TRICYCLIC STEROID HORMONE NUCLEAR RECEPTOR MODULATORS

BACKGROUND OF THE INVENTION

Nuclear hormone receptors are an evolutionarily conserved class of intracellular receptor proteins which have been termed "ligand dependent transcription factors". Evans *et al.*, SCIENCE, 240: 889 (1988). The nuclear hormone receptor gene superfamily encodes structurally-related receptor proteins for glucocorticoids (e.g. cortisol, corticosterone, cortisone), androgens, mineralocorticoids (e.g. aldosterone), progestins, estrogen, and thyroid hormone. Also included within this superfamily of nuclear receptors are receptor proteins for vitamin D, retinoic acid, 9-cis retinoic acid, as well as those receptors for which no cognate ligands have been identified ("orphan receptors") Ribeiro *et al.*, Annual Rev. Med., 46:443-453 (1995). Steroid hormone receptors represent a subset of the nuclear hormone receptor superfamily. So named according to the cognate ligand which complexes with the receptor in its native state, the steroid hormone nuclear receptors include the glucocorticoid receptor (GR), the androgen receptor (AR), the mineralocorticoid receptor (MR), the estrogen receptor (ER), and the progesterone receptor (PR). Tenbaum *et al.*, Int. J. Biochem. Cell. Bio., 29(12):1325-1341(1997).

In contrast to membrane bound receptors, nuclear hormone receptors encounter their respective ligands following entry of the ligand into the cell. Once ligand binding occurs, the ligand-receptor complex modulates transcription of target genes within the cell nucleus. For example, most ligand-free nuclear receptors are bound in a complex with heat shock proteins (hsps) in the cytoplasm. Following entry of circulating hormone into the cell, binding elicits a conformational change in the receptor, dissociating the receptor from the hsp. The ligand bound receptors translocate to the nucleus, where they act as monomers as well as hetero-and homodimers in binding to particular hormone response elements (HREs) in the promoter regions of target genes. The HRE-receptor complex then, in turn, regulates transcription of proximally-located genes. (see Ribeiro *et al.*, supra.). On the other hand, thyroid hormone receptors (TRs) and other non-steroid receptors such as vitamin D receptor (VDR) and retinoic acid receptors (RAR) are bound to their respective HRE in the absence of hsps and/or cognate ligand. Hormones released

from the circulation enter the cell, binding in the nucleus to these receptors which, in turn, hetero-dimerize to other nuclear receptors such as 9-cis retinoic acid (RXR). As with the steroid hormone nuclear receptors, following ligand binding, the ligand-bound receptor complex again regulates transcription of neighboring genes.

Mineralocorticoids and glucocorticoids exert profound influences on a multitude of physiological functions by virtue of their diverse roles in growth, development, and maintenance of homeostasis. The actions are mediated by the MR and GR which share approximately 94% homology in their respective DNA binding regions, and approximately 57% homology in their respective ligand-binding domains. Kino *et al.*, J. of Endocrinology, 169, 437-445 (2001). In visceral tissues, such as the kidney and the gut, MR regulates sodium retention, potassium excretion, and water balance in response to aldosterone. In addition, MR expression in the brain appears to play a role in the control of neuronal excitability, in the negative feedback regulation of the hypothalamic-pituitary-adrenal axis, and in the cognitive aspects of behavioral performance. Castren *et al.*, J. of Neuroendocrinology, 3, 461-466 (1993). GR, which is ubiquitously expressed in almost all tissues and organ systems, is crucial for the integrity of central nervous system function and the maintenance of cardiovascular, metabolic, and immune homeostasis. Kino *et al.*, J. of Endocrinology, 169, 437-445 (2001).

Elevations in aldosterone levels, or excess stimulation of mineralocorticoid receptors, are linked to several pathological disorders or pathologic disease states including, Conn's Syndrome, primary and secondary hyperaldosteronism, increased sodium retention, increased magnesium and potassium excretion (diuresis), increased water retention, hypertension (isolated systolic and combined systolic/diastolic), arrhythmias, myocardial fibrosis, myocardial infarction, Bartter's Syndrome, and disorders associated with excess catecholamine levels. Hadley, M.E., ENDOCRINOLOGY, 2nd Ed., pp. 366-381, (1988); and Brilla *et al.*, Journal of Molecular and Cellular Cardiology, 25 (5), pp. 563-575 (1993). Additionally, elevated aldosterone levels have been increasingly implicated with congestive heart failure (CHF). In CHF, the failing heart triggers hormonal mechanisms in other organs in response to the attending reductions in blood flow and blood pressure seen with CHF. In particular, the kidney activates the renin-angiotensin-aldosterone system (RAAS) causing an increase in aldosterone production by the adrenals which, in turn, promotes water and sodium

retention, potassium loss, and further edema. Although historically it was believed that aldosterone participated in the etiology of CHF only as a result of its salt retaining effects, several recent studies have implicated elevated aldosterone levels with events in extra-adrenal tissues and organs, such as myocardial and vascular fibrosis, direct vascular damage, and baroreceptor dysfunction. Pitt *et al.*, New Eng. J. Med., 341:709-717 (1999). These findings are particularly significant since angiotensin converting enzyme (ACE) inhibitors, which were once thought to completely abolish aldosterone production, are now believed to only transiently suppress aldosterone production which has been shown to occur in extra-adrenal tissues including the heart and vasculature. Weber, New Eng. J. Med., 341:753-755 (1999); Fardella and Miller, Annu. Rev. Nutr., 16:443-470 (1996).

The involvement of aldosterone acting via MR in CHF was confirmed in the recently completed RALES (Randomized Aldactone Evaluation Study) study. Pitt *et al.*, New Eng. J. Med., 341:709-717 (1999). The RALES study demonstrated that the use of Aldactone™ (spironolactone), a well-known competitive MR antagonist, in combination with standard CHF therapy, reduced cardiac related mortality by 30% and frequency of hospitalization by 35% in patients suffering from advanced CHF. However, spironolactone therapy has also been associated with attending side effects such as gastric bleeding, diarrhea, azotemia, hyperchloremic metabolic acidosis an type-4 renal tubule acidosis, nausea, gynecomastia, erectile dysfunction, hyperkalemia, and irregular menses. Thus, the mineralocorticoid receptor represents a viable target for CHF therapy either alone or in combination with conventional CHF therapies such as vasodilators (ACE inhibitors), inotropics (digoxin), diuretics, or beta blockers. Molecules, preferably non-steroids, which bind to the mineralocorticoid receptor and modulate receptor activity without the attending side effects of current therapies would be particularly desirable.

Finally, published international PCT application WO 02/17895 discloses that aldosterone antagonists are useful in the treatment of subjects suffering from one or more cognitive dysfunctions including, but not limited to psychoses, cognitive disorders (such as memory disturbances), mood disorders (such as depression and bipolar disorder), anxiety disorders, and personality disorders. In particular, Smythe *et al.*, *Pharm. Biochem and Behav.*, (1997); 56(3); 507-513 and Young et al, *Arch. Gen. Psychiatry*, (2003); 60; 24-28, respectively, report that mineralocorticoid receptors, and modulation of MR activity, are involved in anxiety and major depression. In addition, Sasano *et al.*,

Anticancer Research, 17; 2001-2007 (1997) reports that expression of MR may be related to differentiation of breast carcinomas. Thus MR modulators may also have utility in treating cancer, particularly of the breast.

Glucocorticoids (e.g. cortisol, corticosterone, and cortisone), and the glucocorticoid receptor, have also been implicated in the etiology of a variety of pathological disorders or pathologic disease states. For example, cortisol hyposecretion is implicated in the pathogenesis of Addison's Disease and may result in muscle weakness, increased melanin pigmentation of the skin, weight loss, hypotension, and hypoglycemia. On the other hand, excessive or prolonged secretion of glucocorticoids has been correlated to Cushing's Syndrome and may also result in obesity, hypertension, glucose intolerance, hyperglycemia, diabetes mellitus, osteoporosis, polyuria, and polydipsia. Hadley, M.E., ENDOCRINOLOGY, 2nd Ed., pp. 366-381, (1988). Further, Coghlan *et al.*, United States Patent No. 6,166,013, issued December 26, 2000, discloses that GR selective agents could modulate GR activity and, thus, be useful in the treatment of inflammation, tissue rejection, auto-immunity, malignancies such as leukemias and lymphomas, Cushing's syndrome, acute adrenal insufficiency, congenital adrenal hyperplasia, rheumatic fever, polyarteritis nodosa, granulomatous polyarteritis, inhibition of myeloid cell lines, immune proliferation/apoptosis, HPA axis suppression and regulation, hypercortisolemia, modulation of the Th1/Th2 cytokine balance, chronic kidney disease, stroke and spinal cord injury, hypercalcemia, hypergylcemia, acute adrenal insufficiency, chronic primary adrenal insufficiency, secondary adrenal insufficiency, congenital adrenal hyperplasia, cerebral edema, thrombocytopenia, and Little's syndrome. Coghlan *et al.* also discloses that GR modulators are especially useful in disease states involving systemic inflammation such as inflammatory bowel disease, systemic lupus erythematosus, polyartitis nodosa, Wegener's granulomatosis, giant cell arthritis, rheumatoid arthritis, osteoarthritis, hay fever, allergic rhinitis, urticaria, angioneurotic edema, chronic obstructive pulmonary disease, asthma, tendonitis, bursitis, Crohn's disease, ulcerative colitis, autoimmune chronic active hepatitis, organ transplantation, hepatitis, and cirrhosis; and that GR modulating compounds have been used as immunostimulants, repressors, and as wound healing and tissue repair agents.

In addition, Coghlan *et al.* discloses that GR modulators have also found use in a variety of topical diseases such as inflammatory scalp alopecia, panniculitis, psoriasis,

discoid lupus erythematosus, inflamed cysts, atopic dermatitis, pyoderma gangrenosum, pemphigus vulgaris, bullous pemphigoid, systemic lupus erythematosus, dermatomyositis, eosinophilic fasciitis, relapsing polychondritis, inflammatory vasculitis, sarcoidosis, Sweet's disease, type 1 reactive leprosy, capillary hemangiomas, contact dermatitis, atopic dermatitis, lichen planus, exfoliative dermatitis, erythema nodosum, acne, hirsutism, toxic epidermal necrolysis, erythema multiform, and cutaneous T-cell lymphoma.

Finally, GR Modulators may also have utility in treating respiratory disorders, such as emphysema, and neuroinflammatory disorders, such as multiple sclerosis and Alzheimer's Disease.

Thus, it is clear that a ligand which has affinity for steroid hormone nuclear receptors, and particularly for MR and/or GR, could be used to modulate (i.e. repress, antagonize, agonize, partially antagonize, partially agonize) receptor activity and target gene expression, thereby influencing a multitude of physiological functions related to alterations in steroid hormone levels and/or steroid hormone receptor activity. In this regard, such ligands could be useful to treat a wide range of pathological disorders susceptible to steroid hormone nuclear receptor modulation.

Several art references disclose tricyclic derivative molecules useful as, *inter alia*, photographic coupling and developing agents, thromboxane A2 modulators, and as histamine H2 antagonists. Further, tricyclic-derivative compounds have also been disclosed as having pharmacological utility as, *inter alia*, antidepressants and anti-inflammatory agents. Surprisingly, however, and in accordance with the present invention, applicants have discovered a series of tricyclic compounds, particularly dibenzosuberane, dibenzoxapine, dibenzazapine, and dibenzthiepine derivatives, with affinity for steroid hormone nuclear receptors, and particularly for MR and GR. Such compounds could modulate receptor activity and, thus, have utility in treating pathological disorders related to alterations in steroid hormone level and/or to alterations in steroid hormone nuclear receptor activity. As a further embodiment, the present invention also provides a novel series of novel non-steroidal tricyclic compounds that exhibit steroid hormone nuclear receptor affinity and modulating activity. Such methods and compounds could address a long felt and continuing need for safe and effective pharmaceutical interventions without the attending side effects of steroidal-type agents. The treatment of steroid hormone related disorders is hereby furthered.

The following references describe examples of the state of the art as it relates to the present invention.

U.S. Patent No. 4,282,233 discloses tricyclic molecules (i.e. Loratadine (Claritin™) as H2 antagonists.

U.S. Patent No. 4,999,363 (and family members) discloses tricyclic molecules as thromboxane A2 antagonists.

U.S. Patent Nos. 5,378,701 and 5,478,840 and 5,607,955 disclose tricyclic molecules as angiotensin II antagonists.

U.S. Patent No. 6,362,188 B1 discloses tricyclic molecules as farnesyl protein transferase inhibitors.

Published International PCT Application WO 99/33786 discloses tricyclic propanamide derivative molecules as anti-inflammatory agents.

Published International PCT Application WO 96/19458 and U.S. Patent Nos. 5,696,130; 5,994,544; 6,017,924, and 6,121,450 disclose quinoline derivative analogs as steroid hormone receptor modulators.

Published International PCT Application WO 00/06137 and U.S. Patent No. 6,166,013 disclose triphenylmethane compounds as glucocorticoid receptor modulators.

U.S. Patent No. 6,147,066 discloses anti-mineralocorticoid receptor compounds for use in treating drug withdrawal syndrome.

U.S. Patents Nos. 6,008,210 and 6,093,708 disclose spirolactone compounds, such as spironolactone and epoxymexrenone, with affinity for the mineralocorticoid receptor for use in the treatment of myocardial fibrosis.

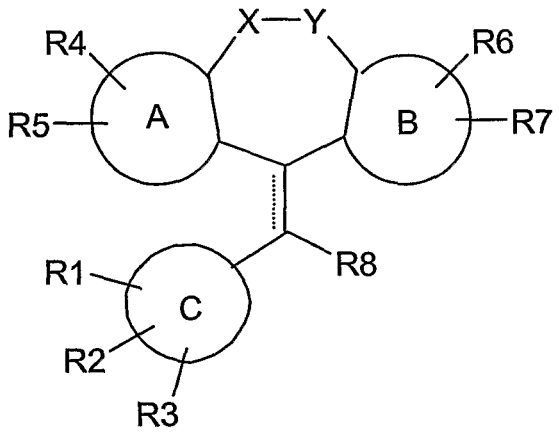
U.S. Patent No. 5,024,912 discloses 5H Dibenzo (A,D) cycloheptenylidene and 5H Dibenzo (A,D) cycloheptanylidene derivatives as electrophotographic photosensitive agents.

U.S. Patents Nos. 4,741,976, 4,539,507, 5,093,210, and 5,166,022 disclose the use of tricyclic molecules in electroluminescent devices.

SUMMARY OF THE INVENTION

The present invention is directed to the discovery that the tricyclic compounds of the present invention, as defined below, are modulators of steroid hormone nuclear

receptors. Accordingly, the present invention provides a method of treating a pathological disorder susceptible to steroid hormone nuclear receptor modulation comprising administering to a patient in need thereof an effective amount of a compound of the formula:

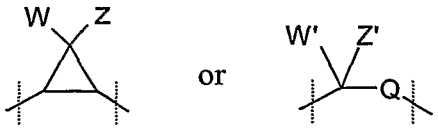


Formula I

wherein,

A, B, and C each independently represent an aryl, heterocycle, or benzofused-heterocyclic ring;

X and Y together represent $-CH_2-CH_2-$, $-CH=CH-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-S-$, $-S-CH_2-$, $-CH_2-SO-$, $-SO-CH_2-$, $-CH_2-SO_2-$, $-SO_2-CH_2-$, $-CH_2-NR^{10}-$, $-NR^{10}-CH_2-$, $-NR^{10}-CO-$, $-CO-NR^{10}-$, or a group of the formula



wherein W and Z each independently represent hydrogen, fluoro, or chloro; W' and Z' each independently represent hydrogen, fluoro, chloro, or methyl; and Q represents NH, O, S, or CH_2;

"- - - - -" represents a single or double bond;

R^1 represents hydrogen, halo, hydroxy, cyano, nitro, amino, oxo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, CH_2NH_2, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, $C(CF_3)_2OH$, SO_2NH_2, $SO_2NR^9R^{10}$, SO_2R^{11}, $NHSO_2R^{11}$, $N(CH_3)SO_2CH_3$, NR^9R^{10}, $CH_2NH(OH)$,

$CH_2NH(SO_2R^{11})$, $NHCOR^{12}$, COR^{12}, $CHNR^{13}$, OR^{14}, SR^{14}, $(C_3$-$C_7)$cycloalkyl, aryl, substituted aryl, $(C_1$-$C_4)$alkyl-aryl, $(C_1$-$C_4)$alkyl-substituted aryl, heterocycle, substituted heterocycle, $(C_1$-$C_4)$alkyl-heterocycle, or $(C_1$-$C_4)$alkyl-substituted heterocycle;

provided that where "C" represents an aryl group, R^1 is other than oxo, $(C_2$-$C_6)$alkenyl, or $(C_2$-$C_6)$alkynyl;

R^2 through R^8 each independently represent hydrogen, halo, hydroxy, cyano, nitro, amino, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, hydroxy$(C_1$-$C_6)$alkyl, hydroxy$(C_1$-$C_6)$alkoxy, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, CH_2NH_2 , halo$(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkoxy, $C(CF_3)_2OH$, SO_2NH_2, $SO_2NR^9R^{10}$, SO_2R^{11}, $NHSO_2R^{11}$, NR^9R^{10}, $CH_2NH(OH)$, $CH_2NH(SO_2R^{11})$, $NHCOR^{12}$, COR^{12} , $CHNR^{13}$, OR^{14}, SR^{14}, $(C_3$-$C_7)$cycloalkyl, aryl, substituted aryl, $(C_1$-$C_4)$alkyl-$(C_1$-$C_6)$alkoxy, $(C_1$-$C_4)$alkyl-aryl, $(C_1$-$C_4)$alkyl-substituted aryl, heterocycle, substituted heterocycle, $(C_1$-$C_4)$alkyl-heterocycle, or $(C_1$-$C_4)$alkyl-substituted heterocycle;

provided that where "A", "B", or "C" represents an aryl group, each of R^2 through R^7 is other than $(C_2$-$C_6)$alkenyl or $(C_2$-$C_6)$alkynyl;

R^9 represents independently at each occurrence cyano, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_4)$alkyl-$(C_1$-$C_6)$alkoxy , halo$(C_1$-$C_6)$alkyl, hydroxy$(C_1$-$C_6)$alkyl, $(C_3$-$C_7)$cycloalkyl, NH-$(C_1$-$C_6)$alkylamine, N,N-$(C_1$-$C_6)$dialkylamine, aryl, substituted aryl, $(C_1$-$C_4)$alkyl-aryl, $(C_1$-$C_4)$alkyl-substituted aryl, heterocycle, substituted heterocycle, $(C_1$-$C_4)$alkyl-heterocycle, or $(C_1$-$C_4)$alkyl-substituted heterocycle;

R^{10} represents independently at each occurrence hydrogen or $(C_1$-$C_6)$alkyl or R^9 and R^{10} together with the nitrogen atom to which they are attached, form a substituted or unsubstituted heterocycle group;

R^{11} represents independently at each occurrence amino, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, halo$(C_1$-$C_6)$alkyl, $(C_3$-$C_7)$cycloalkyl, aryl, substituted aryl, $(C_1$-$C_4)$alkyl-aryl, $(C_1$-$C_4)$alkyl-substituted aryl, heterocycle, substituted heterocycle, $(C_1$-$C_4)$alkyl-heterocycle, or $(C_1$-$C_4)$alkyl-substituted heterocycle;

R^{12} represents independently at each occurrence hydrogen, amino, $(C_1$-$C_6)$alkyl, hydroxy$(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkyl-$(C_1$-$C_6)$alkoxy, $(C_3$-$C_7)$cycloalkyl, NH-$(C_1$-$C_6)$alkylamine, N,N-$(C_1$-$C_6)$dialkylamine, aryl, substituted aryl, $(C_1$-$C_4)$alkyl-aryl, $(C_1$-$C_4)$alkyl-substituted aryl, heterocycle, substituted heterocycle, $(C_1$-$C_4)$alkyl-heterocycle, or $(C_1$-$C_4)$alkyl-substituted heterocycle;

R^{13} represents independently at each occurrence OH, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_7)$cycloalkyl, aryl, heterocycle, or a substituted aryl or heterocycle;

R^{14} represents independently at each occurrence $(C_3\text{-}C_7)$cycloalkyl, aryl, substituted aryl, acyl, $(C_1\text{-}C_4)$alkyl-aryl, $(C_1\text{-}C_4)$alkyl-substituted aryl, heterocycle, substituted heterocycle, $(C_1\text{-}C_4)$alkyl-heterocycle, $(C_1\text{-}C_4)$alkyl-substituted heterocycle, or $(C_1\text{-}C_4)$alkyl-$(C_3\text{-}C_7)$cycloalkyl;

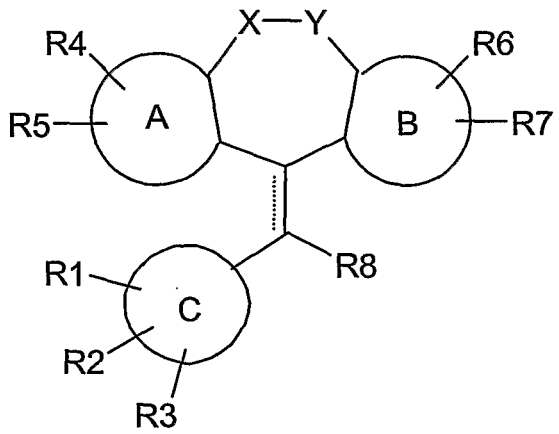
or a pharmaceutically acceptable salt thereof.

Examples of such disorders include Conn's Syndrome, primary and secondary hyperaldosteronism, increased sodium retention, increased magnesium and potassium excretion (diuresis), increased water retention, hypertension (isolated systolic and combined systolic/diastolic), arrhythmias, myocardial fibrosis, myocardial infarction, Bartter's Syndrome, disorders associated with excess catecholamine levels, diastolic and systolic congestive heart failure (CHF), peripheral vascular disease, diabetic nephropathy, cirrhosis with edema and ascites, esophageal varicies, Addison's Disease, muscle weakness, increased melanin pigmentation of the skin, weight loss, hypotension, hypoglycemia, Cushing's Syndrome, obesity, hypertension, glucose intolerance, hyperglycemia, diabetes mellitus, osteoporosis, polyuria, polydipsia, inflammation, autoimmune disorders, tissue rejection associated with organ transplant, malignancies such as leukemias and lymphomas, acute adrenal insufficiency, congenital adrenal hyperplasia, rheumatic fever, polyarteritis nodosa, granulomatous polyarteritis, inhibition of myeloid cell lines, immune proliferation/apoptosis, HPA axis suppression and regulation, hypercortisolemia, modulation of the Th1/Th2 cytokine balance, chronic kidney disease, stroke and spinal cord injury, hypercalcemia, hypergylcemia, acute adrenal insufficiency, chronic primary adrenal insufficiency, secondary adrenal insufficiency, congenital adrenal hyperplasia, cerebral edema, thrombocytopenia, and Little's syndrome, systemic inflammation, inflammatory bowel disease, systemic lupus erythematosus, discoid lupus erythematosus, polyartitis nodosa, Wegener's granulomatosis, giant cell arthritis, rheumatoid arthritis, osteoarthritis, hay fever, allergic rhinitis, contact dermatitis, atopic dermatitis, exfoliative dermatitis, urticaria, angioneurotic edema, chronic obstructive pulmonary disease, asthma, tendonitis, bursitis, Crohn's disease, ulcerative colitis, autoimmune chronic active hepatitis, hepatitis,

cirrhosis, inflammatory scalp alopecia, panniculitis, psoriasis, inflamed cysts, pyoderma gangrenosum, pemphigus vulgaris, bullous pemphigoid, dermatomyositis, eosinophilic fasciitis, relapsing polychondritis, inflammatory vasculitis, sarcoidosis, Sweet's disease, type 1 reactive leprosy, capillary hemangiomas, lichen planus, , erythema nodosum, acne, hirsutism, toxic epidermal necrolysis, erythema multiform, cutaneous T-cell lymphoma, emphysema, Alzheimer's Disease, and multiple sclerosis.

As a particular aspect, the present invention provides a method of treating a pathological disorder susceptible to mineralocorticoid or glucocorticoid receptor modulation comprising administering to a patient in need thereof an effective amount of a compound of Formula I, as described more fully herein and above. As a more particular aspect, the present invention provides a method of treating a pathological disorder susceptible to mineralocorticoid or glucocorticoid receptor antagonism comprising administering to a patient in need thereof an effective amount of a compound of Formula I, as described herein and above. As an even more particular aspect, the present invention provides a method of treating systolic and/or diastolic congestive heart failure or inflammation or rheumatoid arthritis comprising administering to a patient in need thereof an effective amount of a compound of Formula I, as described herein and above.

Certain of the tricyclic compounds corresponding to Formula I are believed to be novel and, thus, to constitute another embodiment of the present invention. As such, the present invention also provides a novel compound of Formula I:

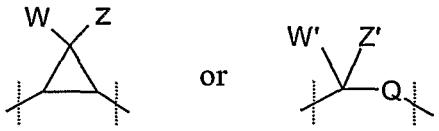


Formula I

wherein,

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X and Y together represent $-CH_2-CH_2-$, $-CH=CH-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-S-$, $-S-CH_2-$, $-CH_2-SO-$, $-SO-CH_2-$, $-CH_2-SO_2-$, $-SO_2-CH_2-$, $-CH_2-NR^{10}-$, $-NR^{10}-CH_2-$, $-NR^{10}-CO-$, $-CO-NR^{10}-$, or a group of the formula



wherein W and Z each independently represent hydrogen, fluoro, or chloro; W' and Z' each independently represent hydrogen, fluoro, chloro, or methyl; and Q represents NH, O, S, or CH_2;

"- - - - -" represents a single or double bond;

R^1 represents halo, hydroxy, cyano, nitro, amino, oxo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, CH_2NH_2, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, $C(CF_3)_2OH$, SO_2NH_2, $SO_2NR^9R^{10}$, SO_2R^{11}, $NHSO_2R^{11}$, $N(CH_3)SO_2CH_3$, NR^9R^{10}, $CH_2NH(OH)$, $CH_2NH(SO_2R^{11})$, $NHCOR^{12}$, COR^{12}, $CHNR^{13}$, OR^{14}, SR^{14}, (C_3-C_7)cycloalkyl, aryl, substituted aryl, (C_1-C_4)alkyl-aryl, (C_1-C_4)alkyl-substituted aryl, heterocycle, substituted heterocycle, (C_1-C_4)alkyl-heterocycle, or (C_1-C_4)alkyl-substituted heterocycle;

provided that where "C" represents an aryl group, R^1 is other than oxo, (C_2-C_6)alkenyl, or (C_2-C_6)alkynyl;

further provided that where "C" represents a benzofused-heterocycle then R^1 may also represent hydrogen;

R^2 through R^8 each independently represent hydrogen halo, hydroxy, cyano, nitro, amino, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, CH_2NH_2, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, $C(CF_3)_2OH$, SO_2NH_2, $SO_2NR^9R^{10}$, SO_2R^{11}, $NHSO_2R^{11}$, NR^9R^{10}, $CH_2NH(OH)$, $CH_2NH(SO_2R^{11})$, $NHCOR^{12}$, COR^{12}, $CHNR^{13}$, OR^{14}, SR^{14}, (C_3-C_7)cycloalkyl, aryl, substituted aryl, (C_1-C_4)alkyl-aryl, (C_1-C_4)alkyl-(C_1-C_6)alkoxy, (C_1-C_4)alkyl-substituted aryl, heterocycle, substituted heterocycle, (C_1-C_4)alkyl-heterocycle, or (C_1-C_4)alkyl-substituted heterocycle;

provided that where "A", "B", or "C" represents an aryl group, each of R^2 through R^7 is other than (C_2-C_6)alkenyl or (C_2-C_6)alkynyl;

further provided that where "C" represents a phenyl ring and R^1 represents halo then at least one of R^2 and R^3 is other than hydrogen, (C_1-C_6)alkyl, aryl, substituted aryl, (C_1-C_4)alkyl-aryl, (C_1-C_4)alkyl-substituted aryl, CHF_2, or CF_3;

further provided that where "C" represents a six-membered ring and R^1 represents cyano, amino, NR^9R^{10}, or $NHCOCH_3$ and R^2 and R^3 are each hydrogen, then R^1 is not bound at the 4-position of said six-membered ring;

further provided that where "C" represents a six-membered ring and R^1 represents nitro, and R^2 and R^3 are each hydrogen, then R^1 is not bound at the 2, 4, or 6-position of said six-membered ring;

R^9 represents independently at each occurrence cyano, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_4)alkyl-(C_1-C_6)alkoxy , halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, NH-(C_1-C_6)alkylamine, N,N-(C_1-C_6)dialkylamine, aryl, substituted aryl, (C_1-C_4)alkyl-aryl, (C_1-C_4)alkyl-substituted aryl, heterocycle, substituted heterocycle, (C_1-C_4)alkyl-heterocycle, or (C_1-C_4)alkyl-substituted heterocycle;

R^{10} represents independently at each occurrence hydrogen or (C_1-C_6)alkyl or R^9 and R^{10} together with the nitrogen atom to which they are attached, form a substituted or unsubstituted heterocycle group;

R^{11} represents independently at each occurrence amino, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, aryl, substituted aryl, (C_1-C_4)alkyl-aryl, (C_1-C_4)alkyl-substituted aryl, heterocycle, substituted heterocycle, (C_1-C_4)alkyl-heterocycle, or (C_1-C_4)alkyl-substituted heterocycle;

R^{12} represents independently at each occurrence hydrogen, amino, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkyl-(C_1-C_6)alkoxy, (C_3-C_7)cycloalkyl, NH-(C_1-C_6)alkylamine, N,N-(C_1-C_6)dialkylamine, aryl, substituted aryl, (C_1-C_4)alkyl-aryl, (C_1-C_4)alkyl-substituted aryl, heterocycle, substituted heterocycle, (C_1-C_4)alkyl-heterocycle, or (C_1-C_4)alkyl-substituted heterocycle;

R^{13} represents independently at each occurrence OH, (C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, aryl, heterocycle, or a substituted aryl or heterocycle;

R^{14} represents independently at each occurrence (C_3-C_7)cycloalkyl, aryl, substituted aryl, acyl, (C_1-C_4)alkyl-aryl, (C_1-C_4)alkyl-substituted aryl, heterocycle,

substituted heterocycle, (C_1-C_4)alkyl-heterocycle, (C_1-C_4)alkyl-substituted heterocycle, or (C_1-C_4)alkyl-(C_3-C_7)cycloalkyl;

or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a method of treating a pathological disorder susceptible to steroid hormone nuclear receptor modulation comprising administering to a patient in need thereof an effective amount of a novel compound of Formula I, or a pharmaceutically acceptable salt thereof, as described more fully herein and above. Examples of such disorders include Conn's Syndrome, primary and secondary hyperaldosteronism, increased sodium retention, increased magnesium and potassium excretion (diuresis), increased water retention, hypertension (isolated systolic and combined systolic/diastolic), arrhythmias, myocardial fibrosis, myocardial infarction, Bartter's Syndrome, disorders associated with excess catecholamine levels, diastolic and systolic congestive heart failure (CHF), peripheral vascular disease, diabetic nephropathy, cirrhosis with edema and ascites, esophageal varicies, Addison's Disease, muscle weakness, increased melanin pigmentation of the skin, weight loss, hypotension, hypoglycemia, Cushing's Syndrome, obesity, hypertension, glucose intolerance, hyperglycemia, diabetes mellitus, osteoporosis, polyuria, polydipsia, inflammation, autoimmune disorders, tissue rejection associated with organ transplant, malignancies such as leukemias and lymphomas, acute adrenal insufficiency, congenital adrenal hyperplasia, rheumatic fever, polyarteritis nodosa, granulomatous polyarteritis, inhibition of myeloid cell lines, immune proliferation/apoptosis, HPA axis suppression and regulation, hypercortisolemia, modulation of the Th1/Th2 cytokine balance, chronic kidney disease, stroke and spinal cord injury, hypercalcemia, hypergylcemia, acute adrenal insufficiency, chronic primary adrenal insufficiency, secondary adrenal insufficiency, congenital adrenal hyperplasia, cerebral edema, thrombocytopenia, and Little's syndrome, systemic inflammation, inflammatory bowel disease, systemic lupus erythematosus, discoid lupus erythematosus, polyartitis nodosa, Wegener's granulomatosis, giant cell arthritis, rheumatoid arthritis, osteoarthritis, hay fever, allergic rhinitis, contact dermatitis, atopic dermatitis, exfoliative dermatitis, urticaria, angioneurotic edema, chronic obstructive pulmonary disease, asthma, tendonitis, bursitis, Crohn's disease, ulcerative colitis, autoimmune chronic active hepatitis, hepatitis, cirrhosis, inflammatory scalp alopecia, panniculitis, psoriasis, inflamed cysts, pyoderma

gangrenosum, pemphigus vulgaris, bullous pemphigoid, dermatomyositis, eosinophilic fasciitis, relapsing polychondritis, inflammatory vasculitis, sarcoidosis, Sweet's disease, type 1 reactive leprosy, capillary hemangiomas, lichen planus, , erythema nodosum, acne, hirsutism, toxic epidermal necrolysis, erythema multiform, and cutaneous T-cell lymphoma.

As a particular aspect, the present invention provides a method of treating a pathological disorder susceptible to mineralocorticoid or glucocorticoid receptor modulation comprising administering to a patient in need thereof an effective amount of a novel compound of Formula I, as described herein and above. More particularly, the present invention provides a method of treating a pathological disorder susceptible to mineralocorticoid or glucocorticoid receptor antagonism comprising administering to a patient in need thereof an effective amount of a novel compound of Formula I, as described herein and above. As an even more particular aspect, the present invention provides a method of treating systolic and/or diastolic congestive heart failure or inflammation comprising administering to a patient in need thereof an effective amount of a novel compound of Formula I, as described herein and above.

In addition, the present invention also provides a method of modulating a steroid hormone nuclear receptor comprising administering to a patient in need thereof an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof. More particularly, the present invention provides a method of modulating MR or GR comprising administering to a patient in need thereof an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, as described herein and above. As an even more particular aspect, the present invention provides a method of modulating MR or GR comprising administering to a patient in need thereof an effective amount of a novel compound of Formula I, as described herein and above. More particular still, the present invention provides a method of antagonizing MR or GR comprising administering to a patient in need thereof an effective amount of a compound of Formula I, or a novel compound of Formula I, all as described herein and above.

In addition, the present invention provides pharmaceutical compositions of compounds of Formula I, including any pharmaceutically acceptable salts and hydrates thereof, comprising a compound of Formula I in combination with a pharmaceutically acceptable carrier, diluent or excipient. More particularly, the present invention provides

pharmaceutical compositions comprising a novel compound of Formula I in combination with a pharmaceutically acceptable carrier, diluent or excipient. This invention also encompasses novel intermediates, and processes for the synthesis of the compounds of Formula I.

The present invention also provides the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating a pathological disorder susceptible to steroid hormone nuclear receptor modulation. More particularly, the present invention provides the use of a novel compound of Formula I, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating a pathological disorder susceptible to steroid hormone nuclear receptor modulation. As an even more particular aspect, the present invention provides the use of a novel compound of Formula I for the manufacture of a medicament for treating congestive heart failure or inflammation.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compounds with affinity for steroid hormone nuclear receptors, particularly MR and/or GR, which could be used to modulate (i.e. repress, antagonize, agonize, partially antagonize, partially agonize) receptor activity and gene expression, thereby influencing physiological functions related to steroid hormone levels and/or steroid hormone receptor activity. In this regard, such ligands are believed to be useful in treating or preventing a multitude of pathological disorders susceptible to steroid hormone nuclear receptor modulation. Thus, methods for the treatment or prevention of pathological disorders susceptible to steroid hormone nuclear receptor modulation constitute an important embodiment of the present invention. As a particular aspect, the present invention provides compounds useful as mineralocorticoid or glucocorticoid receptor modulators. As a more particular aspect, the present invention provides compounds useful as mineralocorticoid or glucocorticoid receptor antagonists. In addition, certain of the compounds of Formula I are believed to be novel which constitute yet another important embodiment of the present invention.

As will be understood by the skilled artisan, some of the compounds useful for the methods of the present invention may be available for prodrug formulation. As used herein, the term "prodrug" refers to a compound of Formula I which has been structurally

modified such that *in vivo* the prodrug is converted, for example, by hydrolytic, oxidative, reductive, or enzymatic cleavage, into the parent molecule ("drug") as given by Formula I. Such prodrugs may be, for example, metabolically labile ester derivatives of the parent compound where said parent molecule bears a carboxylic acid group. Conventional procedures for the selection and preparation of suitable prodrugs are well known to one of ordinary skill in the art. Conversely, some compounds of Formula I may be suitable as antedrugs. "Antedrugs" are themselves pharmacologically active agents, containing metabolically labile functional groups, that upon administration are subsequently deactivated in vivo. Lee *et al.*, *Arch. Pharm. Res.*, 25(2); 111-136 (2002) provides a discussion of such antedrugs and their utility.

It is also understood that many of the steroid hormone nuclear receptor modulators of the present invention may exist as pharmaceutically acceptable salts and, as such, pharmaceutically acceptable salts are therefore included within the scope of the present invention. The term "pharmaceutically acceptable salt" as used herein, refers to salts of the compounds of Formula I, which are substantially non-toxic to living organisms. Typical pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a pharmaceutically acceptable mineral or organic acid or an organic or inorganic base. Such salts are known as acid addition and base addition salts. It is further understood by the skilled reader that salt forms of pharmaceutical compounds are commonly used because they are often more readily crystallized, or more readily purified, than are the free bases. In all cases, the use of the pharmaceutical compounds of the present invention as salts is contemplated in the description herein. Hence, it is understood that where compounds of Formula I are capable of forming salts, the pharmaceutically acceptable salts and isoforms thereof are encompassed in the names provided herein.

Acids commonly employed to form acid addition salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as *p*-toluenesulfonic, methanesulfonic acid, oxalic acid, *p*-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like. Examples of such pharmaceutically acceptable salts are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, bromide, iodide, hydroiodide,

dihydroiodide, acetate, propionate, decanoate, caprylate, acrylate, formate, hydrochloride, dihydrochloride, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, hydroxybenzoate, methoxybenzoate, phthalate, xylenesulfonate, phenyl acetate, phenyl propionate, phenyl butyrate, citrate, lactate, α-hydroxybutyrate, glycolate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, napththalene-2-sulfonate, mandelate and the like. Base addition salts include those derived from inorganic bases, such as ammonium or alkali or alkaline earth metal hydroxides, carbonates, bicarbonates, and the like. Such bases useful in preparing the salts of this invention thus include sodium hydroxide, potassium hydroxide, ammonium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like.

As used herein, the term "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures which are not interchangeable. The three-dimensional structures are called configurations. As used herein, the term "enantiomer" refers to one of two stereoisomers whose molecules are nonsuperimposable mirror images of one another. The term "chiral center" refers to a carbon atom to which four different groups are attached. As used herein, the term "diastereomers" refers to stereoisomers which are not enantiomers. In addition, two diastereomers which have a different configuration at only one chiral center are referred to herein as "epimers". The terms "racemate", "racemic mixture" or "racemic modification" refer to a mixture of equal parts of enantiomers.

The compounds of the present invention may have one or more chiral centers and may, therefore, exist in a variety of stereoisomeric configurations. As a consequence of these chiral centers the compounds of the present invention may occur as racemates, mixtures of enantiomers, and as individual enantiomers as well as diastereomers and mixtures of diastereomers. All such racemates, enantiomers, and diastereomers are within the scope of the present invention. Enantiomers of the compounds provided by the present invention can be resolved, for example, by one of ordinary skill in the art using standard techniques such as those described by J. Jacques, *et al.*, "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, Inc., 1981.

The terms "R" and "S" are used herein as commonly used in organic chemistry to denote specific configuration of a chiral center. The term "R" (rectus) refers to that configuration of a chiral center with a clockwise relationship of group priorities (highest to second lowest) when viewed along the bond from the chiral carbon toward the lowest priority group. The term "S" (sinister) refers to that configuration of a chiral center with a counterclockwise relationship of group priorities (highest to second lowest) when viewed along the bond from the chiral carbon toward the lowest priority group. The priority of groups is based upon their atomic number (in order of decreasing atomic number). A partial list of priorities and a discussion of stereochemistry is contained in "Nomenclature of Organic Compounds: Principles and Practice", (J.H. Fletcher, *et al.*, eds., 1974) at pages 103-120.

The specific stereoisomers and enantiomers of compounds of Formula I can be prepared by one of ordinary skill in the art utilizing well known techniques and processes, such as those disclosed by Eliel and Wilen, "Stereochemistry of Organic Compounds", John Wiley & Sons, Inc., 1994, Chapter 7; Separation of Stereoisomers, Resolution, Racemization; and by Collet and Wilen, "Enantiomers, Racemates, and Resolutions", John Wiley & Sons, Inc., 1981. For example, specific stereoisomers and enantiomers can be prepared by stereospecific syntheses using enantiomerically and geometrically pure, or enantiomerically or geometrically enriched starting materials. In addition, the specific stereoisomers and enantiomers can be resolved and recovered by techniques such as chromatography on chiral stationary phases, enzymatic resolution or fractional recrystallization of addition salts formed by reagents used for that purpose.

As will be appreciated by one of ordinary skill in the art, molecules containing a carbon-carbon double bond may exist as geometric isomers. Two methods are commonly used to designate the specific isomers, the "cis-trans" method and the "E and Z" method depending on whether the groups attached to each of the ethylene carbons are the same or different. A discussion of geometric isomerism and the naming of specific isomers is found in March, "Advanced Organic Chemistry", John Wiley & Sons, 1992, Chapter 4. All such geometric isomers, as well as mixtures of individual isomers, are contemplated and provided by the present invention.

Where used herein, the term "Pg" refers to a suitable oxygen or nitrogen protecting group. Suitable oxygen or nitrogen protecting groups, as used herein, refers to those

groups intended to protect or block the oxygen or nitrogen group against undesirable reactions during synthetic procedures. Whether the term "Pg", as used herein, represents an oxygen protecting group or a nitrogen protecting group will be readily apparent to the ordinarily skilled artisan. The suitability of the oxygen or nitrogen protecting group used will depend upon the conditions that will be employed in subsequent reaction steps wherein protection is required, and is well within the knowledge of one of ordinary skill in the art.

Commonly used nitrogen protecting groups are disclosed in Greene, "Protective Groups In Organic Synthesis, 3rd Edition" (John Wiley & Sons, New York (1999)). Suitable nitrogen protecting groups comprise acyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, .alpha.-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and the like; sulfonyl groups such as benzenesulfonyl, p-toluenesulfonyl and the like; carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, .alpha.,.alpha.-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2,-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl, cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, phenylthiocarbonyl and the like; alkyl groups such as benzyl, triphenylmethyl, benzyloxymethyl and the like; and silyl groups such as trimethylsilyl and the like. Commonly used oxygen protecting groups are also disclosed in Greene (supra). Suitable oxygen protecting groups comprise alkyl groups such as methyl ,ethyl, and the like; silyl groups such as t-butyldimethylsilyl, t-butyldiphenylsilyl, triisopropylsilyl, and the like, with t-butyldimethylsilyl being preferred. Other commonly used oxygen protecting groups include benzyl, 4-nitrophenyl methyl, benzoyl, and the like.

As used herein the term "(C_1-C_4)alkyl" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 4 carbon atoms and includes, but is not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and the like.

As used herein the term "(C_1-C_6)alkyl" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms and includes, but is not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, n-hexyl, and the like. It is understood that the term "(C_1-C_4)alkyl" is included within the definition of "(C_1-C_6)alkyl".

As used herein the term "(C_1-C_{10})alkyl" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 10 carbon atoms and includes, but is not limited to methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tertiary butyl, pentyl, isopentyl, hexyl, 2,3-dimethyl-2-butyl, heptyl, 2,2-dimethyl-3-pentyl, 2-methyl-2-hexyl, octyl, 4-methyl-3-heptyl and the like. It is understood that the terms "(C_1-C_4)alkyl" and "(C_1-C_6)alkyl" are included within the definition of "(C_1-C_{10})alkyl".

As used herein, the terms "Me", "Et", "Pr", "i-Pr", "Bu" and "t-Bu" refer to methyl, ethyl, propyl, isopropyl, butyl and tert-butyl respectively.

As used herein, the term "(C_1-C_4)alkoxy" refers to an oxygen atom bearing a straight or branched, monovalent, saturated aliphatic chain of 1 to 4 carbon atoms and includes, but is not limited to methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, and the like. As used herein the term "(C_1-C_6)alkoxy" refers to an oxygen atom bearing a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms and includes, but is not limited to methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, n-pentoxy, n-hexoxy, and the like. It is understood that the term "(C_1-C_4)alkoxy" is included within the definition of "(C_1-C_6)alkoxy".

As used herein, the term "hydroxy(C_1-C_4)alkyl" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 4 carbon atoms bearing a hydroxyl group attached to one of the carbon atoms. As used herein, the term "hydroxy(C_1-C_6)alkyl" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms bearing a hydroxyl group attached to one of the carbon atoms. It is understood that the term "hydroxy(C_1-C_4)alkyl" is included within the definition of "hydroxy(C_1-C_6)alkyl". As used herein, the term "hydroxy(C_1-C_4)alkoxy" refers to an oxygen atom bearing a straight or branched, monovalent, saturated aliphatic chain of 1 to 4 carbon

atoms, further bearing a hydroxyl group attached to one of the carbon atoms. As used herein, the term "hydroxy(C_1-C_6)alkoxy" refers to an oxygen atom bearing a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms, further bearing a hydroxyl group attached to one of the carbon atoms. It is understood that the term "hydroxy(C_1-C_4)alkoxy" is included within the definition of "hydroxy(C_1-C_6)alkoxy".

As used herein, the term "(C_1-C_6)alkyl-(C_1-C_6)alkoxy" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms which has a (C_1-C_6)alkoxy group attached to the aliphatic chain. The term "(C_1-C_4)alkyl-(C_1-C_6)alkoxy" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 4 carbon atoms which has a (C_1-C_6)alkoxy group attached to the aliphatic chain. It is understood that the term "(C_1-C_4)alkyl-(C_1-C_6)alkoxy" is included within the definition of "(C_1-C_6)alkyl-(C_1-C_6)alkoxy". "(C_1-C_6)alkoxymethylene" refers to a methylene group bearing a (C_1-C_6)alkoxy group. "(C_1-C_6)alkoxy(C_1-C_6)alkoxy-methylene refers to a methylene group bearing a (C_1-C_6)alkoxy group which, in turn, bears an additional (C_1-C_6)alkoxy group attached to the aliphatic chain.

As used herein, the terms "halo", "halide" or "hal" of "Hal" refer to a chlorine, bromine, iodine or fluorine atom, unless otherwise specified herein.

As used herein, the term "halo(C_1-C_4)alkyl" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 4 carbon atoms bearing one or more halo groups attached to one or more of the carbon atoms. As used herein, the term "halo(C_1-C_6)alkyl" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms bearing one or more halo groups attached to one or more of the carbon atoms. It is understood that the term "halo(C_1-C_4)alkyl" is included within the definition of "halo(C_1-C_6)alkyl". Typical examples of "halo(C_1-C_6)alkyl" include CF_3, CHF_2, CH_2F, and the like. As used herein, the term "halo(C_1-C_4)alkoxy" refers to an oxygen atom bearing a straight or branched, monovalent, saturated aliphatic chain of 1 to 4 carbon atoms, further bearing one or more halo groups attached to one or more of the carbon atoms. As used herein, the term "halo(C_1-C_6)alkoxy" refers to an oxygen atom bearing a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms, further bearing one or more halo groups attached to one or more of the carbon atoms. It is understood that the term "halo(C_1-C_4)alkoxy" is included within the

definition of "halo(C_1-C_6)alkoxy". Typical examples of "halo(C_1-C_6)alkoxy" include OCF_3, $OCHF_2$, OCH_2F, and the like.

As used herein the term "(C_2-C_6)alkenyl" refers to a straight or branched, monovalent, unsaturated aliphatic chain having from two to six carbon atoms and having a double bond. Typical (C_2-C_6)alkenyl groups include ethenyl (also known as vinyl), 1-methylethenyl, 1-methyl-1-propenyl, 1-butenyl, 1-hexenyl, 2-methyl-2-propenyl, 1-propenyl, 2-propenyl, 2-butenyl, 2-pentenyl, and the like.

As used herein the term "(C_2-C_6)alkynyl" refers to a straight or branched, monovalent, unsaturated aliphatic chain having from two to six carbon atoms and having a triple bond.

As used herein, the term "acyl" refers to a hydrogen or a (C_1-C_6)alkyl group attached to a carbonyl group. Typical acyl groups include formyl, acetyl, propionyl, butyryl, valeryl, and caproyl.

As used herein, the term "aryl" refers to a monovalent carbocyclic group containing one or more fused or non-fused phenyl rings and includes, for example, phenyl, 1- or 2-naphthyl, 1,2-dihydronaphthyl, 1,2,3,4-tetrahydronaphthyl, and the like. The term "substituted aryl" refers to an aryl group substituted with one to three moieties, preferably one or two, chosen from the group consisting of acyl, halogen, hydroxy, cyano, nitro, amino, (C_1-C_6)alkyl, (C_1-C_4)alkylsulfonyl, halo(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_1-C_6)alkylthio, (C_3-C_7)cycloalkyl, (C_1-C_4)alkyl-(C_3-C_7)cycloalkyl, aryl, (C_1-C_4)alkyl-aryl, heterocycle, (C_1-C_4)alkyl-heterocycle, (C_1-C_4)alkoxy-heterocycle, (C_1-C_6)alkoxycarbonyl, , N,N(C_1-C_6)dialkylamine, NH(C_1-C_6)alkylamine, $NHSO_2$(C_1-C_4)alkyl, (C_1-C_4)alkyl-N,N-(C_1-C_6)dialkylamine, (C_1-C_4)alkoxy-N,N-(C_1-C_6)dialkylamine difluoromethyl, difluoromethoxy, trifluoromethyl, trifluoromethoxy, CF_2CF_3, benzoyl, phenoxy, or an aryl or heterocycle group further substituted with one to two moieties selected from the group consisting of :

(C_1-C_4)alkyl,
(C_3-C_7)cycloalkyl,
halo,
hydroxy,
(C_1-C_4)alkoxy,
CF_3,

OCF_3,

CHF_2,

$OCHF_2$,

CF_2CF_3,

cyano,

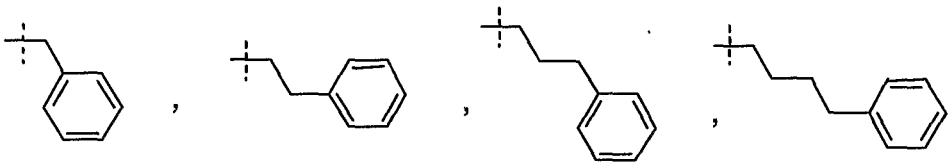
nitro,

amino,

$NH(C_1\text{-}C_4)$alkylamine, and

N,N-($C_1\text{-}C_4$)dialkylamine;

As used herein, the term "$(C_1\text{-}C_6)$alkyl-aryl" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms which has an aryl group attached to the aliphatic chain. "$(C_1\text{-}C_4)$alkyl-aryl" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 4 carbon atoms which has an aryl group attached to the aliphatic chain. It is understood that the term "$(C_1\text{-}C_4)$alkyl-aryl" is included within the definition of "$(C_1\text{-}C_6)$alkyl-aryl. Examples of "$(C_1\text{-}C_6)$alkyl-aryl" include the following:



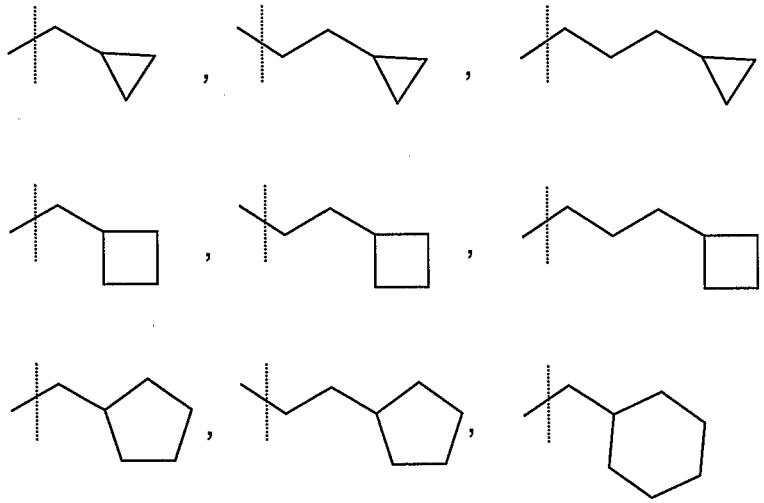
and the like.

As used herein, the term "$(C_1\text{-}C_4)$alkyl-substituted aryl" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 4 carbon atoms which has a substituted aryl group, as described above, attached to the aliphatic chain. Examples of "$(C_1\text{-}C_4)$alkyl-substituted aryl" include methylbenzyl, phenylbenzyl, nitrobenzyl, methoxybenzyl, chlorobenzyl, bromobenzyl, dimethlybenzyl, aminobenzyl, dichlorobenzyl, and the like.

As used herein, the term "aryl$(C_1\text{-}C_6)$alkoxy" refers to an oxygen atom bearing a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms wherein said aliphatic chain, in turn, bears an aryl group.

As used herein the term "(C_3-C_{10})cycloalkyl" refers to a saturated hydrocarbon ring structure composed of one or more fused or unfused rings containing from three to ten carbon atoms. Typical (C_3-C_{10})cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, adamantanyl, and the like. "(C_3-C_7)cycloalkyl" refers to a saturated hydrocarbon ring structure composed of one or more fused or unfused rings containing from three to seven carbon atoms. It is understood that the definition of "(C_3-C_7)cycloalkyl" is included within the definition of "(C_3-C_{10})cycloalkyl". The term "substituted (C_3-C_7)cycloalkyl" refers to a "(C_3-C_7)cycloalkyl group substituted with one or two moieties chosen from the group consisting of halogen, hydroxy, cyano, nitro, amino, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_4)alkyl-(C_3-C_{10})cycloalkyl, (C_1-C_4)alkyl-aryl, (C_1-C_6)alkoxycarbonyl, N,N(C_1-C_6)dialkylamine, NH(C_1-C_6)alkylamine, (C_1-C_4)alkyl-N,N-C_1-C_6dialkylamine, difluoromethyl, difluoromethoxy, trifluoromethyl, and trifluoromethoxy.

As used herein, the term "(C_1-C_4)alkyl-(C_3-C_7)cycloalkyl" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 4 carbon atoms which has a (C_3-C_7)cycloalkyl attached to the aliphatic chain. Included within the term "(C_1-C_4)alkyl-(C_3-C_7)cycloalkyl" are the following:



and the like. As used herein, the term "(C_1-C_4)alkyl-substituted (C_3-C_7)cycloalkyl" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 4 carbon atoms bearing a substituted (C_3-C_7)cycloalkyl group attached to the aliphatic chain.

As used herein the term "(C_3-C_7)cycloalkoxy" refers to an oxygen atom bearing a saturated hydrocarbon ring structure composed of one or more fused or unfused rings containing from three to seven carbon atoms.

As used herein, the term "(C_1-C_6) alkoxycarbonyl" refers to a carbonyl group having a (C_1-C_6)alkyl group attached to the carbonyl carbon through an oxygen atom. Examples of this group include t-butoxycarbonyl, methoxycarbonyl, ethoxycarbonyl and the like. It is understood that the term "(C_1-C_4) alkoxycarbonyl" is included within the definition of "(C_1-C_6) alkoxycarbonyl".

As used herein the term "heterocycle" refers to a saturated or unsaturated, five- or six-membered ring, which contains one to four heteroatoms selected from the group consisting of oxygen, sulfur, and nitrogen. It is understood that the remaining atoms are carbon and that the heterocycle may be attached at any point which provides for a stable structure. Examples of heterocycle groups include thiophenyl, furyl, tetrahydrofuryl, pyrrolyl, imidazolyl, pyrrazolyl, thiazolyl, thiazolidinyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, thiadiazolyl, oxadiazolyl, tetrazolyl, pyridyl, pyridinyl, pyrimidyl, pyrazinyl, pyridiazinyl, triazinyl, imidazolyl, dihydropyrimidyl, tetrahydropyrimdyl, pyrrolidinyl, piperidinyl, piperazinyl, pyrazolidinyl, pyrimidinyl, imidazolidimyl, morpholinyl, pyranyl, thiomorpholinyl, and the like. As used herein, the term "benzofused heterocyclic ring" or "benzofused heterocycle" refers to a saturated or unsaturated, five- or six-membered ring, which contains one to four heteroatoms selected from the group consisting of oxygen, sulfur, and nitrogen, and which is fused to a phenyl group. Representative "benzofused heterocyclic rings" include benzooxazole, benzoimidazole, benzimidazole, benzofuran, benzothiophene, benzothiazole, azaindole, and indole.

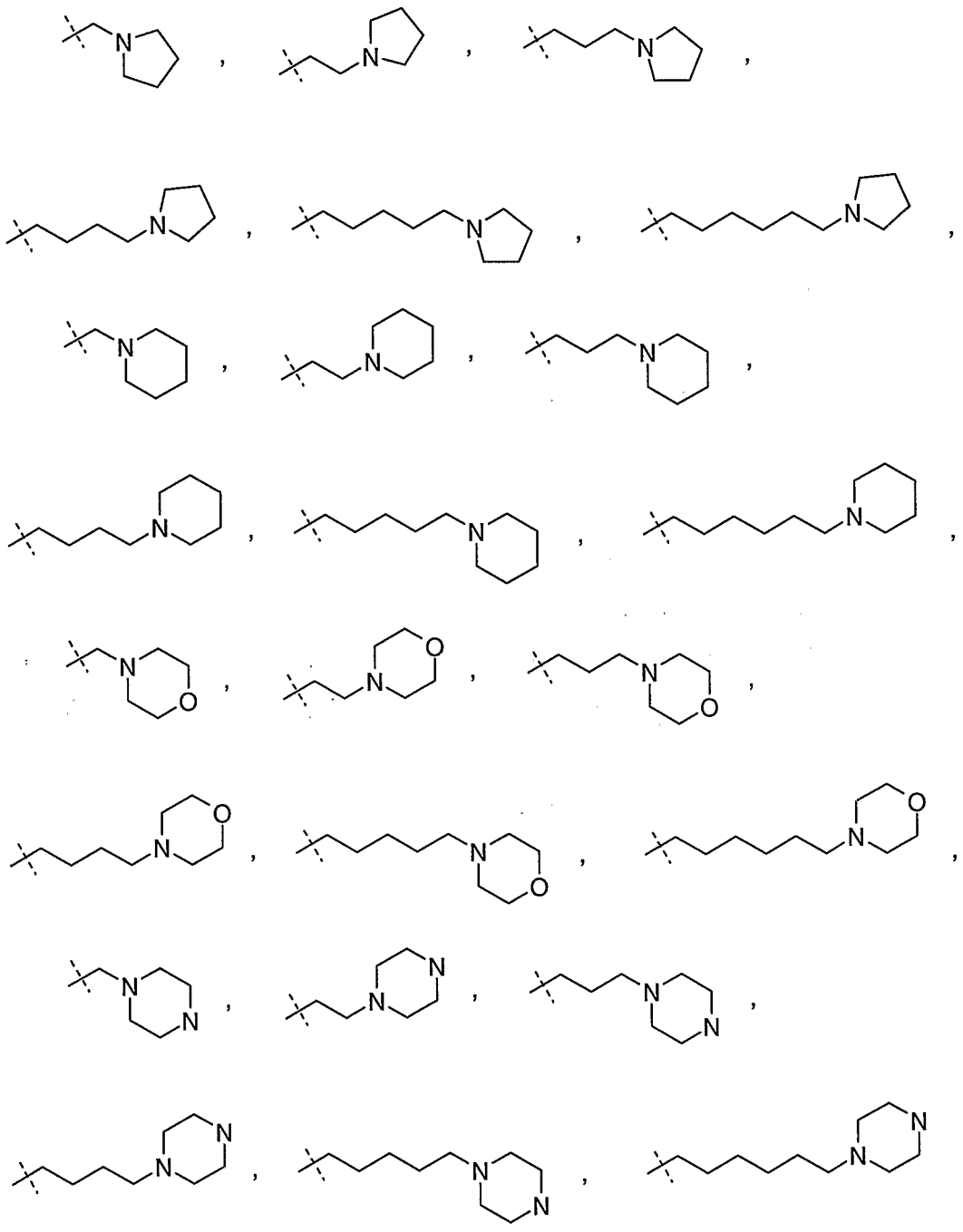
The term "substituted heterocycle" represents a heterocycle group substituted with one or two moieties chosen from the group consisting of acyl, halogen, hydroxy, cyano, nitro, amino, (C_1-C_6)alkyl, (C_1-C_4)alkylsulfonyl, halo(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_1-C_6)alkylthio, (C_3-C_7)cycloalkyl, (C_1-C_4)alkyl-(C_3-C_7)cycloalkyl, aryl, (C_1-C_4)alkyl-aryl, heterocycle, (C_1-C_4)alkyl-heterocycle, (C_1-C_4)alkoxy-heterocycle, (C_1-C_6)alkoxycarbonyl, , N,N(C_1-C_6)dialkylamine, $NHCOCH_3$, NH(C_1-C_6)alkylamine, $NHSO_2$(C_1-C_4)alkyl, (C_1-C_4)alkyl-N,N-C_1-C_6dialkylamine, (C_1-C_4)alkoxy-N,N-C_1-C_6dialkylamine, difluoromethyl, difluoromethoxy, trifluoromethyl, trifluoromethoxy,

CF_2CF_3, or an aryl or heterocycle group further substituted with one to two moieties selected from the group consisting of :

$(C_1$-$C_4)$alkyl,
$(C_3$-$C_7)$cycloalkyl,
halo,
hydroxy,
$(C_1$-$C_4)$alkoxy,
CF_3,
OCF_3,
CHF_2,
$OCHF_2$,
CF_2CF_3,
cyano,
nitro,
amino,
$NH(C_1$-$C_4)$alkylamine, and
N,N-$(C_1$-$C_4)$dialkylamine;

Examples of substituted heterocycle include methylisoxazole, dimethylisoxazole, methylimidazole, trifluoromethyl imidazole, pyridinyl thiophene, and the like. The term "substituted benzofused heterocycle" represents a benzofused heterocycle group substituted with one or two moieties chosen from the group consisting of acyl, halogen, hydroxy, cyano, nitro, amino, $(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkyl, or $(C_1$-$C_6)$alkoxy.

As used herein, the term "$(C_1$-$C_4)$alkyl-heterocycle" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 4 carbon atoms which has a heterocycle group attached to the aliphatic chain. Examples of "$(C_1$-$C_4)$alkyl-heterocycle" include:

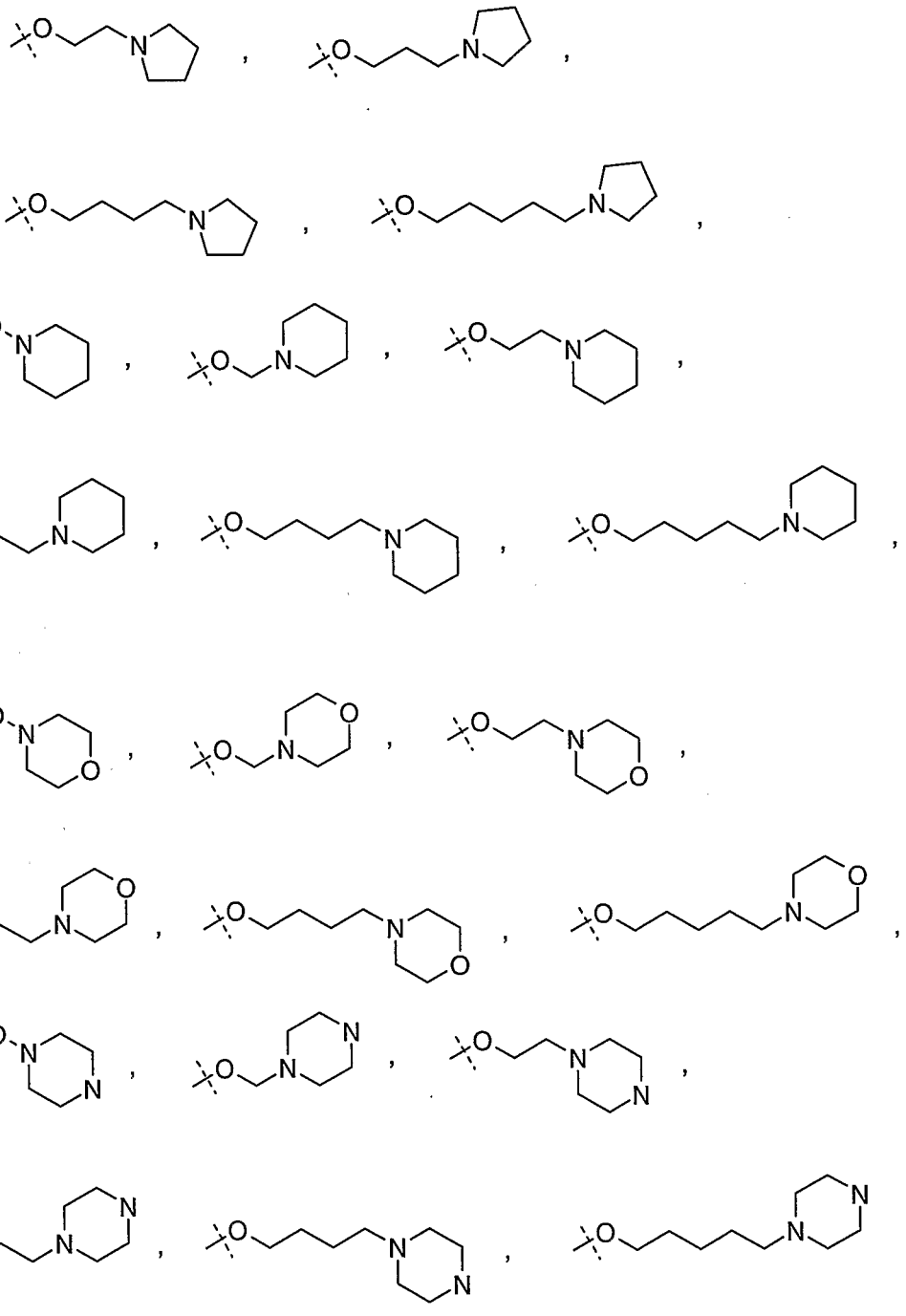


and the like.

The term "(C_1-C_4)alkyl-substituted heterocycle" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 4 carbon atoms bearing a substituted heterocycle group attached to the aliphatic chain.

As used herein, the term "(C_1-C_4)alkoxy-heterocycle" refers to an oxygen atom bearing a straight or branched, monovalent, saturated aliphatic chain of 1 to 4 carbon

atoms which has a heterocycle group attached to the aliphatic chain. Examples of "(C_1-C_4)alkoxy-heterocycle" include:



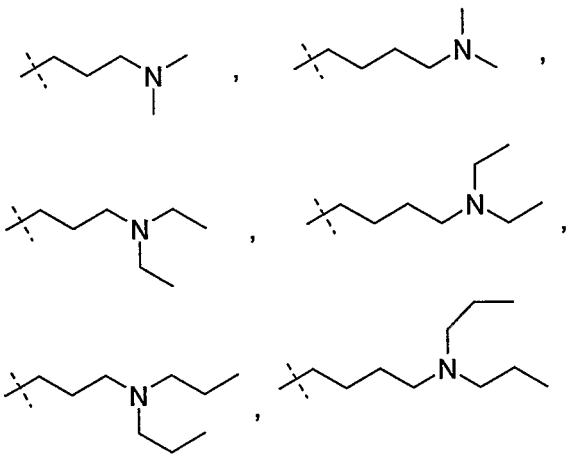
and the like.

The term "(C_1-C_4)alkoxy-substituted heterocycle" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 4 carbon atoms bearing a substituted heterocycle group attached to the aliphatic chain.

As used herein the term "NH(C_3-C_7)cycloalkyl" refers to an amino group substituted with a saturated hydrocarbon ring structure composed of one or more fused or unfused rings containing from three to seven carbon atoms.

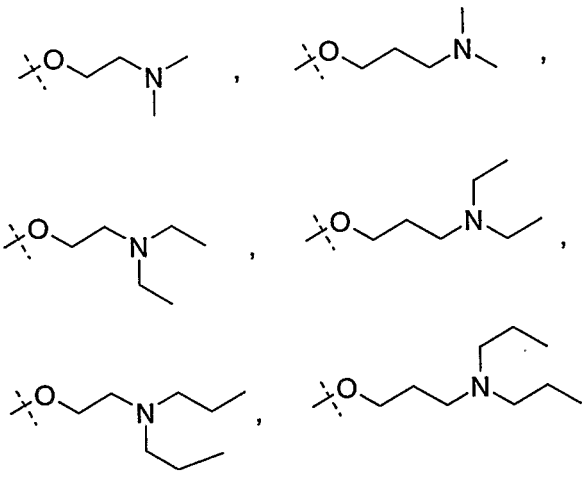
As used herein the term "N,N-(C_1-C_6)dialkylamine" refers to a nitrogen atom substituted with two straight or branched, monovalent, saturated aliphatic chains of 1 to 6 carbon atoms. Included within the term "N,N-(C_1-C_6)dialkylamine" are –$N(CH_3)_2$, -$N(CH_2CH_3)_2$, -$N(CH_2CH_2CH_3)_2$, -$N(CH_2CH_2CH_2CH_3)_2$, and the like. "NH-(C_1-C_6) alkylamine" refers to a nitrogen atom substituted with a straight or branched, monovalent, saturated aliphatic chains of 1 to 6 carbon atoms.

As used herein the term "(C_1-C_6)alkyl-N,N-C_1-C_6dialkylamine" refers to straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms which has an N,N-(C_1-C_6)dialkylamine attached to the aliphatic chain. Included within the term "(C_1-C_6)alkyl-N,N-(C_1-C_6)dialkylamine" are the following:



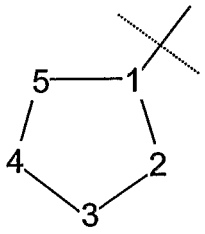
and the like.

As used herein the term "(C_1-C_6)alkoxy-N,N-(C_1-C_6)dialkylamine" refers to an oxygen atom bearing a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms which has an N,N-C_1-C_6 dialkylamine attached to the aliphatic chain. Included within the term "C_1-C_6 alkoxy-N,N-(C_1-C_6)dialkylamine" are the following:

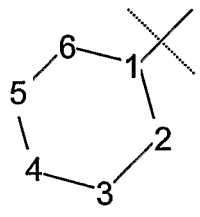


and the like.

The compounds of the present invention have an aryl, heterocycle, or benzofused-heterocycle ring (ring "C" of Formula I) attached to the tricyclic core. Each of these ring structures, in turn, may be singularly or multiply substituted as denoted in Formula I. As a consequence, a uniform method of numbering is needed to denote the positions on the rings where substitution occurs or may occur. As such, where ring "C" is a five-membered ring, the following numbering pattern is used to denote the positions on the ring where substitution occurs, or may occur

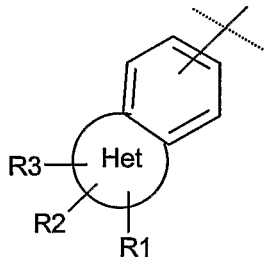


Where ring "C" is a six-membered ring, the following numbering pattern is used to denote the positions on the ring where substitution occurs, or may occur



As stated, the compounds of the present invention may have a benzofused-heterocycle ring (ring "C" of Formula I) attached to the tricyclic core. Each of these ring

structures, in turn, may be singularly or multiply substituted as denoted in Formula I. More particularly, where ring "C" is a benzofuzed-heterocycle, ring "C" attaches to the tricyclic core of Formula I through the phenyl portion of the bicyclic system and the substituents R^1-R^3 attach to ring "C" through the heteroatom containing portion of the bicyclic ring system. This particular configuration of ring "C", when "C" represents a benzofuzed heterocycle, in relation to the tricyclic core of Formula I and the substituents R^1-R^3 is given by the following:



Representative examples where ring "C" is a benzofused-heterocycle include benzoimidazole, benzothiazole, benzooxazole, benzothiadiazole, indazole, indole, oxindole, and benzimidazole.

Representative examples where ring "C" is a benzofused-heterocycle and at least one of R^1-R^3 is other than hydrogen, include benzoimidazolone, benzothiazolone, benzooxazolone, indoline, N-methylbenzoimidazolone, N-ethylbenzoimidazolone, N-propylbenzoimidazolone, N-isopropylbenzoimidazolone, N-isobutylbenzoimidazolone, N-trifluoroethylbenzoimidazolone, N-phenylbenzoimidazolone, N-pyridinylbenzoimidazolone, N-imidazolylbenzoimidazolone, N-thiazolylbenzoimidazolone, N-oxazolylbenzoimidazolone, N-morpholinoethylbenzoimidazolone, N-morpholinopropylbenzoimidazolone, N-methylpiperazinylethylbenzoimidazolone, N-(1-piperdinyl)ethylbenzoimidazolone, N-(1-pyrrolidinyl)ethylbenzoimidazolone, N-(1-piperdin-4-yl)ethylbenzoimidazolone, N-(1-methylpiperdin-4-yl)benzoimidazolone, N-(1-pyrrolidin-3-yl)benzoimidazolone, and N-(1-methylpyrrolidin-3-yl)benzoimidazolone, and the like.

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The designation "  " refers to a bond that protrudes backward out of the plane of the page.

As used herein, the term "steroid hormone nuclear receptor modulator" refers to those nuclear hormone receptor ligands which bind to any one of GR, MR, AR, ER, or PR, of the larger class of nuclear hormone receptors, and either agonize, antagonize, partially agonize, partially antagonize, or repress the receptor's activity.

As used herein the term "mineralocorticoid receptor" or "MR" refers to the mineralocorticoid receptor subtype, of the larger class of nuclear hormone receptors, which binds the mineralocorticoid hormone aldosterone, as its cognate ligand. The term "mineralocorticoid receptor modulator" or "mineralocorticoid modulator" or "MR modulator" as used herein, refers to those nuclear hormone receptor ligands which bind to the mineralocorticoid receptor subtype and modulate (i.e. agonize, antagonize, partially agonize, partially antagonize, or repress) the receptor activity. As a particular embodiment, the present invention provides antagonists of MR activity.

As used herein the term "glucocorticoid receptor" or "GR" refers to the glucocorticoid receptor subtype, of the larger class of nuclear hormone receptors, which binds the glucocorticoid hormones cortisol, corticosterone, or cortisone as its cognate ligand. The term "glucocorticoid receptor modulator" or "glucocorticoid modulator" or "GR modulator", as used herein, refers to those nuclear hormone receptor ligands which bind to the glucocorticoid receptor subtype and modulate (i.e. agonize, antagonize, partially agonize, partially antagonize, or repress) the receptor activity.

As used herein, the term "disorder susceptible to steroid hormone nuclear receptor modulation" refers to any pathological disorder, of any origin, known or believed to be responsive to administration of a modulator (i.e. agonist, antagonist, partial agonist, or partial antagonist) of a steroid hormone nuclear receptor. Such pathological disorders include Conn's Syndrome, primary and secondary hyperaldosteronism, increased sodium retention, increased magnesium and potassium excretion (diuresis), increased water retention, hypertension (isolated systolic and combined systolic/diastolic), arrhythmias, myocardial fibrosis, myocardial infarction, Bartter's Syndrome, disorders associated with excess catecholamine levels, diastolic and systolic congestive heart failure (CHF), peripheral vascular disease, diabetic nephropathy, cirrhosis with edema and ascites, esophageal varicies, Addison's Disease, muscle weakness, increased melanin pigmentation of the skin, weight loss, hypotension, hypoglycemia, Cushing's Syndrome, obesity, hypertension, glucose intolerance, hyperglycemia, diabetes mellitus, osteoporosis,

polyuria, polydipsia, inflammation, autoimmune disorders, tissue rejection associated with organ transplant, malignancies such as leukemias and lymphomas, acute adrenal insufficiency, congenital adrenal hyperplasia, rheumatic fever, polyarteritis nodosa, granulomatous polyarteritis, inhibition of myeloid cell lines, immune proliferation/apoptosis, HPA axis suppression and regulation, hypercortisolemia, modulation of the Th1/Th2 cytokine balance, chronic kidney disease, stroke and spinal cord injury, hypercalcemia, hypergylcemia, acute adrenal insufficiency, chronic primary adrenal insufficiency, secondary adrenal insufficiency, congenital adrenal hyperplasia, cerebral edema, thrombocytopenia, and Little's syndrome, systemic inflammation, inflammatory bowel disease, systemic lupus erythematosus, discoid lupus erythematosus, polyartitis nodosa, Wegener's granulomatosis, giant cell arthritis, rheumatoid arthritis, osteoarthritis, hay fever, allergic rhinitis, contact dermatitis, atopic dermatitis, exfoliative dermatitis, urticaria, angioneurotic edema, chronic obstructive pulmonary disease, asthma, tendonitis, bursitis, Crohn's disease, ulcerative colitis, autoimmune chronic active hepatitis, hepatitis, cirrhosis, inflammatory scalp alopecia, panniculitis, psoriasis, inflamed cysts, pyoderma gangrenosum, pemphigus vulgaris, bullous pemphigoid, dermatomyositis, eosinophilic fasciitis, relapsing polychondritis, inflammatory vasculitis, sarcoidosis, Sweet's disease, type 1 reactive leprosy, capillary hemangiomas, lichen planus, , erythema nodosum, acne, hirsutism, toxic epidermal necrolysis, erythema multiform, cutaneous T-cell lymphoma, emphysema, Alzheimer's Disease, and multiple sclerosis.

As used herein the term "congestive heart failure" (CHF) or "congestive heart disease" refers to a disease state of the cardiovascular system whereby the heart is unable to efficiently pump an adequate volume of blood to meet the requirements of the body's tissues and organ systems. Typically, CHF is characterized by left ventricular failure (systolic dysfunction) and fluid accumulation in the lungs, with the underlying cause being attributed to one or more heart or cardiovascular disease states including coronary artery disease, myocardial infarction, hypertension, diabetes, valvular heart disease, and cardiomyopathy. The term "diastolic congestive heart failure" refers to a state of CHF characterized by impairment in the ability of the heart to properly relax and fill with blood. Conversely, the term "systolic congestive heart failure" refers to a state of CHF

characterized by impairment in the ability of the heart to properly contract and eject blood.

As appreciated by one of skill in the art, pathological disorders may present as a "chronic" condition, or an "acute" episode. The term "chronic", as used herein, means a condition of slow progress and long continuance. As such, a chronic condition is treated when it is diagnosed and treatment continued throughout the course of the disease. Conversely, the term "acute"means an exacerbated event or attack, of short course, followed by a period of remission. Thus, the treatment of pathological disorders contemplates both acute events and chronic conditions. In an acute event, compound is administered at the onset of symptoms and discontinued when the symptoms disappear. As described above, a chronic condition is treated throughout the course of the disease.

As used herein the term "patient" refers to a mammal, such a mouse, gerbil, guinea pig, rat, dog or human. It is understood, however, that the preferred patient is a human. As used herein, the terms "treating", "treatment", or "to treat" each mean to alleviate symptoms, eliminate the causation of resultant symptoms either on a temporary or permanent basis, and to prevent, slow the appearance, or reverse the progression or severity of resultant symptoms of the named disorder. As such, the methods of this invention encompass both therapeutic and prophylactic administration.

As used herein the term "effective amount" refers to the amount or dose of the compound, upon single or multiple dose administration to the patient, which provides the desired effect in the patient under diagnosis or treatment. An effective amount can be readily determined by the attending diagnostician, as one skilled in the art, by the use of known techniques and by observing results obtained under analogous circumstances. In determining the effective amount or dose of compound administered, a number of factors are considered by the attending diagnostician, including, but not limited to: the species of mammal; its size, age, and general health; the degree of involvement or the severity of the disease involved; the response of the individual patient; the particular compound administered; the mode of administration; the bioavailability characteristics of the preparation administered; the dose regimen selected; the use of concomitant medication; and other relevant circumstances.

A typical daily dose will contain from about 0.01 mg/kg to about 100 mg/kg of each compound used in the present method of treatment. Preferably, daily doses will be

about 0.05 mg/kg to about 50 mg/kg, more preferably from about 0.1 mg/kg to about 25 mg/kg.

Oral administration is a preferred route of administering the compounds employed in the present invention whether administered alone, or as a combination of compounds capable of acting as a mineralocorticoid receptor modulator. Oral administration, however, is not the only route, nor even the only preferred route. Other preferred routes of administration include transdermal, percutaneous, pulmonary, intravenous, intramuscular, intranasal, buccal, sublingual, or intrarectal routes. Where the steroid hormone nuclear receptor modulator is administered as a combination of compounds, one of the compounds may be administered by one route, such as oral, and the other may be administered by the transdermal, percutaneous, pulmonary, intravenous, intramuscular, intranasal, buccal, sublingual, or intrarectal route, as particular circumstances require. The route of administration may be varied in any way, limited by the physical properties of the compounds and the convenience of the patient and the caregiver.

The compounds employed in the present invention may be administered as pharmaceutical compositions and, therefore, pharmaceutical compositions incorporating compounds of Formula I, and more particularly the novel compounds of Formula I, are important embodiments of the present invention. Such compositions may take any physical form that is pharmaceutically acceptable, but orally administered pharmaceutical compositions are particularly preferred. Such pharmaceutical compositions contain, as an active ingredient, an effective amount of a compound of Formula I, including the pharmaceutically acceptable salts and hydrates thereof, which effective amount is related to the daily dose of the compound to be administered. Each dosage unit may contain the daily dose of a given compound, or may contain a fraction of the daily dose, such as one-half or one-third of the dose. The amount of each compound to be contained in each dosage unit depends on the identity of the particular compound chosen for the therapy, and other factors such as the indication for which it is given. The pharmaceutical compositions of the present invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing well known procedures.

The following discussion provides typical procedures for preparing pharmaceutical compositions incorporating the compounds of the present invention.

However, the following is in no way intended to limit the scope of the pharmaceutical compositions provided by the present invention.

Compositions are preferably formulated in a unit dosage form, each dosage containing from about 1 to about 500 mg of each compound individually or in a single unit dosage form, more preferably about 5 to about 300 mg (for example 25 mg). The term "unit dosage form" refers to a physically discrete unit suitable as unitary dosages for a patient, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier, diluent, or excipient.

The inert ingredients and manner of formulation of the pharmaceutical compositions are conventional. The usual methods of formulation used in pharmaceutical science may be used here. All of the usual types of compositions may be used, including tablets, chewable tablets, capsules, solutions, parenteral solutions, intranasal sprays or powders, troches, suppositories, transdermal patches and suspensions. In general, compositions contain from about 0.5% to about 50% of the compounds in total, depending on the desired doses and the type of composition to be used. The amount of the compound, however, is best defined as the "effective amount", that is, the amount of each compound which provides the desired dose to the patient in need of such treatment. The activity of the compounds employed in the present invention do not depend on the nature of the composition, hence, the compositions are chosen and formulated solely for convenience and economy.

Capsules are prepared by mixing the compound with a suitable diluent and filling the proper amount of the mixture in capsules. The usual diluents include inert powdered substances such as starches, powdered cellulose especially crystalline and microcrystalline cellulose, sugars such as fructose, mannitol and sucrose, grain flours, and similar edible powders.

Tablets are prepared by direct compression, by wet granulation, or by dry granulation. Their formulations usually incorporate diluents, binders, lubricants and disintegrators as well as the compound. Typical diluents include, for example, various types of starch, lactose, mannitol, kaolin, calcium phosphate or sulfate, inorganic salts such as sodium chloride and powdered sugar. Powdered cellulose derivatives are also useful. Typical tablet binders are substances such as starch, gelatin and sugars such as

lactose, fructose, glucose and the like. Natural and synthetic gums are also convenient, including acacia, alginates, methylcellulose, polyvinylpyrrolidine and the like. Polyethylene glycol, ethylcellulose and waxes can also serve as binders.

Tablets are often coated with sugar as a flavor and sealant. The compounds may also be formulated as chewable tablets, by using large amounts of pleasant-tasting substances such as mannitol in the formulation, as is now well-established practice. Instantly dissolving tablet-like formulations are also now frequently used to assure that the patient consumes the dosage form, and to avoid the difficulty in swallowing solid objects that bothers some patients.

A lubricant is often necessary in a tablet formulation to prevent the tablet and punches from sticking in the die. The lubricant is chosen from such slippery solids as talc, magnesium and calcium stearate, stearic acid and hydrogenated vegetable oils.

Tablet disintegrators are substances which swell when wetted to break up the tablet and release the compound. They include starches, clays, celluloses, algins and gums. More particularly, corn and potato starches, methylcellulose, agar, bentonite, wood cellulose, powdered natural sponge, cation-exchange resins, alginic acid, guar gum, citrus pulp and carboxymethylcellulose, for example, may be used, as well as sodium lauryl sulfate.

Enteric formulations are often used to protect an active ingredient from the strongly acid contents of the stomach. Such formulations are created by coating a solid dosage form with a film of a polymer which is insoluble in acid environments, and soluble in basic environments. Exemplary films are cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate and hydroxypropyl methylcellulose acetate succinate.

When it is desired to administer the compound as a suppository, the usual bases may be used. Cocoa butter is a traditional suppository base, which may be modified by addition of waxes to raise its melting point slightly. Water-miscible suppository bases comprising, particularly, polyethylene glycols of various molecular weights are in wide use, also.

Transdermal patches have become popular recently. Typically they comprise a resinous composition in which the drugs will dissolve, or partially dissolve, which is held in contact with the skin by a film which protects the composition. Many patents have

appeared in the field recently. Other, more complicated patch compositions are also in use, particularly those having a membrane pierced with innumerable pores through which the drugs are pumped by osmotic action.

It is understood by one of ordinary skill in the art that the procedures as described above can also be readily applied to a method of treating pathological disorders susceptible to steroid hormone nuclear receptor modulation , and particularly congestive heart failure.

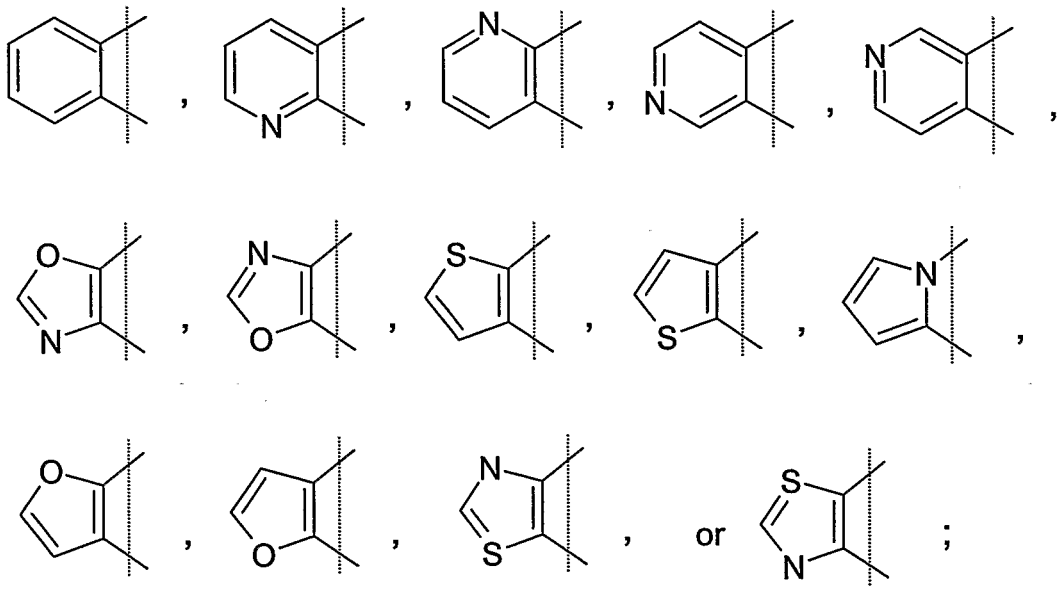
Particular Aspects of the Methods and Uses of the Invention

The following list sets out several groupings of particular substituents and particular variables for compounds of Formula I. It will be understood that certain methods and uses as described herein, employing compounds of Formula I having such particular substituents or variables, represent particular aspects of the methods and uses of the present invention. It will be further understood that each of these groupings of particular substituents and particular variables may be combined with other provided groupings, to create still additional particular aspects of the methods and uses of the present invention.

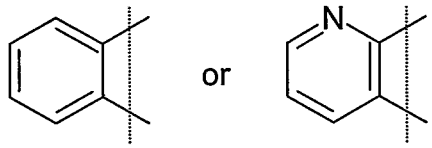
Thus, a particular aspect of the methods and uses of the present invention is one wherein the compound to be administered is a compound of Formula I, wherein:

(a) "A" represents phenyl, pyridine, pyrimidine, pyrazine, thiophene, oxazole, imidazole, or thiazole;

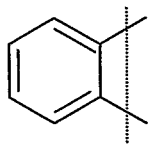
(b) "A" represents a ring selected from the following



(c) "A" represents the following



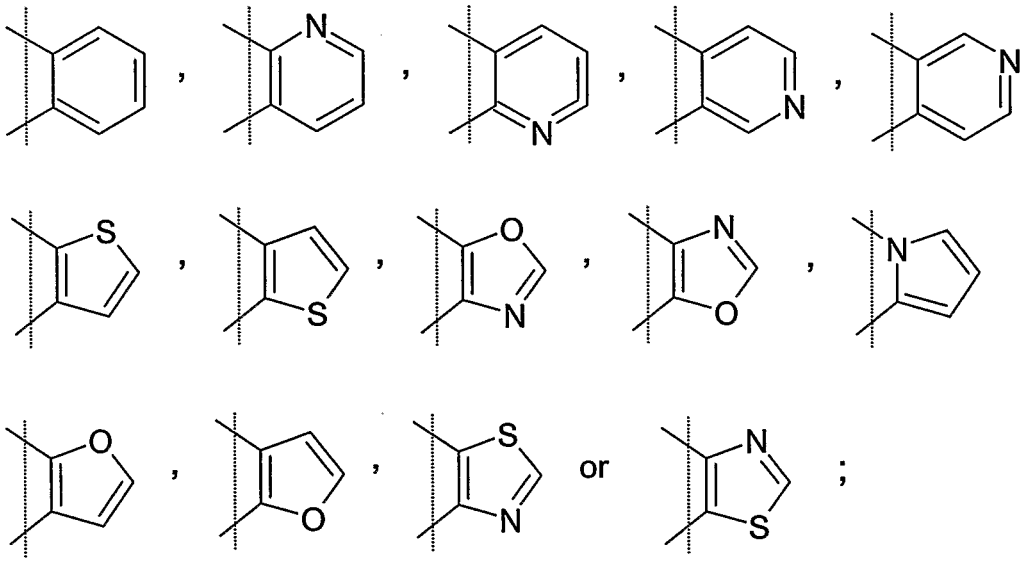
(d) "A" represents



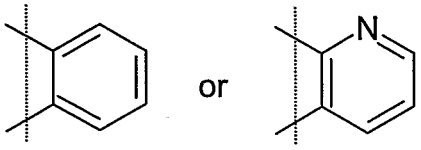
(e)

(e) "B" represents phenyl, pyridine, pyrimidine, pyrazine, thiophene, oxazole, imidazole, or thiazole;

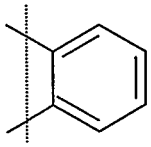
(f) "B" represents an aryl or heterocyclic ring selected from the following



(g) "B" represents the following

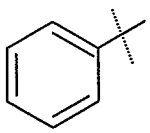
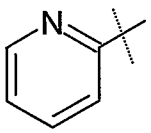
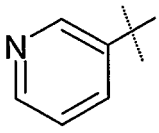
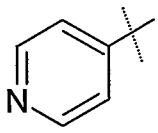


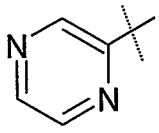
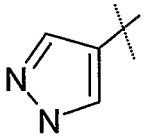
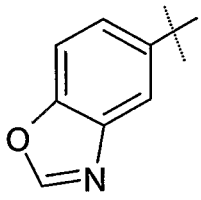
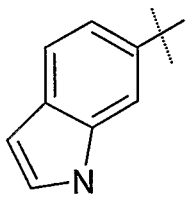
(h) "B" represents

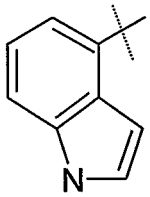
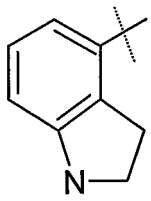
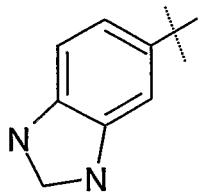
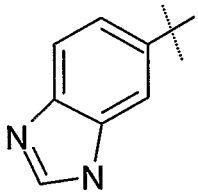


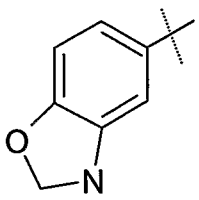
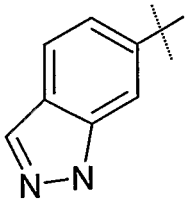
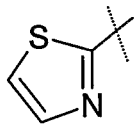
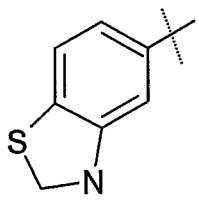
(i) C represents an aryl, heterocycle, or benzofused heterocycle selected from the following

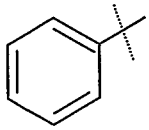
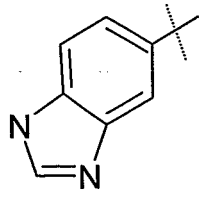
(j) C represents the following


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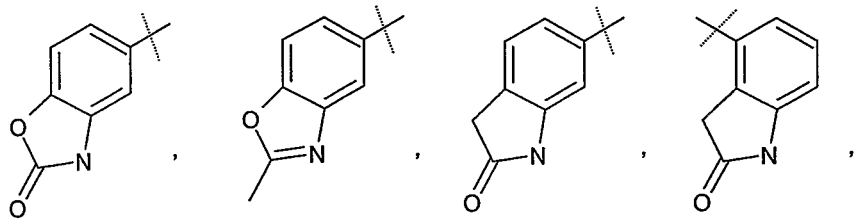

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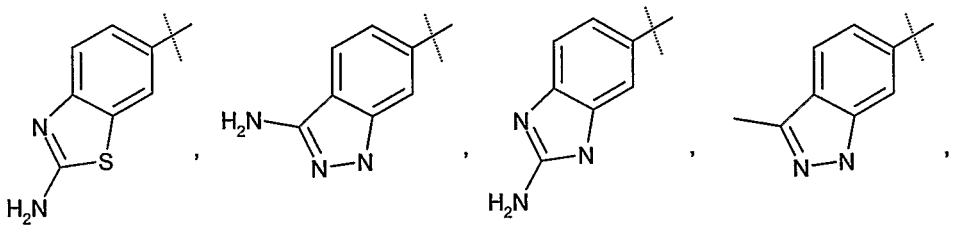

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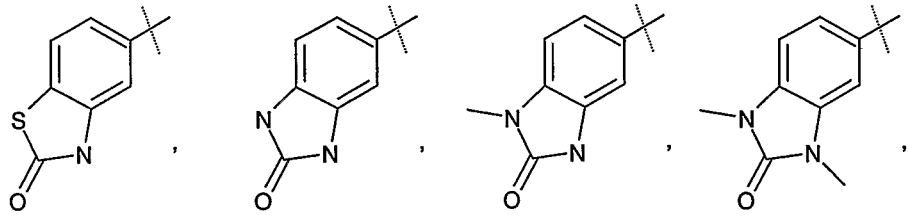

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or


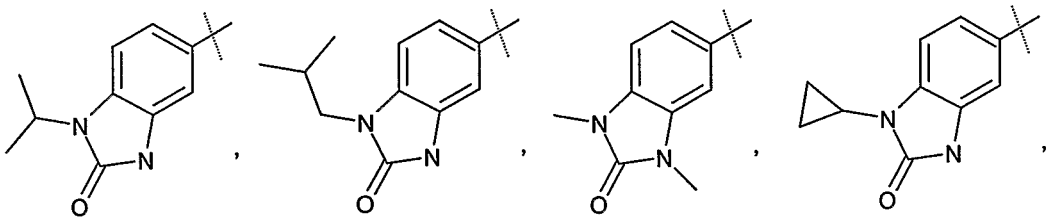

or


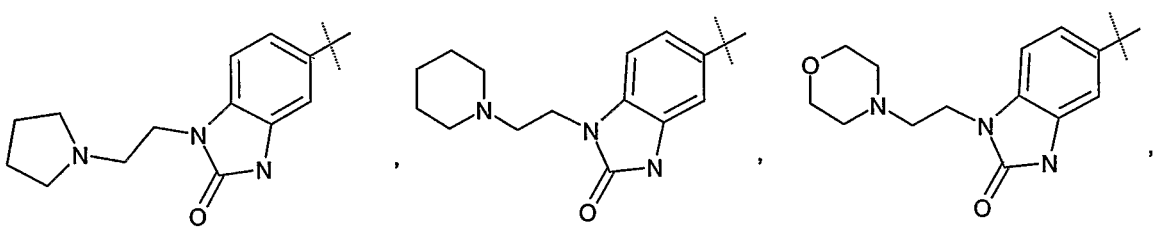
(k) "C" represents a benzofused heterocycle having a non-hydrogen substituent at at least one of R1-R3, wherein said benzofused heterocycle having a non-hydrogen substituent is given by the following:



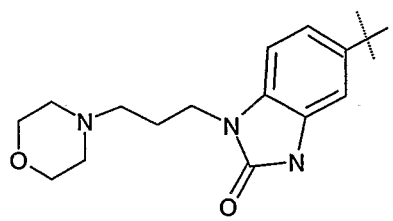




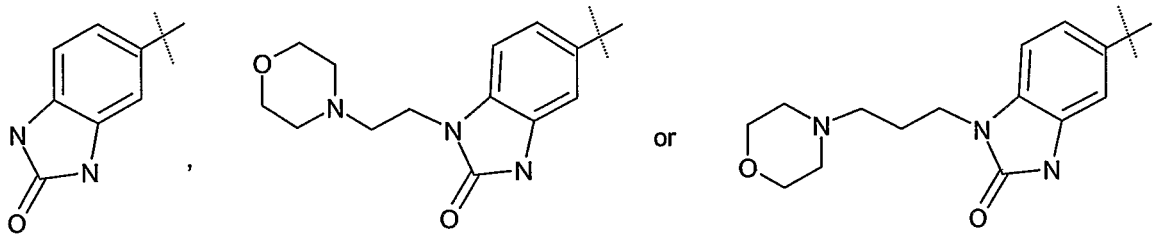




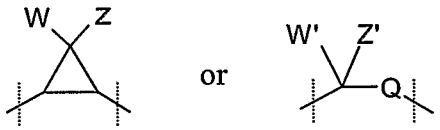
or



(l) "C" represents a benzofused heterocycle having a non-hydrogen substituent at at least one of R1-R3, wherein said benzofused heterocycle having a non-hydrogen substituent is given by the following:

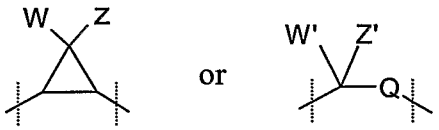


(m.) X-Y represents $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-S-$, $-S-CH_2-$, $-NR^{10}-CO-$, $-CO-NR^{10}-$, $-CH_2-NR^{10}-$, $-NR^{10}-CH_2-$, $-CH=CH-$, or a group of the formula



wherein W and Z each represent hydrogen, fluoro, or chloro; and W' and Z' each represent hydrogen, fluoro, chloro, or methyl, and Q represents NH, O, S, or CH_2;

(n) X-Y represents $-CH_2-CH_2-$, $-CH_2-O-$, $-CH=CH-$, or a group of the formula



wherein W and Z each represent hydrogen, fluoro, or chloro; and W' and Z' each represent fluoro, chloro, or methyl, and Q represents NH, O, S, or CH_2;

(o) X-Y represents $-O-CH_2-$, $-CH_2-S-$, $-S-CH_2-$, $-NR^{10}-CO-$, $-CO-NR^{10}-$, $-CH_2-NR^{10}-$, or $-NR^{10}-CH_2-$;

(p) X-Y represents $-CH_2-CH_2-$;

(q) X-Y represents $-CH_2-O-$;

(r) X-Y represents $-O-CH_2-$;

(s) X-Y represents $-CH_2-S-$;

(t) X-Y represents $-S-CH_2-$;

(u) X-Y represents $-NR^{10}-CO-$;

(v) X-Y represents $-NR^{10}-CO-$ wherein R10 represents hydrogen or methyl;

(w) X-Y represents $-CO-NR^{10}-$;

(x) X-Y represents $-CO-NR^{10}-$ wherein R10 represents hydrogen or methyl;

(y) X-Y represents $-CH_2-NR^{10}-$;

(z) X-Y represents $-CH_2-NR^{10}-$ wherein R10 represents hydrogen or methyl;

(aa) X-Y represents $-NR^{10}-CH_2-$;

(bb) X-Y represents $-NR^{10}-CH_2-$ wherein R10 represents hydrogen or methyl;

(cc) X-Y represents $-CH=CH-$;

(dd) "-----" represents a double bond.

Additional particular aspects of the methods and uses of the present invention are those wherein the compound to be administered is a compound of Formula I, wherein R^1 is as follows:

(a) R^1 represents hydrogen, halo, hydroxy, cyano, nitro, amino, oxo , (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, CH_2NH_2, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, SO_2NH_2 , $SO_2NR^9R^{10}$, SO_2R^{11}, NH SO_2R^{11}, $N(CH_3)SO_2CH_3$, $CH_2NH(SO_2R^{11})$, NR^9R^{10}, $NHCOR^{12}$, COR^{12} , $CHNR^{13}$, OR^{14} , SR^{14}, C_3-C_7)cycloalkyl, heterocycle , (C_1-C_4)alkyl-heterocycle, or substituted heterocycle, provided that where "C" represents an aryl group then R^1 is other than oxo , (C_2-C_6)alkenyl, or (C_2-C_6)alkynyl;

(b) R^1 represents SO_2R^{11}, $N(CH_3)SO_2CH_3$, OR^{14}, SR^{14}, (C_3-C_7)cycloalkyl, (C_1-C_4)alkyl-heterocycle or oxo provided "C" does not represent an aryl group when R^1 is oxo;

(c) R^1 represents hydrogen, halo, hydroxy, cyano, nitro, amino, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, CH_2NH_2, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, SO_2NH_2, $SO_2NR^9R^{10}$, $NHSO_2R^{11}$, $CH_2NH(SO_2R^{11})$, NR^9R^{10}, $NHCOR^{12}$, COR^{12}, $CHNR^{13}$, heterocycle, substituted heterocycle, provided that where "C" represents an aryl group then R^1 is other than (C_2-C_6)alkenyl or (C_2-C_6)alkynyl;

(d) R^1 represents halo, hydroxy, cyano, amino, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxymethyl, CH_2NH_2, CHF_2, CF_3, $OCHF_2$, OCF_3, SO_2NH_2, $SO_2NR^9R^{10}$, NH SO_2R^{11}, $CH_2NH(SO_2R^{11})$, NR^9R^{10}, $NHCOR^{12}$, COR^{12}, CHN(OH), heterocycle, substituted heterocycle;

Further particular aspects are those methods and uses wherein the compound to be administered is a compound of Formula I wherein R^1 is as follows:

(a) R^1 represents halo;

(b) R^1 represents bromo, chloro, or fluoro;

(c) R^1 represents hydroxy attached at the 3, 4, or 5 position of ring "C" when "C" represents a six-membered ring;

(d) R^1 represents cyano;

(e) R^1 represents amino;

(f) R^1 represents oxo provided "C" does not represent an aryl group;

(g) R^1 represents methyl, ethyl, propyl, or isopropyl;

(h) R^1 represents methyl;

(i) R^1 represents methoxy or ethoxy;

(j) R^1 represents methoxy;

(k) R^1 represents hydroxymethyl;

(l) R^1 represents aminomethyl;

(m)R^1 represents difluoromethyl, trifluoromethyl, difluoromethoxy, or trifluoromethoxy;

(n) R^1 represents difluoromethyl, trifluoromethyl, or difluoromethoxy;

(o) R^1 represents sulfonamido;

(p) R^1 represents $SO_2NR^9R^{10}$;

(q) R^1 represents $SO_2NR^9R^{10}$, wherein R^9 represents $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_4)$alkyl-$(C_1\text{-}C_6)$alkoxy , halo$(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_7)$cycloalkyl, aryl, substituted aryl, $(C_1\text{-}C_4)$alkyl-aryl, $(C_1\text{-}C_4)$alkyl-substituted aryl, heterocycle, substituted heterocycle, $(C_1\text{-}C_4)$alkyl-heterocycle, or $(C_1\text{-}C_4)$alkyl-substituted heterocycle and R^{10} represents hydrogen or methyl, or R^9 and R^{10} together with the nitrogen to which they are attached form a substituted or unsubstituted heterocycle;

(r) R^1 represents $SO_2NR^9R^{10}$, wherein R^9 represents $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_4)$alkyl-$(C_1\text{-}C_6)$alkoxy , halo$(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_7)$cycloalkyl, aryl, $(C_1\text{-}C_4)$alkyl-aryl, heterocycle and R^{10} represents hydrogen or methyl, or R^9 and R^{10} together with the nitrogen to which they are attached form a substituted or unsubstituted heterocycle;

(s) R^1 represents N-(methyl)-sulfonamido, N-(ethyl)-sulfonamido, N,N-(dimethyl) sulfonamido, N-(propyl) sulfonamido, N-(benzyl)-sulfonamido, N-(2-methoxy ethyl) sulfonamido, morpholino-sulfonyl, N-(phenyl)-sulfonamido, N-(cyclopropyl)-sulfonamido, 4-(4-trifluoromethyl-phenyl)-piperidinyl sulfonamido, or N-(2,2,2-trifluoro-ethyl)-sulfonamido;

(t) R^1 represents SO_2R^{11} wherein R^{11} represents amino, $(C_1\text{-}C_6)$alkyl, or morpholino;

(u) R^1 represents SO_2R^{11} wherein R^{11} represents methyl;

(v) R^1 represents NH SO_2R^{11};

(w) R^1 represents NH SO_2R^{11} wherein R^{11} represents amino, $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy , $(C_3\text{-}C_7)$cycloalkyl, aryl, substituted aryl, heterocycle, or substituted heterocycle;

(x) R^1 represents NH SO_2R^{11} wherein R^{11} represents amino, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy , $(C_3\text{-}C_7)$cycloalkyl, aryl, substituted aryl, heterocycle, or substituted heterocycle;

(y) R^1 represents NH SO_2R^{11} wherein R^{11} represents (C_1-C_6)alkyl, (C_1-C_6)alkoxy , (C_3-C_7)cycloalkyl, NH-(C_1-C_6)alkylamine, aryl, substituted aryl, heterocycle, or substituted heterocycle;

(z) R^1 represents NH SO_2R^{11} wherein R^{11} represents methyl, ethyl, propyl, isopropyl, butyl, or 2-methyl propyl;

(aa) R^1 represents NH SO_2R^{11} wherein R^{11} represents methyl;

(bb) R^1 represents NH SO_2R^{11} wherein R^{11} represents methyl and wherein said NH SO_2R^{11} group is attached at the 3, 4, or 5 position of ring "C" when "C" represents a six-membered ring.

(cc) R^1 represents NH SO_2R^{11} wherein R^{11} represents methyl and wherein said NH SO_2R^{11} group is attached at the 3 or 5 position of ring "C" when "C" represents a six-membered ring.

(dd) R^1 represents NH SO_2R^{11} wherein R^{11} represents trifluoromethyl or difluoromethyl;

(ee) R^1 represents NH SO_2R^{11} wherein R^{11} represents cyclopropyl;

(ff) R^1 represents NH SO_2R^{11} wherein R^{11} represents phenyl;

(gg) R^1 represents NH SO_2R^{11} wherein R^{11} represents phenyl substituted one to two times with a substituent individually selected from the group consisting ofmethyl, methoxy, chloro, fluoro,and trifluoromethyl;

(hh) R^1 represents NH SO_2R^{11} wherein R^{11} represents 4-methylphenyl, 4-fluorophenyl, 4-chlorophenyl, 4-methoxyphenyl, 3,4-dichlorophenyl, or 3-trifluoromethylphenyl,;

(ii) R^1 represents NH SO_2R^{11} wherein R^{11} represents heterocycle;

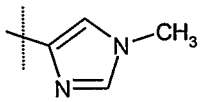
(jj) R^1 represents NH SO_2R^{11} wherein R^{11} represents thiophene or imidazole;

(kk) R^1 represents NH SO_2R^{11} wherein R^{11} represents substituted heterocycle;

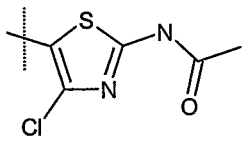
(ll) R^1 represents NH SO_2R^{11} wherein R^{11} represents substituted imidazole, isoxazole, thiazole, or thiophene;

(mm) R^1 represents NH SO_2R^{11} wherein R^{11} represents substituted imidazole, isoxazole, or thiophene;

(nn) R^1 represents NH SO_2R^{11} wherein R^{11} represents 1,2-dimethyl-1H imidazole, 3,5-dimethylisoxazole, 1-methyl-1H imidazole, or 5-pyridin-2-yl-thiophene, or a group of the formula :



or



(oo) R^1 represents NH SO_2R^{11} wherein R^{11} represents 1,2-dimethyl-1H imidazole, 3,5-dimethylisoxazole, 1-methyl-1H imidazole, or 5-pyridin-2-yl-thiophene;

(pp) R^1 represents N(CH3)SO2CH3;

(qq) R^1 represents $CH_2NHSO_2CH_3$

(rr) R^1 represents NR^9R^{10};

(ss) R^1 represents NR^9R^{10}, wherein R^9 represents $(C_1\text{-}C_6)$alkyl or cyano and R^{10} represents hydrogen or methyl;

(tt) R^1 represents NR^9R^{10}, wherein R^9 represents $(C_1\text{-}C_6)$alkyl and R^{10} represents hydrogen or methyl;

(uu) R^1 represents methylamine or dimethylamine;

(vv) R^1 represents $NHCOR^{12}$;

(ww) R^1 represents $NHCOR^{12}$ wherein R^{12} represents H, amino, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, hydroxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C)$alkyl-$(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkyl, NH-methylamine,NH-ethylamine, or heterocycle;

(xx) R^1 represents $NHCOR^{12}$ wherein R^{12} represents H, amino, $(C_1\text{-}C_6)$alkyl, or heterocycle;

(yy) R^1 represents $NHCOR^{12}$ wherein R^{12} represents H, amino,methyl, trifluoromethyl, hydroxymethyl, methoxymethyl,

(zz) R^1 represents $NHCOR^{12}$ wherein R^{12} represents NH-methylamine, NH-ethylamine, or N,N-dimethylamine;

(aaa) R^1 represents acetamido, isonicotinamido, or $NHCONH_2$;

(bbb) R^1 represents COR^{12};

(ccc) R^1 represents COR^{12} wherein R^{12} represents H, amino, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, hydroxy$(C_1\text{-}C_6)$alkyl;

(ddd) R^1 represents COR^{12} wherein R^{12} represents H, amino, $(C_1\text{-}C_6)$alkyl, or heterocycle;

(eee) R^1 represents COR^{12} wherein R^{12} represents $(C_1\text{-}C_6)$alkoxy or hydroxy$(C_1\text{-}C_6)$alkyl;

(fff) R^1 represents CHO, $CONH_2$;

(ggg) R^1 represents $COOCH_3$;

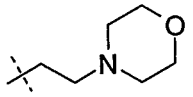
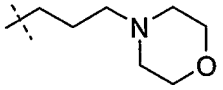
(hhh) R^1 represents $COCH_2OH$;

(iii) R^1 represents $CONH(CH_3)$ or $CONH(CH_2CH_3)$;

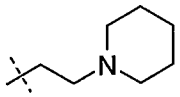
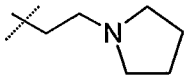
(jjj)R^1 represents OR^{14} wherein R^{14} represents $(C_1\text{-}C)$alkyl-heterocycle or acetyl;

(kkk) R^1 represents OR^{14} wherein R^{14} represents acetyl;

(lll)R^1 represents OR^{14} wherein R^{14} represents a group of the formula

 or  ;

(mmm) R^1 represents OR^{14} wherein R^{14} represents a group of the formula

 or  ;

(nnn) R^1 represents SR^{14} wherein R^{14} represents methyl;

(ooo) R1 represents cyclopropyl;

(ppp) R^1 represents heterocycle;

(qqq) R^1 represents pyrazine, pyridine, pyrazole, imidazole, or isoxazole;

(rrr) R^1 represents pyrazin-2-yl, pyridin-2-yl, 1H pyrazol-5yl, or pyridin-3-yl;

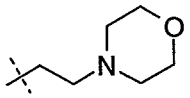
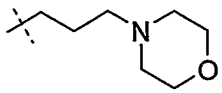
(sss) R^1 represents substituted heterocycle;

(ttt)R^1 represents substituted pyrazine, substituted pyridine, substituted pyrazole, substituted imidazole, or substituted isoxazole; or

(uuu) R^1 represents 4-trifluoromethyl-1H imidazolyl, 3,5-dimethyl isoxazolyl.

(aaaa) R^1 represents (C1-C4)alkyl-heterocycle;

(bbbb) R^1 represents a group of the formula

 or  ;

Additional particular aspects of the methods and uses of the present invention are those wherein the compound to be administered is a compound of Formula I, wherein R^2 is as follows:

(a) R^2 represents hydrogen, halo, hydroxy, cyano, amino, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, hydroxymethyl, CH_2NH_2, halo$(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkoxy, SO_2NH_2, $SO_2NR^9R^{10}$, NH SO_2R^{11}, $CH_2NH(SO_2R^{11})$, NR^9R^{10}, $NHCOR^{12}$, COR^{12}, CHN(OH), $(C_3$-$C_7)$cycloalkyl, heterocycle, $(C_1$-$C_4)$alkyl-heterocycle, or substituted heterocycle;

(b) R^2 represents hydrogen, $(C_3$-$C_7)$cycloalkyl, or $(C_1$-$C_4)$alkyl-heterocycle;

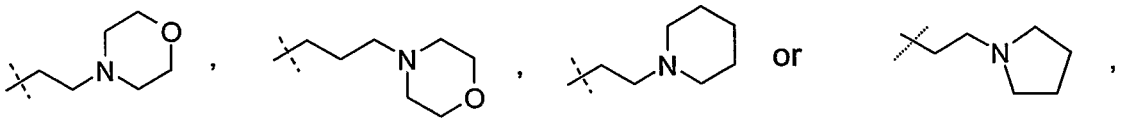
(c) R^2 represents hydrogen, halo, hydroxy, cyano, amino, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, hydroxymethyl, CH_2NH_2, halo$(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkoxy, SO_2NH_2, $SO_2NR^9R^{10}$, NH SO_2R^{11}, $CH_2NH(SO_2R^{11})$, NR^9R^{10}, $NHCOR^{12}$, COR^{12}, CHN(OH), heterocycle, or substituted heterocycle;

(d) R^2 represents hydrogen, halo, hydroxy, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, CHF_2, CF_3, $OCHF_2$, or OCF_3;

Further particular aspects are those methods and uses wherein the compound to be administered is a compound of Formula I wherein R^2 is as follows:

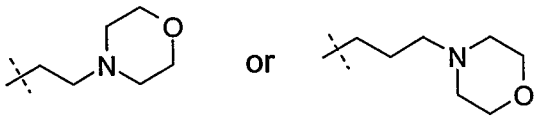
(a) R^2 represents halo;

(b) R^2 represents cyclopropyl, or a group of the formula

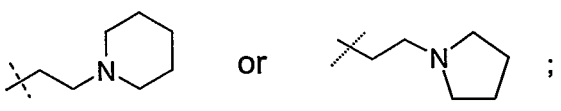


(c) R^2 represents cyclopropyl;

(d) R^2 represents a group of the formula



(e) R^2 represents a group of the formula



(f) R^2 represents bromo, chloro, or fluoro;

(g) R^2 represents hydroxy;

(h) R^2 represents $(C_1\text{-}C_6)$alkyl;

(i) R^2 represents methyl, isopropyl, or 2-methylpropyl;

(j) R^2 represents methyl;

(k) R^2 represents $(C_1\text{-}C_6)$alkoxy;

(l) R^2 represents methoxy;

(m)R^2 represents CHF_2 , CF_3 , $OCHF_2$, or OCF_3; or

(n) R^2 represents hydrogen.

Additional particular aspects of the methods and uses of the present invention are those wherein the compound to be administered is a compound of Formula I, wherein R^3 is as follows:

(a) R^3 represents hydrogen, halo, hydroxy, cyano, amino, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, hydroxymethyl, CH_2NH_2 , halo$(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkoxy, SO_2NH_2 , $SO_2NR^9R^{10}$, NH SO_2R^{11}, $CH_2NH(SO_2R^{11})$, NR^9R^{10}, $NHCOR^{12}$, COR^{12}, CHN(OH), heterocycle , or substituted heterocycle;

(b) R^3 represents hydrogen, halo, or $(C_1\text{-}C_6)$alkyl;

(c) R^3 represents halo;

(d) R^3 represents bromo, chloro, of fluoro;

(e) R^3 represents $(C_1\text{-}C_6)$alkyl;

(f) R^3 represents methyl; or

(g) R^3 represents hydrogen.

Additional particular aspects of the methods and uses of the present invention are those wherein the compound to be administered is a compound of Formula I, wherein R^4 through R^7 are as follows:

(a) R^4 through R^7 each independently represent hydrogen, halo, hydroxy, cyano, amino, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, hydroxymethyl, CH_2NH_2 , CHF_2, CF_3, $OCHF_2$,OCF_3, SO_2NH_2, SO_2CH_3 , $SO_2NR^9R^{10}$, NH SO_2R^{11}, $CH_2NH(SO_2R^{11})$, NR^9R^{10}, $NHCOR^{12}$, COR^{12}, CHN(OH), OR^{14}, SR^{14}, aryl, heterocycle, or substituted heterocycle;

(b) R^4 through R^7 each independently represent hydrogen, SO_2NH_2, SO_2CH_3, OR^{14}, SR^{14}, or aryl;

(c) R^4 through R^7 each independently represent hydrogen, halo, hydroxy, cyano, amino, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxymethyl, CH_2NH_2, CHF_2, CF_3, $OCHF_2$,OCF_3, SO_2NH_2, $SO_2NR^9R^{10}$, NH SO_2R^{11}, $CH_2NH(SO_2R^{11})$, NR^9R^{10}, $NHCOR^{12}$, COR^{12}, CHN(OH), heterocycle, or substituted heterocycle;

(d) R^4 through R^7 each independently represent hydrogen, halo, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or OR^{14}.

Further particular aspects are those methods and uses wherein the compound to be administered is a compound of Formula I wherein R^4 through R^7 are as follows:

(a) R^4 through R^7 each independently represent halo;

(b) R^4 through R^7 each independently represent bromo, chloro, or fluoro;

(c) R^4 through R^7 each independently represent hydroxy;

(d) R^4 through R^7 each independently represent (C_1-C_6)alkyl,;

(e) R^4 through R^7 each independently represent methyl, ethyl, isopropyl, or 2-methylpropyl

(f) R^4 through R^7 each independently represent methyl;

(g) R^4 through R^7 each independently represent (C_1-C_6)alkoxy;

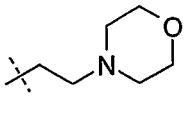
(h) R^4 through R^7 each independently represent methoxy, methylethoxy, ethoxy, or propyloxy;

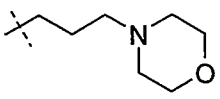
(i) R^4 through R^7 each independently represent methoxy;

(j) R^4 through R^7 each independently represent OR^{14};

(k) R^4 through R^7 each independently represent OR^{14} wherein R^{14} represents (C_1-C_4)alkyl-aryl, (C_1-C_4)alkyl-substituted aryl, (C_1-C_4)alkyl-heterocycle, or (C_1-C_4)alkyl-(C_3-C_7)cycloalkyl;

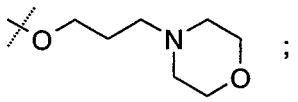
(l) R^4 through R^7 each independently represent OR^{14} wherein R^{14} cyclopropylmethyl, benzyl, phenylethyl, methoxyphenyl ethyl or a group of the formula



or


;

(m)R^4 through R^7 each independently represent a group of the formula



;

(n) R^4 through R^7 each independently represent cyclopropylmethoxy;

(o) R^4 through R^7 each independently represent trifluoromethyl, difluoromethyl, trifluoromethoxy, or difluoromethoxy;

(p) R^4 through R^7 each independently represent cyano, or amino;

(q) R^4 through R^7 each independently represent hydroxymethyl or aminomethyl;

(r) R^4 through R^7 each independently represent SO_2NH_2, SO_2CH_3, or SCH_3;

(s) R^4 through R^7 each independently represent $NHCOR^{12}$ or COR^{12};

(t) R^4 through R^7 each independently represent $NHCOR^{12}$ or COR^{12} wherein R^{12} represents independently at each occurrence hydrogen, amino, methyl, or methoxy;

(u) R^4 through R^7 each independently represent phenyl;

(v) R^4 through R^7 each independently represent NH SO_2R^{11};

(w)R^4 through R^7 each independently represent NH SO_2R^{11} wherein R^{11} represents $(C_1\text{-}C_6)$alkyl;

(x) R^4 through R^7 each independently represent NH SO_2CH_3;

(y) R^4 through R^7 each independently represent NR^9R^{10};

(z) R^4 through R^7 each independently represent NR^9R^{10} wherein R^9 represents methyl and R^{10} represent methyl;

(aa) R^4 through R^7 each independently represent hydrogen.

Still additional particular aspects of the methods and uses of the present invention are those wherein the compound to be administered is a compound of Formula I, wherein R^4 and R^6 are as follows:

(a) R^4 and R^6 each independently represent hydrogen, halo, hydroxy, cyano, amino, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkyl, hydroxymethyl, CH_2NH_2, SO_2NH_2, SO_2CH_3, NH SO_2R^{11}, NR^9R^{10}, $NHCOR^{12}$, COR^{12}, OR^{14}, SR^{14}, or aryl;

(b) R^4 and R^6 each independently represent hydrogen, halo, hydroxy, cyano, amino, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propyloxy, methylethoxy, difluromethyl, trifluoromethyl, hydroxymethyl, SO_2CH_3, NH SO_2R^{11} wherein R11 represents $(C_1\text{-}C_6)$alkyl, NR^9R^{10} wherein R^9 and R^{10} represents $(C_1\text{-}C_6)$alkyl, $NHCOR^{12}$ wherein R^{12} represents $(C_1\text{-}C_6)$alkyl; COR^{12} wherein R12 represents hydrogen, amino, or $(C_1\text{-}C_6)$alkoxy; OR^{14} wherein R^{14} represents $(C_1\text{-}C_4)$alkyl-$(C_3\text{-}C_7)$cycloalkyl, $(C_1\text{-}C_4)$alkyl-aryl, $(C_1\text{-}C_4)$alkyl-substituted aryl, or $(C_1\text{-}C_4)$alkyl-heterocycle; SR^{14} wherein R^{14} represents $(C_1\text{-}C_6)$alkyl; or aryl;

(c) R^4 and R^6 each independently represent chloro, bromo, or fluoro;

(d) R^4 and R^6 each independently represent hydroxy;

(e) R^4 and R^6 each independently represent cyano, or amino;

(f) R^4 and R^6 each independently represent methyl, ethyl, propyl, or isopropyl;

(g) R^4 and R^6 each independently represent methoxy, ethoxy, propyloxy, or methylethoxy;

(h) R^4 and R^6 each independently represent difluromethyl, trifluoromethyl, or hydroxymethyl;

(i) R^4 and R^6 each independently represent SO_2CH_3;

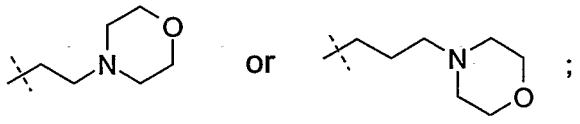
(j) R^4 and R^6 each independently represent NH SO_2CH_3;

(k) R^4 and R^6 each independently represent dimethylamine;

(l) R^4 and R^6 each independently represent CHO, $CONH_2$, or $COOCH_3$;

(m) R^4 and R^6 each independently represent OR^{14} wherein R^{14} represents $(C_1\text{-}C_4)$alkyl-$(C_3\text{-}C_7)$cycloalkyl, $(C_1\text{-}C_4)$alkyl-aryl, $(C_1\text{-}C_4)$alkyl-substituted aryl, or $(C_1\text{-}C_4)$alkyl-heterocycle;

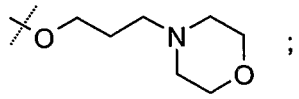
(n) R^4 and R^6 each independently represent OR^{14} wherein R^{14} represents cyclopropylmethyl, phenylethyl, methoxyphenyl ethyl, or a group of the formula



;

(o) R^4 and R^6 each independently represent cyclopropylmethoxy;

(p) R^4 and R^6 each independently represent a group of the formula



(q) R^4 and R^6 each independently represent SCH_3;

(r) R^4 and R^6 each independently represent phenyl; or

(s) R^4 and R^6 each independently represent hydrogen.

Still additional particular aspects of the methods and uses of the present invention are those wherein the compound to be administered is a compound of Formula I, wherein R^5 and R^7 are as follows:

(a) R^5 and R^7 each independently represent hydrogen, hydroxxy, halo, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy;

(b) R^5 and R^7 each independently represent hydroxy;

(c) R^5 and R^7 each independently represent chloro, bromo, or fluoro;

(d) R^5 and R^7 each independently represent methyl, or methoxy; or

(e) R^5 and R^7 each independently represent hydrogen.

Yet additional particular aspects of the methods and uses of the present invention are those wherein the compound to be administered is a compound of Formula I, wherein R^8 is as follows:

(a) R^8 represents hydrogen, halo, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl , (C_1-C_4)alkyl -(C_1-C_6)alkoxy, COR^{12}, (C_3-C_7)cycloalkyl, aryl or substituted aryl;

(b) R^8 represents bromo, chloro, or fluoro;

(c) R^8 represents methyl, ethyl, propyl, isopropyl, or 2-methylpropyl;

(d) R^8 represents hydroxymethyl;

(e) R^8 represents (C_1-C_4)alkyl -(C_1-C_6)alkoxy;

(f) R^8 represents methoxymethyl;

(g) R^8 represents COR^{12} wherein R^{12} represents methoxy, ethoxy, hydroxyamethyl, or methoxymethyl;

(h) R^8 represents (C_3-C_7)cycloalkyl;

(i) R^8 represents phenyl, methoxyphenyl, methylphenyl, or phenyl-phenyl; or

(j) R^8 represents hydrogen.

In addition, it will be understood that a most particular aspect of the methods and uses of the present invention are those wherein the compound to be administered is any compound of Formula I exemplified herein.

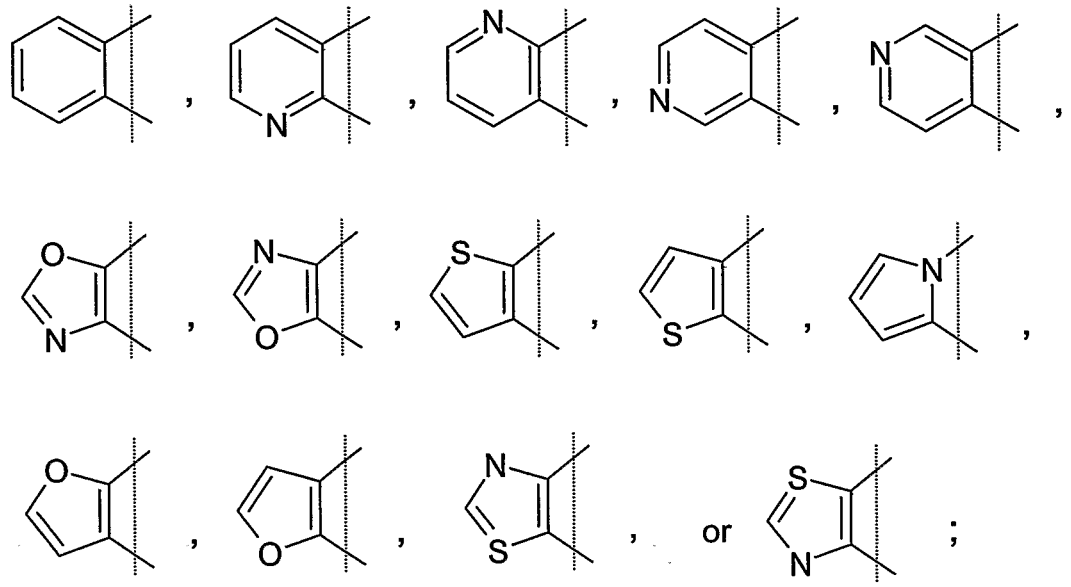
Particular Aspects of the Novel Compounds of the Invention

As discussed previously, certain compounds of Formula I are believed to be novel and, thus, to represent another embodiment of the present invention. The following list sets out several groupings of particular substituents and particular variables of the novel compounds of Formula I. It will be understood that novel compounds of Formula I having such particular substituents and variables represent particular aspects of the present invention. It will be further understood that each of these groupings may be combined with other provided groupings, to create still additional particular aspects of the present invention.

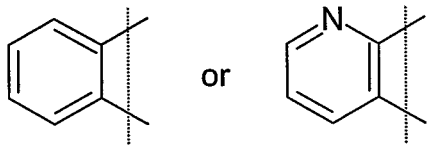
Thus, a particular aspect of the novel compounds of Formula I is one wherein:

(a) "A" represents phenyl, pyridine, pyrimidine, pyrazine, thiophene, oxazole, imidazole, or thiazole;

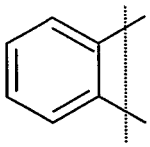
(b) "A" represents a ring selected from the following



(c) "A" represents the following

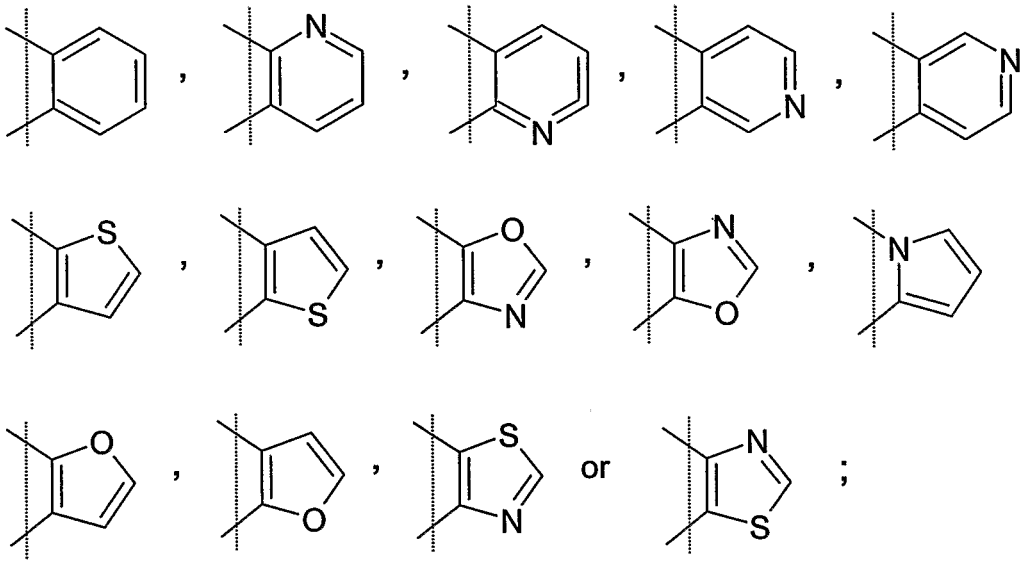


(d) "A" represents



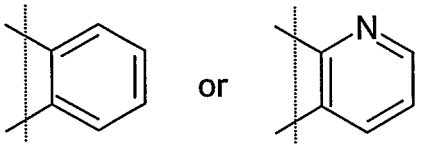
(f) "B" represents phenyl, pyridine, pyrimidine, pyrazine, thiophene, oxazole, imidazole, or thiazole;

(g) "B" represents an aryl or heterocyclic ring selected from the following

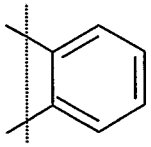


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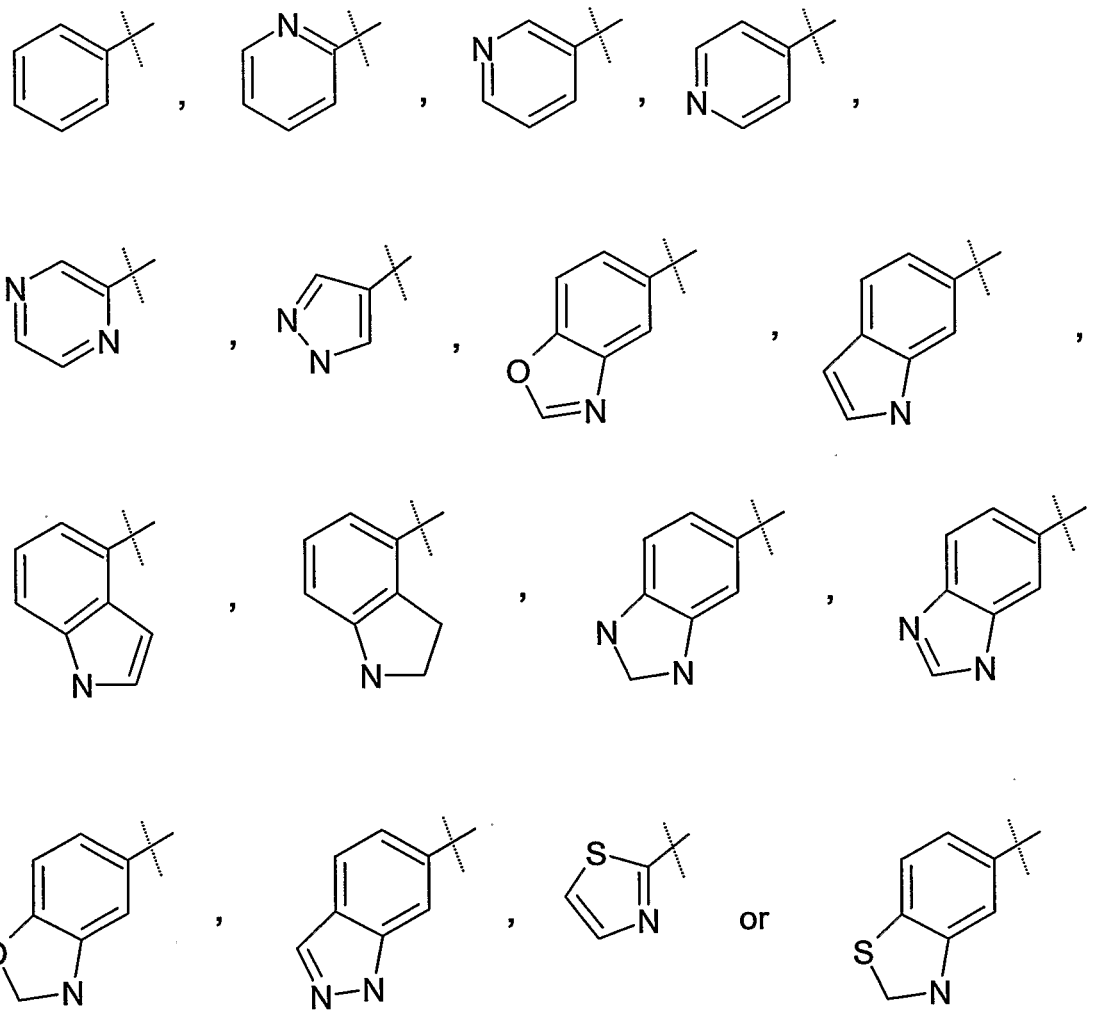
(h) "B" represents the following



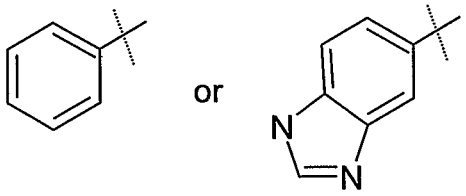
(i) "B" represents



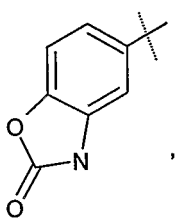
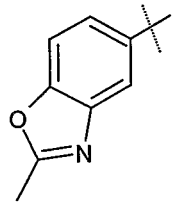
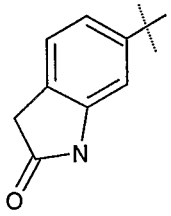
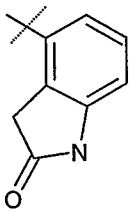
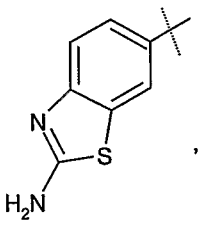
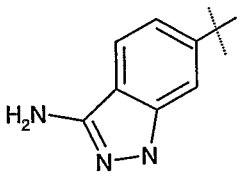
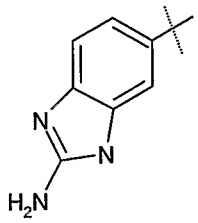
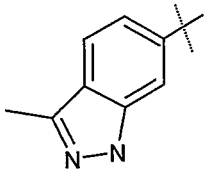
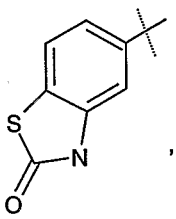
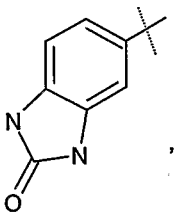
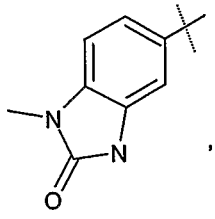
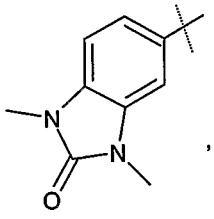
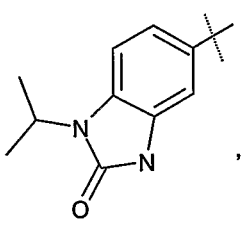
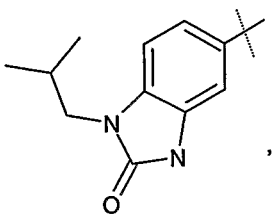
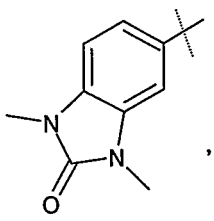
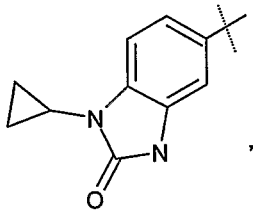
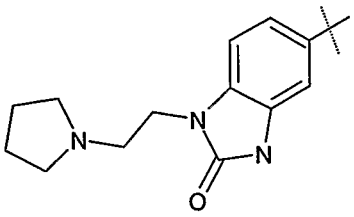
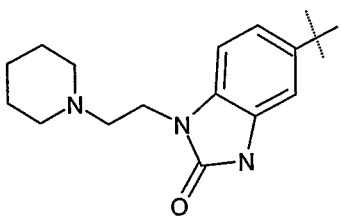
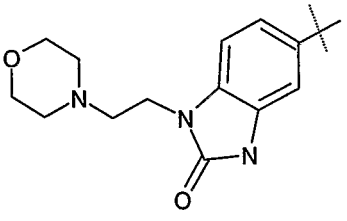
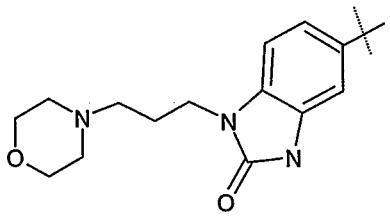
(j) "C" represents an aryl, heterocycle, or benzofused heterocycle selected from the following



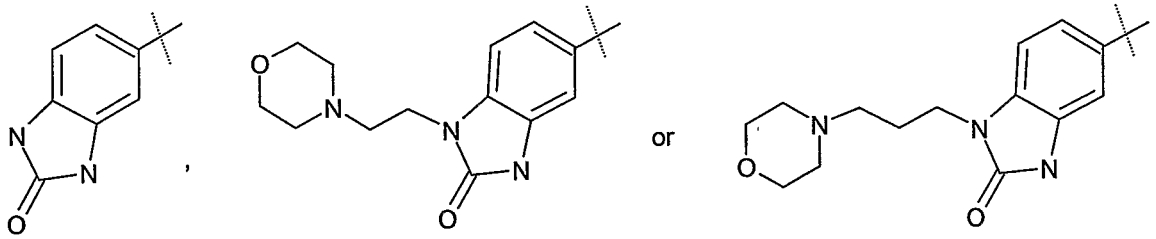
(j) "C" represents the following



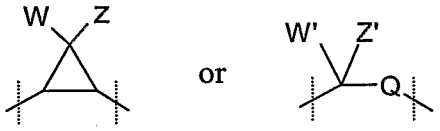
(k) "C" represents a benzofused heterocycle having a non-hydrogen substituent at at least one of R1-R3, wherein said benzofused heterocycle having a non-hydrogen substituent is given by the following:


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or


(p) "C" represents a benzofused heterocycle having a non-hydrogen substituent at at least one of R1-R3, wherein said benzofused heterocycle having a non-hydrogen substituent is given by the following:

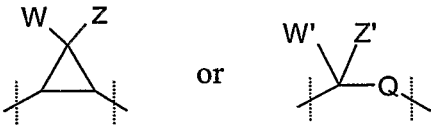


(m) X-Y represents $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-S-$, $-S-CH_2-$, $-NR^{10}-CO-$, $-CO-NR^{10}-$, $-CH_2-NR^{10}-$, $-NR^{10}-CH_2-$, $-CH=CH-$, or a group of the formula



wherein W and Z each represent hydrogen, fluoro, or chloro; and W' and Z' each represent hydrogen, fluoro, chloro, or methyl, and Q represents NH, O, S, or CH_2;

(n) X-Y represents $-CH_2-CH_2-$, $-CH_2-O-$, $-CH=CH-$, or a group of the formula



wherein W and Z each represent hydrogen, fluoro, or chloro; and W' and Z' each represent fluoro, chloro, or methyl, and Q represents NH, O, S, or CH_2;

(o) X-Y represents $-O-CH_2-$, $-CH_2-S-$, $-S-CH_2-$, $-NR^{10}-CO-$, $-CO-NR^{10}-$, $-CH_2-NR^{10}-$, or $-NR^{10}-CH_2-$;

(p) X-Y represents $-CH_2-CH_2-$;

(q) X-Y represents $-CH_2-O-$;

(r) X-Y represents $-O-CH_2-$;

(s) X-Y represents $-CH_2-S-$;

(t) X-Y represents $-S-CH_2-$;

(u) X-Y represents $-NR^{10}-CO-$;

(v) X-Y represents $-NR^{10}-CO-$ wherein R10 represents hydrogen or methyl;

(w) X-Y represents $-CO-NR^{10}-$;

(x) X-Y represents $-CO-NR^{10}-$ wherein R10 represents hydrogen or methyl;

(y) X-Y represents $-CH_2-NR^{10}-$;

(z) X-Y represents $-CH_2-NR^{10}-$ wherein R10 represents hydrogen or methyl;

(aa) X-Y represents $-NR^{10}-CH_2-$;

(bb) X-Y represents $-NR^{10}-CH_2-$ wherein R10 represents hydrogen or methyl;

(cc) X-Y represents $-CH=CH-$;

(dd) "-----" represents a double bond.

Additonal particular aspects of the novel compounds of the present invention are those wherein the novel compound is a compound of Formula I, wherein R^1 is as follows:

(a) R^1 represents halo, hydroxy, cyano, nitro, amino, oxo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, CH_2NH_2, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, SO_2NH_2, $SO_2NR^9R^{10}$, SO_2R^{11}, $NHSO_2R^{11}$, $N(CH_3)SO_2CH_3$, $CH_2NH(SO_2R^{11})$, NR^9R^{10}, $NHCOR^{12}$, COR^{12}, $CHNR^{13}$, OR^{14}, SR^{14}, (C_3-C_7)cycloalkyl, heterocycle, (C_1-C_4)alkyl-heterocycle, or substituted heterocycle, provided that where "C" represents an aryl group then R^1 is other than oxo, (C_2-C_6)alkenyl or (C_2-C_6)alkynyl; further provided that where "C" represents a phenyl ring and R^1 represents halo then at least one of R^2 and R^3 is other than hydrogen, (C_1-C_6)alkyl, aryl, substituted aryl, (C_1-C_4)alkyl-aryl, (C_1-C_4)alkyl-

substituted aryl, CHF_2, or CF_3; further provided that where "C" represents a benzo-fused heterocycle then R^1 may also represent hydrogen
further provided that where "C" represents a six-membered ring and R^1 represents cyano, amino, NR^9R^{10}, or $NHCOCH_3$ and R^2 and R^3 are each hydrogen, then R^1 is not bound at the 4-position of said six-membered ring; further provided that where "C" represents a six-membered ring and R^1 represents nitro, and R^2 and R^3 are each hydrogen, then R^1 is not bound at the 2, 4, or 6-position of said six-membered ring;

(b) R^1 represents SO_2R^{11}, $N(CH_3)SO_2CH_3$, OR^{14}, SR^{14}, $(C_3\text{-}C_7)$cycloalkyl, $(C_1\text{-}C_4)$alkyl-heterocycle or oxo provided "C" does not represent an aryl group when R^1 is oxo;

(c) R^1 represents halo, hydroxy, cyano, nitro, amino, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, hydroxy$(C_1\text{-}C_6)$alkyl, hydroxy$(C_1\text{-}C_6)$alkoxy, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, CH_2NH_2, halo$(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkoxy, SO_2NH_2, $SO_2NR^9R^{10}$, $NHSO_2R^{11}$, $CH_2NH(SO_2R^{11})$, NR^9R^{10}, $NHCOR^{12}$, COR^{12}, $CHNR^{13}$, heterocycle, or substituted heterocycle, provided that where "C" represents an aryl group then R^1 is other than $(C_2\text{-}C_6)$alkenyl or $(C_2\text{-}C_6)$alkynyl; further provided that where "C" represents a phenyl ring and R^1 represents halo then at least one of R^2 and R^3 is other than hydrogen, $(C_1\text{-}C_6)$alkyl, aryl, substituted aryl, $(C_1\text{-}C_4)$alkyl-aryl, $(C_1\text{-}C_4)$alkyl-substituted aryl, CHF_2, or CF_3; further provided that where "C" represents a benzo-fused heterocycle then R^1 may also represent hydrogen
further provided that where "C" represents a six-membered ring and R^1 represents cyano, amino, NR^9R^{10}, or $NHCOCH_3$ and R^2 and R^3 are each hydrogen, then R^1 is not bound at the 4-position of said six-membered ring; further provided that where "C" represents a six-membered ring and R^1 represents nitro, and R^2 and R^3 are each hydrogen, then R^1 is not bound at the 2, 4, or 6-position of said six-membered ring;

(d) R^1 represents halo, hydroxy, cyano, amino, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, hydroxymethyl, CH_2NH_2, CHF_2, CF_3, $OCHF_2$, OCF_3, SO_2NH_2, $SO_2NR^9R^{10}$, NH SO_2R^{11}, $CH_2NH(SO_2R^{11})$, NR^9R^{10}, $NHCOR^{12}$, COR^{12}, CHN(OH), heterocycle, substituted heterocycle, provided that where "C"

represents a phenyl ring and R^1 represents halo then at least one of R^2 and R^3 is other than hydrogen, (C_1-C_6)alkyl, aryl, substituted aryl, (C_1-C_4)alkyl-aryl, (C_1-C_4)alkyl-substituted aryl, CHF_2, or CF_3; further provided that where "C" represents a benzo-fused heterocycle then R^1 may also represent hydrogen; further provided that where "C" represents a six-membered ring and R^1 represents cyano, amino, NR^9R^{10}, or $NHCOCH_3$ and R^2 and R^3 are each hydrogen, then R^1 is not bound at the 4-position of said six-membered ring;

Further particular aspects are those methods and uses wherein the compound to be administered is a compound of Formula I wherein R^1 is as follows:

(a) R^1 represents halo provided that where "C" represents a phenyl ring then at least one of R^2 and R^3 is other than hydrogen, (C_1-C_6)alkyl, aryl, substituted aryl, (C_1-C_4)alkyl-aryl, (C_1-C_4)alkyl-substituted aryl, CHF_2, or CF_3;

(b) R^1 represents bromo, chloro, or fluoro provided that where "C" represents a phenyl ring then at least one of R^2 and R^3 is other than hydrogen, (C_1-C_6)alkyl, aryl, substituted aryl, (C_1-C_4)alkyl-aryl, (C_1-C_4)alkyl-substituted aryl, CHF_2, or CF_3;

(c) R^1 represents hydroxy attached at the 3, 4, or 5 position of ring "C" when "C" represents a six-membered ring;

(d) R^1 represents cyano provided that where "C" represents a six-membered ring and R^2 and R^3 are each hydrogen, then R^1 is not bound at the 4-position of said six-membered ring;

(e) R^1 represents amino provided that where "C" represents a six-membered ring and R^2 and R^3 are each hydrogen, then R^1 is not bound at the 4-position of said six-membered ring;

(f) R^1 represents oxo provided "C" does not represent an aryl group;

(g) R^1 represents methyl, ethyl, propyl, or isopropyl;

(h) R^1 represents methyl;

(i) R^1 represents methoxy or ethoxy;

(j) R^1 represents methoxy;

(k) R^1 represents hydroxymethyl;

(l) R^1 represents aminomethyl;

(m)R^1 represents difluoromethyl, trifluoromethyl, difluoromethoxy, or trifluoromethoxy;

(n) R^1 represents difluoromethyl, trifluoromethyl, or difluoromethoxy;

(o) R^1 represents sulfonamido;

(p) R^1 represents $SO_2NR^9R^{10}$;

(q) R^1 represents $SO_2NR^9R^{10}$, wherein R^9 represents $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_4)$alkyl-$(C_1\text{-}C_6)$alkoxy , halo$(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_7)$cycloalkyl, aryl, substituted aryl, $(C_1\text{-}C_4)$alkyl-aryl, $(C_1\text{-}C_4)$alkyl-substituted aryl, heterocycle, substituted heterocycle, $(C_1\text{-}C_4)$alkyl-heterocycle, or $(C_1\text{-}C_4)$alkyl-substituted heterocycle and R^{10} represents hydrogen or methyl, or R^9 and R^{10} together with the nitrogen to which they are attached form a substituted or unsubstituted heterocycle;

(r) R^1 represents $SO_2NR^9R^{10}$, wherein R^9 represents $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_4)$alkyl-$(C_1\text{-}C_6)$alkoxy , halo$(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_7)$cycloalkyl, aryl, $(C_1\text{-}C_4)$alkyl-aryl, heterocycle and R^{10} represents hydrogen or methyl, or R^9 and R^{10} together with the nitrogen to which they are attached form a substituted or unsubstituted heterocycle;

(s) R^1 represents N-(methyl)-sulfonamido, N-(ethyl)-sulfonamido, N,N-(dimethyl) sulfonamido, N-(propyl) sulfonamido, N-(benzyl)-sulfonamido, N-(2-methoxy ethyl) sulfonamido, morpholino-sulfonyl, N-(phenyl)-sulfonamido, N-(cyclopropyl)-sulfonamido, 4-(4-trifluoromethyl-phenyl)-piperidinyl sulfonamido, or N-(2,2,2-trifluoro-ethyl)-sulfonamido;

(t) R^1 represents SO_2R^{11} wherein R^{11} represents amino, $(C_1\text{-}C_6)$alkyl, or morpholino;

(u) R^1 represents SO_2R^{11} wherein R^{11} represents methyl;

(v) R^1 represents NH SO_2R^{11};

(w)R^1 represents NH SO_2R^{11} wherein R^{11} represents amino, halo$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy , $(C_3\text{-}C_7)$cycloalkyl, aryl, substituted aryl, heterocycle, or substituted heterocycle;

(x) R^1 represents NH SO_2R^{11} wherein R^{11} represents amino, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy , $(C_3\text{-}C_7)$cycloalkyl, aryl, substituted aryl, heterocycle, or substituted heterocycle;

(y) R^1 represents NH SO_2R^{11} wherein R^{11} represents (C_1-C_6)alkyl, (C_1-C_6)alkoxy , (C_3-C_7)cycloalkyl, aryl, substituted aryl, heterocycle, or substituted heterocycle;

(z) R^1 represents NH SO_2R^{11} wherein R^{11} represents methyl, ethyl, propyl, isopropyl, butyl, or 2-methyl propyl;

(aa) R^1 represents NH SO_2R^{11} wherein R^{11} represents methyl;

(bb) R^1 represents NH SO_2R^{11} wherein R^{11} represents methyl and wherein said NH SO_2R^{11} group is attached at the 3, 4, or 5 position of ring "C" when "C" represents a six-membered ring.

(cc) R^1 represents NH SO_2R^{11} wherein R^{11} represents methyl and wherein said NH SO_2R^{11} group is attached at the 3 or 5 position of ring "C" when "C" represents a six-membered ring.

(dd) R^1 represents NH SO_2R^{11} wherein R^{11} represents trifluoromethyl or difluoromethyl;

(ee) R^1 represents NH SO_2R^{11} wherein R^{11} represents cyclopropyl;

(ff) R^1 represents NH SO_2R^{11} wherein R^{11} represents phenyl;

(gg) R^1 represents NH SO_2R^{11} wherein R^{11} represents phenyl substituted one to two times with a substituent individually selected from the group consisting ofmethyl, methoxy, chloro, fluoro, and trifluoromethyl;

(hh) R^1 represents NH SO_2R^{11} wherein R^{11} represents 4-methylphenyl, 4-fluorophenyl, 4-chlorophenyl, 4-methoxyphenyl, 3,4-dichlorophenyl, or 3-trifluoromethylphenyl;

(ii) R^1 represents NH SO_2R^{11} wherein R^{11} represents heterocycle;

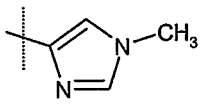
(jj) R^1 represents NH SO_2R^{11} wherein R^{11} represents thiophene or imidazole;

(kk) R^1 represents NH SO_2R^{11} wherein R^{11} represents substituted heterocycle;

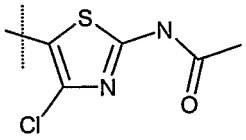
(ll) R^1 represents NH SO_2R^{11} wherein R^{11} represents substituted imidazole, isoxazole, thiazole or thiophene;

(mm) R^1 represents NH SO_2R^{11} wherein R^{11} represents substituted imidazole, isoxazole, or thiophene;

(nn) R^1 represents NH SO_2R^{11} wherein R^{11} represents 1,2-dimethyl-1H imidazole, 3,5-dimethylisoxazole, 1-methyl-1H imidazole, or 5-pyridin-2-yl-thiophene, or a group of the formula :



or



(oo) R^1 represents NH SO_2R^{11} wherein R^{11} represents 1,2-dimethyl-1H imidazole, 3,5-dimethylisoxazole, 1-methyl-1H imidazole, or 5-pyridin-2-yl-thiophene;

(pp) R^1 represents N(CH3)SO2CH3;

(qq) R^1 represents $CH_2NHSO_2CH_3$

(rr) R^1 represents NR^9R^{10} provided that where "C" represents a six-membered ring and R^2 and R^3 are each hydrogen, then R^1 is not bound at the 4-position of said six-membered ring;

(ss) R^1 represents NR^9R^{10}, wherein R^9 represents $(C_1\text{-}C_6)$alkyl or cyano and R^{10} represents hydrogen or methyl provided that where "C" represents a six-membered ring and R^2 and R^3 are each hydrogen, then R^1 is not bound at the 4-position of said six-membered ring;;

(tt) R^1 represents NR^9R^{10}, wherein R^9 represents $(C_1\text{-}C_6)$alkyl and R^{10} represents hydrogen or methyl provided that where "C" represents a six-membered ring and R^2 and R^3 are each hydrogen, then R^1 is not bound at the 4-position of said six-membered ring;;

(uu) R^1 represents NR^9R^{10}, wherein R^9 represents $(C_1\text{-}C_6)$alkyl and R^{10} represents hydrogen or methyl provided that where "C" represents a six-membered ring and R^2 and R^3 are each hydrogen, then R^1 is not bound at the 4-position of said six-membered ring;

(vv) R^1 represents methylamine or dimethylamine, provided that where "C" represents a six-membered ring and R^2 and R^3 are each hydrogen, then R^1 is not bound at the 4-position of said six-membered ring;

(ww) R^1 represents $NHCOR^{12}$ provided that where "C" represents a six-membered ring and R^2 and R^3 are each hydrogen, then R^1 is not bound at the 4-position of said six-membered ring when R^1 represents $NHCOCH_3$;

(xx) R^1 represents $NHCOR^{12}$ wherein R^{12} represents H, amino, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, hydroxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C)$alkyl-$(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkyl, NH-methylamine,NH-ethylamine, or heterocycle, provided that where "C" represents a six-membered ring and R^2 and R^3 are each hydrogen, then R^1 is not bound at the 4-position of said six-membered ring when R^1 represents $NHCOCH_3$;;

(yy) R^1 represents $NHCOR^{12}$ wherein R^{12} represents H, amino, $(C_1\text{-}C_6)$alkyl, or heterocycle provided that where "C" represents a six-membered ring and R^2 and R^3 are each hydrogen, then R^1 is not bound at the 4-position of said six-membered ring when R^1 represents $NHCOCH_3$;

(zz) R^1 represents $NHCOR^{12}$ wherein R^{12} represents H, amino,methyl, trifluoromethyl, hydroxymethyl, methoxymethyl, provided that where "C" represents a six-membered ring and R^2 and R^3 are each hydrogen, then R^1 is not bound at the 4-position of said six-membered ring when R^1 represents $NHCOCH_3$;

(aaa) R^1 represents $NHCOR^{12}$ wherein R^{12} represents NH-methylamine, NH-ethylamine, or N,N-dimethylamine;

(bbb) R^1 represents $NHCOCH_3$, isonicotinamido, or $NHCONH_2$ provided that where "C" represents a six-membered ring and R^2 and R^3 are each hydrogen, then R^1 is not bound at the 4-position of said six-membered ring when R^1 represents $NHCOCH_3$;

(ccc) R^1 represents COR^{12};

(ddd) R^1 represents COR^{12} wherein R^{12} represents H, amino, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, hydroxy$(C_1\text{-}C_6)$alkyl;

(eee) R^1 represents COR^{12} wherein R^{12} represents H, amino, $(C_1\text{-}C_6)$alkyl, or heterocycle;

(fff) R^1 represents COR^{12} wherein R^{12} represents $(C_1\text{-}C_6)$alkoxy or hydroxy$(C_1\text{-}C_6)$alkyl;

(ggg) R^1 represents CHO, $CONH_2$;

(hhh) R^1 represents $COOCH_3$;

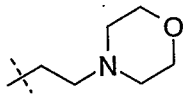
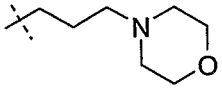
(iii)R^1 represents $COCH_2OH$;

(jjj)R^1 represents $CONH(CH_3)$ or $CONH(CH_2CH_3)$;

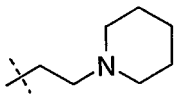
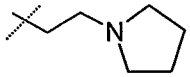
(kkk) R^1 represents OR^{14} wherein R^{14} represents (C_1-C)alkyl-heterocycle or acetyl;

(lll)R^1 represents OR^{14} wherein R^{14} represents acetyl;

(mmm) R^1 represents OR^{14} wherein R^{14} represents a group of the formula

 or  ;

(nnn) R^1 represents OR^{14} wherein R^{14} represents a group of the formula

 or  ;

(ooo) R^1 represents SR^{14} wherein R^{14} represents methyl;

(ppp) R1 represents cyclopropyl;

(qqq) R^1 represents heterocycle;

(rrr) R^1 represents pyrazine, pyridine, pyrazole, imidazole, or isoxazole;

(sss) R^1 represents pyrazin-2-yl, pyridin-2-yl, 1H pyrazol-5yl, or pyridin-3-yl;

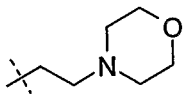
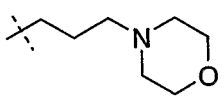
(ttt)R^1 represents substituted heterocycle;

(uuu) R^1 represents substituted pyrazine, substituted pyridine, substituted pyrazole, substituted imidazole, or substituted isoxazole; or

(vvv) R^1 represents 4-trifluoromethyl-1H imidazolyl, 3,5-dimethyl isoxazolyl.

(www) R^1 represents (C1-C4)alkyl-heterocycle;

(xxx) R^1 represents a group of the formula

 or  ;

Additional particular aspects of the novel compounds of the present invention are those wherein the compound of Formula I is one wherein R^2 is as follows:

(a) R^2 represents hydrogen, halo, hydroxy, cyano, amino, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxymethyl, CH_2NH_2, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, SO_2NH_2, $SO_2NR^9R^{10}$, NH SO_2R^{11}, $CH_2NH(SO_2R^{11})$, NR^9R^{10}, $NHCOR^{12}$, COR^{12}, CHN(OH), (C_3-C_7)cycloalkyl, heterocycle, (C_1-C_4)alkyl-heterocycle , or substituted heterocycle;

(b) R^2 represents hydrogen, (C_3-C_7)cycloalkyl, or (C_1-C_4)alkyl-heterocycle;

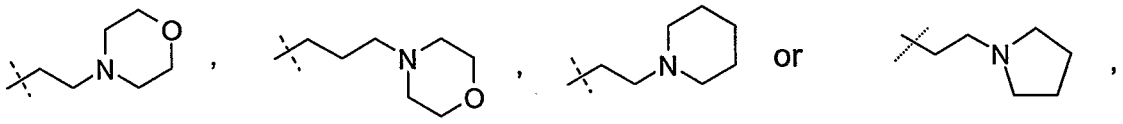
(c) R^2 represents hydrogen, halo, hydroxy, cyano, amino, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxymethyl, CH_2NH_2, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, SO_2NH_2, $SO_2NR^9R^{10}$, NH SO_2R^{11}, $CH_2NH(SO_2R^{11})$, NR^9R^{10}, $NHCOR^{12}$, COR^{12}, CHN(OH), heterocycle, or substituted heterocycle;

(d) R^2 represents hydrogen, halo, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, CHF_2, CF_3, $OCHF_2$, or OCF_3;

Further particular aspects are those novel compounds wherein the compound of Formula I is one wherein R^2 is as follows:

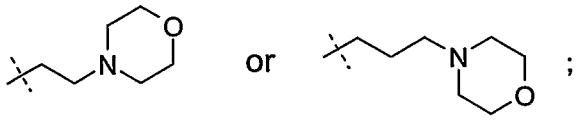
(a) R^2 represents halo;

(b) R^2 represents cyclopropyl, or a group of the formula

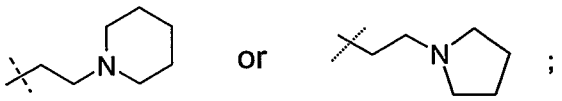


(c) R^2 represents cyclopropyl;

(d) R^2 represents a group of the formula



(e) R^2 represents a group of the formula



(f) R^2 represents bromo, chloro, or fluoro;

(g) R^2 represents hydroxy;

(h) R^2 represents (C_1-C_6)alkyl;

(i) R^2 represents methyl, isopropyl, or 2-methylpropyl;

(j) R^2 represents methyl;

(k) R^2 represents (C_1-C_6)alkoxy;

(l) R^2 represents methoxy;

(m)R^2 represents CHF_2 , CF_3 , $OCHF_2$, or OCF_3; or

(n) R^2 represents hydrogen.

Additional particular aspects of the novel compounds of the present invention are those wherein the compound of Formula I is one wherein R^3 is as follows:

(a) R^3 represents hydrogen, halo, hydroxy, cyano, amino, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxymethyl, CH_2NH_2 , halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, SO_2NH_2 , $SO_2NR^9R^{10}$, NH SO_2R^{11}, $CH_2NH(SO_2R^{11})$, NR^9R^{10}, $NHCOR^{12}$, COR^{12}, CHN(OH), heterocycle , or substituted heterocycle;

(b) R^3 represents hydrogen, halo, or (C_1-C_6)alkyl;

(c) R^3 represents halo;

(d) R^3 represents bromo, chloro, of fluoro;

(e) R^3 represents (C_1-C_6)alkyl;

(f) R^3 represents methyl; or

(g) R^3 represents hydrogen.

Additional particular aspects of the novel compounds of the present invention are those wherein the compound of Formula I is one wherein R^4 through R^7 are as follows:

(a) R^4 through R^7 each independently represent hydrogen, halo, hydroxy, cyano, amino, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxymethyl, CH_2NH_2 , CHF_2, CF_3, $OCHF_2$,OCF_3, SO_2NH_2, SO_2CH_3 , $SO_2NR^9R^{10}$, NH SO_2R^{11}, $CH_2NH(SO_2R^{11})$, NR^9R^{10}, $NHCOR^{12}$, COR^{12}, CHN(OH), OR^{14}, SR^{14}, aryl, heterocycle, or substituted heterocycle;

(b) R^4 through R^7 each independently represent hydrogen, SO_2NH_2, SO_2CH_3, OR^{14}, SR^{14}, or aryl;

(c) R^4 through R^7 each independently represent hydrogen, halo, hydroxy, cyano, amino, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxymethyl, CH_2NH_2 , CHF_2, CF_3, $OCHF_2$,OCF_3, SO_2NH_2, $SO_2NR^9R^{10}$, NH SO_2R^{11}, $CH_2NH(SO_2R^{11})$, NR^9R^{10}, $NHCOR^{12}$, COR^{12}, CHN(OH), heterocycle, or substituted heterocycle;

(c) R^4 through R^7 each independently represent hydrogen, halo, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or OR^{14};

Further particular aspects are those compounds of Formula I wherein R^4 through R^7 are as follows:

(a) R^4 through R^7 each independently represent halo;

(b) R^4 through R^7 each independently represent bromo, chloro, or fluoro;

(c) R^4 through R^7 each independently represent hydroxy;

(d) R^4 through R^7 each independently represent (C_1-C_6)alkyl;

(e) R^4 through R^7 each independently represent methyl, ethyl, isopropyl, or 2-methylpropyl;

(f) R^4 through R^7 each independently represent methyl;

(g) R^4 through R^7 each independently represent (C_1-C_6)alkoxy;

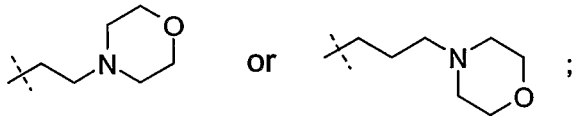
(h) R^4 through R^7 each independently represent methoxy, methylethoxy, ethoxy, or propyloxy;

(i) R^4 through R^7 each independently represent methoxy;

(j) R^4 through R^7 each independently represent OR^{14};

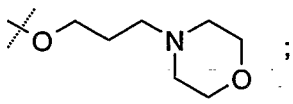
(k) R^4 through R^7 each independently represent OR^{14} wherein R^{14} represents (C_1-C_4)alkyl-aryl, (C_1-C_4)alkyl-substituted aryl, (C_1-C_4)alkyl-heterocycle, or (C_1-C_4)alkyl-(C_3-C_7)cycloalkyl;

(l) R^4 through R^7 each independently represent OR^{14} wherein R^{14} cyclopropylmethyl, benzyl, phenylethyl, methoxyphenyl ethyl or a group of the formula



;

(m)R^4 through R^7 each independently represent a group of the formula



;

(n) R^4 through R^7 each independently represent cyclopropylmethoxy;

(o) R^4 through R^7 each independently represent trifluoromethyl, difluoromethyl, trifluoromethoxy, or difluoromethoxy;

(p) R^4 through R^7 each independently represent cyano, or amino;

(q) R^4 through R^7 each independently represent hydroxymethyl, or aminomethyl;

(r) R^4 through R^7 each independently represent SO_2NH_2, SO_2CH_3, or SCH_3;

(s) R^4 through R^7 each independently represent $NHCOR^{12}$ or COR^{12};

(t) R^4 through R^7 each independently represent $NHCOR^{12}$ or COR^{12} wherein R^{12} represents independently at each occurrence amino, methyl, or methoxy;

(u) R^4 through R^7 each independently represent phenyl;

(v) R^4 through R^7 each independently represent $NH\ SO_2R^{11}$;

(w) R^4 through R^7 each independently represent $NH\ SO_2R^{11}$ wherein R^{11} represents $(C_1\text{-}C_6)$alkyl;

(x) R^4 through R^7 each independently represent $NH\ SO_2CH_3$;

(y) R^4 through R^7 each independently represent NR^9R^{10};

(z) R^4 through R^7 each independently represent NR^9R^{10} wherein R^9 represents methyl and R^{10} represent methyl;

(aa) R^4 through R^7 each independently represent hydrogen.

Still additional particular aspects of the novel compounds of the present invention are those wherein the compound is a compound of Formula I, wherein R^4 and R^6 are as follows:

(a) R^4 and R^6 each independently represent hydrogen, halo, hydroxy, cyano, amino, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkyl, hydroxymethyl, CH_2NH_2, SO_2NH_2, SO_2CH_3, $NH\ SO_2R^{11}$, NR^9R^{10}, $NHCOR^{12}$, COR^{12}, OR^{14}, SR^{14}, or aryl;

(b) R^4 and R^6 each independently represent hydrogen, halo, hydroxy, cyano, amino, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propyloxy, methylethoxy, difluromethyl, trifluoromethyl, hydroxymethyl, SO_2CH_3, $NH\ SO_2R^{11}$ wherein R11 represents $(C_1\text{-}C_6)$alkyl, NR^9R^{10} wherein R^9 and R^{10} represents $(C_1\text{-}C_6)$alkyl, $NHCOR^{12}$ wherein R^{12} represents $(C_1\text{-}C_6)$alkyl; COR^{12} wherein R12 represents hydrogen, amino, or $(C_1\text{-}C_6)$alkoxy; OR^{14} wherein R^{14} represents $(C_1\text{-}C_4)$alkyl-$(C_3\text{-}C_7)$cycloalkyl, $(C_1\text{-}C_4)$alkyl-aryl, $(C_1\text{-}C_4)$alkyl-substituted aryl, or $(C_1\text{-}C_4)$alkyl-heterocycle; SR^{14} wherein R^{14} represents $(C_1\text{-}C_6)$alkyl; or aryl;

(c) R^4 and R^6 each independently represent chloro, bromo, or fluoro;

(d) R^4 and R^6 each independently represent hydroxy;

(e) R^4 and R^6 each independently represent cyano, or amino;

(f) R^4 and R^6 each independently represent methyl, ethyl, propyl, or isopropyl;

(g) R^4 and R^6 each independently represent methoxy, ethoxy, propyloxy, or methylethoxy;

(h) R^4 and R^6 each independently represent difluromethyl, trifluoromethyl, or hydroxymethyl;

(i) R^4 and R^6 each independently represent SO_2CH_3;

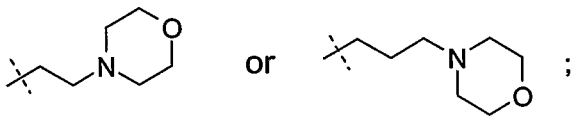
(j) R^4 and R^6 each independently represent NH SO_2CH_3;

(k) R^4 and R^6 each independently represent dimethylamine;

(l) R^4 and R^6 each independently represent CHO, $CONH_2$, or $COOCH_3$;

(m) R^4 and R^6 each independently represent OR^{14} wherein R^{14} represents (C_1-C_4)alkyl-(C_3-C_7)cycloalkyl , (C_1-C_4)alkyl-aryl, (C_1-C_4)alkyl-substituted aryl , or (C_1-C_4)alkyl-heterocycle;

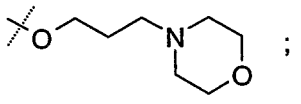
(n) R^4 and R^6 each independently represent OR^{14} wherein R^{14} represents cyclopropylmethyl, phenylethyl, methoxyphenyl ethyl, or a group of the formula



;

(o) R^4 and R^6 each independently represent cyclopropylmethoxy;

(p) R^4 and R^6 each independently represent a group of the formula



;

(q) R^4 and R^6 each independently represent SCH_3; and

(r) R^4 and R^6 each independently represent phenyl;

(s) R^4 and R^6 each independently represent hydrogen;

Still additional particular aspects of the novel compounds of the present invention are those wherein the compound is a compound of Formula I, wherein R^5 and R^7 are as follows:

(a) R^5 and R^7 each independently represent hydrogen, hydroxxy, halo, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy;

(b) R^5 and R^7 each independently represent hydroxy;

(c) R^5 and R^7 each independently represent chloro, bromo, or fluoro;

(d) R^5 and R^7 each independently represent methyl, or methoxy;

(e) R^5 and R^7 each independently represent hydrogen;

Yet additional particular aspects of the novel compounds of the present invention are those wherein the compound of Formula I is one wherein R^8 is as follows:

(a) R^8 represents hydrogen, halo, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl , (C_1-C_4)alkyl -(C_1-C_6)alkoxy , COR^{12}, (C_3-C_7)cycloalkyl, aryl or substituted aryl;

(b) R^8 represents bromo, chloro, or fluoro;

(c) R^8 represents methyl, ethyl, propyl, isopropyl, or 2-methylpropyl;

(d) R^8 represents hydroxymethyl;

(e) R^8 represents (C_1-C_4)alkyl-(C_1-C_6)alkoxy;

(f) R^8 represents methoxymethyl;

(g) R^8 represents COR^{12} wherein R^{12} represents methoxy, ethoxy, hydroxyamethyl, or methoxymethyl;

(h) R^8 represents (C_3-C_7)cycloalkyl;

(i) R^8 represents phenyl, methoxyphenyl, methylphenyl, or phenyl-phenyl;

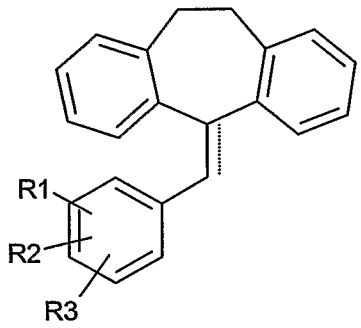
(j) R^8 represents hydrogen.

In addition, it will be understood that a most particular aspect of the novel compounds of the present invention are those wherein the compound is any novel compound of Formula I exemplified herein.

Compounds of the present invention, including novel compounds, can be further divided into sections as represented by Formulas I(a) through I(g) below. As such, methods and uses employing compounds of Formula I(a) - I(g), as well as novel compounds of Formula I(a) - I(g), represent more particular aspects of the present

invention. Section 1, as given by Formula I(a), contains derivatives of Formula I having substitution on the "C" ring but not on the "A" or "B" rings. Section 2, as given by Formula I(b), contains derivatives of Formula I having substitution on the "C" ring and further on the "A" and/or "B" rings. Section 3, as given by Formula I(c), contains derivatives of Formula I wherein the "C" ring further represents a heterocyclic or benzofused heterocyclic. Section 4, as given by Formula I(d), contains derivatives of Formula I wherein the "A" and / or "B" ring further represents a heterocyclic ring. Section 5, as given by Formula I(e), contains derivatives of Formula I wherein the bridge depicted by –X—Y– represents a fused cyclopropyl structure. Section 6, as given by Formula I(f), contains derivatives of Formula I wherein the bridge depicted by –X—Y– contains a heteroatom or heteroatom containing group at either the X or Y position. Finally, Section 7, as given by Formula I(g), contains derivatives of Formula I wherein R^8 is other than hydrogen and the bridge depicted by –X—Y– contains either a heteroatom or heteroatom containing group at either the X or Y position or both X and Y are CH_2.

Formula I(a)



wherein

"- - - - -" represents a double bond;

R^1 represents hydrogen, halo, hydroxy, cyano, nitro, amino, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, halo$(C_1$-$C_6)$alkyl, hydroxy$(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkoxy, $SO_2NR^9R^{10}$, SO_2R^{11}, $NHSO_2R^{11}$, $CH_2NHSO_2R^{11}$, $N(CH_3)SO_2R^{11}$, NR^9R^{10}, $NHCOR^{12}$, COR^{12}, CH_2NH_2, SR^{14}, heterocycle, or substituted heterocycle;

R^2 represents hydrogen, halo, hydroxy, (C1-C6)alkyl, (C1-C6)alkoxy, or halo(C1-C6)alkyl;

R^3 represents hydrogen or halo;

R^9 represents independently at each occurrence cyano, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_4)$alkyl-$(C_1\text{-}C_6)$alkoxy , halo$(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_7)$cycloalkyl, aryl, or $(C_1\text{-}C_4)$alkyl-aryl;

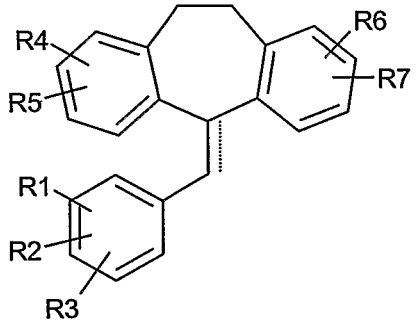
R^{10} represents independently at each occurrence hydrogen or $(C_1\text{-}C_6)$alkyl, or R^9 and R^{10} together with the nitrogen to which they are attached form a substituted or unsubstituted heterocycle

R^{11} represents independently at each occurrence amino, $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, NH-$(C_1\text{-}C_6)$alkylamine, N,N-$(C_1\text{-}C_6)$dialkylamine, aryl, substituted aryl, heterocycle, or substituted heterocycle;

R^{12} represents independently at each occurrence H, amino, $(C_1\text{-}C_6)$alkyl, or heterocycle; and

R^{14} represents $(C_1\text{-}C_6)$alkyl.

Formula I(b)



wherein

"- - - - -" represents a double bond;

R^1 represents hydrogen, halo, hydroxy, cyano, amino, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkoxy, $NHSO_2R^{11}$, NR^9R^{10}, $CH_2NH(SO_2R^{11})$, $NHCOR^{12}$, COR^{12}, OR^{14};

R^2 represents hydrogen or halo;

R^3 represents hydrogen;

R^4 and R^6 each independently represent hydrogen, halo, hydroxy, cyano, amino, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkyl, $NHSO_2R^{11}$, NR^9R^{10}, $NHCOR^{12}$, COR^{12}, OR^{14}, SO_2R^{11} , SR^{14}, aryl, or heterocycle;

R^5 and R^7 each independently represent hydrogen, halo, hydroxy, or (C_1-C_6)alkoxy;

R^9 represents independently at each occurrence cyano or (C_1-C_6)alkyl;

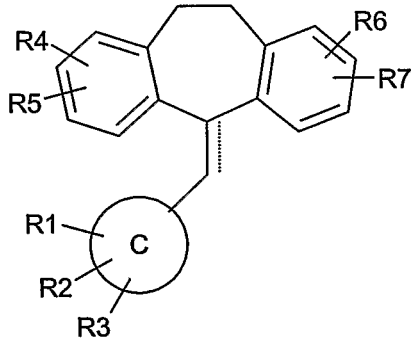
R^{10} represents independently at each occurrence hydrogen or (C_1-C_6)alkyl;

R^{11} represents independently at each occurrence amino, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, NH-(C_1-C_6)alkylamine, N,N-(C_1-C_6)dialkylamine, aryl, substituted aryl, heterocycle, or substituted heterocycle;

R^{12} represents independently at each occurrence H, amino, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxy(C_1-C_6)alkyl, (C_1-C)alkyl-(C_1-C_6)alkoxy, halo(C_1-C_6)alkyl, NH-methylamine, NH-dimethylamine , NH-ethylamine, or heterocycle; and

R^{14} represents independently at each occurrence (C_1-C_6)alkyl, (C_1-C_4)alkyl-aryl, (C_1-C_4)alkyl-substituted aryl, (C_1-C_4)alkyl-heterocycle, or (C_1-C_4)alkyl-(C_3-C_7)cycloalkyl.

Formula I(c)



wherein

"- - - - -" represents a double bond

"C" represents a heterocycle or benzofused heterocycle ring;

R^1 represents hydrogen, halo, hydroxy, amino, oxo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, $NHSO_2R^{11}$, or (C_1-C_4)alkyl-heterocycle;

R^2 represents hydrogen, halo, (C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, heterocycle, or (C_1-C_4)alkyl-heterocycle;

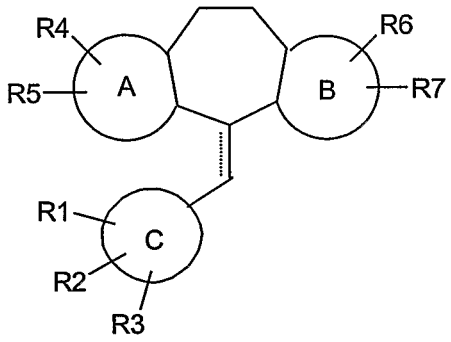
R3 represents hydrogen;

R4 and R6 each independently represent hydrogen, halo, hydroxy, cyano, amino, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or halo(C_1-C_6)alkyl;

R5 and R7 each independently represent hydrogen, halo, hydroxy, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy; and

R11 represents (C_1-C_6)alkyl.

Formula I(d)



wherein

"A" and "B", each independently represent phenyl or a heterocycle, provided at least one of "A" and "B" is a heterocycle;

"C" is as previously defined;

"-----" represents a double bond

R^1 represents hydrogen, halo, hydroxy, amino, oxo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkyl, $NHSO_2R^{11}$, $NHCOR^{12}$, COR^{12}, (C_3-C_7)cycloalkyl, heterocycle, or (C_1-C_4)alkyl-heterocycle, provided that when "C" represents aryl then R1 is other than oxo;

R^2 represents hydrogen, halo, hydroxy, (C_1-C_6)alkyl, or (C_3-C_7)cycloalkyl ;

R^3 represents hydrogen;

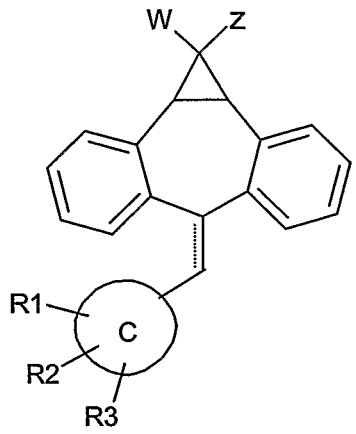
R^4 and R^6 each independently represent hydrogen, halo, hydroxy, cyano, amino, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkyl, or $NHCOR^{12}$;

R^5 and R^7 each independently represent hydrogen or halo;

R^{11} represents (C_1-C_6)alkyl or aryl; and

R^{12} represents independently at each occurrence (C_1-C_6)alkyl or (C_1-C_6)alkoxy.

Formula I(e)



Wherein

W and Z each independently represent hydrogen, fluoro, or chloro

"- - - - -" represents a double bond

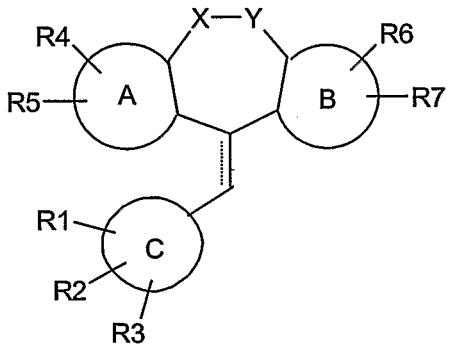
"C" represents phenyl or benzofused heterocycle;

R^1 represents hydrogen, hydroxy, amino, oxo, or $NHSO_2R^{11}$, provided that when "C" represents aryl then R1 is other than oxo;

R^2 and R^3 each represent hydrogen; and

R^{11} represents $(C_1\text{-}C_6)$alkyl.

Formula I(f)



wherein

"- - - - -" represents a double bond;

"A" and "B" represent phenyl or heterocycle and "C" is as previously defined;

X and Y together represent $-CH_2-O-$, $-O-CH_2-$, $-CH_2-S-$, $-S-CH_2-$, $-CH_2-SO-$, $-SO-CH_2-$, $-CH_2-SO_2-$, $-SO_2-CH_2-$, $-CH_2-NR^{10}-$, $-NR^{10}-CH_2-$, $-NR^{10}-CO-$, or $-CO-NR^{10}-$, wherein R^{10} is as previously defined;

R^1 represents hydrogen, halo, hydroxy, amino, oxo, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkyl, hydroxy$(C_1\text{-}C_6)$alkyl, $NHSO_2R^{11}$, $CH_2NH(SO_2R^{11})$, $NHCOR^{12}$, COR^{12}, OR^{14} , $(C_3\text{-}C_7)$cycloalkyl, or $(C_1\text{-}C_4)$alkyl-heterocycle, provided that when "C" represents aryl then R1 is other than oxo;

R^2 represents hydrogen, halo, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_7)$cycloalkyl, heterocycle, or $(C_1\text{-}C_4)$alkyl-heterocycle;

R^3 represents hydrogen, or $(C_1\text{-}C_6)$alkyl;

R^4 and R^6 each independently represent hydrogen, halo, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkyl, or COR^{12}; and

R^5 and R^7 each independently represent hydrogen, halo, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$alkoxy.

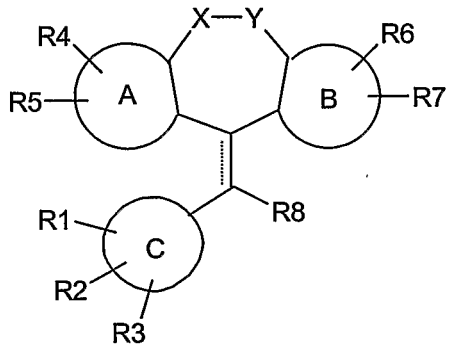
R^{10} represents independently at each occurrence hydrogen $(C_1\text{-}C_6)$alkyl;

R^{11} represents independently at each occurrence $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, aryl, substituted aryl, or $(C_3\text{-}C_7)$cycloalkyl;

R^{12} represents independently at each occurrence $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, NH-methylamine, NH-dimethylamine , or NH-ethylamine; and

R^{14} represents acetyl.

Formula I(g)



wherein

"- - - - -" represents a double bond;

"A" and "B" represent phenyl or heterocycle and "C" is as defined previously;

X and Y together represent $-CH_2-O-$, $-O-CH_2-$, $-CH_2-S-$, $-S-CH_2-$, $-CH_2-SO-$, $-SO-CH_2-$, $-CH_2-SO_2-$, $-SO_2-CH_2-$, $-CH_2-NR^{10}-$, $-NR^{10}-CH_2-$, $-NR^{10}-CO-$, or $-CO-NR^{10}-$;

R1 represents hydrogen, halo, hydroxy, amino, oxo, and $NHSO_2R^{11}$, provided that when "C" represents aryl then R1 is other than oxo;

R2 and R3 each individually represent hydrogen or halo;

R4 and R6 each independently represent hydrogen, halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or OR^{14};

R5 and R7 each independently represent hydrogen or halo;

R8 represents halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxy(C_1-C_6)alkyl, (C_1-C_4)alkyl-(C_1-C_6)alkoxy, COR^{12}, aryl, or substituted aryl;

R^{10} represents hydrogen or (C_1-C_6)alkyl;

R^{11} represents (C_1-C_6)alkyl;

R^{12} represents (C_1-C_6)alkoxy; and

R^{14} represents (C_1-C_4)alkyl-(C_3-C_7)cycloalkyl.

Further particular aspects of the methods and uses employing compounds of Formula I(a) – I(g) are provided by the groupings of particular substituents and particular variables, as set forth above, for the methods and uses employing compounds of Formula I, generally. Further particular aspects of the novel compounds of Formula I(a) – I(g) are provided by the groupings of particular substituents and particular variables, as set forth above, for the novel compounds of Formula I, generally.

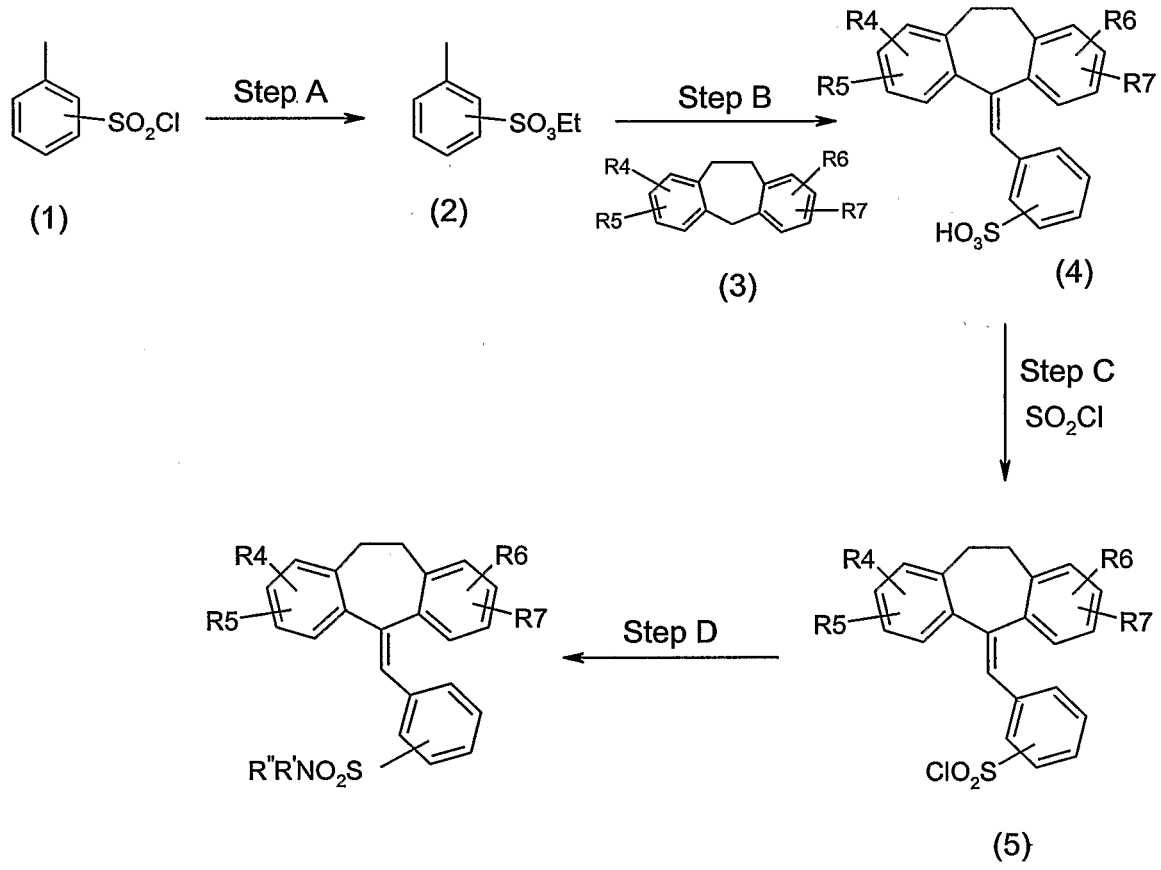
All of the compounds of Formula I, including the novel compounds of Formula I, can be can be chemically prepared, for example, by following the synthetic routes set forth in the Schemes below. However, the following discussion is not intended to be limiting to the scope of the present invention in any way. For example, the specific synthetic steps for the routes described for the synthesis of compounds of a particular section herein, may be combined in different ways, or in conjunction with steps from different schemes, to prepare additional compounds of Formula I or compounds of a different section. For example, the conditions described in Scheme VII, Step C may be employed to synthesize the final products of many of the compounds of Formula I

including, for example, derivatives wherein the bridge depicted by –X—Y– contains a heteroatom or heteroatom containing group at either the X or Y position.

All substituents, unless otherwise indicated, are as previously defined. The reagents and starting materials are readily available to one of ordinary skill in the art. For example, certain reagents or starting materials can be prepared by one of ordinary skill in the art following procedures disclosed in J. Prakt. Chem. 333 (4) (1991); J. Marsh, Advanced Organic Chemistry (4th edition); J. Med. Chem. (1990); J.S. Buck and W.S. Ide, Organic Synthesis Coll. Vol. II, 622-623, (1943) J.P. Wolfe and S.L. Buchwald, Organic Synthesis, (78) 23-31 (2000); Tetrahedron Letters, 39 (51) 9365-9368 (1998); F. Kurzer, Organic Synthesis, Coll. Vol. (IV) 49 (1963); and Synthetic Communications, 1129-1135 (1991). Additional reagents, starting materials, or useful procedures may be found in M Kurokawa, F Sato, Y Masuda, T Yoshida and Y Ochi, *Chem. Pharm. Bull.*, 39; 10; (1991) 2564-5273, Y Ohishi, H Yoshitaka, M Mitsuo, T Mukai, K Kimura, M Nagahara, *Chem. Pharm. Bull.*, 38; 4; (1990) 1066-1068, Inman, Raiford, *JACS*; 56 (1934) 1586-1587, Clark, Pessolano, *JACS*; 80 (1958) 1662, P. Bollinger, P. Cooper.; H. U. Gubler, A. Leutwiler, T. Payne *Helv. Chim . Acta* ;73; (1990);1197, G. Vassilikogiannakis, M. Hatzimarinaki, M. Orfanapoulos *J. Org. Chem.*, 65, 8180; Y. Girard, J. G. Atkinson, P. C. Belanger, J. J. Fuentes, J. Rokach, C. S. Rooney, D. C. Remy, C. A. Hunt *J. Org. Chem.*,48; (1983); 3220, D. S. Matteson, D. Majumder *Organometallics*, 2;(1983); 230; *Journal of Heterocyclic Chemistry*, 73; (1971) *Journal of Medicinal Chemistry*, 33; (1990); 3095, *Journal of Organic Chemistry,* 60;(1995);7508, Bergmann, E.D., Solomonovici, A., *Synthesis*, (1970); 183-189, Poirier et al., *Org. Letters*,3; 23; (2001); 3795-3798, Spanish Patent ES2092957 A1(1996); Brown, C., et al., J. Chem. Soc., Perkin Trans. I, 3007 (1982); Deck, L.M., et al., Org. Prep. Proceed. Int., 22(4); 495-500, (1990); Lee, J.C., et al., Synth. Comm., 25(9), 1367-1370 (1995); Ho, Z.C., et al., Tetrahedron, 52(41), 13189-13200 (1996); M Murata, T Takashi, S Watanabe and Y Yusuru, *J. Org. Chem.*; 65 (1) 164-168 (2000); and T. Ishiyama, M. Murata, N. Miyaura, *J. Org. Chem.*, 60(23), 7508-7510 (1995). Other necessary reagents and starting material may be made by procedures which are selected from standard techniques of organic and heterocyclic chemistry, techniques which are analogous to the syntheses of known structurally similar compounds, and the procedures described in the Examples below, including any novel procedures.

Scheme I provides procedures for the synthesis of compounds of Formula I wherein the bond represented by " ----- " attached to the tricyclic core is a double bond and at least one of R^1 through R^3 is, for example, an N-substituted- or unsubstituted-sulfonamido group.

Scheme I



In Scheme I, Step A, a substituted or unsubstituted toluenesulfonyl chloride derivative of formula (1) is reacted with an excess of ethanol in an inert solvent such as dioxane at about 0 to 50°C for about 10 to 48 hours, according to a procedure similar to that in J. Prakt. Chem. 333 (4) (1991). The HCl produced is neutralized in situ with a base, such as triethylamine or pyridine, with the progress of the reaction being followed by tlc. After work-up, the crude product can be purified using silica gel to give sulfate ester of formula (2).

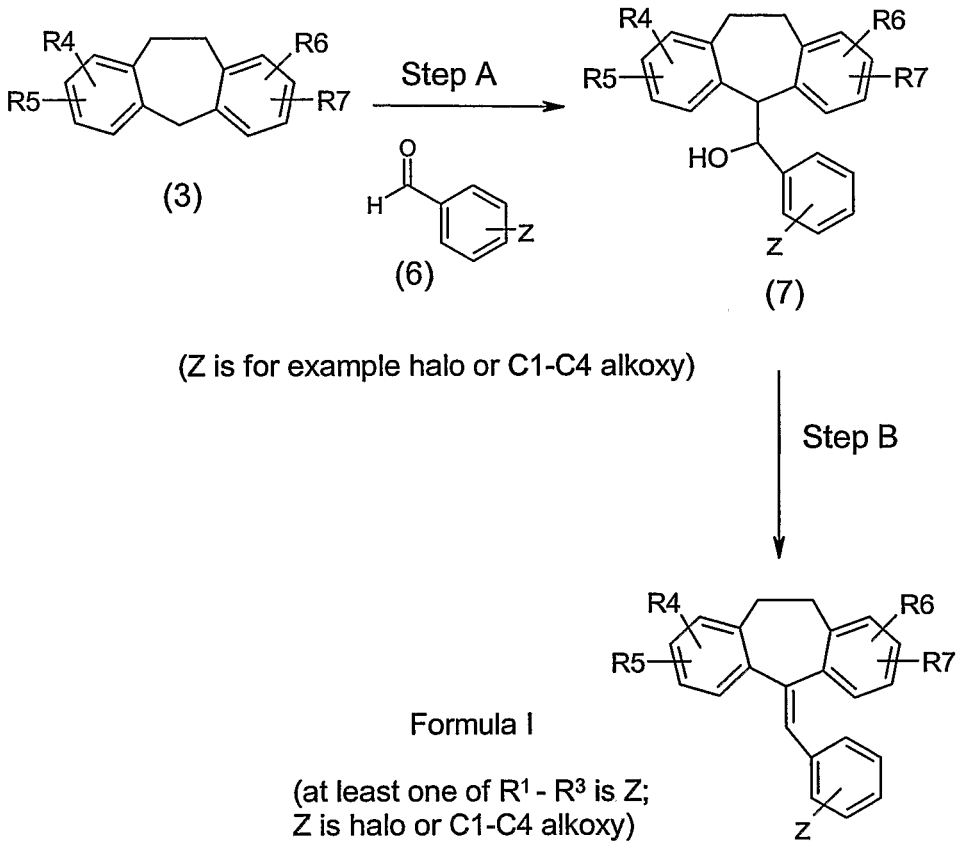
In Scheme I, Step B, the anion of the methyl sulfate ester of formula (2) is first generated using an appropriate base, such as n-butyl-Li, sec-butyl-Li, or t-butyl-Li at about –78 to 25°C, in an inert solvent such as THF. For a general discussion of anion formation see J. Marsh, Advanced Organic Chemistry (4th edition) 606-610. After generation of the anion is complete, a tricyclic, for example substituted or unsubstituted dibenzosuberane (formula (3)), is added. During acidic work-up, the carbinol dehydrates to the olefin and the sulfate ester hydrolyzes to the corresponding sulfonic acid to provide the compound of formula (4).

In Scheme I, Step C, using thionyl chloride and following methods well known to one of ordinary skill in the art, the sulfonic acid is converted to the corresponding sulfonyl chloride of formula (5). Inert solvents, such as methylene chloride, may be used and a catalytic amount of N,N-dimethylformamide increases the reaction rate. (J. Marsh, Advanced Organic Chemistry (4th ed.); 499) provides a detailed description and additional literature references.

In Scheme I, Step D, the sulfonyl chloride is reacted with an excess of a substituted or unsubstituted amine, at about 10 to 60°C for 2 to 24 hours, in an inert solvent such as THF, dioxane or methylene chloride (which may contain an acid scavenger such as pyridine or triethylamine) to provide the compound of Formula I, wherein at least one of R^1 through R^3 is, for example, an N-substituted- or unsubstituted-sulfonamido group. The product can then be purified using standard techniques such silica gel chromatography, eluting with suitable eluent such as ethyl acetate and hexane.

Scheme II provides procedures for the synthesis of compounds of Formula I wherein the bond represented by " ----- " attached to the tricyclic core is a double bond and at least one of R^1through R^3 is, for example, halo or (C1-C4)alkoxy.

Scheme II

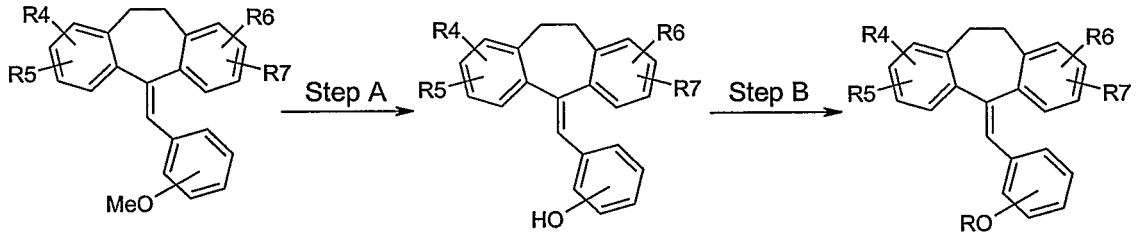


In Scheme II, Step A, the lithium anion of dibenzosuberane is first generated using an appropriate base such as n-butyl-Li, sec-butyl-Li, or t-butyl-Li at about –78 to 25°C in an inert solvent such as THF, diethyl ether, or diglyme, for about 0.5-5 hours. After anion generation is complete, the solution is cooled to about –25 to 10°C and a solution of an unsubstituted or substituted benzaldehyde derivative of formula (6) is added and the corresponding carbinol of formula (7) is isolated.

In Scheme II, Step B, the carbinol is dehydrated to the corresponding olefin derivative using 1-25% concentrated H_2SO_4 in glacial acetic acid at a temperature of about 25 to 100°C, for about 1 to 24 hours. The product of Formula I, wherein at least one of R^1 through R^3 is, for example, halo or $(C_1$-$C_4)$alkoxy, can then be purified using standard techniques such silica gel chromatography, eluting with suitable eluent such as ethyl acetate and hexane.

Scheme III provides procedures for the synthesis of compounds of Formula I wherein the bond represented by "-----" attached to the tricyclic core is a double bond

and at least one of R^1 through R^3 is, for example, hydroxy, difluoromethoxy, trifluoromethoxy, and the like



Formula I (at least one of R^1 - R^3 is OMe)

Formula I (at least one of R^1 - R^3 is OH)

Formula I (at least one of R^1 - R^3 is OR; R is for example CHF_2 or CF_3)

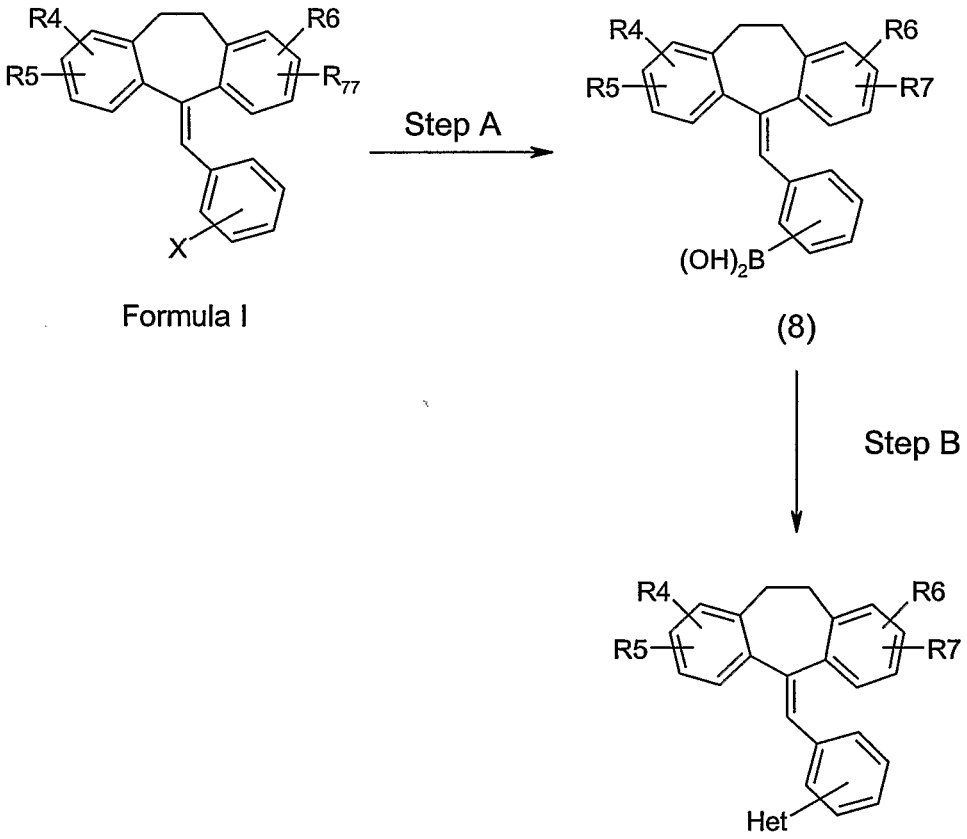
Scheme III

In Scheme III, Step A, a compound of Formula I, wherein at least one of R^1through R^3 is methoxy, is readily converted to a phenol derivative by treatment with either pyridine hydrochloride or boron tribromide. For a more detailed discussion of the formation of phenols from methyl ethers see J. Marsh, Advanced Organic Chemistry (4^{th} edition) 433-434.

In Scheme III, Step B, the phenol derivative of Formula I may be converted, for example, to a fluoromethoxy derivative using standard procedures as detailed in J. Med. Chem. 1230-1241 (1990). The products of Formula I can all be purified using standard techniques known in the art, such as silica gel chromatography with a suitable eluent such as ethyl acetate and hexane.

Schemes IV(a) – IV(d) provide yet additional procedures for the synthesis of compounds of Formula I wherein the bond represented by " ----- " attached to the tricyclic core is a double bond. For example, Scheme IV(a) provides procedures for synthesizing compounds of Formula I wherein at least one of R1 through R^3 is a heterocyclic group.

Scheme IV(a)

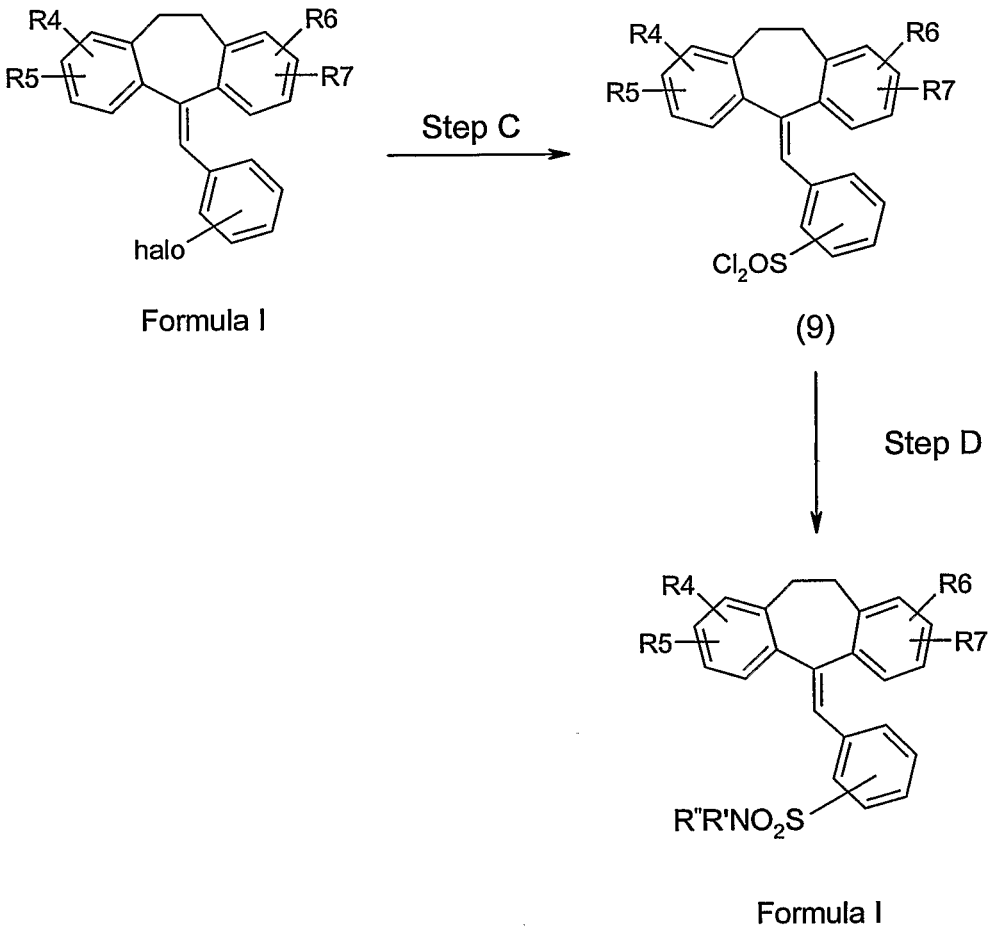


Formula I (8) Formula I

In Scheme IV(a), Step A, the lithium anion of the aryl halide derivative of Formula I (at least one of R^1 through R^3 is halo) is first generated by dissolving the aryl halide derivative in a suitable solvent such as THF, diethyl ether, or dioxane, cooling to a temperature of about –78 to –25°C, followed by addition of an appropriate base such as n-butyl-Li, sec-butyl-Li, or t-butyl-Li. The reaction is stirred for about 10 to 45 minutes to generate the anion. The boronic acid derivatives of formula (8) are prepared by quenching the anion of Formula I with triisopropyl borate followed by acidic hydrolysis.

In Scheme IV(a), Step B, following procedures well known in the art, the compound of formula (8) is treated under standard conditions with a compound of the general formula Het-Hal, (wherein Het is a heterocyclic moiety and Hal is bromo, chloro, or iodo) to provide the compound of Formula I wherein at least one of R^1 through R^3 is a heterocyclic moiety.

Scheme IV(b)



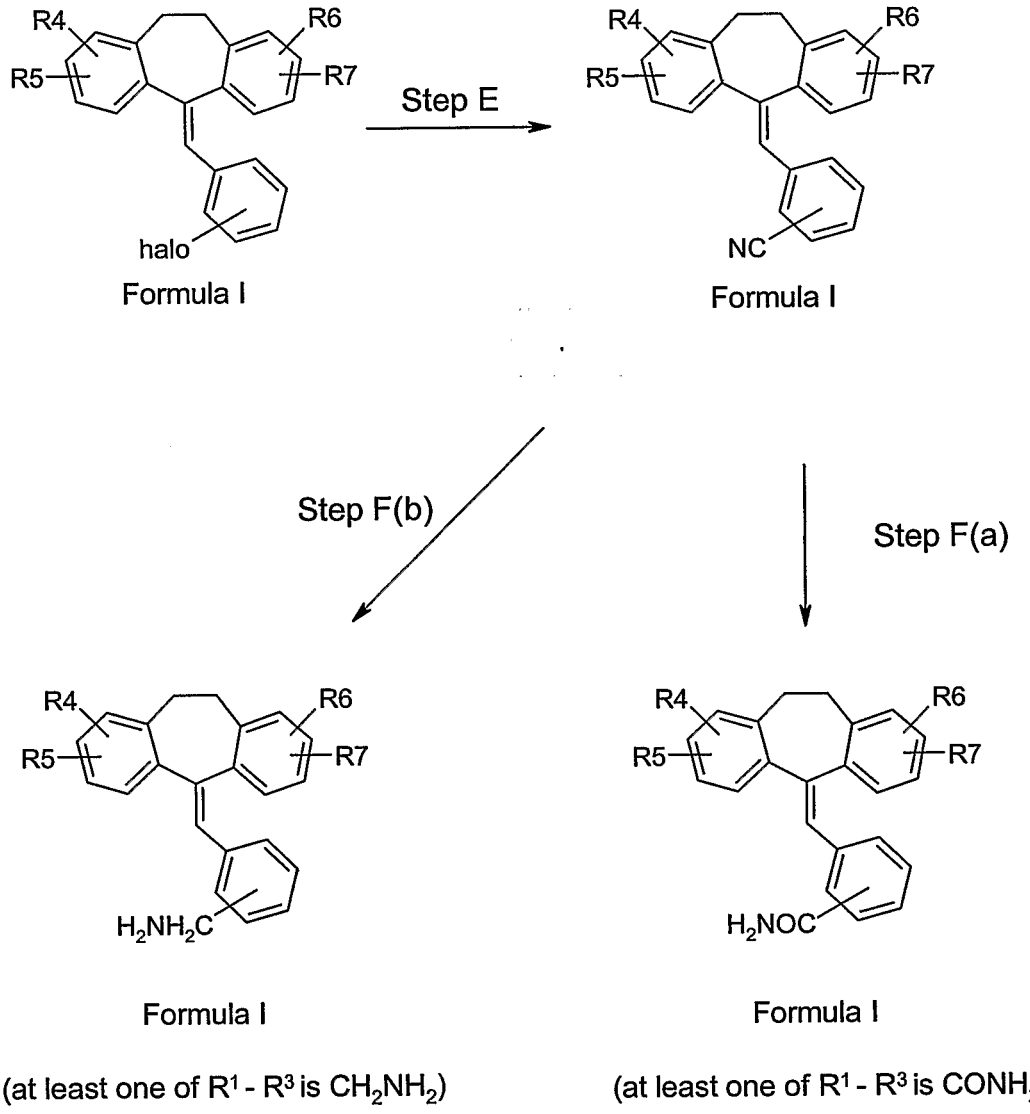
Formula I (9) Formula I

In Scheme IV(a), Step C, the lithium anion of the aryl bromide derivative of Formula I (at least one of R^1 through R^3 is halo) is first generated by dissolving the aryl halide derivative in a suitable solvent such as THF, diethyl ether, or dioxane, cooling to a temperature of about –78 to –25°C, followed by addition of an appropriate base such as n-butyl-Li, sec-butyl-Li, or t-butyl-Li. The reaction is stirred for about 10 to 45 minutes to generate the anion. Using standard techniques, the aryl sulfonyl chloride of formula (9) is prepared by quenching the aryl halide anion with sulfuryl chloride.

In Scheme IV(b), Step D, the aryl sulfonyl chloride derivative of formula (9) is treated with N-substituted- or unsubstituted- amines, as previously described in Scheme I above, to provide the compound of Formula I, wherein at least one of R^1 through R^3 is, for example, an N-substituted- or unsubstituted sulfonamide. The product can then be

purified using standard techniques such silica gel chromatography, eluting with suitable eluent such as ethyl acetate and hexane.

Scheme IV(c)



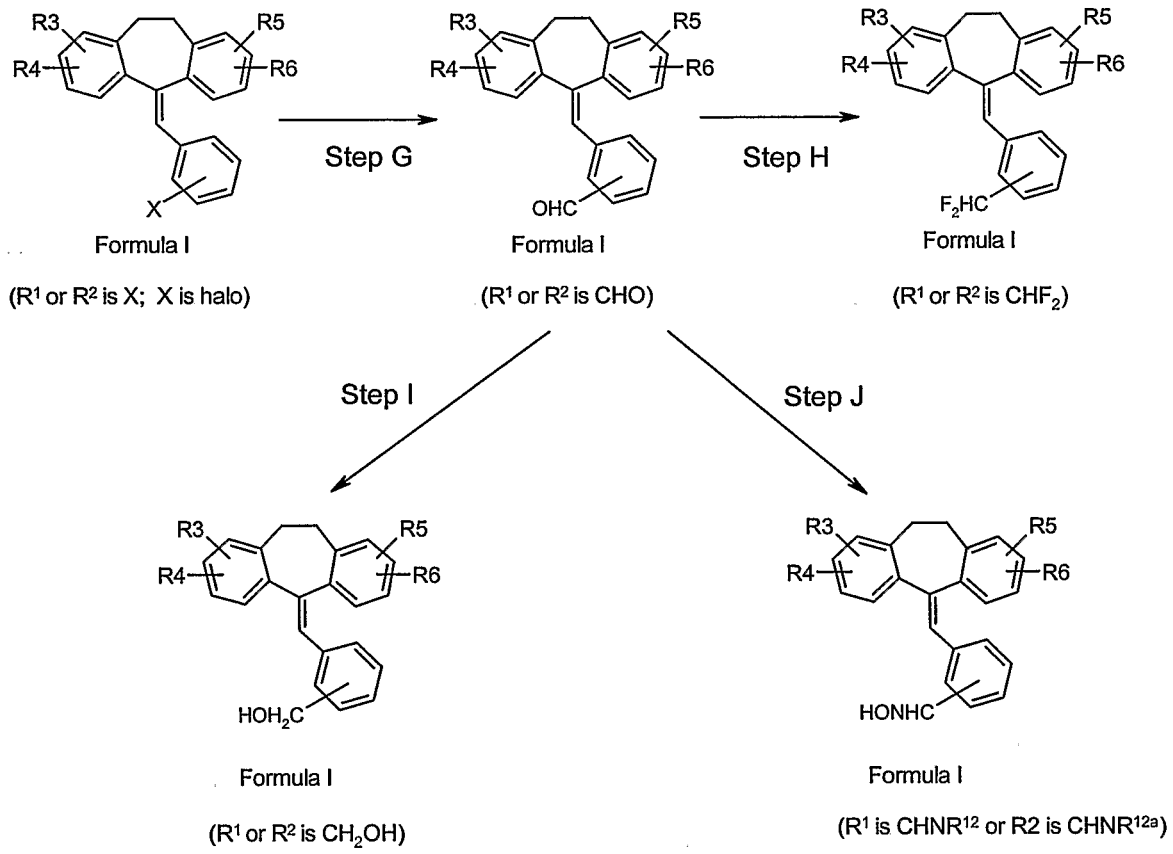
In Scheme IV(c), Step E, the aryl halide derivative is dissolved in a suitable solvent, such as N-methylpyrrolidinone (NMP), and sparged with nitrogen for 5-15 minutes. Solid CuCN and CuI are added and the reaction is heated to a temperature ranging from about 100 to 150°C for 1 to 24 hour. The reaction is then cooled and shaken with aqueous ferric chloride and ethyl acetate, to provide the benzonitrile derivative of

Formula I. The product can then be purified using standard techniques such silica gel chromatography, eluting with suitable eluent such as ethyl acetate and hexane.

In Scheme IV(c), Step F(a), the benzonitrile is first dissolved in a suitable solvent, such as DMSO, then solid K_2CO_3 is added, followed by about 30% H_2O_2. The reaction is stirred for about 3 hours followed by quenching with water. The product of Formula I, wherein at least one of R^1 through R^3 is, for example COR^{12} is then collected and dried under vacuum. Alternatively, in Step F(b), the benzonitrile may be reduced to the corresponding aminomethyl. For example, the corresponding nitrile is first dissolved in diethyl ether. Lithium aluminum hydride is then added and the reaction is stirred at room temperature for 1-24 h. The reaction is quenched by using procedures known in the art and as described in Fieser and Fieser, Reagents for Organic Synthesis, Vol. 1 pp 581-595. The inorganic solids are then filtered and washed with ether. After drying ($MgSO_4$) and concentration, the crude compound is obtained wherein at least one of R1 through R3 is aminomethyl. Further purification can be accomplished using column chromatography with the appropriate solvents.

Scheme IV(d) provides procedures for the synthesis of compounds of Formula I wherein at least one of R^1 through R^3 is, for example, a fluoromethyl, hydroxy, or an oxime.

Scheme IV(d)



In Scheme IV(d), Step G, the lithium anion of the aryl halide derivative of Formula I is first generated by dissolving the aryl bromide derivative in a suitable solvent such as THF, diethyl ether, or dioxane, cooling to a temperature of about –78 to –25°C, followed by addition of an appropriate base such as n-butyl-Li, sec-butyl-Li, or t-butyl-Li. The reaction is stirred for about 10 to 45 minutes to generate the anion. Using standard techniques, the aldehyde derivative of Formula I (at least one of R^1 through R^3 is CHO) is then generated by reacting the anion with N,N-dimethylformamide.

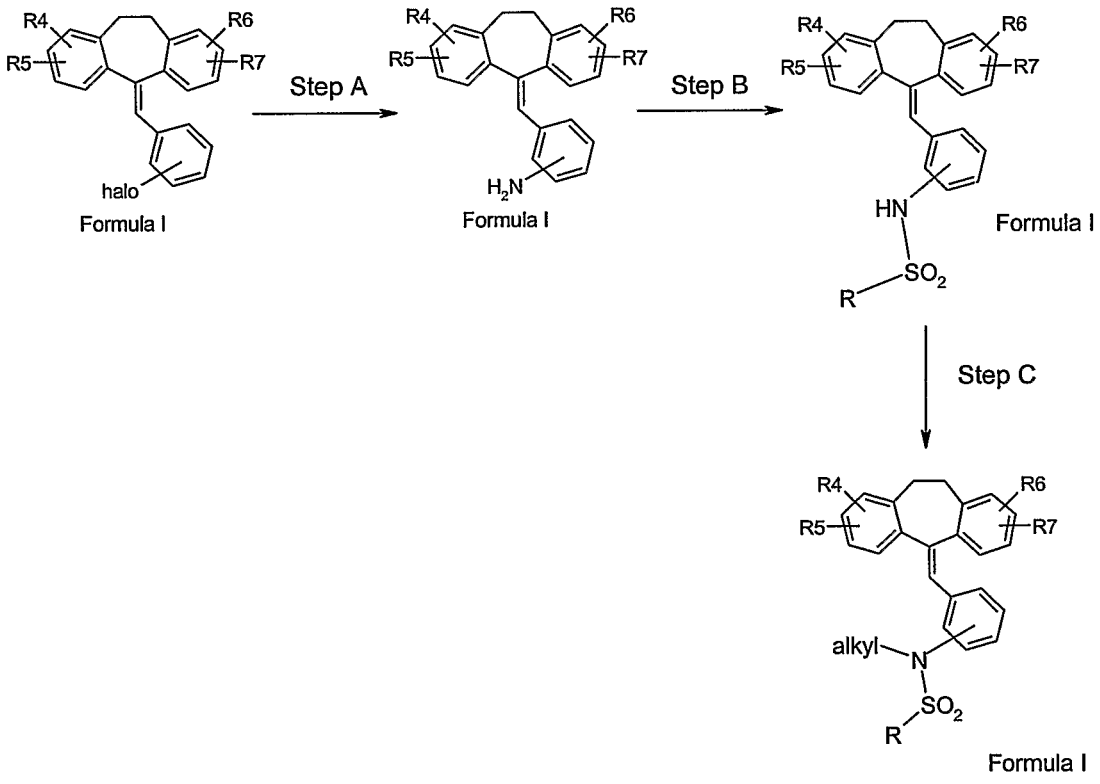
In Scheme IV(d), Step H, the aldehyde derivative is converted into a fluoromethyl derivative by dissolving in dichloromethane and treating with 1 to 5 equivalents of a fluorinating agent such as diethylamino sulfur trifluoride (DAST) and stirring at about 10 to 50°C for 5 to 48 hours.

In Scheme IV(d), Step I, using standard procedures, the aldehyde derivatives of Formula I (at least one of R^1 through R^3 is CHO) are reduced to the corresponding alcohol derivatives by reaction with sodium borohydride in ethanol.

In Scheme IV(d), Step J, using methods as described in J.S. Buck and W.S. Ide, Organic Synthesis Coll. Vol. II, 622-623, (1943) the aldehyde derivative of Formula I is converted to the corresponding oxime derivative of Formula I under standard conditions .

The Formula I products of Steps G, H, I and J, may all be purified using standard techniques such silica gel chromatography, eluting with a suitable eluent such as ethyl acetate and hexane.

Schemes V(a) – V(b) provide procedures for the synthesis of various N-substituted- and unsubstituted-amine derivatives of Formula I (at least one of R^1 through R^3 is, for example, amino, N-substituted amino, or N,N-disubstituted amino) wherein the bond represented by " ----- " attached to the tricyclic core is a double bond.



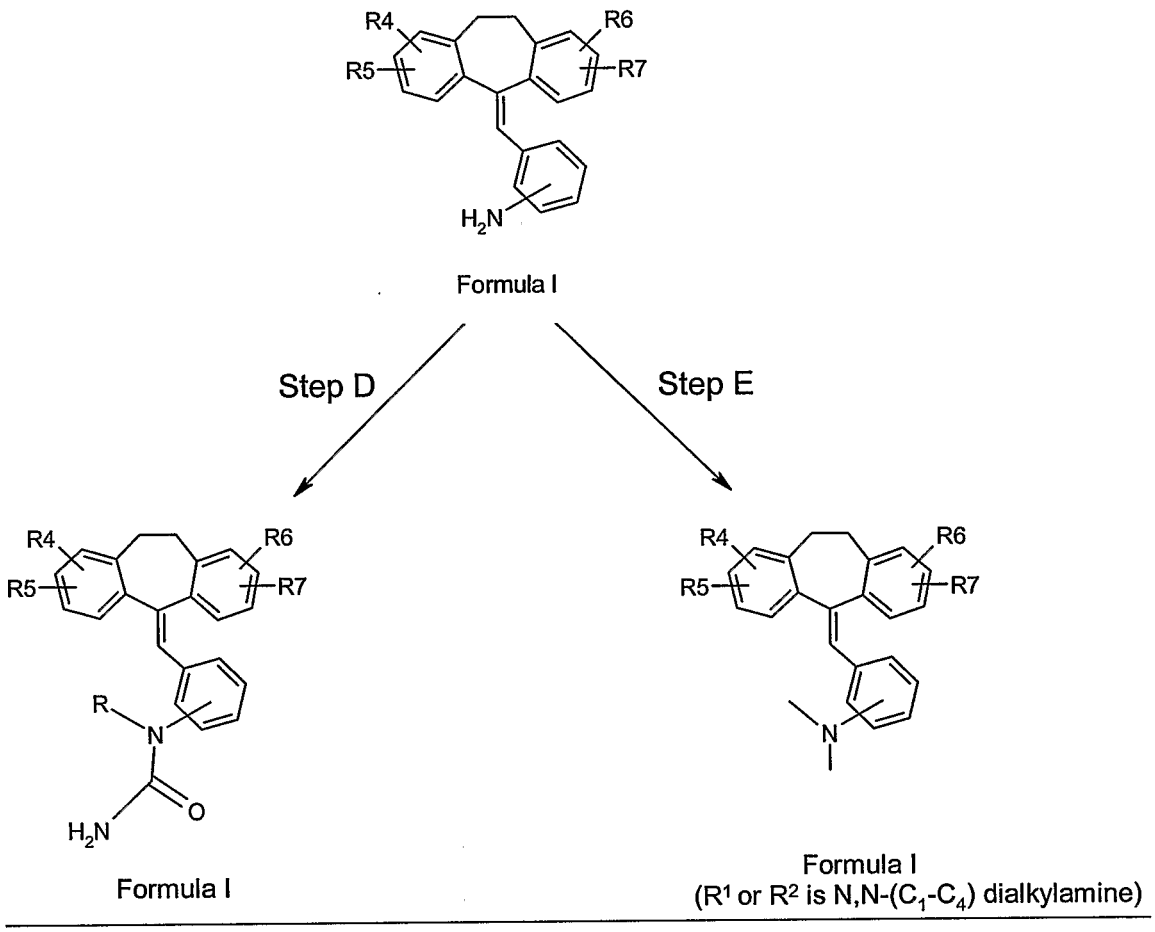
Scheme V(a)

In Scheme V(a), Step A, the halo derivative of Formula I, prepared as described previously in Scheme II, is converted to an arylamine derivative using procedures as described in J.P. Wolfe and S.L. Buchwald, Organic Synthesis, Vol 78 23-31 (2000). After work-up, the crude imine is hydrolyzed to the amine using aqueous hydrochloric acid in tetrahydrofuran. The amines are purified by trituration with toluene/hexane or using silica gel chromatography, eluting with ethyl acetate and hexane.

In Scheme V(a), Step B, the amine derivative of Formula I is converted to a substituted-amine derivative by reaction with a sulfonyl chloride in pyridine at a temperature of about 10 to 50°C for about 5 to 48 hours. The crude product of Formula I wherein at least one of R^1 through R^3 is, for example an N-[sulfonyl]-amino moiety can then be purified using silica gel chromatograph, eluting with a mixture of ethyl acetate and hexane.

In Scheme V(a), Step C, the N-[sulfonyl]-amines may be converted to disubstituted-amine derivatives according to procedures as detailed in Tetrahedron Letters, 39 (51) 9365-9368 (1998). The anion is generated using sodium hydride in N,N-dimethylformamide at temperatures ranging from about 0 to 30°C for about 0.25 to 2 hours. After addition of excess iodomethane, the reaction is stirred at room temperature for about 1 to 24 hours and then the crude product of Formula I, wherein at least one of R^1 through R^3 is, for example, a disubstituted N,N-[alkyl , sulfonyl]-amine can then be purified using silica gel chromatograph, eluting with a mixture of ethyl acetate and hexane.

Scheme V(b)



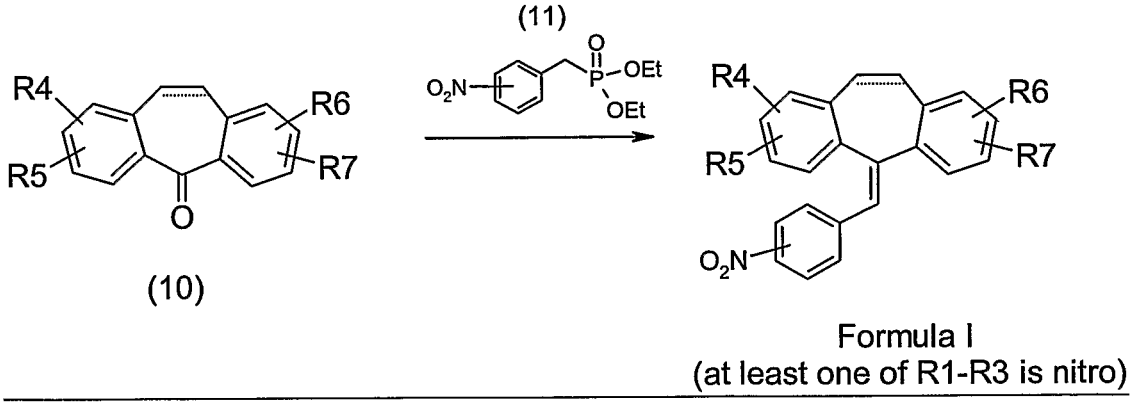
In Scheme V(b), Step D, the amine derivative of Formula I prepared as described in Scheme V(a), above, is converted to the corresponding urea using procedures as described by F. Kurzer, Organic Synthesis, Coll. Vol. (IV) 49 (1963). For example, a compound of Formula I, wherein at least one of R^1 is NH_2 is combined with HOAc and water. A solution of sodium cyanate in water is then added to the mixture of the amine derivative. The reaction is stirred at room temperature for about 2 hours and then poured into water. The compound of Formula I, wherein at least one of R^1 through R^3 is, for example $NRCONH_2$ is then extracted with EtOAc, dry ($MgSO_4$) and concentrated to provide crude product. The crude product may then be purified by standard techniques such as silica gel chromatography, eluting with a mixture of ethyl acetate and hexane. (Alternatively in Step D, the amine derivative of Formula I is converted into an amide derivative of Formula I, by reacting with an acid halide in pyridine at about 10 to 50°C for about 5 to 48 hours. The crude product of can then be purified using silica gel chromatography, eluting with a mixture of ethyl acetate and hexane).

In Scheme V(b), Step E, the amine derivative of Formula I is mono- or di-alkylated using standard procedures well known to those of ordinary skill in the art. For a detailed descriptions of such methods, see Synthetic Communications, 1129-1135 (1991). The crude products of Formula I, wherein at least one of R^1 through R^3 is, for example NH-(C1-C4) alkylamine or N,N-(C1-C4)dialkylamine, can then be purified using silica gel chromatography, eluting with a mixture of ethyl acetate and hexane.

To provide compounds of Formula I wherein the bond represented by "-----" attached to the dibenzosuberane core is a single bond, the olefin moiety of the compounds of Formula I, prepared according to Schemes I-V above, can be readily reduced using a catalyst such as palladium on carbon (5 to 10%) in a solvent such as ethanol or methanol. The pressure of hydrogen used may vary from atmospheric to 60 psi. The reaction is performed at temperatures ranging from about 20 to 50°C for 1 to 20 hours. For more details on hydrogenation of olefins, see H.O. House, Modern Synthetic Reactions, 2nd edition, pp. 1-34 (1972).

Schemes VI provides yet additional procedures for the synthesis of compounds of Formula I. Scheme VI is particularly useful where at least one of R^1 through R^3 is, for example, nitro or amino; wherein X and Y represent –CH=CH– ; and wherein the bond represented by "-----" attached to the tricyclic core is a double bond.

Scheme VI



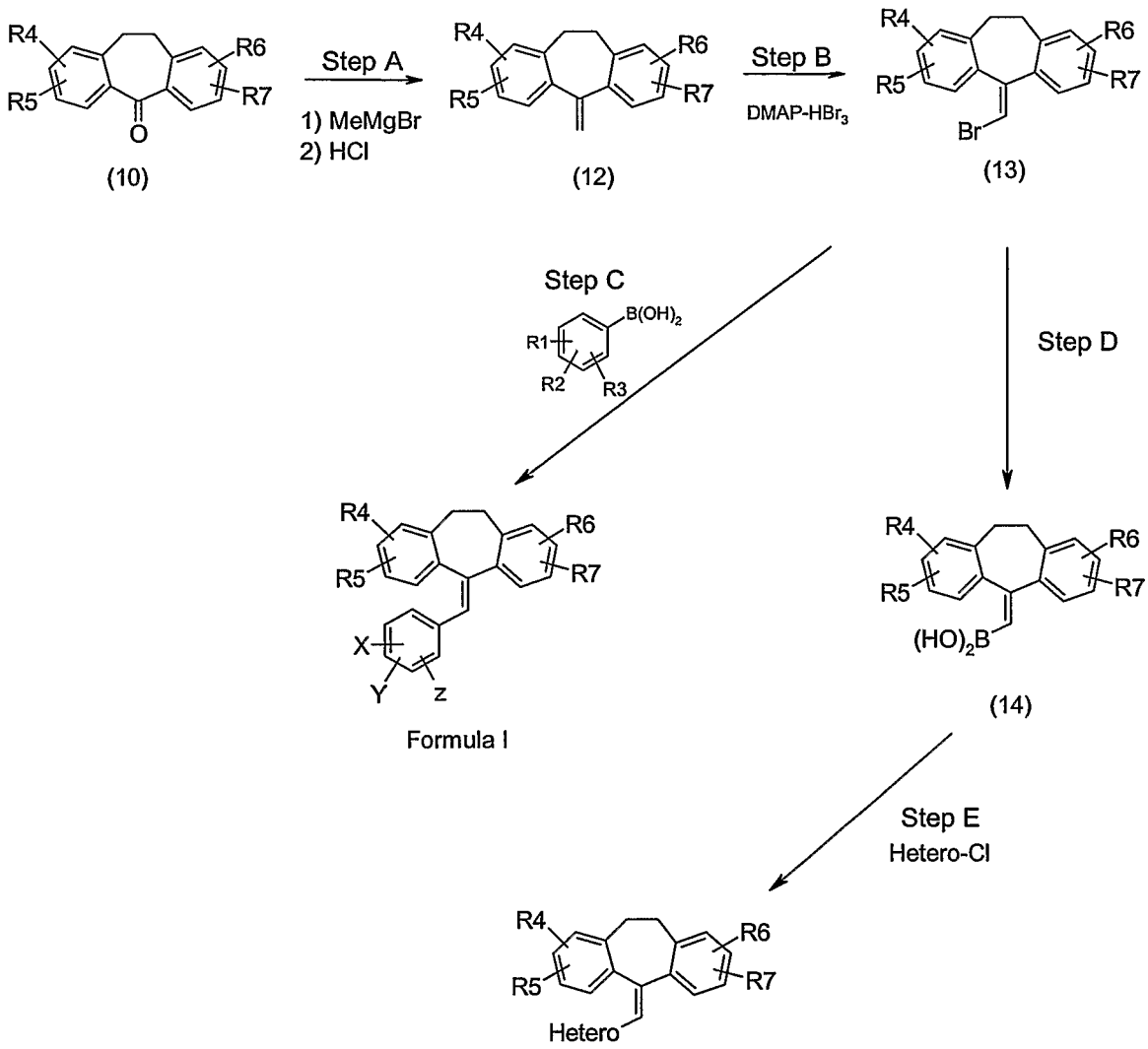
In Scheme VI, the phosphonate of structure (11) is first dissolved in a suitable solvent, such as DMF, DMSO or acetonitrile at room temperature under an inert atmosphere. An appropriate base, such as sodium hydride, is then added. After stirring

from 0.5 to 6 hours, the dibenzosuberone- or dibenzosuberenone-derivative of structure (10), dissolved in a suitable solvent such as DMF, is then added. The reaction is stirred for about 6 to 24 hours and then quenched with aqueous HCl. The product, wherein at least one of R1 through R3 is, for example nitro, is then extracted into EtOAc, dried ($MgSO_4$) and concentrated. The product is purified using column chromatography, eluted with EtOAc/hexanes. (For a more detailed discussion of this Horner-Emmons procedure, see

J. Marsh, Advanced Organic Chemistry (4^{th} edition) pp 959-960 and references cited therein).

Scheme VII provides procedures for the synthesis of compounds of Formula I employing Suzuki coupling conditions. In particular, the procedures of Scheme VII are useful for synthesizing compounds of Formula I wherein a heterocyclic or substituted heterocyclic ring is attached to the tricyclic core of Formula I; and wherein the bond represented by " ----- " attached to the tricyclic core is a double bond.

Scheme VII



Formula I

In Scheme VII, Step A, the dibenzosuberone derivative (10) is dissolved in an appropriate solvent such as diethyl ether, dioxane or tetrahydrofuran and 1 to 5 equivalents of methylmagnesium bromide is added. After 2-24 hours, the intermediate carbinol derivative is converted to the exomethylene derivative by cooling to 0°C and adding HCl. After stirring for about 1-18 hours, the reaction is shaken with EtOAc and water. The organic solution is dried ($MgSO_4$) and concentrated. The crude product of structure (12) is purified by short path column chromatography (silica gel, hexane containing EtOAc).

In Step B, the compound of structure (12) is dissolved in a solvent such as methylene chloride, chloroform, carbon tetrachloride or 1,2-dichloroethane and treated with a slight excess of dimethylaminopyridine tribromide. The reaction is stirred at room temperature for about 1-24 hours. The excess brominating reagent is quenched with Na_2SO_3 and the reaction is partitioned between water and organic solvent. The solvent is dried (Na_2SO_4) and concentrated under reduced pressure to yield the crude product of structure (13). The crude compound of structure (13) is purified by short path column chromatography (silica gel, hexane containing EtOAc).

In Step D, derivatives of structure (14) are prepared by adding t-BuLi portionwise (exotherm) to a solution of the vinyl bromide (13) in dry THF at –78°C under N_2. The reaction is stirred at –78°C for 45min and trimethyl borate is then added. The reaction is warmed to room temperature and stirred for about an additional 30min. The mixture is then concentrate using standard procedures, ethylene glycol and toluene are added, and the reaction refluxed overnight. The reaction is then cooled to room temperature, the layers separated and the ethylene glycol layer extracted with toluene. the toluene layers are then combined and concentrated to provide the compound of structure (14). The crude product (14) can then be purified by silica gel chromatography eluting with ethyl acetate:hexanes:triethylamine.

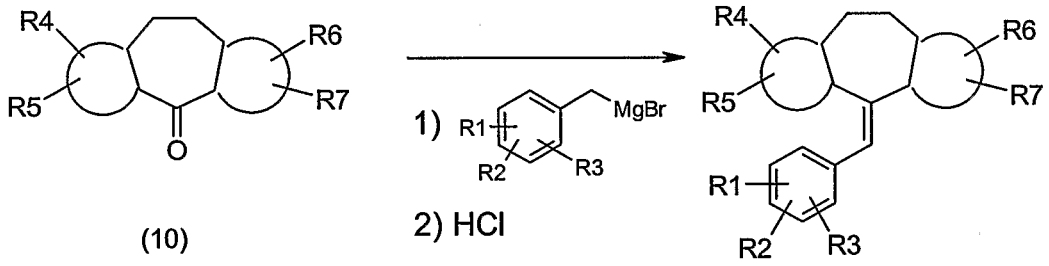
In Step C, the vinyl bromide of structure (13) and aryl boronic acid are mixed in dioxane. 2.0M aqueous Na_2CO_3 is then added and the reaction sparged with N_2 for 5min. $Pd(PPh_3)_4$ is added and the reaction vial immediately sealed. The reaction is heated to about t 70-100°C for about 8-24 h. The reaction is then quenched with H_2O and the product of Formula I extracted into CH_2Cl_2. After drying (Na_2SO_4) and concentration, the crude product is purified using chromatography on silica gel, eluting with ethyl acetate/hexanes to obtain the purified product of Formula I.

In Step E, a mixture of the vinyl borate of structure (14), a substituted or unsubstituted chloroheterocycle, cesium fluoride and [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium (II) (1:1 complex with CH_2Cl_2) in dioxane is heated at about 50-100°C for about 12-72 h. The solvent is removed using a stream of nitrogen and the resulting residue is shaken with H_2O and CH_2Cl_2 and loaded onto a Varian ChemElut CE1005 solid-phase extraction cartridge. Elute with CH_2Cl_2, and concentrate using standard procedure to obtain the crude product of Formula I, wherein a heterocycle or

substituted heterocycle is attached to the tricyclic core. The crude product can then be purified by mass-guided reverse-phase HPLC to obtain the purified product of Formula I. Alternatively, in Step E, a mixture of vinyl borate (14), a substituted or unsubstituted chloroheterocycle, K_2CO_3 and ethanol is sparged with N_2 for 10min. $Pd(PPh_3)_4$ is then added and the reaction sealed immediately. The reaction is heated at about 70-100°C for about 12-72 h. The mixture is then concentrated under N_2, then H_2O (1mL) and ethyl acetate (1mL) are added. The residue is load onto a Varian ChemElut CE1005 solid-phase extraction cartridge. Elute with ethyl acetate, collect, and concentrate the crude reaction. The crude product can then be purified on silica gel, eluting with ethyl acetate/hexanes to obtain the pure product of Formula I wherein a substituted or unsubstituted heterocycle is attached to the tricyclic core.

Scheme VIII provides yet additional procedures for the synthesis of compounds of Formula I, particularly those wherein rings A and/or B are heterocyclic rings.

Scheme VIII



Formula I

In Scheme VIII, a solution of the appropriate substituted or unsubstituted benzyl magnesium bromide in THF is added to a solution of (10) in THF under Ar. The resulting solution is stirred for about 1-24 h at about 25 °C before quenching with saturated, aqueous ammonium chloride. The mixture is filtered and the magnesium salts washed with diethyl ether. The filtrate is then with water and brine, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting tertiary alcohol can then be purified by column chromatography (hexanes/ethyl acetate).

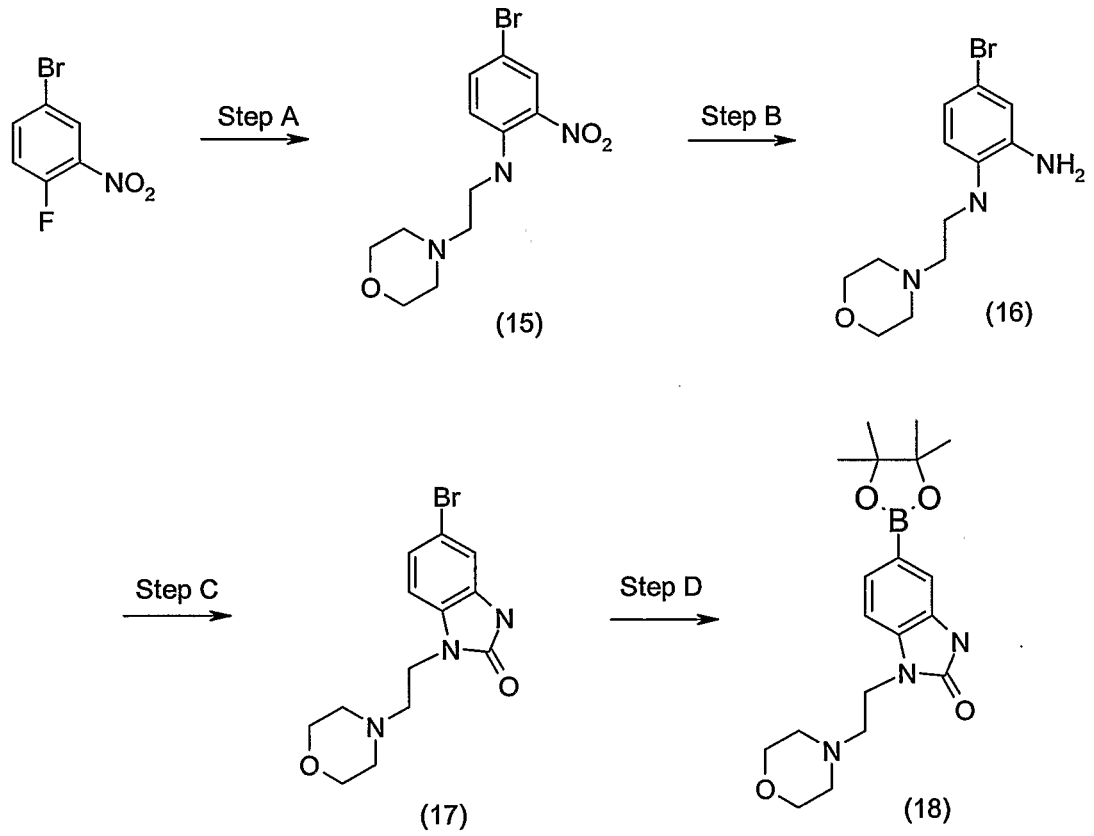
The crude carbinol is dissolved in $CHCl_3$ and concentrated hydrochloric acid is then added. The resulting dark solution is stirred for 2 h at about 25 °C. Water and $CHCl_3$ are added, the layers separated, and the organic layer washed successively with

saturated, aqueous sodium bicarbonate and brine. The crude product of Formula I is then dried ($MgSO_4$) and concentrated via rotary evaporation. The crude material may then be purified by flash chromatograpy(hexanes/ethyl acetate) to provide the purified final product of Formula I (wherein A and / or B are, for example, heterocyclic rings).

Additional Schemes for the synthesis of compounds of the invention:

Scheme IX provides procedures useful for the synthesis of compounds of Formula I wherein the "C" ring represents an N-substituted benzimidazole derivative.

Scheme IX



In Scheme IX, Step A, 5-bromo-2-fluoro-nitrobenzene is mixed with about 2 equivalents of a substituted amine, for example 4-(2-aminoethyl)morpholine, in THF. The reaction is stirred at room temperature for about 18h. The THF is removed under reduced pressure and the residue partitioned between water and ethyl acetate. The organic layer is dried (MgSO4) and concentrated to provide compound of structure (15).

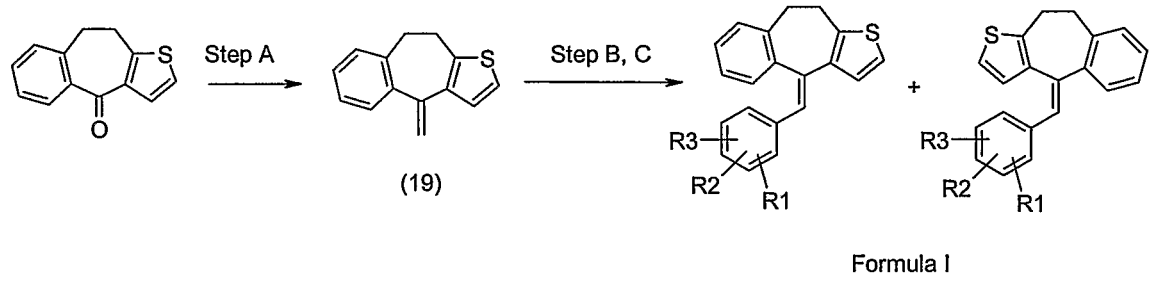
In Scheme IX, Step B, the compound of structure (15)is dissolved in ethyl acetate or THF and 5% Pt/C (sulfided)is added. The slurry is placed under 60psi hydrogen gas at room temperature for about 8h. The reaction is then filtered and concentrated to provide, for example, the compound of structure (16) as a dark red oil. Compound (16) may then be purified, for example by using a short plug of silica gel and 10% 2N NH3 in MeOH/dichloromethane.

In Scheme IX, Step C, the compound of structure (16) is mixed with NaHCO3, water, and methanol. Slowly, phenyl chloroformate (about 1.5 equivalents)is added and the reaction is stirred for about 1h at room temperature. 5N NaOH (about 1.5 equivalents) is then added and the reaction is stirred overnight at room temperature. The solid of structure (17) is collected by vacuum filtration and washed with methanol.

In Scheme IX, Step D, under a blanket of nitrogen, a solution of compound (17)in THF is cooled to about 5°C and 3N ethylmagnesium bromide is added. After about 1/2h, the reaction is cooled to about –72°C and slowly 1.7M t-BuLi is added. The reaction is allowed to warm to about –55°C, then trimethyl borate is added and the reaction is allowed to stir at room temperature overnight. 5N HCl is then added and the reaction stirred for about 4h. The pH is adjusted to about 6-7 and the crude boronic acid is extracted into ethyl acetate, dried and concentrated to give the crude acid which is then slurried with toluene and pinacol is added. The reaction is heated briefly and stirred overnight. Ethyl acetate and aqueous NaHCO3 are added, the organics extracted with water and the dried (MgSO4) organic layer is evaporated to give the purified product of compound (18).

Schemes X-XIII provide procedures useful for the synthesis of compounds of Formula I wherein the "A" and/or "B" ring represents a heterocyclic ring, which may be substituted or unsubstituted. Also, Scheme X demonstrates an alternative procedure to that described in SchemeVII, Step A for converting the ketone moiety to a methylene by use of the Tebbe reagent.

Scheme X

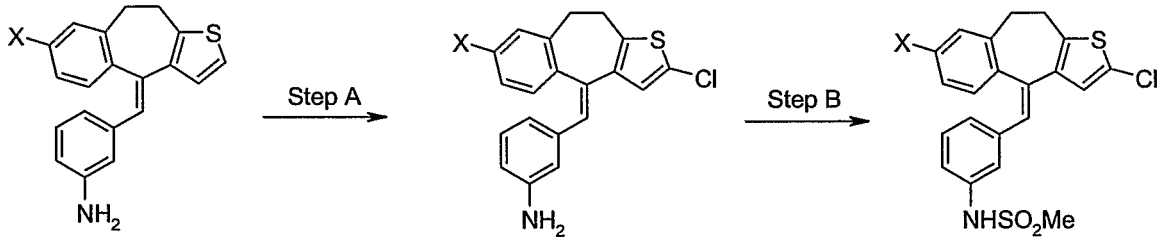


Formula I

In Scheme X, Step A, to a solution of , for example, 9,10-dihydro-1-thia-benzo[*f*]azulene-4-one (see P. Bollinger, P. Cooper.; H. U. Gubler, A. Leutwiler, T. Payne *Helv. Chim . Acta* **1990**, *73*, 1197) at about –40°C is added about 3 equiv of a 0.5 M solution of Tebbe reagent in toluene and about 3 equiv of pyridine in THF (0.1 M) under Ar. The resulting mixture is stirred for about 2 h then allowed to warm to 0 °C over ca. 30 min period before diluting with diethyl ether. 5 N sodium hydroxide is then added carefully until bubbling ceases, then solid Na_2SO_4, and the reaction stirred for about 1 h. The mixture is then filered through Celite®, then the filtrate by rotary evaporation. The crude residue of compound (19) may then be purified by standard techniques such as column chromatography (hexanes) to give the purified product of structure (19).

In Scheme X, Steps B and C, the compound of structure (19) may be treated according to the procedures as described in Scheme VII, Steps B and C to provide the compound of Formula I.

Scheme XI



Formula I(i) (X = H or Cl)

Formula I(ii) (X = H or Cl)

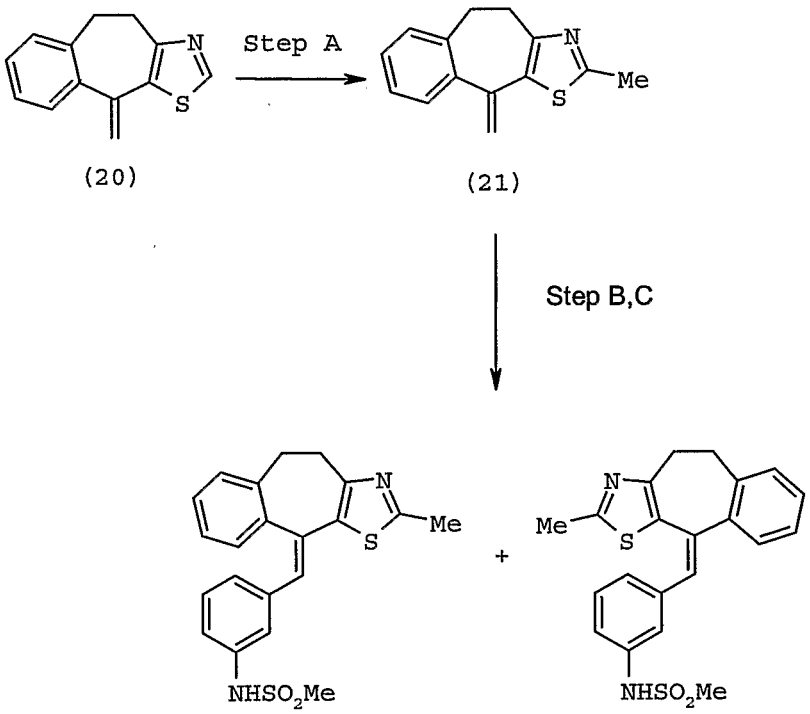
Formula I(iii) (X = H or Cl)

In Scheme XI, procedures for the synthesis of compounds of Formula I wherein "A" or "B" represents a chlorothiophene are provided. In Scheme XI, Step A, about 2 equiv of *n*-BuLi-hexanes is added dropwise to a solution of a compound of Formula I(i), for example 3-(9,10-Dihydro-1-thia-benzo[f]azulen-4-ylidenemethyl)-phenylamine, in

THF at about 0 °C under Ar. The resultant dark solution is stirred for about 1 h before adding about 2.5 equiv of hexachloroethane in THF. The reaction is stirred for about 2 h, quenched with excess water, and acidified to neutral pH. The aqueous layer is extracted with diethyl ether (3 X) and then dried ($MgSO_4$), and the combined organic layers are concentrated under reduced pressure. The crude product (Formula I(ii)) may then be purifed using standard techniques, such as by column chromatography to give the 2-chlorothiophene derivative compound.

In Scheme XI, Step B, the amino group of Ring "C" may be treated according to procedures as described in Scheme V(a), Step B to provide further methanesulfonamide derivatives of Formula I(iii).

Scheme XII



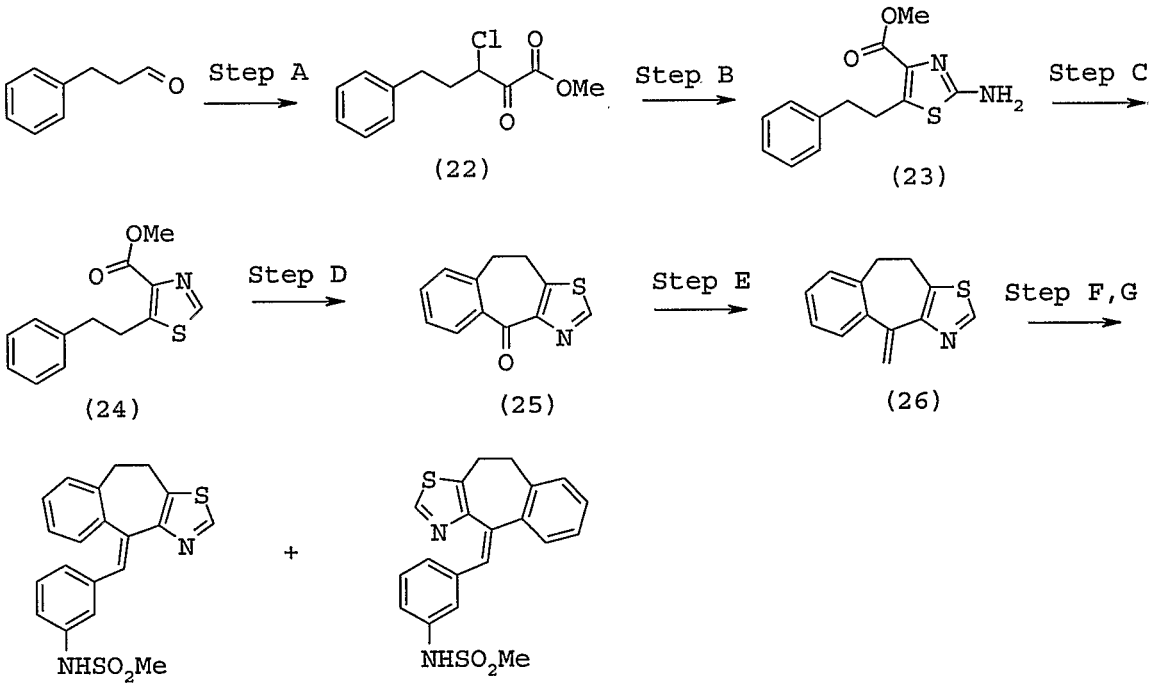
Formula I

Scheme XII provides procedures for the synthesis of derivatives of Formula I wherein Ring "A" and or "B" represents a methylated heterocycle, particularly a methylated thiazole. In Scheme XII, Step A, add about 1.2 equiv of *n*-BuLi-hexanes dropwise to a solution of compound (20)(4-methylene-9,10-dihydro-4H-3-thia-1-aza-

benzo[f]azulene) in THF at about -78 °C under Ar. The resultant dark green solution is stirred for about 5 min before adding about 1.2 equiv of iodomethane in THF. The reaction is allowed to warm and stirred at room temperature for about 18 h before quenching with excess water. The layers are separated and the aqueous layer extracted with,for example, diethyl ether (3 X) and then dried ($MgSO_4$. The combined organic layers may then be concentrated under reduced pressure and the product (Structure (21))used in the next step without further purification.

In Scheme XII,Steps B and C, the compound of structure (21) is treated according to procedures as described Scheme VII, Steps B and C to provide the compound of Formula I wherein Ring "A" and or "B" represents a methylated heterocycle.

Scheme XIII



Formula I

Scheme XIII provides additional procedures for the synthesis of compounds of Formula I wherein Ring "A" and or "B" represents a thiazole. In Scheme XIII, Step A, a flask is charged with equimolar methyl dichloroacetate and 3-phenyl-prionaldehyde in diethyl ether. The solution is cooled to about 0 °C and about 1 equiv of sodium methoxide in methanol is added over a 1 h period. The mixture is vigourously stirred for

about 2 h at about 0 C and then allow to warm to room temperature before adding brine. The layers are separated, dried ($MgSO_4$) and the organic concentrated to give the crude residue of compound (22).

In Scheme XIII, Step B, reflux the compound of structure (22) and thiourea in MeOH for about 4 h, then basify with ammonia-MeOH and add brine. The reaction is then extract with, for example ethyl acetate, then the combined organic layers are washed with brine, dried($MgSO_4$), and concentrated under reduced pressure to give the compound of structure (23).

In Scheme XIII,Step C, about one equiv of the compound of structure (23) and about 3 equiv of isoamyl nitrite in THF are refluxed for about 3 h. Evaporate The volatile components are evaporated to provide the compound of structure (24).

In Scheme XIII, Step D, a thick slurry of the compound of structure (24) and polyphosphoric acid (PPA) is rapidly stirred and heated to about 140 °C for about 24 h and then about 150 °C for about 5 h. Carefully the hot mixture is added to ice-cold aqueous sodium hydroxide. The reaction is then extracted, for example with EtOAc, and the combined organic layers washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue of structure(25) may then be purified by standard techniques, such as by column chromatography (10% to 50% EtOAc:hexanes) to provide the purified compound of structure (25).

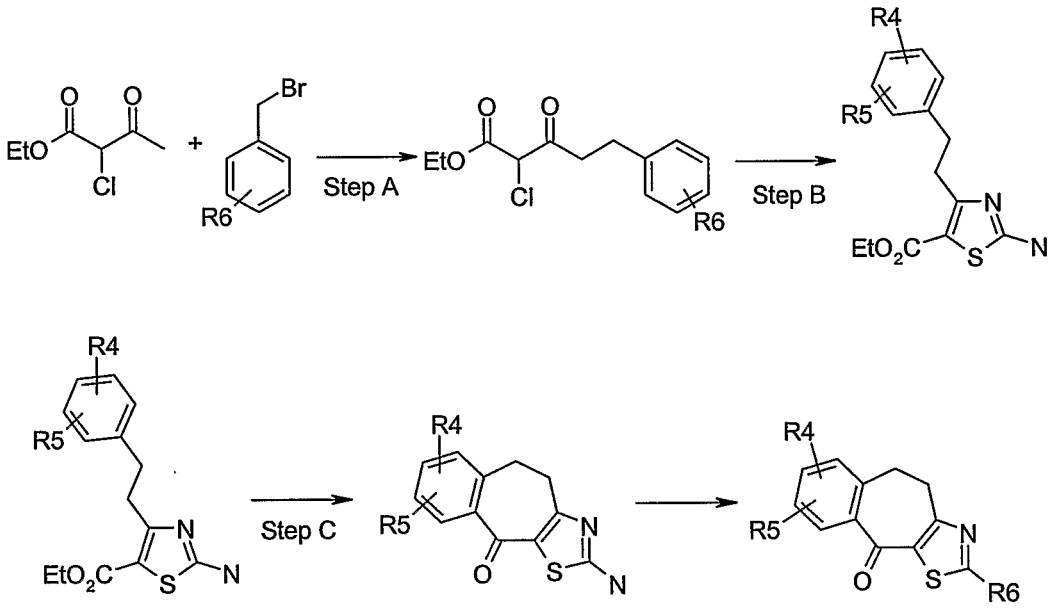
In Scheme XIII, Step E, the compound of structure(25) is treated according to procedures as described in Scheme VII, Step A to provide compound of structure (26).

In Scheme XIII, Steps F and G, the compound of structure (26) is treated according to procedures as described Scheme VII, Steps B and C to provide the compound of Formula I wherein Ring "A" and or "B" represents a thiazole ring.

Alternatively, the desired starting thiazole ketone can be prepared as as shown in Scheme XIII(b), below. In step A, 2-chloro-3-oxo-butyric acid ethyl ester in THF is treated with first NaH (1 equivalent) then n-BuLi (1 equivalent) while the temperature is held at about –60 to -10°C and then the appropriately substituted benzyl bromide added. In Step B, the intermediate 2-chloro-3-oxo-5-phenyl-pentanoic acid ethyl ester derivative is reacted with thiourea in refluxing ethanol for 1-24 hours. This ester can be cyclized using PPA and heating at from 160-250°C for 1-15 hours. As described in Scheme

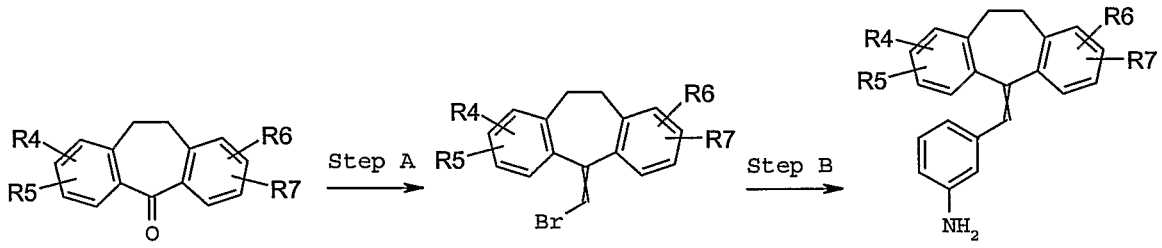
XIII(a), Step C , the amino moiety can be converted to –H. This intermediate ketone can be converted to final products as in Scheme XIII(a), Steps E, F and G.

Scheme XIII(b)



Scheme XIV provides additional procedures for the synthesis of compounds of Formula I wherein ring "A" and or "B" is substituted.

Scheme XIV



(27) (28) Formula I

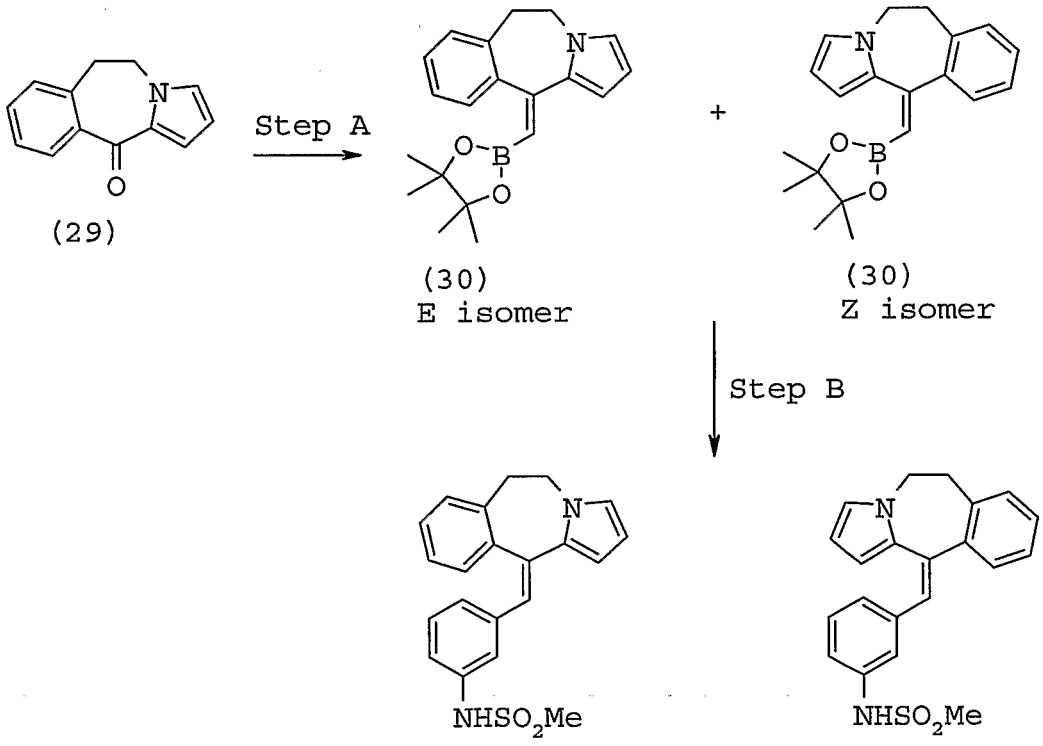
In Scheme XIV, Step A, a mixture of 2-3 equiv of bromomethyltriphenylphosphonium bromide (see G. Vassilikogiannakis, M. Hatzimarinaki, M. Orfanapoulos *J. Org. Chem.*, **65**, 8180) in THF (0.5 M) is cooled to about –78 °C and about 2-3 equiv of LiHMDS-THF is added dropwise to give a bright

yellow mixture. The reaction is stirred for about 1 h at about –78 °C and then for about 10 min at 0 °C. The mixture is re-cooled to about –78 °C and the compound of structure (27) is added. The dark mixture to is allowed to warm to room temperature and stirred for about 3.5 h before adding saturated, aqueous saturated ammonium chloride and diluting with pentane. The mixture is filtered through celite, the filtrate concentrated under reduced pressure, and purifed by standard techniques such as column chromatography (1% to 2% to 3% to 5% EtOAc:hexanes) to give the compound of structure (28) as a 1:1 mixture of geometric isomers.

In Scheme XIV, Step B, the compound of structure (28) is treated according to procedures as described in Scheme VII, Step C to provide the compound of Formula I.

Scheme XV provides additional procedures for the synthesis of compounds of Formula I wherein ring "A" and or "B" represents a heterocyclic ring and additionally shows methodology to prepare useful intermediate vinyl borate ester derivatives.

Scheme XV

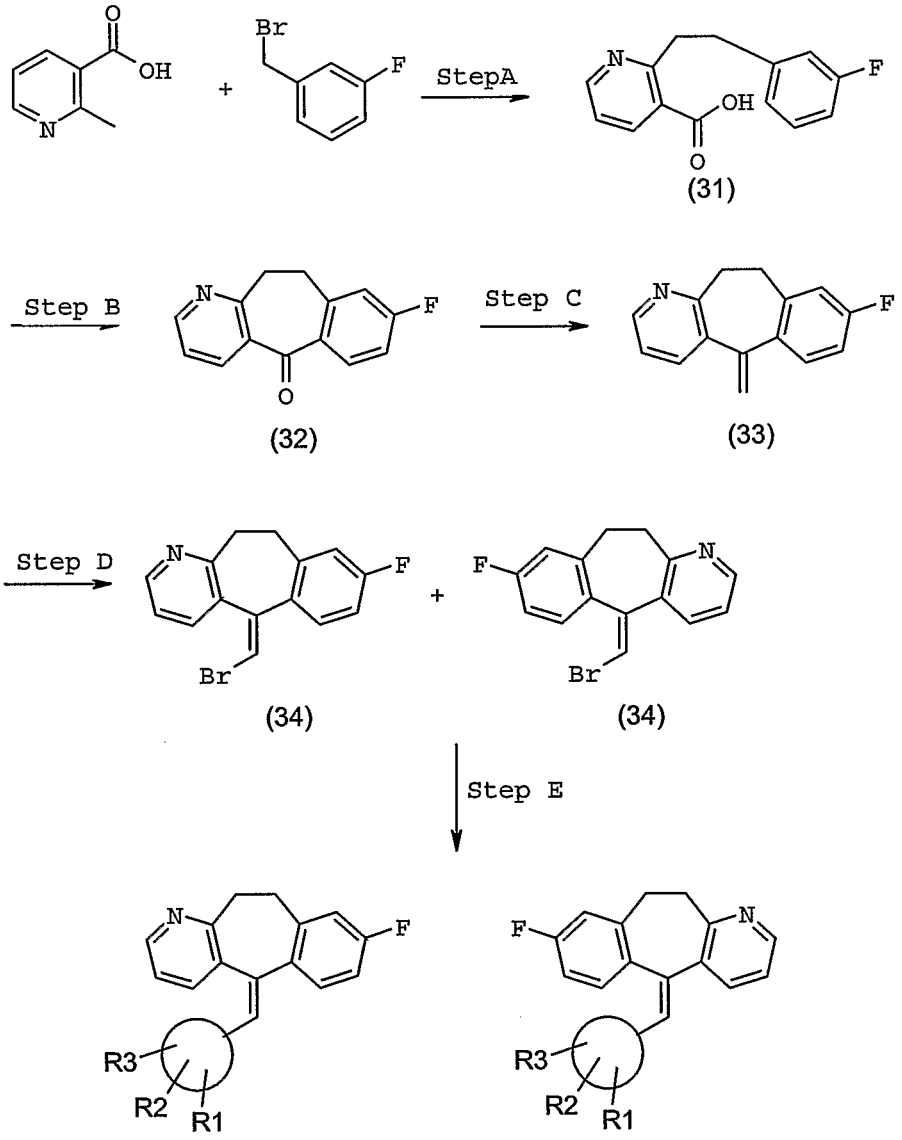


In Scheme XV, Step A, about one equiv of, for example, 5,6-dihydro-benzo[d]pyrrolo[1,2-a]azepin-11-one (structure(29))(see Y. Girard, J. G. Atkinson, P. C. Belanger, J. J. Fuentes, J. Rokach, C. S. Rooney, D. C. Remy, C. A. Hunt *J. Org. Chem.* **1983**, *48*, 3220) in THF is added to a solution of about 2.5 equiv of pinicol lithio(trimethylsilyl)methaneboronate (see D. S. Matteson, D. Majumder *Organometallics***1983**, *2*, 230), about 1 equiv TMEDA, about 2.5 equiv of tetramethylpiperidine (TMP), and THF at about –78 °C. The solution is allowed to warm to room temperature and stirred for about 3.5 h before quenching with excess water. The reaction is extracted with Et_2O (4 X), dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue may then be purified by standard techniques such as column chromatography (5% to 10% EtOAc:hexanes) to give the pure E-isomer and Z-isomer of structure (30).

In Scheme XV, Step B, the compound of structure (30) is treated according to procedures as described in Scheme VII, Step C to provide the E and Z isomer of the compound of Formula I.

Scheme XVI provides yet additional procedures for synthesizing compounds of Formula I wherein ring "A" and or "B" represents a heterocyclic ring.

Scheme XVI



Formula I

In Scheme XVI, Step A, diisopropylamine is dissolved in dry tetrahydrofuran and the resulting mixture cooled to about –78 °C. Butyllithium is then added and the reaction mixture is warmed to about 0 °C then a fine slurry of 2-methyl-nicotinic acid in THF (25 mL) is added portionwise during about 10 min. The resulting slurry is stirred for about 1h, then 3-fluorobenzyl bromide is added and the mixture is stirred for about 5 min. The reaction is quenched with water and extracted with diethyl ether. The pH of the aqueous layer is adjusted to about 3.1 with concentrated aqueous hydrochloric acid solution. The resulting slurry is treated with ethyl acetate and stirred to dissolve all solids. The layers are separated and the aqueous layer extracted with ethyl acetate. Concentrate the

combined extracts are then concentrated to dryness to provide the compound of structure (31).

In Scheme XVI, Step B, the compound of Structure (31) is combined with polyphosphoric acid (about 100 g) and heated to about 160 °C for about 6 h. The reaction mixture is allowed to slowly cool over 12h, then reheated to about 160 °C and poured into ice. The transfer is completed using water and the pH of the aqueous mixture adjusted to about 8.0 with 50% aqueous sodium hydroxide solution. The product of structure (32) is extracted with methylene chloride. The combined organic extracts are dried with magnesium sulfate, filtered and concentrated. The compound of structure (32) may then be purified using standard techniques such as flash chromatography (25% ethyl acetate/hexanes to 50% ethyl acetate/hexanes) to provide the purified product of the compound of structure (32). (See *Journal of Heterocyclic Chemistry* **1971**, 73).

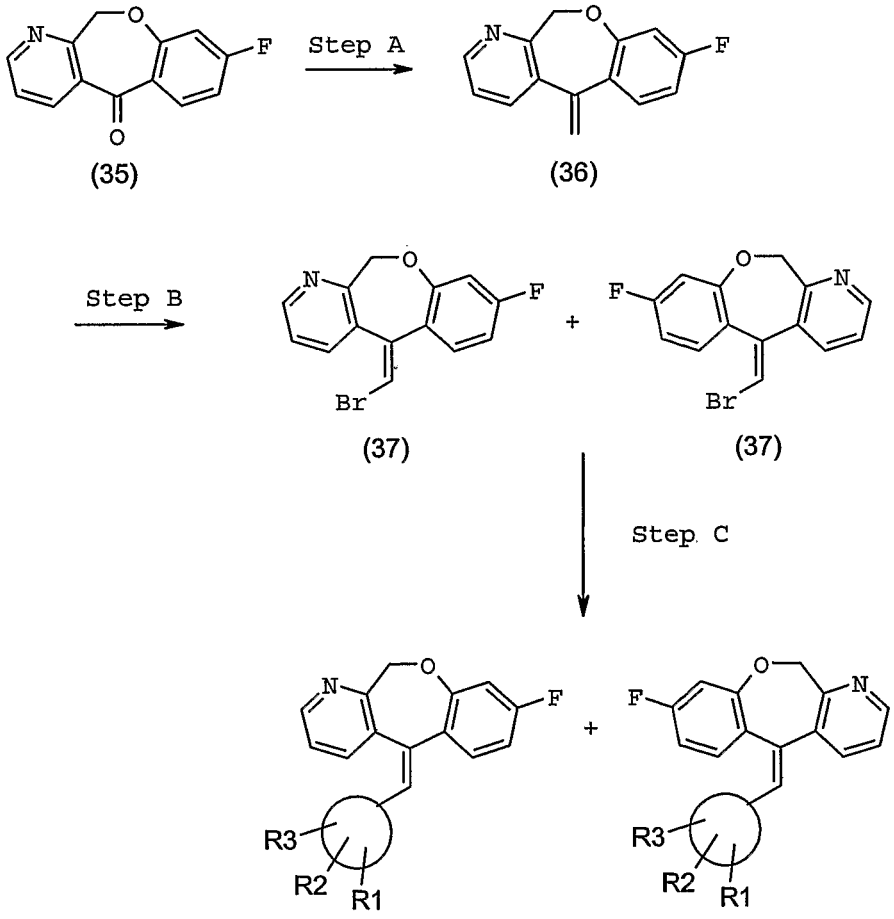
In Scheme XVI, Step C, a mixture of compound (32) and dry THF is chilled to about 0 °C. This mixture is treated with methyl magnesium bromide, the cooling removed, and the mixture is stirred at room temperature for about 15 min. The reaction is quenched , while cooling with an ice-water bath, by adding saturated aqueous ammonium chloride solution (50 mL). The layers are separated and the aqueous layer extracted with methylene chloride (2x50 mL). The combined organic layers are dried with magnesium sulfate, filtered, and concentrated to provide the intermediate product of structure (33) as a thick crude oil. Without further purification, this residue is dissolved in a solution of sulfuric acid in acetic acid (3% by volume, 50 mL) and the mixture stirred at room temperature for about 12-18 h. The reaction mixture is concentrated to remove excess solvent and the resulting orange residue dissolved in 1N aqueous sodium hydroxide solution (25 mL) and ethyl acetate (50 mL). the pH of the resulting mixture is adjusted to about 8 with 5N aqueous sodium hydroxide solution. The layers are separted, and the aqueous extracted with ethyl acetate (2x50 mL). The combined organic layers are dried with magnesium sulfate, filtered, and concentrated to provide the compound of structure (33).

In Scheme XVI, Step D, the compound of structure (33) is treated according to procedures as described in Scheme VII, Step B, to provide E and Z isomer of compound (34).

In Scheme XVI, Step E, the compound of structure (34) is treated according to procedures as described in Scheme VII, Step C to provide the E and Z isomer of the compound of Formula I.

Scheme XVII provides yet additional procedures for synthesizing compounds of Formula I wherein ring "A" and or "B" represents a heterocyclic ring and wherein the bridge depicted by –X—Y– contains a heteroatom or heteroatom containing group at either the X or Y position.

Scheme XVII



Formula I

In Scheme XVII, Step A, the compound of structure (35), for example, (8-fluoro-11H-10-oxa-1-aza-dibenzo[a,d]cyclohepten-5-one) (see *Journal of Medicinal Chemistry* 1990, *33*, 3095)and anhydrous tetrahydrofuran (25 mL) are combined and the solution

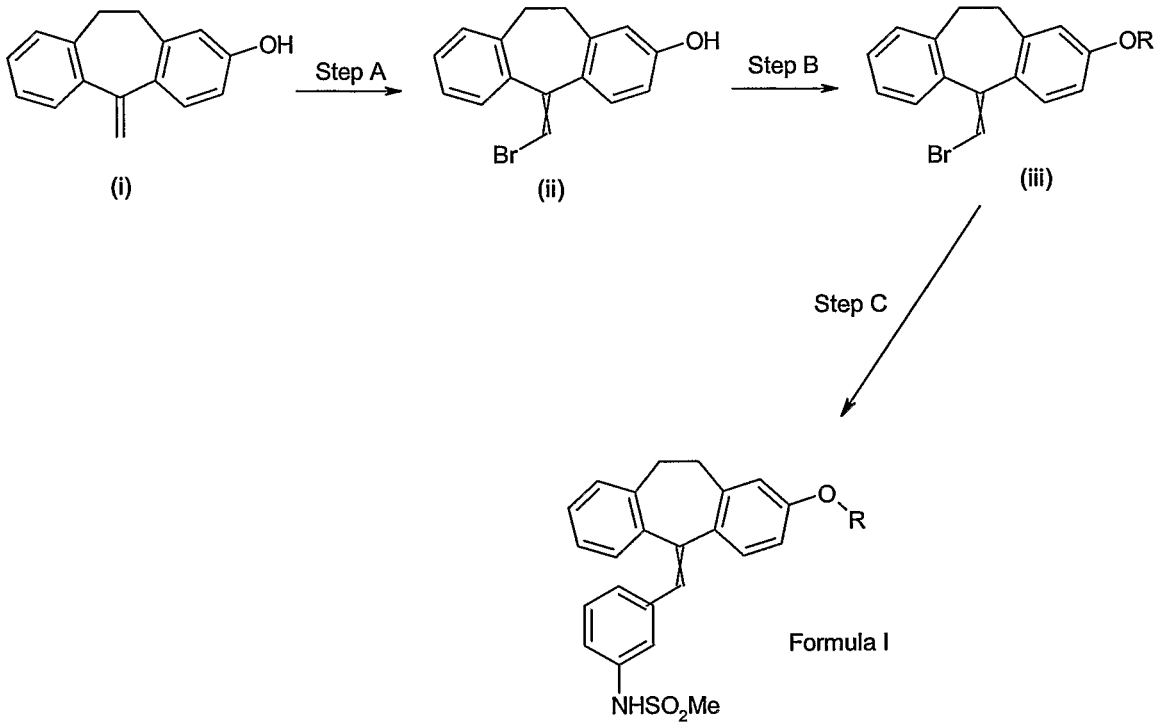
cooled to about 0 °C . Tebbe reagent (0.5M/L solution in toluene) is then added, cooling is removed, and the mixture stirred for about 10 min. The reaction is quenched by adding saturated aqueous Rochelle's salt solution and the biphasic mixture stirred rapidly for about 10 min. The layers are then separated and the aqueous layer extracted with ethyl acetate. The combined organic layers are dried with magnesium sulfate, filtered and concentrated. The crude product of compound (36) may then be purified using standard techniques such as flash chromatography (25% ethyl acetate/hexanes) to provide the purified product of structure (36).

In Scheme XVII, Step B, the compound of structure (36) is treated according to procedures as described in Scheme VII, Step B, to provide E and Z isomer of compound (37).

In Scheme XVII, Step C, the compound of structure (37) is treated according to procedures as described in Scheme VII, Step C to provide the E and Z isomer of the compound of Formula I.

Scheme XVIII provides general procedures for the synthesis of compounds of Formula I wherein ring "A" and or "B" is contains an ether moeity

Scheme XVIII



In Scheme XVIII, Step A, the compound of structure (i) (5-methylene-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-2-ol), prepared from commercially available 2-hydroxy-10,11-dihydro-dibenzo[a,d]cyclohepten-5-one using procedures as described Scheme VII, Step A, is treated under conditions as described in SchemeVII, Step B to provide the compound of structure (ii) (5-bromomethylene-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-2-ol)

In Scheme XVIII, Step B, 2.5 equivalents of PS-TBD Resin (commercially available: Argonaut Technologies) is added to a fritted vessel. The bottom of the vessel is capped and about 1.0 equivalent of 5-bromomethylene-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-2-ol in acetonitrile is added. About 0.8 equivalents of the appropriate alkyl halide in acetonitrile is then added and the top of the vessel is capped and the vessel rotated for about 48-96 hours. The vessel is then uncapped and the filtrate collected into a screw-cap vial. The resin is washed with acetonitrile followed by dichloromethane. The filtrate is combined with the washings and concentrate under vacuum.

In Scheme XVIII, Step C, into the screw capped vial containing the bromomethylene ether, about 1.2 equivalents of potassium carbonate and about 1.1

equivalents of , for example, N-[3-(4,4,5,5-tetramethyl-[1,3,2]-dioxaboronan-2-yl)-phenyl]-methanesulfonamide, is added. The solution is purged with nitrogen for about 5 min. then about 0.1 equivalents of palladium tetrakis(triphenylphosphine) is added into the vial. The vial is capped and heated to about 90-100 °C for about 16 hours with continuous stirring. The reaction is then loaded onto Chem-Elute column (Varian Sample Prep) primed with water and the column is eluted with ethyl acetate. The filtrate is then concentrated under vacuum and may be purified by standard techniques such as silica gel chromatography.

Determination of Biological Activity

To demonstrate that compounds of the present invention have affinity for steroid hormone nuclear receptors, and thus have the capacity to modulate steroid hormone nuclear receptors, soluble MR and GR binding assays are performed. All ligands, radioligands, solvents, and reagents employed in the binding assays are readily available from commercial sources, or can be readily synthesized by the ordinarily skilled artisan.

Mineralocorticoid Receptor Binding Assay:

The full length human MR gene is cloned from a human kidney or human brain cDNA library. Briefly, using synthetic oligonucleotide primers (Eli Lilly and Company, Indianapolis) directed to nucleotides 20-54 and 3700-3666 of the human MR, polymerase chain reaction (PCR) is performed under standard conditions using a human cDNA library. The PCR reaction is performed in a final volume of 50µl containing about 1µl of a 50X stock solution of polymerase; about 1µl of a 50X stock solution of dNTP; about 5µl of an appropriate PCR buffer; about 1µl of each primer; about 5µl of a H. kidney or H. brain cDNA library; and about 36µl of water. The reaction is allowed to denature for about 30 seconds at 95 degrees Celsius, anneal for about 30 seconds at 55 degrees Celsius, and extend for about 5 minutes at 72 degrees Celsius, the sequence being repeated for a total of about 35 cycles. The desired PCR product (3.68 Kb) is confirmed by gel electrophoresis and subsequently cut from the gel and stored at about –20 degrees Celsius until extraction. To extract the cDNA product from the agarose gel, the QIAEX II Gel Extraction protocol (QIAGEN, Inc.) is employed according to the manufacturer's instructions. Following extraction, the MR cDNA is cloned into an appropriate cloning

vector (Zero Blunt TOPO PCR Cloning Kit (Invitrogen, Inc.) and a pAcHLT-baculovirus transfer vector (B.D./Pharminogen), then expressed in SF9 insect cells, essentially according to manufacturer's instructions. Sf9 cells are grown at a scale where gram quantity cell pellets are obtained for subsequent use in the MR binding assay. Harvested cell pellets are lysed by repeated freeze-thaw cycles (about 4) in a suitable lysis buffer then centrifuged at about 1 X 10^3G (with the supernatant being saved for future assays).

MR binding assays are performed in a final total volume of about 250µl containing about 20-25µg of protein and 0.5nM of [^{3}H]-aldosterone plus varying concentrations of test compound or vehicle. The assay binding buffer consists of 30mM sodium molybdate, 30mM of TRIS-HCl, 5mM sodium phosphate, 5mM sodium pyrophosphate, and about 10% glycerol, pH=7.5.

Briefly, assays are prepared at RT in 96-well Falcon 3072 plates, each well containing 210µl of binding buffer, 10µl of [^{3}H]-aldosterone, 10µl of test compound/vehicle, and 20µl of the resuspended receptor protein extract. Incubations are carried out at 4 degrees Celsius with shaking for about 16 hours. 200µl aliquots of each incubation are filtered onto Millipore HA 0.45micron 96-well filter plates, pre-moistened with cold 30mM TRIS-HCl. The filter plates are suctioned dry with vacuum and immediately washed 3X with cold 30mM TRIS-HCl. The plates are then punched out and the amount of receptor-ligand complex is determined by liquid scintillation counting using 4ml of Ready Protein Plus™ liquid scintillation cocktail.

IC_{50} values (defined as the concentration of test compound required to decrease [^{3}H]-aldosterone binding by 50%) are then determined. Ki values for each respective test compound can then be calculated by application of the Cheng-Prusoff equation as described in Cheng *et al.*, Relationship Between The Inhibition Constant (Ki) and The Concentration of Inhibitor Which Causes 50% Inhibition (IC_{50}) of an Enzymatic Reaction, Biochem. Pharmacol., 22: 3099-31088; (1973).

Glucocorticoid Receptor Binding Assay:

To demonstrate the GR modulating potency of compounds of the present invention the following source of glucocorticoid receptor is employed. A549 human lung epithelial cells (ATCC) are grown at a scale where gram quantity cell pellets are obtained. Harvested cell pellets are washed twice in cold phosphate buffered saline, centrifuged,

and resuspended in cold assay binding buffer. The assay binding buffer consists of 10% glycerol, 50mM Tris-HCl (pH7.2), 75mM sodium chloride, 1.5mM magnesium chloride, 1.5mM EDTA, and 10mM sodium molybdate. Cell suspensions were lysed via sonication, centrifuged, and the "extract" supernatant is snap frozen and stored at –80C until needed.

GR binding assays are performed in a final volume of 140ul containing 50-200ug of A549 cell extract and 1.86nM [^{3}H]-dexamethasone (Amersham) plus varying concentrations of test compound or vehicle. Briefly, assays are prepared at RT in 96-well Fisher 3356 plates, each well containing 100ul of A549 cell extract, 20ul of [^{3}H]-dexamethasone, and 20ul of test compound/vehicle. Incubations are carried out at 4 degrees Celsius for 16 hours. After incubation, 70ul of 3X dextran-coated charcoal solution is added to each reaction, mixed, and incubated for 8 minutes at RT. 3X-dextran-coated charcoal solution consists of 250ml assay binding buffer, 3.75g Norit A charcoal (Sigma), and 1.25g dextran T-70 (Amersham). Charcoal/unbound radioligand complexes are removed by centrifugation of the plate and 140ul of supernatant from each well is transferred to another 96 well Optiplate (Packard Instruments). 200ul of Microscint-20 scinillant (Packard Instruments) is added to each well and amount of receptor bound radioligand is determined using Packard Instruments TopCount instrument.

IC_{50} values, defined as the concentration of test compound required to decrease [^{3}H]-dexamethasone binding by 50%, are then determined. Ki values for each respective test compound can then be calculated by application of the Cheng-Prusoff equation as described in Cheng *et al.*, Relationship Between The Inhibition Constant (Ki) and The Concentration of Inhibitor Which Causes 50% Inhibition (IC_{50}) of an Enzymatic Reaction, Biochem. Pharmacol., 22: 3099-31088; (1973).

Binding assay protocols for PR, AR, and ER, similar to those described above for MR and GR, can be readily designed by the ordinarily skilled artisan. United States Patent No. 6,166,013 provides examples of such protocols. Representative compounds of the present invention have a Ki in the MR or GR binding assay of $\leq 50\mu M$. Table I (see infra.) provides MR and GR binding data for a representative sample of the exemplified compounds of the present invention.

To demonstrate the ability of compounds of the present invention to modulate the activity of a steroid hormone receptor (i.e. either agonize, antagonize, partially agonize, or partially antagonize), bioassays are performed which detect modulation of target gene expression in cells transiently transfected with a nuclear receptor protein and a hormone response element-reporter gene construct. The solvents, reagents, and ligands employed in the functional assay are readily available from commercial sources, or can be synthesized by one of ordinary skill in the art.

Functional Assay of Mineralocorticoid Receptor Modulation:

For the MR transient transfection assay, COS-7 cells are transfected with full length human MR and a 2XGRE-luciferase gene construct. Following transfection, the ability of test compounds to modulate expression of the luciferase reporter gene product is monitored. Briefly, on day one, COS cells are harvested from cell culture plates using standard procedures such as treatment with Trypsin-EDTA (GIBCO BRL). Culture medium is then added to the cells and the cell-medium mixture is plated in 96 – well plates coated with poly-(d)-lysine (approximately 3 X 10^4 cells/well). Cells are grown for about 4 hours then transfected with Fugene-6 reagent with plasmids containing human MR, previously cloned into pc.DNA 3.1 expression vector, and 2XGRE-reporter gene construct (GRE-luciferase), previously cloned into pTAL-luc vector. Transfection is carried out in DMEM with 5% fetal calf serum, charcoal treated. 24 hours later cells are exposed to various concentrations of aldosterone in the presence and absence of test compound and incubated for an additional 24 hours. The reaction is terminated by the addition of lysis buffer followed by luciferin (luciferase substrate). Luciferase expression, as an indicator of ligand induced MR transactivation, is monitored by chemiluminescence measured using a microtiter plate luminometer (MLX). The kinetic inhibition constant (K_b or K_p) can then be determined by analysis of dose-response curves for aldosterone, in the presence and absence of test compound, using standard techniques.

Table I

Mineralocorticoid and Glucocorticoid Receptor Binding Assay Values

Example No.	MR Ki (nM)	GR Ki (nM
206(a)	+++	+++
262	+++	+++
197(a)	+++	+++
125	+++	+++
267	+++	+++
199(a)	+++	+++
199(b)	+++	+++
207	+++	+++
274	+++	+++
141	+++	+++
182	+++	+++
184(a)	+++	+++
181(a)	+++	+++
268	+++	+++
208(b)	+++	+++
50	+++	+++
208(a)	+++	+++
162	+++	+++
183	+++	+++
205(b)	+++	+++
187	+++	+++
206(b)	+++	+++
184(b)	+++	+++
188(a)	+++	+++

214	+++	+++
205(a)	+++	+++
211(a)	+++	+++
222(a)	+++	+++
178	+++	+++
163	+++	+++
200(a)	+++	+++
91	+++	+++
200(b)	+++	+++
185(b)	+++	++
191	+++	+++
258	+++	+++
201	+++	+++
161	+++	+++
189	+++	+++
161(b)	+++	+++
90	+++	+++
48	+++	+++
253	+++	+++
75	+++	+++
208(c)	+++	+++
92	+++	+++
57	+++	+++
49	+++	+++
186	+++	+++
192	+++	+++
198(a)	+++	+++
215	+++	+++

223	+++	+
149	+++	+++
112	+++	+++
221(a)	+++	+++
155	+++	+++
216	+++	+++
263	+++	++
188(b)	+++	+++
86	+++	+++
202	+++	++
171	+++	+++
185(a)	+++	+++
205(c)	+++	+++
261	+++	+++
167	+++	+++
173(a)	+++	+++
126	+++	+++
181(b)	+++	+++
254	+++	+++
81	+++	+
1	+++	+++
65	+++	+
251	+++	+++
153	+++	++
45	+++	++
177	+++	++
71	+++	+++
151	+++	++

157	+++	++
193	+++	+++
74	+++	+++
231	+++	+++
121	+++	+
175	+++	+
105	+++	+++
272	+++	+
54	+++	+++
211(b)	+++	++
271	+++	+++
133	+++	++
5	+++	+++
135	+++	+
229	+++	++
132	+++	++
4	+++	++
198(b)	+++	++
129	+++	+++
62	+++	+
221(b)	+++	+++
72	+++	+
104	+++	+++
259	+++	+
128	+++	++
108	+++	+++
110	+++	+++
145	+++	+++

245	+++	+
130	+++	+
2	+++	+++
95	+++	++
93	+++	+++
70	+++	++
253	+++	+
106	+++	+++
228	+++	++
114	+++	+++
116	+++	+++
220	+++	+
170(b)	+++	+++
118	+++	+++
85	+++	+++
224	+++	+++
47	+++	++
80	+++	+++
94	+++	+++
210	+++	++
78	+++	++
69	+++	+++
194	+++	+++
107	+++	NT
236	+++	+++
87	+++	+++
31	+++	+
35	+++	+++

27	+++	++
64	+++	+++
117	+++	+++
148	+++	++
120	+++	+
60	+++	+
259	+++	+
249	+++	+++
113	+++	+++
212	+++	++
225	+++	+
152	+++	+
219	+++	++
154	+++	++
42	+++	+
6	+++	+++
256	+++	++
180	+++	++
84	+++	+
225	+++	NT
143	+++	+
217	+++	+
96	+++	+
68	+++	+++
169	+++	+++
255	+++	+++
173(b)	+++	+
196	+++	+++

137	+++	++
168	+++	++
99	+++	++
82	+++	++
218	+++	++
131	+++	+
166	+++	+
52	+++	+
77	+++	+++
32	+++	++
79	+++	+++
109	+++	+++
170(a)	+++	++
174	+++	++
195(a)	+++	++
233	+++	+
227	+++	++
88	+++	++
244	+++	+
237	+++	+
73	+++	++
76	++	+++
3	++	++
230	++	+
264	++	+
41	++	+

Table I (Continued)

Mineralocorticoid and Glucocorticoid Receptor Binding Assay Values

Example No.	MR Ki (nM)	GR Ki (nM)
699	+++	+++
700	+++	+++
701	+++	+++
702	+++	+
521	+++	+++
522	+++	+++
363	+++	+++
364	+++	+++
498	+++	++
499	+++	+++
703	+++	+++
287	+++	+++
365	+++	+++
366	+++	+++
367	+++	+
368	+++	+
369	+++	+
447	+++	+++
448	+++	+
449	+++	+
500	+++	+++
501	+++	+++
502	+++	+++
370	+++	++
371	+++	+++

372	+++	++
465	+++	++
466	+++	++
373	+++	+
374	+++	+++
375	+++	+++
722	+++	+++
723	+++	+++
376	+++	+++
377	+++	+
301	+++	+++
302	+++	+++
450	+++	+++
451	+++	+
334	+++	+++
335	+++	+++
452	+++	++
378	+++	++
379	+++	+
524	+++	+++
503	+++	+++
303	+++	+++
380	+++	++
453	+++	++
336	+++	+
504	+++	+++
337	++	
338	+++	++

339	+++	+++
454	+++	+++
481	+++	+++
407	+++	+++
408	+++	+++
409	+++	+++
410	+++	+++
304	+++	+++
340	+++	+++
341	+++	+++
558	+++	
342	+++	+++
488	+++	+++
525	+++	+++
526	+++	+
527	+++	+
528	+++	++
529	+++	+
530	+++	+++
531	+++	+++
532	+++	++
533	+++	++
534	+++	+
535	++	+
305	+++	++
306	+++	++
278	+++	
381	+++	+++

286	+++	+
382	+++	+++
559	+++	+++
307	+++	++
455	+++	+
456	+++	+
411	+++	+++
412	+++	++
347	+++	+++
348	+++	+++
308	+++	+
309	+++	++
427	+++	+
578	+++	+
579	+++	+++
739	+++	+++
580	+++	+
581	+++	+
740	+++	+++
582	+++	+
330	+++	+++
583	+++	+
584	++	+
585	+++	+
586	+++	+
587	+++	+
279	+++	+
383	+++	+++

560	+++	++
536	+++	+++
588	+++	+++
589	+++	+++
310	+++	++
483(a)	+++	+++
483(b)	+++	+++
280	+++	++
457	+++	+++
349	+++	+++
537	+++	+
458	+++	+++
311	+++	+++
312	+++	+++
313	+++	
314	+++	+++
413	+++	+++
414	+++	+++
467	+++	+++
538	+++	+++
331		+++
332		+++
627	+++	+++
628	+++	+++
468	+++	+++
469	+++	+++
470	+++	+
471	+++	+++

290	+++	++
291	+++	+++
659	++	+
629	+++	+++
630	+++	+++
315	+++	+
350	+++	+++
316	+++	+++
351	+++	+++
317	+++	+
318	+++	++
741	+++	+++
539	+++	+++
540	+++	+++
541	+++	++
542	+++	+
543	+++	+
544	+++	++
292	+++	+++
459	+++	++
293	+++	+++
631	+++	++
611	+++	
294	+++	+
660	+++	+++
604	+++	++
783	+++	+++
384	+++	+++

632	+++	+++
633	+++	+++
385	+++	++
561	+++	++
352	+++	+++
295	+++	+++
296	+++	+
545	+++	+
661	+++	+++
662	+++	+++
634	+++	+++
635	+++	++
281	+++	+
297	+++	+
386	+++	+++
387	+++	+++
636	+++	+++
637	+++	+++
663	+++	+++
664	+++	+++
665	+++	+++
666	+++	+++
415	+++	+++
416	+++	+++
417	+++	+++
418	+++	++
460	+++	++
461	+++	+++

462	+++	++
605	+++	+++
606	+++	+++
562	+++	+++
667	++	+
668	+++	++
669	+++	+++
343	++	+++
484(a)	++	+++
590	+++	++
840	+++	+++
793	+++	+++
794	+++	+++
795	+++	+++
796	+++	+++
388	+++	+++
389	+++	+++
753	+++	+++
344	+++	+++
463	+++	+
464	+++	+
638	+++	++
612	+++	+
742	+++	+++
743	+++	+++
744	+++	+++
745	+++	+++
390	+++	+++

391	+++	+++
472	+++	+
473	+++	+
797	+++	+++
798	+++	+++
639	+++	+
319	+++	+++
704	+++	+++
705	+++	+++
799	+++	+++
800	+++	+++
724	+++	+++
725	+++	+++
801	+++	+++
802	+++	+++
670	+++	+++
671	+++	+++
672	+++	+++
673	+++	+++
674	+++	+++
675	+++	+++
676	+++	+++
677	+++	+++
678	+++	
679	+++	+++
680	+++	++
681	+++	+++
682	+++	+++

754		+++
726	+++	+++
727	+++	+++
728	+++	+++
729	+++	+++
392	+++	+++
393	+++	+++
320	+++	+++
321	+++	+++
353	+++	+++
640	+++	+++
549	+++	+
484(b)	+++	+++
482	+++	+++
546	+++	+++
547	+++	+++
746	+++	+++
747	+++	+++
748	+++	+++
755	+++	+++
322	+++	+++
323	+++	+++
324		++
563	+++	+++
564	+++	+++
838	+++	+++
839	+++	+++
706	+++	+++

707	+++	+++
708	+++	+++
709	+++	+++
565	+++	+
683	+++	+++
684	+++	+++
550	+++	+++
551	+++	+++
771	+++	+++
772	+++	+++
325	+++	+++
641	+++	++
642	+++	++
643	+++	+
730	+++	+++
731	+++	+++
732	+++	+++
733	+++	+++
609	+++	++
710	+++	+++
591	+++	+
592	+++	+
711	+++	++
712	+++	+++
607	+++	++
713	+++	+++
326	+++	+++
327	+++	+++

773	+++	+++
774	+++	+++
841	+++	+++
842	+++	+++
566	+++	+
593	+++	+
749	+++	+++
750	+++	+++
751	+++	+++
623	+++	+++
624	+++	+++
734	+++	+++
735	+++	+++
714	+++	+
715	+++	++
775	+++	+++
776	+++	+++
803	+++	+++
804	+++	+++
716	+++	++
717	+++	
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817	+++	+++
818	+++	+++
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299	+++	++
644	+++	++

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837	+++	+++
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810	+++	+++
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420	+++	+++
421	+++	+++
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598	+++	+++
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777	+++	+++
778	+++	+++
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346	+++	+
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830	+++	+++

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618	+++	
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780	+++	+++
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814	+++	+++
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647	+++	++
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719	+++	
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815	+++	
816	+++	
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792	+++	
756	+++	
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426	+++	
781	+++	
782	+++	
720	+++	
825	+++	
826	+++	
485(a)		
328		
329		+++
439	+++	+++

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489	+++	+
490	++	+
621	+++	
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359	+++	+++

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569	+++	+
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445	+++	+
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493	+++	
494	+++	+++
685	+++	+++
686		+++
517	+++	++

574	+++	+++
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576	+++	+
577	+++	+++
687	+++	+++
518	+++	+++
487	+++	++
766	+++	+
767	+++	+++
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769	+++	+++
770	+++	+++
403	+++	+++
404	+++	+++
689		+++
690		++

691	++	+++
692	+++	+++
693	+++	+++
694	+++	+++
695	+++	+++
696	+++	+++
405	+++	+++
406	+++	+++
362	+++	++
496	+++	+++
497	+++	+++
697	+++	
698	++	+++
477	+++	+
478	+++	+

Legend:

"+" represents a value of ≤ 10,000nM

"++" represents a value of ≤ 1,000nM

"+++" represents a value of ≤ 500nM

"--" indicates the value was not determined

The following preparations and examples further illustrate the invention and represent typical synthesis of the compounds of Formula I, including any novel compounds, as described generally above. The reagents and starting materials are readily available to, or may be readily synthesized by, one of ordinary skill in the art. As used herein, the following terms have the meanings indicated: "i.v." refers to intravenously; "p.o." refers to orally; "i.p." refers to intraperitoneally; "eq" or "equiv." refers to equivalents; "g" refers to grams; "mg" refers to milligrams; "L" refers to liters; "mL"

refers to milliliters; "μL" refers to microliters; "mol" refers to moles; "mmol" refers to millimoles; "psi" refers to pounds per square inch; "mm Hg" refers to millimeters of mercury; "min" refers to minutes; "h" or "hr" refers to hours; "°C" refers to degrees Celsius; "TLC" refers to thin layer chromatography; "HPLC" refers to high performance liquid chromatography; "R_f" refers to retention factor; "R_t" refers to retention time; "δ" refers to part per million down-field from tetramethylsilane; "THF" refers to tetrahydrofuran; "DMF" refers to N,N-dimethylformamide; "DMSO" refers to dimethyl sulfoxide; "aq" refers to aqueous; "EtOAc" refers to ethyl acetate; "iPrOAc" refers to isopropyl acetate; "MeOH" refers to methanol; "MTBE" refers to tert-butyl methyl ether; "PPh_3" refers to triphenylphosphine; "DEAD" refers to diethyl azodicarboxylate; "RT" refers to room temperature; "Pd-C" refers to palladium over carbon; $NaBH(OAc)_3$ refers to sodium triacetoxyborohydride; "Bn" refers to benzyl; "$BnNH_2$" refers to benzyl amine; H_2 refers to hydrogen; "K_i" refers to the dissociation constant of an enzyme-antagonist complex and serves as an index of ligand binding; and "ID_{50}" and "ID_{100}" refer to doses of an administered therapeutic agent which produce, respectively, a 50 % and 100% reduction in a physiological response.

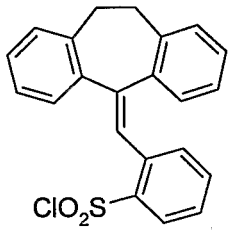
Instrumental Analysis

Unless otherwise indicated, ^1H NMR spectra are recorded on a either a 300 MHz or 400 MHz Varian spectrometer at ambient temperature. Data are reported as follows: chemical shift in ppm from internal standard tetramethylsilane on the δ scale, multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet and m = multiplet), integration, coupling constant (Hz) and assignment. Positive and negative electrospray mass spectral data are obtained on a Micromass Platform LCZ equipped with an autosampler. Analytical thin layer chromatography is performed on EM Reagent 0.25-mm silica gel 60-F plates. Visualization is accomplished with UV light. HPLC analysis is performed on an Agilent 1100 Series HPLC using an acetonitrile/0.03M phosphate buffer (80/20) as the mobile phase using an Agilent Eclipse XDB-C8 analytical 4.6x150mm 5-micron column. Melting points are determined on a Mettler Toledo FP62 melting point apparatus. GC-MS data are obtained on an Agilent HP6890 GC using a HP-5MS (30m, 0.25mm i.d., 0.25μm film) column.

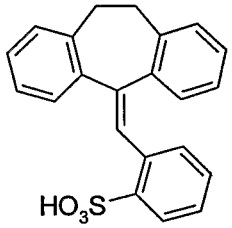
Section 1 (derivatives of Formula I having substitution on the "C" ring but not on the "A" or "B" rings.)

Preparation 1

2-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-benzenesulfonyl chloride



A. Preparation of 2-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-benzenesulfonic acid (LY622781, ER0-A01318-26B)



1. Treat a mixture of o-toluenesulfonyl chloride (22g, 115mmol) in dioxane (200mL) with triethylamine (28mL, 200mmol) and cool to 10°C. Add ethanol (50mL) and allow the reaction to warm to room temperature. After 18 h, acidify the reaction and remove most of the solvent under reduced pressure. Partition the residue between water/EtOAc. Dry the organic layer with $MgSO_4$ and concentrate to give 22.6g colorless oil. Purify using flash chromatography (10% EtOAc/hexane) to give 7.4g of pure ester. ^1H NMR (CDCl3) δ1.50 (t, 3H), 2.64 (s, 3H), 4.08 (q, 2H), 7.34 (m, 2H), 7.50 (t, 1H), 7.96 (d, 2H). (Literature ref: J. Prakt. Chem. 333 (4) 625-635 (1991).

2. Under a blanket of nitrogen, cool (6.4g, 32mmol) toluene-2-sulfonic acid ethyl ester in THF (140mL) to –70°C. Add n-butyllithium (1.6M, 22.5mL, 36mmol) slowly. An orange solid forms. After 20 minutes, add a solution of dibenzosuberone (6.32g, 30mmol) in THF (15mL). Allow warming to room temperature and stir for 2 h. Concentrate to

remove most of the THF and dissolve the residue in EtOAc and shake vigorously with 5N HCl for 5 minutes. Dry the organic layer ($MgSO_4$) and concentrate to give 10.8g crude product as a dark red oil. Purify the crude product by flash chromatography (300g silica gel, 5% HOAc/EtOAc) to give crude sulfonic acid. Remove residual HOAc by repeatedly azeotroping with toluene to yield 910mg orange solid. ^1H NMR (DMSO-d6) δ2.80-3.44 (br m, 4H), 6.54 (d, 1H), 6.78-7.76 (m,12H); MS (ES) 361 (M-1).

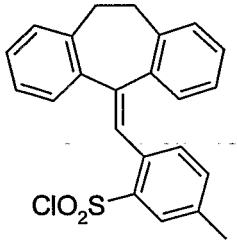
B. Preparation of 2-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-benzenesulfonyl chloride (ER0-A01318-30)

Treat a mixture of 2-(10,11-dihydro dibenzo[a,d]cyclohepten-5-ylidenemethyl)-benzenesulfonic acid (710mg, 2mmol) in thionyl chloride (10mL) with 5 drops DMF and reflux for 40 minutes. TLC (10% EtOAc/hexane) shows a new higher R_f material and no starting material. The material is then concentrated to give 760mg crude sulfonyl chloride, which is used without further purification. (Note: To confirm the structure, a small aliquot is reacted with methylamine. The MS (ES) of the corresponding sulfonamide is readily detected).

Following the procedures essentially as described in Preparation 1 above, and using the appropriately substituted arylsulfonyl chloride, the following sulfonyl chlorides were prepared:

Preparation 2

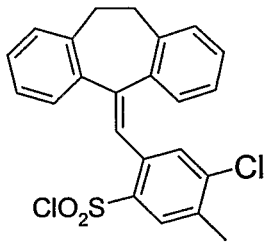
2-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-5-methyl-benzenesulfonyl chloride



To confirm the structure, a small aliquot is reacted with methylamine. The MS (ES) of the corresponding sulfonamide is readily detected

Preparation 3

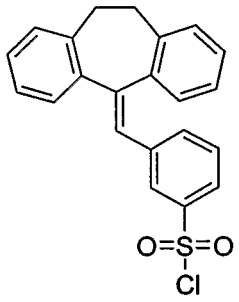
4-Chloro-2-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-5-methyl-benzenesulfonyl chloride



To confirm the structure, a small aliquot is reacted with methylamine. The MS (ES) of the corresponding sulfonamide is readily detected

Preparation 4

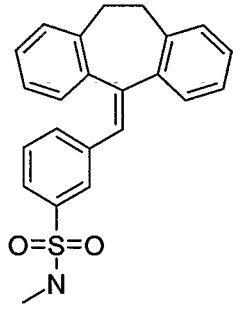
3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-benzenesulfonyl chloride



To confirm the structure, a small aliquot is reacted with methylamine. The MS (ES) of the corresponding sulfonamide is readily detected

Example 1

3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-N-methyl-benzenesulfonamide

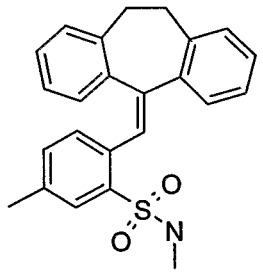


Treat a solution of 3-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-benzenesulfonyl chloride (95mg, 0.25mmol) in THF (2mL) with methylamine (300□L 40% aqueous solution, 3.5mmol) at room temperature. Stir reaction overnight at room temperature, then concentrate under a stream of N_2. Take residue up in 2mL CH_2Cl_2 and shake with 2mL 1N HCl. Load the biphasic solution onto a Varian ChemElut 1005 solid-phase extraction column and elute with 10-15mL CH_2Cl_2. Collect organics and concentrate under N_2 stream. Purify via silica gel chromatography (1:3 ethyl acetate:hexanes) to afford 45mg (48%) of yellow solid, mp 153.9°C. ^{1}H NMR ($CDCl_3$) δ 2.48 (s, 3H), 2.79-3.61 (br m, 4H), 4.19 (br s, 1H), 6.78-7.63 (m, 13H); MS (ES) 376 (M+H). HPLC shows 94% purity.

Following the procedures essentially as described in Example 1 above, reaction of the appropriate sulfonyl chloride from Preparations 1-4 and the appropriate amine gives the following compounds:

Example 2

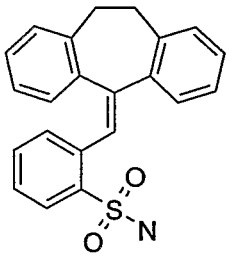
2-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-5,N-dimethyl-benzenesulfonamide



Prepared in 49% from the sulfonyl chloride (500mg, 1.27mmol) and methanesulfonyl chloride to give white needles (EtOH), mp 174.9°C. ^{1}H NMR δ 2.36 (s, 3H), 2.77 (d, 3H), 3.29 (br s, 4H), 4.51 (q, 1H), 6.73-7.29 M, 10H), 7.58 (m, 1H), 7.82 (s, 1H); MS (ES) 390 (M+1). HPLC shows 99.6% purity.

Example 3

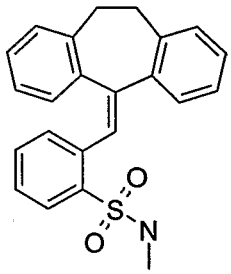
2-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-benzenesulfonamide



Prepared in 18% yield as a white solid, ^{1}H NMR ($CDCl_3$) δ 3.29 (br s, 4H), 4.97 (br s, 2H), 6.76-7.65 (m, 13H); MS (ES) 361 (M-1).

Example 4

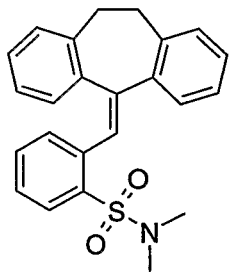
2-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-N-methyl-benzenesulfonamide



Prepared in 16% yield as a white solid, mp 149°C, MS (ES) 376 (M+1), 374 (M-1).

Example 5

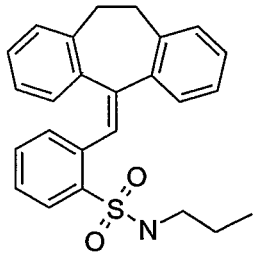
2-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-N,N-dimethyl-benzenesulfonamide



Prepared in 28% yield as a white solid, ^{1}H NMR ($CDCl_3$) δ 2.90(s, 6H), 3.18 (br s, 4H), 6.79-7.95 (m, 13H); MS (ES) 390 (M+1).

Example 6

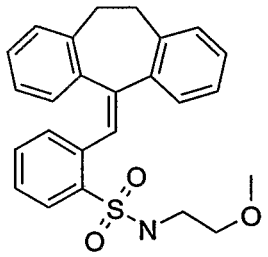
2-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-N-propyl-benzenesulfonamide



Prepared in 23% yield as a white solid, mp 155.6°C, ^{1}H NMR ($CDCl_3$) δ 0.98 (t, 3H), 1.61 (q, 2H), 3.05 (q, 2H), 3.30 (br s, 4H), 4.57 (br t, 1H), 6.78-7.42 (m, 13H); MS (ES) 404 (M+1), 402 (M-1).

Example 7

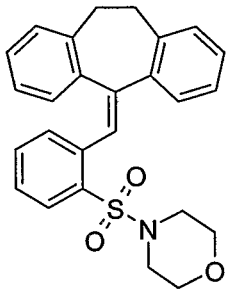
2-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-N-(2-methoxy-ethyl)-benzenesulfonamide



Prepared in 10% yield to give a white solid. ^{1}H NMR ($CDCl_3$) δ 2.85-3.70 (m, 11H), 5.13 (br t, 1H), 6.84-8.01 (m, 13H); MS (ES) 420 (M+H), 418 (M-H).

Example 8

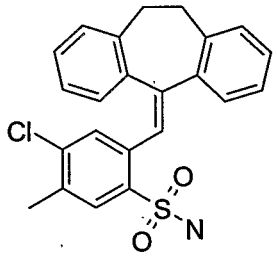
4-[2-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-benzenesulfonyl]-morpholine



Prepared in 29% yield as a white solid, mp 139.3°C. ^{1}H NMR ($CDCl_3$) δ 2.76-3.89 (m, 12H), 6.57-7.93 (m, 13H). MS (ES) 432 (M+H).

Example 9

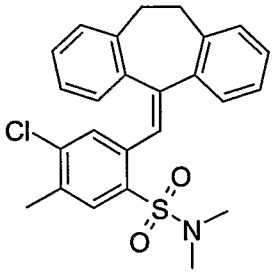
4-Chloro-2-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-5-methyl-benzenesulfonamide



MS (ES) 408 (M-H). HPLC shows 81% purity.

Example 10

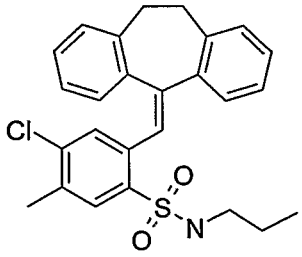
4-Chloro-2-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-5,N,N-trimethyl-benzenesulfonamide



White solid, mp 199.9°C. ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3H), 2.95 (s, 6H), 2.98-3.66 (br m, 4H), 6.79-7.80 (m, 11H); MS (ES) 438 (M+H), 436 (M-H. ; HPLC shows 98% purity.

Example 11

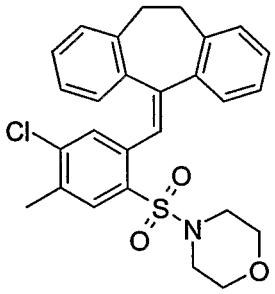
4-Chloro-2-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-5-methyl-N-propyl-benzenesulfonamide



White solid. MS (ES) 452 (M+H), 450 (M-H). HPLC shows 97% purity.

Example 12

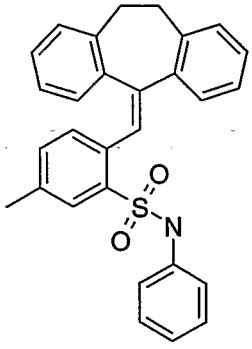
4-[4-Chloro-2-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-5-methyl-benzenesulfonyl]-morpholine



White solid, mp 194.7°C. ^{1}H NMR ($CDCl_3$) δ 2.20 (s, 3H), 2.65-3.67 (m, 12H), 6.63-7.60 (m, 11H); MS (ES) 480 (M+H). HPLC shows 98% purity.

Example 13

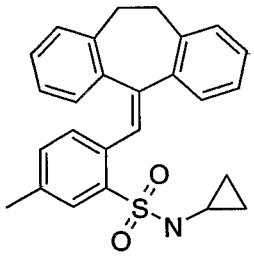
2-[2-(2-Ethyl-phenyl)-penta-1,4-dienyl]-5-methyl-N-phenyl-benzenesulfonamide; compound with propene



White solid, mp 220.4°C. ^{1}H NMR ($CDCl_3$) δ 2.31 (s, 3H), 2.85-3.60 (br m, 4H), 4.54 (br t, 1H), 6.10-7.84 (m, 17H); MS (ES) 452 (M+H), 450 (M-H). HPLC shows 93% purity.

Example 14

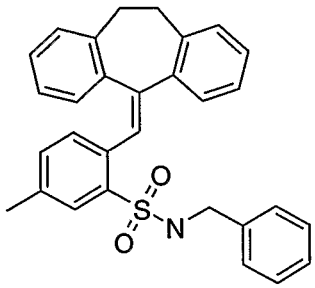
N-Cyclopropyl-2-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-5-methyl-benzenesulfonamide



White solid, mp 160.8°C. MS (ES) 416 (M+H), 414 (M-H). HPLC shows 86% purity.

Example 15

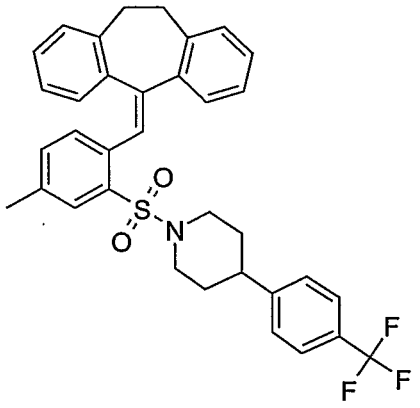
N-Benzyl-2-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-5-methyl-benzenesulfonamide



Colorless oil, slowly crystallized, mp 138.3°C. ^{1}H NMR ($CDCl_3$)δ 2.34 (s, 3H), 2.87-3.69 (br s, 4H), 4.28 (d, 2H), 4.82 (br t, 1H), 6.70-7.85 (m, 17H); MS (ES) 464 (M-H). HPLC shows 96% purity.

Example 16

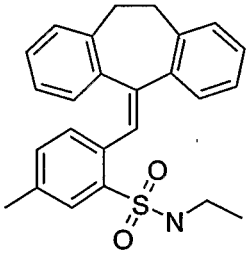
1-[2-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-5-methyl-benzenesulfonyl]-4-(4-trif luoromethyl-phenyl)-piperidine



White foam. MS (ES) 588 (M+H). HPLC shows 96% purity.

Example 17

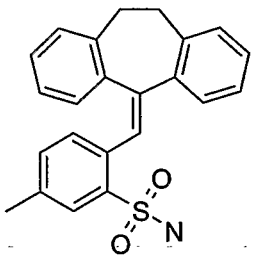
2-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-N-ethyl-5-methyl-benzenesulfonamide



White foam, mp 172.4°C. MS (ES) 402 (M-H). HPLC shows 95% purity.

Example 18

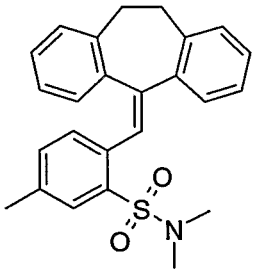
2-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-5-methyl-benzenesulfonamide



^{1}H NMR ($CDCl_3$) δ2.38 (s, 3H), 2.80-3.80 (br m, 4H), 6.77-7.92 (m, 12H); MS (ES) 375 (M-H. HPLC shows 78% purity.

Example 19

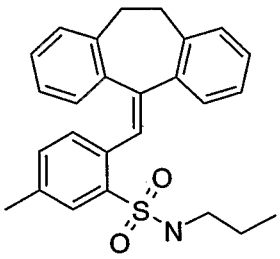
2-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-5,N,N-trimethyl-benzenesulfonamide



White solid, mp 186.6°C. MS (ES) 404 (M+H).

Example 20

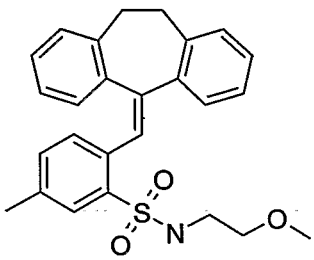
2-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-5-methyl-N-propyl-benzenesulfonamide



White solid, mp 149.8°C. MS (ES) 418 (M+H), 416 (M-H). HPLC shows 96% purity.

Example 21

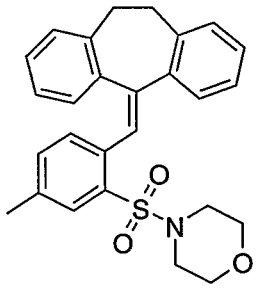
2-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-N-(2-methoxy-ethyl)-5-methyl-benzenesulfonamide



^{1}H NMR ($CDCl_3$) δ 2.33 (s, 3H), 2.85-3.20 (m, 11H), 5.12 (br t, 1H), 6.61-7.33 (m, 12H); MS (ES) 434 (M+H), 432 (M-H). HPLC shows 98% purity.

Example 22

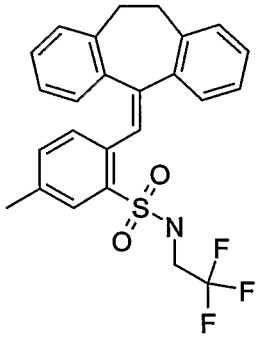
4-[2-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-5-methyl-benzenesulfonyl]-morpholine



White solid, mp 157.2°C. ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 3H), 2.85-4.00 (m, 12H), 6.72-7.75 (m, 12H); MS (ES) 446 (M+H). HPLC shows 95% purity.

Example 23

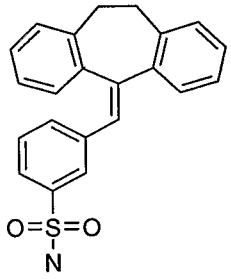
2-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-5-methyl-N-(2,2,2-trifluoro-ethyl)-benzenesulfonamide



White needles, mp 100.7°C. ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 3H), 3.0-3.6 (br s, 4H), 3.76 (m, 2H), 5.05 (br t, 1H), 6.75-7.62 (m, 11H), 7.78 (s, 1H); MS (ES) 457 (M+H), 456 (M-H). HPLC shows 99% purity.

Example 24

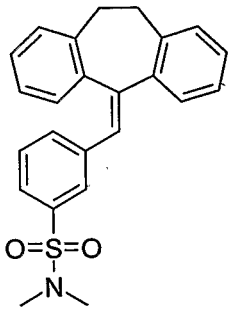
3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-benzenesulfonamide



White crystalline solid, mp 204.0°C. ^{1}H NMR (DMSO-d_6) δ 2.77-3.45 (br m, 4H), 6.81-7.68 (br m, 15H); MS (ES) 384 (M+Na). HPLC shows 98% purity.

Example 25

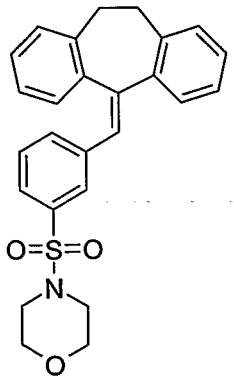
3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-N,N-dimethyl-benzenesulfonamide



White crystalline solid, mp 167.3°C. ^{1}H NMR ($CDCl_3$) δ 2.54 (s, 6H), 2.80-3.64 (br m, 4H), 6.86 (s, 1H), 6.91-7.56 (m, 12H); MS (ES) 390 (M+H). HPLC shows 96% purity.

Example 26

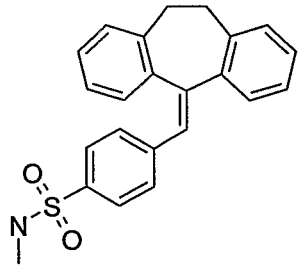
4-[3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-benzenesulfonyl]-morpholine



Off-white crystalline solid. ^{1}H NMR ($CDCl_3$) δ 2.73 (m, 4H), 2.82-3.63 (br m, 4H), 3.70 (m, 4H), 6.86 (s, 1H), 6.92-7.51 (m, 12H); MS (ES) 432 (M+H). HPLC shows 96% purity.

Example 27

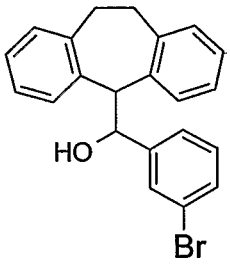
4-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-N-methyl-benzenesulfonamide



White solid, mp 189.7°C. ^{1}H NMR ($CDCl_3$) δ 2.65 (d, 3H), 2.81-3.65 (br m, 4H), 4.23 (br m, 1H), 6.85 (s, 1H), 6.94-7.67 (m, 12H); MS (ES) 376 (M+H), 374 (M-H). HPLC shows 98% purity.

Preparation 5

(3-Bromo-phenyl)-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methanol



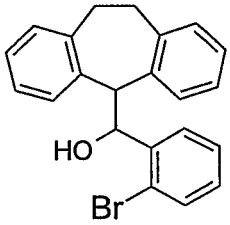
Under nitrogen, cool a THF (300mL) solution of dibenzosuberane (23.9g, 123mmol) to 0°C and add n-BuLi (1.6M, 90mL, 144mmol). Remove the cooling bath and the reaction stir at ambient temperature for 1 h. Cool the orange solution to 5°C and add a solution of 3-bromobenzaldehyde (22.8g, 123mmol) in THF (100mL). After 30 min., quench the reaction with saturated NH_4Cl (200mL) and remove most of the THF under reduced pressure. Shake the residue with brine/EtOAc. Dry the organic layer ($MgSO_4$) and concentrate to give 49.2g colorless oil. HPLC shows 86% purity. The compound is sufficiently pure to carry on to the next reaction. Purify a small portion on silica gel using

EtOAc/hexane to give a colorless oil that rapidly crystallized, mp 93.9°C, ^{1}H NMR (CDCl3) δ3.00 (m,2H), 3.57 (m,2H),3.94 (d,1H), 5.30 (d,1H), 6.38 (d,1H), 6.76-7.34 (m,12H); MS (EI) 360 (M-$H_2$0).

Using the procedures essentially as described in Preparation 5, and the appropriately substituted benzaldehyde, the following crude alcohol intermediates are made. Unless otherwise stated, these intermediate carbinols are not isolated or characterized, buth rather, used in the synthesis of compounds of Formula I without purther purification.

Preparation 6

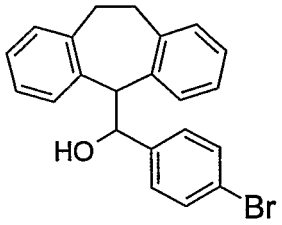
(2-Bromo-phenyl)-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methanol



Light yellow solid, mp146.9°C. MS (FD) 361 (M-$H_2$0).

Preparation 7

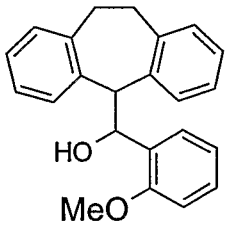
(4-Bromo-phenyl)-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methanol



Viscous yellow oil, MS (EI) 360 (M-H_2O). HPLC (ISO80-10M) t=1.86min.

Preparation 8

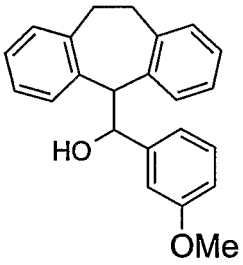
(2-Methoxy-phenyl)-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methanol



Pale yellow solid, mp113.1°C.

Preparation 9

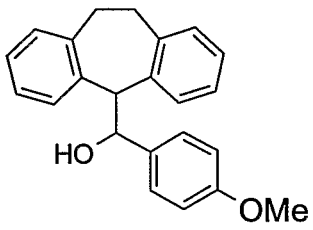
(3-Methoxy-phenyl)-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methanol



Pale yellow solid, mp132.1°C.

Preparation 10

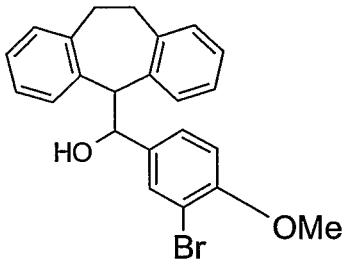
(4-Methoxy-phenyl)-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methanol



Pale yellow solid, mp103.1°C.

Preparation 11

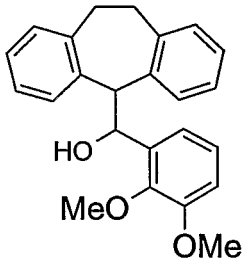
(3-Bromo-4-methoxy-phenyl)-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methanol



HPLC (ISO80-10M) t=1.75min.

Preparation 12

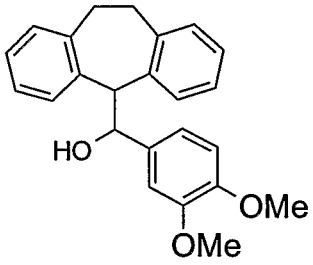
(2,3-Dimethoxy-phenyl)-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methanol



Used without further characterization or purification.

Preparation 13

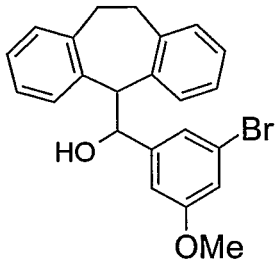
(3,4-Dimethoxy-phenyl)-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methanol



HPLC (ISO80-10M) t=1.43min.

Preparation 14

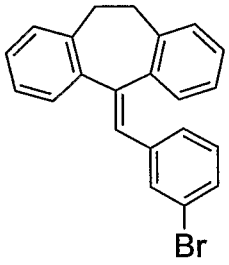
(3-bromo-5-methoxy-phenyl)-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methanol



Used without further characterization or purification.

Example 28

5-(3-Bromo-benzylidene)-10,11-dihydro-5H- dibenzo-[a,d]cycloheptene

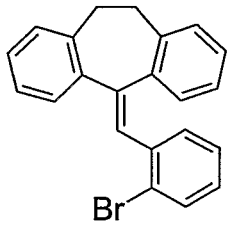


Add the crude product from Preparation 5 above (48.85g, 129mmol) to a premixed solution of HOAc (300mL) and concentrated H_2SO_4 (6mL). Reflux the solution for 2.5 h and then cool to ambient temperature. Shake the reaction with EtOAc (1L)/water (1L). Wash the organic layer again with water and then 1N NaOH (2x). Dry the organic layer ($MgSO_4$) and concentrate to give 54g crude product. Recrystallize from hexane to afford 26.6g (57%)light tan crystals, mp 104.7°C, ^{1}H NMR (CDCl3) δ 2.97 (br d, 2H), 3.43 (br d, 2H), 6.50 (s, 1H), 6.86-7.47 (m, 12H); MS (FAB+) 360. HPLC shows 98.3% purity. Anal: Calcd. for $C_{22}H_{17}Br$: C, 73.14; H, 4.74. Found: C, 73.22; H, 4.84.

Following the procedures essentially as described in Example 28 above, reaction of the appropriate crude alcohol intermediate from Preparations 6-14 above, gives the following compounds:

Example 29

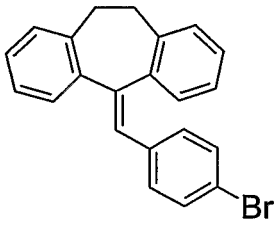
5-(2-Bromo-benzylidene)-10,11-dihydro-5H-dibenzo-[a,d]cycloheptene



Recrystallize from hexane, mp 122.7°C, ^{1}H NMR (CDCl3) δ 2.80-3.64 (br s, 4H), 6.60-7.20 (m, 11H), 7.45-7.57 (m,2H); MS (EI) 360.

Example 30

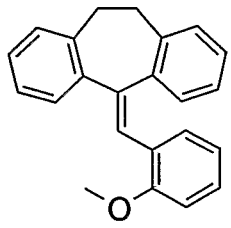
5-(4-Bromo-benzylidene)-10,11-dihydro-5H-dibenzo-[a,d]cycloheptene



Viscous oil, ^{1}H NMR (CDCl3) δ 2.80-3.64 (br m, 4H), 6.74-7.55 (m, 13H); MS (EI) 360. HPLC shows 96.4% purity.

Example 31

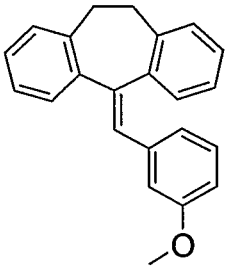
5-(2-Methoxy-benzylidene)-10,11-dihydro-5H-dibenzo-[a,d]cycloheptene



Recrystallize from hexane, mp 129.3°C, ^{1}H NMR (CDCl3) δ 2.80-3.64 (br m, 4H), 3.86 (s, 3H), 6.59-7.58 (m, 13H). HPLC shows 100% purity.

Example 32

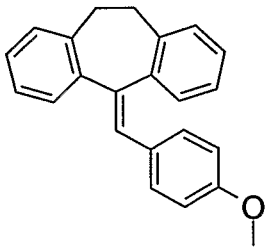
5-(3-Methoxy-benzylidene)-10,11-dihydro-5H-dibenzo-[a,d]cycloheptene



Triturate with hexane, mp 83.0°C; ^{1}H NMR (CDCl3) δ 2.80-3.60 (m, 4H), 3.55 (s, 3H), 6.48-7.50 (m, 13H). HPLC shows 98.8% purity.

Example 33

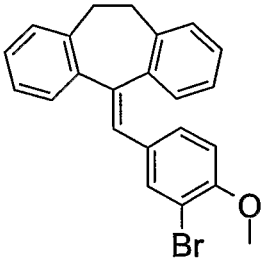
5-(4-Methoxy-benzylidene)-10,11-dihydro-5H-dibenzo-[a,d]cycloheptene



Purify on silica gel using CH_2Cl_2. Recrystallize from hexane/CH_2Cl_2, mp 116.8°C. ^{1}H NMR (CDCl3) δ 2.94 (br d, 2H), 3.46 (br d, 2H), 3.77 (s, 3H), 6.65-7.48 (m, 13H).

Example 34

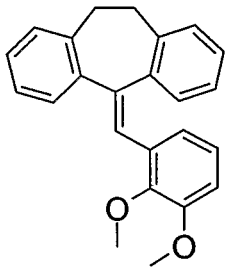
5-(3-Bromo-4-methoxy-benzylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene



Recrystallize from hexane/toluene, mp 140.7°C. ^{1}H NMR (CDCl3) δ2.94 (br d, 2H), 3.45 (br d, 2H), 3.83 (s, 3H), 6.64-7.48 (m, 12H). HPLC shows 95% purity.

Example 35

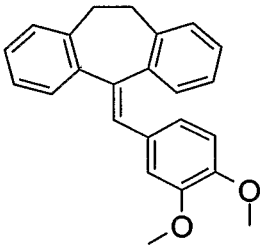
5-(2,3-Dimethoxy-benzylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene



Purify on silica gel using EtOAc/hexane. Light yellow solid, mp 130.6°C. ^{1}H NMR (CDCl3) δ 2.94 (br d, 2H), 3.45 (br d, 2H), 3.82 (s, 3H), 3.95 (s, 3H), 6.27 (dd, 1H), 6.65-7.27 (m, 9H), 7.57, m, 1H); MS (ES) 343 (M+H). HPLC shows 91% purity.

Example 36

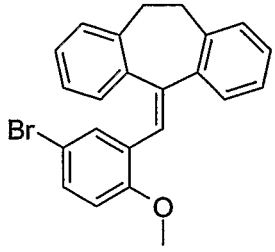
5-(3,4-Dimethoxy-benzylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene



Purify on silica gel using EtOAc/hexane to give a white solid, mp 102.8°C. ^{1}H NMR (CDCl3) δ 2.80-3.60 (br dd, 4H), 3.42 (s, 3H), 3.83 (s, 3H), 6.42 (s, 1H), 6.72 (m, 3H), 7.06-7.47 (m, 8H). HPLC shows 97% purity.

Example 40

5-(5-Bromo-2-methoxy-benzylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene

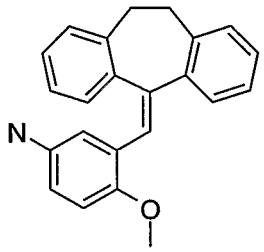


Following the procedures essentially as described for Preparation 5 and Example 28 above, using dibenzosuberane (15.0g, 77.2mmol) and 5-bromo-o-anisaldehyde (16.6g, 77.2mmol), recrystallization from boiling toluene/hexanes affords 19.78g (65%) of the

title compound as a tan solid. ^{1}H-NMR ($CDCl_3$) δ 2.76-3.70 (br m, 4H), 3.81 (s, 3H), 6.69 (d, 1H), 6.76 (d, 1H), 6.88-7.29 (m, 9H), 7.53 (m, 1H); HPLC shows 100% purity.

Example 41

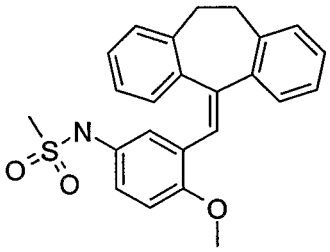
3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-4-methoxy-phenylamine



Following the procedures essentially as described in Example 86 below, and using 5-(5-bromo-2-methoxy-benzylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (10.0g, 25.56mmol), affords 6.52g (78%) of the title compound as a solid. MS (ES) 328 (M+H); HPLC shows 99% purity.

Example 42

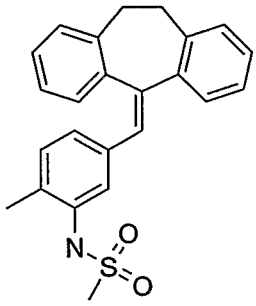
N-[3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-4-methoxy-phenyl]-methanesulfonamide



Following the procedures essentially as described in Example 90 below, and using 3-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-4-methoxy-phenylamine (500mg, 1.53mmol), affords 398mg (64%) of the title compound as a white foam. MS (ES) 423 (M+H), 404 (M-H); HPLC shows 100% purity.

Example 45

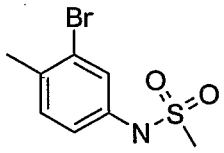
N-[5-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-2-methyl-phenyl]-methanesulfonamide



Following the procedure essentially as described for Example 219, below, and using 5-bromomethylene-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (300mg, 1.05mmol) and (3-amino-4-methylphenyl)boronic acid hydrochloride (217mg, 1.16mmol), yields 245mg (75%) 5-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-2-methyl-phenylamine as a brown oil. Then, following procedures essentially as described in Example 90, below, and using 5-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-2-methyl-phenylamine (100mg, 0.321mmol), affords 35mg (28%) of the title compound as a colorless oil. MS (ES) 407 ($M+NH_4$), 388 (M-H); HPLC shows 98% purity.

Example 46

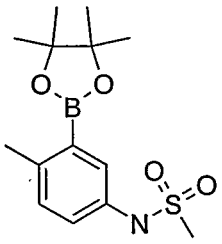
N-(3-Bromo-4-methyl-phenyl)-methanesulfonamide



Following the procedures essentially as described for Example 90, below, and using 3-bromo-4-methylaniline (5.00g, 26.9mmol), recrystallization from boiling toluene/hexanes affords 6.08g (86%) of the title compound as a tan crystalline solid. MS (ES) 263 (M-H), HPLC shows 100% purity.

Preparation 15

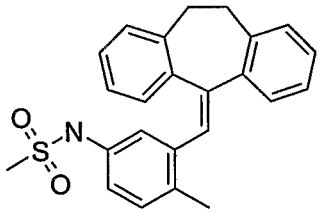
N-[4-Methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-methanesulfonamide



Mix N-(3-bromo-4-methyl-phenyl)-methanesulfonamide (500mg, 1.89mmol), bis(pinacolato)diboron (576mg, 2.27mmol), and potassium acetate (557mg, 5.67mmol) in DMSO (6mL). Sparge solution with N_2 for 10min, then add Pd(dppf)Cl_2 (1:1 complex with CH_2Cl_2, 154mg, 0.189mmol) and heat to 85°C overnight. Cool reaction mixture to room temperature, dilute with ethyl acetate (100mL), and wash organics four times with H_2O. Dry ($MgSO_4$) and concentrate organics to a brown oil. Chromatograph on silica gel (40g), eluting with 20% to 40% ethyl acetate/hexanes affords 415mg (71%) of the title compound as a colorless oil. MS (ES) 329 (M+NH_4), 310 (M-H); HPLC shows 96% purity.

Example 47

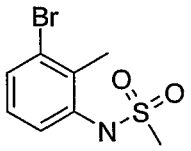
N-[3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-4-methyl-phenyl]-methanesulfonamide



Following the procedures essentially as described in Example 219, below, and using N-[4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-methanesulfonamide (120mg, 0.386mmol) and 5-bromomethylene-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (100mg, 0.351mmol) affords 83mg (61%) of the title compound as a yellow solid. MS (ES) 407 (M+NH_4), 388 (M-H); HPLC shows 91% purity.

Preparation 16

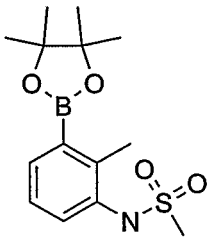
N-(3-Bromo-2-methyl-phenyl)-methanesulfonamide



Following procedures essentially as described in Example 90, below, and using 2-methyl-3-bromoaniline (5.00g, 26.87mmol), recrystallization from boiling toluene/hexanes affords 6.77g (95%) of the title compound as a light green solid. MS (ES) 263 (M-H); HPLC shows 100% purity.

Preparation 17

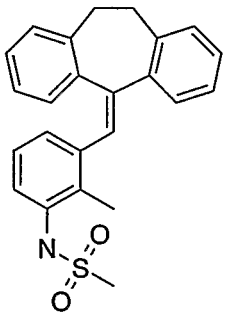
N-[2-Methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-methanesulfonamide



Mix N-(3-bromo-2-methyl-phenyl)-methanesulfonamide (500mg, 1.89mmol), bis(pinacolato)diboron (576mg, 2.27mmol), and potassium acetate (557mg, 5.67mmol) in DMSO (6mL). Sparge solution with N_2 for 5min, then add Pd(dppf)Cl_2 (1:1 complex with CH_2Cl_2, 154mg, 0.189mmol) and heat to 85°C overnight. Cool reaction mixture to room temperature, dilute with ethyl acetate (100mL), and wash organics three times with H_2O. Dry ($MgSO_4$) and concentrate organics to a brown oil. Chromatograph on silica gel (40g), eluting with 20% to 40% ethyl acetate/hexanes affords 458mg (78%) of the title compound as a colorless oil. MS (ES) 310 (M-H); HPLC shows 76% purity.

Example 48

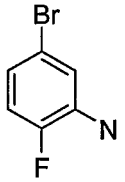
N-[3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-2-methyl-phenyl]-methanesulfonamide



Following the procedures essentially as described in Example 219, below, and using N-[2-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-methanesulfonamide (120mg, 0.386mmol) and 5-bromomethylene-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (100mg, 0.351mmol), purification by UV-guided semi-preparatory reverse-phase HPLC affords 18mg (13%) of the title compound as a yellow oil. MS (ES) 407 (M+NH_4), 388 (M-H); HPLC shows 96% purity.

Preparation 18

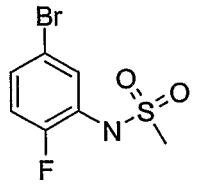
5-Bromo-2-fluoro-phenylamine



Dissolve 4-bromo-1-fluoro-2-nitrobenzene (5.00g, 22.73mmol) and $SnCl_2$ (dihydrate, 25.46g, 113.6mmol) in ethanol (100mL) and heat to reflux overnight. Cool to room temperature and concentrate in-vacuo. Dissolve residue in ethyl acetate and basify with saturated aqueous $NaHCO_3$. Filter through a pad of Celite and extract filtrate with ethyl acetate. Dry ($MgSO_4$) and concentrate organics to a brown oil. Chromatograph on 90g silica gel, eluting with 5% to 10% ethyl acetate/hexanes affords 2.85g (66%) of the title compound as a tan oil. MS (ES) 191 (M+H); HPLC shows 99% purity.

Preparation 19

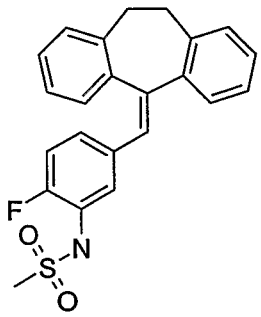
N-(5-Bromo-2-fluoro-phenyl)-methanesulfonamide



Dissolve 5-bromo-2-fluoro-phenylamine (1.40g, 7.37mmol), N,N-dimethylamino-4-pyridine (90mg, 0.737mmol), and methanesulfonyl chloride (1.69g, 14.74mmol) in CH2Cl2 (10mL) and pyridine (10mL). Stir under N_2 for 4h and concentrate in-vacuo. Dilute residue with 1.00N aqueous HCl (20mL) and extract into ethyl acetate. Dry ($MgSO_4$) and concentrate organics to a yellow solid. Dissolve in THF (20mL) and add 1.0M tetrabutylammonium fluoride/THF (4.83mL, 4.83mmol). Heat to reflux for 3h, then add H_2O and brine. Extract into ethyl acetate, then dry ($MgSO_4$) and concentrate organics to a white solid. Recrystallization from boiling toluene/hexanes affords 768mg (39%) of the title compound as a white solid. MS (ES) 267 (M-H); HPLC shows 100% purity.

Example 49

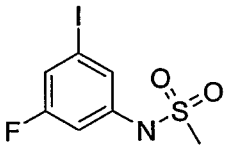
N-[5-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-2-fluoro-phenyl]-methanesulfonamide



Following the procedures essentially as described in Example 219 (below) and using (10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidene)-boronic acid (0.197M in dioxane, 3.35mL, 0.660mmol) and N-(5-bromo-2-fluoro-phenyl)-methanesulfonamide (147mg, 0.550mmol) affords 141mg (65%) of the title compound as a purple foam. MS (ES) 411 (M+NH4), 392 (M-H); HPLC shows 91% purity.

Preparation 20

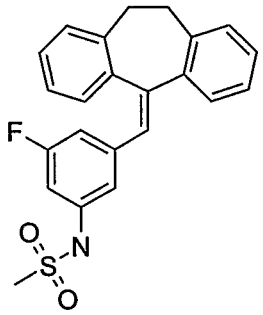
N-(3-Fluoro-5-iodo-phenyl)-methanesulfonamide



Dissolve 3-fluoro-5-iodoaniline (600mg, 2.53mmol) (prepared as described in published PCT International Application WO96/23783 A1, published August 8, 1996), methanesulfonyl chloride (896mg, 7.83mmol), triethylamine (1.91g, 18.9mmol), and N,N-dimethylamino-4-pyridine (31mg, 0.253mmol) in CH_2Cl_2 (10mL) and stir at room temperature overnight. Dilute with 1.00N aqueous HCl (20mL) and extract into ethyl acetate. Dry ($MgSO_4$) and concentrate organics to a yellow solid. Dissolve solid in THF (50mL) and add 1.0M tetrabutylammonium fluoride (2.8mL). Heat to reflux for 3.5h. Cool to room temperature, dilute with H_2O, and extract into ethyl acetate. Dry ($MgSO_4$) and concentrate organics. Chromatograph on silica gel (40g), eluting with 20% to 35% ethyl acetate/hexanes affords 618mg (78%) of the title compound as a white solid. MS (ES) 314 (M-H); HPLC shows 100% purity.

Example 50

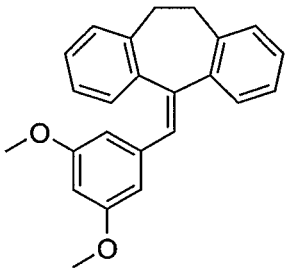
N-[3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-5-fluoro-phenyl]-methanesulfonamide



Following procedures essentially as described in Example 219, below, and using 10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidene)-boronic acid (0.198M in dioxane, 5.1mL, 1.02mmol) and N-(3-fluoro-5-iodo-phenyl)-methanesulfonamide (268mg, 0.850mmol), purification by UV-guided reverse-phase semi-preparatory HPLC affords 108mg (32%) of the title compound as a colorless oil. MS (ES) 394 (M+H), 392 (M-H); HPLC shows 99% purity.

Example 51

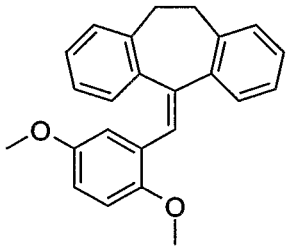
5-(3,5-Dimethoxy-benzylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene



Following procedures essentially as described in Preparation 5 and Example 28, above, and using dibenzosuberone (2.00g, 10.29mmol) and 3,5-dimethoxybenzaldehyde (1.71g, 10.29mmol), affords 1.43g (41%) of the title compound as a yellow foam. ^{1}H-NMR ($CDCl_3$) δ 2.79-3.64 (br m, 4H), 3.55 (s, 6H), 6.20 (d, 2H), 6.25 (t, 1H), 6.72 (s, 1H), 7.06-7.30 (m, 7H), 7.48 (m, 1H); HPLC shows 99% purity.

Example 52

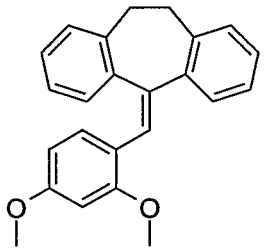
5-(2,5-Dimethoxy-benzylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene



Following procedures essentially as described in Preparation 5 and Example 28, above, and using dibenzosuberone (2.00g, 10.29mmol) and 2,5-dimethoxybenzaldehyde (1.71g, 10.29mmol) affords 1.27g (36%) of the title compound as a yellow solid. ^{1}H-NMR ($CDCl_3$) δ 2.74-3.67 (br m, 4H), 3.34 (s, 3H), 3.83 (s, 3H), 6.27 (d, 1H), 6.65 (dd, 1H), 6.77 (d, 1H), 6.98-7.28 (m, 8H), 7.56 (dd, 1H); HPLC shows 99% purity.

Example 53

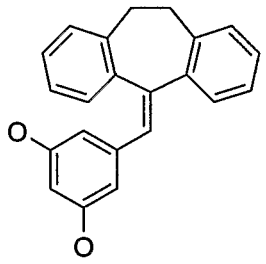
5-(2,4-Dimethoxy-benzylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene



Following procedures essentially as described in Preparation 5 and Example 28, above, and using dibenzosuberone (2.00g, 10.29mmol) and 2,4-dimethoxybenzaldehyde (1.71g, 10.29mmol) affords 231mg (7%) of the title compound as a white foam. ^{1}H-NMR ($CDCl_3$) δ 2.70-3.67 (br m, 4H), 3.73 (s, 3H), 3.84 (s, 3H), 6.15 (dd, 1H), 6.41 (d, 1H), 6.61 (d, 1H), 6.9-7.27 (m, 8H), 7.56 (dd, 1H); HPLC shows 98% purity.

Example 54

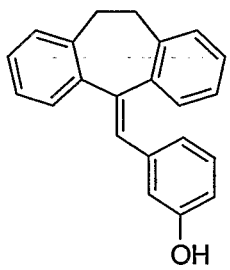
5-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-benzene-1,3-diol



Following procedures essentially as described in Example 57, below, and using 5-(3,5-dimethoxy-benzylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (664mg, 1.94mmol), affords 608mg (99%) of the title compound as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ 2.73-3.62 (br m, 4H), 4.89 (br s, 2H), 6.07 (d, 2H), 6.14 (t, 1H), 6.64 (s, 1H), 7.04-7.28 (7H), 7.44 (m, 1H); HPLC shows 98% purity.

Example 57

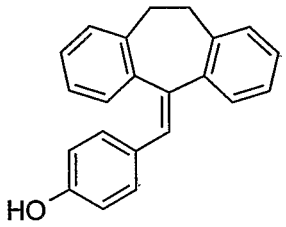
3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenol



Stir a molten mixture of 5-(3-methoxy-benzylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (1.11g, 3.55mmol) and pyridine hydrochloride (10g, 87mmol) at 215°C for 40 min. Cool the reaction mixture to 100°C, dilute with 1N HCl, and extract with ethyl acetate. Dry organics ($MgSO_4$), filter, and concentrate to a brown oil containing the title compound. Purification via silica gel chromatography (1:6 ethyl acetate:hexanes) affords 940mg (89%) of a tan oil. ^1H NMR ($CDCl_3$) δ 2.76-3.63 (br m, 4H), 4.59 (s, 1H), 6.45 (s, 1H), 6.64 (m, 2H), 6.75 (s, 1H), 6.99-7.52 (m, 9H); MS (ES) 299 (M+H), 297 (M-H). HPLC shows 97% purity.

Example 60

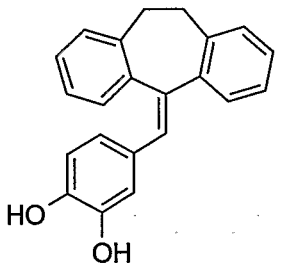
4-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenol



Following procedures essentially as described in Example 57, above, and using 5-(4-methoxy-benzylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene gives the title compound in 60% yield as a white crystalline solid, mp 56.9°C. ^1H NMR ($CDCl_3$) δ 2.77-3.60 (br m, 4H), 4.71 (s, 1H), 6.62 (d, 2H), 6.73 (s, 1H), 6.92 (d, 2H), 7.02-7.50 (m, 8H); MS (ES) 297 (M-H). HPLC shows 97% purity.

Example 62

4-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-benzene-1,2-diol

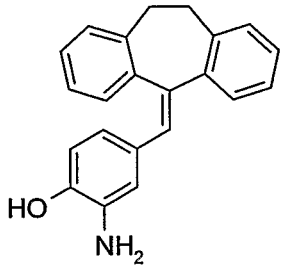


Following procedures essentially as described in Example 57, above, and using 5-(3,4-dimethoxy-benzylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene gives the title compound in 79% yield as a brown foam, mp 138.0°C. ^1H NMR ($CDCl_3$) δ 2.76-3.62 (br

m, 4H), 4.84 (s, 1H), 5.07 (s, 1H), 6.47 (s, 1H), 6.55 (m, 11H); MS (ES) 313 (M-H). HPLC shows 95% purity.

Example 63

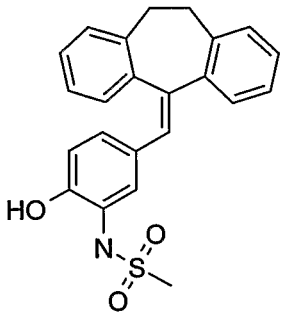
2-Amino-4-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenol



Following procedures essentially as described in Example 57, above, and using 5-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-2-methoxy-phenylamine gives the title compound in 75% yield as a brown foam, mp 158.8°C. ^{1}H NMR ($CDCl_3$) δ 2.72-4.45 (br m, 6H), 6.31-7.54 (br m, 13H). MS (ES) 314 (M+H), 312 (M-H). HPLC shows 98% purity.

Example 64

N-[5-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-2-hydroxy-phenyl]-methanesulfonamide

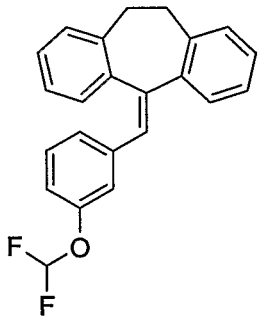


Cool a solution of N-[5-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-2-methoxy-phenyl]-methanesulfonamide (100mg, 0.247mmol) in CH_2Cl_2 (5mL) to 0°C. Add 23.3□L (62mg, 0.247mmol) BBr_3 and warm up to room temperature. Stir for 20min, then add 30.0□L (79.5mg, 0.317mmol) more BBr_3. Stir at room temperature for 1 h, then dilute reaction with 90mL saturated aqueous $NaHCO_3$. Stir overnight. Separate the layers, and extract the aqueous layer with CH_2Cl_2. Combine and dry organics

($MgSO_4$), filter, and concentrate to afford 94mg (97%) of a white foam, mp 122.6°C. ^1H NMR ($CDCl_3$) δ 2.70 (s, 3H), 2.79-3.59 (br m, 4H), 5.94 (s, 1H), 6.39 (s, 1H), 6.70-7.98 (m, 12H); MS (ES) 414 (M+Na), 390 (M-H). HPLC shows 99% purity.

Example 65

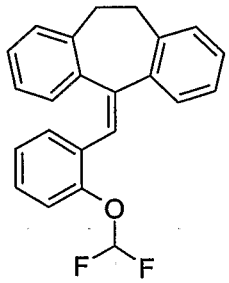
5-(3-Difluoromethoxy-benzylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene



Add pellets of KOH (376mg, 6.7mmol) to a solution of 3-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenol (200mg, 0.67mmol) in isopropanol (10mL). Bubble chlorodifluoromethane (Freon 22) slowly into the reaction mixture for 2 h. Concentrate the reaction mixture, and take the residue up in 1N HCl. Extract into ethyl acetate, dry organics ($MgSO_4$), filter, and concentrate to a milky tan oil containing the title compound. Purify via silica gel chromatography (1:20 ethyl acetate:hexanes) to afford 108mg (20%) of a white solid, mp 91.3°C. ^1H NMR ($CDCl_3$) δ 2.66-3.56 (br m, 4H), 6.12 (t, 1H, J=80Hz), 6.55-7.43 (m, 13H); MS (EI) 348. HPLC shows 97% purity.

Example 66

5-(2-Difluoromethoxy-benzylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene

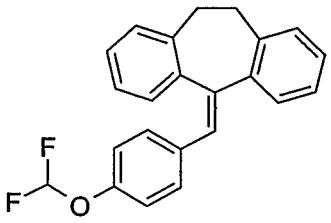


Following the procedures essentially as described in Example 65 above, 5-(2-difluoromethoxy-benzylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene gives the title

compound in 20% yield as a white solid, mp 81.1°C. ^{1}H NMR ($CDCl_3$) δ 2.76-3.72 (br m, 4H), 6.57 (t, 1H, J=72Hz), 6.75-7.57 (m, 13H); MS (EI) 348. HPLC shows 95% purity.

Example 67

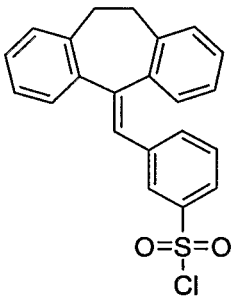
5-(4-Difluoromethoxy-benzylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene



Following the procedures essentially as described in Example 65 above, 5-(4-difluoromethoxy-benzylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene gives the title compound in 46% yield as a white solid, mp 65.8°C. ^{1}H NMR ($CDCl_3$) δ 2.76-3.64 (br m, 4H), 6.44 (t, 1H, J=76Hz), 6.76 (s, 1H), 6.84-7.50 (m, 12H); MS (EI) 348. HPLC shows 100% purity.

Preparation 21

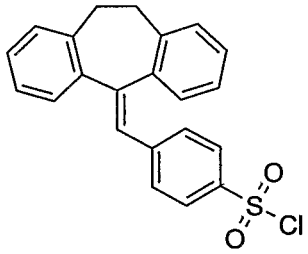
3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-benzenesulfonyl chloride



Under a blanket of nitrogen, cool 5-(3-bromo-benzylidene)-10,11-dihydro-5H-dibenzo-[a,d]cycloheptene (2.8g, 7.75mmol) in THF (40mL) to –78°C and add n-BuLi (1.6M, 5.8mL, 9.3mmol) via syringe. After 20 min, add sulfuryl chloride (800µl, 10mmol). The color lightened immediately. Quench the reaction with saturated NH_4Cl and mix the reaction with water/EtOAc. Dry ($MgSO_4$) and concentrate to give 2.7g pale yellow oil. Purify on silica gel using a gradient of 100% hexane to 30% EtOAc/hexane to give 380mg (13%) sulfonyl chloride. Stir a small aliquot with dimethylamine for several hours. MS (ES) gives the correct mass for the dimethylsulfonamide derivative.

Preparation 22

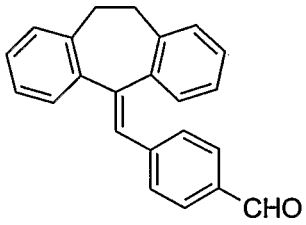
4-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-benzenesulfonyl chloride



Prepared using Procedure E to give 142mg (8%) sulfonyl chloride as a pale yellow oil.

Example 68

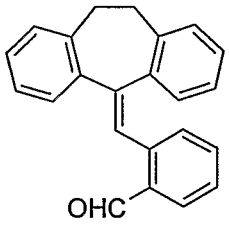
4-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-benzaldehyde



Under nitrogen, cool 5-(4-bromo-benzylidene)-10,11-dihydro-5H-dibenzo-[a,d]cycloheptene (2.2g, 6.1mmol) in THF (40mL) to –65°C and add n-BuLi (1.6M, 5mL, 8mmol) via syringe. After 15 minutes, add DMF (1mL, 14mmol). After 1 h, the quench the reaction with saturated NH_4Cl and partition between water/EtOAc. Dry ($MgSO_4$) and concentrate to yield 1.8g crude aldehyde. Purify on silica gel using hexane/EtOAc to give 940mg colorless oil that slowly crystallized to give a white solid, mp 106.4°C; ^1H NMR (CDCl3) δ 2.80-3.60 (br dd, 4H), 6.84 (s, 1H), 6.92-7.63 (m, 12H), 9.90 (s, 1H); MS (EI) 310. HPLC shows 96% purity.

Example 69

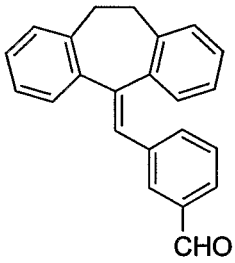
2-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-benzaldehyde



Following procedures essentially as described in Example 68, the title compound was prepared from the corresponding bromide derivative to give white crystals (hexane/EtOAc, 42%), mp 198.9°C. ^{1}H NMR (CDCl3) δ 2.80-3.60 (br s, 4H), 6.67-7.86 (m, 13H), 10.42 (s,1H); MS (EI) 310. HPLC shows 97% purity.

Example 70

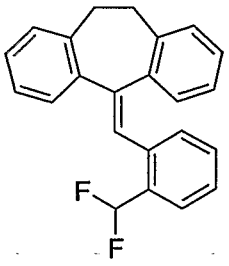
3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-benzaldehyde



Following procedures essentially as described in Example 68 the title compound was isolated as a white solid (38%), mp 86.7°C. ^{1}H NMR (CDCl3) δ2.80-3.60 (br dd, 4H), 6.84 (s, 1H), 6.93-7.65 (m, 12H), 9.81 (s, 1H); MS (EI) 310. HPLC shows 97% purity.

Example 71

5-(2-Difluoromethyl-benzylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene

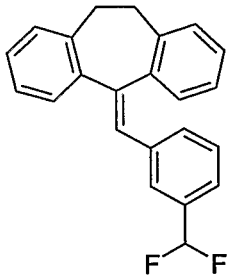


Dissolve 2-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-benzaldehyde (100mg, 0.32mmol) in CH_2Cl_2 (3mL) and add (diethylamino)sulfur trifluoride (DAST) (210□l, 1.6mmol). Stir the reaction overnight at ambient temperature. Shake the crude reaction with saturated $NaHCO_3/CH_2Cl_2$. Dry ($MgSO_4$) and concentrate to give 110mg

crude product. Purify on silica gel using hexane/CH_2Cl_2 to give 50mg (47%) title compound as a white solid, mp. 13.3°C. ^{1}H NMR (CDCl3) δ 2.80-3.60 (br s, 4H), 6.72-7.58 (m, 14H); MS (EI) 332. HPLC shows 98% purity.

Example 72

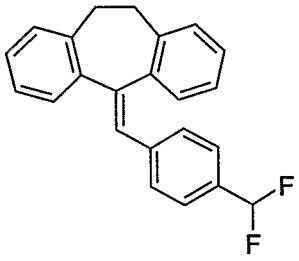
5-(3-Difluoromethyl-benzylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene



Following procedures essentially as described in Example 71, the title compound was prepared as a light yellow solid (39%), mp 92.5°C. ^{1}H NMR (CDCl3) δ 2.96 (br d, 2H), 3.44 (br d, 2H), 6.45 (t, 1H, J=70Hz), 6.80 (s, 1H), 6.94-7.33 (m, 11H), 7.48 (m, 1H); MS (EI) 332. HPLC shows 94% purity.

Example 73

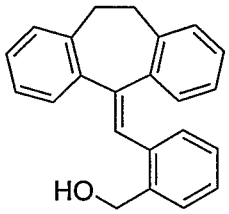
5-(4-Difluoromethyl-benzylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene



Following procedures essentially as described in Example 71, the title compound was prepared as a colorless oil (39%); ^{1}H NMR (CDCl3) δ 2.80-3.60 (br dd, 4H), 6.47 (t, 1H, J=55Hz), 6.72 (s, 1H), 6.87-7.24 (m, 11H), 7.42 (m, 1H); MS (EI) 332. HPLC shows 100% purity.

Example 74

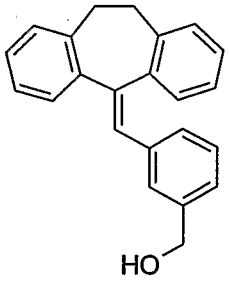
[2-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methanol



Treat a solution of 2-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-benzaldehyde (125mg, 0.4mmol) in EtOH (4mL) with $NaBH_4$ (30mg, 0.8mmol). After 4 h at room temperature, quench the reaction with 1N HCl and concentrate. Shake the residue en with water/EtOAc. Dry the organic layer ($MgSO_4$) and concentrate to give 130mg crude product. Purify on silica gel (EtOAc/hexane) to give 90mg (72%) colorless oil which slowly crystallized, mp 121.8°C. ^{1}H NMR (CDCl3) δ 3.28 (br s, 4H), 4.85 (s, 2H), 6.77-7.60 (m, 13H; MS (EI) 312. HPLC shows 98% purity.

Example 75

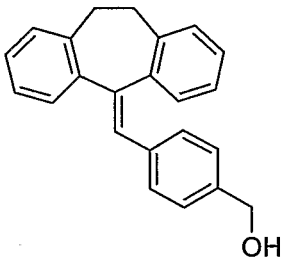
[3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methanol



Following procedures essentially as described in Example 74, the title compound was obtained as a colorless oil which slowly crystallized. ^{1}H NMR (CDCl3) δ 3.03 (br d, 2H), 3.47 (br d, 2H), 4.55 (s, 2H), 6.84 (s, 1H), 6.93-7.31 (m, 11H), 7.52 (m, 1H); MS (EI) 312. HPLC shows 93% purity.

Example 76

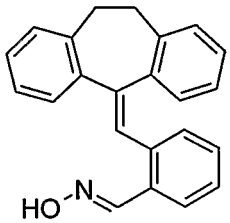
[4-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methanol



Following procedures essentially as described in Example 74, the title compound was obtained as a colorless oil (65%); ^{1}H NMR (CDCl3) δ3.03 (br d, 2H), 3.47 (br d, 2H), 4.62 (s, 2H), 6.78 (s, 1H), 7.02-7.34 (m, 11H), 7.520 (m, 1H); MS (EI) 312.

Example 77

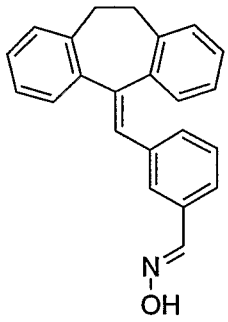
2-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-benzaldehyde oxime



Dissolve 2-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-benzaldehyde (110mg,0.35mmol) in EtOH (4mL). In a separate flask, dissolve hydroxylamine hydrochloride (35mg, 0.5mmol) in water (1mL). Add this solution the aldehyde solution and stir at room temperature for 18h. Pour the reaction into water (300mL) and extract the product into EtOAc. Dry ($MgSO_4$) and concentrate to give 140mg crude product. Purity on silica gel using EtOAc/hexane to give 82mg (72%) title compound as a white solid. ^{1}H NMR (CDCl3) δ 3.31 (br s, 4H), 6.73-7.33 (m, 11H), 7.55 (m, 1H), 7.70 (dd, 1H), 8.58 (s, 1H); MS (ES) 326 (M+1), 324 (M-1). HPLC shows 98% purity.

Example 78

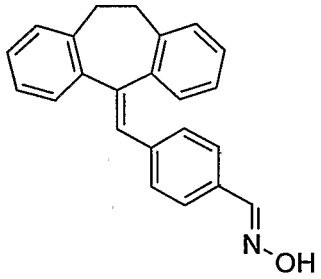
3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-benzaldehyde oxime



Following procedures essentially as described in Example 77, the title compound was prepared in 55% yield from 3-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-benzaldehyde (50mg, 0.161mmol). ^{1}H NMR (CDCl3) δ 2.92 (br d, 2H), 3.36 (br d, 2H), 6.72 (s, 1H), 6.87-7.43 (m, 12H), 7.87 (s, 1H); MS (ES) 326 (M+1).

Example 79

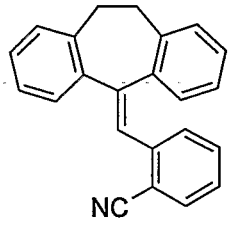
4-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-benzaldehyde oxime



Following procedures essentially as described in Example 77, the title compound was prepared in 55% yield from 4-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-benzaldehyde (117mg, 0.38mmol). ^{1}H NMR (CDCl3) δ 2.77 (br d, 2H), 3.21 (br d, 2H), 6.57 (s, 1H), 6.61-7.64 (m,12H), 7.82 (s, 1H); MS (ES) 326 (M+1). HPLC shows 97% purity.

Example 80

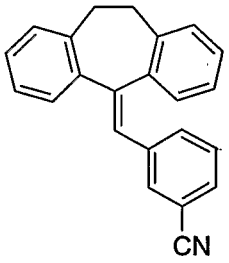
2-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-benzonitrile



Sparge a mixture of 5-methylene-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (2.0g, 9.7mmol) (prepared as described in Journal of Organic Chemistry, 53 (8) 1768-1774 (1988)), 2-bromobenzonitrile ((1.77g, 9.7mmol), NaOAc (1g, 12 mmol) and dimethylacetamide (100mL) with nitrogen for 15 minutes. Add Hermann catalyst (320mg, 0.46mmol)(Chem. Eur. J. 1357-1364 (1997)) and heat at 150°C for 6 days. Cool the reaction and partition between water (1L) and EtOAc (500mL). Wash the organic layer with water (3 x 1L). Dry ($MgSO_4$) and concentrate under reduced pressure to give 3.3g brown oil. Purify on silica gel using EtOAc/hexane 500mg nitrile that is 81% pure by glc. Recrystallize (EtOH) to give 213mg (7%) pale yellow plates, mp 185.4°C. ^1H NMR ($CDCl_3$) δ 3.04 (br d, 2H), 3.47 (br s, 2H), 6.82-7.34 (m, 11H), 7.62 (m, 2H); MS (ES) 308 (M+1). HPLC shows 98% purity.

Example 81

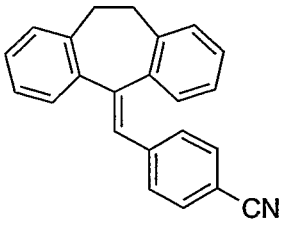
3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-benzonitrile



Purge a solution of 5-(3-bromo-benzylidene)-10,11-dihydro-5H-dibenzo-[a,d]cycloheptene (4.2g, 11.6mmol) in N-methylpyrrolidinone (80mL) with nitrogen for 10 minutes. Add CuI (6.7g, 35mmol) and CuCN (3.1g, 35mmol) and heat to 130°C. After 1 hour, cool the reaction to ambient temperature and shake with aqueous $FeCl_3$ (200mL) and EtOAc (200mL). Wash the organic layer with water, dry with $MgSO_4$ and concentrate to obtain 6.4g crude product. Purify on silica gel using EtOAc/hexane to obtain 2.55g (71%) title compound as a white solid, mp 115.7°C. ^1H NMR ($CDCl_3$) δ 3.02 (br d, 2H), 3.40 (br d, 2H), 6.77 (s, 1H), 6.93 (dd, 1H), 7.02-7.49 (m,11H); MS (EI) 307. HPLC shows 98% purity.

Example 82

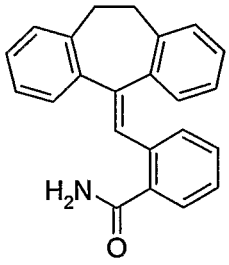
4-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-benzonitrile



Following procedures essentially as described in Example 81and using 5-(4-bromo-benzylidene)-10,11-dihydro-5H-dibenzo-[a,d]cycloheptene (4.2g, 11.6mmol) gives 2.02g (57%) as tan viscous oil. ^{1}H NMR ($CDCl_3$) δ 3.06 (br d, 2H), 3.48 (br d, 2H), 6.85 (s, 1H), 6.98 (dd, 1H), 7.06-7.57 (m, 11H; MS (EI) 307. HPLC shows 97% purity.

Example 83

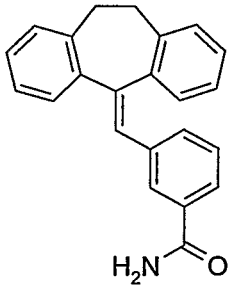
2-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-benzamide



Dissolve 2-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-benzonitrile (100mg, 0.32mmol) in DMSO (3mL) and add solid K_2CO_3 (50mg) followed by 30% H_2O_2 (100□l). Stir the reaction for 3 h. and quench by pouring into water. Collect the white solid and dry in a vacuum oven to yield 84mg (81%). ^{1}H NMR (DMSO-d_6) δ2.95 (br s, 2H), 3.38 (br s, 2H), 6.67-7.56 (m, 12H), 7.90 (s, 1H); MS (ES) 326 (M+1), 324 (M-1). HPLC shows 95% purity.

Example 84

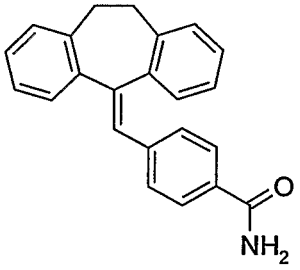
3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-benzamide



Following procedures essentially as described in Example 83 and starting with 3-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-benzonitrile (480mg, 1.56mmol) gives 445mg (88%)as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 2.95 (br s, 2H), 3.40 (br s, 2H), 6.85-7.54 (m, 10H), 7.61 (d, 1H), 7.72 (s, 1H), 7.84 (s, 1H); MS (ES) 326 (M+1), 324 (M-1). HPLC shows 94% purity.

Example 85

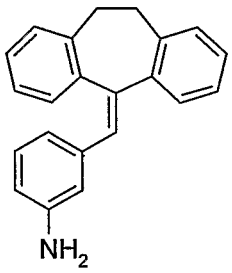
4-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-benzamide



Following procedures essentially as described in Example 83 and starting with 4-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-benzonitrile (230mg, 0.75mmol) gives 226mg (93%) white powder. ^{1}H NMR (DMSO-d_6) δ 2.95 (br s, 2H), 3.38 (br s, 2H), 6.82-7.54 (m, 11H), 7.67 (d, 1H), 7.87 (s, 1H); MS (ES) 326 (M+1). HPLC shows 96% purity.

Example 86

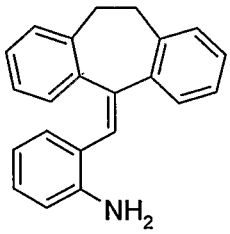
3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenylamine



Dissolve 5-(3-bromo-benzylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (3.00g, 8.30mmol) in toluene (75mL) and add the following reagents: tris(dibenzylidine acetone)dipalladium(0) (380mg, 0.415mmol), racemic BINAP (517mg, 0.830mmol), sodium t-butoxide (1.12g, 11.6mmol), and benzophenone imine (3.48mL, 3.76g, 20.76mmol). Heat the mixture to reflux overnight. Cool to room temperature and dilute with H_2O. Extract into ethyl acetate and dry organics ($MgSO_4$). Concentrate organics and take the residue up in a 1:1 mixture of THF and 1N HCl. After 2 h, extract into ethyl acetate and dry organics ($MgSO_4$). Concentrate to a brown solid containing the title compound. Boil the solid in a 5:1:0.1 mixture of toluene:ethyl acetate:THF. Cool the suspension to –26°C and filter, collect 1.98g (80%) of a white solid, mp 204.3°C. ^1H NMR (DMSO-d_6) δ 2.90 (br s, 2H), 3.36 (br d, 2H), 6.77-7.51 (m, 15H); MS (ES) 298 (M+H). HPLC shows 99% purity.

Example 87

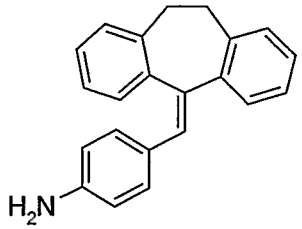
2-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenylamine



Following procedures essentially as described in Example 86, 5-(2-bromo-benzylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene gives the title compound in 85% yield as a yellow foam, mp 145.2°C after purification using silica gel chromatography (75:24:1 hexanes:CH2Cl2:2M NH3/MeOH). ^1H NMR ($CDCl_3$) δ 3.25 (br s, 4H), 3.80 (s, 2H), 6.45-7.51 (m, 13H); MS (ES) 298 (M+H). HPLC shows 95% purity.

Example 88

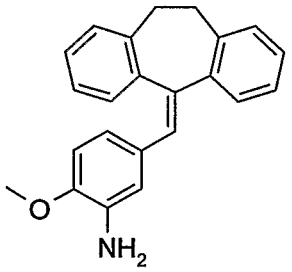
4-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenylamine



Following procedures essentially as described in Example 86, 5-(4-bromo-benzylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene gives the title compound in 54% yield as an orange solid, mp >250°C after purification by triturating with hot CH_2Cl_2. ^1H NMR (DMSO-d_6) δ 2.86 (br s, 2H), 3.32 (br d, 2H), 6.74 (s, 1H), 6.89-7.48 (m, 14H); MS (ES) 298 (M+H). HPLC shows 98% purity.

Example 89

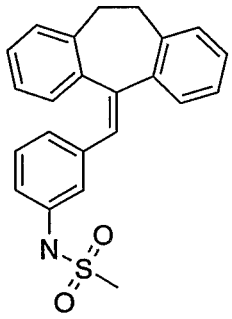
5-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-2-methoxy-phenylamine



Following procedures essentially as described in Example 86, 5-(3-bromo-4-methoxy-benzylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene gives the title compound in 36% yield as a yellow foam, mp 62.7°C after purification via silica gel chromatography (1:9 ethyl acetate:hexanes). ^1H NMR ($CDCl_3$) δ 2.69-3.73 (br m, 6H), 3.80 (s, 3H), 6.36 (s, 1H), 6.48 (dd, 1H), 6.60 (d, 1H), 6.66 (s, 1H), 7.00-7.50 (m, 8H); MS (ES) 328 (M+H). HPLC shows 98% purity.

Example 90

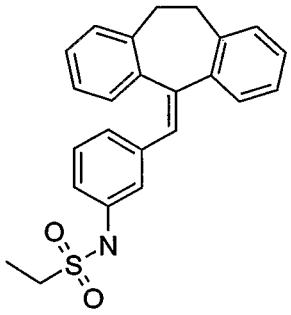
N-[3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methanesulfonamide



Dissolve 3-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenylamine (400mg, 1.34mmol) in anhydrous pyridine (10mL) and add methanesulfonyl chloride (616mg, 416□L, 5.38mmol). Stir overnight at room temperature, then concentrate. Take residue up in ethyl acetate and 1N HCl and separate the layers. Extract aqueous layer with ethyl acetate, combine organics, and dry ($MgSO_4$). Concentrate to a brown oil. Purify via silica gel chromatography (2:3 ethyl acetate:hexanes) to yield 350mg (70%) of yellow foam, mp 66.3°C. ^1H NMR ($CDCl_3$) δ 2.71 (s, 3H), 2.75-3.56 (br m, 4H), 6.09 (s, 1H), 6.64-7.43 (m, 13H); MS (ES) 398 (M+23), 374 (M-H). HPLC shows 96% purity.

Example 91

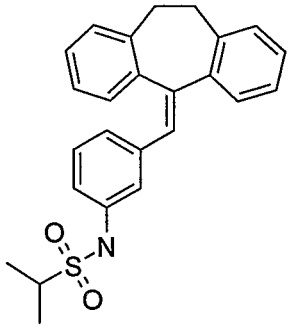
Ethanesulfonic acid [3-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-amide



Following procedures essentially as described in Example 90, 3-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenylamine and ethanesulfonyl chloride gives the title compound in 74% yield as a brown solid, mp 180.2°C. ^1H NMR ($CDCl_3$) δ 1.25 (t, 3H), 2.80-3.60 (br m, 6H), 6.06 (br s, 1H), 6.71-7.51 (m, 13H); MS (ES) 412 (M+Na), 388 (M-H). HPLC shows 99% purity.

Example 92

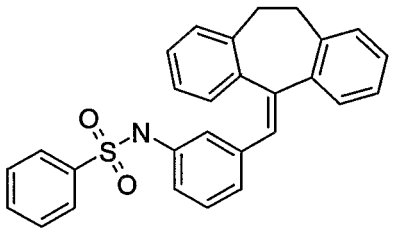
Propane-2-sulfonic acid [3-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-amide



Following procedures essentially as described in Example 90, 3-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenylamine and isopropylsulfonyl chloride gives the title compound in 22% yield as a white solid, mp 187.7°C. ^{1}H NMR ($CDCl_3$) δ 1.28 (d, 6H), 2.80-3.60 (br m, 5H), 6.47 (s, 1H), 6.75-7.50 (m, 13H); MS (ES) 426 (M+Na), 402 (M-H). HPLC shows 94% purity.

Example 93

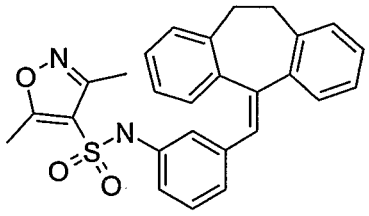
N-[3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-benzenesulfonamide



Following procedures essentially as described in Example 90, 2-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenylamine and benzenesulfonyl chloride gives the title compound in 82% yield as a white solid, mp 121.9°C. ^{1}H HMR ($CDCl_3$) δ 2.76-3.56 (br m, 4H), 6.64-7.77 (m, 19H); MS (ES) 460 (M+Na), 436 (M-H). HPLC shows 98% purity.

Example 94

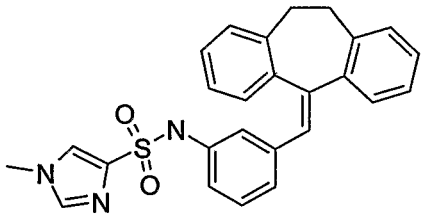
3,5-Dimethyl-isoxazole-4-sulfonic acid [3-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-amide



Following procedures essentially as described in Example 90, 2-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenylamine and 3,5-dimethyl-isoxazole-4-sulfonyl chloride gives the title compound in 80% yield as a white solid, mp 149.3°C. ^{1}H NMR ($CDCl_3$) δ 2.21 (s, 3H), 2.40 (s, 3H), 2.77-3.54 (br m, 4H), 6.57 (s, 1H), 6.69 (d, 2H), 6.86-7.48 (m, 11H); MS (ES) 479 (M+Na) 455 (M-H). HPLC shows 95% purity.

Example 95

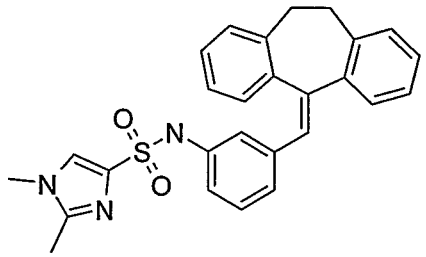
1-Methyl-1H-imidazole-4-sulfonic acid [3-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-amide



Following procedures essentially as described in Example 90, 2-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenylamine and 1-methyl-1H-imidazole-4-sulfonyl chloride gives the title compound in 40% yield as a white solid, mp 257.0°C. ^{1}H NMR (DMSO-d_6) δ 2.90 (br s, 2H), 3.35 (br s, 2H), 3.64 (s, 3H), 6.46 (d, 1H), 6.67 (s, 1H), 6.80-7.46 (m, 11H), 7.79 (d, 2H), 6.11 (s, 1H); MS (ES) 464 (M+Na). HPLC shows 100% purity.

Example 96

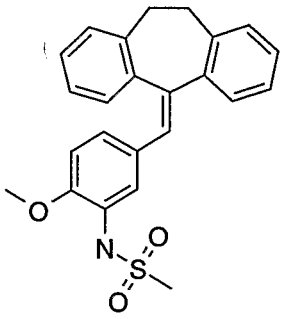
1,2-Dimethyl-1H-imidazole-4-sulfonic acid [3-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-amide



Following procedures essentially as described in Example 90, 2-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenylamine and 1,2-dimethyl-1H-imidazole-4-sulfonyl chloride gives the title compound in 1% yield as a white solid. MS (ES) 456 (M+H). HPLC shows 100% purity.

Example 97

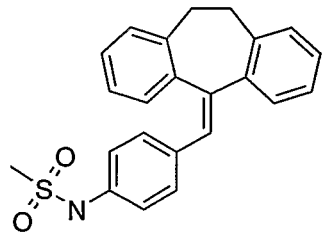
N-[5-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-2-methoxy-phenyl]-methanesulfonamide



Following procedures essentially as described in Example 90-, 5-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-2-methoxy-phenylamine and methanesulfonyl chloride gives the title compound in 77% yield as a tan foam, mp 192.1°C. ^{1}H NMR ($CDCl_3$) δ 2.74 (s, 3H), 2.80-4.61 (br m, 4H), 4.81 (s, 3H), 6.67-7.50 (m, 13H); MS (ES) 423 ($M+NH_4$), 404 (M-H). HPLC shows 100% purity.

Example 99

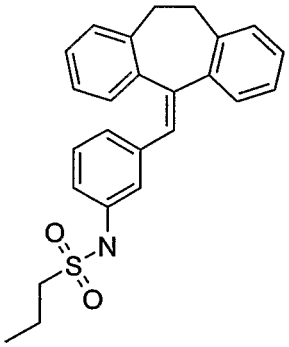
N-[4-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methanesulfonamide



Following procedures essentially as described in Example 90, 4-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenylamine and methanesulfonyl chloride gives the title compound in 48% yield as a tan solid, mp 210.7°C. ^{1}H NMR ($CDCl_3$) δ 2.72-3.58 (br m, 7H), 6.49 (s, 1H), 6.74 (s, 1H), 6.96-7.49 (m, 12H); MS (ES) 398 (M+Na), 374 (M-H). HPLC shows 98% purity.

Example 104

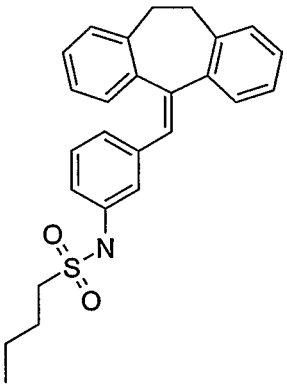
Propane-1-sulfonic acid [3-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-amide



Following procedures essentially as described in Example 90, 3-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenylamine (50mg, 0.168mmol) and 1-propanesulfonyl chloride (144mg, 1.01mmol) affords 34mg (50%) of the title compound as a white foam. MS (ES) 426 (M+Na), 402 (M-H); HPLC shows 99% purity.

Example 105

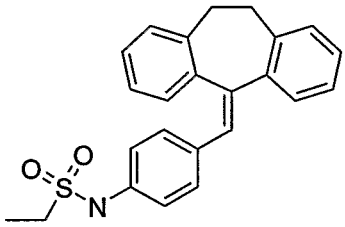
Butane-1-sulfonic acid [3-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-amide



Following procedures essentially as described in Example 90, 3-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenylamine (50mg, 0.168mmol) and 1-butanesulfonyl chloride (158mg, 1.01mmol) affords 41mg (58%) of the title compound as a colorless oil. MS (ES) 440 (M+Na); HPLC shows 99% purity.

Example 106

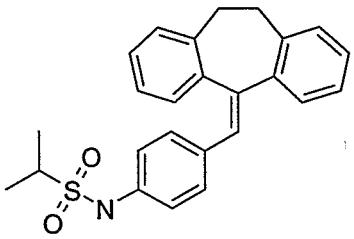
Ethanesulfonic acid [4-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-amide



Following procedures essentially as described in Example 90, 4-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenylamine (100mg, 0.336mmol) and ethanesulfonyl chloride (129mg, 1.01mmol) affords 74mg (57%) of the title compound as a colorless oil. MS (ES) 412 (M+Na), 388 (M-H); HPLC shows 97% purity.

Example 107

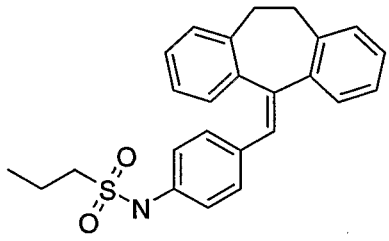
Propane-2-sulfonic acid [4-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-amide



Following procedures essentially as described in Example 90, 4-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenylamine (100mg, 0.336mmol) and 2-propanesulfonyl chloride (144mg, 1.01mmol) affords the title compound. MS (ES) 426 (M+Na), 402 (M-H); HPLC shows 93% purity.

Example 108

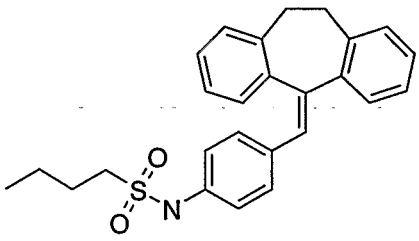
Propane-1-sulfonic acid [4-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-amide



Following procedures essentially as described in Example 90, 4-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenylamine (100mg, 0.336mmol) and 1-propanesulfonyl chloride (144mg, 1.01mmol) affords 69mg (51%) of the title compound as a colorless oil. MS (ES) 426 (M+Na), 402 (M-H); HPLC shows 99% purity.

Example 109

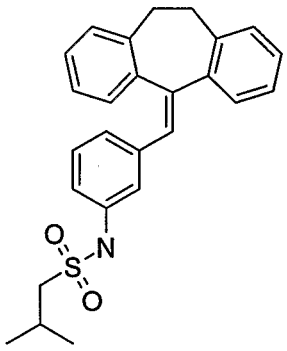
Butane-1-sulfonic acid [4-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-amide



Following procedures essentially as described in Example 90, 4-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenylamine (100mg, 0.336mmol) and 1-butanesulfonyl chloride (158mg, 1.01mmol) affords 88mg (63%) of the title compound as a yellow oil. MS (ES) 440 (M+Na), 416 (M-H); HPLC shows 98% purity.

Example 110

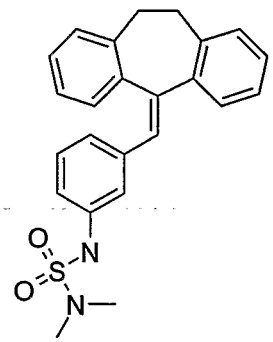
2-Methyl-propane-1-sulfonic acid [3-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-amide



Following procedures essentially as described in Example 90, 3-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenylamine (50mg, 0.168mmol) and 2-methyl-propane-1-sulfonyl chloride (53mg, 0.336mmol) (prepared as described in Quast, H., Synthesis (1974), (7), 489-90) affords 15mg (21%) of the title compound as a brown oil. MS (ES) 435 (M+NH_4), 416 (M-H); HPLC shows 100% purity.

Example 112

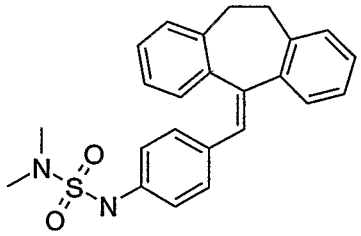
Dimethylsulfamic acid [3-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-amide



Following procedures essentially as described in Example 90, 3-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenylamine (100mg, 0.336mmol) and dimethylsulfamoyl chloride (144mg, 1.01mmol) affords 92mg (68%) of the title compound as a yellow oil. MS (ES) 427 (M+Na), 403 (M-H); HPLC shows 93% purity.

Example 113

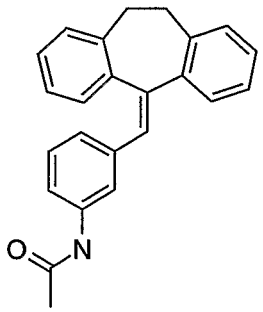
Dimethylsulfamic acid [4-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-amide



Following procedures essentially as described in Example 90, 4-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenylamine (100mg, 0.336mmol) and dimethylsulfamoyl chloride (144mg, 1.01mmol) affords 83mg (61%) of the title compound as a white solid. MS (ES) 427 (M+Na), 403 (M-H); HPLC shows 87% purity.

Example 114

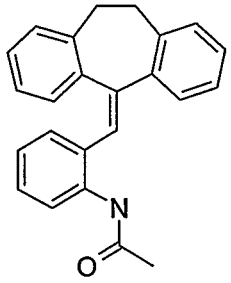
N-[3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-acetamide



Following procedures essentially as described in Example 90, 3-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenylamine and acetyl chloride give the title compound in 25% yield as a white solid. ^{1}H NMR (CDCl3) δ 2.12 (s, 3H), 2.76-3.61 (br m, 4H), 6.71 (d, 1H), 6.75 (s, 1H), 6.96-7.50 (m, 13H); MS (ES) 340 (M+H). HPLC shows 100% purity.

Example 115

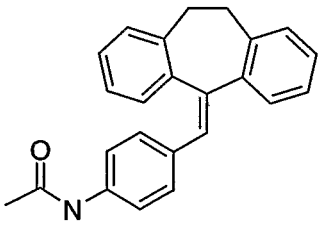
N-[2-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-acetamide



Following procedures essentially as described in Example 90, 2-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenylamine and acetyl chloride give the title compound in 70% yield as a yellow solid, mp 189.7°C. ^{1}H NMR ($CDCl_3$) δ 2.16 (s, 3H), 3.26 (br s, 4H), 6.78 (s, 1H), 6.84-7.50 (m, 11H), 7.82 (d, 1H); MS (ES) 340 (M+H) 338 (M-H). HPLC shows 94% purity.

Example 116

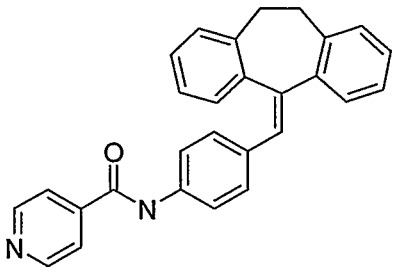
N-[4-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-acetamide



Following procedures essentially as described in Example 90, 4-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenylamine and acetyl chloride give the title compound in 51% yield as an off-white solid, mp 134.8°C. ^{1}H NMR ($CDCl_3$) δ 2.12 (s, 3H), 2.78-3.61 (br m, 4H), 6.75 (s, 1H), 6.95-7.52 (m, 13H); MS (ES) 340 (M+H). HPLC shows 95% purity.

Example 117

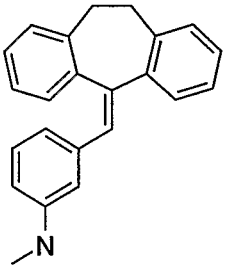
N-[4-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-isonicotinamide



Following procedures essentially as described in Example 90, 4-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenylamine and isonicotinoyl chloride give the title compound in 17% yield as a yellow solid, mp 252.1°C. ^{1}H NMR (DMSO-d_6) δ 2.94 (br s, 2H), 3.87 (br s, 2H), 6.82 (s, 1H), 6.90-7.62 (m, 12H), 7.83 (d, 2H), 8.79 (d, 2H), 10.47 (s, 1H); MS (ES) 403 (M+H), 401 (M-H). HPLC shows 93% purity.

Example 118

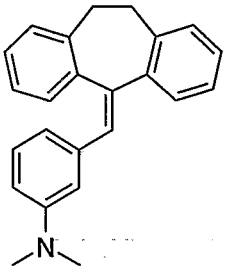
[3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methyl-amine



and

Example 119

[3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-dimethyl-amine



Using a procedure described in Syn. Comm. 1129-1135 (1991), dissolve 3-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenylamine (100mg, 0.336mmol) in toluene (5mL) and add $(Bu)_4NBr$ (2mg, 0.006mmol), K_2CO_3 (46mg, 0.336), and NaOH

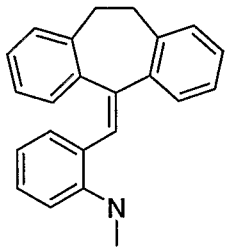
(54mg, 1.34mmol). Stir for 1 h at 35°C, and then add Me_2SO_4 (33L, 44mg, 0.353mmol). Stir for 2 h, then warm up to 55°C. Stir overnight, then add 20□L Me_2SO_4 (26mg, 0.211mmol). Stir at 55°C for 6 h, then cool to room temperature. Dilute reaction with H_2O and ethyl acetate. Separate layers and extract aqueous layer with ethyl acetate. Combine organics, dry ($MgSO_4$), and concentrate to an oil containing the two title compounds. Separation and purification of the title compounds is effected via silica gel chromatography (1:19 ethyl acetate:hexanes).

[3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methyl-amine (Example 118) is obtained in 17% yield (18mg) as a colorless oil. ^1H NMR ($CDCl_3$) δ 2.59 (s, 3H), 2.70-3.65 (br m, 5H), 6.26 (s, 1H), 6.40 (d, 1H), 6.46 (d, 1H), 6.74 (s, 1H), 6.97-7.53 (m, 9H); MS (ES) 312 (M+H). HPLC shows 99% purity.

[3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-dimethyl-amine (Example 119) is obtained in 14% yield (15mg) as a colorless oil. ^1H NMR ($CDCl_3$) δ 2.62 (s, 6H), 2.68-3.58 (br m, 4H), 6.33 (s, 1H), 6.44 (m, 2H), 6.67 (s, 1H), 6.95-7.44 (m, 9H); MS (ES) 326 (M+H). HPLC shows 98% purity.

Example 120

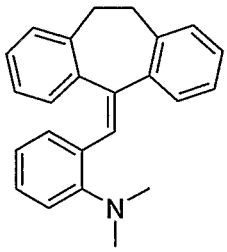
[2-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methyl-amine



and

Example 121

[2-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-dimethyl-amine



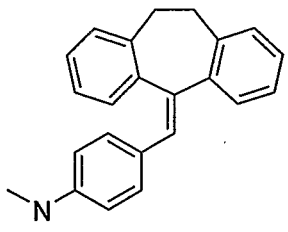
Following procedures essentially as described in Examples 118 and 119, 2-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenylamine gives the title compounds.

[2-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methyl-amine (Example 85) is obtained in 21% yield as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 2.91 (s, 3H), 3.26 (br s, 4H), 3.94 (br s, 1H), 6.47 (t, 1H), 6.62 (d, 1H), 6.70 (s, 1H), 6.71 (d, 1H), 6.86-7.51 (m, 9H); MS (ES) 312 (M+H). HPLC shows 98% purity.

[2-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-dimethyl-amine (Example 86) is obtained in 16% yield as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 2.96 (s, 6H), 3.24 (br s, 4H), 6.66 (m, 2H), 6.94-7.28 (m, 10H), 7.57 (d, 1H); MS (ES) 326 (M+H). HPLC shows 96% purity.

Example 122

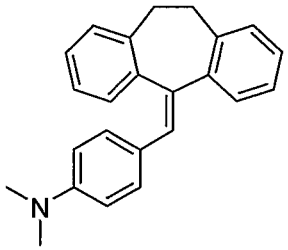
[4-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methyl-amine



and

Example 123

[4-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-dimethyl-amine



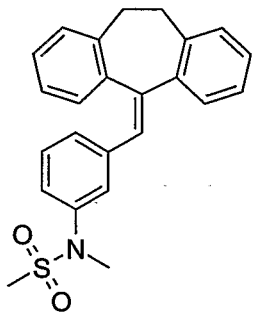
Following procedures essentially as described in Examples 118 and 119, 4-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenylamine gives the title compounds.

[4-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methyl-amine (Example 122) is obtained in 47% yield as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 2.66-3.55 (br m, 4H), 2.72 (s, 3H), 4.60 (s, 1H), 6.33 (d, 2H), 6.61 (s, 1H), 6.80 (d, 2H), 6.96-7.43 (m, 8H); MS (ES) 312 (M+H). HPLC shows 98% purity.

[4-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-dimethyl-amine(Example 123) is obtained in 2% yield as a white solid. ^{1}H NMR ($CDCl_3$) δ 2.71-3.65 (br m, 4H), 2.90 (s, 6H), 6.51 (d, 2H), 6.69 (s, 1H), 6.92 (d, 2H), 7.04-7.50 (m, 8H); MS (ES) 326 (M+H). HPLC shows 99% purity.

Example 124

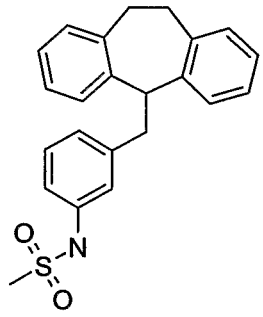
N-[3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-N-methyl-methanesulfonamide



Dissolve N-[3-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methanesulfonamide (100mg, 0.265mmol) in DMF (4mL) and add NaH (13mg of a 60% suspension in mineral oil, 0.318mmol). Stir at room temperature for 50min, then add MeI (33□L, 75mg, 0.530mmol). Stir at room temp for 1h. Dilute reaction mixture with H2O and ethyl acetate. Separate layers, and wash organics with H_2O. Dry organics ($MgSO_4$) and concentrate to 101mg (100%) of a pale yellow solid, mp 124.2°C. ^{1}H NMR ($CDCl_3$) δ 2.53 (s, 3H), 2.72-3.54 (br m, 4H), 6.74 (s, 1H), 6.78 (s, 1H), 6.91-7.43 (m, 11H); MS (ES) 412 (M+Na). HPLC shows 97% purity.

Example 125

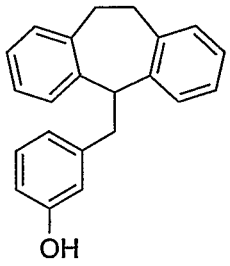
N-[3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylmethyl)-phenyl]-methanesulfonamide



Dissolve N-[3-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methanesulfonamide (100mg, 0.265) in ethanol (25mL) and add 10% Pd/C (56mg). Pressurize to 60psi with H_2 and shake overnight at room temperature. Filter reaction through a pad of Celite and concentrate filtrate to 54mg (54%) of white foam, mp 149.0°C. ^{1}H NMR ($CDCl_3$) δ 2.70 (s, 3H), 2.98 (br q, 2H), 3.28 (d, 2H), 3.40 (br q, 2H), 4.11 (br s, 1H), 6.16 (s, 1H), 6.58 (s, 1H), 6.82-7.20 (m, 11H); MS (ES) 395 (M+Na), 376 (M-H). HPLC shows 94% purity.

Example 126

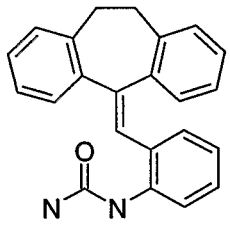
3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylmethyl)-phenol



Following procedures similar to those as described in Example 125, 3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenol and a H_2 balloon gave the title compound in 64% yield as a white solid, mp 76.6°C. ^1H NMR ($CDCl_3$) δ 3.06 (br q, 2H), 3.33 (d, 2H), 3.47 (br q, 2H), 4.2 (br s, 1H), 4.74 (s, 1H), 6.40 (s, 1H), 6.39 (m, 2H), 6.96-7.17 (m, 9H); MS (ES) 299 (M-H). HPLC shows 93% purity.

Example 127

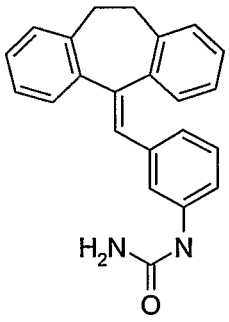
[2-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-urea



According to the procedure of F. Kurzer, Org. Syn. Coll. Vol (IV) 49 (1963), mix 2-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenylamine ((133mg, 0.54mmol) with HOAc (4mL) and water (2mL). Dissolve sodium cyanate (80mg, 1.2mmol) in water (1mL) and add this solution to the amine derivative. Stir the reaction at room temperature for 2 h. and then pour into water (100mL). Extract the title compound into EtOAc, dry ($MgSO_4$) and concentrate to give 240mg crude product. Purify on silica gel using EtOAc/hexane to give 150mg (48%) product as a colorless oil. MS (ES) 341 (M+1), 339 (M-1). HPLC shows 96.6% purity.

Example 128

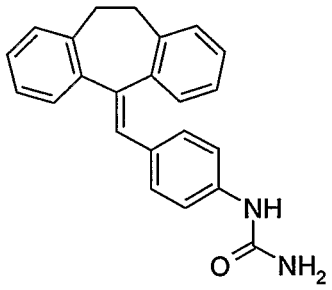
[3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-urea



Following procedures essentially as described in Example 127 and using 3-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenylamine (200mg, 0.67mmol) provides the title compound in 66% yield as a colorless oil. MS (ES) 341 (M+1), 339 (M-1). HPLC shows 100% purity.

Example 129

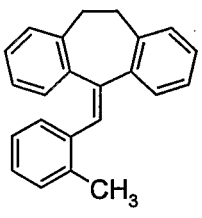
[4-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-urea



Following procedures essentially as described in Example 127 and using 4-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenylamine (143mg, 0.58mmol) provides the title compound in 41% yield as a colorless oil. MS (ES) 341 (M+1), 339 (M-1). HPLC shows 100% purity.

Example 130

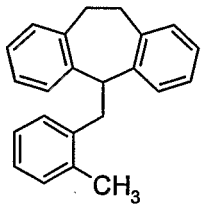
5-(2-Methyl-benzylidene)-10,11-dihydro-5H-dibenzo [a,d]cycloheptene



Combine 5-bromomethylene-10,11-dihydro-5H-dibenzo [a,d] cycloheptene (0.5 g, 1.75 mmol) and o-tolylboronic acid (0.238 g, 1.75 mmol) using procedures essentially as described in Example 219, below. Pass through a plug of silica gel equilibrated with hexanes. Concentrate the filtrate to give the title product: MS (m/e) 296 (M+); Analysis for $C_{23}H_{20}$: Calcd: C, 93.19 H, 6.80. Found: C, 93.42 H, 6.79.

Example 131

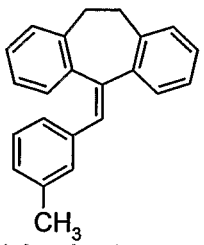
5-(2-Methyl-benzyl)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene



Add the 5-(2-methyl-benzylidene)-10,11-dihydro-5H-dibenzo [a,d]cycloheptene (0.19 g, 0.64 mmol) to a mixture of 10% Pd/C (0.075 g) suspended in absolute ethanol (4.0 mL) and ethyl acetate (2.0 mL) and hydrogenate under a balloon of hydrogen at room temperature and pressure. Stir for 17 h, remove the catalyst via filtration through a pad of Celite, evaporate the filtrate and pass through a plug of silica gel equilibrated with hexanes. Concentrate the filtrate to give the title product: MS (m/e) 298 (M+). Analysis for $C_{23}H_{22}$: Calcd: C, 91.99 H, 7.39. Found: C, 91.95 H, 7.39.

Example 132

5-(3-Methyl-benzylidene)-10,11-dihydro-5H-dibenzo [a,d]cycloheptene

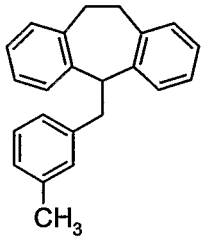


Combine 5-bromomethylene-10,11-dihydro-5H-dibenzo [a,d] cycloheptene (0.5 g, 1.75 mmol) and m-tolylboronic acid (0.238 g, 1.75 mmol) using procedures essentially as described in Example 219, below. Pass through a plug of silica gel equilibrated with

hexanes. Concentrate the filtrate to give the title product: MS (m/e): 296 (M+); HPLC (ISO80-10M)) t=17.78min (95%).

Example 133

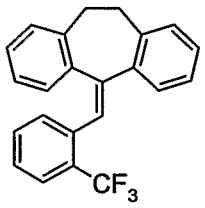
5-(3-Methyl-benzyl)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene



Add 5-(3-methyl-benzylidene)-10,11-dihydro-5H-dibenzo [a,d]cycloheptene (0.18 g, 0.61 mmol), to a mixture of 10% Pd/C (0.045 g) suspended in absolute ethanol (4.0 mL) and ethyl acetate (2.0 mL) and hydrogenate under a balloon of hydrogen at room temperature and pressure. Stir for 17 h, remove the catalyst via filtration through a pad of Celite. Evaporate the filtrate and pass through a plug of silica gel equilibrated with hexanes. Concentrated the filtrate to give the title product. MS (m/e): 298 (M+). HPLC (ISO80-10M) t=11.00 (98%).

Example 134

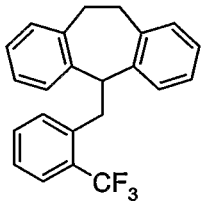
5-(2-Trifluoromethyl-benzylidene)-10,11-dihydro-5H-dibenzo [a,d]cycloheptene



Combine 5-bromomethylene-10,11-dihydro-5H-dibenzo [a,d] cycloheptene (0.5 g, 1.75 mmol) and 2-(trifluoromethyl)phenyl boronic acid (0.33 g, 1.75 mmol) using procedures essentially as described in Example 219, below. Pass through a plug of silica gel equilibrated with hexanes. Concentrate the filtrate to give the title product. Analysis for $C_{23}H_{17}F_3$: Calcd: C, 78.84 H, 4.89; Found: C, 78.65 H, 4.96. HPLC (ISO80-10M)) t=16.67min (99%).

Example 135

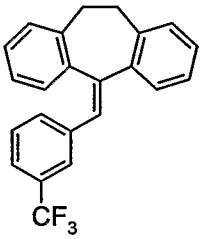
5-(2-Trifluoromethyl-benzyl)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene



Add 5-(2-trifluoromethyl-benzylidene)-10,11-dihydro-5H-dibenzo [a,d]cycloheptene (0.16 g, 0.45 mmol) to a mixture of 10% Pd/C (0.075 g) suspended in absolute ethanol (4.0 mL) and ethyl acetate (2.0 mL) and hydrogenate under a balloon of hydrogen at room temperature and pressure. Stir for 17 h, remove the catalyst via filtration through a pad of Celite. Evaporate the filtrate and pass through a plug of silica gel equilibrated with hexanes. Concentrated the filtrate to give the title product. MS (m/e): 352 (M+). Analysis for $C_{23}H_{19}F_3$: Calcd: C, 78.39 H, 5.43. Found: C, 78.84 H, 5.11.

Example 136

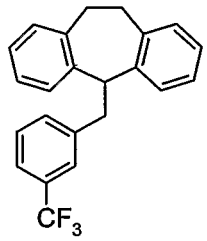
5-(3-Trifluoromethyl-benzylidene)-10,11-dihydro-5H-dibenzo [a,d]cycloheptene



Combine 5-bromomethylene-10,11-dihydro-5H-dibenzo [a,d] cycloheptene (0.5 g, 1.75 mmol) and 3-(trifluoromethyl)phenyl boronic acid (0.33 g, 1.75 mmol) using procedures essentially as described in Example 219, below. Pass through a plug of silica gel equilibrated with hexanes. Concentrate the filtrate to give the title product. Analysis for $C_{23}H_{17}F_3$: Calcd: C, 78.84 H, 4.89; Found: C, 79.03 H, 5.03. HPLC (ISO80-10M)) t=16.30min (98%).

Example 137

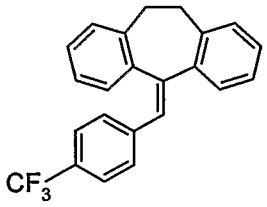
5-(3-Trifluoromethyl-benzyl)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene



Add 5-(3-trifluoromethyl-benzylidene)-10,11-dihydro-5H-dibenzo [a,d]cycloheptene (0.145 g, 0.41 mmol), to a mixture of 10% Pd/C (0.04 g) suspended in absolute ethanol (4.0 mL) and ethyl acetate (4.0 mL) and hydrogenate under a balloon of hydrogen at room temperature and pressure. Stir for 17 h, remove the catalyst via filtration through a pad of Celite. Evaporate the filtrate and pass through a plug of silica gel equilibrated with hexanes. Concentrated the filtrate to give the title product. MS (m/e): 352 (M+); GC retention time=7.11 min.

Example 138

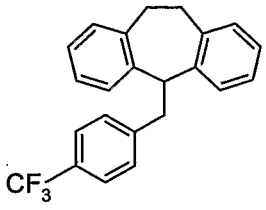
5-(4-Trifluoromethyl-benzylidene)-10,11-dihydro-5H-dibenzo [a,d]cycloheptene



Combine 5-bromomethylene-10,11-dihydro-5H-dibenzo [a,d] cycloheptene (0.5 g, 1.75 mmol) and 4-(trifluoromethyl)phenyl boronic acid (0.33 g, 1.75 mmol using procedures essentially as described in Example 219, below. Pass through a plug of silica gel equilibrated with hexanes. Concentrate the filtrate to give the title product: MS (m/e): 350 (M+). HPLC (ISO80-10M)) t=17.32 min.

Example 139

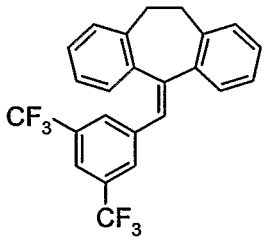
5-(4-Trifluoromethyl-benzyl)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene



Add the 5-(4-trifluoromethyl-benzylidene)-10,11-dihydro-5H-dibenzo [a,d]cycloheptene (0.14 g, 0.45 mmol), to a mixture of 10% Pd/C (0.05 g) suspended in absolute ethanol (4.0 mL) and ethyl acetate (4.0 mL) and hydrogenate under a balloon of hydrogen at room temperature and pressure. Stir for 17 h, remove the catalyst via filtration through a pad of Celite. Evaporate the filtrate and pass through a plug of silica gel equilibrated with hexanes. Concentrate the filtrate to gives the title product. MS (m/e): 352 (M+); Analysis for $C_{23}H_{19}F_3$: Calcd: C, 78.39 H, 5.43. Found: C, 78.70 H, 5.16.

Example 140

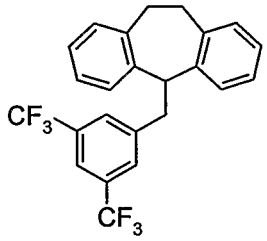
5-(3,5-Bis-trifluoromethyl-benzylidene)-10,11-dihydro-5H-dibenzo [a,d]cycloheptene



Combine 5-bromomethylene-10,11-dihydro-5H-dibenzo [a,d] cycloheptene (0.5 g, 1.75 mmol) and 3,5-bis (trifluoromethyl)phenyl boronic acid (0.449 g, 1.75 mmol) using procedures essentially as described in Example 219, below. Pass through a plug of silica gel equilibrated with hexanes. Concentrate the filtrate to give the title product. Analysis for $C_{24}H_{16}F_6$: Calcd: C, 68.90 H, 3.85. Found: C, 68.64 H, 3.80. HPLC (ISO80-10M)) t=5.64min (98%).

Example 141

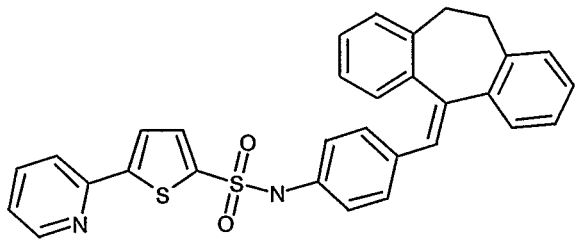
5-(3,5-Bis-Trifluoromethyl-benzyl)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene



Add 5-(3,5-bis-trifluoromethyl-benzylidene)-10,11-dihydro-5H-dibenzo [a,d]cycloheptene (0.28 g, 0.67 mmol) to a mixture of 10% Pd/C (0.08 g) suspended in absolute ethanol (4.0 mL) and ethyl acetate (4.0 mL) and hydrogenate under a balloon of hydrogen at room temperature and pressure. Stir for 17 h, remove the catalyst via filtration through a pad of Celite. Evaporate the filtrate and pass through a plug of silica gel equilibrated with hexanes. Concentrate the filtrate to give the title product. MS (m/e): 420 (M+); Analysis for $C_{24}H_{18}F_6$: Calcd: C, 68.56 H, 4.31. Found: C, 68.55 H, 4.01.

Example 142

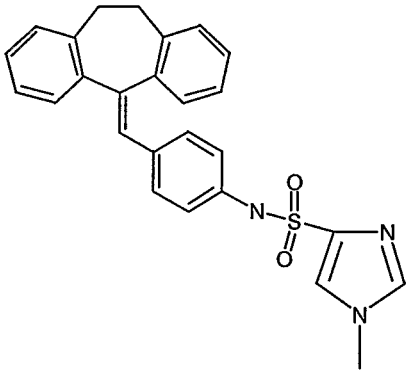
5-Pyridin-2-yl-thiophene-2-sulfonic acid [4-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-amide



Prepared according to procedures essentially as described in Example 90, using 4-(10,11)-dihydro-dibenzo(a,d)cyclohepten-5-ylidene methyl phenylamine (297mg, 1.0mmol) and 5-pyridin-2-yl-thiophene-2-sulfonyl chloride (260mg, 1.0mmol) to give the title compound (HOW MUCH). Purify using column chromatography ethyl acetate/hexane to give 48mg (10%) product. MS (ES) 521 (M+1), 519 (M-1). HPLC shows 97% purity.

Example 143

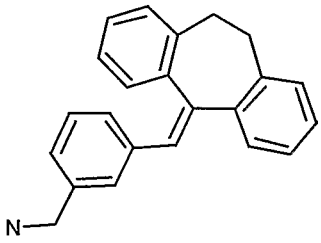
1-Methyl-1H-imidazole-4-sulfonic acid [4-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-amide



Prepared according to procedures essentially as described in Example 90, using 4-(10,11)-dihydro-dibenzo(a,d)cyclohepten-5-ylidene methyl phenylamine (297mg, 1.0mmol) and 1-methyl-1H-imidazole-4-sulfonyl chloride (180mg, 1.0mmol) to give the title compound 44mg (10%) after being purified by mass guided reverse-phase HPLC. MS (ES) 442 (M+1). HPLC shows 97% purity.

Example 144

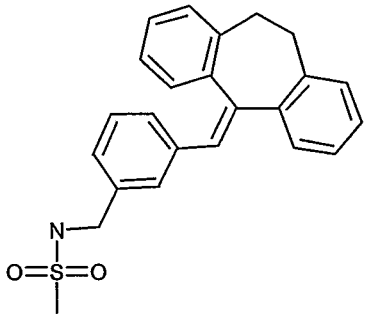
3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-benzylamine



Dissolve 1.0g (3.25mmol) of the corresponding nitrile (prepared as described in Example 81) in diethyl ether (70mL). Add lithium aluminum hydride (250mg, 6.6mmol) and stir at room temperature for 3 h. Quench the reaction by adding 8 drops water, 8 drops 5N NaOH and 16 drops water. Filter the inorganic solids and wash with ether. After drying ($MgSO_4$) and concentration, the title compound was obtained in 98% yield as a colorless oil, MS (ES) 312 (M+1). HPLC shows 98% purity.

Example 145

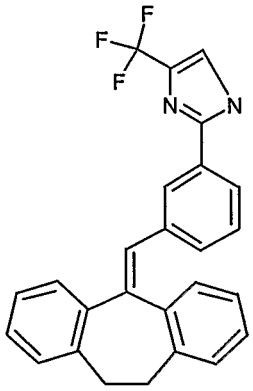
N-[3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-benzyl]-methanesulfonamide



Following procedures essentially as described in Example 90, reaction of the benzylamine (70mg, 0.225mmol) prepared in Example 144 and methanesulfonyl chloride (52□L, 0.68mmol) affords 40mg of the title compound in 46% yield as a colorless oil after purification using column chromatography (30% ethyl acetate/hexane). MS (ES) 388 (M-1). HPLC shows 97% purity.

Example 146

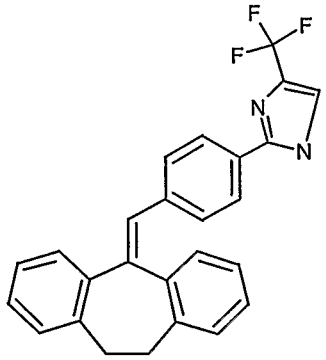
2-[3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-4-trifluoromethyl-1H-imidazole



According to Matthews et al, J. Med. Chem. 33 317 (1990), mix 1,1-dibromo-1',1',1'-trifluoroacetone (216mg, 0.8mmol), NaOAc (112mg, 1.4mmol) and water (2mL). Warm the solution at 60°C for 0.5h. Cool the solution in an ice bath and add 3-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-benzaldehyde(145mg,0.47mmol) in methanol (2mL) and concentrated NH_4OH (2mL) and stir overnight at room temperature. Concentrate and collect the solid. Purify by column chromatography (30% ethyl acetate/hexane) to give 19% title compound. MS (ES) 417 (M+1), 415 (M-1). HPLC shows 86% purity.

Example 147

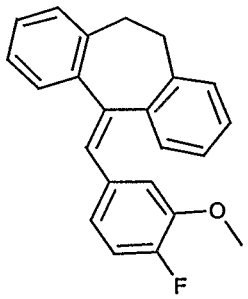
2-[4-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-4-trifluoromethyl-1H-imidazole



Prepare using procedures as described in Example 146 to give the title compound as a pale yellow powder, MS (ES) 417 (M+1), 415 (M-1). HPLC shows 95% purity.

Example 148

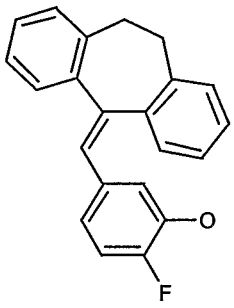
5-(4-Fluoro-3-methoxy-benzylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene



Following procedures essentially as described in Example 28 and using 4-fluoro-3-methoxybenzaldehyde (1.59g, 10.3mmol), dibenzosuberane (1.94g, 10mmol, provides 1.66g of title compound in 49% yield as a light tan oil that slowly crystallized. HPLC shows 93% purity.

Example 149

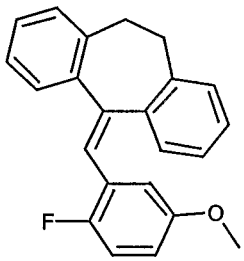
5-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-2-fluoro-phenol



Demethylation of the corresponding methoxy derivative of Example 148 using the procedures as described in Example 57, provides 1.28g (90%) of title compound as a pale tan oil. MS (ES) 315 (M-1). HPLC shows 95% purity.

Example 150

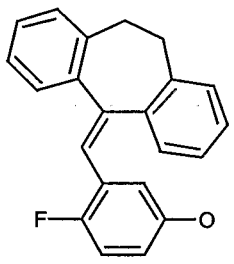
5-(2-Fluoro-5-methoxy-benzylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene



Following procedures essentially as described in Example 28 and using 2-fluoro-5-methoxybenzaldehyde (1.59g, 10.3 mmol) and dibenzosuberane (1.94g, 10 mmol), provides 210mg of title compound as white crystals. mp 110.7°C (hexane). HPLC shows 99% purity.

Example 151

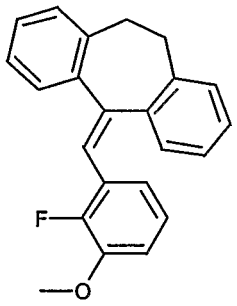
3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-4-fluoro-phenol



Demethylation of the corresponding methoxy derivative of Example 150 using the procedures as described in Example 57, provides 110mg of title compound in 46% yield as a colorless oil. MS (ES) 315 (M-1). HPLC shows 94% purity.

Example 152

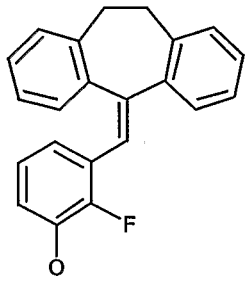
5-(2-Fluoro-3-methoxy-benzylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene



Following procedures essentially as described in Example 28 and using 2-fluoro-3-methoxybenzaldehyde (2.4g, 15.4mmol) and dibenzosuberane (3.0g, 15.4mmol), provides 1.5g of title compound as white crystals. mp 148.9°C. HPLC shows 96% purity.

Example 153

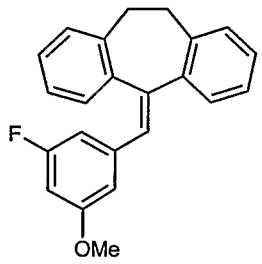
3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-2-fluoro-phenol



Demethylation of the corresponding methoxy derivative of Example 152 using the procedures as described in Example 57, provides 410mg (47%) of title as light tan crystals, mp 143.2°C. MS (ES) 315 (M-1). HPLC shows 94% purity.

Example 154

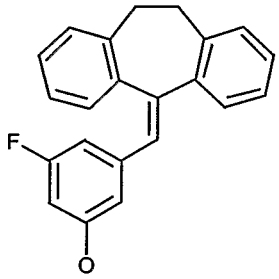
5-(3-Fluoro-5-methoxy-benzylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene



Following procedures essentially as described in Example 219, below, and using 3-fluoro-5-methoxyphenylboronic acid (300mg, 1.76mmol) and 5-bromomethylene-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (450mg, 1.6mmol)provides 275mg of title compound in 52% yield as a pale yellow oil. HPLC shows 97% purity.

Example 155

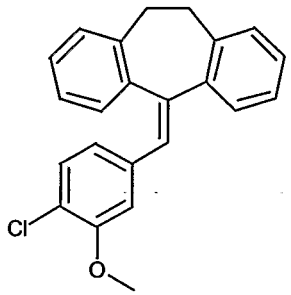
3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-5-fluoro-phenol



Demethylation of the corresponding methoxy derivative of Example 154 using BBr_3 provides the title compound in 62% yield as a colorless, viscous oil. MS (ES) 315(M-1). HPLC shows 94% purity.

Example 156

5-(4-Chloro-3-methoxy-benzylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene

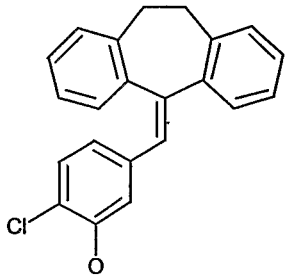


Following procedures essentially as described in Example 219, below, and using 4-chloro-5-methoxyphenylboronic acid (160mg, 0.78mmol) and 5-bromomethylene-10,11-

dihydro-5H-dibenzo[a,d]cycloheptene (222mg, 0.85mmol) provides 80mg of title compound in 23% yield as a colorless oil. HPLC shows 92% purity.

Example 157

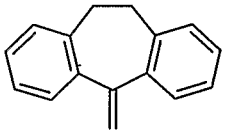
2-Chloro-5-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenol



Demethylation of the corresponding methoxy derivative of Example 154 using BBr_3 provides the title compound in 42% yield as a colorless, oil. MS (ES) 333 (M+1), 331 (M-1).

Preparation 23

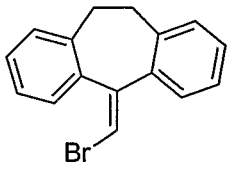
5-Methylene-10,11-dihydro-5H-dibenzo[a,d]cycloheptene



Add methylmagnesium bromide (3M solution in Et_2O, 48.0mL, 144mmol) dropwise to a cooled (0°C) solution of dibenzosuberone (20.0g, 96.03mmol) in THF (140mL) under N_2 (exothermic). Let solution warm up to room temperature and continue stirring for 2h. Cool solution to 0°C and quench with saturated aqueous NH_4Cl (exothermic, emits gas). Extract into ethyl acetate, dry organics ($MgSO_4$) and concentrate in-vacuo. Dissolve residue in 4N HCl/dioxane (40mL) and stir at room temperature overnight. Concentrate and dilute with H_2O. Extract into ethyl acetate, dry organics ($MgSO_4$) and concentrate to a yellow oil. Purify crude product by loading onto a 30g plug of silica gel and eluting with hexanes until eluent shows no UV activity. Combine and concentrate hexane washes to afford 16.72g (84%) of the title compound as a white solid, mp 65.1°C. HPLC shows 98% purity.

Preparation 24

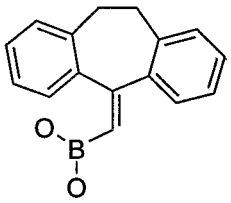
5-Bromomethylene-10,11-dihydro-5H-dibenzo[a,d]cycloheptene



Dissolve 5-methylene-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (10.00g, 48.48mmol) in $CHCl_3$ (125mL) and add 4-(dimethylamino)pyridinium tribromide (19.35g, 53.32mmol). Stir at room temperature for 2.5h and quench with saturated aqueous Na_2SO_3. Separate layers, wash organics with saturated aqueous $NaHCO_3$, then H_2O. The dried organics ($MgSO_4$) and concentrated to a yellow oil. Purify crude product by loading onto a 20g plug of silica gel and eluting with hexanes until eluent shows no UV activity. Combine and concentrate hexane washes to afford 13.01g (94%) of the title compound as a white solid, mp 73.6°C. HPLC shows 99% purity.

Preparation 25

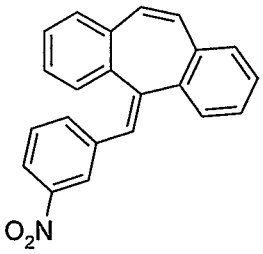
(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidene)-boronic acid



Add t-BuLi (1.7M in pentane, 36.3mL, 61.71mmol) portionwise (exotherm) to a solution of 5-bromomethylene-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (8.00g, 20.05mmol) in dry THF (150mL) at –78°C under N_2. Stir at –78°C for 45min and add trimethyl borate (8.75g, 84.15mmol). Warm to room temperature and stir for 30min. Concentrate reaction mixture to a pale yellow gritty oil, add ethylene glycol (30mL) and toluene (100mL), and reflux overnight. Cool to room temperature, separate layers and extract ethylene glycol layer with toluene. Combine and concentrate toluene layers to a yellow oil. Purify by silica gel chromatography (40g) eluting with 3:1:0.02 ethyl acetate:hexanes:triethylamine to afford 2.68g (35%) of the title compound as a white foam. MS (ES) 249 (M-H); HPLC shows 91% purity.

Example 158

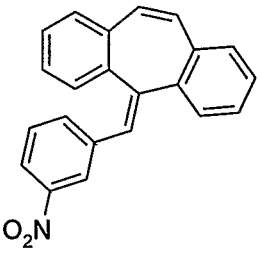
5-(3-Nitro-benzylidene)-5H-dibenzo[a,d]cycloheptene



Dissolve the phosphonate [generate from heating 3-nitobenzyl bromide (786mg, 3.6 mmol) in triethyl phosphite (0.62ml, 3.6 mmol) at 80°C for 12h.] in DMF (10ml) at RT under nitrogen atmosphere. To this mixture, add sodium hydride (87.3mg, 3.6mmol) and stir for 1h. Add dibenzosuberenone (250mg, 1.2mmol) in 2ml of DMF and stir for 18h. Partition the residue between 1N HCl/EtOAc. Dry ($MgSO_4$) and concentrate to give 121.6mg of a pale yellow oil. ^1H NMR ($CDCl_3$) δ7.84 (dt, 1H), 7.72 (t, 1H), 7.45 (d, 1H), 7.4-7.3 (m, 2H), 7.3-7.2 (m, 2H), 7.2-7.0 (m, 4H), 7.0-6.85 (m, 3H), 6.42 (s, 1H).

Example 159

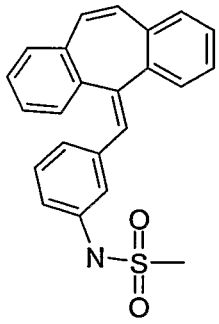
3-Dibenzo[a,d]cyclohepten-5-ylidenemethyl-phenylamine



Dissolve 5-(3-nitro-benzylidene)-5H-dibenzo[a,d]cycloheptene (120mg, 0.4 mmol) in absolute ethanol. Add (10ml tin chloride (416mg, 2.0 mmol) and heat to reflux. After 18 h, cool and partition between 1N NaOH/EtOAc. Dry the organic layers ($MgSO_4$) and concentrate to give 92.3mg of a white solid. MS [EI+] 296 (M+H).

Example 160

N-(3-Dibenzo[a,d]cyclohepten-5-ylidenemethyl-phenyl)-methanesulfonamide Dissolve 3-dibenzo[a,d]cyclohepten-5-ylidenemethyl-phenylamine (90mg, 0.3 mmol) in 5mL of

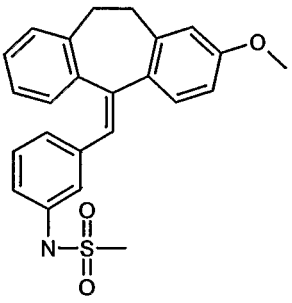


methylene chloride under a nitrogen atmosphere. Add pyridine (0.05mL, 0.6 mmol) then methanesulfonyl chloride (0.03mL, 0.3mmol). Stir at room temperature for 12h, then partition between water/methylene chloride and dry with $MgSO_4$. Concentrate to give 65.9mg of a white solid. ^1H NMR ($CDCl_3$) δ7.84 (d, 1H), 7.72 (s, 1H), 7.45 (d, 1H), 7.4-7.3 (m, 2H), 7.3-7.2 (m, 2H), 7.2-7.0 (m, 4H), 7.0-6.85 (m, 2H), 6.61 (m, 1H), 6.50 (s, 1H), 2.85 (s, 3H). MS [EI+] 374 $(M+H)^+$, 391 (M+18).

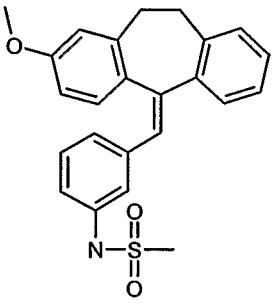
Section 2 (derivatives of Formula I having substitution on both the "C" ring and furtheron the "A" and/or "B" rings.)

Example 161

N-[3-(2-Methoxy-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methanesulfonamide (E-isomer and Z-isomer)



E-isomer



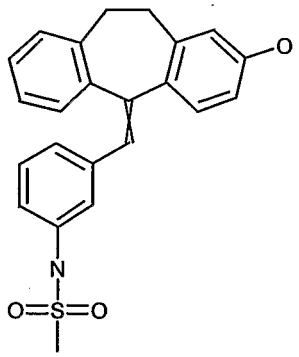
Z-isomer

Following the procedures essentially as described in Example 219, below, and using 5-bromomethylene-2-methoxy-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (E/Z mixture,700mg, 2.22mmol) (Prepared from 2-methoxydibenzosuberone as described in Preparations 23 and 24) with 3-methanesulfonylaminophenylboronic acid (522mg, 2.4mmol) to give 485mg (54%) of an E/Z mixture of isomers. Use UV guided reverse-

phase HPLC with 1/1 acetonitrile/0.1% aqueous trifluoroacetic acid to separate the isomers. The E isomer comes off the column first. MS (ES) 406 (M+1), 404 (M-1). HPLC purity is 99.6%. The second isomer off the column is the Z-isomer, MS (ES) 406 (M+1), 404 (M-1). HPLC purity is 98%.

Example 162

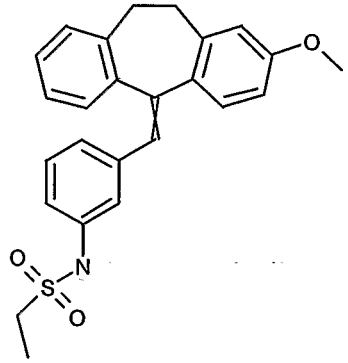
N-[3-(2-Hydroxy-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methanesulfonamide (E/Z mixture)



Demethylate the corresponding methoxy mixture of Example 161 using BBr_3 to give the title compound in 69% yield. MS (ES) 392 (M+1), 390 (M-1). HPLC shows 48% of the faster eluting isomer and 45% of the slower isomer.

Example 163

Ethanesulfonic acid [3-(2-methoxy-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-amide (E/Z mixture)

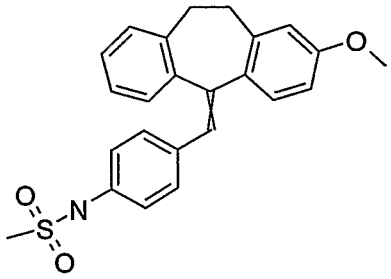


Following the procedures essentially as described in Example 219, below, and using 5-bromomethylene-2-methoxy-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (E/Z mixture,

97mg, 0.31mmol) with 3-ethanesulfonylaminophenylboronic acid (78mg, 0.34mmol) to give 57mg (44%) of an E/Z mixture of the title compound. MS (ES) 420 (M+1) weak, 418 (M-1). HPLC shows 45% of the E isomer and 53% of the Z isomer.

Example 165

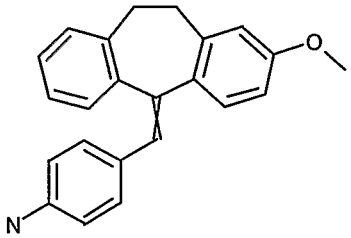
N-[2-(2-Methoxy-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methanesulfonamide (E/Z mixture)



Following the procedures essentially as described in Example 219, below, and using 5-bromomethylene-2-methoxy-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (E/Z mixture,100mg, 0.32mmol) with 4-methanesulfonylaminophenylboronic acid (75mg, 0.35mmol) to give 35mg (27%) of an E/Z mixture of the title compound. MS (ES) 406 (M+1), 404 (M-1). HPLC shows 53% of the E isomer and 44% of the Z isomer.

Example 166

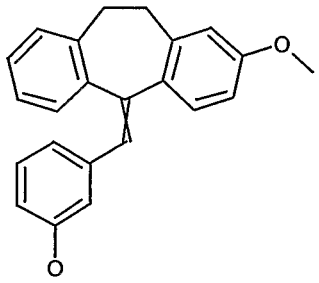
4-(2-Methoxy-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenylamine (E/Z mixture)



Isolate the title compound, which is derived from an impurity in the starting 4-methanesulfonylaminophenylboronic acid in the above reaction. MS (ES) 328 (M+1). HPLC shows 41% of the faster eluting isomer and 58% of the slower isomer.

Example 167

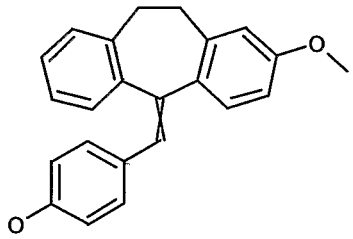
3-(2-Methoxy-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenol



Following the procedures essentially as described in Example 219, below, and using 5-bromomethylene-2-methoxy-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (E/Z mixture,100mg, 0.32mmol) with 3-hydroxyphenylboronic acid (48mg, 0.35mmol) to give 43mg (41%) of an E/Z mixture of the title compound as a tan foam. MS (ES) 327 (M-1). HPLC shows 42% of the E isomer and 55% of the Z isomer.

Example 168

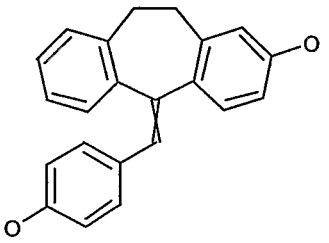
4-(2-Methoxy-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenol (E/Z mixture)



Following the procedures essentially as described in Example 219, below, and using 5-bromomethylene-2-methoxy-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (E/Z mixture,220mg, 0.7mmol) with 4-hydroxyphenylboronic acid (110mg, 0.8mmol) to give 117mg (51%) of an E/Z mixture of the title compound as a tan foam. MS (ES) 327 (M-1). HPLC shows 40% of the E isomer and 54% of the Z isomer.

Example 169

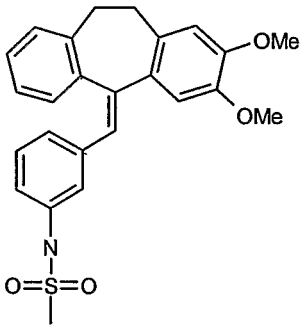
5-(4-Hydroxy-benzylidene)-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-2-ol (E/Z mixture)



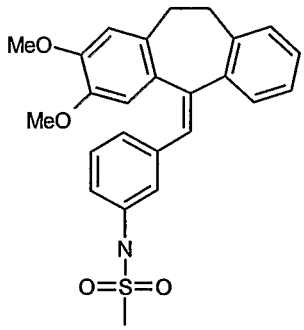
Demethylate the corresponding methoxy derivative mixture from Example 168 using BBr_3 to give the title compound in 80% yield. MS (ES) 315 (M+1), 313 (M-1). HPLC shows 44% of the faster eluting isomer and 52% of the slower isomer.

Example 170 (a) and (b)

N-[3-(2,3-Dimethoxy-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methanesulfonamide (E-isomer) and N-[3-(2,3-Dimethoxy-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methanesulfonamide (Z-isomer)



E-isomer

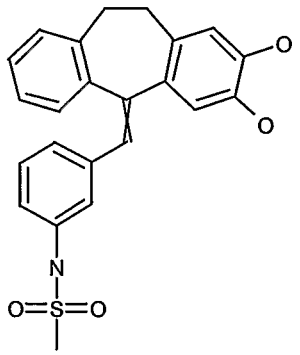


Z-isomer

Following procedures essentially as described in Example 239, below, the title compounds are prepared from the corresponding dimethoxydibenzosuberone and m-bromobenzylmagnesium bromide. These bromo derivatives are converted to the amino derivatives using procedures described in Example 86. The intermediate E and Z amines are reacted with methanesulfonyl chloride as described in Procedure M. The title compounds are purified on silica gel using 33% ethyl acetate/hexane to give 170mg E/Z mixture. Use column chromatography (20% ethyl acetate/hexane) to give 50mg of the E isomer (Example 170(a)); MS (ES) 434 (M-1), HPLC 92% and 35mg of the Z isomer (Example 170(b)); MS (ES) 434 (M-1), HPLC 95%.

Example 171

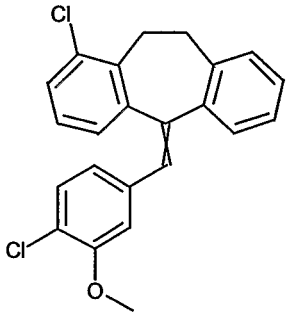
N-[3-(2,3-Dihydroxy-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methanesulfonamide (E/Z mixture)



Demethylate N-[3-(2,3-dimethoxy-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methanesulfonamide (60mg, 0.14mmol) form Example 170 using BBr_3 to give 53mg (93%) the title compound as a tan semi-solid. MS (ES) 408 M+1), 406 (M-1). HPLC shows 47% faster eluting isomer and 53% slower isomer.

Example 172

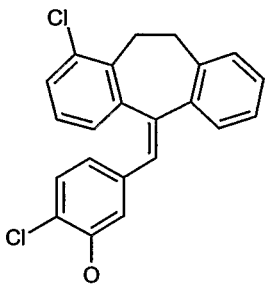
1-Chloro-5-(4-chloro-3-methoxy-benzylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (mixture of E/Z isomers)



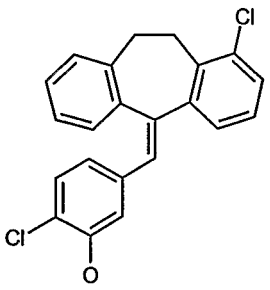
Following procedures essentially as described in Example 219, below, and using 4-chloro-3-methoxyphenylboronic acid (160mg,0.85mmol) with 5-bromomethylene-1-chloro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (249mg, 0.78mmol) to give 440mg crude product. Purify by chromatography to give 210mg (71%) colorless oil. HPLC (ISO90-10M) shows 51% at t=7.62min and 45% at t=9.86min.

Example 173

2-Chloro-5-(1-chloro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenol (Z-isomer, LY2054560, ER0-A01846-65B) and 2-Chloro-5-(1-chloro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenol (E-isomer)



Z isomer

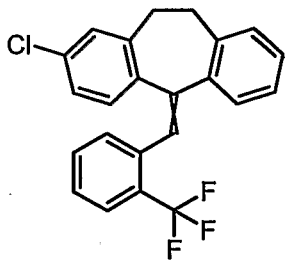


E isomer

Demethylate 1-chloro-5-(4-chloro-3-methoxy-benzylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (mixture of E/Z isomers) (215mg, 0.56mmol) from Example 172 using BBr_3. Separate the isomers using a chromatatron (2% EtOAc/hexane) to give 47mg Z isomer. MS (ES) 365 (M-1). HPLC shows 98% purity. The lower spot is the E isomer, 33mg. MS (ES) 365 (M-1). HPLC shows 96% purity.

Example 174

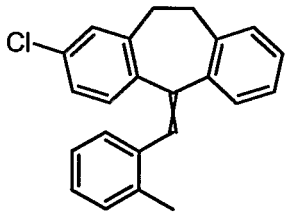
2-Chloro-5-(2-trifluoromethyl-benzylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene



Following procedures essentially as described in Example 219, below, and using 2-(trifluoromethyl)phenylboronic acid (59mg, 0.31mmol) and 5-bromomethylene-2-chloro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (91mg, 0.28mmol) provides 97mg (90%) title compound. GC/MS data: retention times in minutes (MS data for $M^{+\cdot}$ ion): 18.19 (384), 18.38(384)Mass Spec (EI+) 384

Example 175

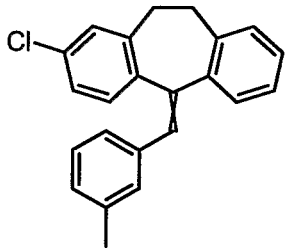
2-Chloro-5-(2-methyl-benzylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene



Following procedures essentially as described in Example 219, below, and using o-tolylboronic acid (91mg, 0.67mmol) and 5-bromomethylene-2-chloro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (178mg, 0.56mmol) provides the title compound. GC/MS data: retention times in minutes (MS data for $M^{+\cdot}$ ion): 19.62 (330), 19.83(330) Mass Spec (EI+) 330.

Example 177

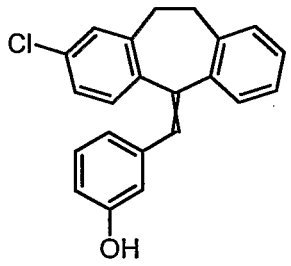
2-Chloro-5-(3-methyl-benzylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene



Following procedures essentially as described in Example 219, below, and using m-tolylboronic acid (61mg, 0.45mmol) and 5-bromomethylene-2-chloro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (119mg, 0.37mmol) provides the title compound.
GC/MS data: retention times in minutes (MS data for $M^{+\cdot}$ ion): 19.60 (330), 19.95(330) Mass Spec (EI+) 330.

Example 178

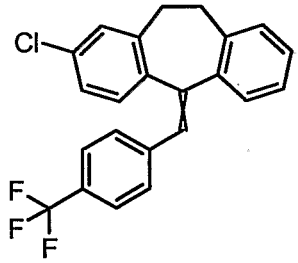
3-(2-Chloro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenol



Following procedures essentially as described in Example 219, below, and using (3-hydroxyphenyl)boronic acid (108mg, 0.78mmol) and 5-bromomethylene-2-chloro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (209mg, 0.65mmol) provides the title compound. Mass Spec (EI+) 332.

Example 179

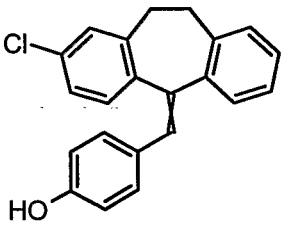
2-Chloro-5-(4-trifluoromethyl-benzylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene



Following procedures essentially as described in Example 219, below, and using 4-(trifluoromethyl)phenylboronic acid (114mg, 0.60mmol) and 5-bromomethylene-2-chloro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (156mg, 0.48mmol) provides the title compound. GC/MS data: retention times in minutes (MS data for $M^{+\cdot}$ ion): 18.52 (384), 18.78(384)Mass Spec (EI+) 384.

Example 180

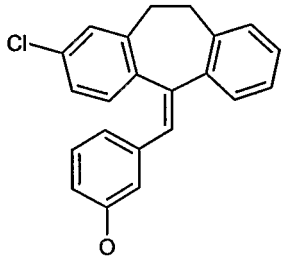
4-(2-Chloro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenol



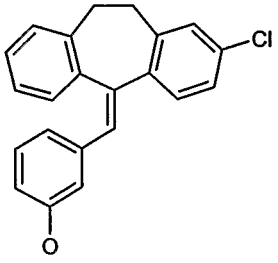
Following procedures essentially as described in Example 219, below, and using (4-hydroxyphenyl)boronic acid (55mg, 0.40mmol) and 5-bromomethylene-2-chloro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (103mg, 0.32mmol) provides the title compound. Mass Spec (EI+) 332.

Example 181

3-(2-Chloro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenol (Z-isomer) and 3-(2-Chloro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenol (E-isomer)



Z isomer

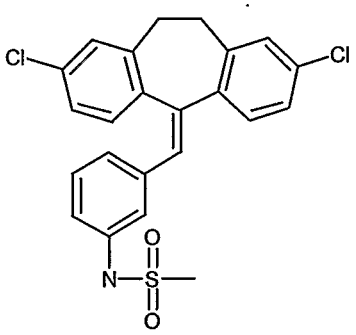


E isomer

Following procedures essentially as described in Example 219, below, and using 3-hydroxyphenylboronic acid (99mg, 0.72mmol) and 5-bromomethylene-10,11-dihydro-5H-2-chlorodibenzo[a,d]cycloheptene (209mg, 0.65mmol) (prepared from 2-chlorodibenzosuberone using procedures as described in Preparations 23 and 24) provides 90mg Z isomer, MS (ES) 332, 334 (M+1), 331, 333 (M-1). HPLC shows 95% purity. The E isomer (51mg) was isolated as a colorless oil, MS (ES) 332, 334 (M+1), 331, 333 (M-1). HPLC shows 99% purity.

Example 182

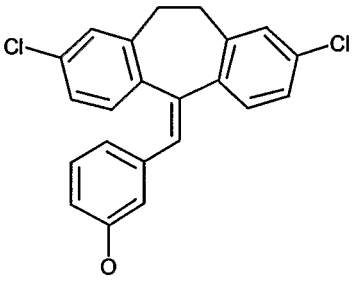
N-[3-(2,8-Dichloro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methanesulfonamide



Following procedures essentially as described in Example 219, below, and using 3-methanesulfonamidophenylboronic acid (154mg, 0.71mmol) and 5-bromomethylene-10,11-dihydro-5H-2,8-dichlorodibenzo[a,d]cycloheptene (230mg, 0.65mmol) (prepared from 2,8-dichlorodibenzosuberone (M. R. Pavia et al, J. Med. Chem. (35) 4238-4248 (1992)) using procedures as described in Preparations 23 and 24) provides 164mg (57%) title compound as a white solid, mp 182.4°C. MS (ES) 444 (M+1), 442 (M-1. HPLC shows 97% purity.

Example 183

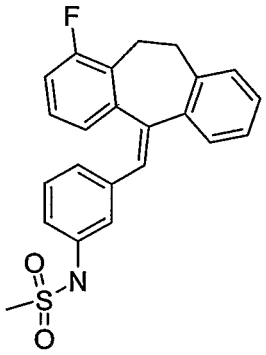
3-(2,8-Dichloro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenol



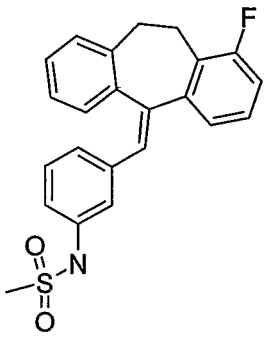
Following procedures essentially as described in Example 219, below, and using 3-hydroxyphenylboronic acid (98mg, 0.71mmol) and 5-bromomethylene-10,11-dihydro-5H-2,8-dichlorodibenzo[a,d]cycloheptene (230mg, 0.65mmol) (prepared from 2,8-dichlorodibenzosuberone (M. R. Pavia et al, J. Med. Chem. (35) 4238-4248 (1992)) using procedures as described in Preparations 23 and 24) provides 178mg title compound in 75% yield as a pale yellow oil. MS (ES) 365 (M-1). HPLC shows 93% purity.

Example 184

N-[3-(1-Fluoro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methanesulfonamide (Z-isomer) and N-[3-(1-Fluoro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methanesulfonamide (E-isomer)



Z isomer

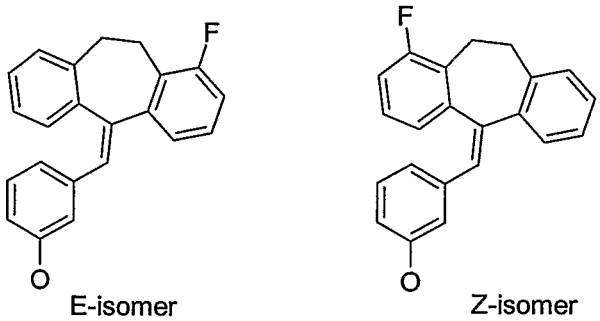


E isomer

Following procedures essentially as described in Example 219, below, and using 3-methanesulfonamidophenylboronic acid (388mg, 1.8mmol) and 5-bromomethylene-1-fluoro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (E/Z mixture,500mg, 1.65mmol) (Prepared from 1-fluorodibenzosuberone (Chem. Abstr. 70 106272a (1969) using procedures as described in Preparations 23 and 24) provides the title compound. Separate the isomers using column chromatography (gradient of 10% EtOAc/hexane to 25% EtOAc/hexane) to give 66mg Z isomer as a white powder, mp 153.5°C, MS (ES) 392 (M-1). HPLC shows 100% purity. Isolate 18mg E isomer as the slower moving spot, MS (ES) 392 (M-1). HPLC shows 97% purity.

Example 185

3-(1-Fluoro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenol (E-isomer) and 3-(1-Fluoro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenol (Z-isomer)

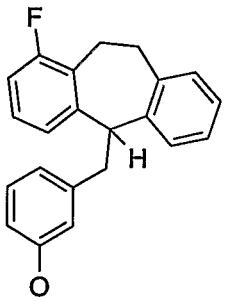


E-isomer Z-isomer

Following procedures essentially as described in Example 219, below, and using 3-hydroxyphenylboronic acid (250mg, 1.8mmol) and 5-bromomethylene-1-fluoro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (E/Z mixture,500mg, 1.65mmol) (Prepared from 1-fluorodibenzosuberone (Chem. Abstr. 70 106272a (1969) using procedures as described in Preparations 23 and 24) provides 750mg crude product of the title compound. Separate the isomers using radial chromatography (hexane→3% EtOAc/hexane) to give 115mg Z-isomer as a pale yellow foam, mp 119.9°C MS (ES) 315 (M-1). HPLC shows >95% purity. The E-isomer is the slower moving material, 69mg yellow foam, mp 158.1°C. MS (ES) 315 (M-1). HPLC shows 99% purity.

Example 186

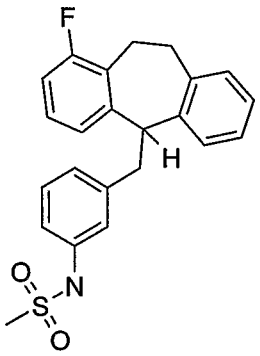
3-(1-Fluoro-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylmethyl)-phenol



Dissolve 3-(1-fluoro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenol (170mg, 0.54mmol) in EtOH (5mL) and add 10% Pd/C (50mg). Stir for 18h under an atmosphere of hydrogen. Filter and concentrate. Purify the crude product using column chromatography (10% EtOAc/hexane → 25% EtOAc/hexane) to give 98mg (57%) product as a colorless oil. MS (ES) 317 (M-1). HPLC shows 99% purity.

Example 187

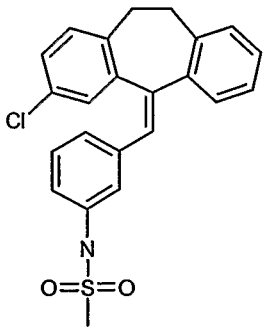
N-[3-(1-Fluoro-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylmethyl)-phenyl]-methanesulfonamide



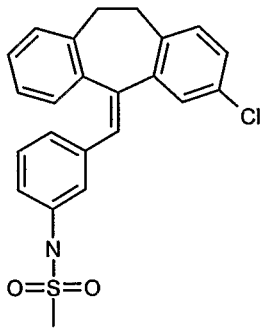
Dissolve 150mg (0.38mmol) N-[3-(1-fluoro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methanesulfonamide in EtOH (5mL) and add 10% Pd/C (50mg). Stir for 18h under an atmosphere of hydrogen. Filter and concentrate. Purify the crude product using column chromatography (10% EtOAc/hexane → 25% EtOAc/hexane) to give 6mg product as a colorless oil. MS (ES) 394 (M-1). HPLC shows 99% purity.

Example 188

N-[3-(3-Chloro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methanesulfonamide (Z-isomer) and N-[3-(3-Chloro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methanesulfonamide (E-isomer)



E-isomer



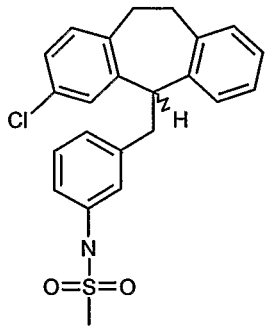
Z-ismoer

Following procedures essentially as described in Example 219, below, and using 3-methanesulfonamidophenyl boronic acid (473mg, 2.2mmol) with 5-bromomethylene-3-chloro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (640mg, 2mmol) provides 1.17 crude product as a brown oil. Purify the crude product using column chromatography eluting with 5% EtOAc/hexane to 25% EtOAc/hexane to give 315mg of the Z-isomer, mp

177.1°C, (MS (ES) 408 (M-1), HPLC 99% purity) and 115mg E-isomer, mp 130.5°C, (MS (ES) 408 (M-1), HPLC 90% purity).

Example 189

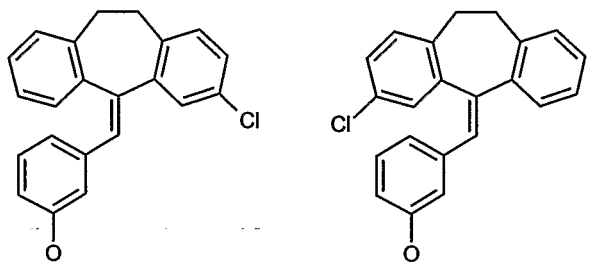
N-[3-(3-Chloro-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylmethyl)-phenyl]-methanesulfonamide



Dissolve N-[3-(3-chloro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methanesulfonamide (200mg, 0.49mmol) in EtOAc (30mL) and add 5%Pt/C (150mg). Stir for 18h under an atmosphere of hydrogen. Add 5%Pt/C (200mg). Stir for 24h under an atmosphere of hydrogen. Filter and concentrate to give 140mg crude product. Purify using reverse-phase UV guided HPLC to give 28mg viscous tan oil, MS (ES) 410 (M-1). HPLC shows 99% purity.

Example 190

3-(3-Chloro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenol (Z-isomer) and 3-(3-Chloro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenol (E-isomer)



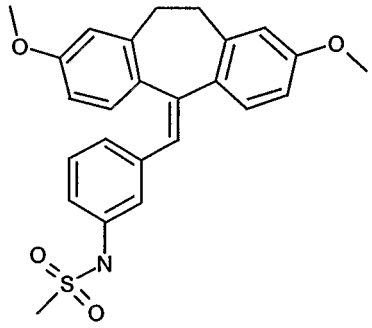
E-isomer Z-isomer

Following procedures essentially as described in Example 219, below, and using 3-hydroxyphenyl boronic acid (300mg, 2.2mmol) with 5-bromomethylene-3-chloro-10,11-

dihydro-5H-dibenzo[a,d]cycloheptene (640mg, 2mmol) to give 880mg crude product. Purify using reverse-phase UV guided HPLC (1/1 CH_3CN/ 0.1% TFA) to give 163mg Z-isomer as a pink foam (HPLC shows 99% purity at t=4.96min) and 43mg E-isomer (MS (ES) 331 (M-1), HPLC shows 95% purity at t=5.22min).

Example 191

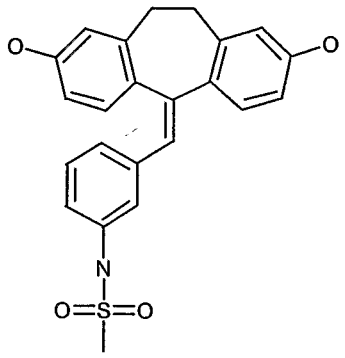
N-[3-(2,8-Dimethoxy-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methanesulfonamide



Following procedures essentially as described in Example 219, below, and using 3-methanesulfonamidophenyl boronic acid (473mg, 2.2mmol) with 5-bromomethylene-2,8-dimethoxy-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (690mg, 2mmol) to give 1.3g crude product. Purify the crude product using column chromatography eluting with 10% EtOAc/hexane to 30% EtOAc/hexane to give 340mg (39%) product as a pale yellow solid, mp 109.6°C. MS (ES) 436 (M+1), 434 (M-1). HPLC shows 91% purity at t=3.11min.

Example 192

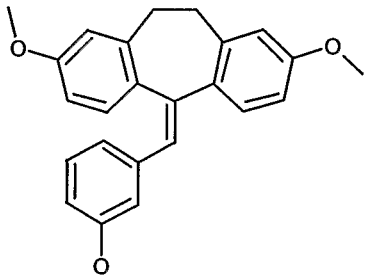
N-[3-(2,8-Dihydroxy-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methanesulfonamide



Demethylate N-[3-(2,8-dihydroxy-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methanesulfonamide (112mg, 0.26mmol) with BBr_3. Purify on silica gel eluting with 25% EtOAc/hexane to 35% EtOAc/hexane to give 72mg (68%) title compound as a colorless oil, MS (ES) 408 (M+1), 406 (M-1). HPLC shows 98% purity.

Example 193

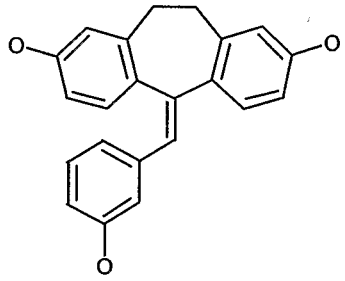
3-(2,8-Dimethoxy-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenol



Following procedures essentially as described in Example 219, below, and using 3-hydroxyphenyl boronic acid (304mg, 2.2mmol) with 5-bromomethylene-2,8-dimethoxy-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (690mg, 2mmol) to give 990mg crude product. Purify the crude product using column chromatography eluting with 8% EtOAc/hexane to 25% EtOAc/hexane to give 240mg (33%) product as a colorless oil. MS (ES) 357 (M-1). HPLC shows 99% purity at t=3.33min.

Example 194

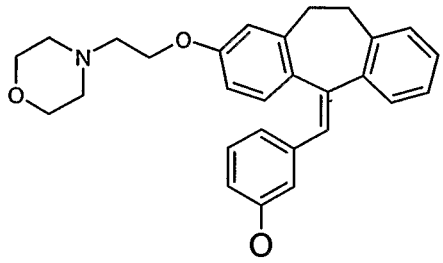
5-(3-Hydroxy-benzylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-2,8-diol



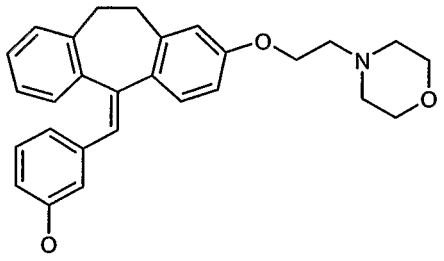
Demethylate 3-(2,8-dimethoxy-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenol (91mg, 0.25mmol) with BBr_3 to give crude title compound. Purify on silica gel eluting with 25% EtOAc/hexane to 35% EtOAc/hexane to give 80mg (96%) as a light pink solid, MS (ES) 331 (m+1), 329 (M-1). HPLC shows 96% purity.

Example 195

3-[2-(2-Morpholin-4-yl-ethoxy)-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl]-phenol (E-isomer) and 3-[2-(2-Morpholin-4-yl-ethoxy)-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl]-phenol (Z-isomer)



Z-isomer



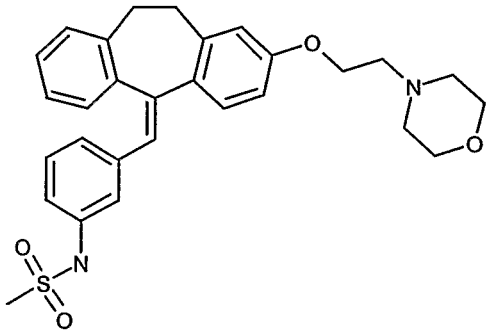
E-isomer

Following procedures essentially as described in Example 219, below, and using 4-[2-(5-bromomethylene-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-2-yloxy)-ethyl]-morpholine (220mg, 0.53mmol) and 3-hydroxyphenylboronic acid (80mg, (0.58mmol). Attempted purification on silica gel eluting with 70% EtOAc/hexane to 100% EtOAc/hexane gave 136mg of an E/Z mixture. Separate the isomers using UV guided reverse-phase using 34% CH_3CN/66% 0.1% aq. TFA. Pool the pure fractions and neutralize with aq.

$NaHCO_3$. Concentrate to remove the organic solvent and extract the product into EtOAc. After drying ($MgSO_4$) and concentration, 40mg of the E-isomer was obtained as a tan foam, MS (ES) 428 (M+1). HPLC 95% purity at t=1.88min. Similarly, 7.2mg of the Z-isomer was obtained as a viscous oil, MS (ES) 428 (M+1). HPLC 96% purity at t=2.27min.

Example 196

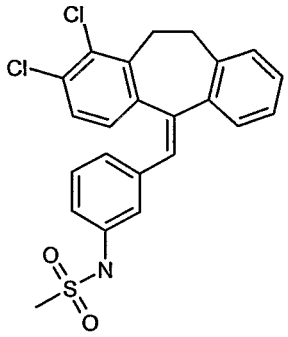
N-{3-[2-(2-Morpholin-4-yl-ethoxy)-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl]-phenyl}-methanesulfonamide



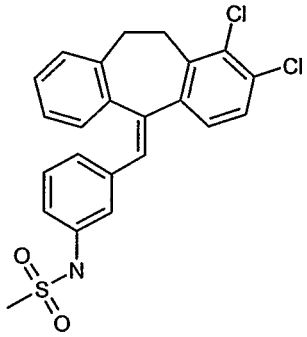
Following procedures essentially as described in Example 219, below, and using 4-[2-(5-bromomethylene-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-2-yloxy)-ethyl]-morpholine (220mg, 0.53mmol) and 3-methanesulfonamidophenylboronic acid (125mg, 0.58mmol). Purification on silica gel eluting with EtOAc then EtOAc/1% $MeOH/NH_3$, gave 57mg of pure E-isomer. MS (ES)505 (M+1), 503(M-1). HPLC shows 92% purity at t=1.79min.

Example 197

N-[3-(1,2-Dichloro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methanesulfonamide (Z-isomer) and N-[3-(1,2-Dichloro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methanesulfonamide (E-isomer)



Z-isomer

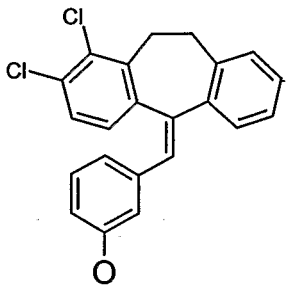


E-isomer

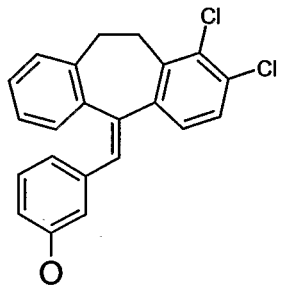
Following procedures essentially as described in Example 219, below, and using 3-methanesulfonamidophenyl boronic acid (473mg, 2.2mmol) with 5-bromomethylene-1,2-dichloro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (700mg, 2mmol) to give 1.29g crude product. Purify the crude product using column chromatography eluting with 10% EtOAc/hexane to 20% EtOAc/hexane, to give the Z-isomer, 330mg yellow foam, mp 190.1°C, MS (ES) 442 (M-1). HPLC shows 98% purity at t=3.55min. Continue to elute and obtain 126mg E-isomer, mp 168.6°C, MS (ES) 442 (M-1). HPLC shows 97% purity at t=3.84min.

Example 198

3-(1,2-Dichloro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenol (Z-isomer) and 3-(1,2-Dichloro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenol (E-isomer)



Z-isomer

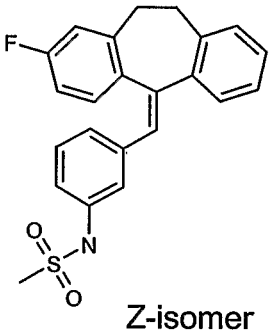


E-isomer

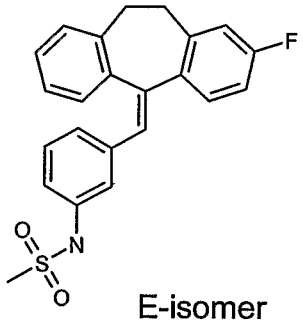
Following procedures essentially as described in Example 219, below, and using 3-hydroxyphenyl boronic acid (310mg, 2.2mmol) with 5-bromomethylene-1,2-dichloro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (700mg, 2mmol) to give 1.39g crude product. Purify the crude product using column chromatography eluting with 5% EtOAc/hexane to 15% EtOAc/hexane to give the Z-isomer, 330mg yellow foam, mp 67.6°C, MS (ES) 365 (M-1). HPLC shows 94% purity at t=4.05min. Continue to elute and obtain 190mg E-isomer, MS (ES) 365 (M-1). HPLC shows 94% purity at t=4.34min .

Example 199

N-[3-(2-Fluoro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methanesulfonamide (Z-isomer) and N-[3-(2-Fluoro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methanesulfonamide (E-isomer)



Z-isomer

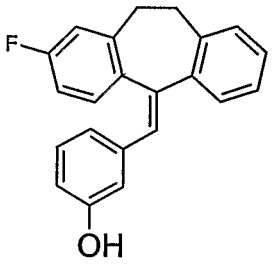


E-isomer

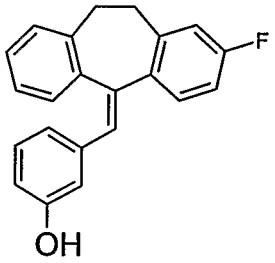
Following procedures essentially as described in Example 219, below, and using 3-methanesulfonamidophenyl boronic acid (596mg, 2.77mmol) with 5-bromomethylene-2-fluoro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (765mg, 2.52mmol) to give 1.49g crude product. Purify the crude product using column chromatography (15% EtOAc/hexane → 25% EtOAc/hexane) to give 212mg Z-isomer as a colorless foam, mp 150.6°C. MS (ES) 392 (M-1). HPLC (ISO60-15M) shows 94% purity at t=12.34min. Continue to elute and obtain 203mg E-isomer as a white foam, mp 145.7°C. MS (ES) 392 (M-1). HPLC (ISO60-15M) shows 94% purity at t=11.86min.

Example 200

3-(2-Fluoro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenol (Z-isomer) and 3-(2-Fluoro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenol (E-isomer)



Z-isomer

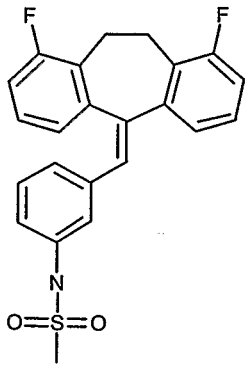


E-isomer

Following procedures essentially as described in Example 219, below, and using 3-hydroxyphenyl boronic acid (415mg, 3.0mmol) with 5-bromomethylene-2-fluoro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (825mg, 2.72mmol) to give 1.07g crude product. Purify the crude product using column chromatography eluting with 5% EtOAc/hexane to 15% EtOAc/hexane to give 120mg pure Z-isomer as a tan viscous oil, MS (ES) 315 (M-1). HPLC (IOS80-10M) shows 94% purity at t=4.02min. Continue to elute and obtain 120mg E-isomer as tan oil, MS (ES) 315 (M-1). HPLC (IOS80-10M) shows 94% purity at t=3.86min.

Example 201

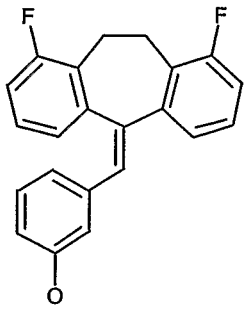
N-[3-(1,9-Difluoro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methanesulfonamide



Following procedures essentially as described in Example 219, below, and using 3-methanesulfonamidophenyl boronic acid (592mg, 2.75mmol) and 5-bromomethylene-1,9-difluoro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (803mg, 2.75mmol), provides 1.52g of the title compound crude product. The crude product is purified using column chromatography (15% EtOAc/hexane to 30% EtOAc/hexane) to give 690 mg (67%) white solid. MS (ES) 410 (M-1). HPLC (ISO90-10M) shows 92% purity at t=2.64min.

Example 202

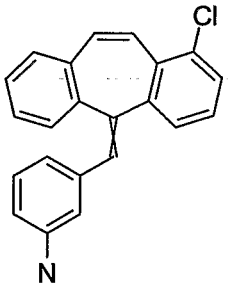
3-(1,9-Difluoro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenol



Following procedures essentially as described in Example 219, below, and using 3-hydroxyphenyl boronic acid (380mg, 2.75mmol) and 5-bromomethylene-1,9-difluoro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (803mg, 2.75mmol), provides to 1.04 g of the title compound as crude product. The crude product is purified using column chromatography eluting with 15% EtOAc/hexane to 30% EtOAc/hexane to give 500mg (60%) product as a light yellow foam, mp 129.5°C. MS (ES) 333 (M-1). HPLC (ISO90-10M) shows 98% at t=2.90min.

Example 203

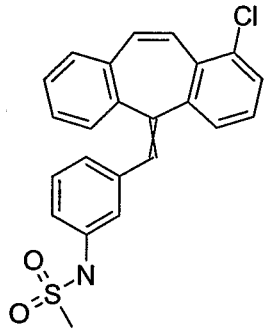
3-(1-Chloro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenylamine



Heat a suspension of NaH (60% suspension in mineral oil, 49mg, 1.2mmol) in DMSO (6mL) to 80°C under N_2 until evolution of H_2 stops. Dissolve (3-nitro-benzyl)-phosphonic acid diethyl ester (prepared according to procedures as described in Okamoto et. al., Bull. Chem. Soc. Jpn. (1987), 60(1), 277-82) (338mg, 1.2mmol) in DMSO (1mL) and add to reaction mixture. Add 1-chloro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-one (prepared according to procedures as described in Humber et al., J. Med. Chem. (1978), 21(12), 1225-31) (200mg, 0.824mmol) at once and heat to 100°C for 48h. Cool to room temperature. Dilute reaction mixture with ethyl acetate (50mL) and wash twice with H_2O. Dry ($MgSO_4$) and concentrate organics to a brown oil. Chromatograph on silica gel (10g), eluting with 2% to 4% ethyl acetate/hexanes to afford a mixture of compounds. Dissolve this mixture in ethanol (10mL) and add $SnCl_2$ (dihydrate, 508mg, 2.25mmol). Heat to reflux for 3h and cool to room temperature. Concentrate reaction mixture, then dissolve residue in diethyl ether. Wash organics with H_2O, 1.00N aqueous NaOH, then twice with H_2O. Dry ($MgSO_4$) and concentrate organics to a yellow oil. Chromatograph on silica gel (10g), eluting with 5% to 10% ethyl acetate/hexanes to afford 28mg (10%) of the title compound as a colorless oil. MS (ES) 330 (M+H); HPLC reveals 36:64 mixture of geometric isomers – 36% at 4.977min, 64% at 5.218min - overall 100% purity.

Example 204

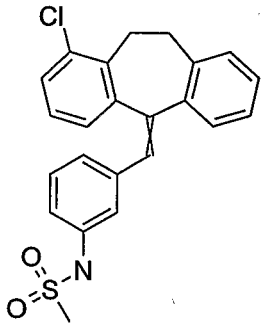
N-[3-(1-Chloro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methanesulfonamide



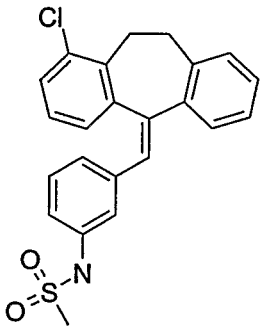
Following procedures essentially as described in Example 90, and using 3-(1-chloro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenylamine (63mg, 0.190mmol), affords 26mg (33%) of the title compound as a white foam. MS (ES) 425 ($M+NH_4$), 406 (M-H); HPLC reveals a mixture of geometric isomers – 41% at 2.879min, 59% at 2.985min – overall 100% purity.

Example 205(a), (b), and (c)

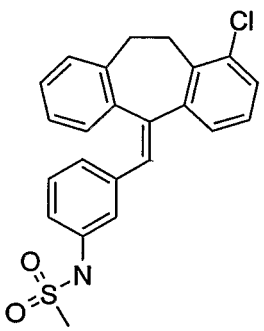
N-[3-(1-Chloro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methanesulfonamide



mixture



Z-isomer

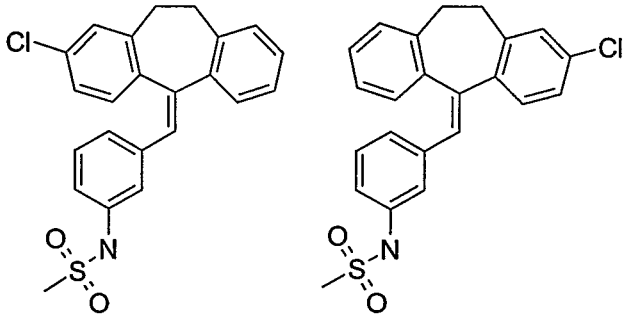


E-isomer

Following procedures essentially as described in Example 219, below, and using 5-bromomethylene-1-chloro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (100mg, 0.313mmol) and 3-methanesulfonylamino-phenylboronic acid (74mg, 0.344mmol), affords 102mg (79%) of the title compound (Example 205(a)) as a mixture of geometric isomers. MS (ES) 408 (M-H); HPLC reveals a 57:43 mixture of geometric isomers – 54% at 3.061min, 40% at 3.197min – overall 94% purity. Separate geometric isomers on a 1000 micron silica gel chromatatron rotor, (10% to 13% ethyl acetate/hexanes) to afford 22mg (17%) of the Z-isomer of the title compound (Example 205(b), (MS (ES) 410 (M+H). HPLC shows 98% purity. Continue to elute to give 11mg (9%) of the E-isomer of the title compound (Example 205(c)) (MS (ES) 410 (M+H), 408 (M-H); HPLC shows 94% purity).

Example 206(a) and (b)

N-[3-(2-Chloro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methanesulfonamide (Z isomer and E isomer)

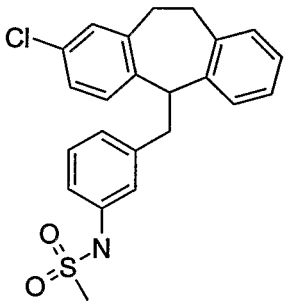


Z-isomer E-isomer

Following procedures essentially as described in Example 219, below, and using 5-bromomethylene-2-chloro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (100mg, 0.313mmol) and 3-methanesulfonylaminophenylboronic acid (74mg, 0.344mmol), affords 37mg (29%) of the Z-isomer (Example 206(a)) of the title compound as a colorless oil (MS (ES) 408 (M-H). HPLC shows 99% purity. Continue to elute and obtain 23mg (18%) of the E-isomer (Example (b)) of the title compound as a colorless oil (MS (ES) 408 (M-H); HPLC shows 92% purity).

Example 207

N-[3-(2-Chloro-10,11-dihydro-5H-dibenzo[a,d]cycloheptenylmethyl)-phenyl]-methanesulfonamide

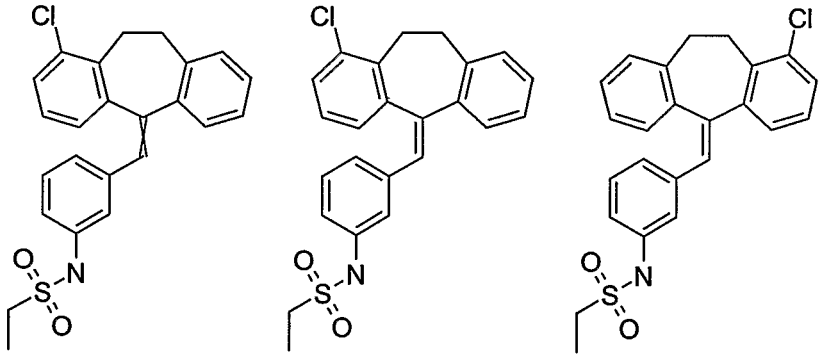


Dissolve N-[3-(2-chloro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methanesulfonamide (mixture of geometric isomers, 100mg, 0.243mmol) in ethanol (15mL) and add 5% Pt/C (20mg). Stir at room temperature under a H_2 balloon for 72h. Filter reaction mixture through a pad of Celite, and concentrate filtrate to a colorless oil. Chromatograph on silica gel (10g), eluting with 15% to 25% ethyl acetate/hexanes. Re-purify by UV-guided semi-preparatory reverse-phase HPLC to afford 44mg (44%) of

the title compound as a colorless oil. MS (ES) 429 ($M+NH_4$), 410 (M-H); HPLC shows 98% purity.

Example 208(a), (b), and (c)

Ethanesulfonic acid [3-(1-chloro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-amide

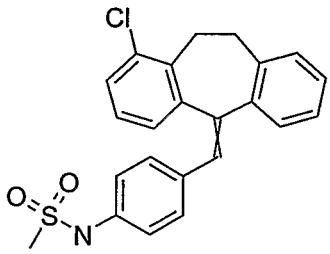


mixture Z-isomer E-isomer

Following procedures essentially as described in Example 219, below, and using 5-bromomethylene-1-chloro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (100mg, 0.313mmol) and 3-ethanesulfonylaminophenylboronic acid (79mg, 0.344mmol), affords 112mg (84%) of a mixture of geometric isomers of the title compound (Example 208(a)) as a yellow solid (MS (ES) 424 (M+H); HPLC shows 94% purity). Separate geometric isomers using a chromatatron rotor (10% ethyl acetate/hexanes) to afford 13mg (10%) of the Z-isomer (Example 208(b)) of the title compound as a white solid, (MS (ES) 424 (M+H), 422 (M-H). HPLC shows 96% purity). Continue to elute and isolate 6mg (5%) of the E-isomer (Example 208(c))of the title compound as a white solid (MS (ES) 424 (M+H), 422 (M-H); HPLC shows 97% purity).

Example 210

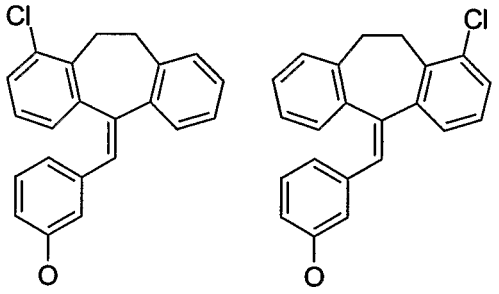
N-[4-(1-Chloro-10,11-dihydro-dibenzo[a,d]cyclohepten-5ylidenemethyl)-phenyl]-methanesulfonamide



Following procedures essentially as described in Example 219, below, and using 5-bromomethylene-1-chloro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (100mg, 0.313mmol) and 4-methanesulfonylaminophenylboronic acid (74mg, 0.344mmol), affords 55mg (43%) of a mixture of geometric isomers of the title compound as a brown oil. MS (ES) 408 (M-H); HPLC shows 96% purity.

Example 211(a) and (b)

3-(1-Chloro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenol

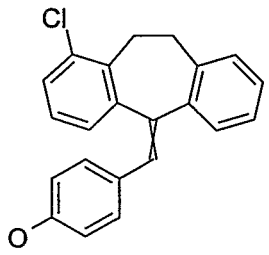


Z-isomer E-isomer

Following procedures essentially as described in Example 219, below, and using 5-bromomethylene-1-chloro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (100mg, 0.313mmol) and 3-hydroxyphenylboronic acid (47mg, 0.344mmol) affords 8mg (8%) of the Z-isomer of the title compound (MS (ES) 331 (M-H). HPLC shows 95% purity. Continue to elute and isolate 27mg (26%) of the E-isomer of the title compound, MS (ES) 331 (M-H). HPLC shows 97% purity.

Example 212

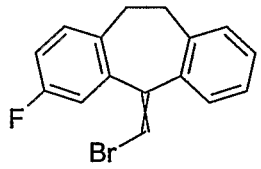
4-(1-Chloro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenol



Following procedures essentially as described in Example 219, below, and using 5-bromomethylene-1-chloro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (100mg, 0.313mmol) and 4-hydroxyphenylboronic acid (47mg, 0.344mmol), affords 84mg (81%) of a mixture of geometric isomers of the title compound as a brown oil. MS (ES) 331 (M-H); HPLC shows 97% purity.

Example 213

5-Bromomethylene-3-fluoro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene

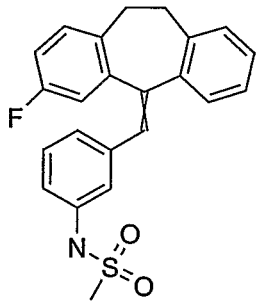


A. Following the procedures essentially as described in Preparation 23, using 3.84g (16.97m) of 3-fluoro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-one (prepared according to procedures as described in published PCT Int. Appl. WO 9856752 A1 19981217 (1998)) to obtain 2.88g (75%) of 3-fluoro-5-methylene-10,11-dihydro-5H-dibenzo[a,d]cycloheptene as a white solid.

B. Following the procedures essentially as described in Preparations 24 and 25, 2.62g (11.70mmol) of the material from Step A, above, affords 3.152g (89%) of a mixture of geometric isomers of the title compound as a yellow oil. MS [EI] 302,304; HPLC shows 99% purity.

Example 214

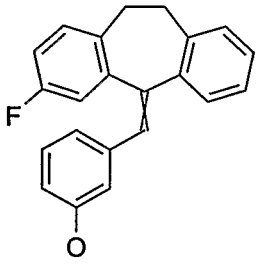
N-[3-(3-Fluoro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methanesulfonamide



Following the procedures essentially as described in Example 219, below, and using 5-bromomethylene-3-fluoro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (200mg, 0.660mmol) and 3-methanesulfonylaminophenylboronic acid (156mg, 0.726mmol), affords 212mg (82%) of a mixture of geometric isomers of the title compound as a yellow solid. MS (ES) 411 (M+NH_4), 392 (M-H); HPLC shows 98% purity.

Example 215

3-(3-Fluoro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenol

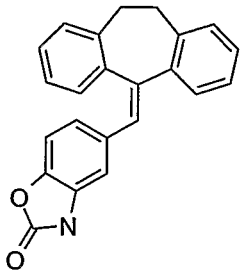


Following the procedures essentially as described in Example 219, below, and using 5-bromomethylene-3-fluoro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (200mg, 0.660mmol) and 3-hydroxyphenylboronic acid (100mg, 0.726mmol), affords 192mg (92%) of a mixture of geometric isomers of the title compound as a yellow oil. MS (ES) 339 (M+Na), 315 (M-H); HPLC shows 95% purity.

Section 3 (derivatives of Formula I wherein the "C" ring further represents a heterocyclic or benzofused heterocyclic ring.)

Example 216

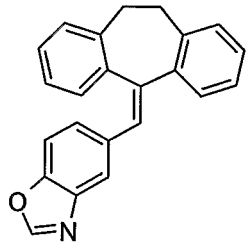
5-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-3H-benzooxazol-2-one



Add phenyl chloroformate (24μL, 0.195mmol) to a suspension of 2-amino-4-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenol (61mg, 0.195mmol) (see Example 63) and $NaHCO_3$ (16mg, 0.195mmol) in water (5mL) and methanol (10mL). Stir for 30min at room temperature and add aqueous NaOH (1.00N, 195□L). Stir overnight and add aqueous HCl (1.00N, 195□L). Extract with CH_2Cl_2, dry organics ($MgSO_4$), and concentrate to a brown oil containing the title compound. Purify on silica gel (10g) eluting with 10% TO 35% ethyl acetate/hexanes, and then triturate with 50% CH_2Cl_2/hexanes to afford 8mg (13%) of a white solid. MS (ES) 357 ($M+NH_4$), 338 (M-H); HPLC shows 94% purity.

Example 217

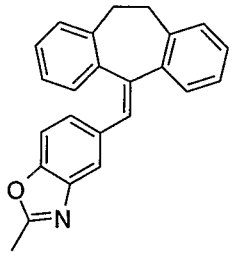
5-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-benzooxazole



Dissolve 2-amino-4-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenol (see Example 63) (60mg, 0.191mmol) in triethylorthoformate (3mL) and heat to reflux for 4.5h. Cool to room temperature and concentrate in-vacuo to a brown oil. Chromatograph on 10g silica gel eluting with 5% to 25% ethyl acetate/hexanes to afford 52mg (84%) of the title compound as a colorless oil. MS (ES) 324 (M+H), 322 (M-H), HPLC shows 94% purity.

Example 218

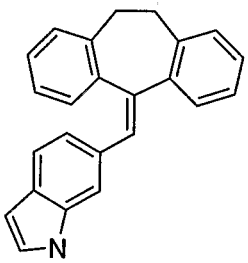
5-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-2-methyl-benzooxazole



Dissolve 2-amino-4-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenol (60mg, 0.191mmol) in triethylorthoacetate (5mL) and heat to reflux for 4h. Cool to room temperature and concentrate in-vacuo to a brown oil. Chromatograph on 10g silica gel eluting with 5% to 25% ethyl acetate/hexanes to afford 51mg (79%) of the title compound as a colorless oil. MS (ES) 338 (M+H); HPLC shows 98% purity.

Example 219

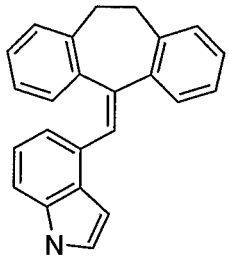
6-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-1H-indole



In a 1-dram vial, mix (10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidene)-boronic acid (100mg, 0.400mmol) and 6-bromoindole (86mg, 0.440mmol) in dioxane (2.5mL) and 2.0M aqueous Na_2CO_3 (400□L, 1.00mmol). Sparge with N_2 for 5min, add $Pd(PPh_3)_4$ (23mg, 0.02mmol), and immediately seal vial. Heat to 85°C overnight, then concentrate under N_2. Add H_2O (1mL) and CH_2Cl_2 (1mL) and load onto a Varian ChemElut CE1005 solid-phase extraction cartridge. Elute, collect, and concentrate 15mL CH_2Cl_2 to obtain crude product. Chromatograph on silica gel (10g), eluting with 0% to 25% ethyl acetate/hexanes to obtain 24mg (19%) of the title compound as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ 2.75-3.60 (br m, 4H), 6.81 (s, 1H), 7.00-7.30 (m, 12H), 7.50 (m, 1H); HPLC shows 99% purity.

Example 220

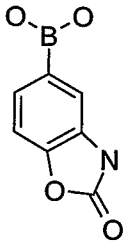
4-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-1H-indole



Following the procedures essentially as described in Example 219, 4-bromoindole (86mg, 0.440mmol) and (10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidene)-boronic acid (100mg, 0.400mmol) afford 6mg (5%) of the title compound as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ 2.77-3.63 (br m, 4H), 6.79 (s, 1H), 6.97-7.29 (m, 12H), 7.49 (m, 1H). HPLC shows 96% purity.

Preparation 26

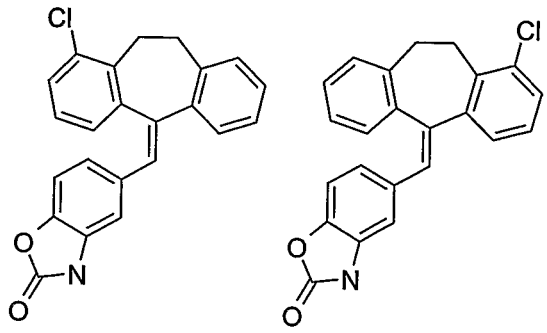
2-Oxo-2,3-dihydro-benzooxazole-5-boronic acid



Add n-BuLi (1.6M in hexanes, 8.76mL, 14.02mmol) portionwise (exotherm) to a solution of 5-bromo-3H-benzooxazol-2-one (1.00g, 4.67mmol) in dry THF (28mL) at –78°C under N_2. Stir at –40°C for 1h and add trimethylborate (1.94g, 18.68mmol) at once. Warm up to room temperature overnight. Add 1N aqueous HCl (50mL) and stir for 3h at room temperature. Extract into ethyl acetate, dry ($MgSO_4$) and concentrate organics to a brown solid. Triturate with hexanes/toluene and collect 766mg (92%) of the title compound as a brown powder. MS (ES) 179 (M+H), 177 (M-H); HPLC shows 80% purity.

Example 221(a) and (b)

5-(1-Chloro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-3H-benzooxazol-2-one (Z isomer and E isomer)

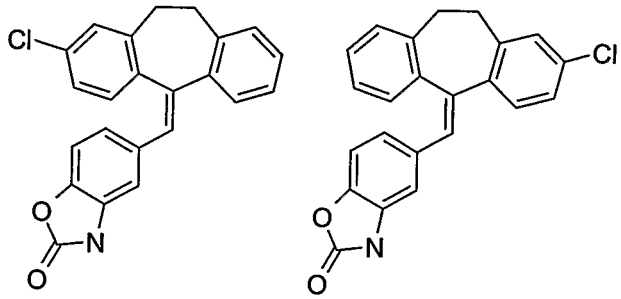


Z-isomer E-isomer

Following procedures essentially as described in Example 219 and using 5-bromomethylene-1-chloro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (200mg, 0.630mmol) and 2-oxo-2,3-dihydro-benzooxazole-5-boronic acid (134mg, 0.750mmol) provides 29mg (12%) of the Z-isomer (Example 221(a)) of title compound as a tan solid (MS (ES) 372 (M-H); HPLC shows 99% purity) and O 23mg (10%) of the E-isomer (Example 221(b)) of the title compound as a tan solid. MS (ES) 372 (M-H); HPLC shows 97% purity.

Example 222(a) and (b)

5-(2-Chloro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-3H-benzooxazol-2-one (Z isomer and E isomer)



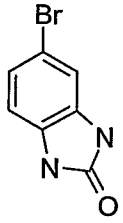
Z-isomer E-isomer

Following procedures essentially as described in Example 219 and using 5-bromomethylene-2-chloro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (200mg, 0.630mmol) and 2-oxo-2,3-dihydro-benzooxazole-5-boronic acid (134mg, 0.750mmol), provides the title compound. Purify by UV-guided semi-prep reverse-phase HPLC to obtain 14mg (6%) of the Z-isomer (Example 222(a)) of title compound as a white solid (MS (ES) 391 ($M+NH_4$), 372 (M-H); HPLC shows 94% purity) and 5mg (2%) of the E-

isomer (Example 222(b)) of the title compound as a white solid. MS (ES) 391 ($M+NH_4$), 372 (M-H); HPLC shows 96% purity.

Preparation 27

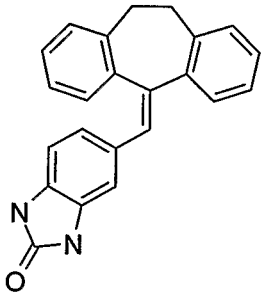
5-Bromo-1,3-dihydro-benzoimidazol-2-one



Add phenyl chloroformate (922mg, 5.89mmol) to a suspension of 4-bromo-benzene-1,2-diamine (1.00g, 5.35mmol) and $NaHCO_3$ (483mg, 5.89mmol) in methanol (20mL) and H_2O (10mL). Stir at room temperature for 3.5h and add 1.00N aqueous NaOH (6mL, 6.00mmol). Stir overnight at room temperature and filter. Wash the filter cake with H_2O and dry in-vacuo overnight to obtain 386mg (34%) of the title compound as a brown powder. MS (ES) 213,215 (M+H), 211,213 (M-H); HPLC shows 95% purity.

Example 223

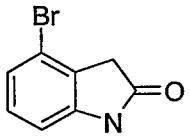
5-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-1,3-dihydro-benzoimidazol-2-one



Following procedures essentially as described in Example 230, below, and using (10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidene)-boronic acid (0.0825M in toluene, 10mL, 0.825mmol) and 5-bromo-1,3-dihydro-benzoimidazol-2-one (117mg, 0.550mmol), provides the title compound. Purify by triturating with CH_2Cl_2 to obtain 85mg (45%) of the title compound as a white powder. MS (ES) 339 (M+H), 337 (M-H); HPLC shows 93% purity.

Preparation 28

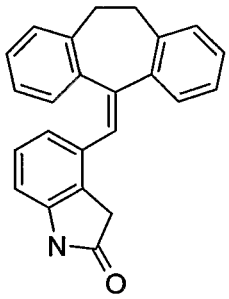
4-Bromo-1,3-dihydro-indol-2-one



Add a solution of I_2 (2.62g, 10.30mmol) in DMF (10mL) dropwise to a solution of 4-bromoindole (2.00g, 10.20mmol) and KOH (1.43g, 25.5mmol) in DMF (40mL). Stir for 30min at room temperature and add saturated aqueous Na_2SO_3. Stir at room temperature for 15min, then dilute reaction mixture with ethyl acetate (100mL). Wash organics three times with H_2O, dry organics ($MgSO_4$) and concentrate to a brown oil. Dissolve oil in 2-methoxyethanol (40mL) and heat to 100°C. Add H_3PO_4 (9mL) and heat to reflux for 48h. Cool to room temperature and dilute with H2O (75mL). Extract into ethyl acetate, dry ($MgSO_4$) and concentrate organics to a dark brown oil. Chromatograph on silica gel (90g), eluting with 20% to 40% ethyl acetate/hexanes to afford 121mg (6%) of the title compound as a tan solid. MS (ES) 212,214 (M+H), 210,212 (M-H); HPLC shows 76% purity.

Example 224

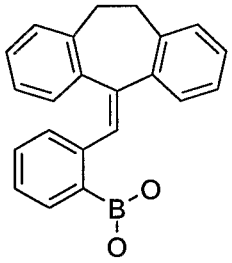
4-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-1,3-dihydro-indol-2-one



Following procedures essentially as described in Example 229 and using (10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidene)-boronic acid (0.0825M in toluene, 7.4Ml, 0.61mmol) (concentrated to dryness before use in reaction). Add 4-bromo-1,3-dihydro-indol-2-one (108mg, 0.510mmol) to provide 37mg (22%) of the title compound as a tan solid. MS (ES) 338 (M+H); HPLC shows 96% purity.

Preparation 29

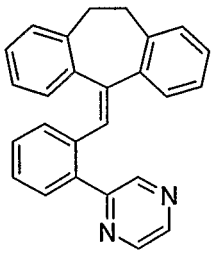
2-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenylboronic acid



Add n-BuLi (1.6M in hexanes, 12.98Ml, 20.76mmol) portionwise (exothermic) to a solution of 5-(2-bromo-benzylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (5.00g, 13.84mmol) in dry THF (50Ml) at –78°C under N_2. Let stir at –78°C for 30min, then add triisopropyl borate (5.21g, 27.68mmol) and warm up to room temperature overnight. Add 50Ml 1.00N HCl and stir for 15min. Extract into ethyl acetate, dry (MgSO4) and concentrate organics to a brown foam. Recrystallize from boiling hexanes, then chromatograph on silica gel (40g), eluting with 20% to 50% ethyl acetate/hexanes to afford the title compound as a white foam, mp 134.1°C. MS (ES) 325 (M-H); HPLC shows 82% purity.

Example 225

2-[2-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-pyrazine

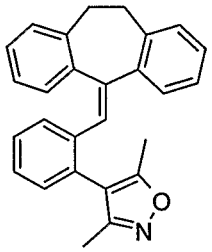


In a 1-dram vial, mix 2-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenylboronic acid (100mg, 0.307mmol), chloropyrazine (69mg, 0.460mmol), cesium fluoride (94mg, 0.614mmol), and [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II) (1:1 complex with CH_2Cl_2, 25mg, 0.031mmol) in dioxane (2mL). Heat to 85°C for 72h, then remove solvent under nitrogen. Take up the resulting residue in H_2O (1mL) and CH_2Cl_2 (1mL) and load onto a Varian ChemElut CE1005 solid-phase extraction cartridge. Elute, collect, and concentrate 15mL CH_2Cl_2 to

obtain crude product. Purify by mass-guided reverse-phase HPLC to obtain 2.3mg (2%) of the title compound. MS (ES) 361 (M+H); HPLC shows 93% purity.

Example 226

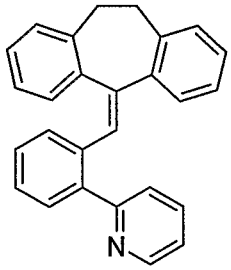
4-[2-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-3,5-dimethyl-isoxazole



Following procedures essentially as described in Example 225 and using 2-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenylboronic acid (100mg, 0.307mmol) and 4-bromo-3,5-dimethylisoxazole (81mg, 0.460mmol), provides the title compound in 2% yield. MS (ES) 378 (M+H); HPLC shows 94% purity.

Example 227

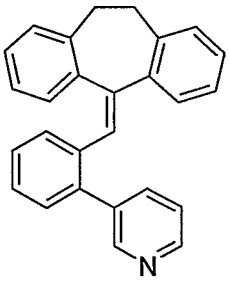
2-[2-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-pyridine



Following procedures essentially as described in Example 225 and using 2-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenylboronic acid (100mg, 0.307mmol) and 2-chloropyridine (52mg, 0.460mmol),provides the title compound. Purify further via silica gel chromatography to obtain 14.7mg (13%) of material that is 84% pure by HPLC. MS (ES) 360 (M+H).

Example 228

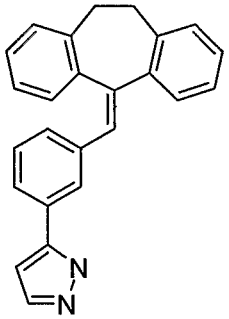
3-[2-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-pyridine



Following procedures essentially as described in Example 225 and using 2-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenylboronic acid (100mg, 0.307mmol) and 3-bromopyridine (73mg, 0.460mmol) provides the title compound. Purify further via silica gel chromatography to obtain 14.9mg (14%) of material that is 98% pure by HPLC. MS (ES) 360 (M+H).

Example 229

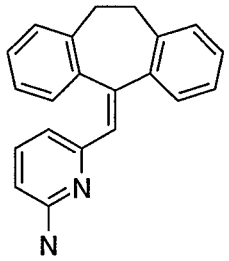
5-[3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-1H-pyrazole



In a 6-dram vial mix (10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidene)-boronic acid (0.0825M in toluene, 10mL, 0.825mmol), 5-(3-bromo-phenyl)-1H-pyrazole (153mg, 0.688mmol), K_2CO_3 (570mg, 4.125mmol) and ethanol (5mL). Sparge reaction mixture with N_2 for 10min and add $Pd(PPh_3)_4$ (56mg, 0.048mmol). Seal vial immediately and heat to 85°C for 72h. Concentrate under N_2, then add H_2O (1mL) and ethyl acetate (1mL). Load onto a Varian ChemElut CE1005 solid-phase extraction cartridge. Elute, collect, and concentrate 30mL ethyl acetate. Chromatograph on 35g silica gel, eluting with 25% to 35% ethyl acetate/hexanes. Re-purify by UV-guided semi-preparatory reverse-phase HPLC to afford 35mg (15%) of the title compound as a milky white oil. MS (ES) 349 (M+H), 347 (M-H); HPLC shows 99% purity.

Example 230

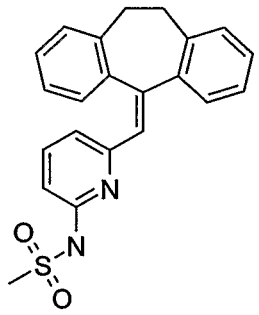
6-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-pyridin-2-ylamine



Following procedures essentially as described in Example 219 and using 2-amino-6-bromopyridine (95mg, 0.550mmol) and (10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidene)-boronic acid (0.197M in dioxane, 3.35mL, 0.660mmol), provides 98mg (60%) of the title compound as a yellow oil. MS (ES) 299 (M+H); HPLC shows 97% purity.

Example 231

N-[6-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-pyridin-2-yl]-methanesulfonamide

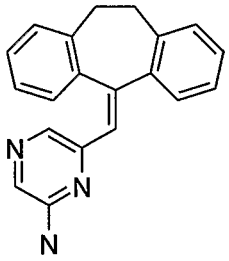


Mix 6-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-pyridin-2-ylamine (70mg, 0.235mmol), triethylamine (68μL, 0.470mmol), N,N-dimethylaminopyridine (3mg, 0.024mmol), and methanesulfonyl chloride (19μL, 0.247mmol) in CH_2Cl_2 (2mL). Stir at room temperature overnight and add 150□L triethylamine and 40μL methanesulfonyl chloride. Stir at room temperature for 6h and add 1.00N aqueous HCl (1mL). Load mixture onto a Varian ChemElut CE1005 solid-phase extraction cartridge, then elute, collect, and concentrate 45mL CH_2Cl_2. Dissolve crude product in THF (5mL), add 1.0M tetrabutylammonium fluoride (0.25mL), and heat to reflux for 1h. Cool to room temperature and dilute with H_2O and brine. Extract into ethyl acetate, dry ($MgSO_4$)

and concentrate organics. Chromatograph on silica gel (10g), eluting with 20% to 35% ethyl acetate/hexanes to afford 61mg (69%) of the title compound as a yellow oil. MS (ES) 377 (M+H), 375 (M-H); HPLC shows 96% purity.

Example 232

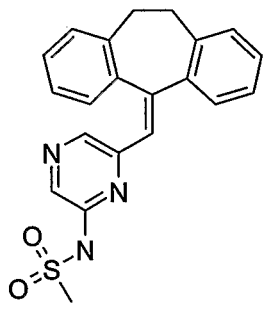
6-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-pyrazin-2-ylamine



Following procedures essentially as described in Example 219 and using 2-amino-6-chloropyrazine (71mg, 0.550mmol) and (10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidene)-boronic acid (0.197M in dioxane, 3.35mL, 0.660mmol), provides the title compound. Purify by recrystallization (ethyl acetate/hexanes) to obtain 48mg (29%) of the title compound as a yellow solid. MS (ES) 300 (M+H); HPLC shows 96% purity.

Example 233

N-[6-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-pyrazin-2-yl]-methanesulfonamide

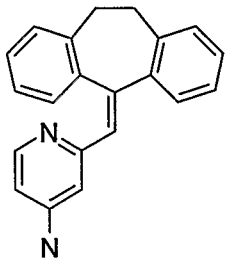


Mix 6-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-pyrazin-2-ylamine (35mg, 0.117mmol), triethylamine (34μL, 0.234mmol), N,N-dimethylaminopyridine (2mg, 0.018mmol), and methanesulfonyl chloride (10μL, 0.123mmol) in CH_2Cl_2 (2mL). Stir at room temperature overnight and add 150μL triethylamine and 40μL

methanesulfonyl chloride. Stir at room temperature for 6h and add 1.00N aqueous HCl (1mL). Load mixture onto a Varian ChemElut CE1005 solid-phase extraction cartridge, then elute, collect, and concentrate 45mL CH_2Cl_2. Dissolve crude product in THF (5mL), add 1.0M tetrabutylammonium fluoride (0.30mL), and heat to reflux for 1h. Cool to room temperature and dilute with H_2O and brine. Extract into ethyl acetate, dry ($MgSO_4$) and concentrate organics. Chromatograph on silica gel (4g), eluting with 20% → 35% ethyl acetate/hexanes to afford 19mg (43%) of the title compound as a white solid. MS (ES) 378 (M+H), 376 (M-H); HPLC shows 100% purity.

Example 234

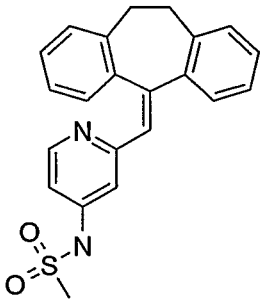
2-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-pyridin-4-ylamine



Following procedures essentially as described in Example 225 and using 4-amino-2-chloropyridine (216mg, 1.68mmol) and (10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidene)-boronic acid (0.197M in dioxane, 10.2mL, 2.01mmol), provides the title compound. Chromatograph on silica gel (35g), eluting with 40% to 60% ethyl acetate/hexanes to afford 250mg (42%) of the title compound as a brown oil. MS (ES) 299 (M+H). HPLC shows 98% purity.

Example 235

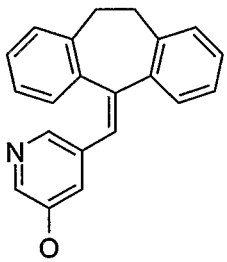
N-[2-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-pyridin-4-yl]-methanesulfonamide



Mix 2-(10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-pyridin-4-ylamine (176mg, 0.590mmol), triethylamine (600μL, 4.13mmol), N,N-dimethylaminopyridine (7mg, 0.059mmol), and methanesulfonyl chloride (137μL, 1.769mmol) in CH_2Cl_2 (10mL). Stir at room temperature for 3h and dilute with H_2O (15mL). Extract into CH_2Cl_2, dry ($MgSO_4$) and concentrate organics. Dissolve crude product in THF (10mL), add 1.0M tetrabutylammonium fluoride (0.89mL), and heat to reflux for 4h. Cool to room temperature and dilute with H_2O. Extract into ethyl acetate, dry ($MgSO_4$) and concentrate organics. Chromatograph on silica gel (10g), eluting with 80% → 90% ethyl acetate/hexanes to afford 150mg (68%) of the title compound as a yellow foam. MS (ES) 377 (M+H), 375 (M-H); HPLC shows 96% purity.

Example 236

5-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-pyridin-3-ol

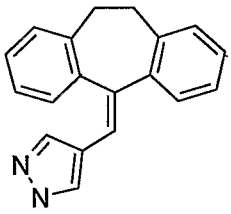


Following procedures essentially as described in Example 225 and using 5-chloro-2-pyridinol (77mg, 0.591mmol) and (10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidene)-boronic acid (0.197M in dioxane, 3.58mL, 0.709mmol), provides the title compound. Chromatograph on silica gel (10g), eluting with 60% to 75% ethyl acetate/hexanes to give 40mg of brown oil. Re-chromatograph on silica gel (5g) eluting with 60% ethyl

acetate/hexanes to afford 15mg (8%) of the title compound as a brown oil. MS (ES) 300 (M+H), 298 (M-H); HPLC shows 95% purity.

Example 237

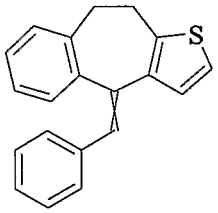
4-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-1H-pyrazole



Following procedures essentially as described in Example 229 and using 4-iodopyrazole (107mg, 0.55mmol) and (10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidene)-boronic acid (0.198M in dioxane, 4.2mL, 0.825mmol), provides 27mg (18%) of the title compound as a colorless oil. MS (ES) 273 (M+H), 271 (M-H). HPLC shows 98% purity.

Example 238

4- Benzylidene-9,10-dihydro-4*H*-1-thia-benzo[*f*]azulene (E and Z isomer)



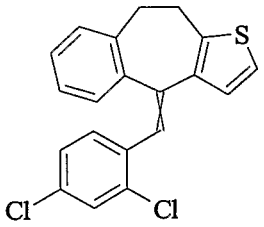
A. Add a 1.0 M solution of benzyl magnesium bromide (0.5mL, 0.5mmol) in THF to a solution of 9,10-dihydro-1-thia-benzo[*f*]azulene-4-one (20.8mg, 0.97mmol) (prepared according to procedures of Bollinger, P.; Cooper, P.; Gubler, H. U.; Leutwiler, A.; Payne, T. *Helv. Chim. Acta* 1990, *73*, 1197) in 1.0 mL of THF under Ar. Stir the resulting solution for 2h at 25 °C before quenching with ca. 100 μL of saturated, aqueous ammonium chloride. Filter the mixture and wash the magnesium salts with copious amounts of diethyl ether. Wash the filtrate with 1-mL portions of water and brine, dry (Na_2SO_4) and concentrate under reduced pressure. The tertiary alcohol can be purified by column chromatography (9:1 hexanes:ethyl acetate).

B. Dissolve the crude oil in 1.5 mL of $CHCl_3$, add ca. 40 μL (2 drops) of concentrated hydrochloric acid, and then stir the resulting dark solution for 2 h at 25 °C. Add 1 mL of water and 1 mL of $CHCl_3$, separate the layers, and wash the organic layer successively with 0.5-mL portions of saturated, aqueous sodium bicarbonate and brine. Dry ($MgSO_4$) and concentrate via rotary evaporation. Purify by flash chromatography (hexanes) to afford 6.7 mg (24%, 2 steps) of a white solid as a 2:1 mixture of E- and Z-isomers. MS (CI): 289 (M+1). ^1H NMR ($CDCl_3$, 400 MHz) δ 2.90-3.60 (m, 4 H), 6.53 (d, J = 5.4 Hz, 1/3 H), 6.66 (s, 1/3 H), 6.86 (d, J = 5.4 Hz, 1/3 H), 6.94 (s, 2/3 H), 7.01-7.34 (m, 10 H), 7.39-7.41 (m, 2/3 H); HPLC shows >95 % purity: t_R = 5.854 min (E + Z; 80:20 MeOH:H_20 to MeOH).

Section 4 (derivatives of Formula I wherein the "A" and / or "B" ring represents a heterocyclic ring.)

Example 239

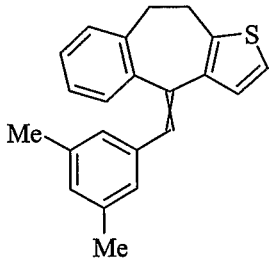
4-(2,4-Dichloro-benzylidene)-9,10-dihydro-4H-1-thia-benzo[*f*]azulene (mixture of E and Z isomers)



Following the procedures essentially as described in Example 238 and using 9,10-dihydro-1-thia-benzo[*f*]azulene-4-one (40.8mg, 0.19mmol) and 2,4-dichlorobenzyl magnesium chloride (0.575 mmol) in THF:diethyl provides, after dehydration, 30.0 mg (44%) of the title compound as a 3:1 mixture of E- and Z-isomers. ^1H NMR ($CDCl_3$) δ 2.88-3.40 (m, 4 H), 6.26 (d, J = 4.8 Hz, 1/4 H), 6.50 (d, J = 8.2 Hz, 3/4 H); 6.63 (s, 1/4 H, Z), 6.74 (s, 3/4 H), 6.76 (td, J = 8.6 Hz, 2.0 Hz, 3/4 H), 6.88 (td, J = 8.2 Hz, 1.2 Hz, 3/4 H), 6.96 (s, 3/4 H), 6.95-6.98 (m, 1/4 H), 7.06 (d, J = 4.8 Hz, 3/4 H), 7.08-7.20 (m, 14/4 H), 7.28 (d, J = 2.0 Hz, 3/4 H), 7.34 (d, J = 2.4 Hz, 1/4 H), 7.35-7.38 (m, 1/4 H); TLC shows .95 % purity: R_f = 0.20 (hexanes).

Example 240

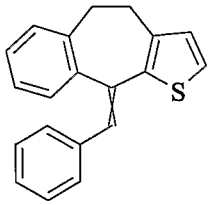
4-(3,5-Dimethyl-benzylidene)-9,10-dihydro-4H-1-thia-benzo[*f*]azulene (mixture of E- and Z- isomers)



Following the procedures essentially as described in Example 238 and using 9,10-dihydro-1-thia-benzo[*f*]azulene-4-one (47.0mg (0.22mmol) and solution of 3,5-dimethylbenzyl magnesium bromide(0.650 mmol) in THF, provides, after dehydration, 39.6 mg (57%) of the title compound as a 1.6:1 mixture of E- and Z-isomers. MS (EI): 316 (M^+); ^1H NMR ($CDCl_3$) δ 2.13 (s, 18/5 H), 2.24 (s, 12/5 H), 2.40-3.80 (m, 4 H), 6.54 (d, J = 5.6 Hz, 2/5 H), 6.53-6.55 (m, 7/5 H), 6.74 (s, 3/5 H), 6.83-6.84 (m, 2/5 H), 6.86 (s, 3/5 H), 6.93 (s, 3/5 H), 7.01-7.02 (m, 1 H), 7.08 (app d, J = 5.6 Hz, 2/5 H), 7.14 (app d, J = 5.6 Hz, 2/5 H), 7.19-7.25 (m, 4 H), 7.30 (d, J = 8.0 Hz, 3/5 H), 7.37-7.39 (m, 2/5 H).

Example 241

E- and Z-4-Benzylidene-9,10-dihydro-4H-3-thia-benzo[*f*]azulene (mixture of E- and Z-isomers)

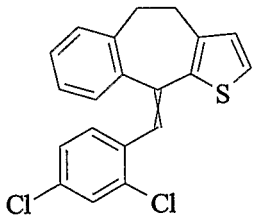


Following the procedures essentially as described in Example 238 and using 9,10-dihydro-3-thia-benzo[*f*]azulene-4-one (32.9mg,0.153mmol) (prepared according to Hallberg, A.; Pedaja, P. *Tetrahedron* 1983, *39*, 819) and solution of benzyl magnesium bromide (0.470 mmol) in THF, provides 15.1 mg (34%) of the title compound as a 4:1 mixture of E- and Z-isomers: MS (CI): 289 (M+1); ^1H NMR ($CDCl_3$) δ 2.98-3.12 (m, 4 H), 6.61 (d, J = 5.2 Hz, 1/5 H), 6.65 (s, 1/5 H); 6.66 (d, J = 5.6 Hz, 4/5 H), 6.96 (s, 4/5 H),

6.97 (d, J = 3.2 Hz, 4/5 H), 6.97 (d, J = 3.2 Hz, 4/5 H), 6.96 (s, 38/5 H), 7.28-7.31 (m, 4/5 H).

Example 242

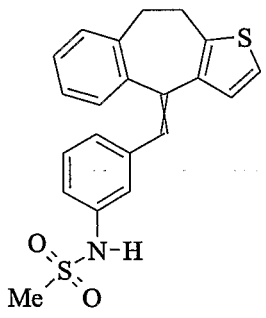
4-(2,4-Dichloro-benzylidene)-9,10-dihydro-4H-3-thia-benzo[*f*]azulene (E- and Z-isomers)



Following the procedures essentially as described in Example 238 and using 9,10-dihydro-3-thia-benzo[*f*]azulene-4-one (23.3mg, 0.108mmol) and solution of 2,4-dichlorobenzyl magnesium chloride (0.325 mmol) in THF provides, after dehydration, 12.5 mg (32%) of the title compound as a 3:1 mixture of E- and Z-isomers: ^{1}H NMR ($CDCl_3$) δ 2.88-3.40 (m, 4 H), 6.26 (d, J = 4.8 Hz, 1/4 H), 6.50 (d, J = 8.2 Hz, 3/4 H); 6.63 (s, 1/4 H, Z), 6.74 (s, 3/4 H), 6.76 (td, J = 8.6 Hz, 2.0 Hz, 3/4 H), 6.88 (td, J = 8.2 Hz, 1.2 Hz, 3/4 H), 6.96 (s, 3/4 H), 6.95-6.98 (m, 15/4 H), 7.28 (d, J = 2.0 Hz, 3/4 H), 7.34 (d, J = 2.4 Hz, 1/4 H), 7.35-7.38 (m, 1/4 H); TLC shows > 95 % purity: R_f = 0.20 (hexanes).

Example 243(a) and (b)

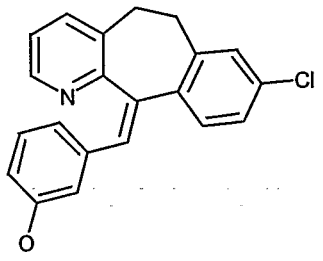
E-N-[3-(9,10-Dihydro-1-thia-benzoazulen-4-ylidenemethyl)-phenyl]-methanesulfonamide (E-isomer) and Z-*N*-[3-(9,10-Dihydro-1-thia-benzoazulen-4-ylidenemethyl)-phenyl]-methanesulfonamide (Z-isomer)



Following the procedures essentially as described in Example 219 and using 4-bromomethylene-9,10-dihydro-4H-1-thia-benzo[*f*]azulene (54.1mg,0.186 mmol) and 3-methylsulfonaminophenyl boronic acid (43.4mg, 0.202mmol), (prepared according to M. L. Quan, J. Wityak, C. Dominguez, J. V. Duncia, C. A. Kettner, C. D. Ellis, A. Y. Liauw, J. M. Park, J. B. Santella, R. M. Knabb, M. J. Thoolen, P. C. Weber and R. R. Wexler *Bioorg. Med. Chem. Lett.* 1997, *13*, 1595), provides the title compound. Purify the crude residue by column chromatography (hexanes to 7:3 hexanes:ethyl acetate) to give 49.7mg (ca. 70 %) of the title compound as a 1:1 mixture of E- and Z-isomers. The isomers were separated via HPLC on a Waters Symmetry C18 5-μm 19-mm x 300-mm semi-preparatory column using a 7:3 MeCN:H_2O (0.1 % TFA) eluent and were identified on the basis of the following spectroscopic properties. E-*N*-[3-(9,10-Dihydro-1-thia-benzoazulen-4-ylidenemethyl)-phenyl]-methanesulfonamide (Example 243)a)) : MS (CI): 382 (M+1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.78 (s, 3 H), 2.90-3.45 (m, 4 H), 6.12 (s, 1 H), 6.72 (app s, 1 H), 6.91 (s, NH, 1 H), 6.93-7.03 (m, 3 H), 7.10-7.23 (m, 4 H), 7.32 (d, J = 7.8 Hz, 1 H); HPLC shows >95 % purity: t_R = 3.194 min (80:20 MeOH:H_2O to MeOH). Z-*N*-[3-(9,10-Dihydro-1-thia-benzoazulen-4-ylidenemethyl)-phenyl]-methanesulfonamide (Example 243(b)): MS (CI): 382 (M+1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.94 (s, 3 H), 3.24 (br s, 4 H), 6.50 (d, J = 5.0 Hz, 1 H), 6.64 (s, 1 H), 6.88 (d, J = 5.0 Hz, 1 H), 7.08-7.18 (m, 3 H), 7.26-7.30 (m, 4 H), 7.38-7.40 (m, 1 H); HPLC shows >95 % purity: t_R = 3.194 min (80:20 MeOH:H_2O to MeOH).

Example 244

3-(8-Chloro-5,6-dihydro-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidenemethyl)-phenol, (Z-isomer)



A. Prepare 11-(3-bromo-benzylidene)-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine according to procedures essentially as described in

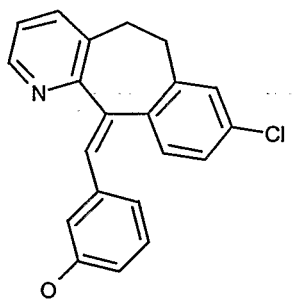
Example 28 using m-bromobenzylmagnesium bromide (7.5mmol)and 8-chloro-5,6-dihydro-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one (600mg, 2.5mmol) in ether (25mL). Separate the E and Z isomers by column chromatography (15% ethyl acetate/hexane).

B. Separately, convert each isomer to the hydroxyl derivative by using the following procedure: Mix 11-(3-bromo-benzylidene)-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (500mg, (1.26mmol),pinacol diborane (416mg, 1.64mmol),KOAc (375mg, 3.8mmol) in DMSO (10mL). Sparge with nitrogen for 10 minutes and then add $Pd(dppf)Cl_2$ (160mg, 0.2mmol) and heat at 80°C for 4h. Shake with water and ethyl acetate. Dry the organic layer ($MgSO_4$) and concentrate to give 650mg crude product. Purify by column chromatography (15% ethyl acetate/hexane) to give 310mg (56%) 8-chloro-11-[3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzylidene]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine. MS (ES) 444 (M+1). Purify by HPLC is 89%.

C. Mix 8-chloro-11-[3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzylidene]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (300mg,0.68mmol), HOAc (1mL), water (1mL), THF (5mL) and 30% H_2O_2 (mL). Stir the reaction at RT for 4h. Quench with aqueous $Na_2S_2O_3$ and extract the product into EtOAc. Dry ($MgSO_4$) and concentrate to give 250mg crude product. Purify by column chromatography (15% ethyl acetate/hexane) to give 66mg 3-(8-chloro-5,6-dihydro-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidenemethyl)-phenol, Z-isomer as a white solid, mp 221.2°C. MS (ES) 334 (M+1), 332 (M-1). HPLC shows 99% purity.

Example 245

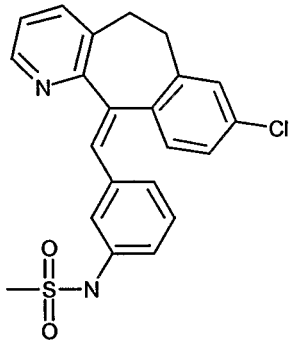
3-(8-Chloro-5,6-dihydro-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidenemethyl)-phenol, (E-isomer)



Prepared as described in Example 244, above, to provide 90mg (57%) product as a white solid, mp >250°C. MS (ES) 334 (M+1), 332 (M-1). HPLC shows 94% purity.

Example 246

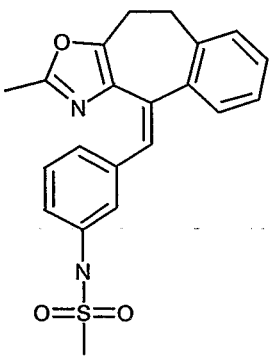
N-[3-(8-Chloro-5,6-dihydro-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidenemethyl)-phenyl]-methanesulfonamide (E isomer,)



Following procedures as described in Example 219 and using 11-bromomethylene-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (E-isomer)(820mg,2.56mmol) and 3-methanesulfonylaminophenylboronic acid (605mg,2.8mmol), provides the title compound in 53% yield as a white foam after purification on silica gel using 50% EtOAc/hexane. MS (ES) 411 (M+1), 409 9M-1). HPLC shows 97% purity.

Example 247

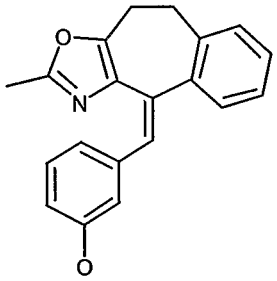
N-[3-(2-Methyl-9,10-dihydro-1-oxa-3-aza-benzo[f]azulen-4-ylidenemethyl)-phenyl]-methanesulfonamide



Prepare the corresponding ketone (2-methyl-9,10-dihydro-1-oxa-3-aza-benzo[f]azulen-4-one) as described by E.E. Galantay, et al,J. Med. Chem. (17) 1316-1327 (1974) and convert to the corresponding Z-isomer of the vinyl bromide using procedures essentially as described in Preparations 23 and 24. Then, following procedures essentially as described in Example 219, combine the ketone with 3-methanesulfonamidophenyl boronic acid (325mg, 1.5mmmol). Purify the crude product using column chromatography (30% EtOAc/hexane to 50% EtOAc/hexane) to provide 180mg (38%) Z-isomer as a light tan solid, mp 184.6°C, MS (ES) 381 (M+1), 379 (M-1). HPLC shows 94% purity at t=1.99min.

Example 248

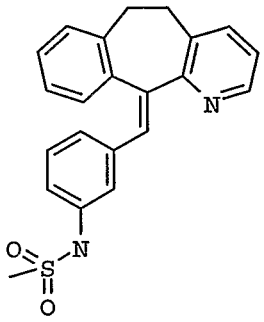
3-(2-Methyl-9,10-dihydro-1-oxa-3-aza-benzo[f]azulen-4-ylidenemethyl)-phenol



Prepare the corresponding ketone (2-methyl-9,10-dihydro-1-oxa-3-aza-benzo[f]azulen-4-one) as described by E.E. Galantay, et al,J. Med. Chem. (17) 1316-1327 (1974) and convert to the corresponding Z-isomer of the vinyl bromide using procedures essentially as described in Preparations 23 and 24. Then, following procedures essentially as described in Example 219, combine the ketone with 3-hydroxyphenyl boronic acid (207mg, 1.5mmmol). Purify the crude product using column chromatography (15% EtOAc/hexane to 30% EtOAc/hexane) to give 26mg title compound, MS (ES) 304 (M+1). HPLC shows 93% purity at t=2.48min.

Example 249

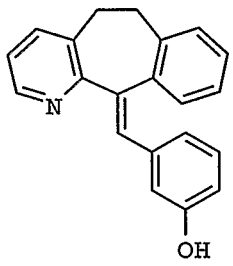
(*E*)-*N*-[3-(5,6-Dihydro-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidenemethyl)-phenyl]-methanesulfonamide (LY2076945, JN9-A01943-65)



Following procedures essentially as described in Example 219, combine 11-bromomethylene-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (250mg, 0.87mmol) and 3-methanesulfonamide-phenyl boronic acid (244mg, 1.1mmol). Purify the product via flash chromatography, eluting the product with solutions of increasing concentrations of ethyl acetate in hexanes (10% to 50%). Combine product fractions, concentrate and dry to yield 190mg (58%) of product as a white solid. LC/MS (APCI-pos): 377.1 (M+H). ^{1}H NMR ($CDCl_3$, 400 MHz): δ8.49 (dd,1H), 7.42 (d,1H), 7.32 (s,1H), 7.29 (d,1H), 7.23-7.11 (m,3H), 7.01 (bd,3H), 6.94 (d,1H), 6.86 (s,2H), 3.6-2.9 (bm, 4H), 2.78 (s,3H).

Example 250

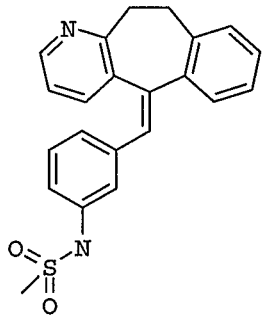
(*E*)-3-(5,6-Dihydro-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidenemethyl)-phenol



Following procedures essentially as described in Example 219, combine 11-bromomethylene-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (250mg, 0.87mmol) and (3-hydroxyphenyl) boronic acid (133mg, 0.96mmol). Purify to provide product 166mg (63%) as an off-white solid. LC/MS: 300.1 (M+H). ^{1}H NMR (DMSO, 400 MHz): δ9.22 (s,1H), 8.40 (d,1H), 7.49 (d,1H), 7.34 (d,1H), 7.24 (d,1H), 7.21 (d,3H), 7.15 (s,1H), 7.04 (t,1H), 6.92 (d,1H), 6.90 (d,1H), 6.52 (d,1H), 6.40-6.42 (m,2H), 3.4-2.8 (m,4H).

Example 251

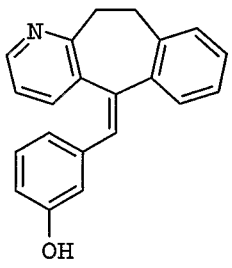
(*Z*)-*N*-[3-(10,11-Dihydro-benzo[4,5]cyclohepta[1,2-*b*]pyridin-5-ylidenemethyl)-phenyl]-methanesulfonamide



Following procedures essentially as described in Example 219, combine (*Z*)-5-bromomethylene-10,11-dihydro-benzo[4,5]cyclohepta[1,2-*b*]pyridine (153mg, 0.53mmol) with 3-methanesulfonamide-phenyl boronic acid (150mg, 0.7mmol). After work-up, purify the crude product by flash chromatography (10% ethyl acetate/hexanes to 25% ethyl acetate/hexanes to 50% ethyl acetate/hexanes) to provide 180mg (90%) of purified product. LC/MS: 377.1 (M+H) 375 (M-H). Purity by LC/MS 95%.

Example 252

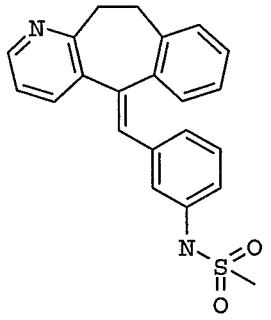
(*Z*)-3-(10,11-Dihydro-benzo[4,5]cyclohepta[1,2-*b*]pyridin-5-ylidenemethyl)-phenol



Following procedures essentially as described in Example 219, combine (*Z*)-5-bromomethylene-10,11-dihydro-benzo[4,5]cyclohepta[1,2-*b*]pyridine (153 mg, 0.53 mmol) 3-hydroxyphenyl boronic acid (85mg, 0.59mmol). After work-up, purify the crude product by flash chromatography (10% ethyl acetate/hexanes to 25% ethyl acetate/hexanes to 50% ethyl acetate/hexanes) to provide 68mg (43%) of purified product. LC/MS: (300.1 (M+H). Purity by HPLC is 95%.

Example 253

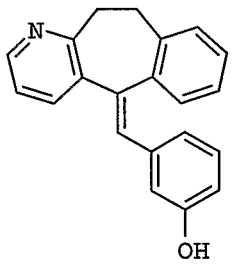
(*E*)-*N*-[3-(10,11-Dihydro-benzo[4,5]cyclohepta[1,2-*b*]pyridin-5-ylidenemethyl)-phenyl]-methanesulfonamide



Following procedures essentially as described in Example 219, combine (*E*)-5-bromomethylene-10,11-dihydro-benzo[4,5]cyclohepta[1,2-*b*]pyridine (105mg, 0.37mmol) 3-methanesulfonamide-phenyl boronic acid (103mg, 0.18mmol). After work-up, purify the crude product by flash chromatography (10% ethyl acetate/hexanes to 25% ethyl acetate/hexanes to 50% ethyl acetate/hexanes) to provide 105mg (76%) of purified product. LC/MS: 377.1 (M+H), 375 (M-H). Purity by LC/MS is 95%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ8.44 (dd,1H), 7.82 (dd,1H), 7.31 (d,2H), 7.26-7.14 (m,3H), 7.03 (dq,2H), 6.95 (dd,1H), 6.87 (d,1H), 6.80-6.77 (m,3H), 3.6-2.9 (bm,4H), 2.80 (s,3H).

Example 254

(*E*)-3-(10,11-Dihydro-benzo[4,5]cyclohepta[1,2-*b*]pyridin-5-ylidenemethyl)-phenol



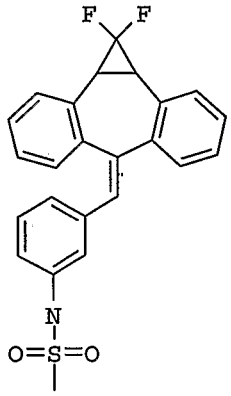
Following procedures essentially as described in Example 219, combine (*E*)-5-bromomethylene-10,11-dihydro-benzo[4,5]cyclohepta[1,2-*b*]pyridine (105mg, 0.37mmol) 3-hydroxyphenyl boronic acid (58mg, 0.4mmol). After work-up, purify the crude product

by flash chromatography (10% ethyl acetate/hexanes to 25% ethyl acetate/hexanes to 50% ethyl acetate/hexanes) to provide 45mg (41%) of purified product. LC/MS: 300.1 (M+H). ^{1}H NMR ($CDCl_3$, 400 MHz): δ8.25 (d,1H), 7.79 (d,1H), 7.18-7.12 (m,1H), 7.01-6.90 (m,5H), 6.68 (s,1H), 6.58 (dd,1H), 6.54 (d,1H), 6.37 (s,1H), 3.5-2.6 (m,4H).

Section 5 (derivatives of Formula I wherein the bridge depicted by –X—Y– represents a fused cyclopropyl structure.)

Example 255

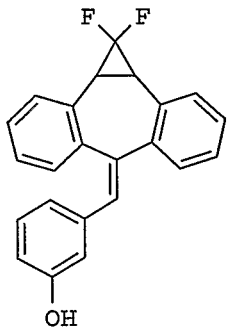
N-[3-(8,8-Difluoro-4-ylidine methyl-2,3,5,6-dibenzobicyclo[5.1.0]octane)-phenyl]-methanesulfonamide



Following procedures essentially as described in Example 219 and using 8,8-difluoro-4-bromomethylene- 2,3,5,6-dibenzobicyclo[5.1.0]octane (163mg, 0.4 mmol) and 3-(methylsulfonamido)phenylboronic acid (116mg, 0.54mmol) to provide the title compound. Evaporate and purify on silica gel (methanol/dichloromethane) to obtain 99mg (48%) of the title compound. Add ethyl acetate to obtain a crystalline material. MS (ES) 423 (M-1).

Example 256

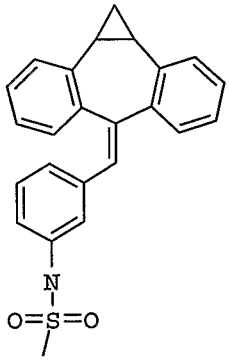
N-[3-(8,8-Difluoro-4-ylidine methyl-2,3,5,6-dibenzobicyclo[5.1.0]octane)-phenol



Following procedures essentially as described in Example 219 and using 8,8-difluoro-4-bromomethylene- 2,3,5,6-dibenzobicyclo[5.1.0]octane (166mg., 0.5mmol) and (3-hydroxypheny)boronic acid (76mg., 0.55mmol). Purify with silica gel (ethyl acetate/hexanes) chromatography to obtain 103 mg (60%) foam. MS (ES) 346 (M-1).

Example 257

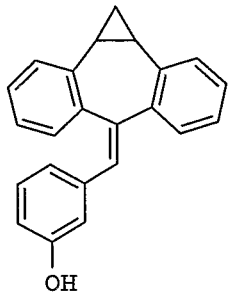
N-[3-(4-Ylidine methyl-2,3,5,6-dibenzobicyclo[5.1.0]octane)-phenyl]-methanesulfonamide



Following procedures essentially as described in Example 219 and using 4-bromomethylene- 2,3,5,6-dibenzobicyclo[5.1.0]octane (208 mg, 0.7 mmol) and 3-(methylsulfonamido)phenylboronic acid (166 mg, 0.77 mmol) to provide the title compound. Purify on silica gel using methanol/dichloromethane and ethyl acetate/hexanes by radial chromatography. Obtain 83.5mg (31%). MS (ES) 387 (M-1).

Example 258

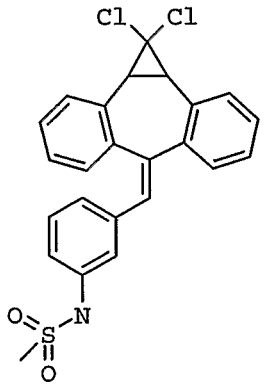
N-[3-(4-Ylidine methyl-2,3,5,6-dibenzobicyclo[5.1.0]octane)-phenol



Following procedures essentially as described in Example 219 and using 4-bromomethylene- 2,3,5,6-dibenzobicyclo[5.1.0]octane (208mg., 0.7mmol) and (3-hydroxypheny)boronic acid (106mg, 0.77 mmol) to provide the title compound. Evaporate the reaction and add to a Celite cartridge using dichloromethane. Elute with dichloromethane. Evaporate the eluent and purify on silica gel ethyl acetate/hexanes chromatography to obtain 60mg (28%)of the title compound as a foam. GC/MS t=21.49min MW=310.

Example 259

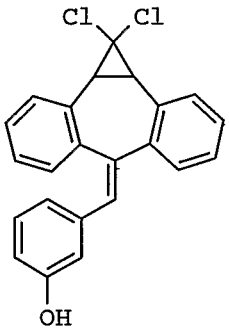
N-[3-(8,8-Dichloro-4-ylidene methyl-2,3,5,6-dibenzobicyclo[5.1.0]octane)-phenyl]-methanesulfonamide



Following procedures essentially as described in Example 219 , combine 8,8-Dichloro-4-bromomethylene-2,3,5,6-dibenzobicyclo[5.1.0]octane (160 mg, 0.44 mmol) and 3-methanesulfonamide-phenyl boronic acid (103 mg, 0.48 mmol to provide the title compound. Purify the product using radial chromatography eluting the product with solutions of increasing concentrations of ethyl acetate in hexanes (5, 10, 15, 20, and 25%). Combine product fractions, concentrate and dry to yield 120 mg (60%) of product as a white solid, mp 199-201°C. LC/MS (ES): 474 ($M+NH_4^+$), 456 (M^+).

Example 260

N-[3-(8,8-Dichloro-4-ylidene methyl-2,3,5,6-dibenzobicyclo[5.1.0]octane)-phenol

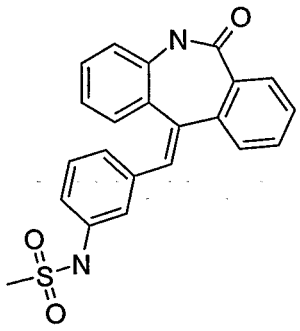


Following procedures essentially as described in Example 219 , combine 8,8-dichloro-4-bromomethylene-2,3,5,6-dibenzobicyclo[5.1.0]octane (160mg, 0.44mmol) and (3-hydroxyphenyl)-boronic acid (70mg, 0.4 mmol) to provide the title compound. Purify the product radial chromatography eluting the product with solutions of increasing concentrations of ethyl acetate in hexanes (5, 10, 15, and 20%). Combine product fractions, concentrate and dry to yield 59mg (36%) of product as a white solid. LC/MS (ES^+): 397 ($M+NH_4^+$), 379 (M^+). ^1H NMR ($CDCl_3$, 400 MHz): δ7.50 (d, 1H), 7.42 (d, 1H), 7.36 (dd, 1H), 7.35-7.26 (m, 3H), 7.12-7.02 (m, 3H), 6.72-6.62 (m, 3H), 6.55 (dd, 1H), 4.89 (s, 1H), 3.46 (d, 1H), 3.35 (d, 1H).

Section 6 (derivatives of Formula I wherein the bridge depicted by –X—Y– contains a heteroatom or heteroatom containing group at either the X or Y position.)

Example 261

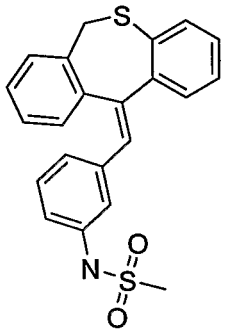
N-[3-(6-Oxo-5,6-dihydro-dibenzo[b,e]azepin-11-ylidenemethyl)-phenyl]-methanesulfonamide



Following procedures essentially as described in Example 158 and using 5H-dibenzo[b,e]azepine-6,11-dione (97mg, 0.31mmol) and methanesulfonyl chloride (26□L, 0.34mmol), followed by procedures essentially as described in Example 90, 83g of the title compound is provided in 68% yield as a white solid. ^{1}H NMR (DMSO) δ10.54(s, 1H), 9.67 (s, 1H), 7.82 (d, 1H), 7.63 (t, 1H), 7.52 (d, 1H), 7.46 (m, 1H), 7.25 (m, 2H), 7.15 (m, 1H), 7.02 (s, 1H), 6.99 (d, 1H), 6.98 (m, 2H), 6.80 (m, 2H), 2.81 (s, 3H). MS [EI+] 391 (M+H).

Example 262

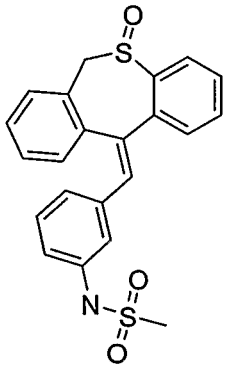
N-[3-(11H-10-Thia-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methanesulfonamide(



Dissolve 3-(11H-10-thia-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenylamine (20mg, 0.06 mmol) in 5mL of methylene chloride under a nitrogen atmosphere. Then, following procedures essentially as described in Example 90 22.3mg of the title compound is provided as a white solid. ^{1}H NMR ($CDCl_3$) δ7.49 (m, 1H), 7.48 (d, 1H), 7.35 (td, 1H), 7.25-7.15 (m, 2H), 7.15-7.10 (m, 2H), 7.10-6.95 (m, 3H), 6.87 (d, 1H), 6.79 (s, 1H), 6.24 (m, 1H), 6.10 (s, 1H), 5.00 (d, 1H), 3.55 (d, 1H), 2.80 (s, 3H). MS [EI+] 394 (M+H), 392 (M-H).

Example 263

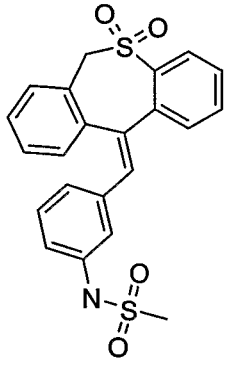
N-[3-(10-Oxo-10,11-dihydro-10λ^4-thia-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methanesulfonamide



In 5mL of acetonitrile add $Fe(NO_3)_3 \cdot 9H2O$ (5.1mg, 0.013mmol) and FeBr3 (1.9mg, .006mmol). Add N-[3-(11H-10-thia-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methanesulfonamide (50mg, 0.13mmol) and stir for 2h at ambient temperature. Extract with methylene chloride, dry ($MgSO_4$) and concentrate. Purify by recrystallization from carbon tetrachloride to yield 13.6mg of a yellow solid. ^1H NMR ($CDCl_3$) δ7.85 (m, 1H), 7.57 (m, 1H), 7.55 (m, 1H), 7.35 (td, 1H), 7.25-7.15 (m, 2H), 7.10 (d, 1H), 7.02 (dd, 1H), 7.00-6.95 (m, 3H), 6.22 (s, 1H), 4.60 (b, 2H), 3.55 (d, 1H), 2.80 (s, 3H). MS [EI+] 410 $(M+H)^+$, 408 $(M-H)^-$.

Example 264

N-[3-(10,10-Dioxo-10,11-dihydro-10λ^6-thia-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-Methanesulfonamide

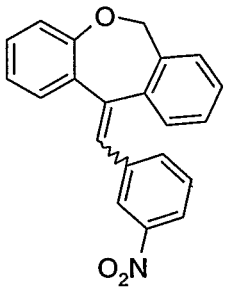


Dissolve N-[3-(10-oxo-10,11-dihydro-10λ^4-thia-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenyl]-methanesulfonamide (35mg, 0.085mmol) in 5mL of methylene chloride at ambient temperature. Add 300mg of silica gel followed by t-butylperoxide (0.012mL, 0.085mmol). Stir overnight, filter and evaporate. Recrystallize from 1:1 ether:pentane to obtain 10.6mg of the product as a yellow solid. ^1H NMR ($CDCl_3$) δ 8.91

(b, 1H), 7.85 (m, 1H), 7.57 (m, 1H), 7.55 (m, 1H), 7.35 (m, 1H), 7.25-7.15 (m, 2H), 7.10 (m, 1H), 7.02 (m, 1H), 7.00-6.95 (m, 1H), 6.30 (d, 2H), 6.15 (d, 1H), 5.25 (t, 1H), 4.40 (t, 1H), 2.80 (s, 3H). MS [EI+] 424 (M-H).

Example 265

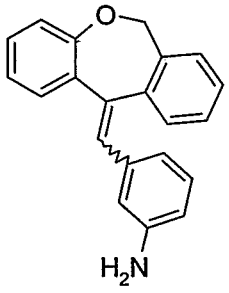
11-(3-Nitro-benzylidene-6,11-dihydro-dibenzo[b,e]oxepine



Following procedures as described in Example 229 combine 11-bromomethylene-6,11-dihydydro-dibenzo[b,e]oxepine (500mg) with m-nitrophenyl boronic acid (290mg). Flash chromatography eluting with 1:1 toluene:hexanes gave 310g of a 3:1 mix of both isomers(54.4% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96-7.94 (d, 1H), 7.87 (s, 1H), 7.52-7.47 (m, 2H), 7.37-7.16 (m, 5H), 7.00-6.95 (t, 3H), 6.85-6.83 (d, 1H).

Example 266

3-(6H-Dibenzo[b,e]oxepin-11-ylidenemethyl)-phenylamine



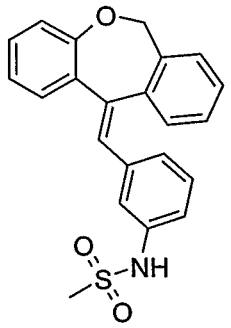
Dissolve 11-(3-Nitro-benzylidene-6,11-dihydro-dibenzo[b,e]oxepine (200mg) in ethanol (10mL) add tin chloride dihydrate (680mg) and reflux for 5h. Concentrate the reaction in vacuo, re-dissolve in ethyl acetate and wash with 1N sodium hydroxide solution. Separate the layers wash with brine and dry over sodium sulfate. Purity using filter

chromatography eluting with 10% ethyl acetate:toluene to give 60mg of product (56% yield).

MS m/z: 300 (M^+ +1).

Example 267

N-[3-(6H-Dibenzo[b,e]oxepine-11-ylidenemethyl)-phenyl]-methanesulfonamide

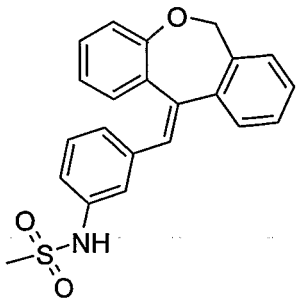


Following the procedures essentially as described in Example 90, the aniline of Example 266 (180mg) is reacted with methanesulfonyl chloride (50L) to provide the title compound. Elute with 1-3-6% ethyl acetate:toluene (silica gel) over a step gradient to give 40mg title product (17.6% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.5-7.46 (t, 2H), 7.34-7.30 (t, 1H), 7.21-7.15 (m, 3H), 7.06-6.9 (m, 5H), 6.83-6.80 (d, 1H), 6.76 (s, 1H), 6.16 (s, 1H), 2.8 (s, 3H).

MS m/z: 376.1 (M^--1).

Example 268

N-[3-(6H-Dibenzo[b,e]oxepin-11-ylidenemethyl)-phenyl]-methanesulfonamide



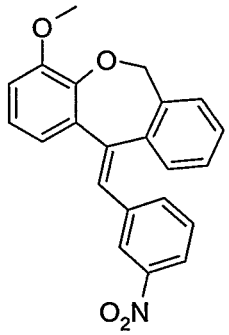
Following the procedures essentially as described in Example 90, the aniline of Example 266 (180mg) is reacted with methanesulfonyl chloride (50L) to provide 5mg (2.2% yield) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.45 (d, 1H), 7.41-7.37 (m,

1H), 7.34-7.32 (m, 2H), 7.20-7.17 (d, 1H), 7.15-6.99 (m, 5H), 6.90-6.88 (d, 1H), 6.67-6.61 (m, 2H), 6.26 (s, 1H), 5.33 (broad s, 2H), 2.87 (s, 3H).

MS m/z: 376.1 (M$^-$-1).

Example 269

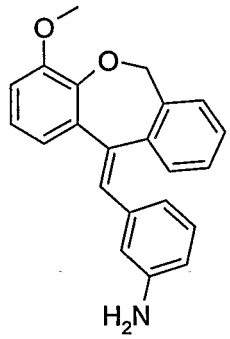
E-4-Methoxy-11-(3-nitro-benzylidene)-6,11-dihydro-dibenzo[b,e]oxepine



Following procedures essentially as described in Example 230, 11-bromomethylene-4-methoxy-6,11-dihydro-dibenzo[b,e]oxepine is combined with m-nitrophenyl boronic acid. The pure E isomer is isolated by recrystallization with hexanes and diethyl ether to give 311 mg of product (33% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.979-7.949 (d, 1H), 7.874 (s, 1H), 7.509-7.491 (d, 1H), 7.365-7.324 (t, 1H), 7.305-7.237 (m, 2H), 7.204-7.162 (t, 1H), 7.123-7.100 (d, 1H), 6.992-6.912 (m, 3H), 6.864-6.840 (d, 1H), 5.75 (broad s, 1H), 5.19 (broad s, 1H), 3.84 (s, 3H).

Example 270

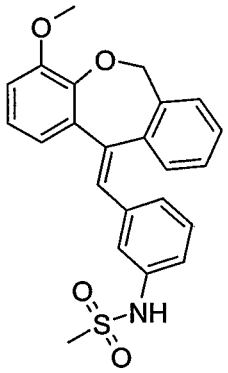
3-(4-Methoxy-6H-dibenzo[b,e]oxepin-11-ylidenemethyl)-phenylamine



Prepare the title compound by $SnCl_2$ reduction of 4-methoxy-11-(3-nitro-benzylidene)-6,11-dihydro-dibenzo[b,e]oxepine (from Example 270) to provide 267mg of product (93.7% yield). This material is used without further characterization.

Example 271

N-[3-(4-Methoxy-6H-dibenzo[b,e]oxepin-11-ylidenemethyl)-phenyl]-methanesulfonamide



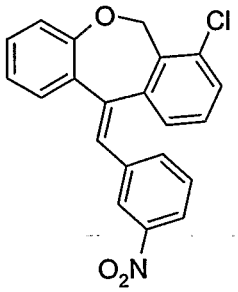
Following procedures essentially as described in Example 90, the title compound is prepared from 3-(4-Methoxy-6H-dibenzo[b,e]oxepin-11-ylidenemethyl)-phenylamine and methanesulfonyl chloride. Flash chromatography eluting with 5 to 10 to 20% ethyl acetate:toluene provides 198mg product (60% yield) of the title final product.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.482-7.463 (d, 1H), 7.321-7.237 (m, 2H), 7.193-7.149 (t, 1H), 7.110-7.086(d, 1H), 7.035-6.973 (m, 2H), 6.936-6.881 (m, 3H), 6.840-6.815 (d, 1H), 6.763 (s, 1H), 6.127 (s, 1H), 3.83 (s, 3H), 2.80 (s, 3H).

MS m/z: 406.1 (M^--1).

Example 272

7-Chloro-11-(3-nitro-benzylidene)-6,11-dihydro-dibenzo[b,e]oxepine

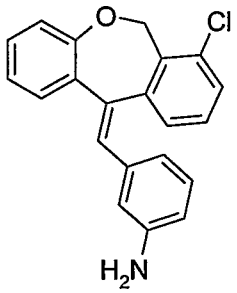


Following procedures essentially as described in Example 230, 11-bromomethylene-7-chloro-6,11-dihydro-dibenzo[b,e]oxepine is combined with m-nitrophenyl boronic acid to provide the title compound. The pure Z isomer is isolated by crystallization (diethyl

ether) to give 1.4g (31.7% yield) product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.038-8.017 (d, 1H), 7.976 (s, 1H), 7.511-7.491 (d, 1H), 7.431-7.410 (d, 1H), 7.369-7.253 (m, 3H), 7.160-7.121 (t, 1H), 7.041-7.005 (m, 2H), 6.928-6.919 (d, 1H), 6.908-6.898 (d, 1H), 5.60 (s, 2H).

Example 273

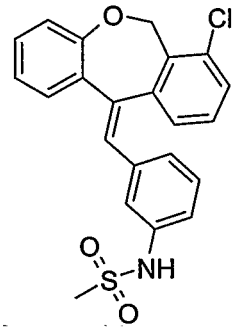
3-(7-Chloro-6H-dibenzo[b,e]oxepin-11-ylidenemethyl)-phenylamine



Prepare the title compound by $SnCl_2$ reduction of 7-chloro-11-(3-nitro-benzylidene)-6,11-dihydro-dibenzo[b,e]oxepine (from Example 272) to provide 900mg (98%)of product. MS m/z: 334.1 (m^+ +1).

Example 274

N-[3-(7-Chloro-6H-dibenzo[b,e]oxepin-11-ylidenemethyl)-phenyl]-methanesulfonamide



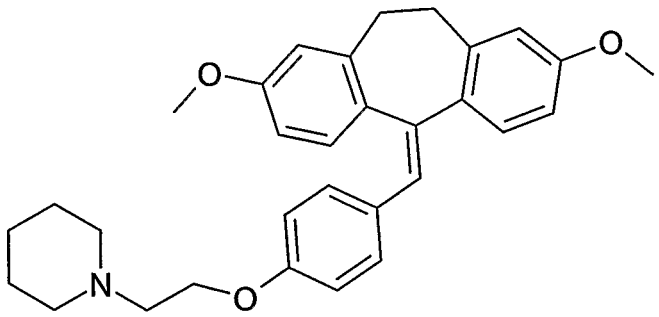
Following procedures essentially as described in Example 90, the title compound is prepared from 3-(7-chloro-6H-dibenzo[b,e]oxepin-11-ylidenemethyl)-phenylamine and methanesulfonyl chloride. Elute on silica gel with 15% ethyl acetate:toluene gave 530mg product (86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.463-7.443 (d, 1H), 7.358-7.337 (d, 1H),

7.230-7.155 (m, 2H), 7.116-7.077 (t, 1H), 7.016-6.840 (m, 7H), 6.264 (s, 1H), 5.563 (s, 2H), 2.88 (s, 3H) MS m/z: 410.1 (M^--1).

Section 2

Preparation 30

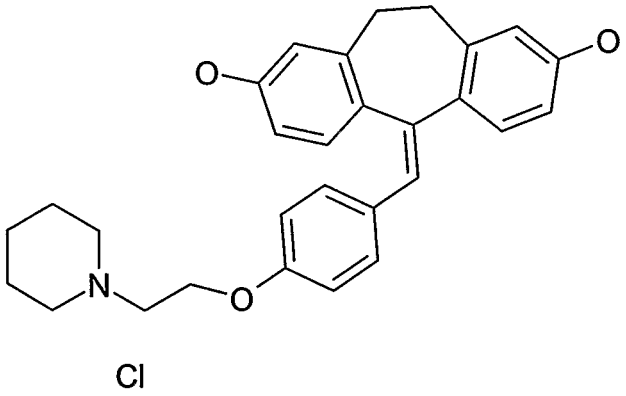
1-{2-[4-(2,8-Dimethoxy-10,11-dihydro-dibenzo[*a,d*]cyclohepten-5-ylidenemethyl)-phenoxy]-ethyl}-piperidine



Mix 5-bromomethylene-2,8-dimethoxy-10,11-dihydro-5H-dibenzo[*a,d*]cycloheptene (270mg, 0.78mmol) and 1-[2-(phenoxy-4-boronic acid)-ethyl]-piperidine (580mg, 2.35 mmol) in 1,4-dioxane (8mL) and aqueous sodium carbonate (2.0 M, 2mL). Sparge solution with N_2 for 15 min, then add $Pd(Ph_3P)_4$ (140mg, 0.12mmol) and heat to 85°C for 2 h. Cool reaction mixture to room temperature, dilute with dichloromethane (100mL), and wash organic once with saturated aqueous ammonium chloride. Dry ($MgSO_4$) and concentrate organics to a brown oil. Chromatography on silica gel (40g), eluting with 5 : 1 dichloromethane : methanol affords 180mg (50%) of the title compound as a light brown oil. MS (ES) 470 (M+H); TLC R_f = 0.40 (5 : 1 dichloromethane : methanol).

Example 275

5-[4-(2-Piperidin-1-yl-ethoxy)-benzylidene]-10,11-dihydro-5H-dibenzo[*a,d*]cycloheptene-2,8-diol hydrochloride

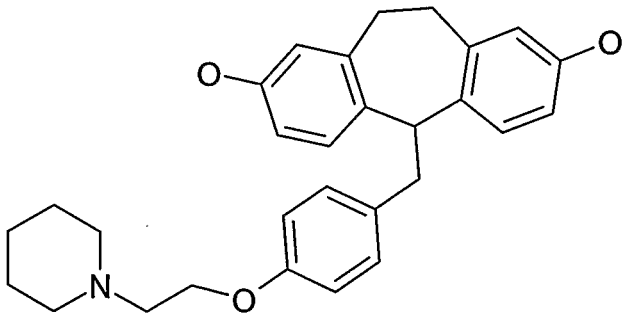


Cl

Mix 1-{2-[4-(2,8-dimethoxy-10,11-dihydro-dibenzo[*a,d*]cyclohepten-5-ylidenemethyl)-phenoxy]-ethyl}-piperidine (180mg, 0.38mmol) and ethereal hydrogen chloride (1.0 M, 1 mL) in dichloromethane (5mL). Concentrate under reduced pressure. Dilute residue with dichloromethane (5mL) and cool to 0°C. Add boron tribromide (100uL, 1.14mmol) and allow to warm to ambient temperature. Dilute with dichloromethane (50mL) and saturated aqueous sodium bicarbonate (10mL). Separate organics, dry over ($MgSO_4$), and concentrate to a brown oil. Chromatography on silica gel (40g), eluting with 5 : 1 dichloromethane : methanol yields the product as a light brown oil. React with ethereal hydrogen chloride (1.0 M, 1mL) in dichloromethane (5mL). Concentrate under reduced pressure. Isolate the hydrochloride salt which weighs 70mg (50%) MS (ES) 442 (M+H); TLC R_f = 0.35 (5 : 1 dichloromethane : methanol); ^{1}H-NMR (DMSO) δ 1.29 – 1.40 (br m, 2H), 1.83 – 1.60 (br m, 4H), 2.59 – 3.26 (br m, 8H), 3.36 – 3.48 (br m, 2H), 4.30 (br s, 2H); 6.42 (dd, J=8.3, 5.9Hz, 1H), 6.47 (d, J=2.3Hz, 1H), 6.57 (dd, J=8.4, 2.7Hz, 1 H), 6.59 (s, 1H), 6.63 (d, J=8.3Hz, 1H), 6.70 (d, J=2.3Hz, 1H), 6.77 (d, J=9.0Hz, 2H), 6.94 (d, J=8.9Hz, 2H), 7.22 (d, J=8.4Hz, 1H), 9.27 (s, 1H), 9.34 (s, 1H), 10.08 (br s, 1H).

Example 276

5-[4-(2-Piperidin-1-yl-ethoxy)-benzyl]-10,11-dihydro-5H-dibenzo[*a,d*]cycloheptene-2,8-diol hydrochloride



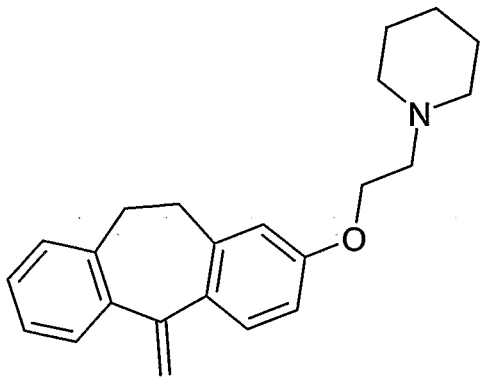
Cl

Mix 5-[4-(2-piperidin-1-yl-ethoxy)-benzylidene]-10,11-dihydro-5H-dibenzo[*a,d*]cycloheptene-2,8-diol (25mg, 0.06mmol) and 10% palladium on carbon (10mg) in ethanol (5mL). Place under ambient hydrogen atmosphere. Stir overnight. Filter through Celite and concentrate under reduced pressure. Chromatography on silica gel (40g), eluting with 5 : 1 dichloromethane : methanol yields the product as a light brown oil. React with ethereal hydrogen chloride (1.0 M, 1 mL) in dichloromethane (5 mL). Concentrate under reduced pressure. Isolate the hydrochloride salt which weighs 25mg (95%) MS (ES) 444 (M+H); TLC $R_f = 0.35$ (5 : 1 dichloromethane : methanol).

Section 7 (derivatives of Formula I wherein R8 is not hydrogen and the bridge depicted by –X—Y– contains either a heteroatom or heteroatom containing group at either the X or Y position or both X and Y are CH_2.)

Preparation 31

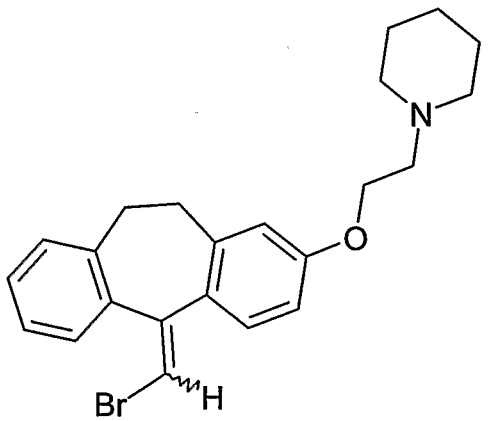
1-[2-(5-Methylene-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-2-yloxy)-ethyl]-piperidine



Dissolve 5-methylene-10,11-dihydro-5H-dibenzo[*a,d*]cyclohepten-2-ol (200mg, 0.90mmol) in dimethylformamide (5mL). Add sodium hydride (90mg, 2.25mmol) followed by 2-chloro-ethyl-1-piperidine hydrochloride (190mg, 1.03mmol). Stir at room temperature overnight. Dilute with dichloromethane (50mL) and saturated aqueous ammonium chloride (15mL). Separate organic, dry over magnesium sulfate , filter and concentrate under reduced pressure. Chromatograph the residue on silica gel (40g), eluting with 5 : 1 dichloromethane : methanol. Isolate the product as a light brown oil which weighs 300mg (100%) MS (ES) 334 (M+H); TLC R_f= 0.45 (5 : 1 dichloromethane : methanol).

Preparation 32

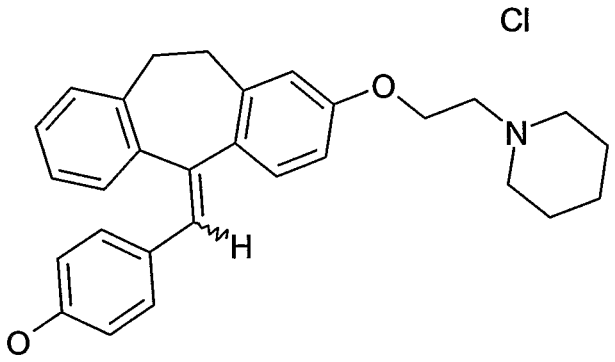
1-[2-(5-Bromomethylene-10,11-dihydro-5H-dibenzo[*a,d*]cyclohepten-2-yloxy)-ethyl]-piperidine



Dissolve 1-[2-(5-methylene-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-2-yloxy)-ethyl]-piperidine (360mg, 1.08mmol) in dichloromethane (15mL). Add dimethylaminopyridinium tribromide (390mg, 1.08mmol). Stir at room temperature for 30min. Dilute with dichloromethane (50mL) and 10% aqueous sodium thiosulfite (15mL). Separate organic, dry over magnesium sulfate , filter and concentrate under reduced pressure. Chromatograph the residue on silica gel (40g), eluting with 5 : 1 dichloromethane : methanol. Isolate the product as a light brown oil which weighs 210mg (47%) MS (ES) 414 (M+H); TLC R_f= 0.48 (5 : 1 dichloromethane : methanol).

Example 277

4-[2-(2-Piperidin-1-yl-ethoxy)-10,11-dihydro-dibenzo[*a,d*]cyclohepten-5-ylidenemethyl]-phenol hydrochloride



Mix 1-[2-(5-bromomethylene-10,11-dihydro-5H-dibenzo[*a,d*]cyclohepten-2-yloxy)-ethyl]-piperidine (210mg, 0.51mmol) and 4-hydroxyphenylboronic acid (110mg, 0.76mmol) in 1,4-dioxane (7mL) and aqueous sodium carbonate (2.0 M, 4mL). Sparge solution with N_2 for 15 min, then add $Pd(Ph_3P)_4$ (60mg, 0.05mmol) and heat to 85°C for 2 h. Cool reaction mixture to room temperature, dilute with dichloromethane (100mL), and wash organic once with saturated aqueous ammonium chloride. Dry ($MgSO_4$) and concentrate organics to a brown oil. Chromatograph the residue on silica gel (40g), eluting with 5 : 1 dichloromethane : methanol. Isolate the product as a light brown oil. . React with ethereal hydrogen chloride (1.0 M, 1 mL) in dichloromethane (5 mL). Concentrate under reduced pressure. Isolate the hydrochloride salt which weighs 110mg (47%) MS (ES) 426 (M+H); TLC R_f = 0.40 (5 : 1 dichloromethane : methanol). NMR data is reported for the free base of the major olefin isomer: ^{1}H-NMR ($CDCl_3$) δ 1.42–1.48 (br m, 2H), 1.58–1.65 (br m, 4H), 2.49–2.58 (br m, 4H), 2.70-3.50 (br m, 4H), 2.77 (t, J=6.2Hz, 2H), 4.70 (t, J=6.3Hz, 2H); 6.49-6.58 (m, 4H), 6.64 (s, 1H), 6.76 (d, J=9.0Hz, 2H), 6.98-7.04 (m, 2H), 7.18 (dt, J=7.4, 1.8Hz, 1H), 7.25 (d, J=7.5Hz, 1H), 7.32 (d, J=8.7Hz, 1H).

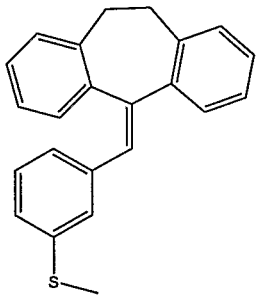
Additional Examples

The following additional preparations and examples further illustrate the invention and represent typical synthesis for the compounds of Formula I, including any novel compounds, as described generally above.

Additional preparations for, and examples of compounds of Formula I having substitution on the "C" ring but not on the "A" or "B" rings. (Section 1 as represented by original Examples 1-160)

Example 278

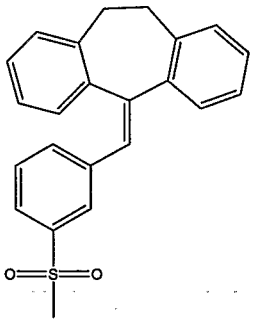
5-(3-Methylsulfanyl-benzylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene



Following procedures as described in Example 219, mix 5-bromomethylene-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (1 equivalent), 4,4,5,5-tetramethyl-2-(3-methylsulfanyl-phenyl)-[1,3,2]dioxaborolane (1.25 equivalents), 2N Na_2CO_3 (2 equivalents) and *tetrakis*triphenylphosphine palladium (0.05 equivalents)in a suitable solvent. Purify the product by silica gel chromatography to obtain a 79% yield of the title compound. MS(ES) = 329(+)

Example 279

5-(3-Methanesulfonyl-benzylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene



Mix 5-(3-methylsulfanyl-benzylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (1 equivalent) and sodium perborate hydrate (2.2 equivalents) in 50:50

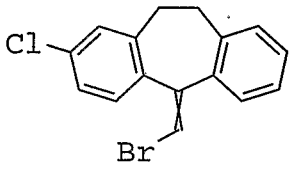
dichloromethane/glacial acetic acid and stir at room temperature for 18 hours. Then warm to 45°C for four hours. Partition between dichloromethane and 0.1N NaOH. Dry and evaporate the organic layer. Purify the product by silica gel chromatography to obtain a 72% yield of the title compound. MS(ES) = 361(+)

Examples 280-288 contained in Table II, herein, provide yet additional examples of compounds of Formula I having substitution on the "C" ring, but not on the "A" or "B" rings. These examples, which further illustrate the present invention are prepared according to the procedures as described generally in the Schemes and literature references described above.

Additional preparations for, and examples of compounds of Formula I having having substitution on both the "C" ring and the "A" and/or "B" rings. (Section 2 as represented by original Examples 161-215)

Preparation 33

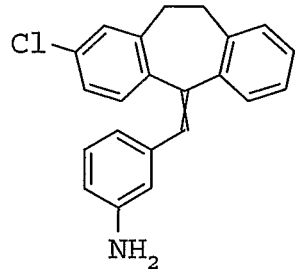
E- and Z-5-Bromomethylene-2-chloro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene



Cool a mixture of 2.8 equiv of bromomethyltriphenylphosphonium bromide (prepared asdescribed in G. Vassilikogiannakis, M. Hatzimarinaki, M. Orfanapoulos *J. Org. Chem.*, **65**, 8180) in THF (0.5 M) to –78 °C and add 2.8 equiv of LiHMDS-THF dropwise to give a bright yellow mixture. Stir for 1 h at –78 °C and then 10 min at 0 °C. Recool the mixture to –78 °C and add 2-chloro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-one. Allow the dark mixture to warm to room temperature and stir for 3.5 h before adding saturated, aqueous saturated ammonium chloride and diluting with pentane. Filter through celite, concentrate filtrate and concentrate under reduced pressure. Purify by column chromatography (1% to 2% to 3% to 5% EtOAc:hexanes) to give title compound (30 %)as a 1:1 mixture of geometric isomers: GC-MS (GRAD60-280°C) t = 7.23 (90 %). MS (EI): 320 (M+).

Example 289

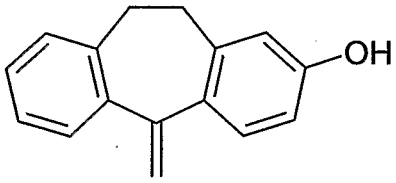
3-(2-Chloro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-phenylamine



Following procedures essentially as described in Example 219, and using 5-bromomethylene-2-chloro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene and 3-aminophenylboronic acid, a mixture of the E and Z isomers of the title compound is prepared.

Preparation 34

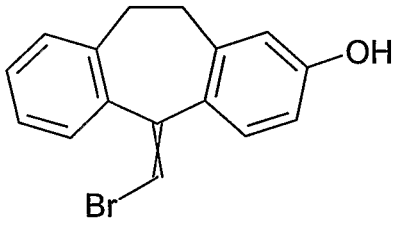
5-Methylene-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-2-ol



Prepared from commercially available 2-hydroxy-10,11-dihydro-dibenzo[a,d]cyclohepten-5-one following procedures essentially as described in Preparation 23. MS (ES-) 221.

Preparation 35

5-Bromomethylene-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-2-ol



Prepared from 5-methylene-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-2-ol using procedures essentially as described in Preparation 24. MS (ES-) 301.

Examples 290-435 contained in Table II, herein, provide yet additional examples of compounds of Formula I having substitution on both the "C" ring and the "A" and/or "B" rings. These examples, which further illustrate the present invention are prepared according to the procedures as described generally in the Schemes and literature references described above.

Additional preparations for, and examples of compounds of Formula I wherein the "C" ring represents a heterocyclic or benzofused heterocyclic ring. (Section 3 as represented by original Examples 216-237)

Preparation 36

1-(2-morpholin-4-yl-ethyl)-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1,3-dihydro-benzoimidazol-2-one.

Following procedures as described in Scheme IX.

Step A: Preparation of (4-bromo-2-nitro-phenyl)-(2-morpholin-4-yl-ethyl)-amine.

Mix 5-bromo-2-fluoro-nitrobenzene (10g, 45mmol) and 4-(2-aminoethyl)morpholine (11.8mL, 90mmol) in THF (100mL). Stir at room temperature for 18h. Remove the THF under reduced pressure and partition the residue between water (200mL) and ethyl acetate (200mL). Dry the organic layer (MgSO4) and concentrate to give 15.3g (100%) title compound. HPLC (ISO80-10M) t=1.83min (94%), MS (ES) 331 (M+1).

Step B: Preparation of 4-bromo-N1-(2-morpholin-4-yl-ethyl)-benzene-1,2-diamine

Dissolve (4-bromo-2-nitro-phenyl)-(2-morpholin-4-yl-ethyl)-amine (15.3g, 46.4mmol) in ethyl acetate (1L) and add 5% Pt/C (sulfided) (382mg). Place the slurry under 60psi hydrogen gas at room temperature of 8h. Filter and concentrate to give 23g crude product as a dark red oil. Purify using a short plug of silica gel and 10% 2N NH3 in MeOH/dichloromethane to give 13.5g of a brown oil. HPLC (ISO60-10M) t=1.46 (94%), MS (ES) 301 (M+1).

Step C: Preparation of 5-bromo-1-(2-morpholin-4-yl-ethyl)-1,3-dihydro-benzoimidazol-2-one.

In a 500-mL round-bottomed flask, mix 4-bromo-N1-(2-morpholin-4-yl-ethyl)-benzene-1,2-diamine 13.25g, 44.1mmol),NaHCO3 (5.4g, 66.2mmol), water (50mL) and methanol (250mL). Slowly add phenyl chloroformate (8.3mL,66.2mmol). Stirr the reaction for 1h at room temperature and then add 5N NaOH (20mL) and stir overnight at room temperature. Collect the solid by vacuum filtration and wash with methanol. HPLC (ISO60-10M) t=1.42 (97%), MS (ES) 326 (M+1).

Step D: Preparation of 1-(2-morpholin-4-yl-ethyl)-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1,3-dihydro-benzoimidazol-2-one.

Under a blanket of nitrogen, cool a THF (150mL) solution of 5-bromo-1-(2-morpholin-4-yl-ethyl)-1,3-dihydro-benzoimidazol-2-one (7.5g, 20mmol) to 5°C and add 3N ethylmagnesium bromide (8mL, 24mmol). After ½h, cool the reaction to –72°C and slowly add 1.7M t-BuLi (170mL, 100mmol). Allow the reaction to warm to –55°C, add trimethyl borate (80mmol) and allow the reaction to stir at room temperature overnight. Add 5N HCl (50mL) and stir for 4h. Adjust the pH to 6-7 and extract the crude boronic acid into ethyl acetate. Dry (MgSO4) and concentrate to give 10.4g crude product. Slurry with toluene (500mL) and add pinacol (64mmol). Heat briefly and then stir overnight. Add ethyl acetate and aqueous NaHCO3. Wash the organic extract with water and evaporate the dried (MgSO4) organic layer to give 5.0g (67%) title boronic ester as a white solid. LC/MS (ISO70-10M) 374 (M+1). Recrystallize from ethyl acetate/hexane.

^{1}H NMR ($CDCl_3$) d 1.34 (s,12H), 2.55 (br s,4H), 2.70 (br s, 2H), 3.68 (br s,4H), 4.02 (br s,2H), 7.03 (s,1H), 7.52 (s, 1H), 7.56 (d, 1H), 8.78 (br s, 1).

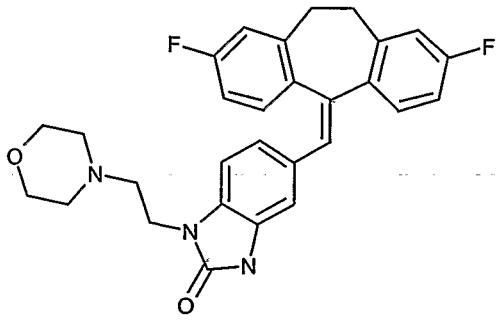
Preparation 37

5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1,3-dihydro-benzoimidazol-2-one

5-Bromo-1,3-dihydro-benzoimidazol-2-one (20.0 g, 93.9 mmol) is dissolved in argon purged anhydrous DMF (150 mL). To this solution is added bis(pinacolato)diboron (28.6 g, 113 mmol), KOAc (27.6 g, 282 mmol), and $PdCl_2$(dppf), 1:1 complex with CH_2Cl_2 (7.67 g, 9.40 mmol). The reaction is heated to 95 °C overnight with mechanical stirring then cooled to room temperature and diluted with brine (500 mL) and EtOAc (750 mL). The mixture is filtered to remove a dark brown solid, which is washed thoroughly with EtOAc. The layers are separated and the organics washed with water (3 x 500 mL), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. Trituration with 1:1 CH_2Cl_2/hexanes affords the product (10.9 g, 44%).
R_f 0.52 (silica gel, 85:15 CH_2Cl_2/MeOH); mp 313–315 °C (dec); ^{1}H NMR (300 MHz, DMSO-d_6) □1.27 (s, 12 H), 6.92 (d, J = 7.7 Hz, 1H), 7.17 (s, 1H), 7.28 (d, J = 7.7 Hz, 1H), 10.62 (s, 1H), 10.74 (s, 1H); APCI MS m/z 261 $[C_{13}H_{17}BN_2O_3 + H]^+$; HPLC = 98.3%, t_R = 18.3 min; Analysis for $C_{13}H_{17}BN_2O_3$: C, 57.07; H, 6.82; N, 10.24. Found: C, 56.69; H, 6.44; N, 10.21.
HPLC conditions:
Waters Symmetry C18 column (4.6 mm x 250 mm); 95:5 to 0:100 water/MeCN; 1.0 mL/min (25 min), □ = 254 nm

Example 436

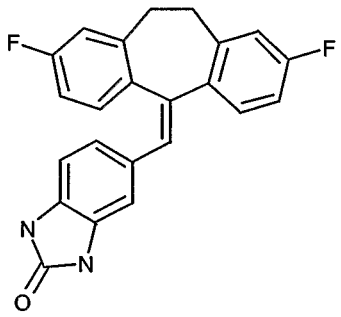
5-(2,8-difluoro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-1-(2-morpholin-4-yl-ethyl)-1,3-dihydro-benzoimidazol-2-one



Following procedures essentially as described in Example 219, mix 1-(2-morpholin-4-yl-ethyl)-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1,3-dihydro-benzoimidazol-2-one (520mg, 1.4mmol), 5-bromomethylene-2,8-difluoro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (510mg, 1.6mmol)(prepared using a procedure essentially as described for the 2,8-dichloro derivative in Example 182), 2N Na_2CO_3 (1mL), dioxane (10mL) and $(Ph_3P)_4Pd$ (67mg, 0.06mmol). Purify the crude product by column chromatography using MeOH/ethyl acetate to give 310mg colorless oil that solidified upon drying, HPLC (ISO80-10M) t=2.03 (97%). MS (ES) 488 (M+1), 486 (M-1). H NMR 10.69 (s, 1H), 7.49 (dd, 1H, *J*=8.4, 6.2 Hz), 7.22 (dd, 1H, *J*=9.7, 2.2 Hz), 7.02 (td, 1H, *J*=12.0, 4.2 Hz), 6.97-6.83 (m, 4H), 6.81 (s, 1H), 6.72 (d, 1H, *J*=7.9 Hz), 6.56 (s, 1H), 3.80 (t, 2H, *J*=6.2 Hz), 3.47 (t, 4H, *J*=4.2 Hz), 3.31 (s, 2H), 2.90 (s, 2H), 2.48 (m, 2H), 2.38 (s, 4H).

Example 437

5-(2,8-difluoro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-1,3-dihydro-benzoimidazol-2-one

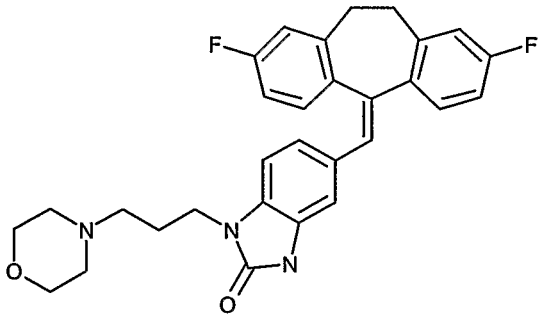


Following procedures essentially as described in Example 219, mix 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1,3-dihydro-benzoimidazol-2-one (535mg, 2.06mmol) (prepared from 5-bromo-1,3-dihydro-benzoimidazol-2-one (Preparation 27) according to the procedure reported by M Murata, T Takashi, S Watanabe and Y Yusuru, J. Org. Chem.; 65 (1) 164-168 (2000)), 5-bromomethylene-2,8-difluoro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (550mg, 1.71mmol), 2N Na_2CO_3 (2mL), dioxane (14mL) and $(Ph_3P)_4Pd$ (200mg, 0.17mmol). Purify the crude product by column chromatography using dichloromethane/ethyl acetate to give 285mg white solid, mp 257°C. HPLC (ISO80-10M) t=2.62 (97%), MS (ES) 373 (M-1). H NMR 10.55 (s, 1H), 10.45 (s, 1H), 7.48 (dd, 1H, *J*=8.4, 6.2 Hz), 7.21 (dd, 1H, *J*=9.7, 2.2 Hz), 7.01 (td, 1H, *J*=12.2, 4.2 Hz),

6.94 (dd, 1H, *J*=10.1, 2.2 Hz), 6.90 (d, 2H, *J*=6.2 Hz), 6.85 (dd, 1H, *J*=8.6, 2.4 Hz), 6.78 (s, 1H), 6.72 (d, 1H, *J*=8.4 Hz), 6.67 (d, 1H, *J*=7.9 Hz), 6.51 (s, 1H), 3.30 (s, 2H), 2.89 (s, 2H), 6.90 (d, 1H, *J*=6.2 Hz).

Example 438

5-(2,8-difluoro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-1-(3-morpholin-4-yl-propyl)-1,3-dihydro-benzoimidazol-2-one



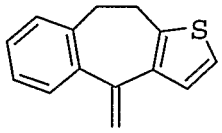
Following procedures essentially as described in Example 219, mix 1-(2-morpholin-4-yl-propyl)-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1,3-dihydro-benzoimidazol-2-one (458mg, 1.18mmol), 5-bromomethylene-2,8-difluoro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (400mg, 1.25mmol), 2N Na_2CO_3 (1.3mL), dioxane (8mL) and $(Ph_3P)_4Pd$ (45mg, 0.04mmol). Purify the crude product by column chromatography using 2% 2N NH_3 in MeOH/dichloromethane to give 170mg title compound as a white foam. HPLC (ISO80-10M) t=1.86 (98%), MS (ES) 502 (M+1), 500 (M-1). H NMR 8.38 (s, 1H), 7.42 (dd, 1H, *J*=8.4, 5.7 Hz), 7.01 (dd, 1H, *J*=9.2, 2.6 Hz), 6.95 (dd, 1H, *J*=8.4, 5.7 Hz), 6.91 (dd, 1H, *J*=8.4, 2.6 Hz), 6.85 (d, 1H, *J*=8.4 Hz), 6.80 (dd, 1H, *J*=9.7, 2.2 Hz), 6.71 (dd, 1H, *J*=8.6, 2.4 Hz), 6.64 (s, 1H), 3.89 (t, 2H, *J*=6.8 Hz), 3.68 (s, 4H), 3.59-2.71 (m, 4H), 1.60 (s, 2H), 1.94 (s, 2H), 2.40 (s, 4H), 6.76 (m, 2H).

Examples 439-474 contained in Table II, herein, provide yet additional examples of compounds of Formula I wherein the "C" ring represents a heterocyclic or benzofused heterocyclic ring. These examples, which further illustrate the present invention are prepared according to the procedures as described generally in the Schemes and literature references described above.

Additional preparations for, and examples of compounds of Formula I wherein the "A" and / or "B" ring represents a heterocyclic ring. (Section 4 as represented by original Examples 238-254)

Preparation 38

4-Methylene-9,10-dihydro-4H-1-thia-benzo[*f*]azulene

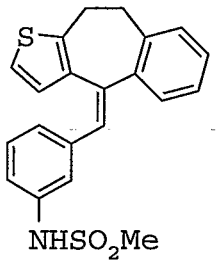


Following procedures as described in Scheme X:

Add 3 equiv of a 0.5 M solution of Tebbe reagent in toluene to a solution (-40 °C) 9,10-dihydro-1-thia-benzo[*f*]azulene-4-one (prepared as described in P. Bollinger, P. Cooper.; H. U. Gubler, A. Leutwiler, T. Payne *Helv. Chim . Acta* (1990), *73*, 1197) and 3 equiv of pyridine in THF (0.1 M) under Ar. Stir the resulting dark red mixture for 2 h then allow to warm to 0 °C over ca. 30 min period before diluting with diethyl ether. Carefully add 5 N sodium hydroxide until bubbling ceases, add solid Na_2SO_4, and then stir for 1 h. Filter the mixture through Celite®, and concentrate the filtrate by rotary evaporation. Purify the crude residue by column chromatography (hexanes) to give the title compound as white crystals (56 %): HPLC (ISO80-20M) t = 1.903 (98 %). MS (APCI): 213 (M+1). ^1H NMR ($CDCl_3$) δ 3.07-3.12 (m, 2 H), 3.14-3.17 (m, 2 H), 5.32 (s, 1 H), 5.63 (s, 1 H), 7.05 (app d, J = 5.4 Hz, 1 H), 7.08 (d, J = 5.4 Hz, 1 H), 7.19-7.26 (m, 3 H), 7.35 (dd, J = 7.6 Hz, 1.6 Hz, 1 H).

Example 475 and Example 476

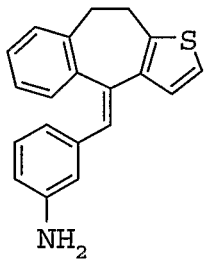




Following procedures essentially as described in Preparation 24 followed by procedures essentially as described in Example 219, and using 4-methylene-9,10-dihydro-4H-1-thia-benzo[*f*]azulene, the title compounds are made.

Example 477

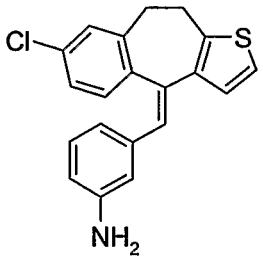
3-(9,10-Dihydro-1-thia-benzo[f]azulen-4-ylidenemethyl)-phenylamine



4-Methylene-9,10-dihydro-4H-1-thia-benzo[*f*]azulene is converted to the vinyl bromide as in Preparation 24 and the vinyl bromide coupled with 3-aminophenylboronic acid using the procedures essentially as described in Example 219.

Example 478

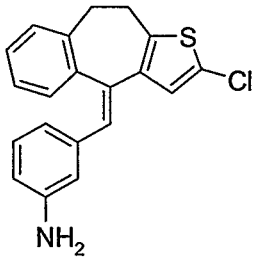
3-(7-Chloro-9,10-dihydro-1-thia-benzo[f]azulen-4-ylidenemethyl)- phenylamine



7-chloro-9,10-dihydro-benzo[4,5]cyclohepta[1,2-b]thiophen-4-one (prepared as described in Bastian *et al*, Helv. Chim. Acta; 49 214-234 (1966)) is converted to the title compound following procedures as described in Scheme VII.

Example 479

3-(2-Chloro-9,10-dihydro-1-thia-benzo[f]azulen-4-ylidenemethyl)-

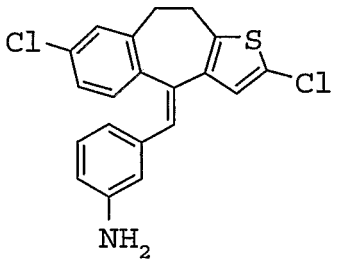


phenylamine

Add 2.2 equiv of *n*-BuLi-hexanes dropwise to a solution of 3-(9,10-dihydro-1-thia-benzo[f]azulen-4-ylidenemethyl)-phenylamine in THF (0.1 M) at 0 °C under Ar. Stir the resultant dark solution for 1 h before adding 2.5 equiv of hexachloroethane in THF. Stir for 2 h, quench with excess water, and acidify to neutral pH. Extract the aqueous layer with diethyl ether (3 X) and then dry ($MgSO_4$) and concentrate the combined organic layers under reduced pressure. Purify the crude residue by column chromatography (0% to 2% to 20% EtOAc:hexanes) to give title compound as an oil (22 %) along with recovered starting material: HPLC (ISO80-20A) t = 1.903 (90 %). MS (APCI): 338 (M+1).

Example 480

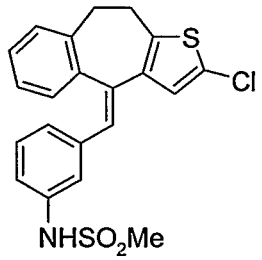
3-(2,7-Dichloro-9,10-dihydro-1-thia-benzo[f]azulen-4-ylidenemethyl)-phenylamine



As in Example 553 (above), using 3-(7-chloro-9,10-dihydro-1-thia-benzo[f]azulen-4-ylidenemethyl)-phenylamine, *n*-BuLi in hexanes, THF, and hexachloroethane. Purify the crude residue by column chromatography (5% to 20% to 30% EtOAc:hexanes) to give title compound as an oil (21 %) along with recovered starting material: ^1H NMR ($CDCl_3$, 400 MHz) δ 2.06-3.02 (m, 4 H), 3.53 (br s, 2 H), 6.32 (s, 1 H), 6.38 (d, J = 7.2 Hz, 1 H), 6.48 (dd, J = 7.2 Hz, 1.6 Hz, 1 H), 6.79 (s, 1 H), 6.93-6.96 (m, 3 H), 7.02 (dd, J = 8.2 Hz, 2.2 Hz, 1 H), 7.27 (d, J = 8.2 Hz, 1 H). TLC R_f = 0.55 (30 % EtOAc:hexanes).

Example 481

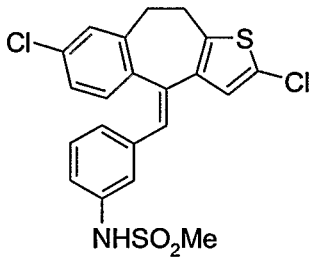
N-[3-(2-Chloro-9,10-dihydro-1-thia-benzo[f]azulen-4-ylidenemethyl)-phenyl]-methanesulfonamide



Following procedures essentially as described in Example 90 and using 3-(2-chloro-9,10-dihydro-1-thia-benzo[f]azulen-4-ylidenemethyl)-phenylamine, the title compound is prepared.

Example 482

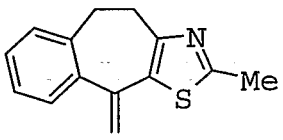
N-[3-(2,7-Dichloro-9,10-dihydro-1-thia-benzo[f]azulen-4-ylidenemethyl)-phenyl]-methanesulfonamide



Following procedures essentially as described in Example 90 and using 3-(2,7-dichloro-9,10-dihydro-1-thia-benzo[f]azulen-4-ylidenemethyl)-phenylamine, the title compound is prepared.

Preparation 39

2-Methyl-4-methylene-9,10-dihydro-4H-3-thia-1-aza-benzo[f]azulene



Add 1.2 equiv of *n*-BuLi-hexanes dropwise to a solution of 4-methylene-9,10-dihydro-4H-3-thia-1-aza-benzo[f]azulene (prepared from 9,10-dihydro-3-thia-1-aza-

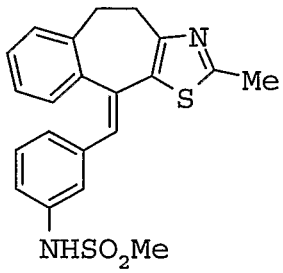
benzo[f]azulen-4-one (see Scheme XIII(b) as in Preparation 23) in THF (0.08 M) at –78 °C under Ar. Stir the resultant dark green solution for 5 min before adding 1.2 equiv of iodomethane in THF. Allow to warm and stir at room temperature for 18 h before quenching with excess water. Separate layers and extract the aqueous layer with diethyl ether (3 X) and then dry ($MgSO_4$) and concentrate the combined organic layers under reduced pressure. Use in the next step without further purification: ^1H NMR ($CDCl_3$, 400 MHz) δ 2.60 (s, 3 H), 3.03-3.13 (m, 4 H), 5.34 (s, 1 H), 5.53 (s, 1 H), 7.20-7.28 (m, 3 H), 7.33 (m, J = 7.2 Hz, 1 H). TLC R_f = 0.30 (10 % EtOAc:hexanes).

Example 483(a)

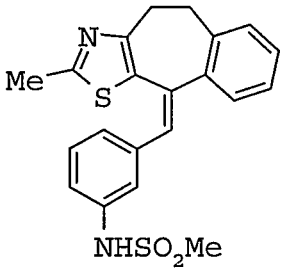
N-[3-(2-Methyl-9,10-dihydro-3-thia-1-aza-benzo[f]azulen-4-ylidenemethyl)-phenyl]-methanesulfonamide (E-isomer) ; and

Example 483(b)

N-[3-(2-Methyl-9,10-dihydro-3-thia-1-aza-benzo[f]azulen-4-ylidenemethyl)-phenyl]-methanesulfonamide (Z-isomer)



E Isomer

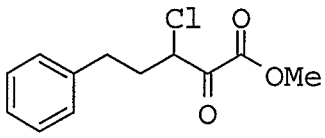


Z Isomer

Following procedures essentially as described in Preparation 24 followed by procedures essentially as described in Example 219, and using 2-methyl-4-methylene-9,10-dihydro-4H-3-thia-1-aza-benzo[f]azulene and 3-methanesulfonylaminophenylboronic acid, the title compounds are made.

Preparation 40

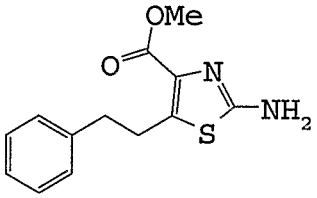
3-Chloro-2-oxo-5-phenyl-pentanoic acid methyl ester



Charge a flask with equimolar methyl dichloroacetate and 3-phenyl-prionaldehyde in diethyl ether (3.0 M). Cool the solution to 0 °C and add 1.1 equiv of sodium methoxide in methanol (2.8 M) over a 1 h period. Vigorously stir the mixture for 2 h at 0 C and then allow to warm to room temperature before adding brine. Separate layers and dry ($MgSO_4$) and concentrate organic layer to give the crude residue in 92 % yield. GC-MS (GRAD60-280°C) t = 13.01 (90 %). MS (EI): 240 (M-).

Preparation 41

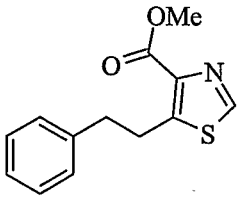
2-Amino-5-phenethyl-thiazole-4-carboxylic acid methyl ester



Reflux equimolar 3-chloro-2-oxo-5-phenyl-pentanoic acid methyl ester and thiourea in MeOH (1.0 M) for 4 h. Basify with ammonia-MeOH and add brine. Extract with ethyl acetate (4 X). Wash combined organic layers with brine, dry ($MgSO_4$), and concentrate under reduced pressure to give (91 %) of title compound. HPLC (GRAD80-100M) t = 2.193 (95 %). MS (APCI): 263 (M+1).

Preparation 42

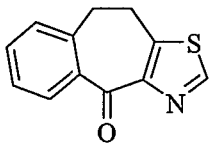
5-Phenethyl-thiazole-4-carboxylic acid methyl ester



Reflux one equiv of 2-amino-5-phenethyl-thiazole-4-carboxylic acid methyl ester and 3 equiv of isoamyl nitrite in THF (0.13M) for 3 h. Evaporate volatile components to give 55 % yield of title compound. HPLC (GRAD80-100M) t = 2.410 (99 %). MS (APCI): 248 (M+1).

Preparation 43

9,10-Dihydro-1-thia-3-aza-benzo[f]azulen-4-one



Rapidly stir and heat a thick slurry of 5-phenethyl-thiazole-4-carboxylic acid methyl ester and polyphosphoric acid (PPA) at 140 °C for 24 h and then 150 °C for 5 h. Carefully add hot mixture to ice-cold aqueous sodium hydroxide. Extract well with EtOAc (4 X). Wash combined organic layers with brine, dry ($MgSO_4$), and concentrate under reduced pressure. Purify the crude residue by column chromatography (10% to 50% EtOAc:hexanes) to give title compound as a brown solid (37 %). HPLC (GRAD80-100M) t = 2.088 (99 %). MS (APCI): 216 (M+1).

Preparation 44

9,10-Dihydro-3-thia-1-aza-benzo[*f*]azulen-4-one

To a room temperature solution of 2-amino-9,10-dihydro-3-thia-1-aza-benzo[*f*]azulen-4-one (5.31 g, 23.1 mmol) in DMF (50 mL) is added isoamyl nitrite (5.95 g, 50.8 mmol) and the reaction stirred for 30 min. The reaction mixture is heated to 80 °C for 2 h, and then cooled to room temperature. The solvent is removed under reduced pressure and ice-cold H_2O (100 mL) is added. The aqueous layer is extracted with EtOAc (2 x 150 mL) and the combined organic layers are dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The dark red oil is subjected to flash chromatography (silica gel, 75:25 Hex/EtOAc) to afford the slightly impure product as an orange-red solid. The product is further purified by trituration using Hex/EtOAc (90:10) to afford the title compound (2.59 g, 52%) as an orange solid: R_f 0.33 (1:1 EtOAc/Hex); mp 83-86 °C; ^{1}H NMR (300 MHz, $CDCl_3$) □8.89 (s, 1H), 7.96 (dd, J = 1.2, 7.7 Hz, 1H), 7.50 (dt, J = 1.4, 7.4 Hz, 1H), 7.37 (m, 1H), 7.30 (d, J = 7.5 Hz, 1H), 3.36 (m, 2H), 3.24 (m, 2H); ESI MS *m/z* 216 $[C_{12}H_9NOS + H]^+$. Anal. Calcd for $C_{12}H_9NOS$: C, 66.95; H, 4.21; N, 6.51. Found: C, 66.81; H, 3.99; N, 6.48.

Preparation 45

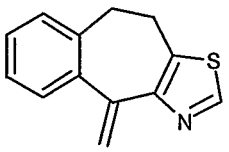
7-Fluoro-9,10-dihydro-3-thia-1-aza-benzo[*f*]azulen-4-one; and

5-Fluoro-9,10-dihydro-3-thia-1-aza-benzo[*f*]azulen-4-one

To a room temperature solution of a 85:15 mixture of 2-amino-7-fluoro-9,10-dihydro-3-thia-1-aza-benzo[*f*]azulen-4-one and 2-amino-5-fluoro-9,10-dihydro-3-thia-1-aza-benzo[*f*]azulen-4-one (6.00 g, 24.2 mmol) in DMF (80 mL) is added *t*-butyl nitrite (5.48 g, 53.2 mmol). The reaction mixture is then heated to 60 °C for 2 h (gas evolution may be observed after 5-10 min of heating), then cooled to room temperature. The solvent is removed under reduced pressure and ice-cold H_2O (100 mL) and EtOAc (700 mL) are added. The organic layer is washed with saturated aqueous $NaHCO_3$ (100 mL) and saturated aqueous NaCl (100 mL). The organic layer is dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting red oil is subjected to flash chromatography (silica gel, 80:20 to 70:30 Hex/EtOAc) to afford the products (3.16 g, 56%) as a partially separable mixture of 5- and 7-fluoro regioisomers. The fractions obtained as a mixture (1.19 g) contain some of the minor isomer (~3:7 5-fluoro/7-fluoro): ^{1}H NMR of 5-fluoro isomer, subtracted from the mixture (300 MHz, $CDCl_3$) □ 8.88 (s, 1H), 7.41 (m, 1H), 7,12-6.98 (m, 2H), 3.32 (m, 2H), 3.39-3.19 (m, 2H).
The fractions obtained pure (1.97 g) contain only the major isomer (7-fluoro) which is isolated as an orange solid: R_f 0.52 (1:1 EtOAc/Hex); mp 122-125 °C; ^{1}H NMR (300 MHz, $CDCl_3$) □ 8.89 (s, 1H), 8.02 (dd, J = 8.7, 6.0 Hz, 1H), 7.06 (m, 1H), 7.00 (dd, J = 9.1, 2.5 Hz, 1H), 3.37 (m, 2H), 3.22 (m, 2H); APCI MS *m/z* 232 [$C_{12}H_8FNOS$ - H]$^-$.
Anal. Calcd for $C_{12}H_8FNOS$: C, 61.79; H, 3.46; N, 6.00. Found: C, 61.70; H, 3.43; N, 6.04.

Preparation 46

4-Methylene-9,10-dihydro-4H-1-thia-3-aza-benzo[f]azulene



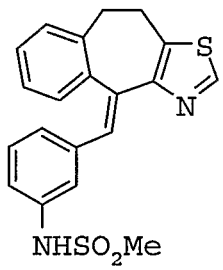
Following procedures essentially as described in Preparation 23, and using 9,10-dihydro-1-thia-3-aza-benzo[f]azulen-4-one, the title compound is made.

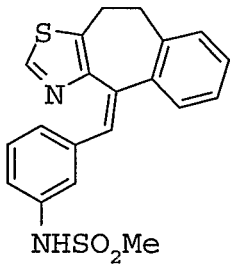
Example 484 (a)

N-[3-(9,10-Dihydro-1-thia-3-aza-benzo[f]azulen-4-ylidenemethyl)-phenyl]-methanesulfonamide (E isomer) and

Example 484 (b)

N-[3-(9,10-Dihydro-1-thia-3-aza-benzo[f]azulen-4-ylidenemethyl)-phenyl]-





methanesulfonamide (Z isomer)

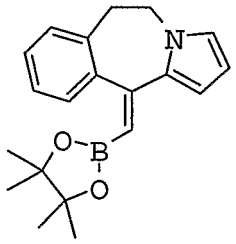
E Isomer Z Isomer

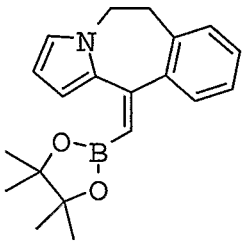
Following procedures essentially as described in Preparation 24 followed by procedures essentially as described in Example 219, and using the product of Preparation 46 and 3-methanesulfonylaminophenylboronic acid , the title compounds are made.

Preparation 47

E-11-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-ylmethylene)-6,11-dihydro-5H-benzo[d]pyrrolo[1,2-a]azepine and

Z-11-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-ylmethylene)-6,11-dihydro-5H-benzo[d]pyrrolo[1,2-a]azepine





E Isomer Z Isomer

Add one equiv of 5,6-dihydro-benzo[d]pyrrolo[1,2-a]azepin-11-one (prepared as described in Y. Girard, J. G. Atkinson, P. C. Belanger, J. J. Fuentes, J. Rokach, C. S. Rooney, D. C. Remy, C. A. Hunt *J. Org. Chem.* **1983**, *48*, 3220) in THF to a solution of 2.5 equiv of pinicol lithio(trimethylsilyl)methaneboronate (as described in D. S. Matteson,

D. Majumder *Organometallics***1983**, *2*, 230), 1 equiv TMEDA, 2.5 equiv of tetramethylpiperidine (TMP), and THF at –78 °C. Allow the solution to warm to room temperature and stir for 3.5 h before quenching with excess water. Extract well with Et_2O (4 X). Dry ($MgSO_4$) and concentrate under reduced pressure. Purify the crude residue by column chromatography (5% to 10% EtOAc:hexanes) to give pure E-isomer (45 %)and Z-isomer (24 %). E-isomer: HPLC (GRAD80-100M) t = 4.340 (99 %). MS (APCI): 322 (M+1).

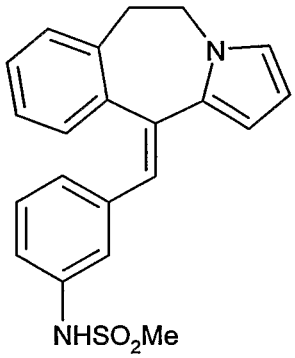
Z-isomer (24 %) HPLC (GRAD80-100M) t = 4.423 (99 %). MS (APCI): 322 (M+1).

Example 485(a)

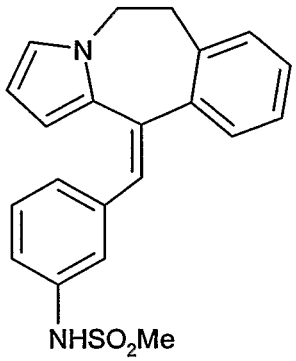
N-[3-(5,6-Dihydro-benzo[d]pyrrolo[1,2-a]azepin-11-ylidenemethyl)-phenyl]-methanesulfonamide (E-isomer) and

Example 485(b)

N-[3-(5,6-Dihydro-benzo[d]pyrrolo[1,2-a]azepin-11-ylidenemethyl)-phenyl]-methanesulfonamide (Z-isomer)



E Isomer

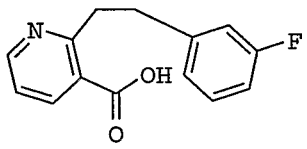


Z Isomer

Following procedures essentially as described in Example 219, and using E- and Z-11-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-ylmethylene)-6,11-dihydro-5H-benzo[d]pyrrolo[1,2-a]azepine and N-(3-iodo-phenyl)-methanesulfonamide, the E and Z isomers of the title compound are prepared.

Preparation 48

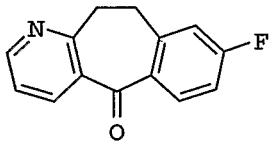
2-[2-(3-Fluoro-phenyl)-ethyl]-nicotinic acid



Dissolve diisopropylamine (3.8 mL, 27.3 mmol) in dry tetrahydrofuran (75 mL). Chill the resulting mixture to –78 °C and add butyl lithium (1.6M solution in hexanes, 17.1 mL, 27.3 mmol). Warm the reaction mixture to 0 °C and add a fine slurry of 2-methyl-nicotinic acid (1.5 g, 10.9 mmol) in THF (25 mL) portionwise during 10 min. Stir the resulting slurry for 1h, then add 3-fluorobenzyl bromide (2.0 mL, 16.4 mmol) and stir 5 min. Quench the reaction with water (100 mL). Extract the reaction mixture with diethyl ether (100 mL). Adjust the pH of the aqueous layer to 3.1 with concentrated aqueous hydrochloric acid solution. Treat the resulting slurry with ethyl acetate and stir to dissolve all solids. Separate the layers and extract the aqueous layer with ethyl acetate. Concentrate the combined extracts to dryness. LCMS (APCI-pos): 244.1 (M+H).

Preparation 49

8-Fluoro-10,11-dihydro-benzo[4,5]cyclohepta[1,2-*b*]pyridin-5-one

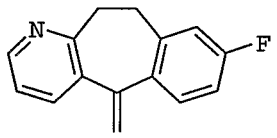


Combine crude 2-[2-(3-fluoro-phenyl)-ethyl]-nicotinic acid (2.06 g, 15.0 mmol) and polyphosphoric acid (100 g) and heat the mixture to 160 °C for 6 h. Allow slow cooling of the reaction mixture over 12h, then reheat the mixture to 160 °C and pour it into ice (200 g). Complete the transfer using water and adjust the pH of the aqueous mixture to ~8.0 with 50% aqueous sodium hydroxide solution. Extract the product with methylene chloride. Dry the combined organic extracts with magnesium sulfate, filter and concentrate. Purify the crude product via flash chromatography (25% ethyl acetate/hexanes to 50% ethyl acetate/hexanes) to provide 1.54 mg (81%) of purified product. LCMS (APCI-pos): 228.1 (M+H). ^{1}HNMR ($CDCl_3$, 400 MHz): δ8.63 (dd, 1H), 8.39 (dd, 1H), 8.01 (dd, 1H), 7.31 (dd, 1H), 7.02 (dt, 1H), 6.95 (dd, 1H), 3.46-3.43 (m, 2H), 3.23-3.21 (m, 2H).

(Literature reference: *Journal of Heterocyclic Chemistry* **1971**, 73).

Preparation 50

8-Fluoro-5-methylene-10,11-dihydro-benzo[4,5]cyclohepta[1,2-*b*]pyridine

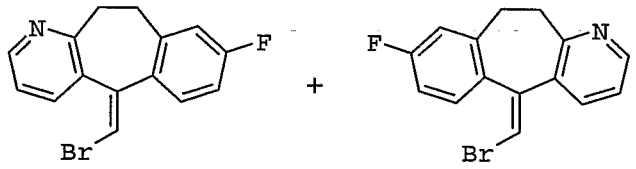


Chill a mixture of 8-fluoro-10,11-dihydro-benzo[4,5]cyclohepta[1,2-*b*]pyridin-5-one (1.3 g, 5.7 mmol) and dry tetrahydrofuran (50 mL) to 0 °C. Treat this mixture with methyl magnesium bromide(3.0M solution in diethyl ether, 5.7 mL, 17.2 mmol). Remove cooling and stir the admixture at room temperature for 15 min. Quench the reaction, while cooling with an ice-water bath, by adding saturated aqueous ammonium chloride solution (50 mL). Separate the layers and extract the aqueous layer with methylene chloride (2x50 mL). Dry the combined organic layers with magnesium sulfate, filter and concentrate to provide the intermediate product as a thick crude oil.

Without further purification, dissolve this residue in a solution of sulfuric acid in acetic acid (3% by volume, 50 mL) and stir the resulting mixture at room temperature for 12-18 h. Concentrate the reaction mixture to remove excess solvent and dissolve the resulting orange residue in 1N aqueous sodium hydroxide solution (25 mL) and ethyl acetate (50 mL). Adjust the pH of the resulting mixture to ~8 with 5N aqueous sodium hydroxide solution. Separate the layers and extract the aqueous layer with ethyl acetate (2x50 mL). Dry the combined organic layers with magnesium sulfate, filter and concentrate to 1.3g (91%) of the title product as an orange-brown oil. LCMS: 226.1 (M+H).

Preparation 51

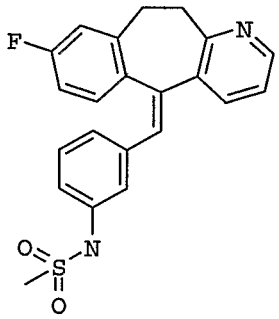
(*E*+*Z*)-5-Bromomethylene-8-fluoro-10,11-dihydro-benzo[4,5]cyclohepta[1,2-*b*]pyridine



Make the title compounds according to Preparation 24, beginning with 8-fluoro-5-methylene-10,11-dihydro-benzo[4,5]cyclohepta[1,2-*b*]pyridine (1.1 g, 5.1 mmol). After workup and purification and separation by flash chromatography (25% ethyl acetate/hexanes to 50% ethyl acetate/hexanes) isolate 700 mg (44%) of (*E*)-5-bromomethylene-10,11-dihydro-8-fluoro-benzo[4,5]cyclohepta[1,2-b]pyridine and 550 mg (34%) of (*Z*)-5-bromomethylene-10,11-dihydro-8-fluoro-benzo[4,5]cyclohepta[1,2-b]pyridine. For (*Z*)-5-bromomethylene-10,11-dihydro-8-fluoro-benzo[4,5]cyclohepta[1,2-*b*]pyridine, LCMS (APCI-pos): 304, 305, 306, 307. ^{1}HNMR ($CDCl_3$, 400 MHz): δ8.45 (dd, 1H), 7.69 (dd, 1H), 7.18 (dd, 1H), 7.13 (dd, 1H), 6.87-6.83 (m, 2H), 6.61 (s, 1H), 3.6-2.4 (m, 4H). For (*E*)-5-bromomethylene-10,11-dihydro-benzo[4,5]cyclohepta[1,2-*b*]pyridine, LCMS (APCI-pos): 304, 305, 306, 307. ^{1}HNMR ($CDCl_3$, 400 MHz): δ8.45 (dd, 1H), 7.56 (dd, 1H), 7.25 (dd, 1H), 7.09 (dd, 1H), 6.99 (dd, 1H), 6.92 (dt, 1H), 6.69 (s, 1H), 3.6-2.8 (m, 4H).

Example 486

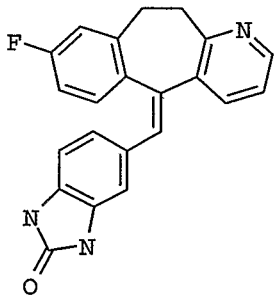
(*E*)-*N*-[3-(8-fluoro-10,11-dihydro-benzo[4,5]cyclohepta[1,2-*b*]pyridin-5-ylidenemethyl)-phenyl]-methanesulfonamide



Following procedures essentially as desctribed in Example 219, beginning with (*E*)-5-bromomethylene-8-fluoro-10,11-dihydro-benzo[4,5]cyclohepta[1,2-*b*]pyridine (200 mg, 0.66 mmol). After work-up, purify the crude product by flash chromatography (50% ethyl acetate/hexanes to 75% ethyl acetate/hexanes) to provide 197 mg (76%) of purified product. LCMS (APCI-pos): 395.1 (M+H). LCMS (APCI-neg): 393.0 (M-H). Purity by LCMS (UV Area percent) 99%. ^{1}HNMR (d6-DMSO, 400 MHz): δ9.62 (s, 1H), 8.41 (dd, 1H), 7.90 (dd, 1H), 7.28-7.24 (m, 2H), 7.14 (t, 1H), 6.96-6.87 (m, 5H), 6.75 (d, 1H), 3.6-2.9 (m, 4H), 2.79 (s, 3H).

Example 487

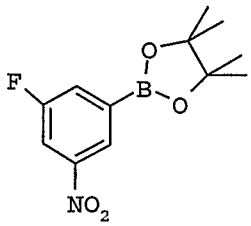
(*E*)-5-(8-Fluoro-10,11-dihydro-benzo[4,5]cyclohepta[1,2-b]pyridin-5-ylidenemethyl)-1,3-dihydro-benzoimidazol-2-one



Following procedures essentially as desctribed in Example 219, beginning with (*E*)-5-bromomethylene-8-fluoro-10,11-dihydro-benzo[4,5]cyclohepta[1,2-*b*]pyridine (100 mg, 0.33 mmol) and 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1,3-dihydro-benzoimidazol-2-one (111 mg, 0.43 mmol). After work-up, purify the crude product by flash chromatography (100% ethyl acetate to 10% ethanol/ethyl acetate) to provide 70 mg (60%) of purified product. LCMS (APCI-pos): 358.0 (M+H). LCMS (APCI-neg): 356.0 (M-H). Purity by LCMS (UV Area percent): 99%. ^{1}HNMR (d6-DMSO, 400 MHz): δ10.56 (s, 1H), 10/46 (s, 1H), 8.38 (dd, 1H), 7.88 (dd, 1H), 7.28 (dd, 1H), 7.23 (dd, 1H), 6.96-6.90 (m, 2H), 6.89 (s, 1H), 6.73 (d, 1H), 6.68 (d, 1H), 6.52 (s, 1H), 3.5-3.3 (m, 2H), 3.1-2.9 (m, 2H).

Preparation 52

2-(3-Fluoro-5-nitro-phenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane

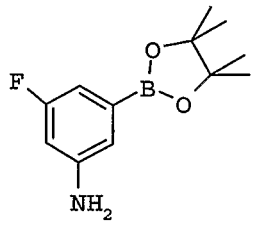


Make according to literature precedent (*Journal of Organic Chemistry* **1995**, *60*, 7508) beginning with 1-fluoro-3-iodo-5-nitrobenzene (1.0 g, 3.7 mmol). Purify the crude product by flash chromatography (1:3- 4% acetic acid in tetrahydrofuran/hexanes) and combine product fractions. Strip to dryness and add 50 mL ethanol and strip to dryness to

provide 945 mg (94%) of purified product. Purity by GCMS: 80%, mass 267.0. ^{1}HNMR ($CDCl_3$, 400 MHz): δ8.43 (bs, 1H), 7.98 (dt, 1H), 7.80 (dd, 1H), 1.36 (s, 12H)

Preparation 53

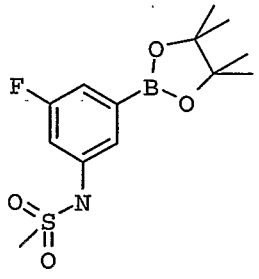
3-Fluoro-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenylamine



Combine 1-fluoro-3-iodo-5-nitrobenzene 2-(3-Fluoro-5-nitro-phenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (940 mg, 3.5 mmol), 5% palladium on carbon (~60% H_2O, 200 mg), and anhydrous ethanol (25 mL). Purge and fill the reaction vessel with hydrogen three times. Stir the reaction mixture under 1 atm of hydrogen. When the reaction is complete by LCMS, filter the reaction mixture through celite to remove the catalyst and wash the filter cake with ethanol. Strip to dryness and purify the crude product by flash chromatography (25% ethyl acetate/hexanes) and combine product fractions. Strip to dryness to provide the crude product. LCMS (APCI-pos): mass 238.2 (M+1), Purity by LCMS (UV area percent): 85%. ^{1}HNMR ($CDCl_3$, 400 MHz): δ6.88-6.83 (m, 2H), 6.47-6.43 (m, 1H), 3.55-3.9 (bs, 2H), 1.32 (s, 12H)

Preparation 54

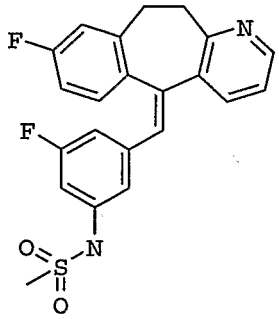
N-[3-Fluoro-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-methanesulfonamide



Combine 3-fluoro-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenylamine (610 mg, 2.6 mmol), methanesulfonyl chloride (240 μL, 3.09 mmol) in pyridine (25 mL). Stir the reaction mixture under nitrogen for 18-24h. Strip to dryness and partition the crude product between methylene chloride (100 mL) and brine (100 mL). Separate the layers and dry the organic layer with magnesium sulfate. Purify the crude product by crystallization (methylene chloride/hexanes) to provide 625 mg of purified product. LCMS (APCI-pos): mass 333.1 ($M+H_2O$), Purity by LCMS (UV area percent): 99%. ^{1}HNMR ($CDCl_3$, 400 MHz): δ7.31-7.20 (m, 3H), 6.44 (s, 1H), 3.03 (s, 3H), 1.34 (s, 12H).

Example 488

(*E*)-N-[3-Fluoro-5-(8-fluoro-10,11-dihydro-benzo[4,5]cyclohepta[1,2-b]pyridin-5-ylidenemethyl)-phenyl]-methanesulfonamide



Following procedures essentially as desctribed in Example 219, beginning with (*E*)-5-bromomethylene-8-fluoro-10,11-dihydro-benzo[4,5]cyclohepta[1,2-*b*]pyridine (50 mg, 0.16 mmol) and N-[3-fluoro-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-methanesulfonamide (62 mg, 0.20 mmol). After work-up, purify the crude product by flash chromatography (50% ethyl acetate/hexanes to 75% ethyl acetate/hexanes) to provide 44 mg (65%) of purified product. LCMS (APCI-pos): 413.0 (M+H). LCMS (APCI-neg): 411.0 (M-H). Purity by LCMS (UV Area percent) 98%. ^{1}HNMR (d6-DMSO, 400 MHz): δ9.91 (s, 1H), 8.42 (dd, 1H), 7.91 (dd, 1H), 7.29-7.25 (m, 2H), 6.92 (s, 2H), 6.90 (d, 1H), 6.77-6.74 (m, 2H), 6.52-6.49(m, 1H), 3.4-2.8 (m, 4H), 2.87 (s, 3H).

Examples 489-601 contained in Table II, herein, provide yet additional examples of compounds of Formula I wherein the "A" and / or "B" ring represents a heterocyclic ring.

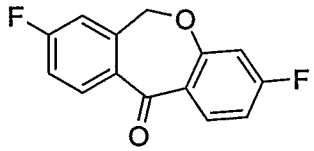
These examples, which further illustrate the present invention are prepared according to the procedures as described generally in the Schemes and literature references described above.

Examples 602-606 contained in Table II, herein, provide yet additional examples of compounds of Formula I wherein the bridge depicted by –X—Y– represents a fused cyclopropyl structure. (Section 5 as represented by original Examples 255-260). These examples, which further illustrate the present invention are prepared according to the procedures as described generally in the Schemes and literature references described above.

Additional preparations for, and examples of compounds of Formula I wherein the bridge depicted by –X—Y– contains a heteroatom or heteroatom containing group at either the X or Y position. (Section 6 as represented by original Examples 261-274)

Preparation 55

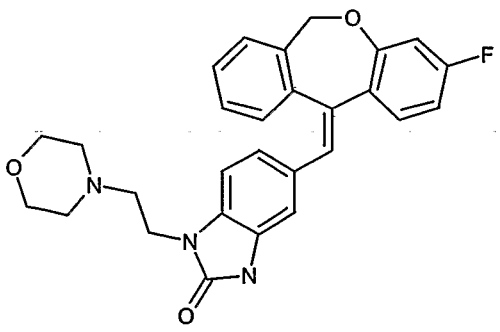
3,8-difluoro-6H-dibenzo[b,e]oxepin-11-one



Prepare starting ketones for oxepine derivatives as described by M Kurokawa, F Sato, Y Masuda, T Yoshida and Y Ochi, Chem. Pharm. Bull., 39; 10; (1991) 2564-5273.

Example 607

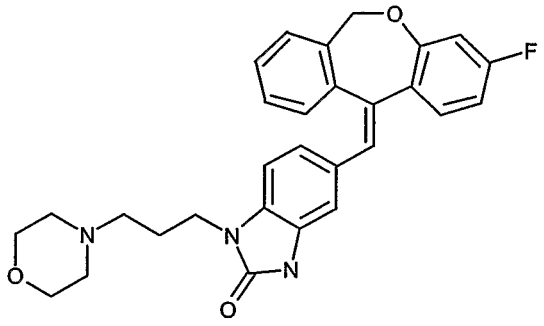
5-(3-Fluoro-6H-dibenzo[b,e]oxepin-11-ylidenemethyl)-1-(2-morpholin-4-yl-ethyl)-1,3-dihydro-benzoimidazol-2-one



Following procedures essentially as described in Example 219, mix 1-(2-morpholin-4-yl-ethyl)-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1,3-dihydro-benzoimidazol-2-one (330mg, 1.1mmol), 11-bromomethylene-3-fluoro-6,11-dihydro-dibenzo[b,e]oxepine (E-isomer, 300mg, 1.03mmol)(prepared following procedures essentially as described in Preparations 55, 23, and 24), 2N Na_2CO_3 (1.4mL), dioxane (10mL) and $(Ph_3P)_4Pd$ (44mg, 0.04mmol). Recrystallize the crude product from toluene and then further purify by using an SCX column by eluting with 1/1 MeOH/dichloromethane then 1/1 2N NH_3 MeOH/dichloromethane. Obtain 51mg of title compound as a white solid, HPLC (ISO80-10M) t=1.82 (99%). MS (ES) 472 (M+1), 470 (M-1). H NMR (DMSO-d_6)δ10.72 (s, 1H), 7.57 (m, 2H), 7.35 (t, 1H, J=7.5 Hz), 7.23 (t, 1H, J=7.5 Hz), 7.00 (d, 1H, J=7.4 Hz), 6.97 (s, 1H), 6.93 (d, 1H, J=8.4 Hz), 6.79 (td, 1H, J=11.9, 4.3 Hz), 6.73 (d, 1H, J=8.4 Hz), 6.60 (m, 2H),5.31 (d, 2H, J=225.4 Hz), 3.80 (t, 2H, J=6.4 Hz), 3.46 (t, 4H, J=4.4 Hz), 2.48 (t, 3H, J=6.2 Hz), 2.38 (s, 4H), 2.48 (t, 2H, J=6.2 Hz).

Example 608

5-(3-fluoro-6H-dibenzo[b,e]oxepin-11-ylidenemethyl)-1-(3-morpholin-4-yl-propyl)-1,3-dihydro-benzoimidazol-2-one

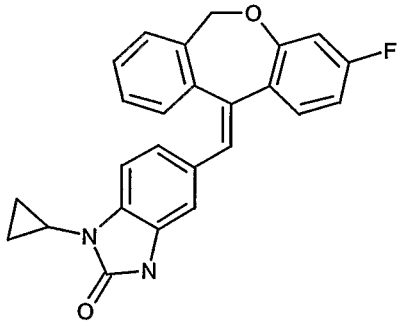


Following procedures essentially as described in Example 219, mix 1-(2-morpholin-4-yl-propyl)-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1,3-dihydro-benzoimidazol-2-one (205mg, 0.53mmol)(prepared following procedures essentially asdescribedin Preparation 36), 11-bromomethylene-3-fluoro-6,11-dihydro-dibenzo[b,e]oxepine (E-isomer, 150mg, 0.5mmol), 2N Na_2CO_3 (0.5mL), dioxane (5mL) and $(Ph_3P)_4Pd$ (53mg, 0.046mmol). Purify the crude product by column chromatography using 2N NH_3 in MeOH/dichloromethane. Triturate the product obtained (192mg) with hexane to give 170mg pure title compound, HPLC (ISO80-10M) t=1.72 (100%). MS (ES) 486 (M+1),

484 (M-1). H NMR (DMSO-d_6)10.68 (s, 1H), 7.57 (m, 2H), 7.35 (t, 1H, *J*=7.5 Hz), 7.22 (t, 1H, *J*=7.7 Hz), 6.96 (m, 3H), 6.78 (td, 1H, *J*=12.0, 4.2 Hz), 6.71 (d, 1H, *J*=7.5 Hz), 6.60 (m, 2H), 5.31 (br d, 2H), 3.72 (t, 2H, *J*=6.6 Hz), 3.46 (t, 4H, *J*=4.2 Hz), 2.48 (m, 4H), 1.71 (m, 2H), 2.20 (m, 6H).

Example 609

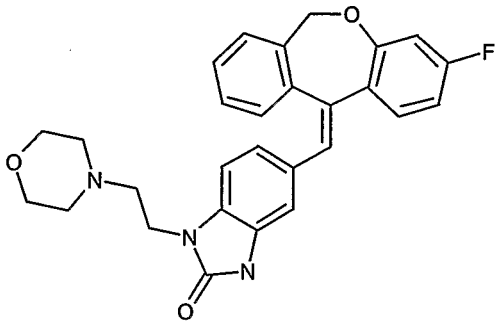
1-cyclopropyl-5-(3-fluoro-6H-dibenzo[b,e]oxepin-11-ylidenemethyl)-1,3-dihydro-benzoimidazol-2-one



Following procedures essentially as described in Example 219, mix 1-cyclopropyl-2-oxo-2,3-dihydro-1H-benzoimidazole-5-boronic acid (120mg, 0.55mmol) (prepared essentially as described in Preparation 36), 11-bromomethylene-3-fluoro-6,11-dihydro-dibenzo[b,e]oxepine (E and Z mixture,177mg, 0.58mmol), 2N Na_2CO_3 (0.7mL), dioxane (8mL) and $(Ph_3P)_4Pd$ (38mg, 0.033mmol). Purify the crude product by column chromatography using THF/hexane to give 65mg title compound as a gray powder. HPLC (ISO80-10M) t=3.53 (93%), MS (ES) 399 (M+1), 397 (M-1). H NMR 10.58 (s, 1H), 7.58 (m, 3H), 7.35 (t, 1H, *J*=7.5 Hz), 7.23 (t, 1H, *J*=7.5 Hz), 6.96 (m, 3H), 7.58 (m, 2H), 6.80 (dd, 1H, *J*=7.9, 2.6 Hz), 6.75 (d, 1H, *J*=7.5 Hz), 6.60 (dd, 1H, *J*=10.6, 2.2 Hz), 6.57 (s, 1H), 5.84-4.79 (m, 2H), 2.75 (m, 1H), 0.93 (m, 2H), 0.77 (m, 2H).

Example 610

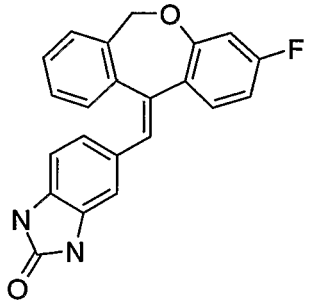
5-(3-fluoro-6H-dibenzo[b,e]oxepin-11-ylidenemethyl)-1-(2-morpholin-4-yl-ethyl)-1,3-dihydro-benzoimidazol-2-one



Following procedures essentially as described in Example 219, mix 1-(2-morpholin-4-yl-ethyl)-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1,3-dihydro-benzoimidazol-2-one (300mg, 1.03mmol), 11-bromomethylene-3-fluoro-6,11-dihydro-dibenzo[b,e]oxepine (E isomer, 330mg, 1.08mmol), 2N Na_2CO_3 (1.4mL), dioxane (10mL) and $(Ph_3P)_4Pd$ (44mg, 0.038mmol). Purify the crude product by column chromatography using 40% THF/hexane to yield 80mg title compound as a pale yellow powder. HPLC (ISO80-10M) t=1.84 (96%), MS (ES) 472 (M+1), 470 (M-1). H NMR (DMSO-d_6)10.72 (s, 1H), 7.57 (m, 2H), 7.35 (t, 1H, *J*=7.5 Hz), 7.23 (t, 1H, *J*=7.5 Hz), 7.00 (d, 1H, *J*=7.5 Hz), 6.97 (s, 1H), 6.93 (d, 1H, *J*=8.4 Hz), 6.79 (td, 1H, *J*=11.9, 4.3 Hz), 6.73 (d, 1H, *J*=8.4 Hz), 6.60 (m, 2H), 5.82-4.79 (m, 2H), 3.80 (t, 2H, *J*=6.4 Hz), 3.46 (t, 4H, *J*=4.4 Hz), 2.48 (m, 2H), 2.38 (s, 4H).

Example 611

5-(3-Fluoro-6H-dibenzo[b,e]oxepin-11-ylidenemethyl)-1,3-dihydro-benzoimidazol-2-one

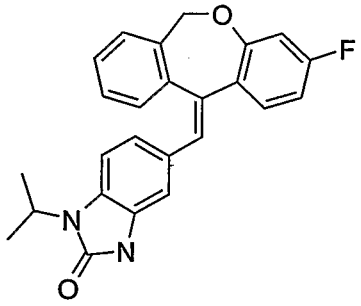


Following procedures essentially as described in Example 219, using 11-bromomethylene-3-fluoro-6,11-dihydro-dibenzo[b,e]oxepine (E-isomer, 1.05 eq.) and 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1,3-dihydro-benzoimidazol-2-one (1 eq.). Purify crude product on silica gel, eluting with 60% to 100% ethyl acetate/$CHCl_3$ to afford a light yellow solid. Triturate with acetone to afford the title compound as a white solid. HPLC (ISO60-10) t=4.09min, 100%; MS [ES] 357 (M-H), 359 (M+H); ^{1}H-NMR

(DMSO-d_6) δ 10.56 (s, 1H), 10.46 (s, 1H), 7.56 (m, 2H), 7.35 (t, 1H, *J*=7.5 Hz), 7.23 (t, 1H, *J*=7.5 Hz), 6.99 (d, 1H, *J*=7.5 Hz), 6.94 (s, 1H), 6.78 (td, 1H, *J*=12.0, 4.2 Hz), 6.71 (d, 1H, *J*=8.4 Hz), 6.66 (d, 1H, *J*=8.4 Hz), 6.59 (dd, 1H, *J*=10.6, 2.6 Hz), 6.57 (s, 1H), 5.83-4.71 (br d, 2H).

Example 612

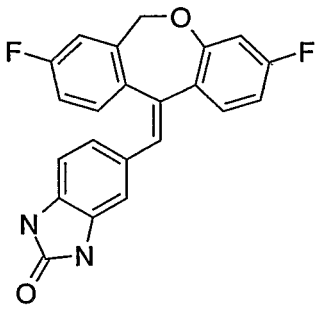
5-(3-Fluoro-6H-dibenzo[b,e]oxepin-11-ylidenemethyl)-1-isopropyl-1,3-dihydro-benzoimidazol-2-one



Following procedures essentially as described in Example 219, mix 11-bromomethylene-3-fluoro-6,11-dihydro-dibenzo[b,e]oxepine (150mg, 0.493mmol), 1-isopropyl-2-oxo-2,3-dihydro-1H-benzoimidazole-5-boronic acid (103mg, 0.468mmol)(prepared according to Scheme IX by using isopropylamine in Step A), Na_2CO_3 (2M in water, 620□L, 1.23mmol), dioxane (4mL), and $Pd(PPh_3)_4$ (29mg, 0.025mmol). Purify the crude product on silica gel (24g), eluting with 25% to 50% THF/hexanes to afford 130mg (69%) of the title compound as a yellow foam. HPLC (ISO80-10) t=3.86min, 98%; MS [ES] 399 (M-H); ^{1}H-NMR ($CDCl_3$) δ 9.10 (s, 1H), 7.44 (m, 2H), 7.32 (t, 1H, *J*=7.5 Hz), 7.22 (t, 1H, *J*=7.5 Hz), 7.11 (d, 1H, *J*=7.5 Hz), 6.93 (d, 1H, *J*=8.4 Hz), 6.86 (s, 1H), 6.75 (d, 1H, *J*=8.4 Hz), 6.69 (s, 1H), 6.66 (td, 1H, *J*=11.7, 4.1 Hz), 6.52 (dd, 1H, *J*=10.3, 2.4 Hz), 5.92-4.73 (m, 2H), 4.66 (m, 1H), 1.51 (d, 6H, *J*=7.0 Hz).

Example 613

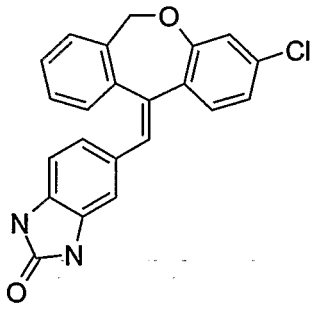
5-(3,8-Difluoro-6H-dibenzo[b,e]oxepin-11-ylidenemethyl)-1,3-dihydro-benzoimidazol-2-one



Following procedures essentially as described in Example 219, mix 11-bromomethylene-3,8-difluoro-6,11-dihydro-dibenzo[b,e]oxepine (E-isomer, 326mg, 1.01mmol), 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1,3-dihydro-benzoimidazol-2-one (250mg, 0.961mmol), Na_2CO_3 (2M in water, 1.20mL, 2.40mmol), dioxane (7mL), and $Pd(PPh_3)_4$ (58mg, 0.051mmol). Purify the crude product on silica gel (12g) eluting with 50% to 70% THF/hexanes to afford two lots of yellow solid weighing 180mg and 151mg. Dissolve the 180mg lot in boiling MeOH (20mL), concentrate to 10mL and cool to –26°C to precipitate 165mg (46%) of the title compound as a white solid. Repeat the recrystallization on the 151mg lot to afford 98mg (27%) of the title compound as a white solid. HPLC (ISO80-10) t=2.38min, 97%; MS [ES] 375 (M-H), 377 (M+H); ^{1}H-NMR (DMSO-d_6) δ 10.57 (s, 1H), 10.46 (s, 1H), 7.57 (dd, 1H, *J*=8.4, 7.0 Hz), 7.49 (dd, 1H, *J*=9.2, 2.6 Hz), 7.08 (td, 1H, *J*=12.5, 4.3 Hz), 7.01 (d, 1H, *J*=5.7 Hz), 6.97 (s, 1H), 6.79 (td, 1H, *J*=12.0, 4.2 Hz), 6.73 (d, 1H, *J*=8.4 Hz), 6.67 (d, 1H, *J*=8.4 Hz), 6.61 (dd, 1H, *J*=10.6, 2.6 Hz), 6.52 (s, 1H), 5.78-4.78 (br d, 2H).

Example 614

5-(3-Chloro-6H-dibenzo[b,e]oxepin-11-ylidenemethyl)-1,3-dihydro-benzoimidazol-2-one

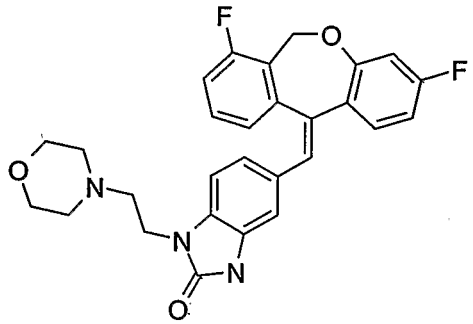


Following procedures essentially as described in Example 219, mix 11-bromomethylene-3-chloro-6,11-dihydro-dibenzo[b,e]oxepine (E-isomer, 40mg, 0.124mmol) (prepared essentially as described in Preparation 55), 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-

yl)-1,3-dihydro-benzoimidazol-2-one (31mg, 0.118mmol), Na_2CO_3 (2M in water, 148□L, 0.295mmol), dioxane (1mL), and $Pd(PPh_3)_4$ (7mg, 0.006mmol). Purify the crude product on silica gel (12g) eluting with 2% to 5% (2M NH_3/MeOH)/CH_2Cl_2 to afford 31mg (69%) of the title compound as a white solid. HPLC (ISO80-10) t=2.85min, 99%; MS [ES] 373 (M-H); ^{1}H-NMR (DMSO-d_6) δ10.57 (s, 1H), 10.47 (s, 1H), 7.56 (dd, 2H, *J*=7.8, 6.1 Hz), 7.35 (t, 1H, *J*=7.5 Hz), 7.24 (t, 1H, *J*=7.7 Hz), 6.98 (m, 3H), 6.82 (d, 1H, *J*=2.2 Hz), 6.69 (m, 2H), 6.57 (s, 1H), 5.89-4.79 (br d, 2H).

Example 615

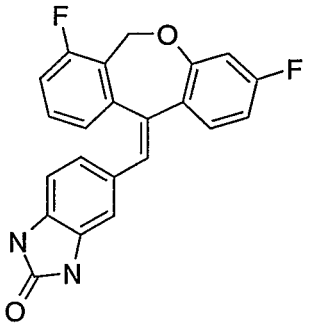
5-(3,7-Difluoro-6H-dibenzo[b,e]oxepin-11-ylidenemethyl)-1-(2-morpholin-4-yl-ethyl)-1,3-dihydro-benzoimidazol-2-one



Following procedures essentially as described in Example 219, mix 11-bromomethylene-3,7-difluoro-6,11-dihydro-dibenzo[b,e]oxepine (E-isomer, 200mg, 0.619mmol) (prepared essentially as described in Preparation 55), 1-(2-morpholin-4-yl-ethyl)-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1,3-dihydro-benzoimidazol-2-one (220mg, 0.589mmol), Na_2CO_3 (2M in water, 736□L, 1.47mmol), dioxane (4mL), and $Pd(PPh_3)_4$ (36mg, 0.031mmol). Purify the crude product on silica gel (64g) eluting with 2% (2M NH_3/MeOH)/CH_2Cl_2 to afford 191mg (66%) of the title compound as a white foam. HPLC (ISO80-10) t=1.95min, 98%; MS [ES] 488 (M-H), 490 (M+H); ^{1}H-NMR (DMSO-d_6) δ 10.69 (s, 1H), 7.58 (dd, 1H, *J*=8.8, 7.0 Hz), 7.24 (m, 2H), 7.02 (s, 1H), 6.96 (d, 1H, *J*=8.4 Hz), 6.80 (m, 3H), 6.64 (m, 2H), 5.56-5.20 (br d, 2H), 3.81 (t, 2H, *J*=6.4 Hz), 3.46 (t, 4H, *J*=4.4 Hz), 2.48 (m, 2H), 2.37 (s, 4H).

Example 616

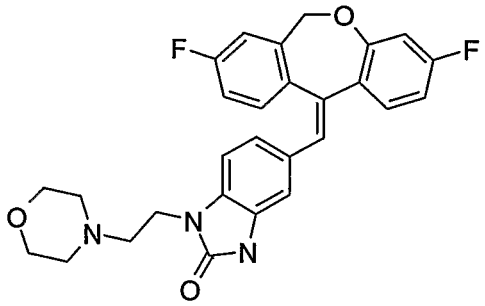
5-(3,7-Difluoro-6H-dibenzo[b,e]oxepin-11-ylidenemethyl)-1,3-dihydro-benzoimidazol-2-one



Following procedures essentially as described in Example 219, mix 11-bromomethylene-3,7-difluoro-6,11-dihydro-dibenzo[b,e]oxepine (E-isomer, 68mg, 0.21mmol), 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1,3-dihydro-benzoimidazol-2-one (52mg, 0.20mmol), Na_2CO_3 (2M in water, 251μL, 0.503mmol), dioxane (2mL), and $Pd(PPh_3)_4$ (12mg, 0.010mmol). Purify on silica gel (12g) eluting with THF to afford a brown solid. Triturate with acetone to afford 56mg (74%) of the title compound as a white solid. HPLC (ISO80-10) t=2.42min, 96%; MS [ES] 375 (M-H); ^{1}H-NMR (DMSO-d_6) δ 10.58 (s, 1H), 10.46 (s, 1H), 7.57 (dd, 1H, *J*=8.8, 7.0 Hz), 7.24 (m, 2H), 7.00 (s, 1H), 6.81 (m, 2H), 6.72 (m, 2H), 6.64 (dd, 1H, *J*=10.6, 2.6 Hz), 6.59 (s, 1H), 5.55-5.19 (br d, 2H).

Example 617

5-(3,8-Difluoro-6H-dibenzo[b,e]oxepin-11-ylidenemethyl)-1-(2-morpholin-4-yl-ethyl)-1,3-dihydro-benzoimidazol-2-one

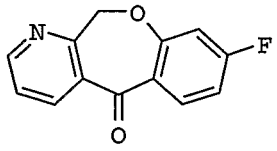


Following procedures essentially as described in Example 219, mix 11-bromomethylene-3,8-difluoro-6,11-dihydro-dibenzo[b,e]oxepine (E-isomer, 40mg, 0.12mmol), 1-(2-morpholin-4-yl-ethyl)-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1,3-dihydro-benzoimidazol-2-one (44mg, 0.12mmol), Na_2CO_3 (2M in water, 155μL, 0.310mmol), dioxane (1mL), and $Pd(PPh_3)_4$ (7mg, 0.006mmol). Purify on silica gel (12g), eluting with 2% to 5% (2M NH_3/MeOH)/CH_2Cl_2 to afford 45mg (78%) of the title compound as a

white foam. HPLC (ISO80-10) t=1.86min, 99%; MS [ES] 488 (M-H), 490 (M+H); ^{1}H-NMR (DMSO-d_6) δ 10.70 (s, 1H), 7.59 (dd, 1H, *J*=8.5, 7.1 Hz), 7.51 (dd, 1H, *J*=8.8, 2.6 Hz), 7.08 (td, 1H, *J*=12.5, 4.3 Hz), 7.01 (m, 2H), 6.96 (d, 1H, *J*=7.9 Hz), 6.80 (td, 1H, *J*=12.0, 4.2 Hz), 6.73 (d, 1H, *J*=7.9 Hz), 6.62 (dd, 1H, *J*=10.3, 2.4 Hz), 6.58 (s, 1H), 5.72-4.85 (br d, 2H), 3.81 (t, 2H, *J*=6.4 Hz), 3.47 (t, 4H, *J*=4.4 Hz), 2.48 (m, 2H), 2.38 (s, 4H).

Preparation 56

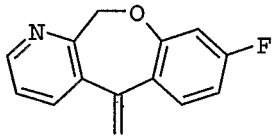
8-Fluoro-11H-10-oxa-1-aza-dibenzo[a,d]cyclohepten-5-one



Prepare according to literature precedent: *Journal of Medicinal Chemistry* **1990**, *33*, 3095.

Preparation 57

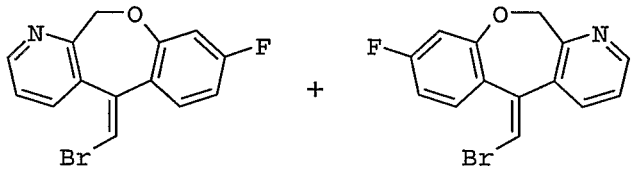
8-Fluoro-5-methylene-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cycloheptene



Combine 8-fluoro-11H-10-oxa-1-aza-dibenzo[a,d]cyclohepten-5-one (567 mg, 2.47 mmol) and anhydrous tetrahydrofuran (25 mL). Chill the solution to 0 °C and add Tebbe reagent (0.5M/L solution in toluene, 5.4 mL, 2.72 mmol). Remove cooling and stir the admixture for 10 min. Quench the reaction by adding saturated aqueous Rochelle's salt solution (75 mL). Stir the biphasic mixture rapidly for 10 min, then separate the layers and extract the aqueous layer with ethyl acetate. Dry the combined organic layers with magnesium sulfate, filter and strip. Purify the crude product by flash chromatography (25% ethyl acetate/hexanes) to provide 416 mg (74%) of purified product. LCMS (APCI-pos): 228.1 (M+H). LCMS (APCI-neg): 226.9 (M-H).

Preparation 58

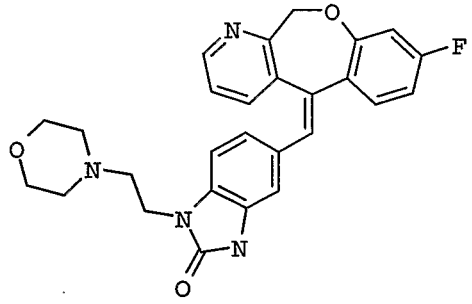
(E+Z)- 5-Bromomethylene-8-fluoro-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cycloheptene



Make the title compounds according to proceduresessentially as described in Preparation 24, beginning with 8-fluoro-5-methylene-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cycloheptene (416 mg, 1.83 mmol). After workup and purification and separation by flash chromatography (25% ethyl acetate/hexanes) isolate 383 mg (68%) of (*E*)-5-bromomethylene-8-fluoro-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cycloheptene and 125 mg (23%) of (*Z*)-5-bromomethylene-8-fluoro-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cycloheptene. For (*E*)-5-bromomethylene-8-fluoro-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cycloheptene, LCMS (APCI-pos): 306, 308. ^{1}HNMR (d6-DMSO, 400 MHz): δ8.55 (d, 1H), 7.86 (d, 1H), 7.49 (dd, 1H), 7.40 (dd, 1H), 7.25 (s, 1H), 6.84 (dt, 1H), 6.73 (dd, 1H), 5.23 (bs, 2H). For (*Z*)-5-bromomethylene-8-fluoro-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cycloheptene, LCMS (APCI-pos): 306, 308. ^{1}HNMR (d6-DMSO, 400 MHz): δ8.50 (dd, 1H), 7.81 (d, 1H), 7.50 (dd, 1H), 7.40 (dd, 1H), 7.09 (s, 1H), 6.99-6.93 (m, 2H), 5.22 (bs, 2H).

Example 618

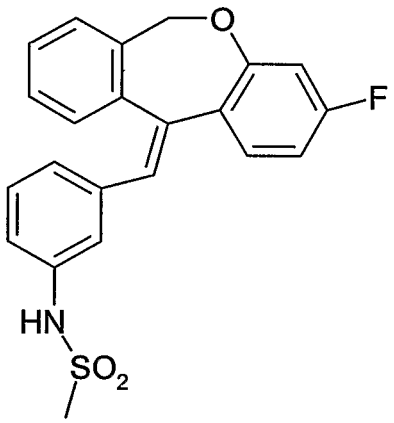
(*E*)-5-(8-Fluoro-11H-10-oxa-1-aza-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-1-(2-morpholin-4-yl-ethyl)-1,3-dihydro-benzoimidazol-2-one



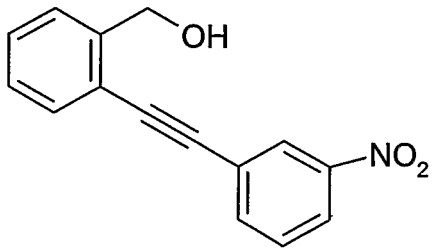
Following procedures essentially as described in Example 219, beginning with (*E*)-5-bromomethylene-8-fluoro-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cycloheptene (192 mg, 0.63 mmol)and 1-(2-morpholin-4-yl-ethyl)-5-(dihyroxyborolan-2-yl)-1,3-dihydro-benzoimidazol-2-one (219 mg, 0.75 mmol). Partition the reaction mixture between ethyl acetate (50 mL) and 1N aqueous hydrochloric acid solution (50 mL). Separate the layers

and extract the aqueous layer with methylene chloride (2x50 mL). Combine the organic layers and extract with 1N aqueous hydrochloric acid solution (50 mL). Adjust the pH of the combined aqueous layers to 8.0 with 5N aqueous sodium hydroxide solution, and extract the product with ethyl acetate (3x 50 mL). Purify the crude product by flash chromatography (25% ethanol/ethyl acetate) to provide 115 mg (39%) of purified product. LCMS (APCI-pos): 473.1 (M+H). Purity by LCMS (UV Area percent) 98%. ^{1}HNMR (d6-DMSO, 400 MHz): δ10.70 (s, 1H), 8.51 (d, 1H), 7.64 (t, 1H), 7.39 (d, 1H), 7.27 (dd, 1H), 7.09 (s, 1H), 6.97 (d, 1H), 6.85 (dt, 1H), 6.73 (d, 1H), 6.69 (dd, 1H), 6.61 (s, 1H), 5.5-5.3 (bs, 2H), 3.81 (t, 2H), 3.30 (s, 4H), 2.48 (s, 4H), 2.34 (bs, 2H).

Example 630



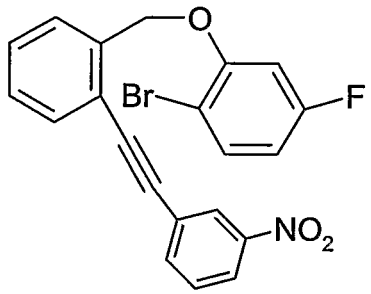
A. Preparation of 2-[2-(3-nitrophenylethynyl)]benzyl alcohol:



2-ethynylbenzyl alcohol (1.65 g, 12.5 mmol), $PdCl_2(PPh_3)_2$ (437 mg, 0.623 mmol), CuI (237 mg, 1.25 mmol) are successively added to a solution of 3-iodonitrobenzene (3.1 g, 12.5 mmol) in 62 mL of Et_3N at rt. The reaction mixture is stirred at rt for 1h. Water (100 mL) is added followed by EtOAc (100 mL). The layers are separated and the aqueous layer extracted with additional 100 mL of EtOAc. The combined organic layer is dried and concentrated to give a dark yellow residue. The residue is purified by column

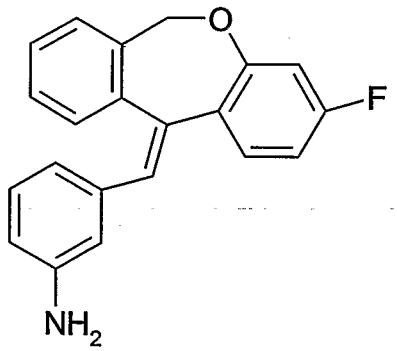
chromatography to give **2** as a yellow solid (2.59 g, 10.25 mmol, 82 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (m, 1 H), 8.21 (m, 1 H), 7.82 (m, 1 H), 7.60 – 7.32 (m, 5 H), 4.94 (d, J = 5.9 Hz, 2 H), 1.97 (t, *J* = 2.3 Hz, 1 H). Yu, H. RG6-R6H-070.

B. Preparation of :



To a mixture of 2-bromo-5-fluorophenol (3.77 g, 19.8 mmol) and the alkyne from Step A, above (5.0 g, 19.8 mmol) in 125 mL of anhydrous THF is added triphenylphosphine (7.8 g, 29.6 mmol) at rt. The reaction mixture is cooled to 0 °C and diisopropylazodicarboxylate (5.99 g, 29.6 mmol) is added dropwise under N_2. The reaction mixture is warmed up to rt and stirred at rt for 2h. 200 mL of water isadded followed by 200 mL of EtOAc. The layers are separated and the aqueous layer further extracted with 200 mL of EtOAc. The combined organic layer is dried and concentrated to give a brown residue. The residue is purified by column chromatography (5% EtOAc/hexane) to give the product (6.70 g, 15.7 mmol, 79 % yield) as an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (m, 1 H), 8.20 (m, 1 H), 7.78 (m, 1 H), 7.69 – 7.35 (m, 6 H), 6.78 (m, 1 H), 6.61 (m, 1 H), 5.18 (s, 2H). Yu, H, RG6-R6H-087.

C. Preparation of :



A mixture of the product of Step B, above (56 mg, 0.131 mmol), Pd $(OAc)_2$ (3 mg, 0.013 mmol) and tri-O-tolylphosphine (8.0 mg, 0.026 mmol) in 0.7 mL of acetonitrile is stirred under N_2 at rt. Formic acid (96 %, 18.2 mmol, 0.394 mmol) is added dropwise followed by piperidine (45 mg, 0.526 mmol). The reaction mixture is heated at 70 °C overnight. TLC shows starting material still remains. Additional Pd $(OAc)_2$ (3 mg, 0.013 mmol), tri-O-tolylphosphine (8.0 mg, 0.026 mmol), formic acid (96 %, 18.2 mmol, 0.394 mmol) and piperidine (45 mg, 0.526 mmol) are added in this sequence. The reaction mixture is heated at 70 °C for additional 4 h with until no starting observed by TLC. The reaction mixture is concentrated to a black residue and purified through 5 g of silica gel to give the aniline product (17 mg, 0.054 mmol, 41% yield) as a beige solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (m, 2 H), 7.31 (dt, J = 9.6 Hz, J = 1.3 Hz, 1 H), 7.21 (dt, J = 9.6 Hz, J = 1.3 Hz, 1 H), 7.11 (m, 1 H), 6.93 (t, J = 9.6 Hz, 1 H), 6.78 (s, 1 H), 6.65 (m, 1 H), 6.53 – 6.29 (m, 4 H), 3.46 (bs, 2 H). Yu, H. RG6-R6H-074.

D. Preparation of Final Title Compound:

To a mixture of the aniline of Step C (1.0 mg, 0.0132 mmol) in 0.1 mL of methylene chloride is added pyridine (0.3 mg, 0.0038 mmol) followed by methanesulfonylchloride (0.4 mg, 0.0035 mmol) at rt under N_2. The reaction mixture is stirred at rt for 2h. The reaction mixture is concentrated to dry and the residue is purified by column chromatogrphy to give Title Compound as a solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (m, 2 H), 7.32 (t, J = 7.5 Hz, 1 H), 7.17 (m, 2 H), 7.00 (m, 2 H), 6.87 (m, 2 H), 6.78 (m, 1 H), 6.67 (dt, J = 11.7 Hz, J = 4.1 Hz, 1 H), 6.53 (dd, J = 10.6 Hz, J = 2.5 Hz, 1 H), 6.07 (s, 1H), 2.81 (s, 3 H).

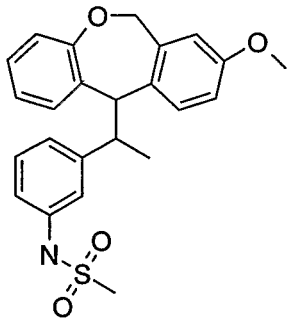
Examples 619-751 contained in Table II, herein, provide yet additional examples of compounds of Formula I wherein the bridge depicted by –X—Y– contains a heteroatom or heteroatom containing group at either the X or Y position.. These examples, which further illustrate the present invention are prepared according to the procedures as described generally in the Schemes and literature references described above.

Additional preparations for, and examples of compounds of Formula I wherein R8 is other than hydrogen and the bridge depicted by –X—Y– contains either a

heteroatom or heteroatom containing group at either the X or Y position or both X and Y are CH_2. (Section 7)

Example 752

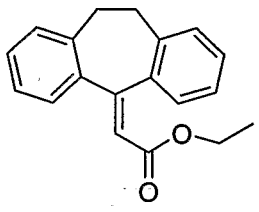
N-{3-[1-(8-Methoxy-6,11-dihydro-dibenzo[b,e]oxepin-11-yl)-ethyl]-phenyl}-methanesulfonamide



Mix N-{3-[1-(8-methoxy-6H-dibenzo[b,e]oxepin-11-ylidene)-ethyl]-phenyl}-methanesulfonamide (prepared essentially a sdescribed in Example 271) (1.0 eq) with 10% Pd/C (65.2 weight %) in EtOH and heat at 60°C overnight under 500 psi hydrogen. Remove the solvent and purify by chromatography (ISCO Combi Flash, 3/1 hexane/ethyl acetate) to give 29% of the title compound as a racemic mixture. HPLC (Xterra C18 2.1x50μm 3.5μM, 5-100% acetonitrile with 0.2% formic acid.) t= 4.55 (100%). MS (ES) 424 (M+1), 422 (M-1).

Preparation 59

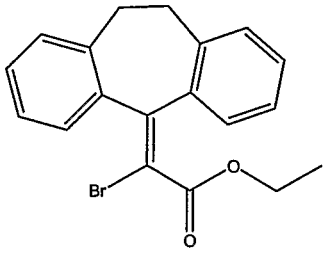
(10,11-dihydro-dibenzo[*a,d*]cyclohepten-5-ylidine)-acetic acid ethyl ester



Prepared as described in Bergmann, E.D., Solomonovici, A., *Synthesis*, **1970**, 183-189.

Preparation 60

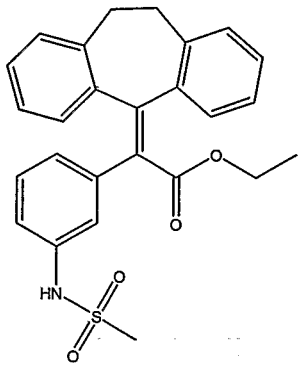
Bromo-(10,11-dihydro-dibenzo[*a,d*]cyclohepten-5-ylidine)-acetic acid ethyl ester



Dissolve (10,11-dihydro-dibenzo[*a,d*]cyclohepten-5-ylidine)-acetic acid ethyl ester (1 equivalent) in a suitable dry solvent and chill to 0° C under a dry atmosphere. Add bromine (1.05 equivalents) dropwise and stir at 0° C for 20 minutes. Remove the ice bath and stir at room temperature for three hours. Return to the ice bath and add potassium *tert*-butoxide (1.1.equivalents)and stir for one hour. Quench the mixture with aqueous Na_2SO_3 and partition between dichloromethane and water and dry the organic layer over anhydrous sodium sulfate. Purify the residue obtained after evaporation by silica gel chromatography to yield 71% of the title compound.

Example 753

(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidene)-(3-methanesulfonylamino-phenyl)-acetic acid ethy lester

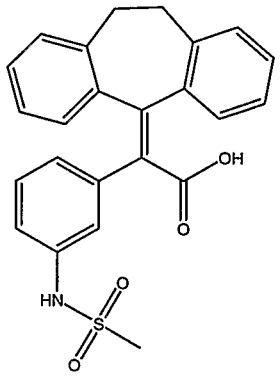


Following procedures essentially as described in Example 219, mix bromo-(10,11-dihydro-dibenzo[*a,d*]cyclohepten-5-ylidine)-acetic acid ethyl ester (1 equivalent), N-[3-

(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-methanesulfonamide (1.25 equivalents), 2N Na_2CO_3 (2 equivalents) and *tetrakis*triphenylphosphine palladium (0.05 equivalents)in a suitable solvent. Purify the product by silica gel chromatography to obtain a 78% yield of the title compound. MS(ES) = 446(+)

Example 754

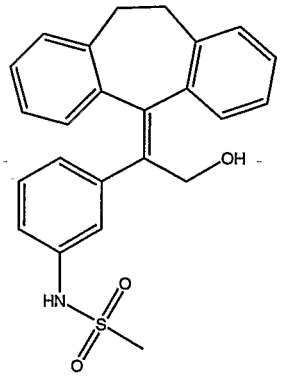
(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidene)-(3-methanesulfonylamino-phenyl)-acetic acid



Treat (10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidene)-(3-methanesulfonylamino-phenyl)-acetic acid ethyl ester with a 50:50 mixture of 1N NaOH and ethanol and heat under reflux conditions for 14 hours. Acidify with 1N HCl and collect the solid by filtration and dry. Purify by reverse phase HPLC to obtain a 20% yield of the title compound. MS(ES)= 437(+NH_3)

Example 755

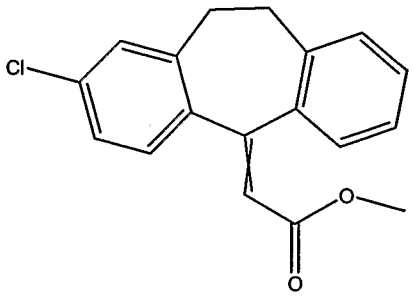
N-{3-[1-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidene)-2-hydroxy-ethyl]-phenyl}-methanesulfonamide



Treat (10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidene)-(3-methanesulfonylamino-phenyl)-acetic acid ethyl ester (1 equivalent) with lithium aluminum hydride (2 equivalents) in a suitable dry solvent and stir at room temperature for four hours. Quench by the dropwise addition of water and partition between dichloromethane and water. Dry the organic layer over anhydrous sodium sulfate and evaporate. Purify the crude residue by silica gel chromatography to obtain a 33% yield on the title compound.
MS(ES)=404(+)

Preparation 61

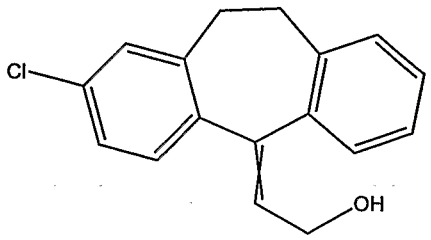
(2-Chloro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidene)-acetic acid methyl ester



Title compound is prepared from 2-chloro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-one as described in Bergmann, E.D., Solomonovici, A., *Synthesis*, **1970**, 183-189.

Preparation 62

2-(2-Chloro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidene)-ethanol



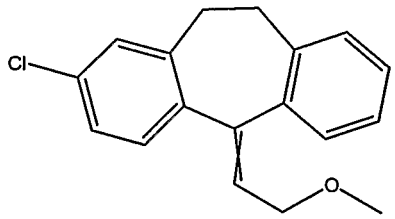
Dissolve (2-chloro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidene)-acetic acid methyl ester (1 equivalent) in a suitable dry solvent and cool to 0°C under a dry atmosphere. Add

1M diisobutylaluminun hydride solution in toluene (3 equivalents) dropwise and stir the mixture for one hour. Quench with aqueous citric acid solution and partition between water and ethyl acetate. Dry and evaporate the organic layer to obtain the title compound in 87% yield.

5

Preparation 63

2-Chloro-5-(2-methoxy-ethylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene



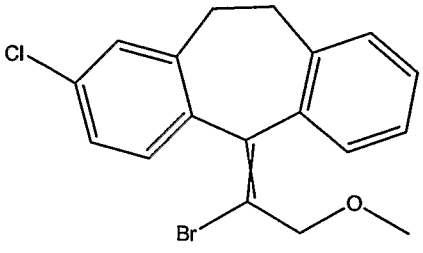
10

Treat 2-(2-chloro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidene)-ethanol (1 equivalent) with sodium hydride (2 equivalents) in a suitable dry solvent at 0°C and stir for 15 minutes. Add dimethyl sulfate dropwise (2 equivalents) and stir at 0°C for one hour. Quench with aqueous citric acid solution and partition between water and ethyl
15 acetate. Dry and evaporate the organic layer. Purify the residue by silica gel chromatography to give the title compound in 82% yield

Preparation 64

5-(1-Bromo-2-methoxy-ethylidene)-2-chloro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene

20

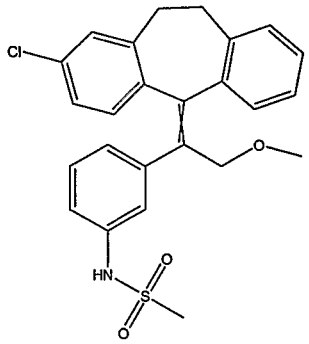


Treat 2-chloro-5-(2-methoxy-ethylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene essentially as described in Preparation 24 to give the title compound in 43% yield.

25

Example 756

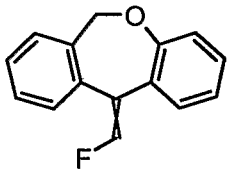
N-{3-[1-(2-Chloro-10,11-dihydro-dibenzo[a,d]cyclohepten-5-ylidene)-2-methoxy-ethyl]-phenyl}-methanesulfonamide



Following procedures essentially as described in Example 219, mix 5-(1-bromo-2-methoxy-ethylidene)-2-chloro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (1 equivalent), N-[3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-methanesulfonamide (1.25 equivalents), 2N Na_2CO_3 (2 equivalents) and *tetrakis*triphenylphosphine palladium (0.05 equivalents)in a suitable solvent. Purify the product by silica gel chromatography to obtain a 62% yield of the title compound. MS(ES)=452(-)

Preparation 65

11-Fluoromethylene-6,11-dihydro-dibenzo[b,e]oxepine

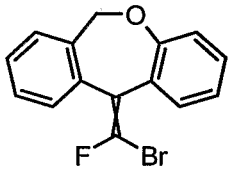


Dissolve 11-Bromomethylene-6,11-dihydro-dibenzo[b,e]oxepine (1 eq.) in dry THF (0.1 M). Cool the solution to – 78C in a dry ice/acetone bath. Slowly add s-butyl lithium (1.2 eq., 1.3 M in cyclohexane) to the above solution. Stir the dark brown solution at – 78 C for two hours. Add a solution of N-fluorobenzene sulfonimide (1.2 eq.) in dry THF (0.4 M) over 2 minutes. Remove the cold bath and allow the reaction mixture to warm to ambient temperature. Stir the reaction mixture at room temperature for 1 hour. Quench the reaction with water. Wash the resulting mixture with saturated aqueous $NaHCO_3$.

Separate the organic phase and dry over sodium sulfate. Filter the mixture and concentrate under reduced pressure to afford a crude product. Purify the crude product by chromatography on silica gel, eluting with 30% CH_2Cl_2 in hexanes. MS (EI) = 226 (M).

Preparation 66

11-Bromo-fluoro-methylene-6,11-dihydro-dibenzo[b,e]oxepine



Dissolve 11-Fluoromethylene-6,11-dihydro-dibenzo[b,e]oxepine in methylene chloride (0.2 M). Add (4-Dimethylamino)pyridinium tribromide (1.05 eq.). Stir the mixture at ambient temperature for 2 hours. Wash the resulting solution with aqueous sodium disulfite, dry with sodium sulfate and concentrate the filtrate. Purify the crude product by silica gel chromatography using 30% methylene chloride in hexanes. MS(EI) = 304/306 (M).

Examples 757-843 contained in Table II, herein, provide yet additional examples of compounds of Formula I wherein R8 is other than hydrogen and the bridge depicted by –X—Y– contains either a heteroatom or heteroatom containing group at either the X or Y position or both X and Y are CH_2. These examples, which further illustrate the present invention are prepared according to the procedures as described generally in the Schemes and literature references described above.

As stated, Table II, below provides formulae and physical data for additional compounds of Formula I. In the table, the heading "Example No." refers to the example number of the compound, "Structure" refers to the chemical formula of the particular compound, "MS Data" refers to the mass spectroscopy data generated for the particular compound, and "HPLC" refers to the high pressure liquid chromatography data generated for the particular compound. Some of the entries in the Table do not contain either MS Data or HPLC values, instead the designation "NMR" appears in the MS Data column. For these Examples, nuclear magnetic resonance data are provided below.

Example 621

1H NMR (400 MHz, CDCl3) 8.02 (d, 1H, J = 5), 7.97 (s, 1H), 7.50 (dd, 1H, J = 5, 1), 7.42 (d, 1H, J = 5.2), 7.35 (t, 1H, J = 9.7, 5), 7.28 (m, 2H), 7.14 (t, 1H, J = 9.7, 5), 7.02 (m, 2H), 6.91 (m, 2H), 5.6 (s, 2H).

Example 658

1H NMR(CDCl3, 400MHz) δ 8.03 (d, J=8.56Hz, 1H), 7.50-6.97 (m, 12H), 6.79 (bs, 1H), 5.70 (d, -J=12.80Hz, 1H), 4.84 (d, -J=12.80Hz, 1H), 3.48 (bs, 3H), 2.73 (bs, 3H)

Example 659

1H NMR(d6-DMSO, 400MHz) δ 9.58 (bs, 1H), 8.09 (d, J=2.20Hz, 1H), 7.75 (dd, J=8.35Hz, 2.20Hz, 1H), 7.58 (d, J=6.59Hz, 1H), 7.34 (dt. J=7.47Hz, 1.32Hz, 1H), 7.23 (dt. J=7.47Hz, 1.32Hz, 1H), 7.05 (s, 1H), 7.00-6.94 (m, 3H), 6.87 (d, J=8.79Hz, 1H), 6.78 (d, J=7.91Hz, 1H), 5.65 (vbs, 1H), 5.13 (vbs, 1H), 3.30 (bs, 3H), 2.78 (s, 3H)

Example 660

1H NMR(CDCl3, 400MHz) δ 7.76-7.72 (m, 2H), 7.44-7.41 (m, 2H), 7.35-7.34 (m, 2H), 7.26-7.17 (m, 2H), 7.06-7.04 (m, 1H), 6.88 (d, J=8.79Hz, 1H), 6.28 (bs, 1H), 5.58 (vbs, 2H), 3.72 (s, 3H), 2.83 (s, 3H)

Example 670

1H NMR(CDCl3, 400MHz) δ 7.45-7.09 (m, 9H), 6.75-6.72 (m, 1H), 6.65-6.61 (m, 2H), 6.38 (bs, 1H), 5.43 (vbs, 2H), 3.87 (s, 3H), 2.88 (s, 3H)

Example 671

1H NMR(CDCl3, 400MHz) δ 7.48-7.46 (m, 1H), 7.34-6.63 (m, 12H), 5.75 (vbs, 1H), 5.10 (m, 1H), 2.83 (s, 3H)

Example 672

1H NMR(CDCl3, 300MHz) δ 7.47-7.06 (m, 8H), 6.86-6.82 (m, 2H), 6.73-6.67 (m, 2H), 6.54-6.52 (m, 1H), 5.31 (vbs, 2H), 2.89 (s, 3H)

Example 673

1H NMR(CDCl3, 300MHz) δ 7.45 (d, J=7.58Hz, 1H), 7.32 (dt, J=7.42, 1.32, 1H), 7.22-7.14 (m, 3H), 7.04-6.98 (m, 2H), 6.92-6.86, (m, 3H), 6.80-6.73 (m, 2H), 6.47 (bs, 1H), 5.25 (vbs, 2H), 2.81 (s, 3H)

Example 675

1H NMR(CDCl3, 300MHz) δ 7.47-6.81 (m, 1H), 5.63 (vbs, 1H), 5.05 (vbs, 1H), 2.82 (s, 3H), 2.18 (s, 1.5H) 2.14 (s, 1.5H)

Example 676

1H NMR(CDCl3, 400MHz) δ 7.41-7.15 (m, 10H), 6.76 (s, 1H), 6.61 (s, 1H), 6.48 (bs, 1H), 5.30 (vbs, 2H), 2.90 (s, 3H), 2.06 (s, 3H)

Example 677

1H NMR(CDCl3, 400MHz) δ 7.63-6.84 (m, 13H), 5.60 (vbs, 1H), 4.95 (vbs, 1H), 2.81 (s, 3H), 2.32 (s, 3H).

Example 679

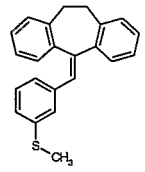
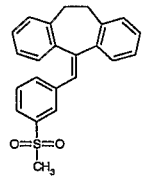
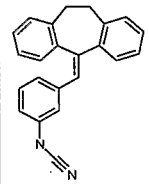
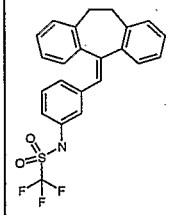
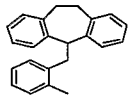
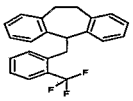
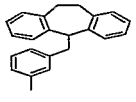
1H NMR(CDCl3, 400MHz) δ 7.64 (s, 1H), 7.44 (d, J=7.47Hz, 1H), 7.39-7.28 (m, 2H), 7.19-7.12 (m, 2H), 7.01-6.98 (m, 2H), 6.91-6.83 (m, 4H), 6.70 (s, 1H), 5.57 (vbs, 1H), 5.00 (vbs, 1H), 2.82 (s, 3H), 2.30 (s, 3H).

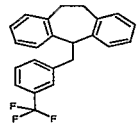
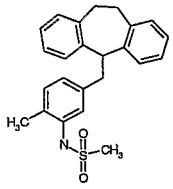
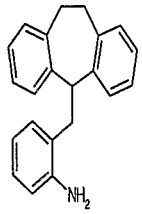
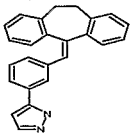
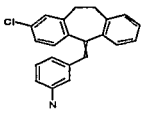
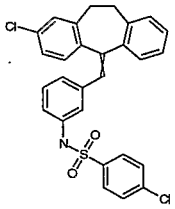
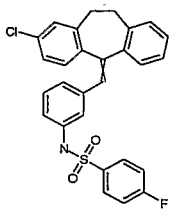
Example 681

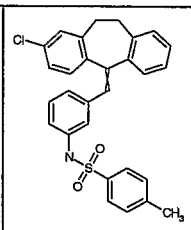
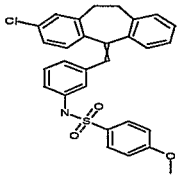
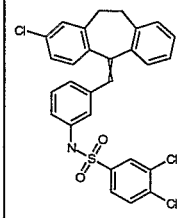
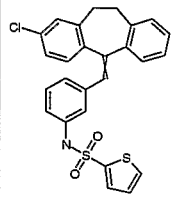
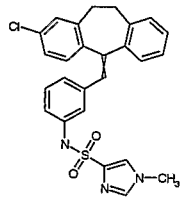
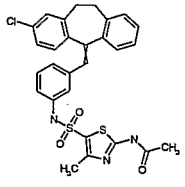
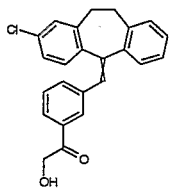
1H NMR(CDCl3, 400MHz) δ 7.45-7.26 (m, 5H), 7.21-7.17 (m, 2H), 7.09 (dd, J=7.91Hz, 1.32Hz, 1H), 7.05 (dd, J=8.79Hz, 2.63Hz, 1H), 6.98 (d, J=2.64Hz, 1H), 6.83 (d, J=8.79Hz, 1H), 6.65 (s, 1H), 6.41 (bs, 1H), 5.33 (vbs, 2H), 2.90 (s, 3H).

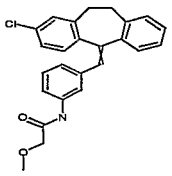
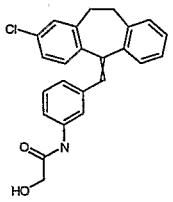
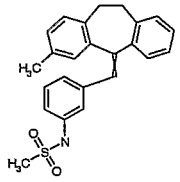
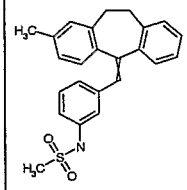
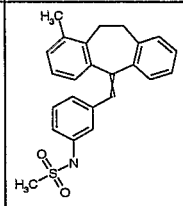
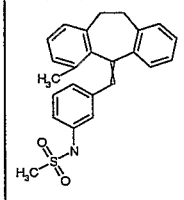
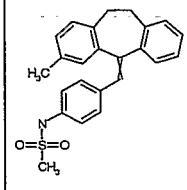
Example 682

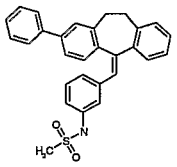
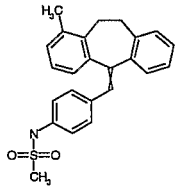
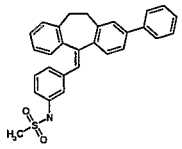
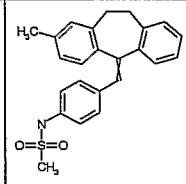
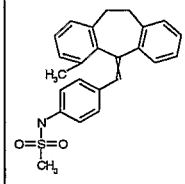
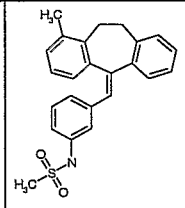
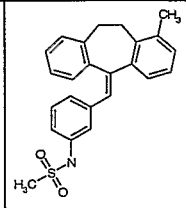
1H NMR(CDCl3, 400MHz) δ 7.46-7.44 (m, 2H), 7.32 (dt, J=7.47Hz, 1.32Hz, 2H), 7.21-7.10 (m, 3H), 7.03-6.98 (m, 2H), 6.91-6.88 (m, 2H), 6.80 (s, 1H), 6.75 (d, J=8.79Hz, 1H), 6.40 (bs, 1H), 5.63 (vbs, 1H), 4.93 (vbs, 1H), 2.82 (s, 3H).

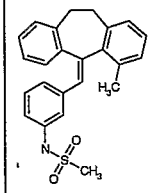
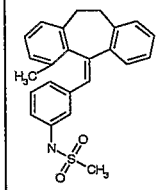
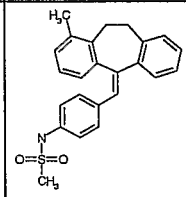
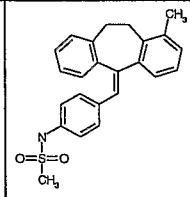
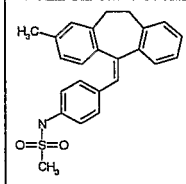
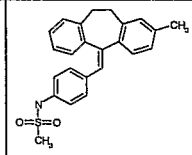
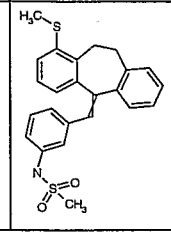
Example No.	Structure	MS Data	HPLC	Section
278		ES 329 (+)	NA	1
279		ES 361 (+)	NA	1
280		ES 321 (-) / 323 (+)	(GRAD) t=3.392 (95%)	1
281		ES 428 (-)	(ISO80-10) t= 5.59 (100%)	1
282		EA; C23H22 th; C, 91.45 H, 7.41 fd; C, 91.99 H, 7.39	t = 2.96 (97.4%)	1
283		TOF MS EI+ = 352	EA; C23H19F3 th; C, 78.39 H, 5.43 fd; C, 78.84 H, 5.11	1
284		TOF MS EI+ = 298	NA	1

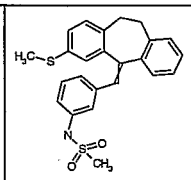
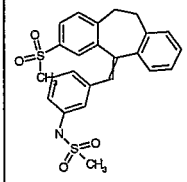
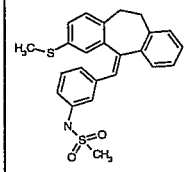
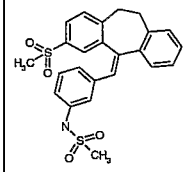
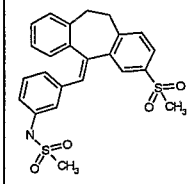
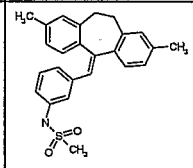
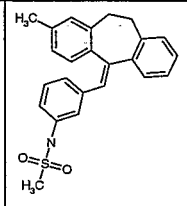
285		TOF MS EI+ = 352	NA	1
286		ES 391 (+)	t= 5.05 min (100%)	1
287		m/z = 300 (M+1)	ISO60-10.M, ret time = 14.15 min.; 100%	1
288		ES 347 (-) / 349 (+)	(ISO90-10) t= 3.15 (99%)	1
289		NA	NA	2
290		APCI 506 (+)	GRAD 80-100M t = 6.048 (100 %)	2
291		APCI 490 (+)	GRAD 80-100M t = 5.638 (100 %)	2

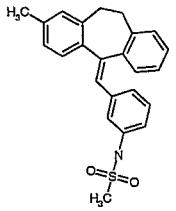
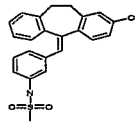
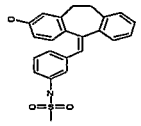
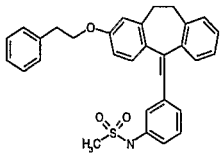
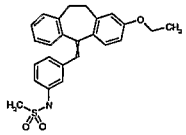
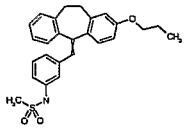
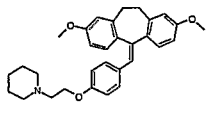
292		APCI 486 (+)/484 (-)	GRAD 80-100M t = 5.638 (100 %)	2
293		APCI 502 (+)/500 (-)	GRAD 80-100M t = 5.464 (100 %)	2
294		APCI 542 (+)/540 (-)	GRAD 80-100M t = 6.221 (100 %)	2
295		APCI 478 (+)	GRAD 80-100M t = 5.200 (100 %)	2
296		APCI 476 (+)	GRAD 80-100M t = 3.876 (100 %)	2
297		APCI 550 (+)	GRAD 80-100M t1=4.316(50%) t2=4.553 (50%) ISOMER MIX	2
298		APCI 374 (+)	GRAD 80-100M t1=5.210(50%) t2=5.340 (50%) ISOMER MIX	2

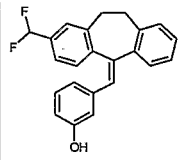
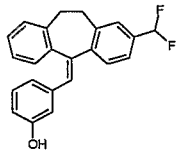
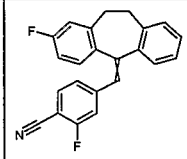
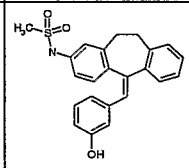
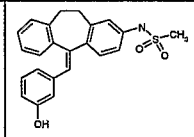
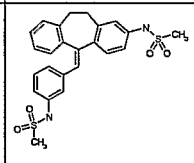
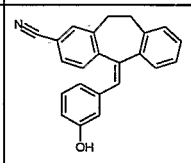
299		APCI 404 (+)	GRAD 80-100M t = 5.343 (100 %)	2
300		APCI 392 (+)	GRAD 80-100M t = 5.282(95 %)	2
301		ES 388 (-) / 390 (+)	(GRAD) t=3.477 (99%)	2
302		ES 388 (-) / 390 (+)	(GRAD) t=3.488 (97 %)	2
303		ES 388 (-) / 390 (+)	(GRAD) t= 3.435 (97%)	2
304		ES 388 (-) / 390 (+)	(GRAD) t=3.424 (100%)	2
305		ES 388 (-) / 390 (+)	(GRAD) t=3.531 (100%)	2

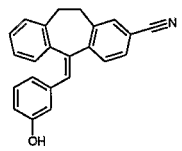
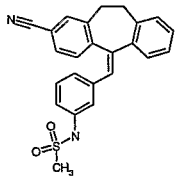
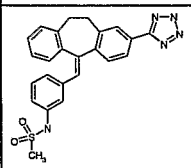
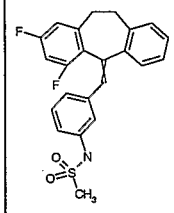
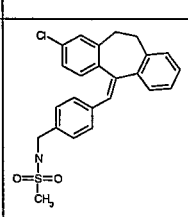
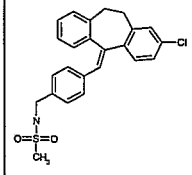
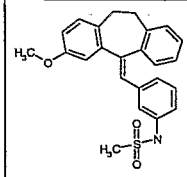
306		ES 450 (-) / 452 (+)	(GRAD) t=3.712 (96%)	2
307		ES 388 (-) / 390 (+)	(GRAD) t=3.467 (99%)	2
308		ES 450 (-) / 452 (+)	(GRAD) t=3.744 (100%)	2
309		ES 388 (-) / 390 (+)	(GRAD) t=3.531 (94%)	2
310		ES 388 (-) / 390 (+)	(GRAD) t=3.445 (100%)	2
311		ES 388 (-) / 390 (+)	(GRAD) t=8.790 (100%)	2
312		ES 388 (-) / 390 (+)	(GRAD) t=11.057 (100%)	2

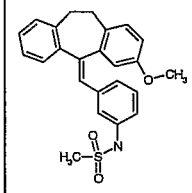
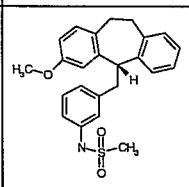
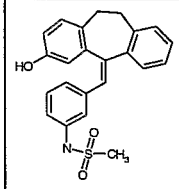
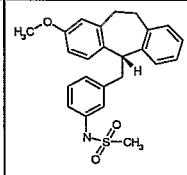
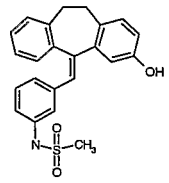
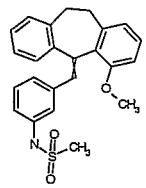
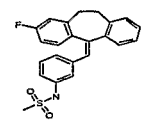
313		ES 388 (-) / 390 (+)	(GRAD) t=8.128 (100%)	2
314		ES 388 (-) / 390 (+)	(GRAD) t=9.738 (100%)	2
315		ES 388 (-) / 390 (+)	(GRAD) t=7.626 (97%)	2
316		ES 388 (-) / 390 (+)	(GRAD) t=6.508 (99%)	2
317		ES 388 (-) / 390 (+)	(GRAD) t=4.790 (99%)	2
318		ES 388 (-) / 390 (+)	(GRAD) t=4.932 (100%)	2
319		ES 420(-) / 422 (+)	(GRAD) t=3.424 (100%)	2

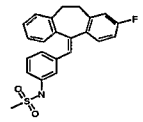
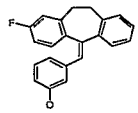
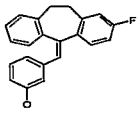
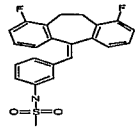
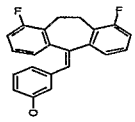
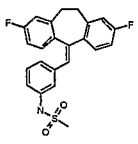
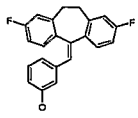
320		ES 420 (-) / 422 (+)	(GRAD) t=3.424 (100%)	2
321		ES 452 (-) / 454 (+)	(GRAD) t=2.779 (100%)	2
322		ES 420 (-) / 422 (+)	(GRAD) t=6.50 (100%)	2
323		ES 452 (-) / 454 (+)	(GRAD) t=13.40 (100%)	2
324		ES 452 (-) / 454 (+)	(GRAD) t=17.90 (100%)	2
325		ES 402 (+) / 404 (-)	NA	2
326		ES 388 (-) / 390 (+)	(GRAD) t=3.381 (97%)	2

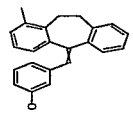
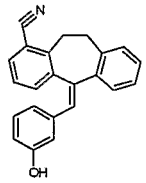
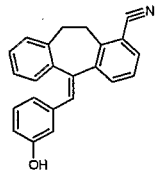
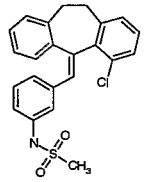
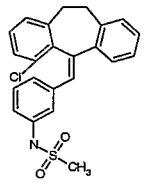
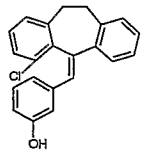
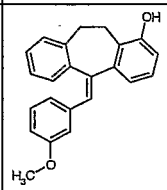
327		ES 388 (-) / 390 (+)	(GRAD) t=3.413 (97%)	2
328		ES- = 390.3, ES+ = 392.2	NA	2
329		ES- = 390.3, ES+ = 392.2	NA	2
330		ES- = 494 (Mixture)	NA	2
331		ES- = 418	NA	2
332		ES- = 432	NA	2
333		ES 470 (+)	t=1.40	2

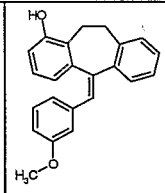
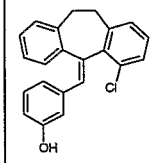
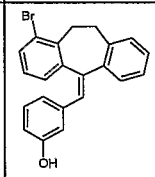
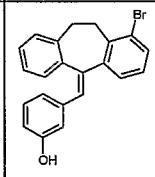
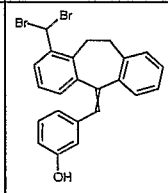
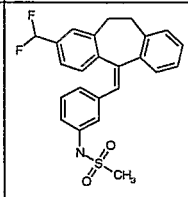
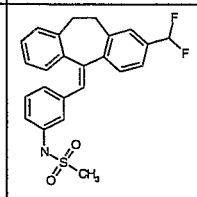
334		ES 347 (-)	(ISO80-10) t= 3.41 (96%)	2
335		ES 347 (-)	(ISO80-10) t= 3.74 (99%)	2
336		EI 343	(ISO80-10) t= 7.08 (47%), 7.31 (52%)	2
337		ES 390 (-) / 392 (+)	(ISO80-10) t= 2.40 (93%)	2
338		ES 390 (-)	(ISO80-10) t= 2.01 (92%)	2
339		ES 467 (-)	(ISO80-10) t= 1.90 (82%)	2
340		ES 322 (-)	(ISO80-10) t= 3.43 (98%)	2

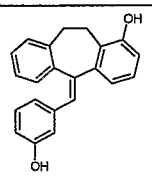
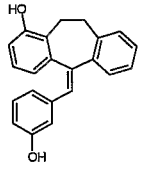
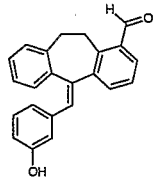
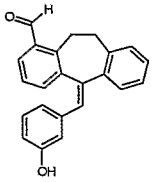
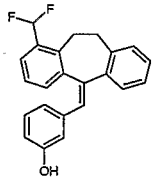
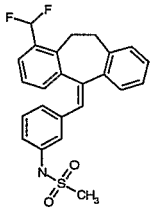
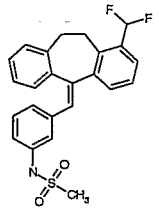
341		ES 322 (-)	(ISO80-10) t= 3.09 (96%)	2
342		ES 399 (-) / 401 (+)	(ISO80-10) t= 3.12 (98%)	2
343		ES 442 (-) / 444 (+)	(ISO80-10) t= 1.88 (98%)	2
344		ES 410 (-) / 412 (+)	(ISO70-10) t= 5.73 (75%), 5.98 (25%)	2
345		ES 422 (-)/ 424 (+)	(GRAD 5-100) t=5.52	2
346		ES 422 (-)/ 424 (+)	(GRAD 5-100) t=5.71	2
347		ES 406 (+)	NA	2

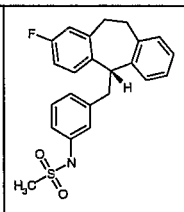
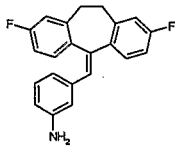
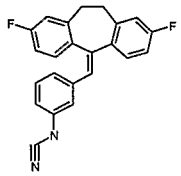
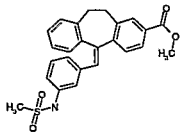
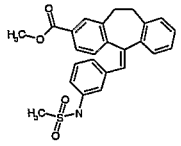
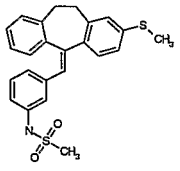
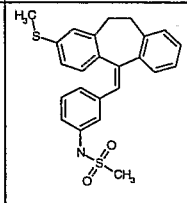
348		ES 406 (+)	NA	2
349		ES 407 (+)	t = 4.89 min	2
350		ES 392 (+)	t = 4.46 min (100%)	2
351		ES 407 (+)	t = 4.80 min (100%)	2
352		ES 392 (+)	t = 4.24 nin (100%)	2
353		ES 405 (+)	t = 5.85 min (100%)	2
354		ES 392 (-)	(ISO60-15M) t=11.22 (100%)	2

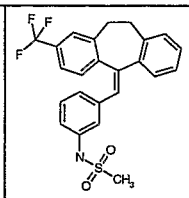
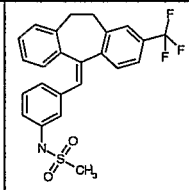
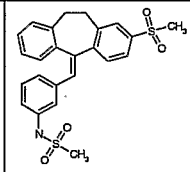
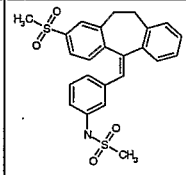
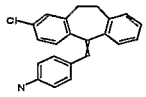
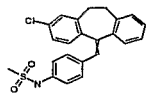
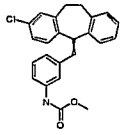
355		ES 392 (-)	(ISO60-15M) t=10.90 (96%)	2
356		ES 315 (-)	(ISO80-10M) t=4.02 (94%)	2
357		ES 315 (-)	(ISO80-10M) t=3.86 (95%)	2
358		ES 410 (-)	(ISO90-10M) t=2.64 (92%)	2
359		ES 333 (-)	(ISO90-10M) t=2.90 (98%)	2
360		ES 410 (-)	(ISO80-10M) t=3.56 (99%)	2
361		ES 333 (-)	(ISO90-10M) t=2.63 (99%)	2

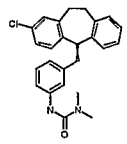
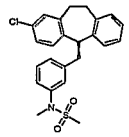
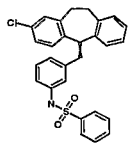
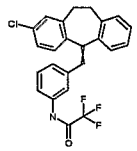
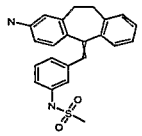
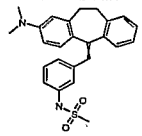
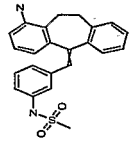
362		ES 311 (-)	(ISO90-10M) t=2.94 (92%)	2
363		ES 322 (-)	(ISO80-10M) t=3.40(96%)	2
364		ES 322 (-)	(ISO80-10M) t=3.10(99%)	2
365		ES 408 (-)	(ISO80-10M) t=4.15(90%)	2
366		ES 408 (-) / 410 (+)	(ISO80-10M) t=3.81 (100%)	2
367		ES 331 (-) / 333 (+)	(ISO80-10M) t=4.10 (99%)	2
368		ES 327 (-) / 329 (+)	(ISO80-10M) t=3.66(100%)	2

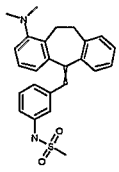
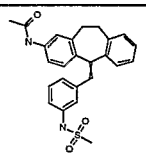
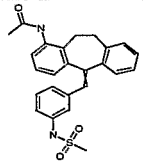
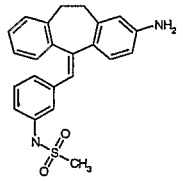
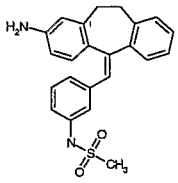
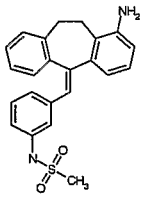
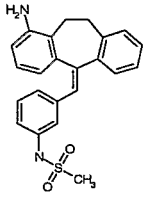
369		ES 327 (-) / 329 (+)	(ISO80-10M) t=4.15(99%)	2
370		ES 332 (-) / 334 (+)	(ISO80-10M) t=4.53(99%)	2
371		ES 377 (-)	(ISO80-10M) t=5.93(96%)	2
372		ES 377 (-)	(ISO80-10M) t=6.28(95%)	2
373		ES 467 (-)	(ISO80-10M) t=5.26(95%)	2
374		ES 424 (-)	(ISO80-10M) t=3.45(92%)	2
375		ES 424 (-)	(ISO80-10M) t=3.06(94%)	2

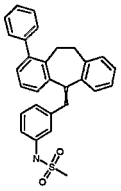
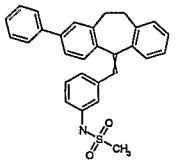
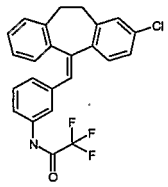
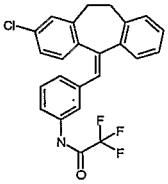
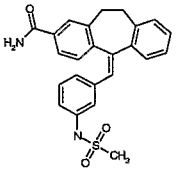
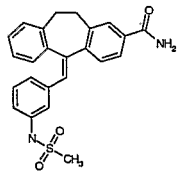
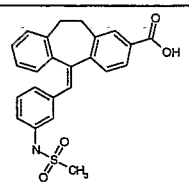
376		ES 313 (-) / 315 (+)	(ISO80-10M) t=2.15(99%)	2
377		ES 313 (-) / 315 (+)	(ISO80-10M) t=2.50(98%)	2
378		ES 325 (-)	(ISO80-10M) t=3.00(93%)	2
379		ES 325 (-)	(ISO80-10M) t=3.22(94%)	2
380		ES 347 (-)	(ISO80-10M) t=3.48 (89%)	2
381		ES 424 (-)	(ISO80-10M) t=3.44 (92%)	2
382		ES 424 (-)	(ISO80-10M) t=3.16 (93%)	2

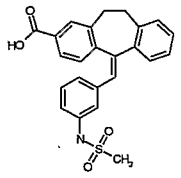
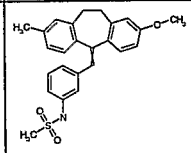
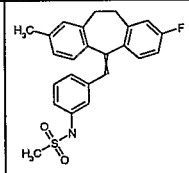
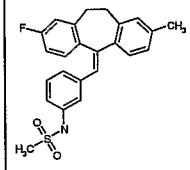
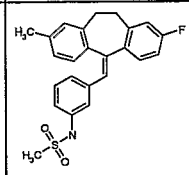
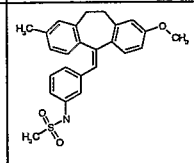
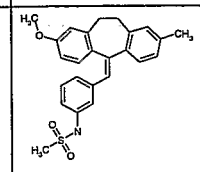
383		ES 394 (-)	(ISO60-15M) t=10.37 (99%)	2
384		ES 334 (+)	(ISO80-10M) t=4.14 (98%)	2
385		ES 357 (-)	(ISO80-10M) t=3.93 (89%)	2
386		ES 432 (-)	(ISO80-10M) t=3.21 (91%)	2
387		ES 432 (-)	(ISO80-10M) t=3.49 (94%)	2
388		NA	(ISO80-10M) t=3.20 (95%)	2
389		NA	(ISO80-10M) t=4.08 (93%)	2

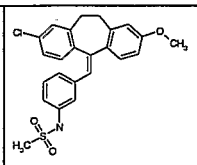
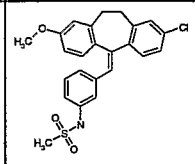
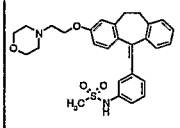
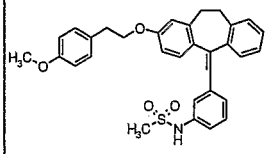
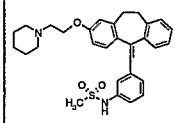
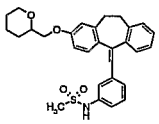
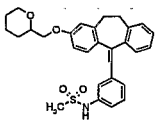
390		ES 442 (-)	(ISO80-10M) t=4.39 (99%)	2
391		ES 442 (-)	(ISO80-10M) t=4.39 (93%)	2
392		ES 452 (-)	(ISO80-10M) t=2.07 (93%)	2
393		ES 452 (-)	(ISO80-10M) t=2.43 (99%)	2
394		332 (ES+) 330 (ES-)	NA	2
395		408 (ES-)	NA	2
396		390 (ES-) 388 (ES+)	NA	2

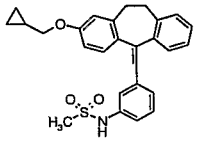
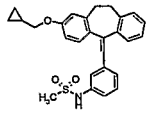
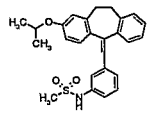
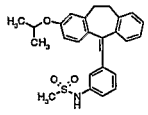
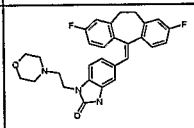
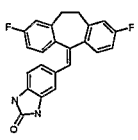
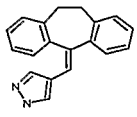
397		402 (EI+)	NA	2
398		MS(ES+) = 424.	NA	2
399		470/472 (ES-)	NA	2
400		426 (ES-)	NA	2
401		389 (ES-)	NA	2
402		419 (ES+)	NA	2
403		Isomers separated NA	NA	2

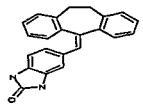
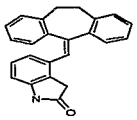
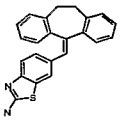
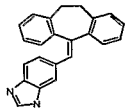
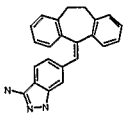
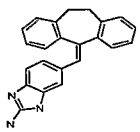
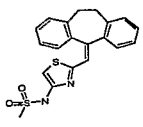
404		419 (ES+)	NA	2
405		433 (ES+)	NA	2
406		433 (ES+)	NA	2
407		391 (ES+)	NA	2
408		391 (ES+)	NA	2
409		391 (ES+)	NA	2
410		391 (ES+)	NA	2

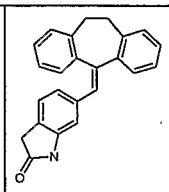
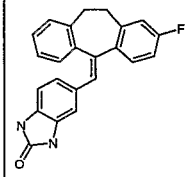
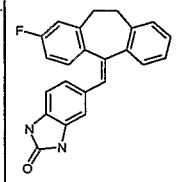
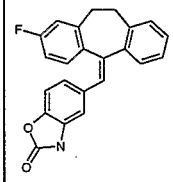
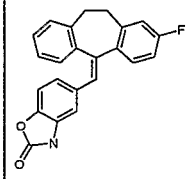
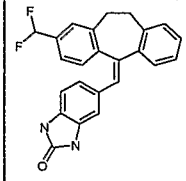
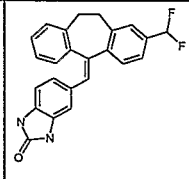
411		450 (ES-)	NA	2
412		450 (ES-)	NA	2
413		426/428 (ES-)	100%	2
414		426/428 (ES-)	100%	2
415		419 (ES+)	93%	2
416		419 (ES+)	97%	2
417		418 (ES-)	NA	2

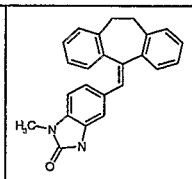
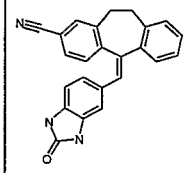
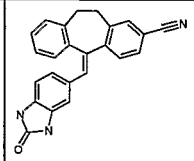
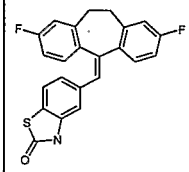
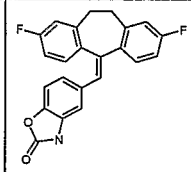
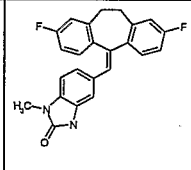
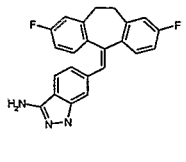
418		418 (ES-)	NA	2
419		ES 420 (+)	(GRAD) t=3.30 (97%)	2
420		ES 408 (+)	(GRAD) t=3.49 (100%)	2
421		NA	(GRAD) t=3.49 (100%)	2
422		N/A	(GRAD) t=3.46 (98.4%)	2
423		ES 418 (-) / 420 (+)	(GRAD) t=2.46 (100%)	2
424		ES 418 (-) / 420 (+)	(GRAD) t=2.46 (100%)	2

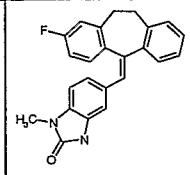
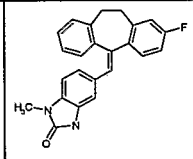
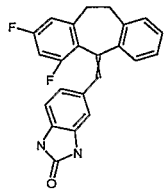
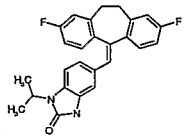
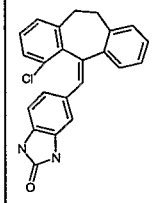
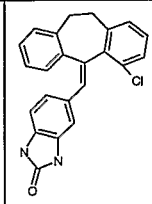
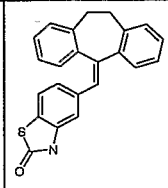
425		ES 438 (-) / 440 (+)	(GRAD) t=2.74 (100%)	2
426		ES 438 (-) / 440 (+)	NA	2
427		ES- = 504, ES+ = 505 (E Isomer)	NA	2
428		ES- = 524 (E Isomer)	NA	2
429		ES- = 501, ES+ = 503 (E Isomer)	NA	2
430		ES- = 488, ES+ = 490 (E Isomer)	NA	2
431		ES- = 488, ES+ = 490 (Z Isomer)	NA	2

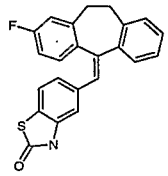
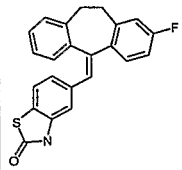
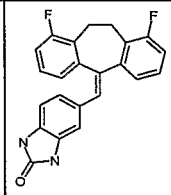
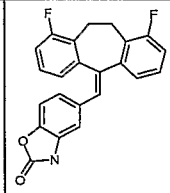
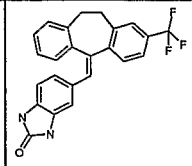
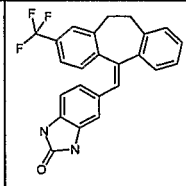
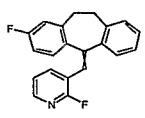
432		ES- = 444 (E Isomer)	NA	2
433		ES- = 444 (Z Isomer)	NA	2
434		ES- = 432 (E Isomer)	NA	2
435		ES- = 432 (Mixture)	NA	2
436		ES 488 (+)	(ISO80-10M) t=2.03 (97%)	3
437		ES 373 (-)	(ISO80-10M) t=2.62 (97%)	3
439		ES 271 (-) / 273 (+)	(ISO90-10) t= 2.55 (98%)	3

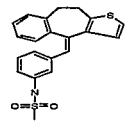
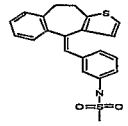
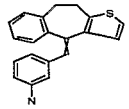
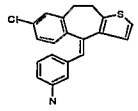
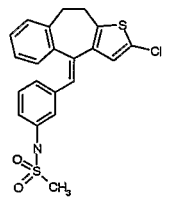
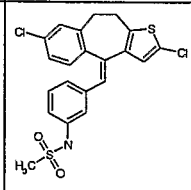
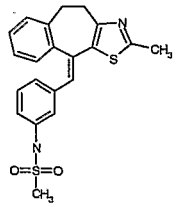
440		ES 337 (-) / 339 (+)	(ISO90-10) t= 2.32 (93%)	3
441		ES 338 (+)	(ISO80-10) t= 3.61 (96%)	3
442		ES 353 (-) / 355 (+)	(ISO80-10) t= 4.03 (98%)	3
443		ES 321 (-) / 323 (+)	(ISO80-10) t= 2.39 (99%)	3
444		ES 336 (-) / 338 (+)	(ISO80-10) t= 2.85 (98%)	3
445		ES 336 (-) / 338 (+)	(ISO80-10) t= 1.96 (100%)	3
446		ES 381 (-) / 383 (+)	(ISO80-10) t= 2.99 (98%)	3

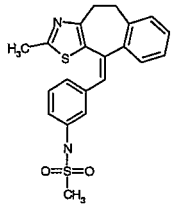
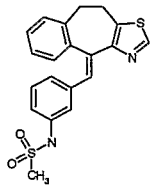
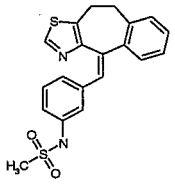
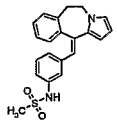
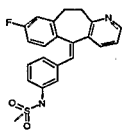
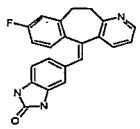
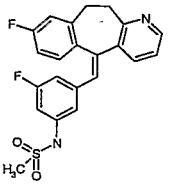
447		ES 336 (-) / 338 (+)	(ISO80-10) t= 3.68 (91%)	3
448		ES 355 (-) / 357 (+)	(ISO80-10) t= 2.64 (78%)	3
449		ES 355 (-) / 357 (+)	(ISO80-10) t= 2.74 (94%)	3
450		ES 356 (-)	(ISO80-10) t= 3.93 (92%)	3
451		ES 356 (-) / 358 (+)	(ISO80-10) t= 3.81 (92%)	3
452		ES 387 (-) / 389 (+)	(ISO80-10) t= 2.58 (96%)	3
453		ES 387 (-) / 389 (+)	(ISO80-10) t= 2.40 (96%)	3

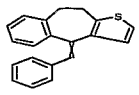
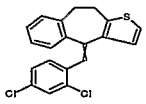
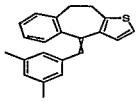
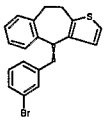
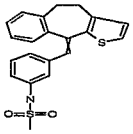
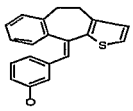
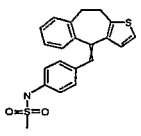
454		ES 351 (-) / 353 (+)	(ISO80-10) t= 3.78 (100%)	3
455		ES 362 (-) / 364 (+)	(ISO80-10) t= 2..41 (84%)	3
456		ES 362 (-) / 364 (+)	(ISO80-10) t= 2.22 (88%)	3
457		ES 390 (-) / 392 (+)	(ISO80-10) t= 4.71 (96%)	3
458		ES 374 (-)	(ISO80-10) t= 3.69 (95%)	3
459		ES 387 (-) / 389 (+)	(ISO80-10) t= 3.72 (95%)	3
460		ES 372 (-) / 374 (+)	(ISO80-10) t= 2.89 (83%)	3

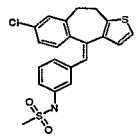
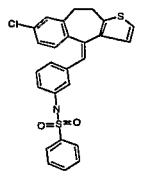
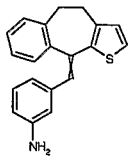
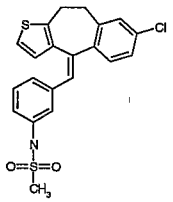
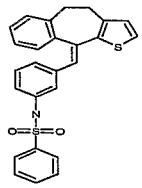
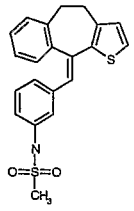
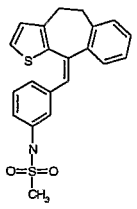
461		ES 369 (-) / 371 (+)	(ISO80-10) t= 3.73 (100%)	3
462		ES 369 (-) / 371 (+)	(ISO80-10) t= 3.64 (99%)	3
463		ES 373 (-)	(ISO70-10) t= 3.54 (78%), 3.64 (22%)	3
464		ES 415 (-) / 417 (+)	(ISO80-10) t= 4.81 (97%)	3
465		ES 371 (-) / 373 (+)	(ISO80-10M) t=2.95(93%)	3
466		ES 371 (-) / 373 (+)	(ISO80-10M) t=2.73(94%)	3
467		ES 354 (-)	(ISO80-10M) t=4.87 (100%)	3

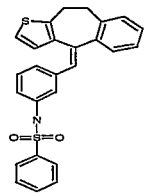
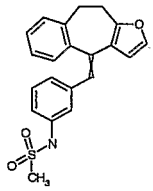
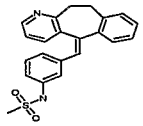
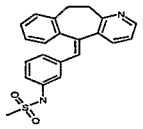
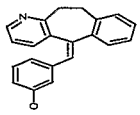
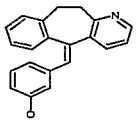
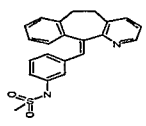
468		ES 372 (-) / 374 (+)	(ISO80-10M) t=5.10 (99%)	3
469		ES 372 (-) / 374 (+)	(ISO80-10M) t=4.97 (99%)	3
470		ES 373 (-) / 375 (+)	(ISO80-10M) t=2.93 (96%)	3
471		ES 374 (-) / 376 (+)	(ISO80-10M) t=4.28 (93%)	3
472		ES 405 (-)	(ISO80-10M) t=3.31 (97%)	3
473		ES 405 (-)	(ISO80-10M) t=3.30 (94%)	3
474		m/z = 320 (M+1)	ISO80-10.M, ret time = 5.63, 5.73 min.; 98.2%	3

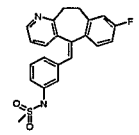
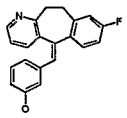
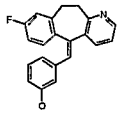
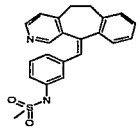
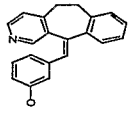
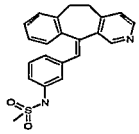
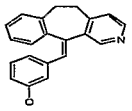
475		APCI 382 (+)	ISO 80:100M t = 3.047 (95 %)	4
476		APCI 382 (+)	ISO 80:100M t = 3.310 (95 %)	4
477		APCI 304 (+)	GRAD 80-100M t=4.037 (98 %)	4
478		EI 337	GRAD60-280 t=24.21 (98 %)	4
481		APCI 416(+)	GRAD 80-100M t = 1.852 (100 %)	4
482		APCI 450 (+)	GRAD 80-100M t = 5.466 (100 %)	4
483(a)		APCI 397 (+)	GRAD 80-100M t = 2.799 (95 %)	4

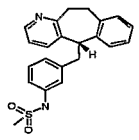
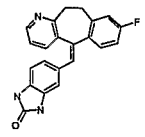
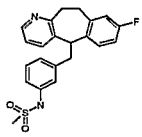
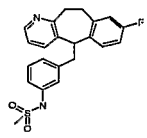
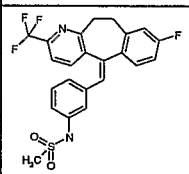
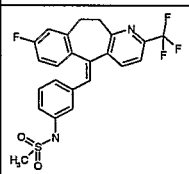
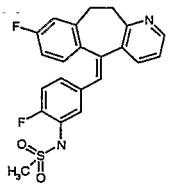
483(b)		APCI 397 (+)	GRAD 80-100M t = 2.598 (95 %)	4
484(a)		APCI 383 (+)	GRAD 80-100M t = 2.128 (100 %)	4
484(b)		APCI 383 (+)	GRAD 80-100M t = 2.219 (98 %)	4
485(a)		APCI 365 (+)	GRAD 80-100M t = 2.823 (99 %)	4
486		395.1 (APCI-pos) 393.0 (APCI-neg)	98%	4
487		358.0 (APCI-pos) 356.0 (APCI-neg)	98%	4
488		413.0 (APCI-pos) 411.0 (APCI-neg)	98%	4

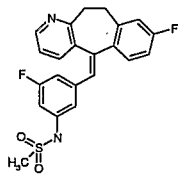
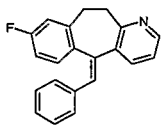
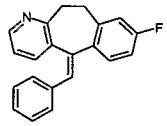
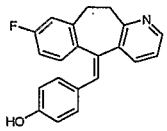
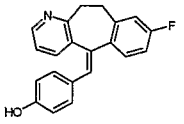
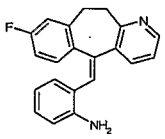
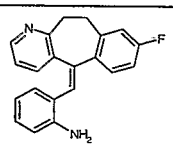
489		APCI 289 (+)	GRAD 80-100M t=5.7550 (100 %)	4
490		NA	NA	4
491		EI 316	GRAD60-280 t1 23.09 (33 %) t2 23.25 (66 %) ISOMERIC MIX	4
492		EI 364	GRAD60-280 t1 20.4 (20 %) t2 20.6 (80 %) ISOMERIC MIX	4
493		APCI 382 (+)	ISO 70:30M t = 4.351 (95 %)	4
494		APCI 303 (+)	ISO 80:20M t = 3.892 (95 %)	4
495		APCI 382 (+)	ISO 80:20M t = 3.413 (95 %)	4

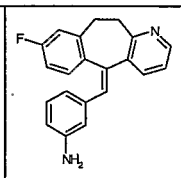
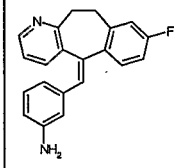
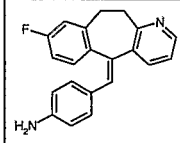
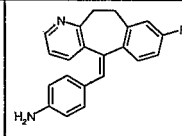
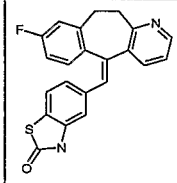
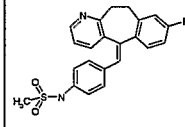
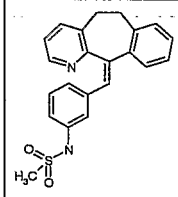
496		APCI 416 (+)	ISO 80:20A t = 3.527 (95 %)	4
497		APCI 440 (+)	ISO 80:100A t = 6.922 (95 %)	4
498		EI 303	GRAD60-280 21.15 (98 %)	4
499		APCI 416 (+)	ISO80-20A t=6.910 (99 %)	4
500		APCI 440 (+)	ISO80-20A t=6.922 (95 %)	4
501		APCI 382 (+)	ISO80-20A t = 5.438 (99 %)	4
502		APCI 382 (+)	ISO80-20A t = 5.430 (95 %)	4

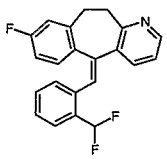
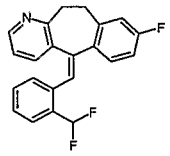
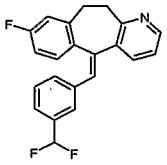
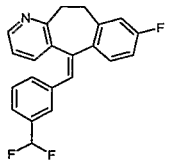
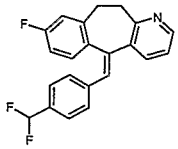
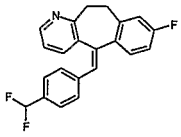
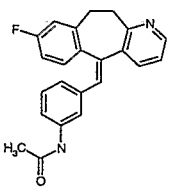
503		APCI 444 (+)	ISO80-20A t = 6.682 (95 %)	4
504		APCI 366 (+)	GRAD 80-100M t = 3.038 (50 %) t = 3.336 (50 %) ISOMERIC MIX	4
505		377.1 (APCI-pos) 375.0 (APCI-neg)	95%	4
506		377.1 (APCI-pos) 375.0 (APCI-neg)	95%	4
507		300.1 (APCI-pos)	95%	4
508		300.1 (APCI-pos)	95%	4
509		377.1 (APCI-pos) 375. (APCI-neg)	98%	4

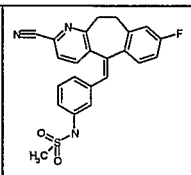
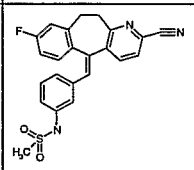
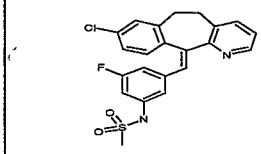
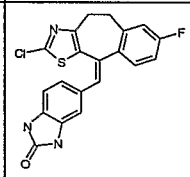
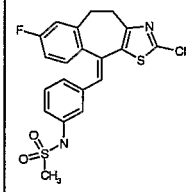
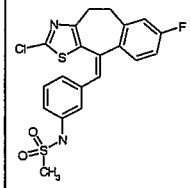
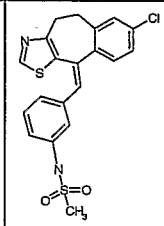
510		395.1 (APCI-pos) 393.0 (APCI-neg)	99%	4
511		318.0 (APCI-pos)	95%	4
512		318.0 (APCI-pos)	95%	4
513		377.1 (APCI-pos) 375. (APCI-neg)	96%	4
514		300.1 (APCI-pos)	95%	4
515		377.1 (APCI-pos) 375. (APCI-neg)	85%	4
516		300.1 (APCI-pos)	85%	4

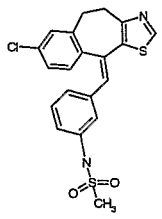
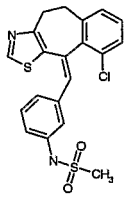
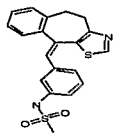
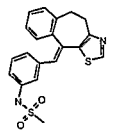
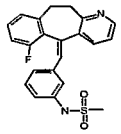
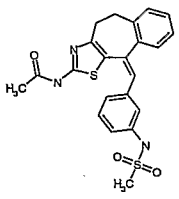
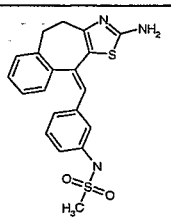
517		379.0 (APCI-pos)	85%	4
518		358.0 (APCI-pos) 356.0 (APCI-neg)	98%	4
519		397.0 (APCI-pos)	98%	4
520		397.0 (APCI-pos)	98%	4
521		463.0 (APCI-pos) 461.0 (APCI-neg)	98%	4
522		463.0 (APCI-pos) 461.0 (APCI-neg)	95%	4
524		413.0 (APCI-pos) 411.0 (APCI-neg)	95%	4

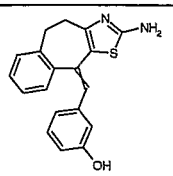
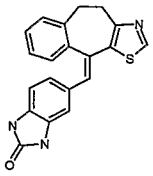
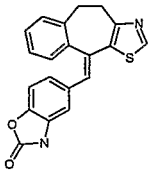
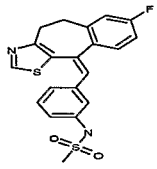
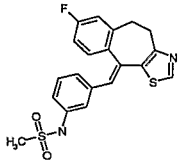
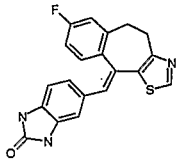
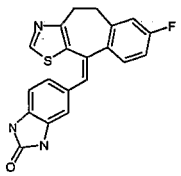
525		413.0 (APCI-pos) 411.0 (APCI-neg)	98%	4
526		302.1 (APCI-pos)	98%	4
527		302.1 (APCI-pos)	98%	4
528		318.0 (APCI-pos) 316.0 (APCI-neg)	98%	4
529		318.0 (APCI-pos) 316.0 (APCI-neg)	98%	4
530		317.1 (APCI-pos)	95%	4
531		317.1 (APCI-pos)	98%	4

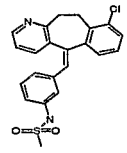
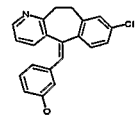
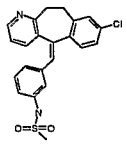
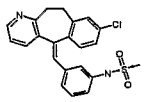
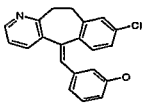
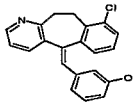
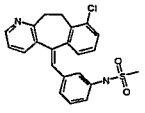
532		317.1 (APCI-pos)	95%	4
533		317.1 (APCI-pos)	90%	4
534		317.1 (APCI-pos)	95%	4
535		317.1 (APCI-pos)	95%	4
536		375.0 (APCI-pos) 373.0 (APCI-neg)	95%	4
537		395.0 (APCI-pos)	95%	4
538		377.1 (APCI-pos)	95%	4

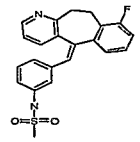
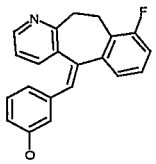
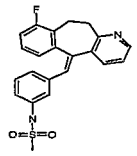
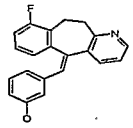
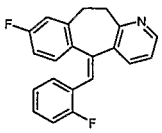
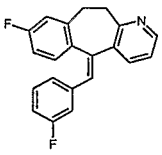
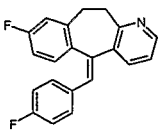
539		352.0 (APCI-pos)	98%	4
540		352.0 (APCI-pos)	99%	4
541		352.0 (APCI-pos)	98%	4
542		352.0 (APCI-pos)	98%	4
543		352.0 (APCI-pos)	98%	4
544		352.0 (APCI-pos)	95%	4
545		359.1 (APCI-pos)	98%	4

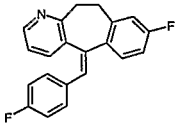
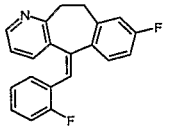
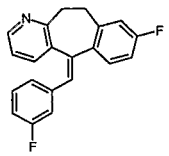
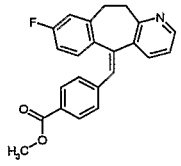
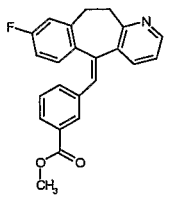
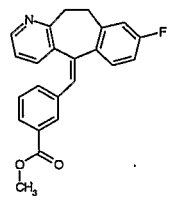
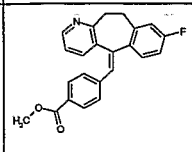
546		420.0 (APCI-pos) 417.9 (APCI-neg)	99%	4
547		420.0 (APCI-pos)	98%	4
548		ES 427 (-) / 429 (+)	(ISO80-10) t= 2.66 (99%)	4
549		ES 396 (-) / 398 (+)	(ISO80-10) t= 2.49 (96%)	4
550		ES 433 (-) / 435 (+)	(ISO80-10) t= 3.75 (92%)	4
551		ES 433 (-) / 435 (+)	(ISO80-10) t= 3.48 (92%)	4
552		APCI 417 (+)	(GRAD 80-100) t=1.31 (96%)	4

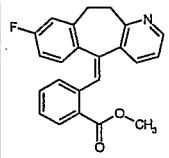
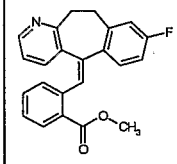
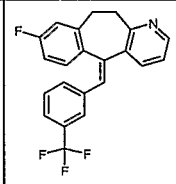
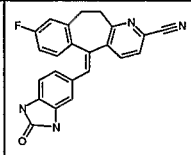
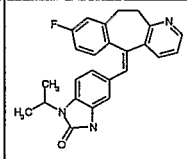
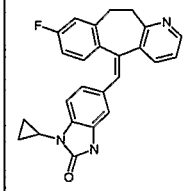
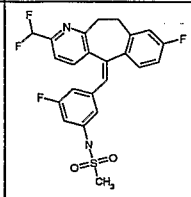
553		ES 417 (+)	(GRAD 70-100) t=2.10 (95%)	4
554		ES 417 (+)	NA	4
555		ES 382 (-) / 384 (+)	(ISO60-10M) t=4.31 (98%)	4
556		ES 382 (-) / 384 (+)	NA	4
557		ES 393 (-) / 395 (+)	(ISO60-10M) t=2.09 (98%)	4
558		ES 438 (-) / 440 (+)	(ISO60-10M) t=3.40 (98%)	4
559		ES 396 (-) / 398 (+)	(ISO40-10M) t=2.45 (92%)	4

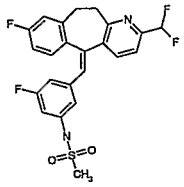
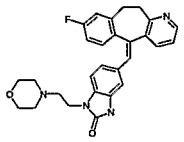
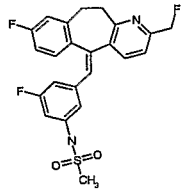
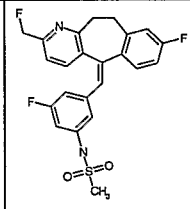
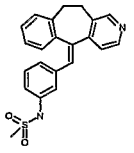
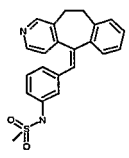
560		ES 319 (-) / 321 (+)	NA	4
561		ES 344 (-) / 346 (+)	(ISO60-10M) t=2.46 (94%)	4
562		ES 345 (-) / 347 (+)	(ISO60-10M) t=4.23 (88%)	4
563		ES 399 (-) / 401 (+)	(ISO80-10M) t=2.42 (100%)	4
564		ES 399 (-) / 401 (+)	(ISO80-10M) t=2.42 (91%)	4
565		ES 362 (-) / 364 (+)	(ISO80-10M) t=1.98 (94%)	4
566		ES 362 (-) / 364 (+)	(ISO60-10M) t=2.55 (97%)	4

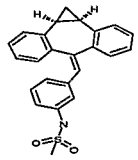
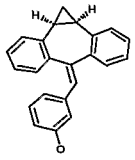
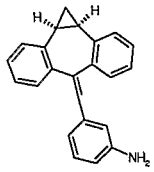
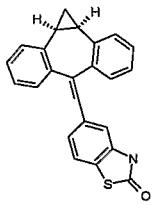
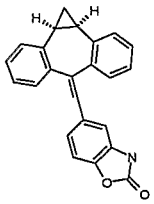
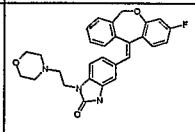
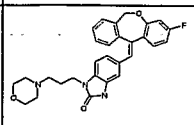
567		APCI 411,413(+)	LCMS(ISO8020M) t=2.60	4
568		APCI 334,336(+)	LCMS(ISO8020M) t=3.28	4
569		APCI 411,413(+)/409,411(-)	LCMS(ISO8020M) t=2.56	4
570		ES 411,413(+)/409,411(-)	LCMS(ISO8020M) t=1.94	4
571		ES 334,336(+)/332,334(-)	LCMS(ISO8020M) t=2.40	4
572		ES 334,336(+)/332,334(-)	LCMS(ISO8020M) t=2.91	4
573		ES 411,413(+)/409,411(-)	LCMS(ISO8020M) t=2.05	4

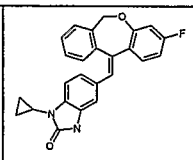
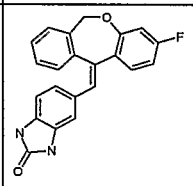
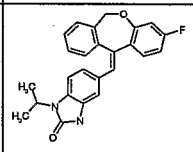
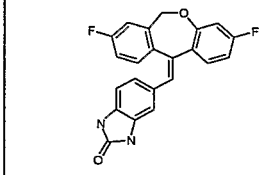
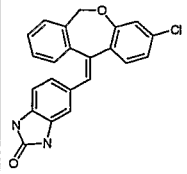
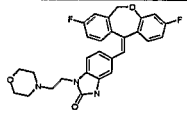
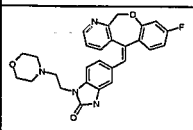
574		APCI 395(+)	LCMS(ISO7030M) t=6.44	4
575		APCI 318(+)	LCMS(ISO7030M) t=8.96	4
576		APCI 395(+)	LCMS(ISO7030M) t=4.51	4
577		APCI 318(+)	LCMS(ISO7030M) t=6.54	4
578		APCI 320(+)	LCMS(GRA80100M) t=4.48	4
579		APCI 320(+)	LCMS(GRA80100M) t=4.05	4
580		APCI 320(+)	LCMS(GRA80100M) t=4.33	4

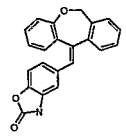
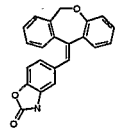
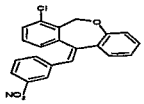
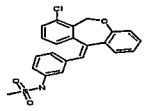
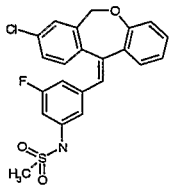
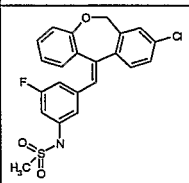
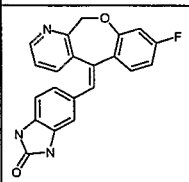
581		APCI 320(+)	LCMS(GRA80100) t=4.32	4
582		APCI 320(+)	LCMS(GRA80100) t=4.58	4
583		APCI 320(+)	LCMS(GRA80100M) t=4.24	4
584		APCI 360(+)	LCMS(GRA80100M) t=3.76	4
585		APCI 360(+)	LCMS(GRA80100) t=3.54	4
586		APCI 360(+)	LCMS(GRA80100M) t=3.82	4
587		APCI 360(+)	LCMS(GRA80100M) t=3.77	4

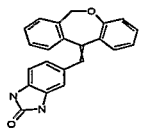
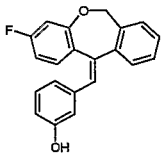
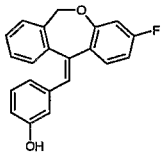
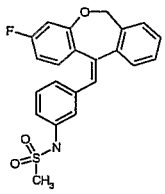
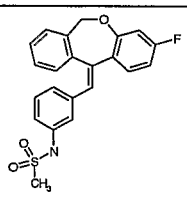
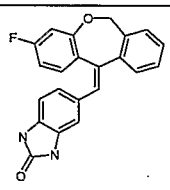
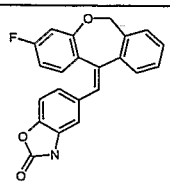
588		APCI 360(+)	LCMS(GRA80100M) t=4.26	4
589		APCI 360(+)	LCMS(GRA80100M) t=3.95	4
590		APCI 370(+)	LCMS(GRA80100M) t=4.70	4
591		APCI 383(+)/381(-)	LCMS(GRA80100M) t=1.98	4
592		APCI 400(+)/398(-)	LCMS(GRA80100M) t=3.08	4
593		APCI 398(+)/396(-)	LCMS(GRA80100M) t=2.97	4
594		APCI 461(-)	LCMS(ISO7030M) t=6.52	4

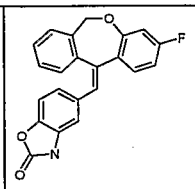
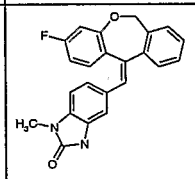
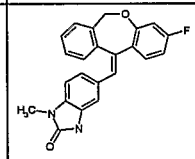
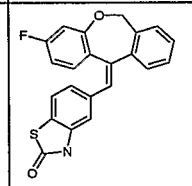
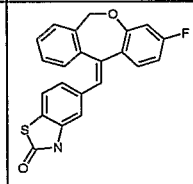
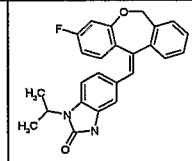
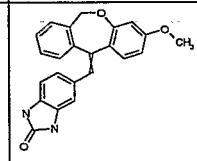
595		APCI 463(+)/461(-)	LCMS(ISO7030M) t=6.52	4
596		APCI 471(+)/469(-)	LCMS(ISO8020M) t=2.41	4
597		APCI 445(+)/443(-)	LCMS(ISO7030M) t=5.49	4
598		APCI 445(+)/443(-)	LCMS(ISO7030M) t=7.35	4
599		EI 286	GRAD60-280 17.84 (95 %)	4
600		APCI 377 (+)	90%	4
601		APCI 377 (+)	90%	4

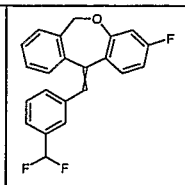
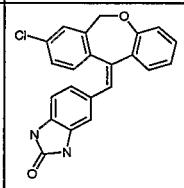
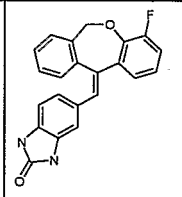
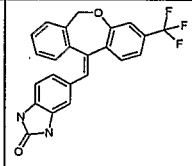
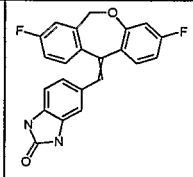
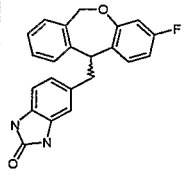
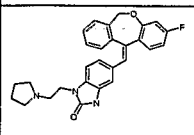
602		ES 386(-)/388(+)	LCMS(ISO8020M) t=3.04	5
603		ES 311(+)	LCMS(ISO8020M) t=3.79	5
604		APCI 310(+)	LCMS(GRA80100M) t=3.60	5
605		APCI 368(+)	LCMS(GRA80100M) t=4.96	5
606		APCI 352(+)	LCMS(GRA80100M) t=4.28	5
607		ES 471 (-) / 473 (+)	(ISO80-10M) t=1.79 (98%)	6
608		ES 484 (-) / 486 (+)	(ISO80-10M) t=1.72 (100%)	6

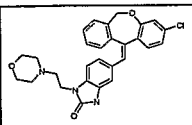
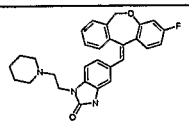
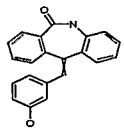
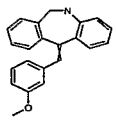
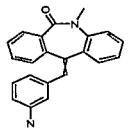
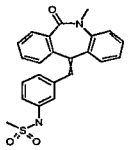
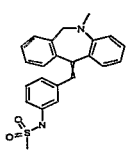
609		ES 397 (-) / 399 (+)	(ISO80-10M) t=3.68 (93%)	6
611		ES 357 (-)	(ISO60-10) t= 3.94 (93%)	6
612		ES 399 (-) / 401 (+)	(ISO80-10) t= 3.74 (96%)	6
613		ES 375 (-)	(ISO80-10) t= 2.38 (98%)	6
614		ES 373 (-)	(ISO80-10) t= 2.85 (99%)	6
617		ES 488 (-) / 490 (+)	(ISO80-10) t= 1.86 (99%)	6
618		473.1 (APCI-pos)	95%	6

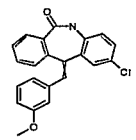
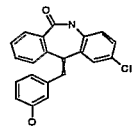
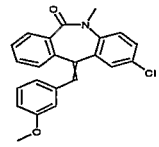
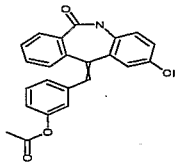
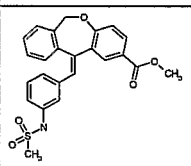
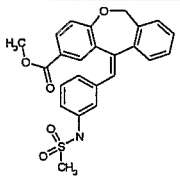
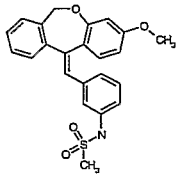
619		ES 340 (-) / 342 (+)	(ISO80-10) t= 2.98 (95%)	6
620		ES 340 (-) / 342 (+)	(ISO80-10) t= 2.96 (92%)	6
621		NMR	NA	6
622		ES 410 (-)	NA	6
623		430.0 (APCI-pos) 427.9, 428.9, 429.9 (APCI-neg)	95%	6
624		430.0 (APCI-pos) 427.9, 428.9, 429.9 (APCI-neg)	95%	6
625		360.0 (APCI-pos)	99%	6

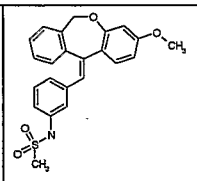
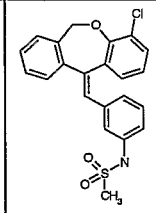
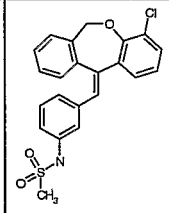
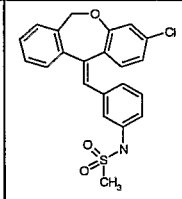
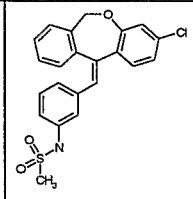
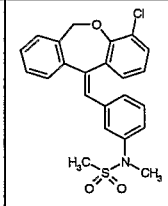
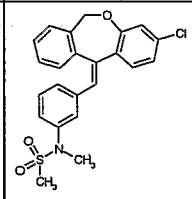
626		ES 339 (-)	(ISO80-10) t= 2.21 (96%)	6
627		ES 317 (-) / 319 (+)	(ISO80-10) t= 3.33 (96%)	6
628		ES 317 (-) / 319 (+)	(ISO80-10) t= 3.21 (96%)	6
629		ES 394 (-) / 396 (+)	(ISO60-10) t= 8.44 (90%)	6
630		ES 394 (-) / 396 (+)	(ISO60-10) t= 8.06 (97%)	6
631		ES 357 (-)	(ISO60-10) t= 4.30 (95%)	6
632		ES 358 (-) / 360 (+)	(ISO80-10) t= 3.11 (90%)	6

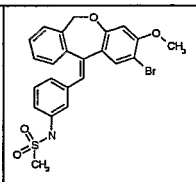
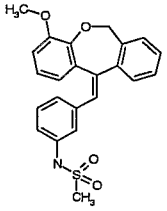
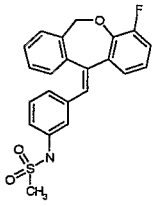
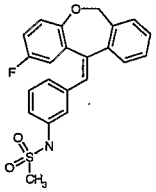
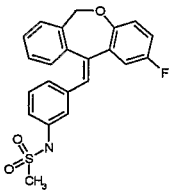
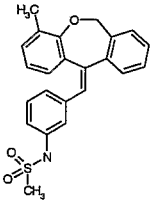
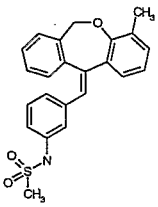
633		ES 358 (-)	(ISO80-10) t= 3.04 (92%)	6
634		ES 371 (-) / 373 (+)	(ISO80-10) t= 3.11 (92%)	6
635		ES 371 (-) / 373 (+)	(ISO80-10) t= 3.00 (92%)	6
636		ES 374 (-)	(ISO80-10) t= 3.91 (97%)	6
637		ES 374 (-)	(ISO80-10) t= 3.65 (93%)	6
638		ES 399 (-) / 401 (+)	(ISO80-10) t= 3.91 (94%)	6
639		ES 369 (-)	(ISO70-10) t= 2.15 (75%), 2.25 (15%)	6

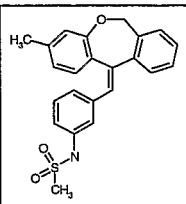
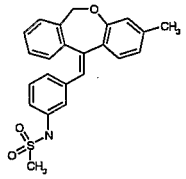
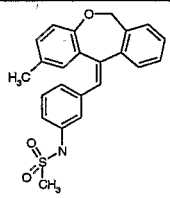
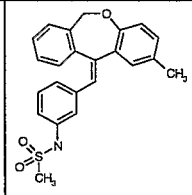
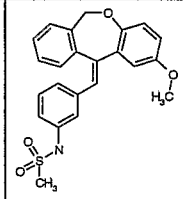
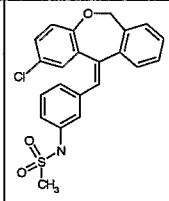
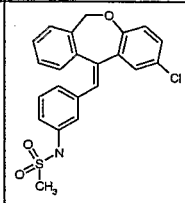
640		EI 352	(ISO80-10) t= 5.64 (100%)	6
641		ES 373 (-)	(ISO80-10) t= 2.68 (99%)	6
642		ES 357 (-)	(ISO80-10) t= 2.15 (99%)	6
643		ES 407 (-)	(ISO80-10) t= 2.82 (99%)	6
644		ES 375 (-)	(ISO80-10) t= 2.36 (96%)	6
645		ES 359 (-)	(ISO60-10) t= 3.71 (100%)	6
646		ES 454 (-) / 456 (+)	(ISO80-10) t= 1.75 (98%)	6

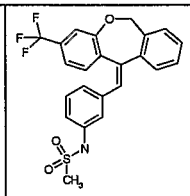
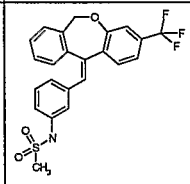
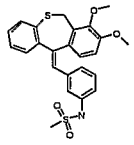
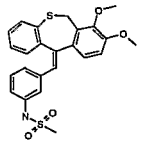
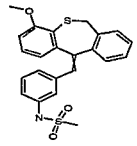
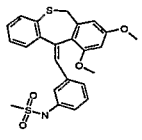
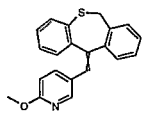
647		ES 486 (-) / 488 (+)	(ISO80-10) t= 2.07 (95%)	6
648		ES 470 (+)	(ISO80-10) t= 1.80 (96%)	6
649		ES 313.9 (+)	NA	6
650		ES 314.0 (+)	NA	6
651		ES 327.0 (+)	NA	6
652		ES 405.0 (+)	NA	6
653		ES 391.0 (+)	NA	6

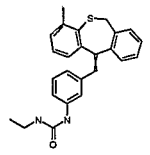
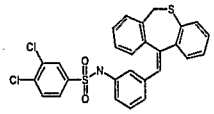
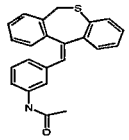
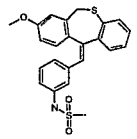
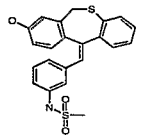
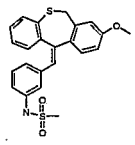
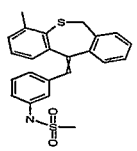
654		ES 361.0 (+)	NA	6
655		ES 347.9 (+)	NA	6
656		ES 375.9 (+)	NA	6
657		ES 389.9 (+)	NA	6
658		NMR	NA	6
659		NMR	NA	6
660		ES 406.1 (+)	NA	6

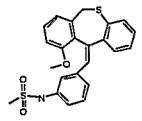
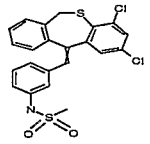
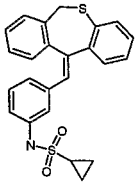
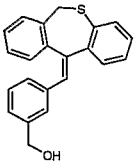
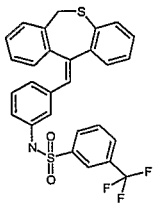
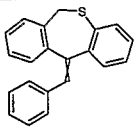
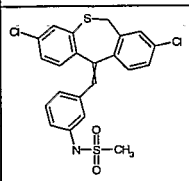
661		ES 406.1 (+)	NA	6
662		ES 410.0 (+)	NA	6
663		ES 410.0 (+)	NA	6
664		ES 410.0 (+)	NA	6
665		NA	>95% (254nM)	6
666		NA	>99% (254nM)	6
667		ES 424 (-)	NA	6

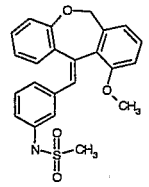
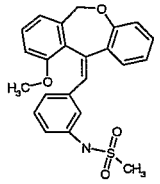
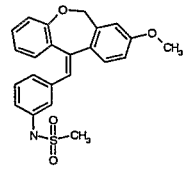
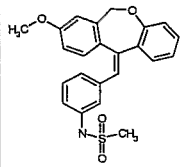
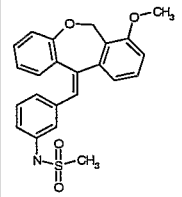
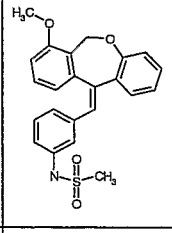
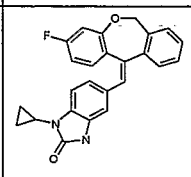
668		ES 486 (+)	NA	6
669		NMR	NA	6
670		NMR	NA	6
671		NMR	NA	6
672		NMR	NA	6
673		ES 390.1 (-)	NA	6
674		NMR	NA	6

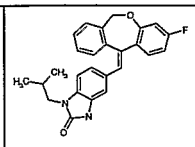
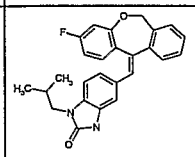
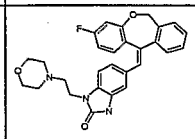
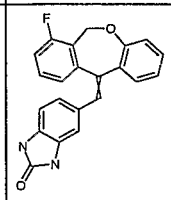
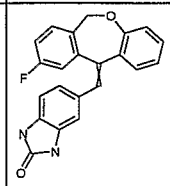
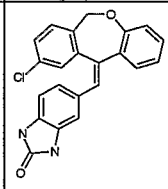
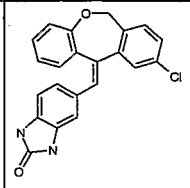
675		NMR	NA	6
676		NMR	NA	6
677		ES 390.1 (-)	NA	6
678		NMR	NA	6
679		ES 406.5 (-)	NA	6
680		NMR	NA	6
681		NMR	NA	6

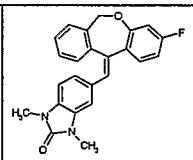
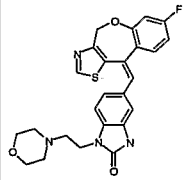
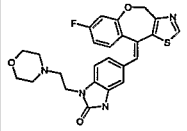
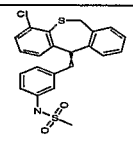
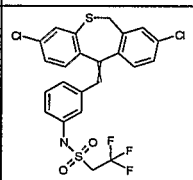
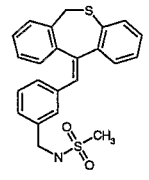
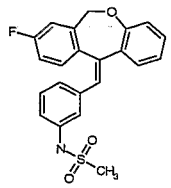
682		ES 444.1 (-)	NA	6
683		ES 444.1 (-)	NA	6
684		CI = 453.93	t =3.24 min (100%)	6
685		CI = 454	t = 3.18 min (100%)	6
686		CI = 424	t= 2.24 min (64 %) t= 2.29 min (34 %)	6
687		CI = 454	t = 3.18 min (100%)	6
688		ES 332 (+)	t = 2.66 min (99 %)	6

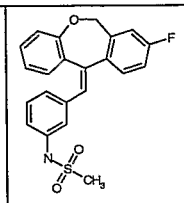
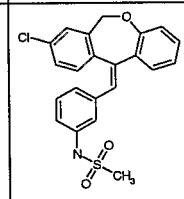
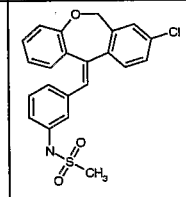
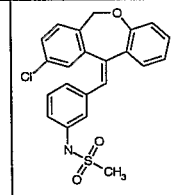
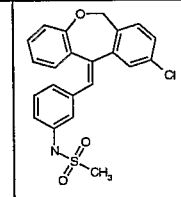
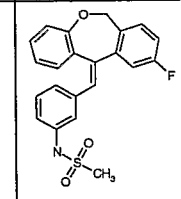
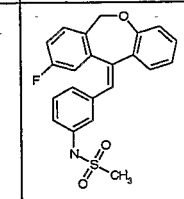
689		APCI = 401	t = 3.88 min (92%)	6
690		ES 522 (+)	t = 3.93 min (98%)	6
691		ES 356 (-)	t = 3.3 min (100)	6
692		APCI = 424	t = 3.29 min (100%)	6
693		APCI = 410	t= 2.97 min (100 %)	6
694		APCI = 424	t = 3.25 min (100%)	6
695		APCI = 408	t = 5.64 min (24 %) t = 5.87 min (76 %)	6

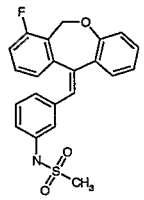
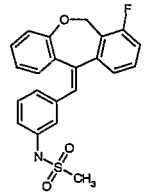
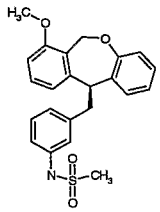
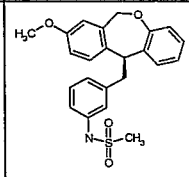
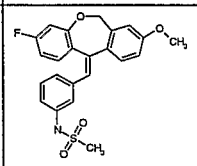
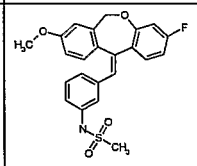
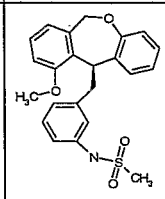
696		APCI = 424	t= 3.12 min (100 %)	6
697		APCI = 462	t = 4.3 min	6
698		ES 418 (-)	t = 3.36 min (100 %)	6
699		APCI 313	t = 3.66 min (100%)	6
700		ES 522 (-)	t = 3.75 min (97 %)	6
701		APCI 301	t = 4.43 min	6
702		APCI = 464	t = 3.69 min (98 %)	6

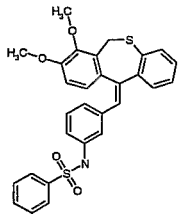
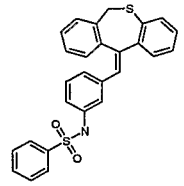
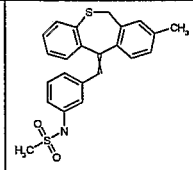
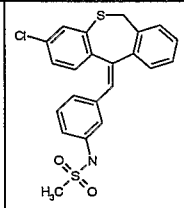
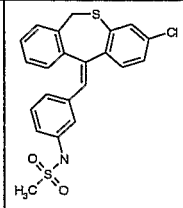
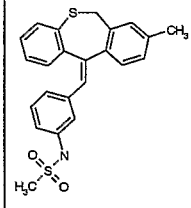
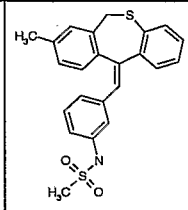
703		ES 407 (+)	t = 4.42 min (100 %)	6
704		ES 407 (+)	t = 4.39 min (100%)	6
705		ES 407 (+)	t = 4.47 min (100 %)	6
706		ES 407 (+)	t = 4.53 min (100%)	6
707		ES 407 (+)	t = 4.61 min (100%)	6
708		ES 407 (+)	t = 4.61 min (100%)	6
709		ES 397 (-) / 399 (+)	(ISO80-10M) t=3.53 (93%)	6

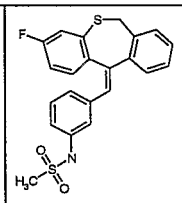
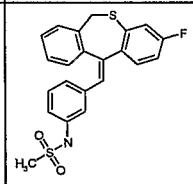
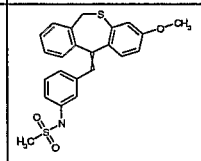
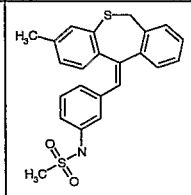
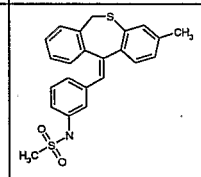
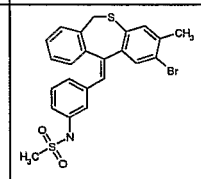
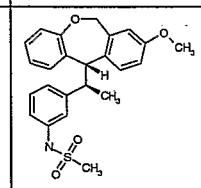
710		ES 413 (-) / 415 (+)	(ISO80-10M) t=4.59 (95%)	6
711		ES 413 (-) / 415 (+)	(ISO80-10M) t=4.82 (95%)	6
712		ES 471 (-) / 473 (+)	(ISO80-10M) t=1.82 (97%)	6
713		ES 357 (-)	(ISO80-10M) t=2.39 (97%)	6
714		ES 357 (-)	(ISO80-10M) t=2.26 (100%)	6
715		ES 374 (-)	(ISO80-10M) t=2.57 (97%)	6
716		ES 374 (-)	(ISO80-10M) t=2.77 (94%)	6

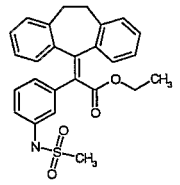
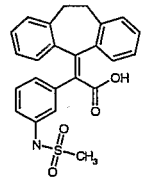
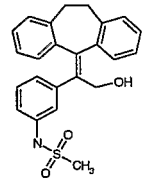
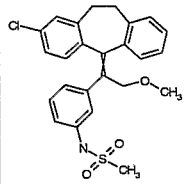
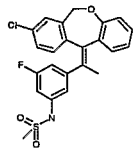
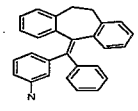
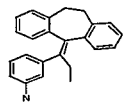
717		ES 387 (+)	(ISO80-10M) t=4.68 (92%)	6
718		ES 477 (-) / 479 (+)	(ISO60-10M) t=1.64 (94%)	6
719		ES 477 (-) / 479 (+)	(ISO60-10M) t=1.51 (88%)	6
720		APCI 428	t = 3.41 min (93%)	6
721		530	96% (220 nm)	6
722		406 (ES-)	NA	6
723		394 (ES-)	100%	6

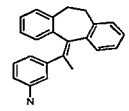
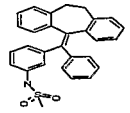
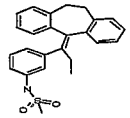
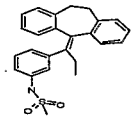
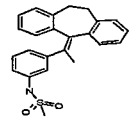
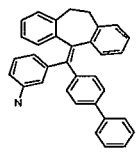
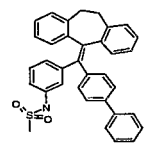
724		394 (ES-)	94.80%	6
725		410 (ES-)	NA	6
726		410 (ES-)	NA	6
727		410/412 (ES-)	NA	6
728		410/412 (ES-)	NA	6
729		394 (ES-)	NA	6
730		394 (ES-)	NA	6

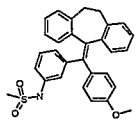
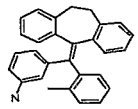
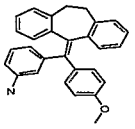
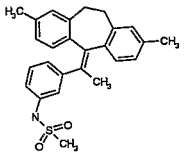
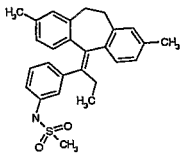
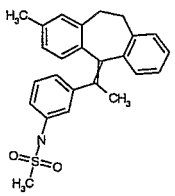
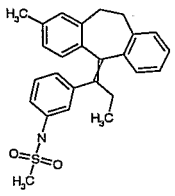
731		394 (ES-)	NA	6
732		394 (ES-)	NA	6
733		ES 408(-) / 410 (+)	t=4.58 (100%)	6
734		ES 408(-) / 409 (+)	t = 4.39 (100%)	6
735		ES 424 (-) / 426 (+)	t = 4.58 (100%)	6
736		ES 424 (-) / 426 (+)	t = 4.62 (100%)	6
737		ES 408 (-) / 410 (+)	t = 4.49 (67%)	6

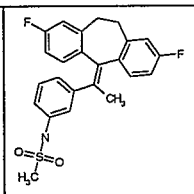
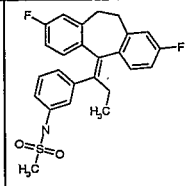
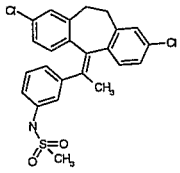
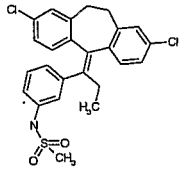
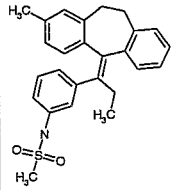
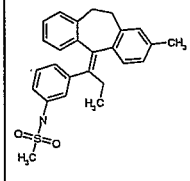
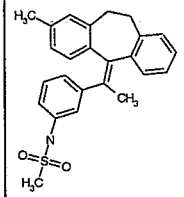
738		ES 514 (-) / 516 (+)	(GRAD) t=3.49 (100%)	6
739		ES 454 (-) / 456 (+)	(GRAD) t=3.44 (100%)	6
740		ES 406 (-) / 408 (+)	(GRAD) t=3.29 (97%)	6
741		ES 426 (-) / 428 (+)	(GRAD) t=2.49 (85%)	6
742		ES 426 (-)	(GRAD) t=2.49 (100%)	6
743		ES 406 (-) / 408 (+)	(GRAD) t=2.43 (100%)	6
744		ES 406 (-) / 408 (+)	(GRAD) t=2.41 (100%)	6

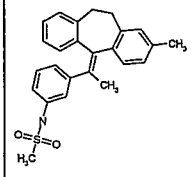
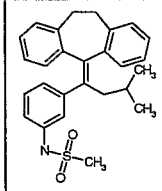
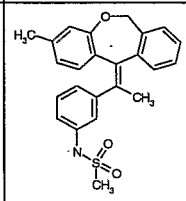
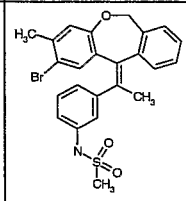
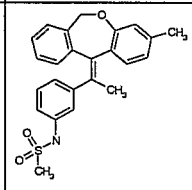
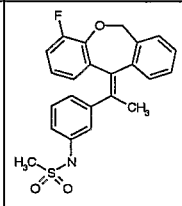
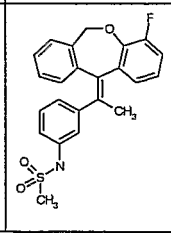
745		ES 410 (-) / 412 (+)	(GRAD) t=2.36 (100%)	6
746		ES 410 (-) / 412 (+)	(GRAD) t=2.36 (91%)	6
747		ES 422 (-) / 424 (+)	(GRAD) t=2.34 (100%)	6
748		ES 406 (-) / 408 (+)	(GRAD) t=2.59 (95%)	6
749		ES 406 (-) / 408 (+)	(GRAD) t=2.61 (100%)	6
750		ES 406 (-) / 408 (+)	(GRAD) t=2.77 (100%)	6
752		ES 424 (-) / 422 (+)	t = 4.55 (100%) t = 6.571 (100%)	7

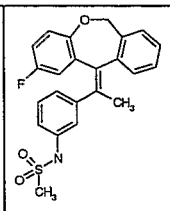
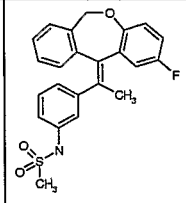
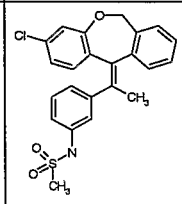
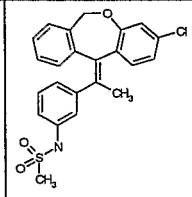
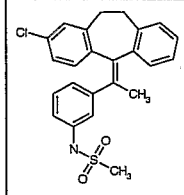
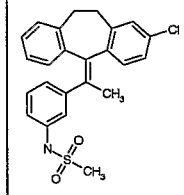
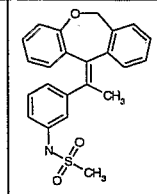
753		ES 446 (+)	NA	7
754		ES 437 (+NH3)	NA	7
755		ES 404(+)	NA	7
756		ES 452 (-)	NA	7
758		APCI 444 (+)	95%	7
759		ES 364 (+)	NA	7
760		ES 326 (+)	NA	7

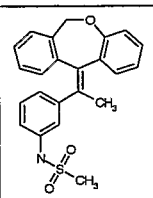
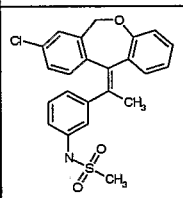
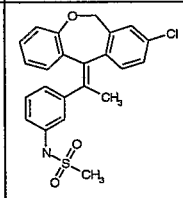
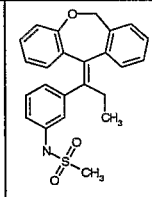
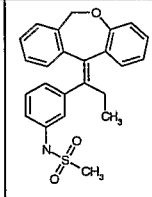
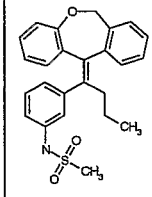
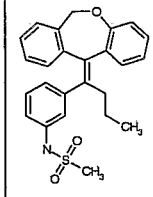
761		ES 312 (+)	NA	7
762		ES 450 (-)	NA	7
763		ES 402 (-)	NA	7
764		ES 402 (-)	NA	7
765		ES 388 (-)	NA	7
766		ES 450 (+)	NA	7
767		ES 526 (-)	NA	7

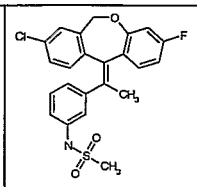
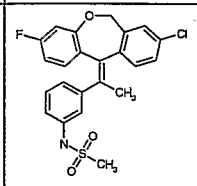
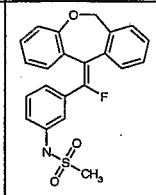
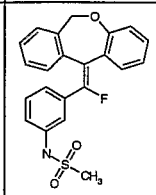
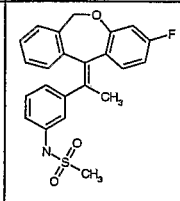
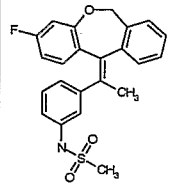
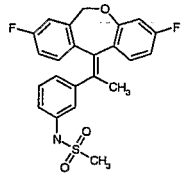
768		ES 480 (-)	NA	7
769		ES 388 (+)	NA	7
770		ES 464 (+)	NA	7
771		ES 416 (-) / 418 (+)	(GRAD) t=3.648 (98%)	7
772		ES 430(-) / 432 (+)	(GRAD) t=3.733 (98%)	7
773		ES 402(-) / 404 (+)	(GRAD) t=3.445 (100%)	7
774		ES 416 (-) / 418 (+)	(GRAD) t=3.541 (100%)	7

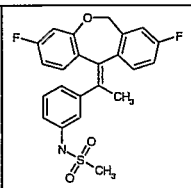
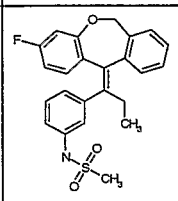
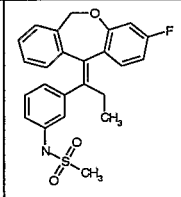
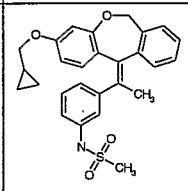
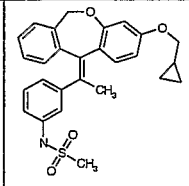
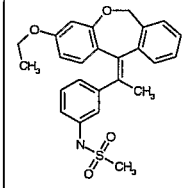
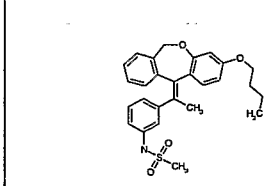
775		ES 424 (-) / 443 (+NH4)	(GRAD) t=3.349 (100%)	7
776		ES 438 (-) / 440 (+)	(GRAD) t=3.456 (100%)	7
777		ES 456 (-) / 475 (+NH4)	(GRAD) t=3.733 (99%)	7
778		ES 470 (-) / 489 (+NH4)	(GRAD) t=3.819 (95%)	7
779		ES 416 (-) / 435 (+NH4)	(GRAD) t=3.552 (100%)	7
780		ES 416 (-) / 435 (+NH4)	(GRAD) t=3.595 (97%)	7
781		ES 402 (-) / 412 (+NH4)	(GRAD) t=3.477 (100%)	7

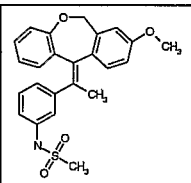
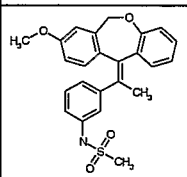
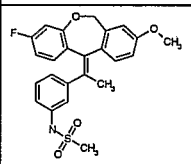
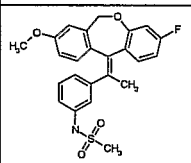
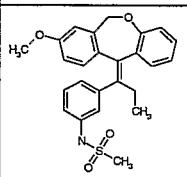
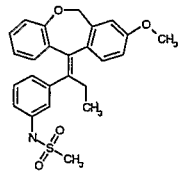
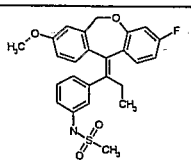
782		ES 402 (-) / 412 (+NH4)	(GRAD) t=3.509 (100%)	7
783		ES 430 (-)	NA	7
784		ES 404.1 (-)	NA	7
785		ES 482.0 (-)	NA	7
786		ES 404.1 (-)	NA	7
787		ES 408.0 (-)	NA	7
788		ES 408.0 (-)	NA	7

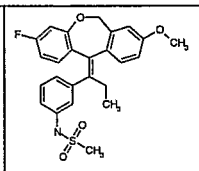
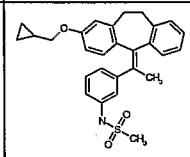
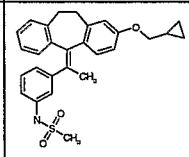
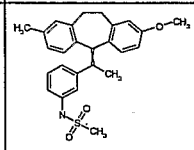
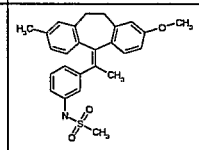
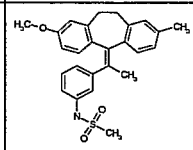
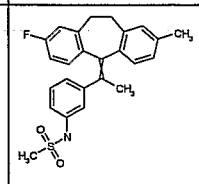
789		ES 408.0 (-)	NA	7
790		ES 408.0 (-)	NA	7
791		ES 424.0 (-)	NA	7
792		ES 424.0 (-)	NA	7
793		422/424 (ES-)	100%	7
794		422/424 (ES-)	99.60%	7
795		390 (ES-)	99.80%	7

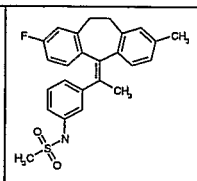
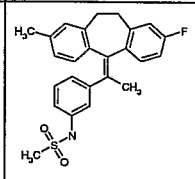
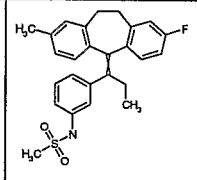
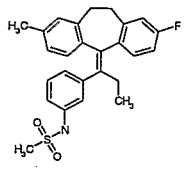
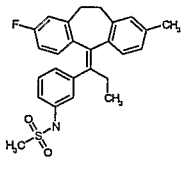
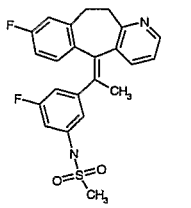
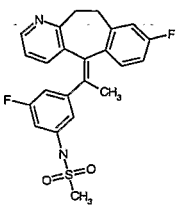
796		390 (ES-)	100%	7
797		424/426 (ES-)	NA	7
798		424/426 (ES-)	NA	7
799		404 (ES-)	99.70%	7
800		404 (ES-)	97.40%	7
801		418 (ES-)	NA	7
802		418 (ES-)	NA	7

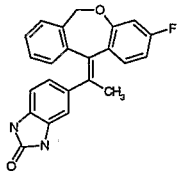
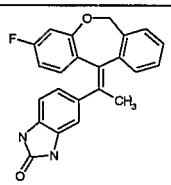
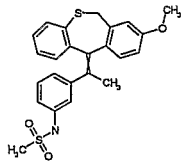
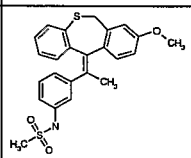
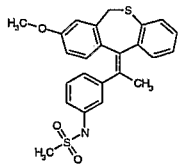
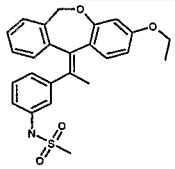
803		442/444 (ES-)	NA	7
804		442/444 (ES-)	NA	7
805		MS(ES+) = 424.	NA	7
806		394 (ES-)	NA	7
807		408 (ES-)	NA	7
808		408 (ES-)	NA	7
809		426 (ES-)	NA	7

810		426 (ES-)	NA	7
811		422 (ES-)	NA	7
812		422 (ES-)	NA	7
813		MS(ES-) = 460.	NA	7
814		460 (ES-)	NA	7
815		434 (ES-)	NA	7
816		462 (ES-)	NA	7

817		ES 420 (-) / 422 (+)	t=4.50 (100%)	7
818		ES 420 (-) / 422 (+)	t = 4.57 (100%)	7
819		ES 438 (-) / 440 (+)	t = 4.63 (100%)	7
820		ES 438 (-) / 440 (+)	t = 4.69 (100%)	7
821		ES 434 (-) / 436 (+)	t = 4.77 (100%)	7
822		ES 434 (-) / 436 (+)	t = 4.68 (100%)	7
823		ES 452 (-) / 454 (+)	t = 4.84 (100%)	7

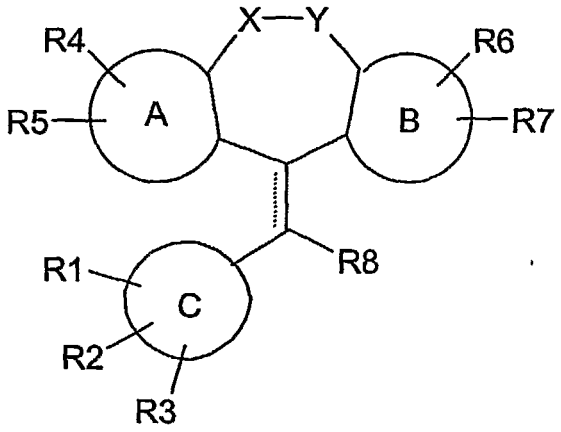
824		ES 452 (-) / 454 (+)	t = 4.74 (100%)	7
825		ES 458 (-) / 460 (+)	t = 5.30 (100%)	7
826		ES 458 (-) / 460 (+)	t = 5.27 (100%)	7
827		NA	(GRAD) t=3.40 (86%)	7
828		ES 432 (-)	(GRAD) t=3.35 (98.8%)	7
829		ES 432 (-)	(GRAD) t=3.48 (97%)	7
830		NA	(GRAD) t=3.53 (100%)	7

831		NA	(GRAD) t=3.52 (100%)	7
832		NA	(GRAD) t=3.48 (100%)	7
833		ES 434 (-)	(GRAD) t=2.54 (96%)	7
834		ES 434 (-)	(GRAD) t=2.54 (96%)	7
835		ES 434 (-)	NA	7
836		APCI 427(+)/425(-)	LCMS(ISO7030M) t=4.88	7
837		APCI 427(+)/425(-)	LCMS(ISO7030M) t=6.89	7

838		373.0 (APCI-pos)	95%	7
839		373.0 (APCI-pos)	95%	7
840		ES 436 (-) / 438 (+)	(GRAD) t=2.35 (100%)	7
841		ES 436 (-) / 438 (+)	(GRAD) t=2.54 (100%)	7
842		ES 436 (-) / 438 (+)	(GRAD) t=2.54 (100%)	7
843		MS (ES-) 434	NA	7

We claim:

1. A method of treating a pathological disorder susceptible to steroid hormone nuclear receptor modulation comprising administering to a patient in need thereof an effective amount of a compound of the formula:

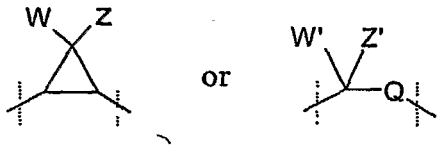


Formula I

wherein,

A, B, and C each independently represent an aryl, heterocycle, or benzofused-heterocyclic ring;

X and Y together represent $-CH_2-CH_2-$, $-CH=CH-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-S-$, $-S-CH_2-$, $-CH_2-SO-$, $-SO-CH_2-$, $-CH_2-SO_2-$, $-SO_2-CH_2-$, $-CH_2-NR^{10}-$, $-NR^{10}-CH_2-$, $-NR^{10}-CO-$, $-CO-NR^{10}-$, or a group of the formula



wherein W and Z each independently represent hydrogen, fluoro, or chloro; W' and Z' each independently represent hydrogen, fluoro, chloro, or methyl; and Q represents NH, O, S, or CH_2;

"- - - -" represents a single or double bond;

R^1 represents hydrogen, halo, hydroxy, cyano, nitro, amino, oxo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, CH_2NH_2, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, $C(CF_3)_2OH$, SO_2NH_2, $SO_2NR^9R^{10}$, SO_2R^{11}, $NHSO_2R^{11}$, $N(CH_3)SO_2CH_3$, NR^9R^{10}, $CH_2NH(OH)$,

$CH_2NH(SO_2R^{11})$, $NHCOR^{12}$, COR^{12}, $CHNR^{13}$, OR^{14}, SR^{14}, (C_3-C_7)cycloalkyl, aryl, substituted aryl, (C_1-C_4)alkyl-aryl, (C_1-C_4)alkyl-substituted aryl, heterocycle, substituted heterocycle, (C_1-C_4)alkyl-heterocycle, or (C_1-C_4)alkyl-substituted heterocycle;

provided that where "C" represents an aryl group, R^1 is other than oxo, (C_2-C_6)alkenyl, or (C_2-C_6)alkynyl;

R^2 through R^8 each independently represent hydrogen, halo, hydroxy, cyano, nitro, amino, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, CH_2NH_2, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, $C(CF_3)_2OH$, SO_2NH_2, $SO_2NR^9R^{10}$, SO_2R^{11}, $NHSO_2R^{11}$, NR^9R^{10}, $CH_2NH(OH)$, $CH_2NH(SO_2R^{11})$, $NHCOR^{12}$, COR^{12}, $CHNR^{13}$, OR^{14}, SR^{14}, (C_3-C_7)cycloalkyl, aryl, substituted aryl, (C_1-C_4)alkyl-(C_1-C_6)alkoxy, (C_1-C_4)alkyl-aryl, (C_1-C_4)alkyl-substituted aryl, heterocycle, substituted heterocycle, (C_1-C_4)alkyl-heterocycle, or (C_1-C_4)alkyl-substituted heterocycle;

provided that where "A", "B", or "C" represents an aryl group, each of R^2 through R^7 is other than (C_2-C_6)alkenyl or (C_2-C_6)alkynyl;

R^9 represents independently at each occurrence cyano, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_4)alkyl-(C_1-C_6)alkoxy, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, NH-(C_1-C_6)alkylamine, N,N-(C_1-C_6)dialkylamine, aryl, substituted aryl, (C_1-C_4)alkyl-aryl, (C_1-C_4)alkyl-substituted aryl, heterocycle, substituted heterocycle, (C_1-C_4)alkyl-heterocycle, or (C_1-C_4)alkyl-substituted heterocycle;

R^{10} represents independently at each occurrence hydrogen or (C_1-C_6)alkyl or R^9 and R^{10} together with the nitrogen atom to which they are attached, form a substituted or unsubstituted heterocycle group;

R^{11} represents independently at each occurrence amino, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, aryl, substituted aryl, (C_1-C_4)alkyl-aryl, (C_1-C_4)alkyl-substituted aryl, heterocycle, substituted heterocycle, (C_1-C_4)alkyl-heterocycle, or (C_1-C_4)alkyl-substituted heterocycle;

R^{12} represents independently at each occurrence hydrogen, amino, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkyl-(C_1-C_6)alkoxy, (C_3-C_7)cycloalkyl, NH-(C_1-C_6)alkylamine, N,N-(C_1-C_6)dialkylamine, aryl, substituted aryl, (C_1-C_4)alkyl-aryl, (C_1-C_4)alkyl-substituted aryl, heterocycle, substituted heterocycle, (C_1-C_4)alkyl-heterocycle, or (C_1-C_4)alkyl-substituted heterocycle;

R^{13} represents independently at each occurrence OH, (C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, aryl, heterocycle, or a substituted aryl or heterocycle;

R^{14} represents independently at each occurrence (C_3-C_7)cycloalkyl, aryl, substituted aryl, acyl, (C_1-C_4)alkyl-aryl, (C_1-C_4)alkyl-substituted aryl, heterocycle,

substituted heterocycle, (C_1-C_4)alkyl-heterocycle, (C_1-C_4)alkyl-substituted heterocycle, or (C_1-C_4)alkyl-(C_3-C_7)cycloalkyl;

or a pharmaceutically acceptable salt thereof.

2. The method according to claim 1 wherein said disorder is susceptible to mineralocorticoid receptor or glucocorticoid receptor modulation.

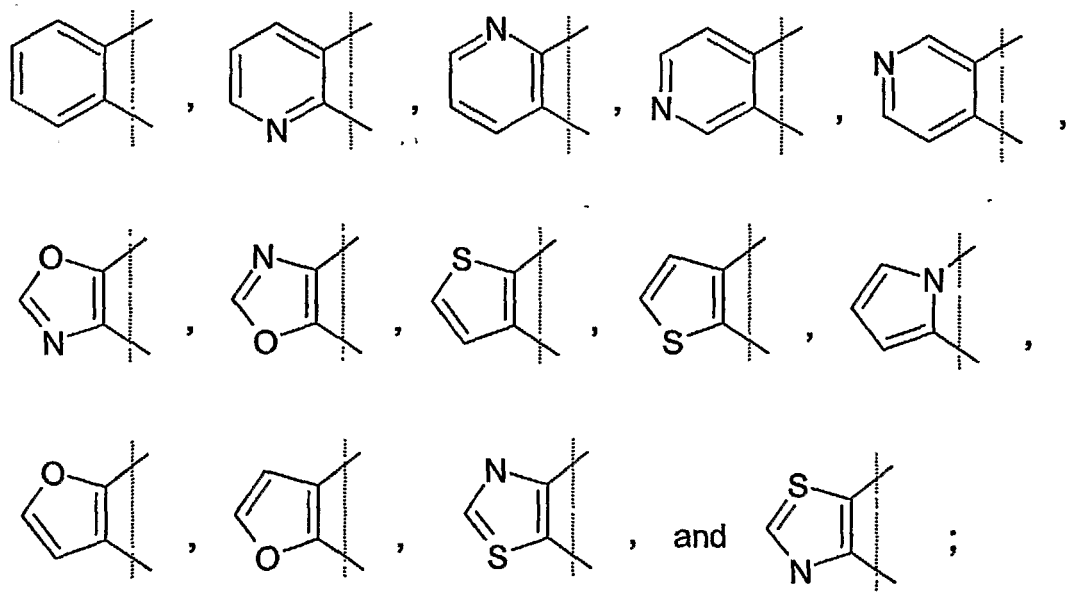
3. The method according to claim 2 wherein said disorder is selected from the group consisting Conn's Syndrome, primary and secondary hyperaldosteronism, increased sodium retention, increased magnesium and potassium excretion (diuresis), increased water retention, hypertension (isolated systolic and combined systolic/diastolic), arrhythmias, myocardial fibrosis, myocardial infarction, Bartter's Syndrome, disorders associated with excess catecholamine levels, diastolic and systolic congestive heart failure (CHF), psychoses, cognitive disorders, memory disturbances, depression, bipolar disorder, anxiety disorders, personality disorders, breast cancer, peripheral vascular disease, diabetic nephropathy, cirrhosis with edema and ascites, esophageal varicies, Addison's Disease, muscle weakness, increased melanin pigmentation of the skin, weight loss, hypotension, hypoglycemia, Cushing's Syndrome, obesity, hypertension, glucose intolerance, hyperglycemia, diabetes mellitus, osteoporosis, polyuria, polydipsia, inflammation, autoimmune disorders, tissue rejection associated with organ transplant, malignancies such as leukemias and lymphomas, acute adrenal insufficiency, congenital adrenal hyperplasia, rheumatic fever, polyarteritis nodosa, granulomatous polyarteritis, inhibition of myeloid cell lines, immune proliferation/apoptosis, HPA axis suppression and regulation, hypercortisolemia, modulation of the Th1/Th2 cytokine balance, chronic kidney disease, stroke and spinal cord injury, hypercalcemia, hypergylcemia, acute adrenal insufficiency, chronic primary adrenal insufficiency, secondary adrenal insufficiency, congenital adrenal hyperplasia, cerebral edema, thrombocytopenia, and Little's syndrome, systemic inflammation, inflammatory bowel disease, systemic lupus erythematosus, discoid lupus erythematosus, polyartitis nodosa, Wegener's granulomatosis, giant cell arthritis, rheumatoid arthritis, osteoarthritis, hay fever, allergic rhinitis, contact dermatitis, atopic dermatitis, exfoliative dermatitis, urticaria, angioneurotic edema, chronic obstructive pulmonary disease, asthma, tendonitis, bursitis, Crohn's disease, ulcerative colitis, autoimmune chronic active

hepatitis, hepatitis, cirrhosis, inflammatory scalp alopecia, panniculitis, psoriasis, inflamed cysts, pyoderma gangrenosum, pemphigus vulgaris, bullous pemphigoid, dermatomyositis, eosinophilic fasciitis, relapsing polychondritis, inflammatory vasculitis, sarcoidosis, Sweet's disease, type 1 reactive leprosy, capillary hemangiomas, lichen planus, , erythema nodosum, acne, hirsutism, toxic epidermal necrolysis, erythema multiform, and cutaneous T-cell lymphoma, emphysema, Alzheimer's Disease, or multiple sclerosis.

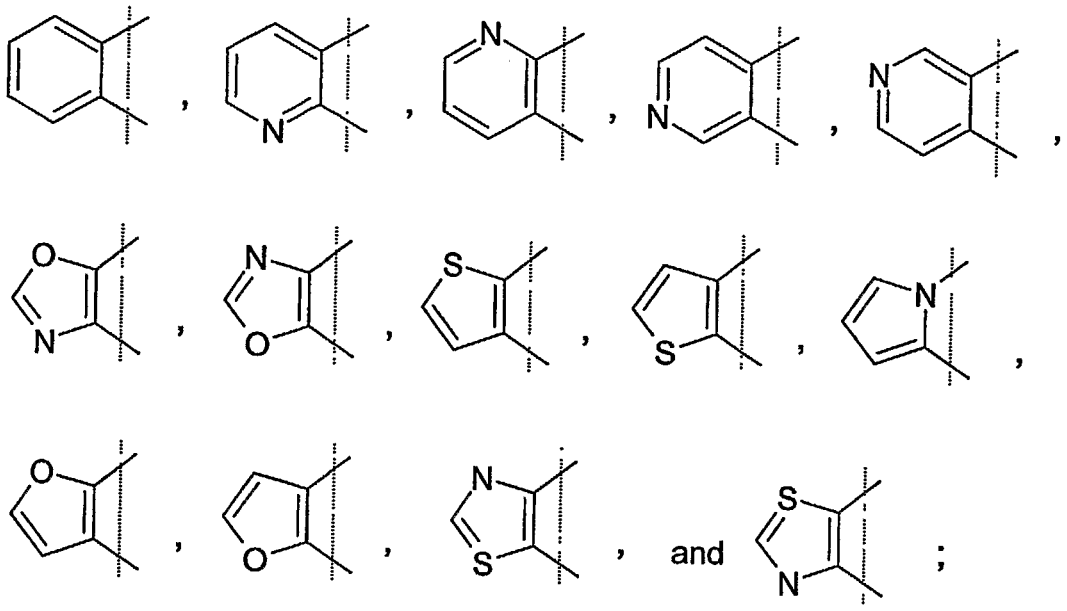
4. The method according to claim 3 wherein said disorder is diastolic or systolic congestive heart failure, inflammation, rheumatoid arthritis, autoimmune disorder, asthma, or chronic obstructive pulmonary disease .

5. A method according to any one of claims 1-4 wherein the compound of Formula I is one wherein,

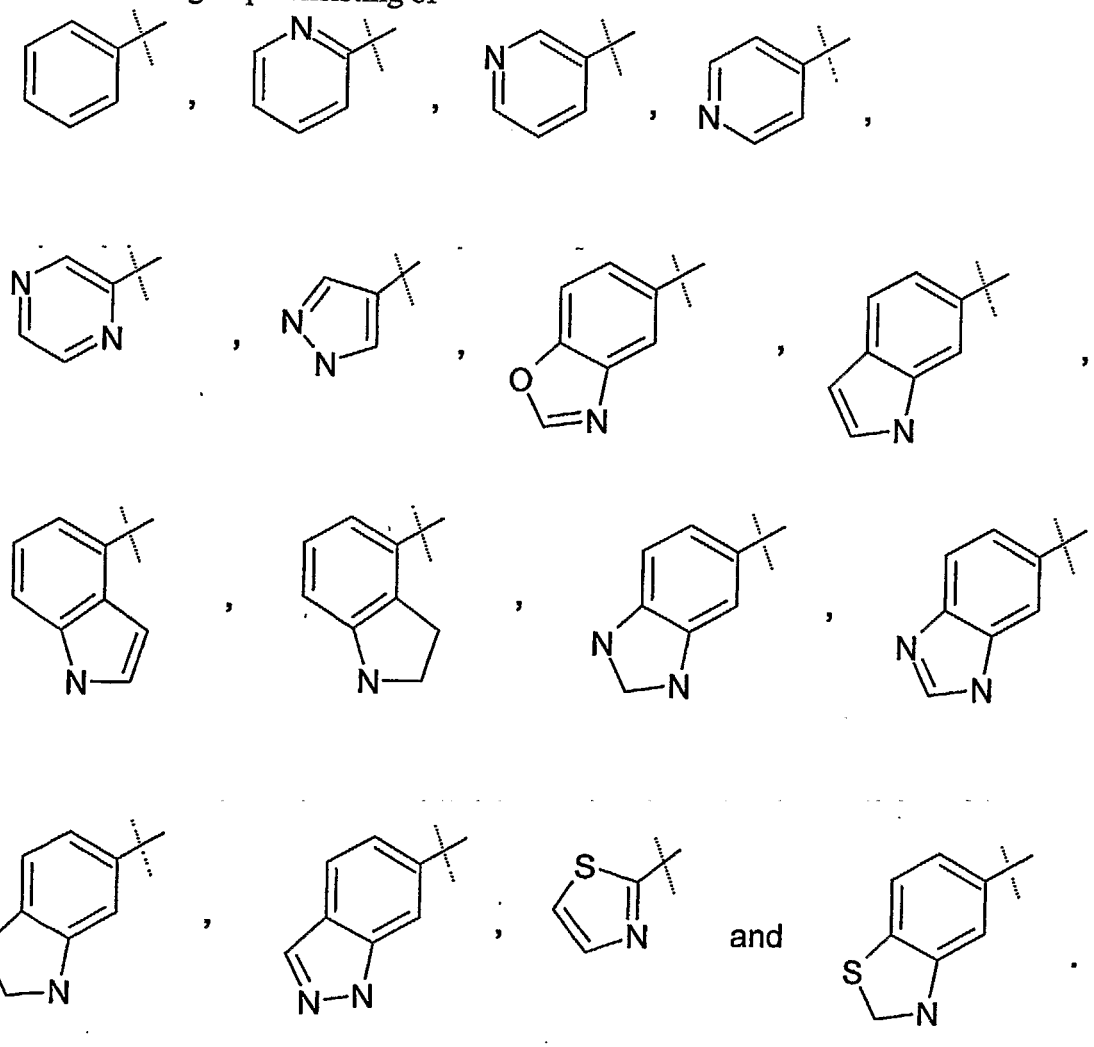
"A" represents an aryl or heterocycle ring selected from the group consisting of



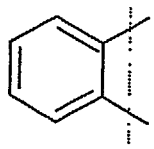
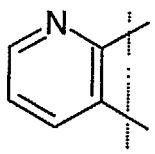
"B" represents an aryl or heterocyclic ring selected from the group consisting of



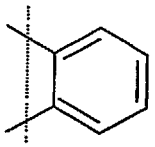
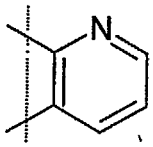
"C" represents an aryl , heterocyclic, or benzofused heterocycle ring selected from the group consisting of



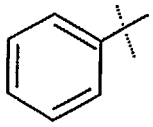
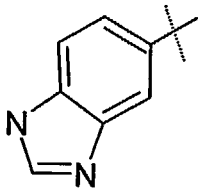
6. The method according to claim 5 wherein "A" represents

 or  ;

"B" represents

 or  ;

and "C" represents

 or  .

7. A method according to any one of Claims 1-6 wherein X-Y represents $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-S-$, $-S-CH_2-$, $-NR^{10}-CO-$, $-CO-NR^{10}-$, $-CH_2-NR^{10}-$, $-NR^{10}-CH_2-$, or $-CH=CH-$.

8. The method according to Claim 7 wherein X-Y represents $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-S-$, $-S-CH_2-$, $-NR^{10}-CO-$, $-CO-NR^{10}-$, $-CH_2-NR^{10}-$, $-NR^{10}-CH_2-$, or $-CH=CH-$, wherein R10 represents hydrogen or methyl.

9. The method according to Claim 8 wherein X-Y represents $-CH_2-CH_2-$, $-CH_2-O-$, or $-O-CH_2-$.

10. A method according to any one of Claims 1-9 wherein " - - - - - " represents a double bond.

11. A method according to any one of Claims 1-10 wherein R^1 represents hydrogen, halo, hydroxy, cyano, nitro, amino, oxo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxy(C_1-C_6)alkyl, CH_2NH_2, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, SO_2NH_2,

$SO_2NR^9R^{10}$, SO_2R^{11}, NH SO_2R^{11}, NR^9R^{10}, $NHCOR^{12}$, COR^{12}, $CHNR^{13}$, OR^{14}, SR^{14}, heterocycle, $(C_1\text{-}C_4)$alkyl-heterocycle, or substituted heterocycle, provided that where "C" represents an aryl group then R^1 is other than oxo.

12. The method according to Claim 11 wherein R^1 represents halo, amino, oxo, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, hydroxymethyl, difluromethyl, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $SO_2NR^9R^{10}$, NH SO_2R^{11}, $NHCOR^{12}$, COR^{12}, OR^{14}, or $(C_1\text{-}C_4)$alkyl-heterocycle, provided that where "C" represents an aryl group then R^1 is other than oxo.

13. The method according to Claim 12 wherein when R^1 represents $SO_2NR^9R^{10}$, R^9 represents $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_4)$alkyl-$(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_7)$cycloalkyl, aryl, $(C_1\text{-}C_4)$alkyl-aryl, heterocycle and R^{10} represents hydrogen or methyl, or R^9 and R^{10} together with the nitrogen to which they are attached form a substituted or unsubstituted heterocycle.

14. The method according to Claim 12 wherein when R^1 represents NH SO_2R^{11}, R^{11} represents amino, $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_3\text{-}C_7)$cycloalkyl, aryl, substituted aryl, heterocycle, or substituted heterocycle.

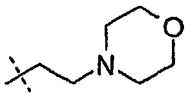
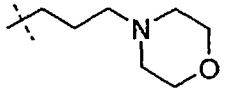
15. The method according to Claim 14 wherein R^{11} represents methyl, ethyl, propyl, isopropyl, butyl, or 2-methyl propyl.

16. The method according to Claim 12 wherein when R^1 represents $NHCOR^{12}$, R^{12} represents H, amino, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, hydroxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C)$alkyl-$(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkyl, NH-methylamine, NH-dimethylamine, NH-ethylamine, or heterocycle.

17. The method according to Claim 12 wherein when R^1 represents COR^{12}, R^{12} represents H, amino, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, or hydroxy$(C_1\text{-}C_6)$alkyl.

18. The method according to Claim 12 wherein when R^1 represents OR^{14}, R^{14} represents $(C_1\text{-}C)$alkyl-heterocycle.

19. The method according to Claim 12 wherein $(C_1\text{-}C)$alkyl-heterocycle represents a group of the formula

 or  .

20. A method according to any one of Claims 1-19 wherein R^2 represents hydrogen, halo, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, or (C_1-C_4)alkyl-heterocycle.

21. The method according to Claim 20 wherein R^2 represents hydrogen or (C_1-C_4)alkyl-heterocycle.

22. The method according to Claim 21 wherein R^2 represents hydrogen.

23. A method according to any one of Claims 1-22 wherein R^3 represents hydrogen, halo, or (C_1-C_6)alkyl.

24. The method according to Claim 23 wherein R^3 represents hydrogen.

25. A method according to any one of Claims 1-24 wherein R^4-R^7 each independently represent hydrogen, halo, hydroxy, cyano, amino, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, SO_2NH_2, SO_2CH_3, NH SO_2R^{11}, NR^9R^{10}, $NHCOR^{12}$, COR^{12}, OR^{14}, SR^{14}, or aryl.

26. The method according to Claim 25 wherein R^4-R^7 each independently represent hydrogen, halo, hydroxy, cyano, amino, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, CHF_2, CF_3, $OCHF_2$,OCF_3, NH SO_2R^{11}, NR^9R^{10}, $NHCOR^{12}$, COR^{12}, OR^{14}, or aryl.

27. The method according to Claim 26 wherein R^4-R^7 each independently represent hydrogen, halo, hydroxy, cyano, amino, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, CHF_2, CF_3, $OCHF_2$,OCF_3, NH SO_2CH_3, dimethylamino, $NHCOCH_3$, COR^{12} wherein R^{12} represents hydrogen, amino, or methoxy; OR^{14} wherein R^{14} represents (C_1-C_4)alkyl-aryl, (C_1-C_4)alkyl-substituted aryl, (C_1-C_4)alkyl-heterocycle, or (C_1-C_4)alkyl-(C_3-C_7)cycloalkyl; or aryl.

28. The method according to Claim 27 wherein R^4-R^7 each independently represent hydrogen, hydroxy, halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or OR^{14} wherein R^{14}

represents (C_1-C_4)alkyl-aryl, (C_1-C_4)alkyl-substituted aryl, (C_1-C_4)alkyl-heterocycle, or (C_1-C_4)alkyl-(C_3-C_7)cycloalkyl.

29. The method according to Claim 28 wherein R^4 and R^6 each independently represent hydrogen, halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or OR^{14} wherein R^{14} represents (C_1-C_4)alkyl-aryl, (C_1-C_4)alkyl-substituted aryl, (C_1-C_4)alkyl-heterocycle, or (C_1-C_4)alkyl-(C_3-C_7)cycloalkyl.

30. The method according to Claim 28 wherein R^5 and R^7 each independently represent hydrogen, hydroxy, halo, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy.

31. A method according to any one of Claims 1-30 wherein R^8 represents hydrogen, halo, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl , (C_1-C_4)alkyl -(C_1-C_6)alkoxy , COR^{12}, (C_3-C_7)cycloalkyl, aryl, or substituted aryl.

32. The method according to Claim 31 wherein R^8 represents hydrogen, halo, (C_1-C_6)alkyl, hydroxymethyl, (C_1-C_4)alkyl -(C_1-C_6)alkoxy , COR^{12} wherein R^{12} represents (C_1-C_6)alkoxy; (C_3-C_7)cycloalkyl , phenyl, or substituted aryl.

33. The method according to Claim 32 wherein R^8 represents hydrogen, halo, (C_1-C_6)alkyl, (C_1-C_4)alkyl -(C_1-C_6)alkoxy, or (C_3-C_7)cycloalkyl.

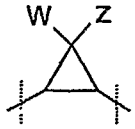
34. The method according to Claim 33 wherein R^8 represents halo, (C_1-C_6)alkyl, or (C_1-C_4)alkyl -(C_1-C_6)alkoxy.

35. The method according to Claim 33 wherein R^8 represents hydrogen.

36. The method according to Claim 1 wherein

"A" and "B" each independently represent phenyl or heterocycle;

X and Y together represent $-CH_2-CH_2-$, $-CH=CH-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-S-$, $-S-CH_2-$, $-CH_2-SO-$, $-SO-CH_2-$, $-CH_2-SO_2-$, $-SO_2-CH_2-$, $-CH_2-NR^{10}-$, $-NR^{10}-CH_2-$, $-NR^{10}-CO-$, $-CO-NR^{10}-$, or a group of the formula



wherein W and Z each independently represent hydrogen, fluoro, or chloro;

"- - - - -" represents a single or double bond;

R^1 represents hydrogen, halo, hydroxy, cyano, nitro, amino, oxo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxy(C_1-C_6)alkyl, CH_2NH_2, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, SO_2NH_2, $SO_2NR^9R^{10}$ wherein R^9 represents (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_4)alkyl-(C_1-C_6)alkoxy, aryl, (C_1-C_4)alkyl-aryl, (C_3-C_7)cycloalkyl and R^{10} represents hydrogen or (C_1-C_6)alkyl or R^9 and R^{10} together represent a substituted or unsubstituted heterocycle; SO_2R^{11} wherein R11 represents (C_1-C_6)alkyl; NH SO_2R^{11} wherein R^{11} represents (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, aryl, substituted aryl, heterocycle, or substituted heterocycle; NR^9R^{10} wherein R^9 represents (C_1-C_6)alkyl or cyano and R^{10} represents hydrogen or methyl; $NHCOR^{12}$ wherein R^{12} represents H, amino, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxy(C_1-C_6)alkyl, (C_1-C)alkyl-(C_1-C_6)alkoxy, halo(C_1-C_6)alkyl, NH-methylamine,NH-ethylamine, or heterocycle; COR^{12} wherein R^{12} represents H, amino, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxy(C_1-C_6)alkyl; OR^{14} wherein R^{14} represents (C_1-C_4)alkyl-heterocycle or acetyl; SR^{14} wherein R^{14} represents (C_1-C_6)alkyl; heterocycle, (C_1-C_4)alkyl-heterocycle, or substituted heterocycle,

provided that where "C" represents an aryl group then R^1 is other than oxo;

R^2 represents hydrogen, halo, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, or (C_1-C_4)alkyl-heterocycle;

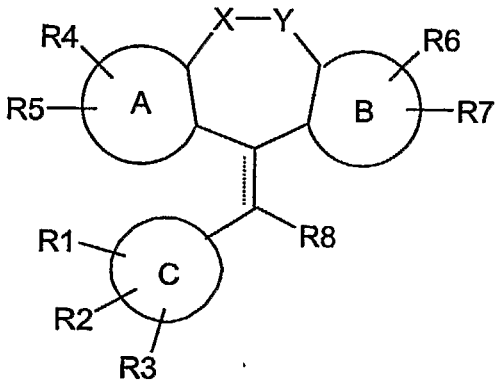
R^3 represents wherein hydrogen, halo, or (C_1-C_6)alkyl;

R^4 and R^6 each independently represent hydrogen, halo, hydroxy, cyano, amino, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkyl, hydroxymethyl, SO_2CH_3, NH SO_2R^{11} wherein R11 represents (C_1-C_6)alkyl; NR^9R^{10} wherein R^9 and R^{10} each represent (C_1-C_6)alkyl, $NHCOR^{12}$ wherein R^{12} represents (C_1-C_6)alkyl; COR^{12} wherein R12 represents hydrogen, amino, or (C_1-C_6)alkoxy; OR^{14} wherein R^{14} represents (C_1-C_4)alkyl-(C_3-C_7)cycloalkyl, (C_1-C_4)alkyl-aryl, (C_1-C_4)alkyl-substituted aryl, or (C_1-C_4)alkyl-heterocycle; SR^{14} wherein R^{14} represents (C_1-C_6)alkyl; or aryl;

R^5 and R^7 each independently represent hydrogen, hydroxy, halo, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy; and

R^8 represents hydrogen, halo, $(C_1\text{-}C_6)$alkyl, hydroxy$(C_1\text{-}C_6)$alkyl , $(C_1\text{-}C_4)$alkyl - $(C_1\text{-}C_6)$alkoxy, COR^{12} wherein R^{12} represents methoxy, ethoxy, hydroxymethyl, or methoxymethyl; $(C_3\text{-}C_7)$cycloalkyl, aryl or substituted aryl.

37. A novel compound of Formula I:

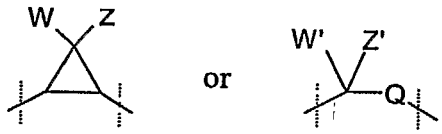


Formula I

wherein,

A, B, and C each independently represent an aryl, heterocycle, or benzofused-heterocyclic ring;

X and Y together represent $-CH_2-CH_2-$, $-CH=CH-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-S-$, $-S-CH_2-$, $-CH_2-SO-$, $-SO-CH_2-$, $-CH_2-SO_2-$, $-SO_2-CH_2-$, $-CH_2-NR^{10}-$, $-NR^{10}-CH_2-$, $-NR^{10}-CO-$, $-CO-NR^{10}-$, or a group of the formula



wherein W and Z each independently represent hydrogen, fluoro, or chloro; W' and Z' each independently represent hydrogen, fluoro, chloro, or methyl; and Q represents NH, O, S, or CH_2;

"- - - - -" represents a single or double bond;

R^1 represents hydrogen, halo, hydroxy, cyano, nitro, amino, oxo, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, hydroxy$(C_1\text{-}C_6)$alkyl, hydroxy$(C_1\text{-}C_6)$alkoxy, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, CH_2NH_2, halo$(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkoxy, $C(CF_3)_2OH$, SO_2NH_2, $SO_2NR^9R^{10}$, SO_2R^{11}, $NHSO_2R^{11}$, $N(CH_3)SO_2CH_3$, NR^9R^{10}, $CH_2NH(OH)$, $CH_2NH(SO_2R^{11})$, $NHCOR^{12}$, COR^{12}, $CHNR^{13}$, OR^{14}, SR^{14}, $(C_3\text{-}C_7)$cycloalkyl, aryl,

substituted aryl, (C_1-C_4)alkyl-aryl, (C_1-C_4)alkyl-substituted aryl, heterocycle, substituted heterocycle, (C_1-C_4)alkyl-heterocycle, or (C_1-C_4)alkyl-substituted heterocycle;

provided that where "C" represents an aryl group, R^1 is other than oxo, (C_2-C_6)alkenyl, or (C_2-C_6)alkynyl;

further provided that where "C" represents a benzo-fused heterocycle then R^1 may also represent hydrogen;

R^2 through R^8 each independently represent hydrogen, halo, hydroxy, cyano, nitro, amino, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, CH_2NH_2, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, $C(CF_3)_2OH$, SO_2NH_2, $SO_2NR^9R^{10}$, SO_2R^{11}, $NHSO_2R^{11}$, NR^9R^{10}, $CH_2NH(OH)$, $CH_2NH(SO_2R^{11})$, $NHCOR^{12}$, COR^{12}, $CHNR^{13}$, OR^{14}, SR^{14}, (C_3-C_7)cycloalkyl, aryl, substituted aryl, (C_1-C_4)alkyl-(C_1-C_6)alkoxy, (C_1-C_4)alkyl-aryl, (C_1-C_4)alkyl-substituted aryl, heterocycle, substituted heterocycle, (C_1-C_4)alkyl-heterocycle, or (C_1-C_4)alkyl-substituted heterocycle;

provided that where "A", "B", or "C" represents an aryl group, each of R^2 through R^7 is other than (C_2-C_6)alkenyl or (C_2-C_6)alkynyl;

further provided that where C represents a phenyl ring and R^1 represents halo then at least one of R^2 and R^3 is other than hydrogen, (C_1-C_6)alkyl, aryl, substituted aryl, (C_1-C_4)alkyl-aryl, (C_1-C_4)alkyl-substituted aryl, CHF_2, or CF_3;

further provided that where C represents a six-membered ring and R^1 represents cyano, amino, NR^9R^{10}, or $NHCOCH_3$ and R^2 and R^3 are each hydrogen, then R^1 is not bound at the 4-position of said six-membered ring;

further provided that where C represents a six-membered ring and R^1 represents nitro, and R^2 and R^3 are each hydrogen, then R^1 is not bound at the 2, 4, or 6-position of said six-membered ring;

R^9 represents independently at each occurrence cyano, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_4)alkyl-(C_1-C_6)alkoxy, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, NH-(C_1-C_6)alkylamine, N,N-(C_1-C_6)dialkylamine, aryl, substituted aryl, (C_1-C_4)alkyl-aryl, (C_1-C_4)alkyl-substituted aryl, heterocycle, substituted heterocycle, (C_1-C_4)alkyl-heterocycle, or (C_1-C_4)alkyl-substituted heterocycle;

R^{10} represents independently at each occurrence hydrogen or (C_1-C_6)alkyl

or R^9 and R^{10} together with the nitrogen atom to which they are attached, form a substituted or unsubstituted heterocycle group;

R^{11} represents independently at each occurrence amino, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_7)$cycloalkyl, aryl, substituted aryl, $(C_1\text{-}C_4)$alkyl-aryl, $(C_1\text{-}C_4)$alkyl-substituted aryl, heterocycle, substituted heterocycle, $(C_1\text{-}C_4)$alkyl-heterocycle, or $(C_1\text{-}C_4)$alkyl-substituted heterocycle;

R^{12} represents independently at each occurrence hydrogen, amino, $(C_1\text{-}C_6)$alkyl, hydroxy$(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkyl-$(C_1\text{-}C_6)$alkoxy, $(C_3\text{-}C_7)$cycloalkyl, NH-$(C_1\text{-}C_6)$alkylamine, N,N-$(C_1\text{-}C_6)$dialkylamine, aryl, substituted aryl, $(C_1\text{-}C_4)$alkyl-aryl, $(C_1\text{-}C_4)$alkyl-substituted aryl, heterocycle, substituted heterocycle, $(C_1\text{-}C_4)$alkyl-heterocycle, or $(C_1\text{-}C_4)$alkyl-substituted heterocycle;

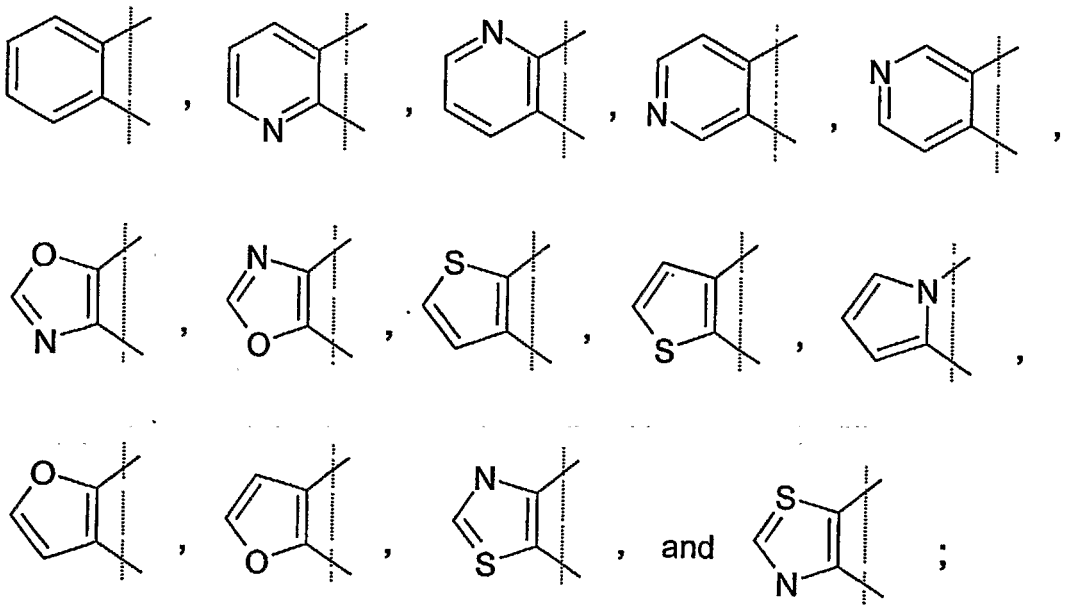
R^{13} represents independently at each occurrence OH, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_7)$cycloalkyl, aryl, heterocycle, or a substituted aryl or heterocycle;

R^{14} represents independently at each occurrence $(C_3\text{-}C_7)$cycloalkyl, aryl, substituted aryl, acyl, $(C_1\text{-}C_4)$alkyl-aryl, $(C_1\text{-}C_4)$alkyl-substituted aryl, heterocycle, substituted heterocycle, $(C_1\text{-}C_4)$alkyl-heterocycle, $(C_1\text{-}C_4)$alkyl-substituted heterocycle, or $(C_1\text{-}C_4)$alkyl-$(C_3\text{-}C_7)$cycloalkyl;

or a pharmaceutically acceptable salt thereof.

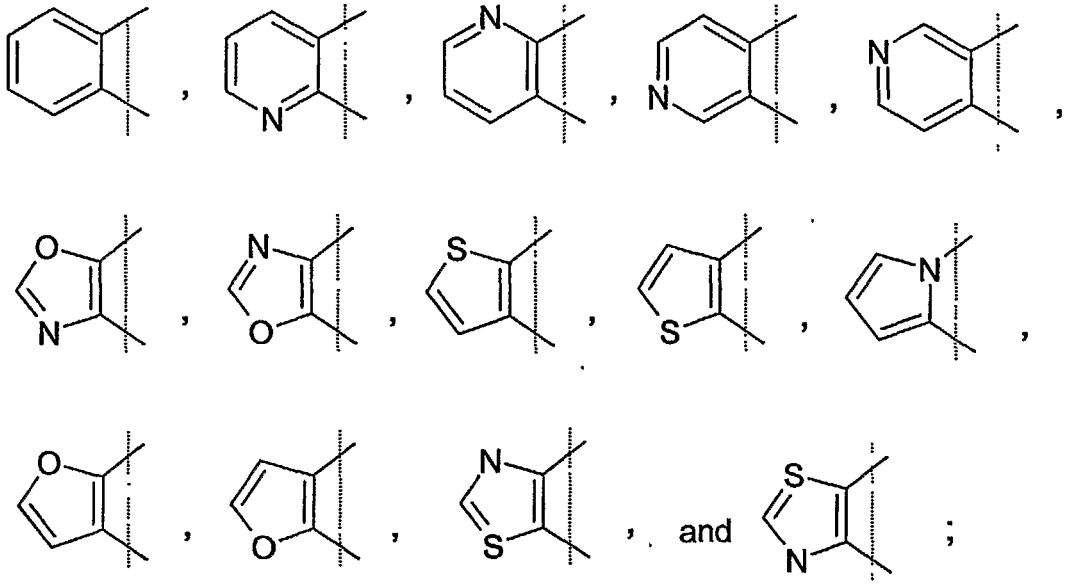
38. The compound according to Claim 37 wherein the compound of Formula I is one wherein,

"A" represents an aryl or heterocycle ring selected from the group consisting of

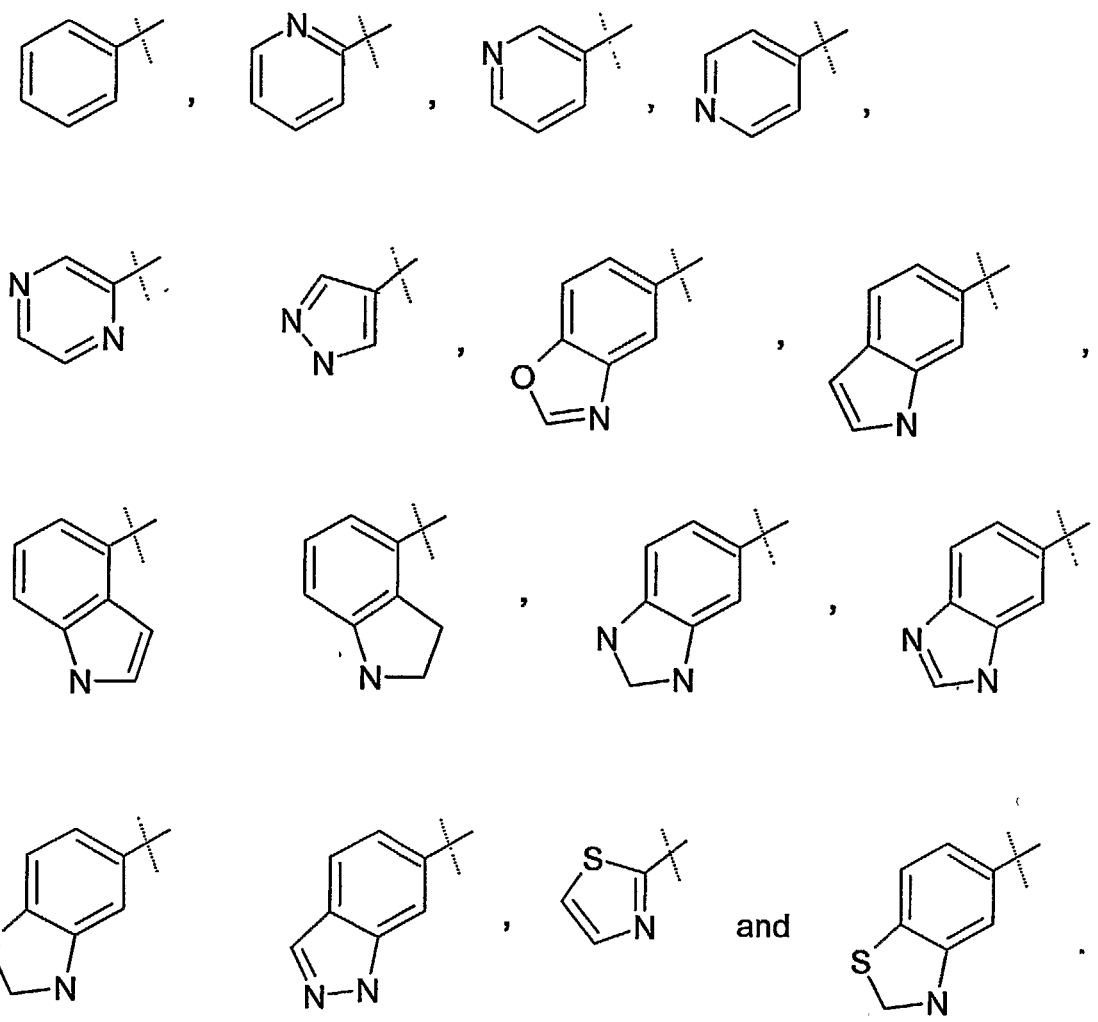


and ;

"B" represents an aryl or heterocyclic ring selected from the group consisting of

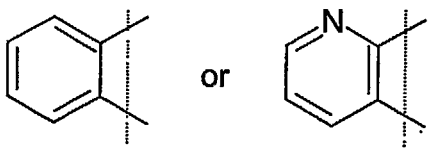


"C" represents an aryl , heterocyclic, or benzofused heterocycle ring selected from the group consisting of

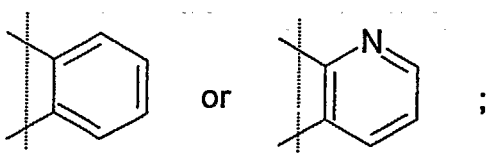


or a pharmaceutically acceptable salt thereof.

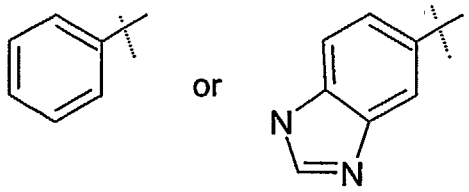
39. The compound according to claim 38 wherein "A" represents



"B" represents



and "C" represents



or a pharmaceutically acceptable salt thereof.

40. A compound according to any one of claims 37-39 wherein X-Y represents $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-S-$, $-S-CH_2-$, $-NR^{10}-CO-$, $-CO-NR^{10}-$, $-CH_2-NR^{10}-$, $-NR^{10}-CH_2-$, or $-CH=CH-$.

41. The compound according to Claim 40 wherein X-Y represents $-CH_2-CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-S-$, $-S-CH_2-$, $-NR^{10}-CO-$, $-CO-NR^{10}-$, $-CH_2-NR^{10}-$, $-NR^{10}-CH_2-$, or $-CH=CH-$, wherein R10 represents hydrogen or methyl.

42. The compound according to Claim 41 wherein X-Y represents $-CH_2-CH_2-$, $-CH_2-O-$, or $-O-CH_2-$.

43. A compound according to any one of Claims 37-42 wherein " - - - - - " represents a double bond.

44. A compound according to any one of Claims 37-43 wherein R^1 represents hydrogen, halo, hydroxy, cyano, nitro, amino, oxo (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxy(C_1-C_6)alkyl, CH_2NH_2, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, SO_2NH_2, $SO_2NR^9R^{10}$, SO_2R^{11}, NH SO_2R^{11}, NR^9R^{10}, $NHCOR^{12}$, COR^{12}, $CHNR^{13}$, OR^{14}, SR^{14}, heterocycle, (C_1-C_4)alkyl-heterocycle, or substituted heterocycle, provided that where "C" represents an aryl group then R^1 is other than oxo.

45. The compound according to Claims 44 wherein R^1 represents halo, amino, oxo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxymethyl, difluromethyl, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $SO_2NR^9R^{10}$, NH SO_2R^{11}, $NHCOR^{12}$, COR^{12}, OR^{14}, or (C_1-C_4)alkyl-heterocycle, provided that where "C" represents an aryl group then R^1 is other than oxo.

46. The compound according to Claim 45 wherein when R^1 represents $SO_2NR^9R^{10}$, R^9 represents (C_1-C_6)alkyl, (C_1-C_4)alkyl-(C_1-C_6)alkoxy, halo(C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, aryl, (C_1-C_4)alkyl-aryl, heterocycle and R^{10} represents hydrogen or methyl, or R^9 and R^{10} together with the nitrogen to which they are attached form a substituted or unsubstituted heterocycle;

47. The compound according to Claim 45 wherein when R^1 represents NH SO_2R^{11}, R^{11} represents amino, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_6)alkoxy , (C_3-C_7)cycloalkyl, aryl, substituted aryl, heterocycle, or substituted heterocycle.

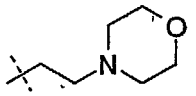
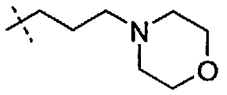
48. The compound according to Claim 47 wherein R^{11} represents methyl, ethyl, propyl, isopropyl, butyl, or 2-methyl propyl.

49. The compound according to Claim 45 wherein when R^1 represents $NHCOR^{12}$, R^{12} represents H, amino, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxy(C_1-C_6)alkyl, (C_1-C)alkyl-(C_1-C_6)alkoxy, halo(C_1-C_6)alkyl, NH-methylamine, NH-dimethylamine, NH-ethylamine, or heterocycle.

50. The compound according to Claim 45 wherein when R^1 represents COR^{12} , R^{12} represents H, amino, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or hydroxy(C_1-C_6)alkyl.

51. The compound according to Claim 45 wherein when R^1 represents OR^{14} , R^{14} represents (C_1-C)alkyl-heterocycle.

52. The compound according to Claim 45 wherein (C_1-C)alkyl-heterocycle represents a group of the formula


or

.

53. A compound according to any one of Claims 37-52 wherein R^2 represents hydrogen, halo, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, or (C_1-C_4)alkyl-heterocycle.

54. The compound according to Claim 53 wherein R^2 represents hydrogen or (C_1-C_4)alkyl-heterocycle.

55. The compound according to Claim 54 wherein R^2 represents hydrogen.

56. A compound according to any one of Claims 37-55 wherein R^3 represents hydrogen, halo, or (C_1-C_6)alkyl.

57. The compound according to Claim 56 wherein R^3 represents hydrogen.

58. A compound according to any one of Claims 37-57 wherein R^4-R^7 each independently represent hydrogen, halo, hydroxy, cyano, amino, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, SO_2NH_2, SO_2CH_3, NH SO_2R^{11}, NR^9R^{10}, $NHCOR^{12}$, COR^{12}, OR^{14}, SR^{14}, or aryl.

59. The compound according to Claim 58 wherein R^4-R^7 each independently represent hydrogen, halo, hydroxy, cyano, amino, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, CHF_2, CF_3, $OCHF_2$,OCF_3, NH SO_2R^{11}, NR^9R^{10}, $NHCOR^{12}$, COR^{12}, OR^{14}, or aryl.

60. The compound according to Claim 59 wherein R^4-R^7 each independently represent hydrogen, halo, hydroxy, cyano, amino, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, CHF_2, CF_3, $OCHF_2$,OCF_3, NH SO_2CH_3, dimethylamine, $NHCOCH_3$, COR^{12} wherein R^{12} represents hydrogen, amino, or methoxy; OR^{14} wherein R^{14} represents (C_1-C_4)alkyl-aryl, (C_1-C_4)alkyl-substituted aryl, (C_1-C_4)alkyl-heterocycle, or (C_1-C_4)alkyl-(C_3-C_7)cycloalkyl; or aryl.

61. The compound according to Claim 60 wherein R^4-R^7 each independently represent hydrogen, hydroxy, halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or OR^{14} wherein R^{14} represents (C_1-C_4)alkyl-aryl, (C_1-C_4)alkyl-substituted aryl, (C_1-C_4)alkyl-heterocycle, or (C_1-C_4)alkyl-(C_3-C_7)cycloalkyl.

62. The compound according to Claim 61 wherein R^4 and R^6 each independently represent hydrogen, halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or OR^{14} wherein R^{14} represents (C_1-C_4)alkyl-aryl, (C_1-C_4)alkyl-substituted aryl, (C_1-C_4)alkyl-heterocycle, or (C_1-C_4)alkyl-(C_3-C_7)cycloalkyl.

63. The compound according to Claim 61 wherein R^5 and R^7 each independently represent hydrogen, hydroxy, halo, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy.

64. A compound according to any one of Claims 37-63 wherein R^8 represents hydrogen, halo, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl , (C_1-C_4)alkyl -(C_1-C_6)alkoxy , COR^{12}, (C_3-C_7)cycloalkyl, aryl, or substituted aryl.

65. The compound according to Claim 64 wherein R^8 represents hydrogen, halo, (C_1-C_6)alkyl, hydroxymethyl, (C_1-C_4)alkyl -(C_1-C_6)alkoxy , COR^{12} wherein R^{12} represents (C_1-C_6)alkoxy; (C_3-C_7)cycloalkyl, phenyl, or substituted aryl.

66. The compound according to Claim 65 wherein R^8 represents hydrogen, halo, (C_1-C_6)alkyl, (C_1-C_4)alkyl -(C_1-C_6)alkoxy , or (C_3-C_7)cycloalkyl.

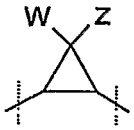
67. The compound according to Claim 66 wherein R^8 represents halo (C_1-C_6)alkyl, (C_1-C_4)alkyl -(C_1-C_6)alkoxy.

68. The compound according to Claim 66 wherein R^8 represents hydrogen.

69. The compound according to Claim 37 wherein

"A" and "B" each independently represent phenyl or heterocycle;

X and Y together represent $-CH_2-CH_2-$, $-CH=CH-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-S-$, $-S-CH_2-$, $-CH_2-SO-$, $-SO-CH_2-$, $-CH_2-SO_2-$, $-SO_2-CH_2-$, $-CH_2-NR^{10}-$, $-NR^{10}-CH_2-$, $-NR^{10}-CO-$, $-CO-NR^{10}-$, or a group of the formula



wherein W and Z each independently represent hydrogen, fluoro, or chloro;

"-----" represents a single or double bond;

R^1 represents halo, hydroxy, cyano, nitro, amino, oxo, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, hydroxy$(C_1$-$C_6)$alkyl, CH_2NH_2, halo$(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkoxy, SO_2NH_2, $SO_2NR^9R^{10}$ wherein R^9 represents $(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_1$-$C_4)$alkyl-$(C_1$-$C_6)$alkoxy, aryl, $(C_1$-$C_4)$alkyl-aryl, $(C_3$-$C_7)$cycloalkyl and R^{10} represents hydrogen or $(C_1$-$C_6)$alkyl or R^9 and R^{10} together represent a substituted or unsubstituted heterocycle; SO_2R^{11} wherein R11 represents $(C_1$-$C_6)$alkyl; NH SO_2R^{11} wherein R^{11} represents $(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_3$-$C_7)$cycloalkyl, aryl, substituted aryl, heterocycle, or substituted heterocycle; NR^9R^{10} wherein R^9 represents $(C_1$-$C_6)$alkyl or cyano and R^{10} represents hydrogen or methyl; $NHCOR^{12}$ wherein R^{12} represents H, amino, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, hydroxy$(C_1$-$C_6)$alkyl, $(C_1$-C)alkyl-$(C_1$-$C_6)$alkoxy, halo$(C_1$-$C_6)$alkyl, NH-methylamine,NH-ethylamine, or heterocycle; COR^{12} wherein R^{12} represents H, amino, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, hydroxy$(C_1$-$C_6)$alkyl; OR^{14} wherein R^{14} represents $(C_1$-$C_4)$alkyl-heterocycle or acetyl; SR^{14} wherein R^{14} represents $(C_1$-$C_6)$alkyl; heterocycle, $(C_1$-$C_4)$alkyl-heterocycle, or substituted heterocycle,

provided that where "C" represents an aryl group then R^1 is other than oxo;

further provided that where "C" represents a benzo-fused heterocycle then R^1 may also represent hydrogen;

R^2 represents hydrogen, halo, hydroxy, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, halo$(C_1$-$C_6)$alkyl, $(C_3$-$C_7)$cycloalkyl, or $(C_1$-$C_4)$alkyl-heterocycle;

R^3 represents wherein hydrogen, halo, or $(C_1$-$C_6)$alkyl;

provided that where C represents a phenyl ring and R^1 represents halo then at least one of R^2 and R^3 is other than hydrogen, $(C_1$-$C_6)$alkyl, aryl, substituted aryl, $(C_1$-$C_4)$alkyl-aryl, $(C_1$-$C_4)$alkyl-substituted aryl, CHF_2, or CF_3;

further provided that where C represents a six-membered ring and R^1 represents cyano, amino, NR^9R^{10}, or $NHCOCH_3$ and R^2 and R^3 are each hydrogen, then R^1 is not bound at the 4-position of said six-membered ring;

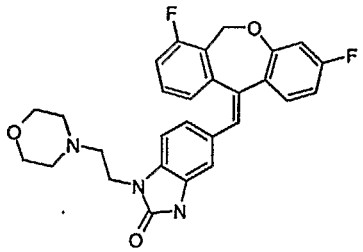
further provided that where C represents a six-membered ring and R^1 represents nitro, and R^2 and R^3 are each hydrogen, then R^1 is not bound at the 2, 4, or 6-position of said six-membered ring;

R^4 and R^6 each independently represent hydrogen, halo, hydroxy, cyano, amino, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkyl, hydroxymethyl, SO_2CH_3, NH SO_2R^{11} wherein R11 represents (C_1-C_6)alkyl; NR^9R^{10} wherein R^9 and R^{10} each represent (C_1-C_6)alkyl, $NHCOR^{12}$ wherein R^{12} represents (C_1-C_6)alkyl; COR^{12} wherein R12 represents hydrogen, amino, or (C_1-C_6)alkoxy; OR^{14} wherein R^{14} represents (C_1-C_4)alkyl-(C_3-C_7)cycloalkyl , (C_1-C_4)alkyl-aryl, (C_1-C_4)alkyl-substituted aryl , or (C_1-C_4)alkyl-heterocycle; SR^{14} wherein R^{14} represents (C_1-C_6)alkyl; or aryl;

R^5 and R^7 each independently represent hydrogen, hydroxy, halo, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy; and

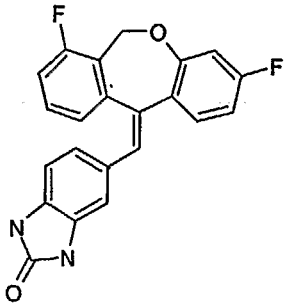
R^8 represents hydrogen, halo, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl , (C_1-C_4)alkyl - (C_1-C_6)alkoxy, COR^{12} wherein R^{12} represents methoxy, ethoxy, hydroxymethyl, or methoxymethyl; (C_3-C_7)cycloalkyl, aryl or substituted aryl.

70. A compound of the formula



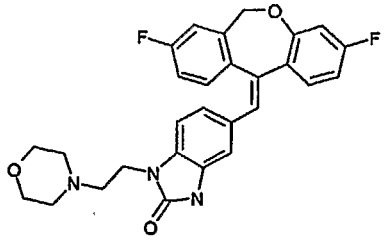
or a pharmaceutically acceptable salt thereof.

71. A compound of the formula



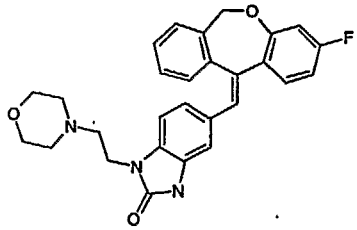
or a pharmaceutically acceptable salt thereof.

72. A compound of the formula



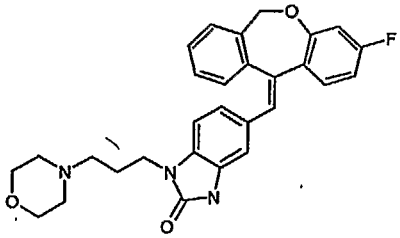
or a pharmaceutically acceptable salt thereof.

73. A compound of the formula



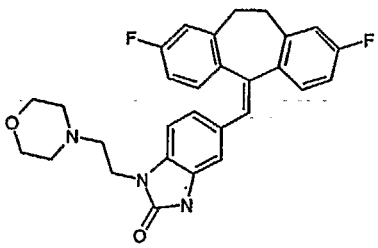
or a pharmaceutically acceptable salt thereof.

74. A compound of the formula



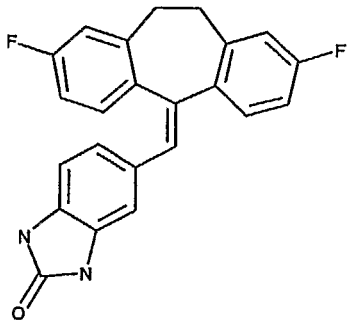
or a pharmaceutically acceptable salt thereof.

75. A compound of the formula



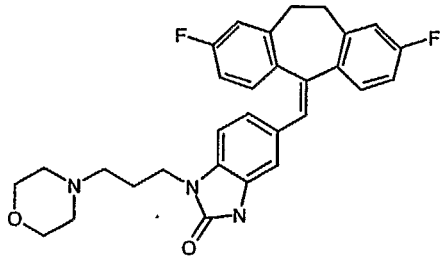
or a pharmaceutically acceptable salt thereof.

76. A compound of the formula



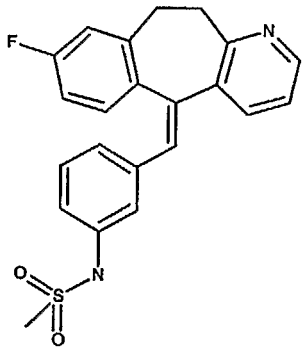
or a pharmaceutically acceptable salt thereof.

77. A compound of the formula



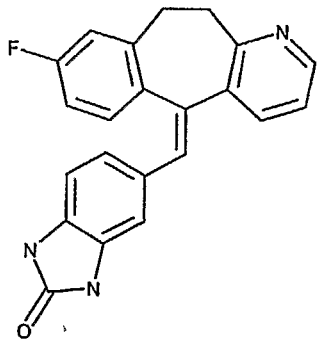
or a pharmaceutically acceptable salt thereof.

78. A compound of the formula



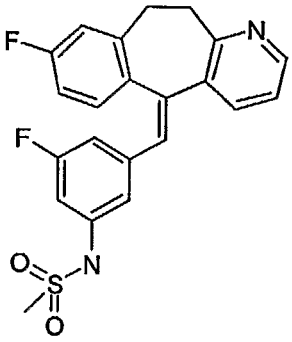
or a pharmaceutically acceptable salt thereof.

79. A compound of the formula



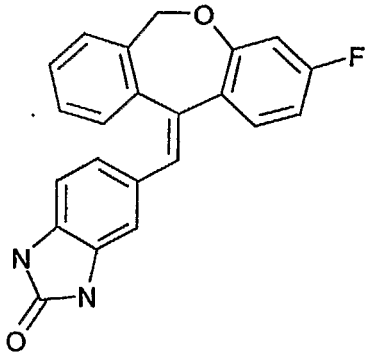
or a pharmaceutically acceptable salt thereof.

80. A compound of the formula



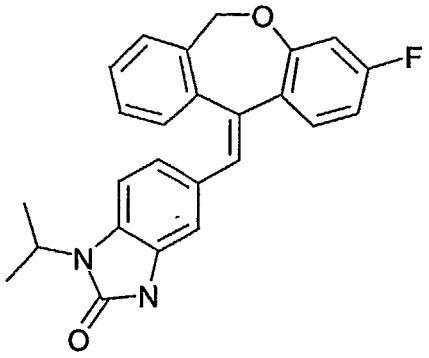
or a pharmaceutically acceptable salt thereof.

81. A compound of the formula



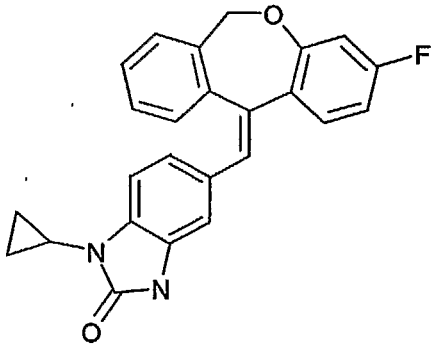
or a pharmaceutically acceptable salt thereof.

82. A compound of the formula



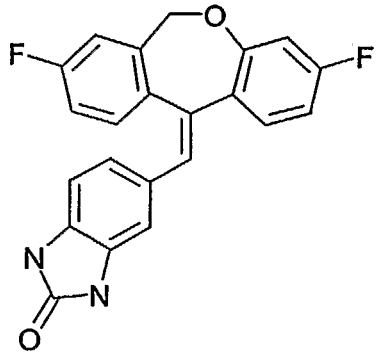
or a pharmaceutically acceptable salt thereof.

83. A compound of the formula



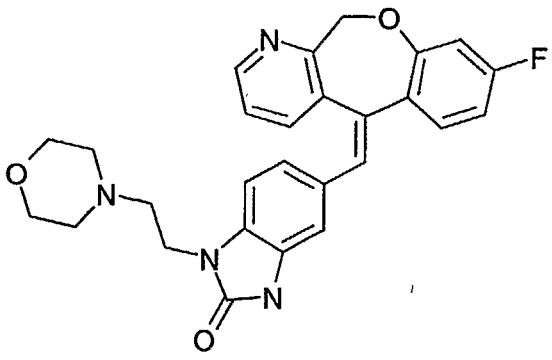
or a pharmaceutically acceptable salt thereof.

84. A compound of the formula



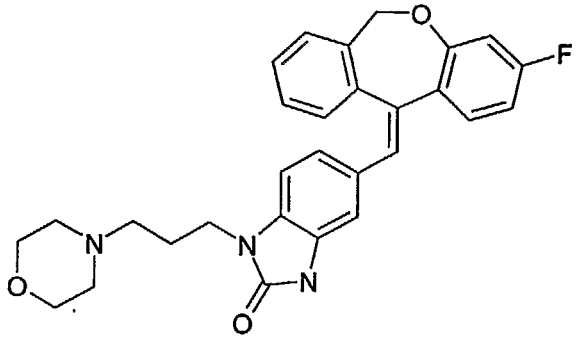
or a pharmaceutically acceptable salt thereof.

85. A compound of the formula



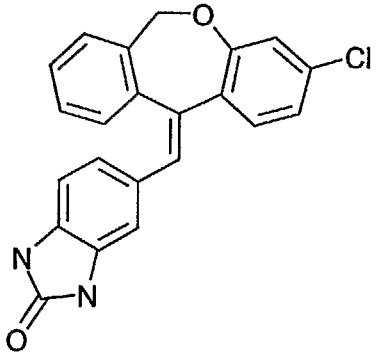
or a pharmaceutically acceptable salt thereof.

86. A compound of the formula



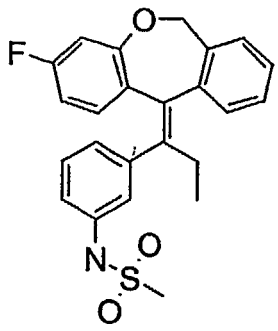
or a pharmaceutically acceptable salt thereof.

87. A compound of the formula



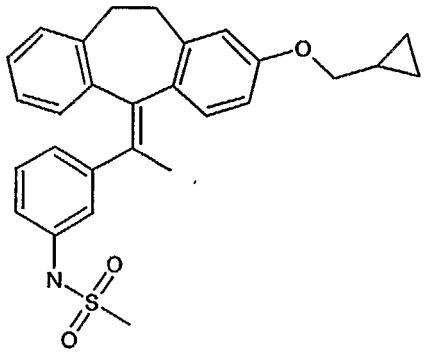
or a pharmaceutically acceptable salt thereof.

88. A compound of the formula



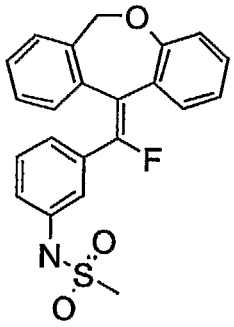
or a pharmaceutically acceptable salt thereof.

89. A compound of the formula



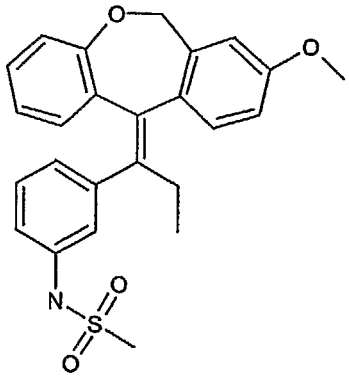
or a pharmaceutically acceptable salt thereof.

90. A compound of the formula



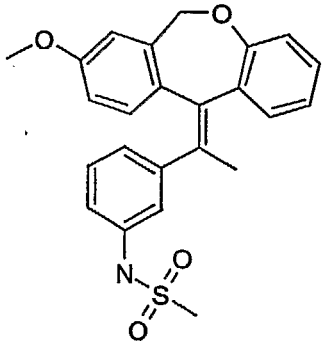
or a pharmaceutically acceptable salt thereof.

91. A compound of the formula



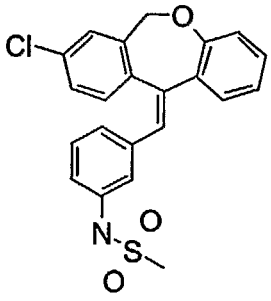
or a pharmaceutically acceptable salt thereof.

92. A compound of the formula



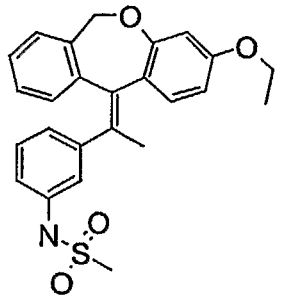
or a pharmaceutically acceptable salt thereof.

93. A compound of the formula



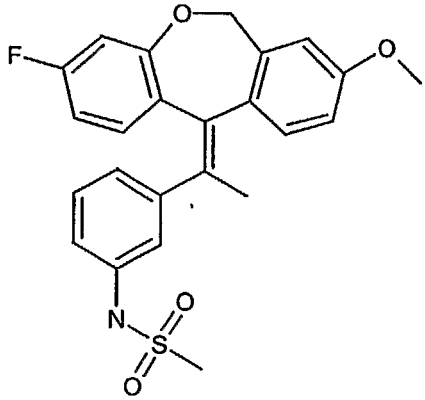
or a pharmaceutically acceptable salt thereof.

94. A compound of the formula



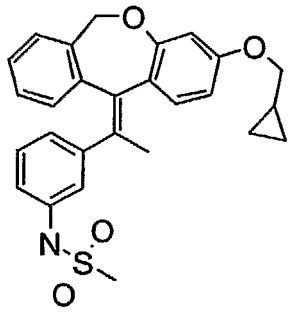
or a pharmaceutically acceptable salt thereof.

95. A compound of the formula



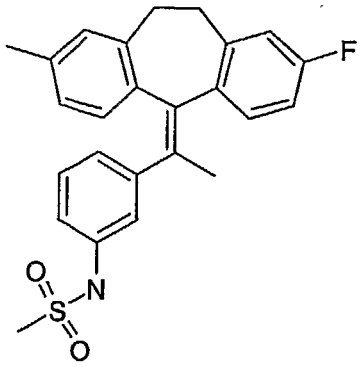
or a pharmaceutically acceptable salt thereof.

96. A compound of the formula



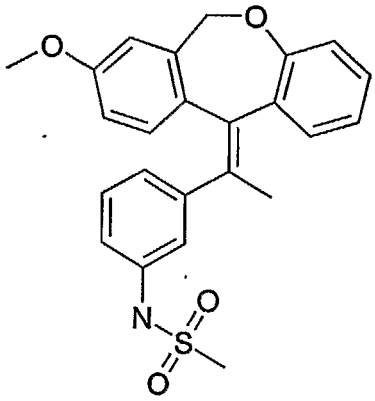
or a pharmaceutically acceptable salt thereof.

97. A compound of the formula



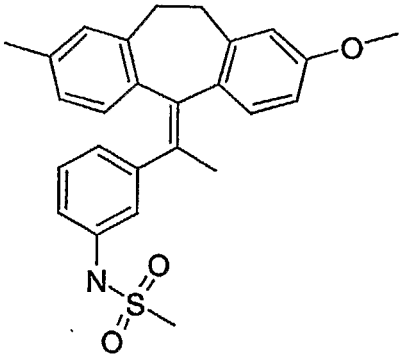
or a pharmaceutically acceptable salt thereof.

98. A compound of the formula



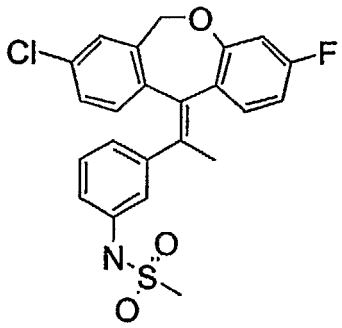
or a pharmaceutically acceptable salt thereof.

99. A compound of the formula



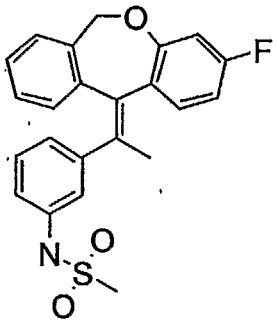
or a pharmaceutically acceptable salt thereof.

100. A compound of the formula



or a pharmaceutically acceptable salt thereof.

101. A compound of the formula



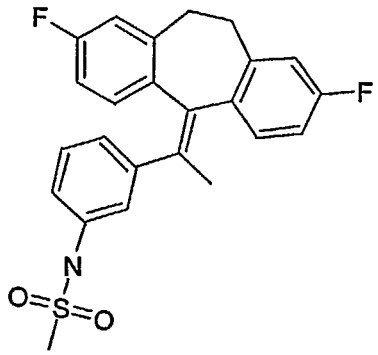
or a pharmaceutically acceptable salt thereof.

102. A compound of the formula



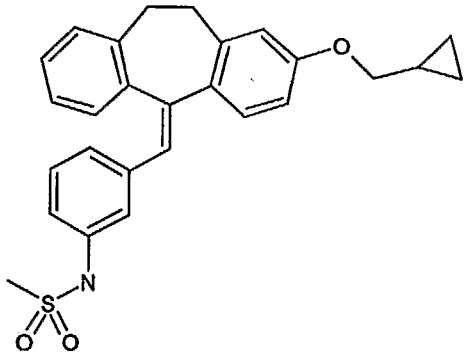
or a pharmaceutically acceptable salt thereof.

103. A compound of the formula



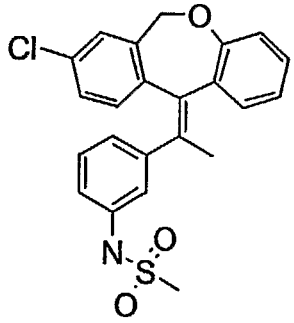
or a pharmaceutically acceptable salt thereof.

104. A compound of the formula



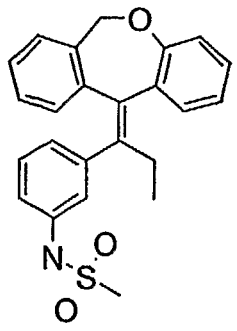
or a pharmaceutically acceptable salt thereof.

105. A compound of the formula



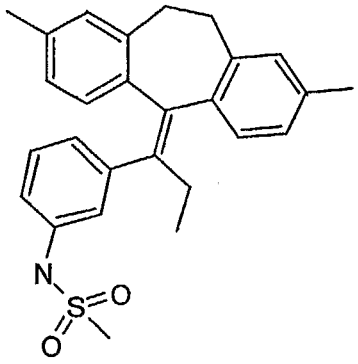
or a pharmaceutically acceptable salt thereof.

106. A compound of the formula



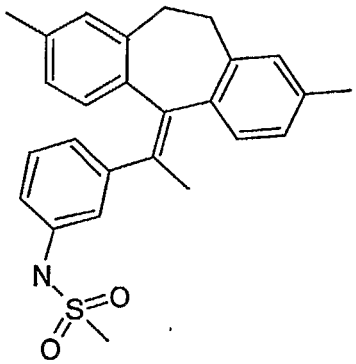
or a pharmaceutically acceptable salt thereof.

107. A compound of the formula



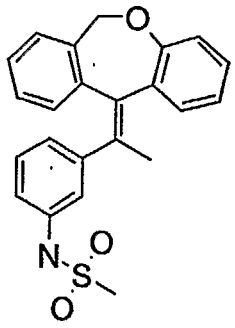
or a pharmaceutically acceptable salt thereof.

108. A compound of the formula



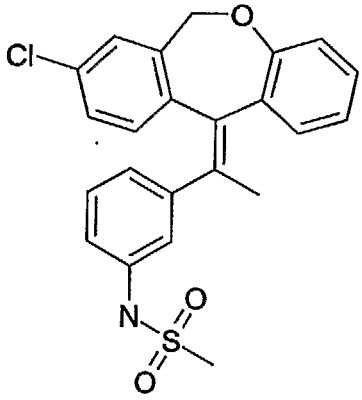
or a pharmaceutically acceptable salt thereof.

109. A compound of the formula



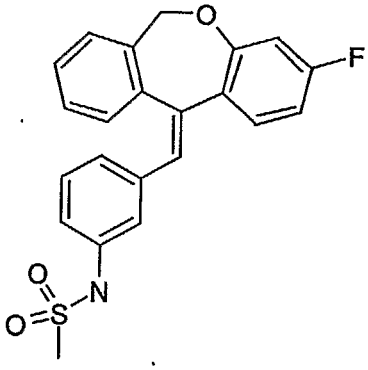
or a pharmaceutically acceptable salt thereof.

110. A compound of the formula



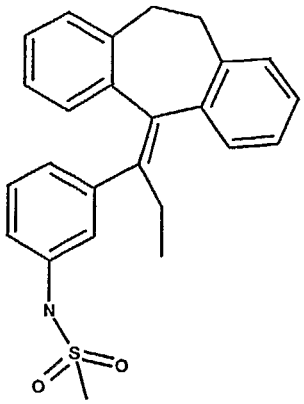
or a pharmaceutically acceptable salt thereof.

111. A compound of the formula



or a pharmaceutically acceptable salt thereof.

112. A compound of the formula



or a pharmaceutically acceptable salt thereof.

113. A method of treating a physiological disorder susceptible to steroid hormone nuclear receptor modulation comprising administering to a patient in need thereof effective amount of a novel compound of Formula I according to claim 37.

114. The method according to claim 113 wherein said disorder is susceptible to mineralocorticoid or glucocorticoid receptor modulation.

115. The method according to Claim 114 wherein said disorder is selected from the group consisting of Conn's Syndrome, primary and secondary hyperaldosteronism, increased sodium retention, increased magnesium and potassium excretion (diuresis), increased water retention, hypertension (isolated systolic and combined systolic/diastolic), arrhythmias, myocardial fibrosis, myocardial infarction, Bartter's Syndrome, disorders associated with excess catecholamine levels, diastolic and systolic congestive heart failure (CHF), psychoses, cognitive disorders, memory disturbances, depression, bipolar disorder, anxiety disorders, personality disorders, breast cancer, peripheral vascular disease, diabetic nephropathy, cirrhosis with edema and ascites, esophageal varicies, Addison's Disease, muscle weakness, increased melanin pigmentation of the skin, weight loss, hypotension, hypoglycemia, Cushing's Syndrome, obesity, hypertension, glucose intolerance, hyperglycemia, diabetes mellitus, osteoporosis, polyuria, polydipsia, inflammation, autoimmune disorders, tissue rejection associated with organ transplant, malignancies such as leukemias and lymphomas, acute adrenal insufficiency, congenital adrenal hyperplasia, rheumatic fever, polyarteritis nodosa, granulomatous polyarteritis, inhibition of myeloid cell lines, immune proliferation/apoptosis, HPA axis suppression and regulation, hypercortisolemia, modulation of the Th1/Th2 cytokine balance, chronic kidney disease, stroke and spinal cord injury, hypercalcemia, hypergylcemia, acute adrenal insufficiency, chronic primary adrenal insufficiency, secondary adrenal insufficiency, congenital adrenal hyperplasia,

cerebral edema, thrombocytopenia, and Little's syndrome, systemic inflammation, inflammatory bowel disease, systemic lupus erythematosus, discoid lupus erythematosus, polyartitis nodosa, Wegener's granulomatosis, giant cell arthritis, rheumatoid arthritis, osteoarthritis, hay fever, allergic rhinitis, contact dermatitis, atopic dermatitis, exfoliative dermatitis, urticaria, angioneurotic edema, chronic obstructive pulmonary disease, asthma, tendonitis, bursitis, Crohn's disease, ulcerative colitis, autoimmune chronic active hepatitis, hepatitis, cirrhosis, inflammatory scalp alopecia, panniculitis, psoriasis, inflamed cysts, pyoderma gangrenosum, pemphigus vulgaris, bullous pemphigoid, dermatomyositis, eosinophilic fasciitis, relapsing polychondritis, inflammatory vasculitis, sarcoidosis, Sweet's disease, type 1 reactive leprosy, capillary hemangiomas, lichen planus, , erythema nodosum, acne, hirsutism, toxic epidermal necrolysis, erythema multiform, cutaneous T-cell lymphoma, emphysema, Alzheimer's Disease, and multiple sclerosis.

116. The method according to claim 115, wherein said disorder is diastolic or systolic congestive heart failure, inflammation, rheumatoid arthritis, an autoimmune disorder, asthma, or chronic obstructive pulmonary disease .

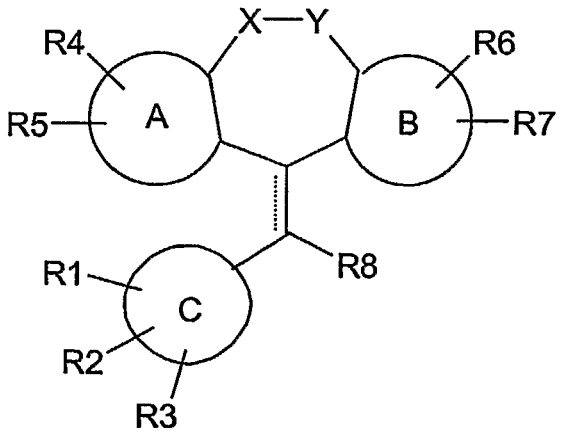
117. The method according to claim 116, wherein said disorder is diastolic or systolic congestive heart failure or rheumatoid arthritis.

118. A method of modulating a steroid hormone nuclear receptor comprising administering to a patient in need thereof an effective amount of a compound of Formula I according to Claim 37.

119. The method of Claim 118 wherein said steroid nuclear receptor is the mineralocorticoid receptor or the glucocorticoid receptor.

120. A pharmaceutical composition comprising an effective amount of a compound of Formula I according to Claim 37 in combination with a pharmaceutically acceptable carrier.

121. The use of a compound of Formula I :

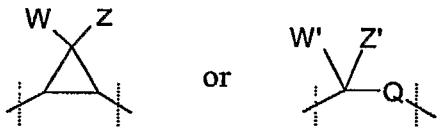


Formula I

wherein,

A, B, and C each independently represent an aryl, heterocycle, or benzofused-heterocyclic ring;

X and Y together represent $-CH_2-CH_2-$, $-CH=CH-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-S-$, $-S-CH_2-$, $-CH_2-SO-$, $-SO-CH_2-$, $-CH_2-SO_2-$, $-SO_2-CH_2-$, $-CH_2-NR^{10}-$, $-NR^{10}-CH_2-$, $-NR^{10}-CO-$, $-CO-NR^{10}-$, or a group of the formula



wherein W and Z each independently represent hydrogen, fluoro, or chloro; W' and Z' each independently represent hydrogen, fluoro, chloro, or methyl; and Q represents NH, O, S, or CH_2;

"- - - - -" represents a single or double bond;

R^1 represents hydrogen, halo, hydroxy, cyano, nitro, amino, oxo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, CH_2NH_2, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, $C(CF_3)_2OH$, SO_2NH_2, $SO_2NR^9R^{10}$, SO_2R^{11}, $NHSO_2R^{11}$, $N(CH_3)SO_2CH_3$, NR^9R^{10}, $CH_2NH(OH)$, $CH_2NH(SO_2R^{11})$, $NHCOR^{12}$, COR^{12}, $CHNR^{13}$, OR^{14}, SR^{14}, (C_3-C_7)cycloalkyl, aryl, substituted aryl, (C_1-C_4)alkyl-aryl, (C_1-C_4)alkyl-substituted aryl, heterocycle, substituted heterocycle, (C_1-C_4)alkyl-heterocycle, or (C_1-C_4)alkyl-substituted heterocycle;

provided that where "C" represents an aryl group, R^1 is other than oxo, (C_2-C_6)alkenyl, or (C_2-C_6)alkynyl;

R^2 through R^8 each independently represent hydrogen, halo, hydroxy, cyano, nitro, amino, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkoxy,

$(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, CH_2NH_2, halo$(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkoxy, $C(CF_3)_2OH$, SO_2NH_2, $SO_2NR^9R^{10}$, SO_2R^{11}, $NHSO_2R^{11}$, NR^9R^{10}, $CH_2NH(OH)$, $CH_2NH(SO_2R^{11})$, $NHCOR^{12}$, COR^{12}, $CHNR^{13}$, OR^{14}, SR^{14}, $(C_3\text{-}C_7)$cycloalkyl, aryl, substituted aryl, $(C_1\text{-}C_4)$alkyl-$(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_4)$alkyl-aryl, $(C_1\text{-}C_4)$alkyl-substituted aryl, heterocycle, substituted heterocycle, $(C_1\text{-}C_4)$alkyl-heterocycle, or $(C_1\text{-}C_4)$alkyl-substituted heterocycle;

provided that where "A", "B", or "C" represents an aryl group, each of R^2 through R^7 is other than $(C_2\text{-}C_6)$alkenyl or $(C_2\text{-}C_6)$alkynyl;

R^9 represents independently at each occurrence cyano, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_4)$alkyl-$(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkyl, hydroxy$(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_7)$cycloalkyl, NH-$(C_1\text{-}C_6)$alkylamine, N,N-$(C_1\text{-}C_6)$dialkylamine, aryl, substituted aryl, $(C_1\text{-}C_4)$alkyl-aryl, $(C_1\text{-}C_4)$alkyl-substituted aryl, heterocycle, substituted heterocycle, $(C_1\text{-}C_4)$alkyl-heterocycle, or $(C_1\text{-}C_4)$alkyl-substituted heterocycle;

R^{10} represents independently at each occurrence hydrogen or $(C_1\text{-}C_6)$alkyl or R^9 and R^{10} together with the nitrogen atom to which they are attached, form a substituted or unsubstituted heterocycle group;

R^{11} represents independently at each occurrence amino, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_7)$cycloalkyl, aryl, substituted aryl, $(C_1\text{-}C_4)$alkyl-aryl, $(C_1\text{-}C_4)$alkyl-substituted aryl, heterocycle, substituted heterocycle, $(C_1\text{-}C_4)$alkyl-heterocycle, or $(C_1\text{-}C_4)$alkyl-substituted heterocycle;

R^{12} represents independently at each occurrence hydrogen, amino, $(C_1\text{-}C_6)$alkyl, hydroxy$(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkyl-$(C_1\text{-}C_6)$alkoxy, $(C_3\text{-}C_7)$cycloalkyl, NH-$(C_1\text{-}C_6)$alkylamine, N,N-$(C_1\text{-}C_6)$dialkylamine, aryl, substituted aryl, $(C_1\text{-}C_4)$alkyl-aryl, $(C_1\text{-}C_4)$alkyl-substituted aryl, heterocycle, substituted heterocycle, $(C_1\text{-}C_4)$alkyl-heterocycle, or $(C_1\text{-}C_4)$alkyl-substituted heterocycle;

R^{13} represents independently at each occurrence OH, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_7)$cycloalkyl, aryl, heterocycle, or a substituted aryl or heterocycle;

R^{14} represents independently at each occurrence $(C_3\text{-}C_7)$cycloalkyl, aryl, substituted aryl, acyl, $(C_1\text{-}C_4)$alkyl-aryl, $(C_1\text{-}C_4)$alkyl-substituted aryl, heterocycle, substituted heterocycle, $(C_1\text{-}C_4)$alkyl-heterocycle, $(C_1\text{-}C_4)$alkyl-substituted heterocycle, or $(C_1\text{-}C_4)$alkyl-$(C_3\text{-}C_7)$cycloalkyl; or a novel compound of Formula I according to Claim 37, or pharmaceutically acceptable salts thereof,

for the manufacture of a medicamernt for the treatment of diastolic or systolic congestive heart failure or rheumatoid arthritis.