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(54) Title: TREATMENT OF CENTRAL NERVOUS SYSTEM DISORDERS WITH IMIDAZOLE ANGIOTENSIN-II RECEPTOR ANTAGONISTS

(57) Abstract

Substituted imidazoles such as 2-butyl-4-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-5-(hydroxymethyl)imidazole and 2-butyl-4-chloro-1-[(2'-carboxybiphenyl-4-yl)-methyl]-5-(hydroxymethyl)imidazole and pharmaceutically acceptable salts thereof are useful for treating central nervous system disorders, such as cognitive and learning disorders, mediated by angiotensin II.

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TITLE

Treatment of Central Nervous System Disorders With Imidazole Angiotensin-II Receptor Antagonists

BACKGROUND OF THE INVENTION

Angiotensin II (AII), in addition to being a circulating hormone, is now thought to act as a neuropeptide in the central nervous system (CNS) and may play a modulatory function on the release and subsequent action of other neurotransmitters (Unger et al. (1988) Circulation 77 (suppl I):40-54). Specific receptors for AII with high affinity have been identified and localized in different regions of the CNS (Mann (1982) Exp. Brain Res. 4 (suppl):242). Stimulation of AII receptors in the CNS elicits a complex but very reproducible and concerted pattern of behavioral, cardiovascular, and endocrine responses (Fitzsimons (1980) Rev. Physiol. Biochem. Pharmacol. 87:117). These include CNS-induced elevation of blood pressure, increased drinking and sodium appetite, release of antidiuretic hormone, oxytocin, luteinizing hormone, and prolactin, and other effects (Scholken et al. (1982) Experientia 38:469). The CNS effects of AII could lead to hypertension and other cardiovascular diseases through inhibition of the baroreceptor reflex, increase in salt consumption, volume expansion, and increased peripheral resistance. Besides the cardiovascular system, AII may also influence the reproductive system and other brain functions, such as memory (Koller et al. (1975) Neuroscience Lett. 14:71-75).

The major functions of AII in the CNS can be classified into three groups which may share, at least in part, overlapping mechanisms of action. The first major function of AII in the CNS is regulation of body fluid volume in response to hypovolemia, involving, for example, regulation of thirst, blood pressure increases, vasopressin release, sodium appetite increase, adrenocorticotropic hormone (ACTH) release, and

aldosterone release (Unger et al. (1988) Circulation 77 (suppl I):40-54, and references cited therein). This CNS function of AII is closely related to the role of AII in hypertension.

A second function of AII in the CNS, although poorly defined, is the regulation of gonadotrophic hormone releasing hormones and pituitary hormones during the reproductive cycle and pregnancy (Unger et al., supra).

A third possible CNS function of AII is a synaptic function. AII appears to interact with neurotransmitters such as acetylcholine (ACh), catecholamines, serotonin, and other peptides (Unger et al., supra). The amount of data supporting this CNS function of AII is limited. Published results suggest that increased AII activity in brain maintains an inhibitory control on cholinergic neurons resulting in impaired cognitive performance.

The role of peptides in learning and memory was initially investigated by DeWied in the late 1960's and early 1970's, and led Morgan and Routtenberg (Science (1977) 196:87-89) to investigate the role of AII in mediating retention of a passive avoidance (PA) response in rats. These authors demonstrated that rats injected with AII into the dorsal neostriatum, a brain area that has a high concentration of AII as well as precursors and metabolic enzymes for AII biosynthesis, showed a disruption in retention of a PA response. The authors demonstrated specificity of the response in terms of both the location in the brain and the peptide used (thyrotropin releasing hormone or lysine-8-vasopressin had no effect). This study showed that increased AII in the dorsal neostriatum results in a cognitive impairment which is most likely a result of AII modulation of neuronal activity that is necessary for consolidation of newly acquired information.

A different approach for investigating the behavioral effects of AII in the CNS was taken by Koller et al. Neuroscience Letters (1975) 14:71-75. These authors injected renin into the lateral ventricle of the brain (IVT) and measured

increases in AII in cerebrospinal fluid (CSF); AII increased from 40 to about 5000 fmol per mL. This increase in AII was accompanied by a disruption of avoidance learning. These results suggested that renin-stimulated biosynthesis of AII could disrupt memory. IVT administration of the angiotensin-converting enzyme (ACE) inhibitors SQ 14225 (captopril), prior to the renin injection, prevented the renin-induced avoidance disruption. We have also shown in our laboratory that renin administered IVT produces a dose-related amnesia in a PA task, and this renin-induced amnesia can be prevented by IVT administration of the ACE inhibitor captopril. These results suggest that increased AII levels in brain leads to a disruption of avoidance performance. Thus, this amnesia can be achieved by direct application into a discrete brain area of AII or renin, a stimulator of endogenous AII biosynthesis.

In the literature on the neuropathology and neurochemistry of Alzheimer's disease (AD) using human CSF and brain tissue, two reports of altered levels of dipeptidyl carboxypeptidase (angiotensin-converting enzyme, ACE) were published. Arrequi et al. J. Neurochemistry (1982) 38:1490-1492 found increased ACE activity in the hippocampus, parahippocampal gyrus, frontal cortex, and caudate nucleus in AD patients. Zubenko et al., Biol. Psych. (1986) 21:1365-1381, found a correlation between the severity of AD with levels of ACE in CSF. Whether the alterations in ACE are causative in the progression of dementia or correlates of the disease progress is not known.

Recent evidence that inhibition of ACE can have a modulatory effect on learning and memory was reported by Usinger et al. Drug Dev. Research (1988) 14:315-324 (also European Patent Application EP 307,872 to Hoechst, published 3/22/89). These authors investigated the effects of the ACE inhibitor Hoe 288 on: uphill avoidance in mice, scopolamine-induced (muscarinic receptor blocker) amnesia of a PA response, and a scopolamine-induced impairment of eight arm

radial maze performance in rats. In the uphill avoidance test, an acute administration of Hoe 288 at 30 mg/kg PO improved performance during retention testing. In the scopolamine-induced PA amnesia, administration of Hoe 288 three times per day at 1, 3 and 10 mg/kg PO, partially reversed the amnesia. Finally, 3 mg/kg IP partially antagonized the effects of muscarinic receptor blockade on performance. Further, these authors demonstrated that acute or repeated administration of the ACE inhibitor induced a significant decrease in ACh in the striatum and hypothalamus.

Similar results were reported by Costall et al., Pharmacol. Biochem. Behav. (1989) 33:573-579, using the ACE inhibitor captopril. These authors demonstrated that the subchronic treatment with captopril increased the rate of acquisition of light/dark habituation performance. Further, anticholinergic scopolamine-induced disruption of performance in this test model was prevented by daily treatment with captopril.

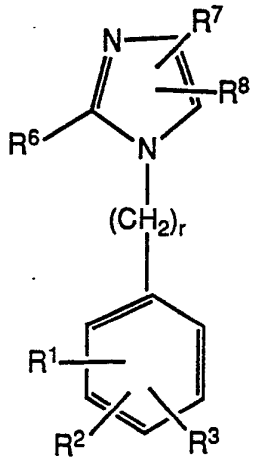
The ACE inhibitor SQ 29852 has also been reported to provide protective effects on memory of previously learned tasks and to ameliorate, at least in part, an anticholinergic effect on performance (European Patent Application EP 288,907 to Squibb, published 11/2/88).

Evidence for a role of AII on cholinergic function was also reported by Barnes et al. (Brain Research (1989) 491:136-143), who examined the affect of AII on an in vitro model of potassium stimulated release of [3H]ACh. AII, but not AI, reduced potassium-stimulated release of ACh without effects on basal levels. This effect was antagonized by the AII antagonist [1-sarcosine, 8-threonine]angiotensin II. These results suggest that AII can inhibit the release of ACh in entorhinal cortex from rat brain.

The results summarized above suggest that increased AII activity in brain may maintain inhibitory control of cholinergic neurons, resulting in impaired cognitive performance.

SUMMARY OF INVENTION

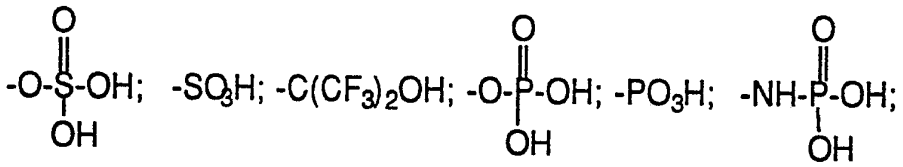
According to the present invention there is provided a method of treating central nervous system (CNS) disorders, such as cognitive and learning disorders, mediated by AII in a mammal comprising administering to the mammal a pharmaceutical composition comprising a compound having the formula (I):



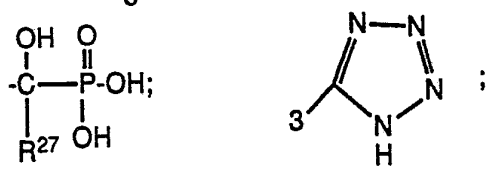
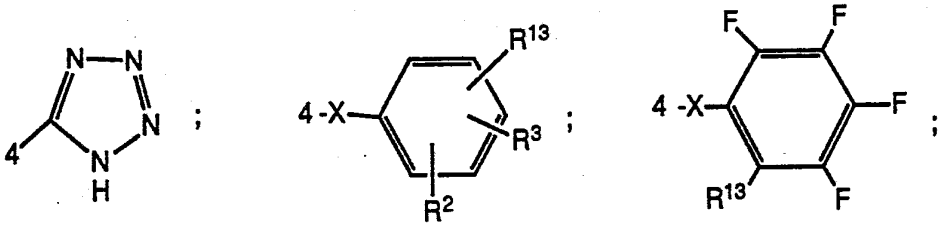
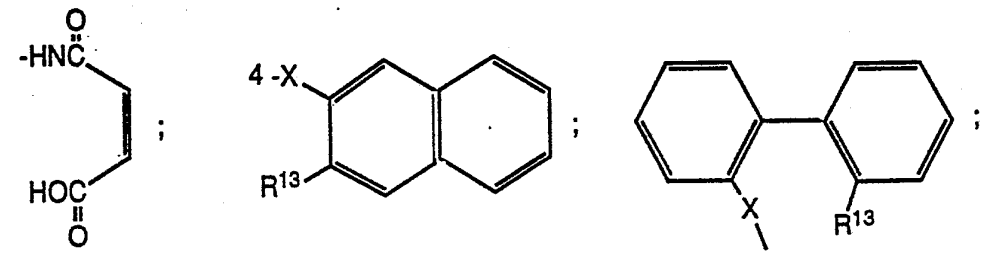
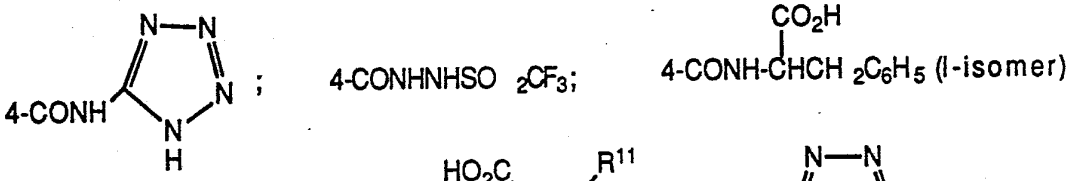
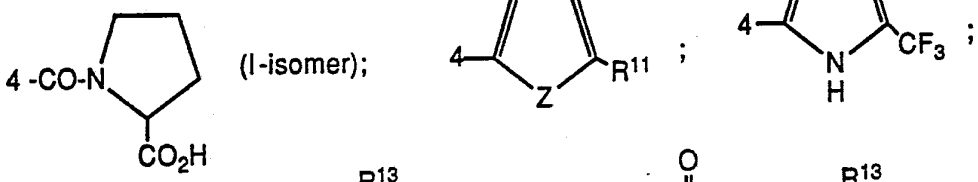
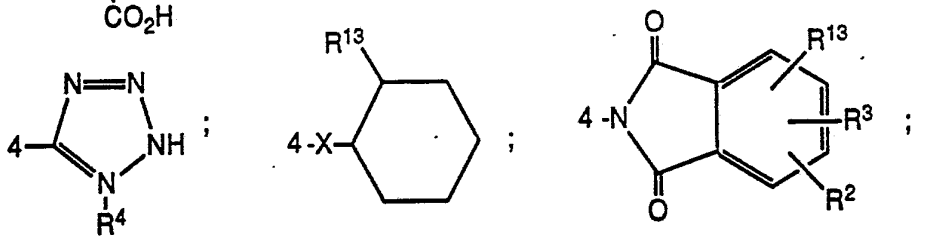
(I)

wherein

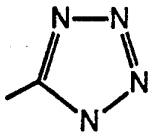
R^1 is 4-CO_2H; 4-CO_2R^9;



4-$NHSO_2CH_3$; -4-$NHSO_2CF_3$; -$CONHOR^{12}$;

R^2 is H; Cl; Br; I; F; NO_2; CN; alkyl of 1 to 4 carbon atoms; acyloxy of 1 to 4 carbon atoms; alkoxy of 1 to 4 carbon atoms; CO_2H; CO_2R^9; $NHSO_2CH_3$; $NHSO_2CF_3$; $CONHOR^{12}$; SO_2NH_2;



; aryl; or furyl;

R^3 is H; Cl, Br, I or F; alkyl of 1 to 4 carbon atoms or alkoxy of 1 to 4 carbon atoms;

R^4 is CN, NO_2 or CO_2R^{11};

R^5 is H, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, alkenyl or alkynyl of 2 to 4 carbon atoms;

R^6 is alkyl of 2 to 10 carbon atoms, alkenyl or alkynyl of 3 to 10 carbon atoms or the same groups substituted with F or CO_2R^{14}; cycloalkyl of 3 to 8 carbon atoms, cycloalkylalkyl of 4 to 10 carbon atoms; cycloalkylalkenyl or cycloalkylalkynyl of 5 to 10 carbon atoms; $(CH_2)_sZ(CH_2)_mR^5$ optionally substituted with F or CO_2R^{14}; benzyl or benzyl substituted on the phenyl ring with 1 or 2 halogens, alkoxy of 1 to 4 carbon atoms, alkyl of 1 to 4 carbon atoms or nitro;

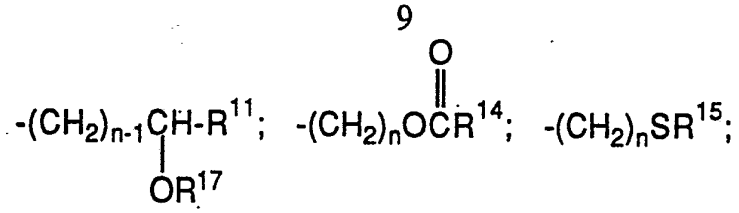
R^7 is H, F, Cl, Br, I, NO_2, C_vF_{2v+1}, where v = 1-6; C_6F_5; CN;

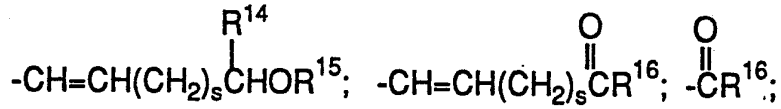
$$-\overset{O}{\overset{\|}{C}}R^{16}\ ;$$

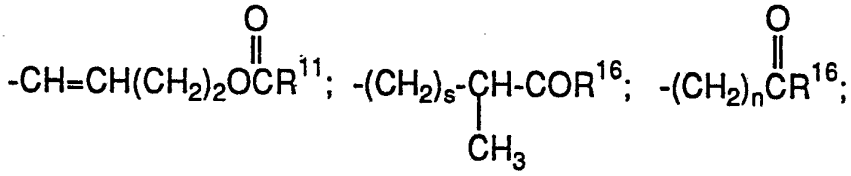
straight or branched alkyl of 1 to 6 carbon atoms; phenyl or phenylalkyl, where alkyl is 1 to 3 carbon atoms; or substituted phenyl or substituted phenylalkyl, where alkyl is 1 to 3 carbon atoms, substituted with one or two substituents selected from alkyl of 1 to 4 carbon atoms, F, Cl, Br, OH, OCH_3, CF_3, and COOR, where R is H, alkyl of 1 to 4 carbon atoms, or phenyl; vinyl; alkynyl of 2-10 carbon atoms; phenylalkynyl where the alkynyl portion is 2-6 carbon atoms; heteroaryl selected from 2- and 3-thienyl, 2- and 3-furyl, 2-, 3-, and 4-pyridyl, 2-pyrazinyl, 2-, 4-, and 5-pyrimidinyl, 3- and 4-pyridazinyl, 2-, 4- and 5-thiazolyl, 2-, 4-, and 5-selenazolyl, 2-, 4-, and 5-oxazolyl; 2- or 3-pyrrolyl, 3-, 4- or 5-pyrazolyl, and 2-, 4- or 5-imidazolyl; o-, m- or p-biphenylyl; o-, m- or p-phenoxyphenyl; substituted phenylalkynyl, heteroaryl, biphenylyl or phenoxphenyl as defined above substituted on

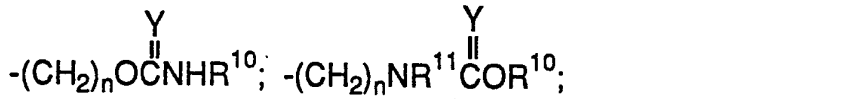
ring carbon with 1 or 2 substituents selected from halogen, alkoxy of 1-5 carbon atoms, alkyl of 1-5 carbon atoms, $-NO_2$, -CN, $-CF_3$, $-COR^{16}$, $-CH_2OR^{17}$, $-NHCOR^{17}$, $CONR^{18}R^{19}$, $S(O)_rR^{17}$, and $SO_2NR^{18}R^{19}$; pyrollyl, pyrazolyl or imidazolyl as defined above substituted on ring nitrogen with alyl of 1-5 carbon atoms or benzyl; or substituted alkyl, alkenyl, or alkynyl of 1 to 10 carbon atoms substituted with a substituted or unsubstituted heteroaryl, biphenylyl or phenoxyphenyl group as defined above; 1- or 2- naphthyl; 5- or 6-naphthoquinonyl; 3-, 4-, or 5-acenaphthyl; 3-, 4-, or 5-acenaphthenyl; 1-, 2- or 9-anthracenyl; 1- or 2-anthraquinonyl; 1-, 2-, 3-, 4-, or 9-phenanthrenyl; 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolinyl; 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinonyl; 2-, 3- ,4-, 5-, 6- or 7-indolyl which can be substituted on ring nitrogen with lower alkyl of 1 to 5 carbon atoms or benzyl; 4-, 5-, 6- or 7-indenyl; 2-, 3-, 4-, 5-, 6- or 7-benzofuryl; 2-, 3-, 4-, 5-, 6- or 7-benzothienyl; 1-, 2-, 3- or 4-dibenzofuryl; 1-, 2-, 3- or 4-dibenzothienyl; 1-, 2-, 3- or 4-fluoenyl; any of the foregoing polycyclic aryl groups substituted with 1 or 2 subsituents selected from halogen, alkoxy of 1-5 carbon atoms, alkyl of 1-5 carbon atoms, $-NO_2$, -CN, $-CF_3$, $-COR^{16}$, $-CH_2OR^{17}$, $-NHCOR^{17}$, $CONR^{18}R^{19}$, $S(O)_rR^{17}$, and $SO_2NR^{18}R^{19}$; the anhydride of 4,5-dicarboxyl-1- or 2-naphthyl; or substituted alkyl of 1 to 10 carbon atoms, alkenyl or alkynyl of 2 to 10 carbon atoms substituted with a substituted or unsubstituted polycyclic aryl group as defined above;

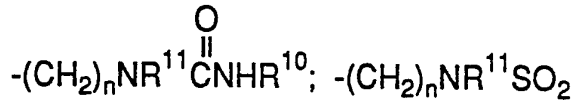
R^8 is H, CN, alkyl of 1 to 10 carbon atoms, alkenyl of 3 to 10 carbon atoms, or the same groups substituted with F; phenylalkenyl wherein the aliphatic portion is 2 to 6 carbon atoms; $-(CH_2)_m$-imidazol-1-yl; $-(CH_2)_m$-1,2,3-triazolyl optionally substituted with one or two groups selected from CO_2CH_3 or alkyl of I to 4 carbon atoms; $-(CH_2)_s$-tetrazolyl;

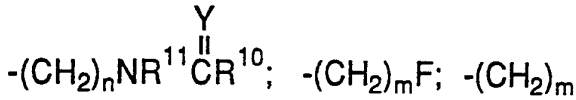


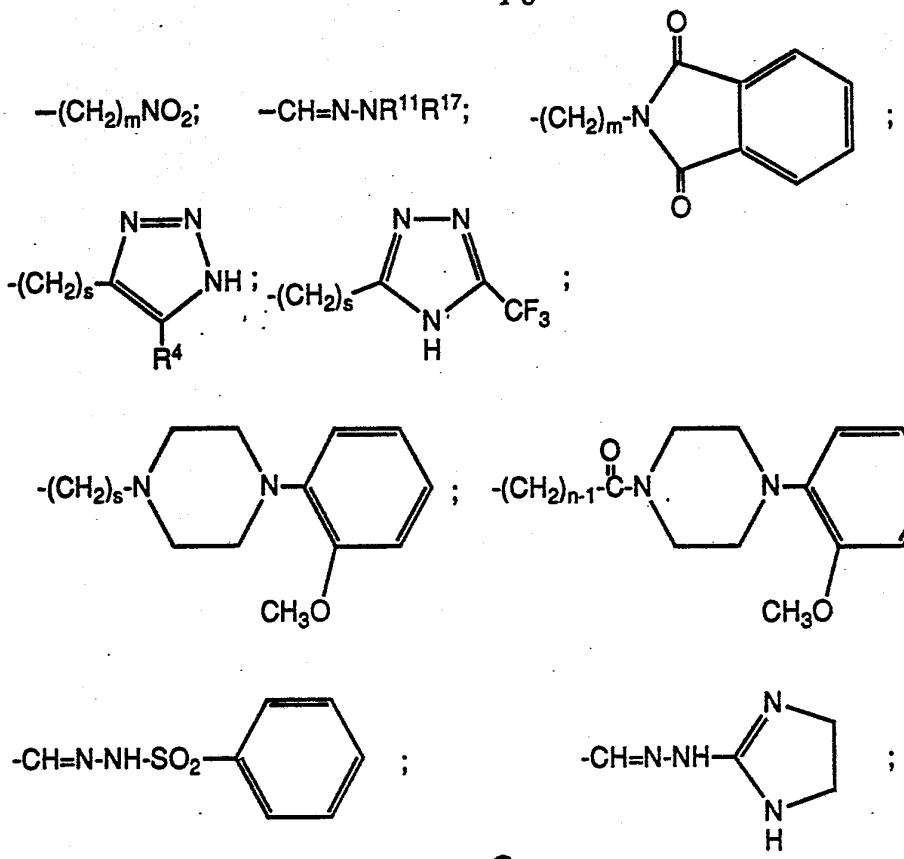












$-(CH_2)_mNO_2$; $-CH=N-NR^{11}R^{17}$;

;

;

;

;

;

;

;

$-(CH_2)_{n-1}CH(OR^{17})-R^{11}$; $-(CH_2)_nOCR^{14}$; $-(CH_2)_nSR^{15}$;

$-CH=CH(CH_2)_sCHOR^{15}$; $-CH=CH(CH_2)_sCR^{16}$; $-CR^{16}$;

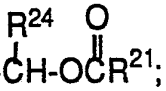
$-CH=CH(CH_2)_sOCR^{11}$; $-(CH_2)_m$-tetrazolyl ;

$-(CH_2)_s-CH(CH_3)-COR^{16}$; $-(CH_2)_nCR^{16}$; $-(CH_2)_nOCHNR^{10}$;

$-(CH_2)_nNR^{11}COR^{10}$; $-(CH_2)_nNR^{11}CNHR^{10}$; $-(CH_2)_nNR^{11}SO_2R^{10}$;

or, $-(CH_2)_nNR^{11}CR^{10}$;

R^9 is;

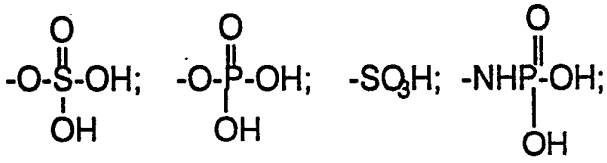


R^{10} is alkyl of 1 to 6 carbon atoms or perfluoroalkyl of 1 to 6 carbon atoms, 1-adamantyl, 1-naphthyl, 1-(1-naphthyl)ethyl, or $(CH_2)_pC_6H_5$;

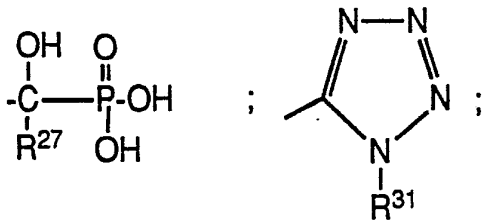
R^{11} is H, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, phenyl or benzyl;

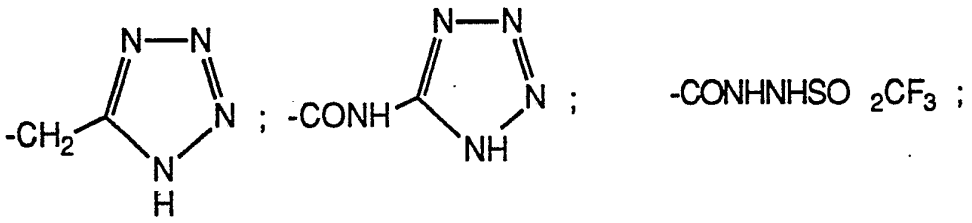
R^{12} is H, methyl or benzyl;

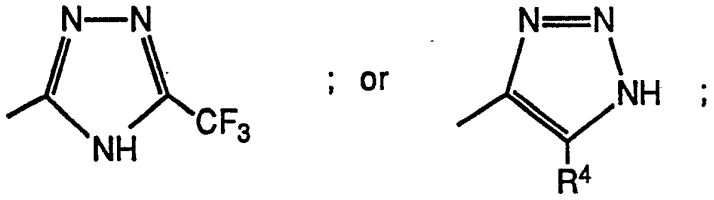
R^{13} is $-CO_2H$; $-CO_2R^9$; $-CH_2CO_2H$, $-CH_2CO_2R^9$;



$-PO_3H$; $-C(CF_3)_2OH$; $-NHSO_2CH_3$; $-NHSO_2CF_3$; $-NHCOCF_3$; $-CONHOR^{12}$; $-SO_2NH_2$;







R^{14} is H, alkyl or perfluoroalkyl of 1 to 8 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, phenyl or benzyl;

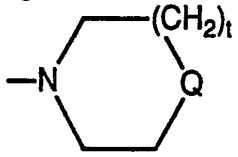
R^{15} is H, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3

to 6 carbon atoms, phenyl, benzyl, acyl of I to 4 carbon atoms, phenacyl;

R^{16} is H, alkyl of I to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, $(CH_2)_pC_6H_5$, OR^{17}, or $NR^{18}R^{19}$;

R^{17} is H, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, phenyl or benzyl;

R^{18} and R^{19} independently are H, alkyl of I to 4 carbon atoms, phenyl, benzyl, a-methylbenzyl, or taken together with the nitrogen form a ring of the formula

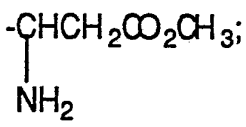


;

Q is NR^{20}, O or CH_2;

R^{20} is H, alkyl of I-4 carbon atoms, or phenyl;

R^{21} is alkyl of 1 to 6 carbon atoms, $-NR^{22}R^{23}$, or

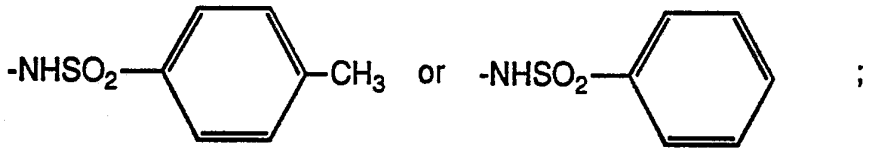


;

R^{22} and R^{23} independently are H, alkyl of 1 to 6 carbon atoms, benzyl, or are taken together as $(CH_2)_u$ where u is 3-6;

R^{24} is H, CH_3 or $-C_6H_5$;

R^{25} is $NR^{27}R^{28}$, OR^{28}, $NHCONH_2$, $NHCSNH_2$,



;

R^{26} is hydrogen, alkyl with from 1 to 6 carbon atoms, benzyl, or allyl;

R^{27} and R^{28} are independently hydrogen, alkyl with from 1 to 5 carbon atoms, or phenyl;

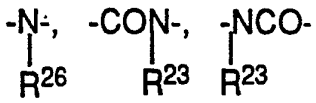
R^{29} and R^{30} are independently alkyl of 1-4 carbon atoms or taken together are $-(CH_2)_q-$;

R^{31} is H, alkyl of 1 to 4 carbon atoms, $-CH_2CH=CH_2$ or

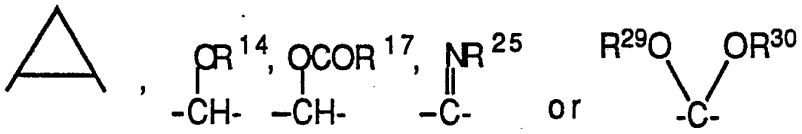
$-CH_2C_6H_4R^{32}$;

R^{32} is H, NO_2, NH_2, OH or OCH_3;

X is a carbon-carbon single bond, -CO-, $-CH_2-$, -O-, -S-, -NH-,



$-OCH_2-$, $-CH_2O-$, $-SCH_2-$, $-CH_2S-$, $NHC(R^{27})(R^{28})$, $-NR^{23}SO_2-$, $-SO_2NR^{23}-$, $-C(R^{27})(R^{28})NH-$, -CH=CH-, -CF=CF-, -CH=CF-, -CF=CH-, $-CH_2CH_2-$, $-CF_2CF_2-$,



Y is O or S;

Z is O, NR^{11}, or S;

m is 1 to 5;

n is 1 to 10;

p is 0 to 3;

q is 2 to 3;

r is 0 to 2;

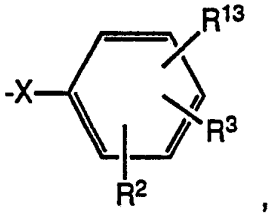
s is 0 to 5;

t is 0 or 1;

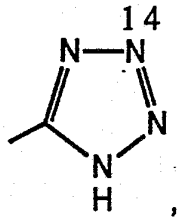
and pharmaceutically acceptable salts of these compounds; provided that:

(1) the R^1 group is not in the ortho position;

(2) when R^1 is

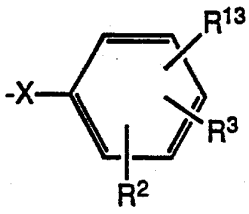


X is a single bond, and R^{13} is CO_2H, or



then R^{13} must be in the ortho or meta position; or when R^1 and X are as above and R^{13} is $NHSO_2CF_3$ or $NHSO_2CH_3$, R^{13} must be ortho;

(3) when R^1 is

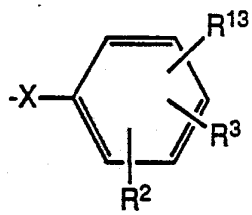


and X is other than a single bond, then R^{13} must be ortho except when X = $NR^{23}CO$ and R^{13} is $NHSO_2CF_3$ or $NHSO_2CH_3$, then R^{13} must be ortho or meta;

(4) when R^1 is 4-CO_2H or a salt thereof, R^6 cannot be S-alkyl;

(5) when R^1 is 4-CO_2H or a salt thereof, the substituent on the 4-position of the imidazole cannot be CH_2OH, CH_2OCOCH_3, or CH_2CO_2H;

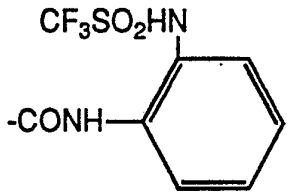
(6) when R^1 is



X is -OCH_2-, and R^{13} is 2-CO_2H, and R^7 is H then R^6 is not C_2H_5S;

(7) when R^1 is

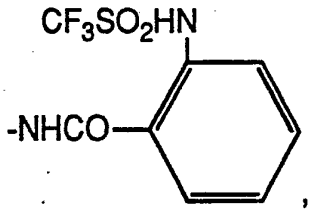
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,

and R^6 is n-hexyl, then R^7 and R^8 are not both hydrogen;

(8) when R^1 is



,

R^6 is not methoxybenzyl;

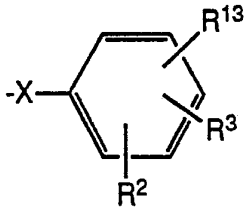
(9) the R^6 group is not -F-$CHCH_2CH_2CH_3$ or CH_2OH;

(10) when r=O, R^1 is

,

X is -NH-C=O, R^{13} is 2-$NHSO_2CF_3$, and R^6 is n-propyl, then R^7 and R^8 are not -CO_2CH_3;

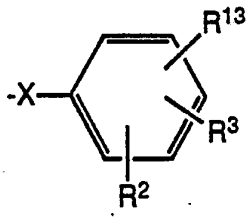
(11) when r=0, R^1 is



,

X is NH-C=O, R^{13} is 2-COOH, and R^6 is n-propyl, then R^7 and R^8 are not -CO_2CH_3;

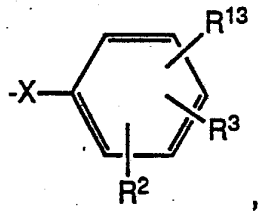
(12) when r=1, R^1=



,

X is a single bond, R^7 is Cl, and R^8 is -CHO, then R^{13} is not 3-(tetrazol-5-yl);

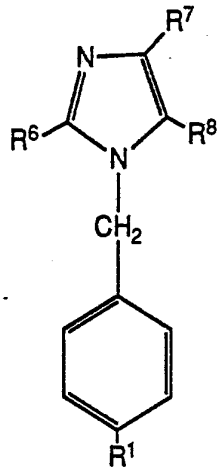
(13) when r=1, R^1=



,

X is a single bond, R^7 is Cl, and R^8 is -CHO, then R^{13} is not 4-(tetrazol-5-yl).

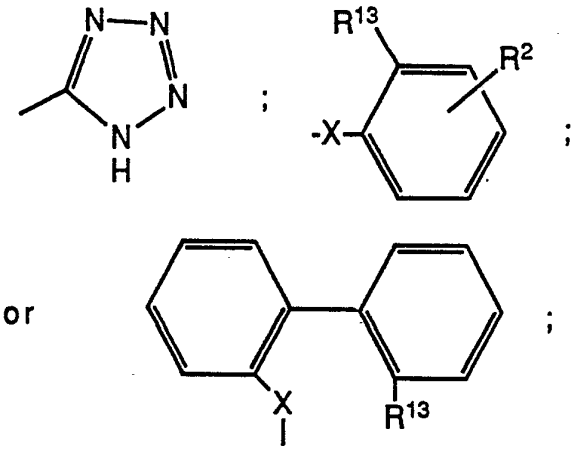
Preferred in the method of this invention are compounds having the formula (II):



(II)

wherein

R^1 is $-CO_2H$; $-NHSO_2CF_3$;



or

R^6 is alkyl of 3 to 10 carbon atoms, alkenyl of 3 to 10 carbon atoms, alkynyl of 3 to 10 carbon atoms, cycloalkyl of 3 to 8 carbon atoms, benzyl substituted on the phenyl ring with up to two groups selected from alkoxy of 1 to 4 carbon atoms, halogen, alkyl of 1 to 4 carbon atoms, and nitro;

R^8 is

$-(CH_2)_s$-tetrazolyl, $-(CH_2)_nOR^{11}$; $-(CH_2)_n OCR^{14}$;

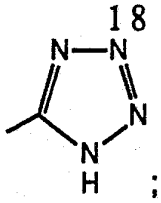
$-CH=CH(CH_2)_sCR^{16}$, $-CH=CH(CH_2)_sCHOR^{15}$;

$-(CH_2)_nCR^{16}$; $-(CH_2)_nNHCOR^{10}$; $-(CH_2)_nNHSO_2R^{10}$;

$-(CH_2)_mF$; or $-CR^{16}$;

phenylalkenyl wherein the aliphatic portion is 2 to 4 carbon atoms; $-(CH_2)_m$-imidazol-l-yl; or $-(CH_2)_m$-1,2,3-triazolyl optionally substituted with one or two groups selected from $-CO_2CH_3$ or alkyl of 1 to 4 carbon atoms;

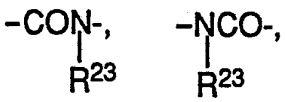
R^{13} is $-CO_2H$, $-CO_2R^9$, $NHSO_2CF_3$; SO_3H; or



;

R^{16} is H, alkyl of 1 to 5 carbon atoms, OR^{17}, or $NR^{18}R^{19}$;

X is carbon-carbon single bond, -CO-, CH_2CH_2-,



-OCH_2-, -CH_2O-, -O-, -SCH_2-, -CH_2S-, -NH-CH_2-, -CH_2NH- or -CH=CH-; and pharmaceutically acceptable salts of these compounds.

More preferred in the process of the invention are compounds of the preferred scope where:

R^2 is H, alkyl of 1 to 4 carbon atoms, halogen, or alkoxy of 1 to 4 carbon atoms;

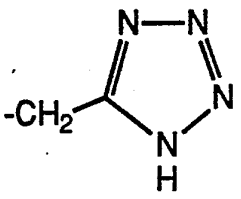
R^6 is alkyl, alkenyl or alkynyl of 3 to 7 carbon atoms;

R^7 is heteroaryl selected from 2- and 3-thienyl, 2- and 3-furyl, 2-, 3-, and 4-pyridyl, p-biphenylyl; H, Cl, Br, I; C_vF_{2v+1}, where v=1-3; $-\overset{O}{\overset{\|}{C}}R^{16}$; straight or branched chain alkyl of 1 to 6 carbon atoms; or phenyl;

R^8 is

$-(CH_2)_mOR^{11}$; $-(CH_2)_mO\overset{O}{\overset{\|}{C}}R^{14}$; $-CH=CH-\overset{R^{14}}{\overset{|}{C}}HOR^{15}$;

$-(CH_2)_m\overset{O}{\overset{\|}{C}}R^{16}$; $-CH_2NHC\overset{O}{\overset{\|}{O}}R^{10}$; $-(CH_2)_mNHSO_2R^{10}$;

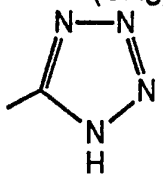


; or $-COR^{16}$;

R^{10} is CF_3, alkyl of I to 6 carbon atoms or phenyl;

R^{11} is H, or alkyl of 1 to 4 carbon atoms;

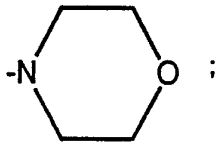
R^{13} is CO_2H; $CO_2CH_2OCOC(CH_3)_3$; $NHSO_2CF_3$;



R^{14} is H, or alkyl of I to 4 carbon atoms;

R^{15} is H, alkyl of I to 4 carbon atoms, or acyl of I to 4 carbon atoms;

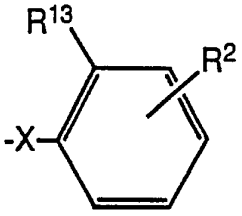
R^{16} is H, alkyl of 1 to 5 carbon atoms; OR^{17}; or



m is I to 5;

X = single bond, -O-; -CO-; -NHCO-; or $-OCH_2-$; and pharmaceutically acceptable salts.

More preferred in the method of the invention are compounds of Formula II, wherein R^1 is



and X is a single bond; and pharmaceutically suitable salts thereof.

Most preferred in the method of the invention are compounds of formula II selected from the following; and pharmaceutically acceptable salts thereof.

- 2-Butyl-4-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-5-(hydroxymethyl)imidazole.
- 2-Butyl-4-chloro-1-[(2'-carboxybiphenyl-4-yl)-methyl]-5-(hydroxymethyl)imidazole.
- 2-Butyl-4-chloro-1-[(2'-carboxybiphenyl-4-

yl)-methyl]-5-[(methoxycarbonyl)aminomethyl] imidazole.

- 2-Butyl-4-chloro-1-[(2'-carboxybiphenyl-4-yl)-methyl]-5-[(propoxycarbonyl)aminomethyl] imidazole.
- 2-Butyl-4-chloro-1-[(2'-carboxybiphenyl-4-yl) methyl]imidazole-5-carboxaldehyde.
- 2-Butyl-1-[(2'-carboxybiphenyl-4-yl)methyl]-imidazole-5-carboxaldehyde.
- 2-(1E-Butenyl)-4-chloro-1-[(2'-carboxybiphenyl-4-yl)methyl]-5-(hydroxymethyl)imidazole.
- 2-(1E-Butenyl)-4-chloro-1-[(2'-carboxybiphenyl-4-yl)methyl]imidazole-5-carboxaldehyde.
- 2-Propyl-4-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-5-(hydroxymethyl) imidazole.
- 2-Propyl-4-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxaldehyde.
- 2-Butyl-4-chloro-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxaldehyde.
- 2-(1E-Butenyl)-4-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-5-hydroxymethyl)imidazole.
- 2-(1E-Butenyl)-4-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxaldehyde.
- 2-Butyl-4-chloro-1-[(2'-(1H-tetrazol-5-yl)-biphenyl-4-yl)methyl]imidazole-5-carboxylic acid.
- 2-Propyl-4-chloro-1-[(2'-(1H-tetrazol-5-yl)-biphenyl-4-yl)methyl]imidazole-5-carboxylic acid.
- 2-Propyl-4-trifluoromethyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxylic acid.
- 2-Propyl-4-trifluoromethyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-5-(hydroxylmethyl)-imidazole.
- 2-Butyl-4-trifluoromethyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboyxlic acid.
- 2-Propyl-4-trifluoromethyl-1-[(2'-(carboxybiphenyl-4-yl)methyl]imidazole-5-carboxaldehyde.

- 2-Propyl-4-pentafluoroethyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-5-(hydroxymethyl)-imidazole.
- 2-Propyl-4-pentafluoroethyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxylic acid.
- 2-Propyl-4-pentafluoroethyl-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxaldehyde.
- 1-[(2'-(1H-Tetrazol-5-yl)biphenyl-4-yl)methyl]-4-phenyl-2-propylimidazole-5-carboxaldehyde
- 1-[(2'-Carboxybiphenyl-4-yl)methyl]-4-phenyl-2-propylimidazole-5-carboxaldehyde

Note that throughout the text when an alkyl substituent is mentioned, the normal alkyl structure is meant (i.e., butyl is n-butyl) unless otherwise specified.

Pharmaceutically suitable salts include both the metallic (inorganic) salts and organic salts; a list of which is given in Remington's Pharmaceutical Sciences, 17th Edition, pg. 1418 (1985). It is well known to one skilled in the art that an appropriate salt form is chosen based on physical and chemical stability, flowability, hydroscopicity and solubility. Prefered salts of this invention for the reasons cited above include potassium, sodium, calcium and ammonium salts.

Also within the scope of this invention are methods of using pharmaceutical compositions comprising a suitable pharmaceutical carrier and a compound of Formula (I), to treat CNS disorders. The pharmaceutical compositions can optionally contain one or more other therapeutic agents.

It should be noted in the foregoing structural formula, when a radical can be a substituent in more than one previously defined radical, that first radical can be selected independently in each previously defined radical. For example, R^1, R^2 and R^3 can each be $CONHOR^{12}$. R^{12} need not be the same substituent in each of R^1, R^2 and R^3 but can be selected independently for each of them.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of Formula (I) useful in this invention are described in and prepared by methods set forth in European Patent Application EPA 0 324 377, published 7/19/89, (page 17, line 5 through page 212, line 32), copending commonly-assigned U.S. patent application USSN 07/375069, filed 6/30/89, (page 16, line 21 through page 133, line 35), and copending commonly-assigned U.S. patent application USSN 07/373,755, filed 6/30/89, (page 16, line 21 through page 153, line 15), the disclosures of which are hereby incorporated by reference.

Two distinct angiotensin II (AII) receptor subtypes have been discovered and characterized by means of the discriminatory effect of dithiothreitol (DTT) and by two structurally dissimilar nonpeptide AII receptor antagonists, denoted as DuP 753 and EXP655, which show reciprocal selectivity for the two subtypes (Chiu et al., Biochem. and Biophys. Res. Comm. (1989)165:196-203). DuP 753 is 2-n-butyl-4-chloro-5-hydroxymethyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-imidazole (Example 89 of European Published Application EPA 0 324 377). EXP655 is 1-(4-amino-3-methylphenyl)methyl-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylic acid (Example 13 of EPA 0 245 637).

Using radioligand-receptor binding techniques, DuP 753 was found to be highly specific for an AII receptor site, desiginated AII receptor subtype-1 or AII-1, displaying an inhibitory constant IC_{50} value of about 1.2×10^{-8} M in rat adrenal cortex. This type of AII receptor was particularly sensitive to inactivation by DTT. EXP655 exhibited very low affinity for the AII-1 site (IC_{50} value of about 3.0×10^{-4} M), but was highly selective for a distinct AII receptor site, designated AII receptor subtype-2 or AII-2, exhibiting an inhibitory constant IC_{50} value of about 1.0×10^{-7} M in rat

adrenal cortex. In contrast to the AII-1 receptor, the AII-2 receptor was resistant to DTT inactivation. Moreover, DuP 753 had very low affinity for the AII-2 receptor (IC_{50} of about 1.4 x 10^{-4} M).

The rat adrenal medulla contains a relatively high density of AII receptors which are predominately the AII-2 subtype, as reported in the Chiu et al. paper.

Whitebread et al., Biochem. and Biophys. Res. Comm. (1989) 163:284-291, also reports the discovery of two AII receptor subtypes.

The compounds of Formula (I) above (which includes DuP 753) block the AII-1 receptor subtype. Compounds of Formula (I) above wherein R^7 or R^8 at the 4-position on the imidazole ring is phenyl, phenylalkyl, phenylalkenyl, phenylalkynyl, substituted phenyl, substituted phenylalkyl, substituted phenylalkenyl or substituted phenylalkynyl, block both the AII-1 and the AII-2 receptor subtypes. For example, Compounds A and B identified below show affinity for both AII-1 and AII-2 receptors in the tests described in the Chiu et al. paper. Compound A (Example 324A of EPA 0 324 377) is 1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-4-phenyl-2-propylimidazole-5-carboxaldehyde. Compound B (Example 322 of EPA 0 324 377) is 1-[(2'-carboxybiphenyl-4-yl)methyl]-4-phenyl-2-propylimidazole-5-carboxaldehyde. The results obtained in the tests for receptor specificity are summarized in Table I:

Table 1

Antagonist Specificity Exhibited by AII Receptor Subtypes

Compound	IC_{50} (M) AII-1	AII-2
AII	1.5×10^{-9}	0.6×10^{-9}
Saralasin	0.7×10^{-9}	0.3×10^{-9}
DuP 753	1.9×10^{-8}	5.8×10^{-5}
EXP655	3.0×10^{-4}	2.8×10^{-8}
Compound A	2.2×10^{-8}	2.4×10^{-6}
Compound B	2.9×10^{-7}	4.3×10^{-6}

AII-1 site binding was determined using adrenal cortex microsomes in the presence of 10^{-5} M EXP655. AII-2 site binding was determined using adrenal medulla microsomes in the presence of 10^{-5} M DuP 753. IC_{50} was determined by displacement of [^{125}I]AII from the receptor by the indicated compound.

Using procedures described by Bennett and Snyder (1976) J. Biol. Chem. 254:7423-7430, we have discovered that the rat brain also contains a high density of AII receptors which are predominately the AII-2 subtype. EXP655 displaced the [^{125}I]AII binding in rat brain membranes in a concentration-dependent manner yielding IC_{50} value of 3.2×10^{-7} M. In contrast, DuP 753 displaced the binding of AII inefficiently, with an IC_{50} value of 1.5×10^{-4} M.

The distribution of AII-1 and AII-2 receptors in certain regions of the brain was determined by the binding of AII antagonists to different sections of brain slices. The results indicate that there are clusters of DTT-sensitive, DuP 753-sensitive AII binding sites (AII-1 receptors) in the brain; however, the majority of binding sites in the brain are DTT-insensitive and EXP655-sensitive, corresponding to AII-2 receptors.

Despite a high density of AII-2 binding sites in the brain, AII-1 receptor antagonists prevent amnesia induced by renin, as shown by the results in the renin-disrupted passive avoidance retention test described below. These results indicate that AII-1 receptor antagonists, such as the compounds of Formula (I), are useful for treatment of CNS disorders,such as learning disorders, cognitive disfunction, schizophrenic polydipsia, centrally induced hypertension, diabetic nephropathy, and excessive milk production. Compound C is the sodium salt of 2-n-propyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-4-trifluoromethylimidazole-5-carboxylic acid (Example 265A of EPA 0 324 377) . Compound D is the sodium salt of 2-n-propyl-5-hydroxymethyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-4-trifluoromethylimidazole (Example 124D of EPA 0 324 377). Both Compounds C and D are AII-1 receptor antagonists.

RENIN-DISRUPTED PASSIVE AVOIDANCE RETENTION

Experimentally naive male Sprague-Dawley rats 100 to 125 days old (Charles River Breeding Laboratories, Kingston, NY), weighing between 175 to 200 gm were used. The animals were housed four per cage (45.0 L x 20.0 H x 26.0 W cm) with free access to food and water. They were maintained on a 12 h light/dark cycle (lights on 0600 h) and at a room temperature of 22 ± 1° C with relative humidity of 50 ± 10 %.

The experimental sessions were conducted in a two-compartment passive avoidance box. One compartment, made of clear plastic with a perforated clear plastic floor, measured 21(L) x 24.5(H) x 17(W) cm and was illuminated with a 60 watt incandescent light bulb placed 36 cm above the floor. The other compartment, made of black plastic, measured 30.5 (L) x 20.3 (H) x 21.5 (W) cm with a floor made of 4 mm stainless steel rods spaced 1.2 cm apart. A grid floor shocker (Coulbourn Instruments) was connected to the steel rods and

provided scrambled footshock. The two compartments were separated by a solenoid-operated slide door (Lafayette Instrument Co., Lafayette, IN). An electronic counter (Coulbourn Instruments), triggered by the opening or closing of the slide door, recorded acquisition and retention latencies (latencies were defined as the time it took an animal to enter the dark compartment).

Passive avoidance training began by placing the rat into the clear compartment of the two-compartment passive avoidance box. Following a 10 sec delay, the slide door to the dark compartment was raised. Once the rat moved completely into the dark compartment (all four paws on the shock grid floor) the slide door was lowered, and after a 10 sec. delay, a 1.0 mA shock was applied to the grid floor for three sec. A second three s shock was delivered after an additional 10 sec delay. The rats were immediately removed from the dark compartment and returned to their home cage. A retention test was given 24 h later. It proceeded in the same manner as the training session except that no shock was applied to the grid floor when the rats were provided access to the dark compartment for a maximum of 300 sec.

Renin at 0.1 to 5 µg/5µL (Sigma Chemicals), and EXP655 at 0.1-100 µg/5µL were dissolved in 0.85% saline solution. All drugs were administered IVT 60 minutes prior to acquisition training in a volume of 5 µl. Doses are expressed as the free base weight of each compound.

Renin injected IVT produces a reliable memory deficit in rats (Table 2). Two AII-1 receptor antagonists, Compounds C and D, when co-administered with renin protected against the amnesia (Tables 3 and 4). EXP655, an AII-2-specific antagonist, was much less effective in preventing the amnesia (Table 5).

TABLE 2

Renin-induced Disruption of Passive Avoidance Retention

[renin], (µg/5µL IVT)	Median Retention Latency, (sec)
0	300
0.1	254
0.5	117
1.0	27
3.0	56.5
5.0	17

TABLE 3

Compound C Blocks Renin-induced Disruption of Passive Avoidance Retention

[renin], (µg/5µL IVT)	[Example 5], (µg/5µL IVT)	Median Retention Latency, (sec)
0	0	300
1.0	0	48
1.0	10	264
1.0	30	300
1.0	100	34.5

TABLE 4

Compound D Blocks Renin-induced Disruption of Passive Avoidance Retention

[renin], (µg/5µL IVT)	[Example 6], (µg/5µL IVT)	Median Retention Latency, (sec)
0	0	300
1.0	0	32
1.0	30	242
1.0	100	10

TABLE 5

Effects of EXP655 On
Renin-induced Disruption
of Passive Avoidance Retention

[renin], (ug/5uL IVT)	[Example 2], (ug/5uL IVT)	Median Retention Latency, (sec)
0	0	300
1.0	0	15.5
1.0	0.1	19
1.0	0.3	22
1.0	1.0	15
1.0	3.0	29
1.0	10	15
1.0	30	67
1.0	100	16

DOSAGE FORMS

The compounds of this invention can be administered for the treatment of AII-mediated CNS disorders according to the invention by any means that effects contact of the active ingredient compound with the site of action, i.e., the CNS, in the body of a warm-blooded animal. For example, administration can be parenteral, i.e., subcutaneous, intravenous, intramuscular, or intra peritoneal. Alternatively, or concurrently, in some cases administration can be by the oral route.

The compounds can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be administered alone, but are generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

For the purpose of this disclosure, a warm-blooded animal is a member of the animal kingdom possessed of a homeostatic mechanism and includes mammals and birds.

The dosage administered will be dependent on the age, health and weight of the recipient, the extent of disease, kind of concurrent treatment, if any, frequency of treatment and the nature of the effect desired. Usually, a daily dosage of active ingredient compound will be from about 1-500 milligrams per day. Ordinarily, from 10 to 100 milligrams per day in one or more applications is effective to obtain desired results.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs syrups, and suspensions. It can also be administered parenterally, in sterile liquid dosage forms.

Gelatin capsules contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as

sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propylparaben, and chlorobutanol.

Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, A. Osol, a standard reference text in this field.

Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules:

A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

Soft Gelatin Capsules:

A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules are washed and dried.

Tablets:

A large number of tablets are prepared by conventional procedures so that the dosage unit is 100 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

Injectable:

A parenteral composition suitable for administration by injection is prepared by stirring 1.5% by weight of active

ingredient in 10% by volume propylene glycol. The solution is made to volume with water for injection and sterilized.

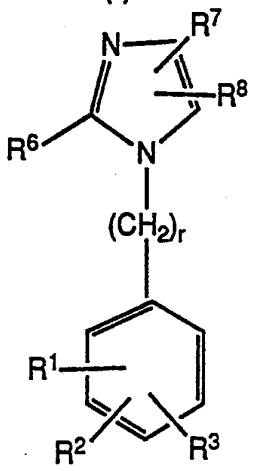
Suspension:

An aqueous suspension is prepared for oral administration so that each 5 milliliters contain 100 milligrams of finely divided active ingredient, 100 milligrams of sodium carboxymethyl cellulose, 5 milligrams of sodium benzoate, 1.0 grams of sorbitol solution, U.S.P., and 0.025 milliliters of vanillin.

The same dosage forms can generally be used when the compounds of this invention are administered stepwise in conjunction with another therapeutic agent. When the drugs are administered in physical combination, the dosage form and administration route should be selected for compatibility with both drugs.

CLAIMS:

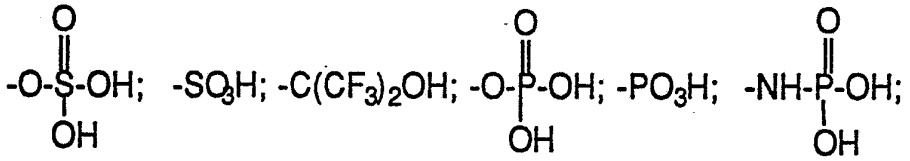
1. A method of treating a central nervous system (CNS) disorder mediated by AII in a mammal, comprising administering to the mammal an effective amount of a compound having the formula (I):



(I)

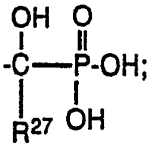
wherein

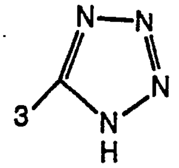
R^1 is 4-CO_2H; 4-CO_2R^9;



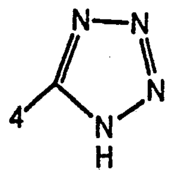
4-$NHSO_2CH_3$; -4-$NHSO_2CF_3$; -$CONHOR^{12}$;

$-SO_2NH_2$;

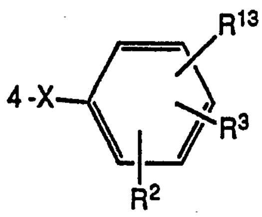




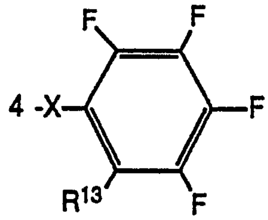
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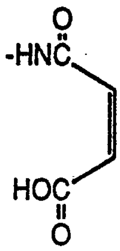
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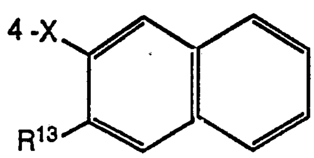
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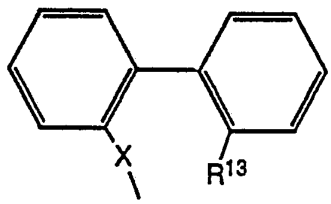
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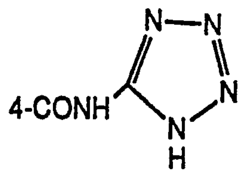
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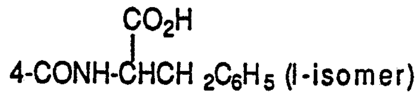


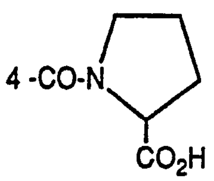
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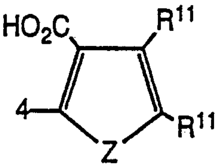
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4-CONHNHSO $_2CF_3$;

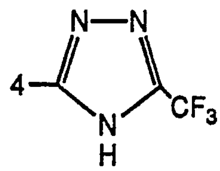




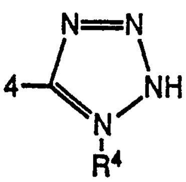
(l-isomer);



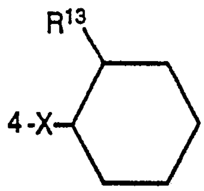
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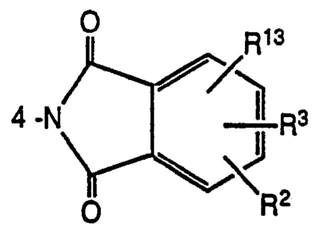
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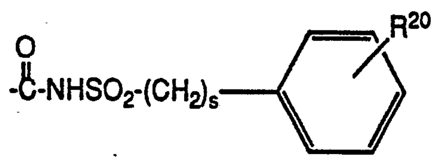


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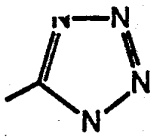
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or



;

R^2 is H; Cl; Br; I; F; NO_2; CN; alkyl of 1 to 4 carbon atoms; acyloxy of 1 to 4 carbon atoms; alkoxy of 1 to 4 carbon atoms; CO_2H; CO_2R^9; $NHSO_2CH_3$; $NHSO_2CF_3$; $CONHOR^{12}$; SO_2NH_2;



; aryl; or furyl;

R^3 is H; Cl, Br, I or F; alkyl of 1 to 4 carbon atoms or alkoxy of 1 to 4 carbon atoms;

R^4 is CN, NO_2 or CO_2R^{11};

R^5 is H, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, alkenyl or alkynyl of 2 to 4 carbon atoms;

R^6 is alkyl of 2 to 10 carbon atoms, alkenyl or alkynyl of 3 to 10 carbon atoms or the same groups substituted with F or CO_2R^{14}; cycloalkyl of 3 to 8 carbon atoms, cycloalkylalkyl of 4 to 10 carbon atoms; cycloalkylalkenyl or cycloalkylalkynyl of 5 to 10 carbon atoms; $(CH_2)_sZ(CH_2)_mR^5$ optionally substituted with F or CO_2R^{14}; benzyl or benzyl substituted on the phenyl ring with 1 or 2 halogens, alkoxy of 1 to 4 carbon atoms, alkyl of 1 to 4 carbon atoms or nitro;

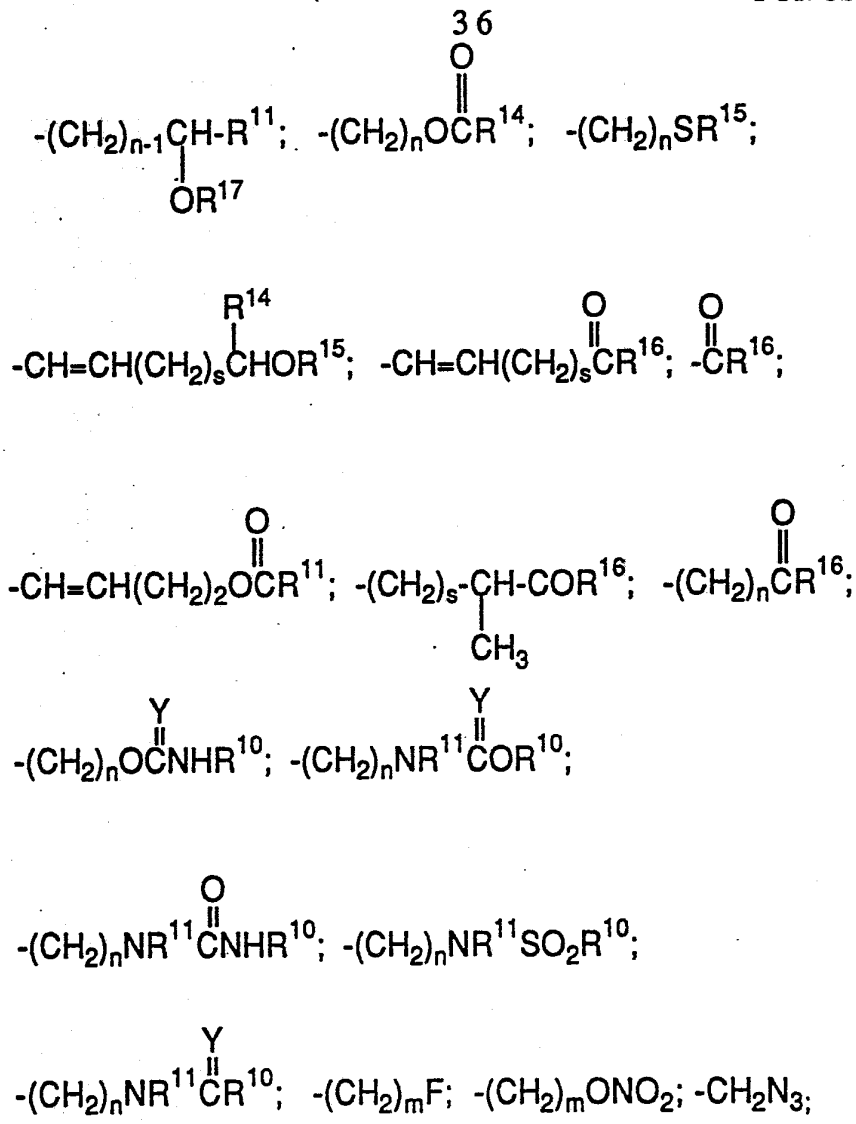
R^7 is H, F, Cl, Br, I, NO_2, C_vF_{2v+1}, where v = 1-6; C_6F_5; CN;

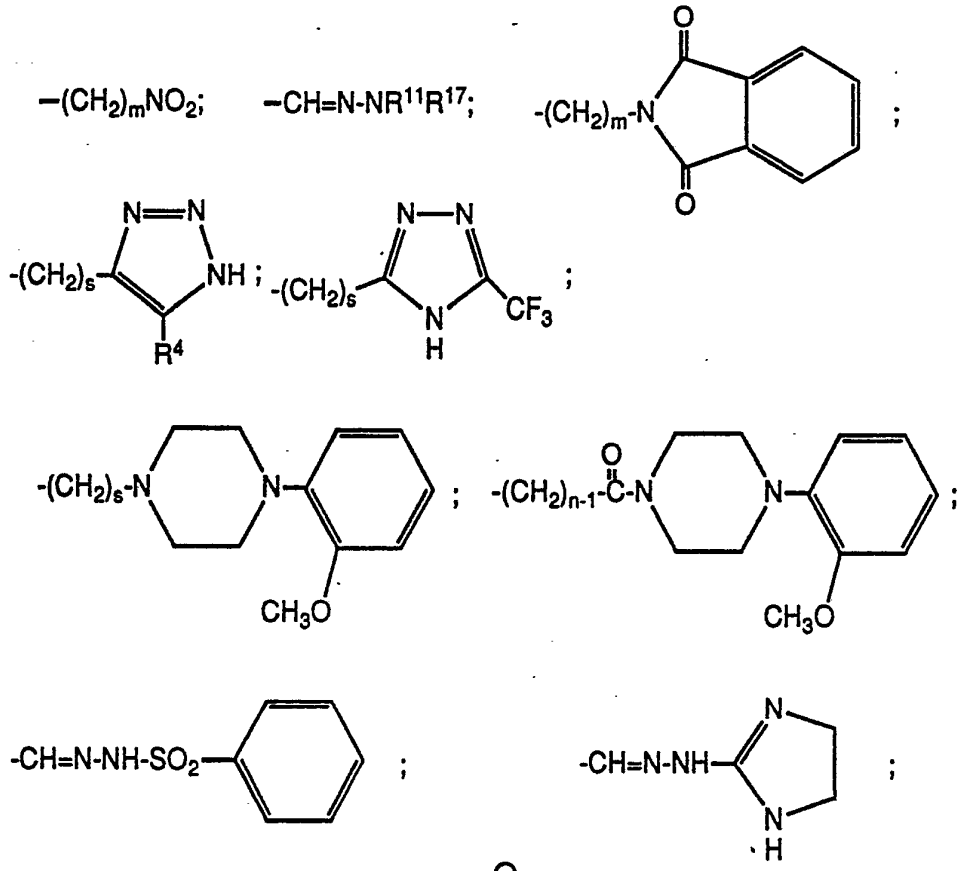
$$-\overset{O}{\overset{\|}{C}}R^{16}\ ;$$

straight or branched alkyl of 1 to 6 carbon atoms; phenyl or phenylalkyl, where alkyl is 1 to 3 carbon atoms; or substituted phenyl or substituted phenylalkyl, where alkyl is 1 to 3 carbon atoms, substituted with one or two substituents selected from alkyl of 1 to 4 carbon atoms, F, Cl, Br, OH, OCH_3, CF_3, and COOR, where R is H, alkyl of 1 to 4 carbon atoms, or phenyl; vinyl; alkynyl of 2-10 carbon atoms; phenylalkynyl where the alkynyl portion if 2-6 carbon atoms; heteroaryl selected from 2- and 3-thienyl, 2- and 3-furyl, 2-, 3-, and 4-pyridyl, 2-pyrazinyl, 2-, 4-, and 5-pyrimidinyl, 3- and 4-pyridainyl, 2-, 4- and 5-thiazolyl, 2-, 4-, and 5-selenazolyl, 2-, 4-, and 5-oxazolyl; 2- or 3-pyrrolyl, 3-, 4- or 5-pyrazolyl, and 2-, 4- or 5-imidazolyl; o-, m- or p-biphenylyl; o-, m- or p-phenoxyphenyl; substituted phenylalkynyl, heteroaryl, biphenylyl or phenoxphenyl as defined above substituted on

ring carbon with 1 or 2 substituents selected from halogen, alkoxy of 1-5 carbon atoms, alkyl of 1-5 carbon atoms, $-NO_2$, -CN, $-CF_3$, $-COR^{16}$, $-CH_2OR^{17}$, $-NHCOR^{17}$, $CONR^{18}R^{19}$, $S(O)_rR^{17}$, and $SO_2NR^{18}R^{19}$; pyrollyl, pyrazolyl or imidazolyl as defined above substituted on ring nitrogen with alyl of 1-5 carbon atoms or benzyl; or substituted alkyl, alkenyl, or alkynyl of 1 to 10 carbon atoms substituted with a substituted or unsubstituted heteroaryl, biphenylyl or phenoxyphenyl group as defined above; 1- or 2- naphthyl; 5- or 6-naphthoquinonyl; 3-, 4-, or 5-acenaphthyl; 3-, 4-, or 5-acenaphthenyl; 1-, 2- or 9-anthracenyl; 1- or 2-anthraquinonyl; 1-, 2-, 3-, 4-, or 9-phenanthrenyl; 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolinyl; 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinonyl; 2-, 3- ,4-, 5-, 6- or 7-indolyl which can be substituted on ring nitrogen with lower alkyl of 1 to 5 carbon atoms or benzyl; 4-, 5-, 6- or 7-indenyl; 2-, 3-, 4-, 5-, 6- or 7-benzofuryl; 2-, 3-, 4-, 5-, 6- or 7-benzothienyl; 1-, 2-, 3- or 4-dibenzofuryl; 1-, 2-, 3- or 4-dibenzothienyl; 1-, 2-, 3- or 4-fluoenyl; any of the foregoing polycyclic aryl groups substituted with 1 or 2 subsituents selected from halogen, alkoxy of 1-5 carbon atoms, alkyl of 1-5 carbon atoms, $-NO_2$, -CN, $-CF_3$, $-COR^{16}$, $-CH_2OR^{17}$, $-NHCOR^{17}$, $CONR^{18}R^{19}$, $S(O)_rR^{17}$, and $SO_2NR^{18}R^{19}$; the anhydride of 4,5-dicarboxyl-1- or 2-naphthyl; or substituted alkyl of 1 to 10 carbon atoms, alkenyl or alkynyl of 2 to 10 carbon atoms substituted with a substituted or unsubstituted polycyclic aryl group as defined above;

R^8 is H, CN, alkyl of 1 to 10 carbon atoms, alkenyl of 3 to 10 carbon atoms, or the same groups substituted with F; phenylalkenyl wherein the aliphatic portion is 2 to 6 carbon atoms; $-(CH_2)_m$-imidazol-1-yl; $-(CH_2)_m$-1,2,3-triazolyl optionally substituted with one or two groups selected from CO_2CH_3 or alkyl of I to 4 carbon atoms; $-(CH_2)_s$-tetrazolyl;





$-(CH_2)_mNO_2$; $-CH=N-NR^{11}R^{17}$;

$-(CH_2)_m-N$;

$-(CH_2)_s$;

$-(CH_2)_s$;

$-(CH_2)_s-N$;

$-(CH_2)_{n-1}-C-N$;

$-CH=N-NH-SO_2$;

$-CH=N-NH$;

$-(CH_2)_{n-1}CH(OR^{17})-R^{11}$; $-(CH_2)_nOCR^{14}$; $-(CH_2)_nSR^{15}$;

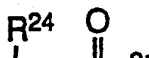
$-CH=CH(CH_2)_sCHOR^{15}$; $-CH=CH(CH_2)_sCR^{16}$; $-CR^{16}$;

$-CH=CH(CH_2)_sOCR^{11}$; $-(CH_2)_m$-tetrazolyl ;

$-(CH_2)_s-CH(CH_3)-COR^{16}$; $-(CH_2)_nCR^{16}$; $-(CH_2)_nOCHNR^{10}$;

$-(CH_2)_nNR^{11}COR^{10}$; $-(CH_2)_nNR^{11}CNHR^{10}$; $-(CH_2)_nNR^{11}SO_2R^{10}$;

or, $-(CH_2)_nNR^{11}CR^{10}$;



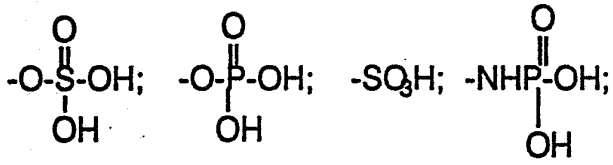
R^9 is -CH-OCR^{21};

R^{10} is alkyl of 1 to 6 carbon atoms or perfluoroalkyl of 1 to 6 carbon atoms, 1-adamantyl, 1-naphthyl, 1-(1-naphthyl)ethyl, or $(CH_2)_pC_6H_5$;

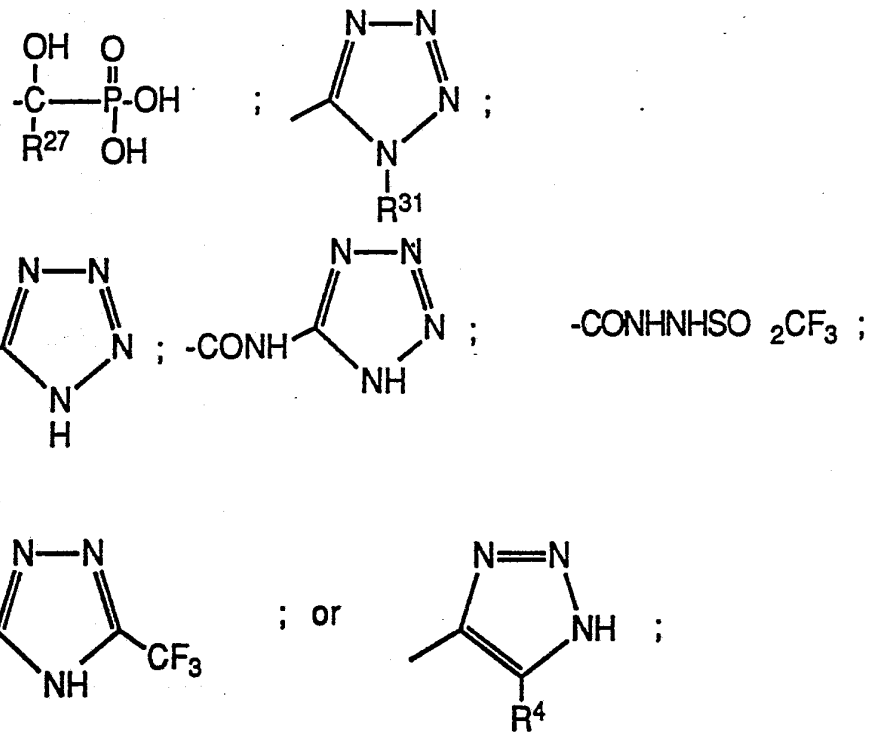
R^{11} is H, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, phenyl or benzyl;

R^{12} is H, methyl or benzyl;

R^{13} is $-CO_2H$; $-CO_2R^9$; $-CH_2CO_2H$, $-CH_2CO_2R^9$;



$-PO_3H$; $-C(CF_3)_2OH$; $-NHSO_2CH_3$; $-NHSO_2CF_3$; $-NHCOCF_3$; $-CONHOR^{12}$; $-SO_2NH_2$;



R^{14} is H, alkyl or perfluoroalkyl of 1 to 8 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, phenyl or benzyl;

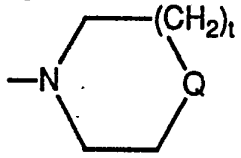
R^{15} is H, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3

to 6 carbon atoms, phenyl, benzyl, acyl of 1 to 4 carbon atoms, phenacyl;

R^{16} is H, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, $(CH_2)_pC_6H_5$, OR^{17}, or $NR^{18}R^{19}$;

R^{17} is H, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, phenyl or benzyl;

R^{18} and R^{19} independently are H, alkyl of 1 to 4 carbon atoms, phenyl, benzyl, a-methylbenzyl, or taken together with the nitrogen form a ring of the formula

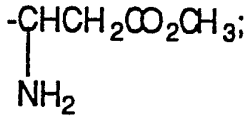


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Q is NR^{20}, O or CH_2;

R^{20} is H, alkyl of 1-4 carbon atoms, or phenyl;

R^{21} is alkyl of 1 to 6 carbon atoms, $-NR^{22}R^{23}$, or

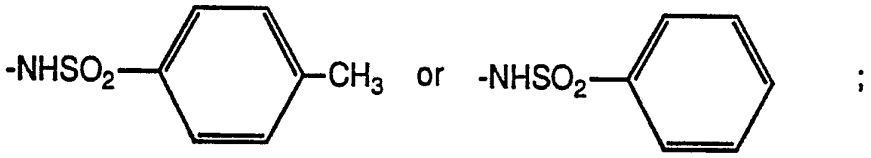


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R^{22} and R^{23} independently are H, alkyl of 1 to 6 carbon atoms, benzyl, or are taken together as $(CH_2)_u$ where u is 3-6;

R^{24} is H, CH_3 or $-C_6H_5$;

R^{25} is $NR^{27}R^{28}$, OR^{28}, $NHCONH_2$, $NHCSNH_2$,



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R^{26} is hydrogen, alkyl with from 1 to 6 carbon atoms, benzyl, or allyl;

R^{27} and R^{28} are independently hydrogen, alkyl with from 1 to 5 carbon atoms, or phenyl;

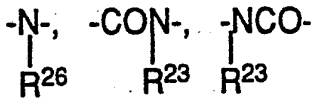
R^{29} and R^{30} are independently alkyl of 1-4 carbon atoms or taken together are $-(CH_2)_q-$;

R^{31} is H, alkyl of 1 to 4 carbon atoms, $-CH_2CH=CH_2$ or

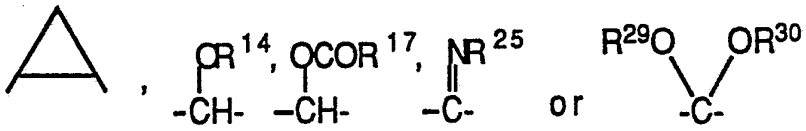
$-CH_2C_6H_4R^{32}$;

R^{32} is H, NO_2, NH_2, OH or OCH_3;

X is a carbon-carbon single bond, -CO-, $-CH_2-$, -O-, -S-, -NH-,



$-OCH_2-$, $-CH_2O-$, $-SCH_2-$, $-CH_2S-$, $NHC(R^{27})(R^{28})$, $-NR^{23}SO_2-$, $-SO_2NR^{23}-$, $-C(R^{27})(R^{28})NH-$, -CH=CH-, -CF=CF-, -CH=CF-, -CF=CH-, $-CH_2CH_2-$, $-CF_2CF_2-$,



Y is O or S;

Z is O, NR^{11}, or S;

m is 1 to 5;

n is 1 to 10;

p is 0 to 3;

q is 2 to 3;

r is 0 to 2;

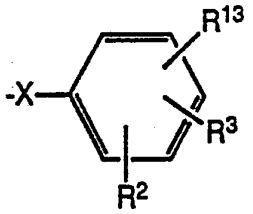
s is 0 to 5;

t is 0 or 1;

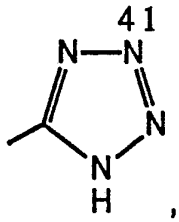
or a pharmaceutically acceptable salt thereof; provided that:

(1) the R^1 group is not in the ortho position;

(2) when R^1 is

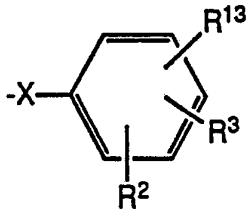


X is a single bond, and R^{13} is CO_2H, or



then R^{13} must be in the ortho or meta position; or when R^1 and X are as above and R^{13} is $NHSO_2CF_3$ or $NHSO_2CH_3$, R^{13} must be ortho;

(3) when R^1 is

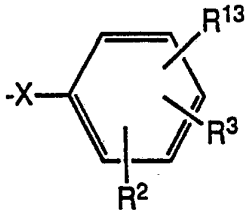


and X is other than a single bond, then R^{13} must be ortho except when X = $NR^{23}CO$ and R^{13} is $NHSO_2CF_3$ or $NHSO_2CH_3$, then R^{13} must be ortho or meta;

(4) when R^1 is 4-CO_2H or a salt thereof, R^6 cannot be S-alkyl;

(5) when R^1 is 4-CO_2H or a salt thereof, the substituent on the 4-position of the imidazole cannot be CH_2OH, CH_2OCOCH_3, or CH_2CO_2H;

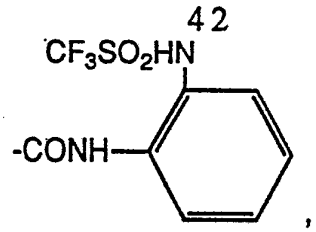
(6) when R^1 is



X is $-OCH_2-$, and R^{13} is 2-CO_2H, and R^7 is H then R^6 is not C_2H_5S;

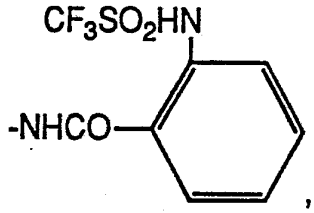
(7) when R^1 is

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and R^6 is n-hexyl, then R^7 and R^8 are not both hydrogen;

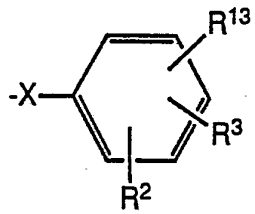
(8) when R^1 is



R^6 is not methoxybenzyl;

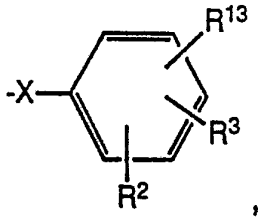
(9) the R^6 group is not -F-$CHCH_2CH_2CH_3$ or CH_2OH;

(10) when r=O, R^1 is



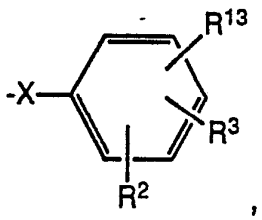
X is -NH-C=O, R^{13} is 2-$NHSO_2CF_3$, and R^6 is n-propyl, then R^7 and R^8 are not -CO_2CH_3;

(11) when r=0, R^1 is



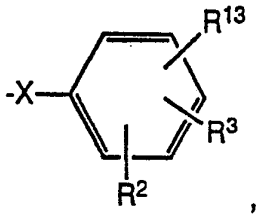
X is NH-C=O, R^{13} is 2-COOH, and R^6 is n-propyl, then R^7 and R^8 are not -CO_2CH_3;

(12) when r=1, R^1=



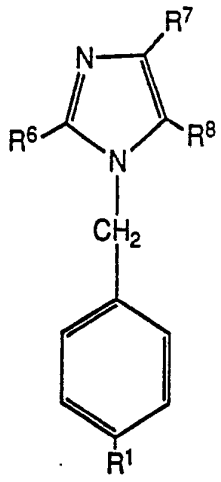
X is a single bond, R^7 is Cl, and R^8 is -CHO, then R^{13} is not 3-(tetrazol-5-yl);

(13) when r=1, R^1=



X is a single bond, R^7 is Cl, and R^8 is -CHO, then R^{13} is not 4-(tetrazol-5-yl).

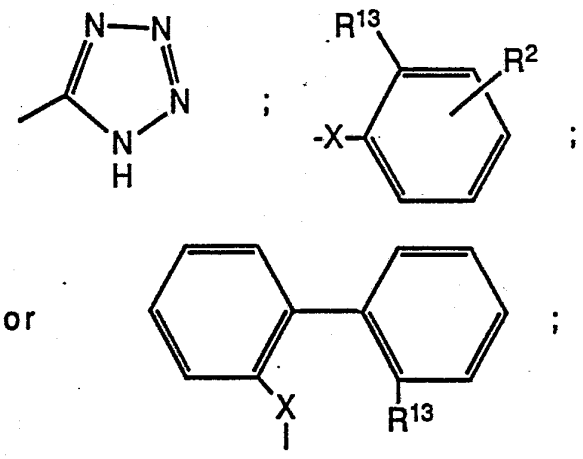
2. Method of claim 1wherein, in the compound of formula (I) is a compound of formula II:



(II)

wherein R^1 is $-CO_2H$; $-NHSO_2CF_3$;

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R^6 is alkyl of 3 to 10 carbon atoms, alkenyl of 3 to 10 carbon atoms, alkynyl of 3 to 10 carbon atoms, cycloalkyl of 3 to 8 carbon atoms, benzyl substituted on the phenyl ring with up to two groups selected from alkoxy of 1 to 4 carbon atoms, halogen, alkyl of 1 to 4 carbon atoms, and nitro;

R^8 is

$-(CH_2)_s$-tetrazolyl, $-(CH_2)_nOR^{11}$; $-(CH_2)_n OCR^{14}$;

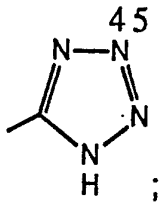
$-CH=CH(CH_2)_sCR^{16}$, $-CH=CH(CH_2)_sCHOR^{15}$;

$-(CH_2)_nCR^{16}$; $-(CH_2)_nNHCOR^{10}$; $-(CH_2)_nNHSO_2R^{10}$;

$-(CH_2)_mF$; or $-CR^{16}$;

phenylalkenyl wherein the aliphatic portion is 2 to 4 carbon atoms; $-(CH_2)_m$-imidazol-l-yl; or $-(CH_2)_m$-1,2,3-triazolyl optionally substituted with one or two groups selected from $-CO_2CH_3$ or alkyl of 1 to 4 carbon atoms;

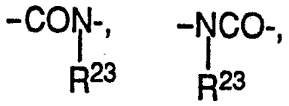
R^{13} is $-CO_2H$, $-CO_2R^9$, $NHSO_2CF_3$; SO_3H; or



;

R^{16} is H, alkyl of 1 to 5 carbon atoms, OR^{17}, or $NR^{18}R^{19}$;

X is carbon-carbon single bond, -CO-, CH_2CH_2-,



-OCH_2-, -CH_2O-, -O-, -SCH_2-, -CH_2S-, -NH-CH_2-, -CH_2NH- or -CH=CH-; or a pharmaceutically acceptable salt thereof.

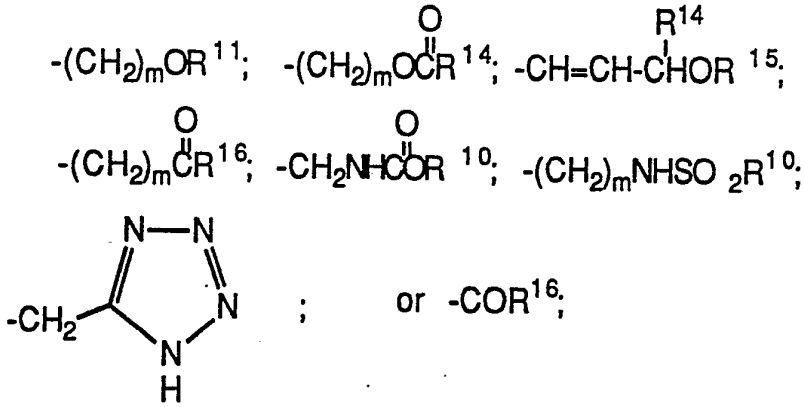
3. Method of claim 2 wherein the compound of formula (II) is a compound wherein:

R^2 is H, alkyl of 1 to 4 carbon atoms, halogen, or alkoxy of 1 to 4 carbon atoms;

R^6 is alkyl, alkenyl or alkynyl of 3 to 7 carbon atoms;

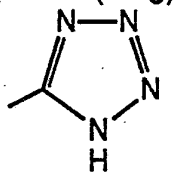
R^7 is heteroaryl selected from 2- and 3-thienyl, 2- and 3-furyl, 2-, 3-, and 4-pyridyl, p-biphenylyl; H, Cl, Br, I; C_vF_{2v+1}, where v=1-3; $-\overset{O}{\overset{\|}{C}}R^{16}$; straight or branched chain alkyl of 1 to 6 carbon atoms; or phenyl;

R^8 is

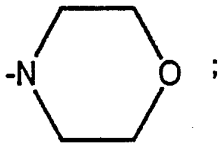


R^{10} is CF_3, alkyl of I to 6 carbon atoms or phenyl;

R^{11} is H, or alkyl of 1 to 4 carbon atoms;
R^{13} is CO_2H; $CO_2CH_2OCOC(CH_3)_3$; $NHSO_2CF_3$;

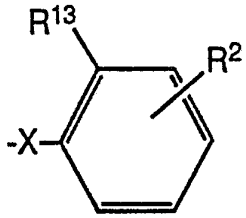


R^{14} is H, or alkyl of I to 4 carbon atoms;
R^{15} is H, alkyl of I to 4 carbon atoms, or acyl of I to 4 carbon atoms;
R^{16} is H, alkyl of 1 to 5 carbon atoms; OR^{17}; or



m is I to 5;
X = single bond, -O-; -CO-; -NHCO-; or $-OCH_2-$; or
a pharmaceutically acceptable salt thereof.

4. Method of claim 3 wherein the compound of formula II is a compound wherein R^1 is



and X is a single bond; or a pharmaceutically suitable salt thereof.

5. Method of claim 4 wherein the compound of formula II is 2-Butyl-4-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-5-(hydroxymethyl)imidazole or a pharmaceutically acceptable salt thereof.

6. Method of claim 4 wherein the compound of formula II is 2-Butyl-4-chloro-1-[(2'-carboxybiphenyl-4-yl)-methyl]-5-(hydroxymethyl)imidazole or a pharmaceutically acceptable salt thereof.

7. Method of claim 4 wherein the compound of formula II is 2-Butyl-4-chloro-1-[(2'-carboxybiphenyl-4-yl)-methyl]-5-[(methoxycarbonyl)aminomethyl] imidazole or a pharmaceutically acceptable salt thereof.

8. Method of claim 4 wherein the compound of formula II is 2-Butyl-4-chloro-1-[(2'-carboxybiphenyl-4-yl)-methyl]-5-[(propoxycarbonyl)aminomethyl] imidazole or a pharmaceutically acceptable salt thereof.

9. Method of claim 4 wherein the compound of formula II is 2-Butyl-4-chloro-1-[(2'-carboxybiphenyl-4-yl) methyl]imidazole-5-carboxaldehyde or a pharmaceutically acceptable salt thereof.

10. Method of claim 4 wherein the compound of formula II is 2-Butyl-1-[(2'-carboxybiphenyl-4-yl)methyl]-imidazole-5-carboxaldehyde or a pharmaceutically acceptable salt thereof.

11. Method of claim 4 wherein the compound of formula II is 2-(1E-Butenyl)-4-chloro-1-[(2'-carboxybi-phenyl-4-yl)methyl]-5-(hydroxymethyl)imidazole or a pharmaceutically acceptable salt thereof.

12. Method of claim 4 wherein the compound of formula II is 2-(1E-Butenyl)-4-chloro-1-[(2'-carboxybi-phenyl-4-yl)methyl]imidazole-5-carboxaldehyde or a pharmaceutically acceptable salt thereof.

13. Method of claim 4 wherein the compound of formula II is 2-Propyl-4-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-5-(hydroxymethyl) imidazole or a pharmaceutically acceptable salt thereof.

14. Method of claim 4 wherein the compound of formula II is 2-Propyl-4-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxaldehyde or a pharmaceutically acceptable salt thereof.

15. Method of claim 4 wherein the compound of formula II is 2-Butyl-4-chloro-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxaldehyde or a pharmaceutically acceptable salt thereof.

16. Method of claim 4 wherein the compound of formula II is 2-(1E-Butenyl)-4-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-5-hydroxymethyl)imidazole or a pharmaceutically acceptable salt thereof.

17. Method of claim 4 wherein the compound of formula II is 2-(1E-Butenyl)-4-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxaldehyde or a pharmaceutically acceptable salt thereof.

18. Method of claim 4 wherein the compound of formula II is 2-Butyl-4-chloro-1-[(2'-(1H-tetrazol-5-yl)-biphenyl-4-yl)methyl]imidazole-5-carboxylic acid or a pharmaceutically acceptable salt thereof.

19. Method of claim 4 wherein the compound of formula II is 2-Propyl-4-chloro-1-[(2'-(1H-tetrazol-5-yl)-biphenyl-4-yl)methyl]imidazole-5-carboxylic acid or a pharmaceutically acceptable salt thereof.

20. Method of claim 4 wherein the compound of formula II is 2-Propyl-4-trifluoromethyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxylic acid or a pharmaceutically acceptable salt thereof.

21 Method of claim 4 wherein the compound of formula II is 2-Propyl-4-trifluoromethyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-5-(hydroxylmethyl)-imidazole or a pharmaceutically acceptable salt thereof.

22. Method of claim 4 wherein the compound of formula II is 2-Butyl-4-trifluoromethyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboyxlic acid or a pharmaceutically acceptable salt thereof.

23. Method of claim 4 wherein the compound of formula II is 2-Propyl-4-trifluoromethyl-1-[(2'-(carboxybiphenyl-4-yl)methyl]imidazole-5-carboxaldehyde or a pharmaceutically acceptable salt thereof.

24. Method of claim 4 wherein the compound of formula II is 2-Propyl-4-pentafluoroethyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-5-(hydroxymethyl)-imidazole or a pharmaceutically acceptable salt thereof.

25. Method of claim 4 wherein the compound of formula II is 2-Propyl-4-pentafluoroethyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxylic acid or a pharmaceutically acceptable salt thereof.

26. Method of claim 4 wherein the compound of formula II is 2-Propyl-4-pentafluoroethyl-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxaldehyde or a pharmaceutically acceptable salt thereof.

27. Method of claim 4 wherein the compound of formula II is1-[(2'-(1H-Tetrazol-5-yl)biphenyl-4-yl)methyl]-4-phenyl-2-propylimidazole-5-carboxaldehyde

28. Method of claim 4 wherein the compound of formula II is1-[(2'-Carboxybiphenyl-4-yl)methyl]-4-phenyl-2-propylimidazole-5-carboxaldehyde

INTERNATIONAL SEARCH REPORT

International Application No PCT/US91/00879

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC (5): A01N 43/50, A01N 43/36
U.S.CL.: 514/399, 514/429

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
U.S.	514/399, 429

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

CAS ON LINE: APS

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
Y	US, A, 4,533,669 (YAMANAKA ET AL) 06 August 1985 See column 1, line 7 to column 3, line 41, and column 9, line 59 to column 12 line 47.	1-28
Y	US, A, 4,602,031 (YAMANAKA ET AL) 22 July 1986 See column 1, line 7 to column3, line 48 and column 9, line 37 to column 12 line 31.	1-28
Y	EP, A, 0-288-907 (SUDILOVSKY) 02 November 1988 See page 1-8.	1-28
Y	EP, A, 0-324-377 (CARINI) 19 July 1989 See entire document.	1-28
Y	EP, A, 0-245,637 (BLANKLEY ET AL) 19 November 1987 See entire document.	1-28
Y	AU, A -22279/88 (EP, A, 307,872) (RUGER ET AL) 16 MaRCH 1989, See entire document.	1-28

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [3]	Date of Mailing of this International Search Report [3]
11 JUNE 1991	21 JUN 1991
International Searching Authority [1]	**Signature of Authorized Officer**
ISA/US	NGUYEN NGOC-HO INTERNATIONAL DIVISION For FREDERICK E. WADDELL Ngoc-Ho Nguyen

Form PCT/ISA/210 (second sheet) (May 1986)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

A	Experimentation, Volume 38, 1982, B. A. Scholkens et al, Intercerebroventricular Angiotensin II increases arterial blood pressure in rhesus monkey by stimulator of the pituitary hormones and the sympathetic nervous system, pages 469-470, See entire document.	1-28
A	Neuroscience Letters, Volume 14; 1975 M. Kohler et al pages 71-75 "Endogenous Brain Angiotensin II Disrupts Passive Avoidance Behavior in Rats", See entire document.	1-28

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers . because they relate to subject matter [1] not required to be searched by this Authority, namely:

2. ☐ Claim numbers , because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [1], specifically:

3. ☐ Claim numbers_____, because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.