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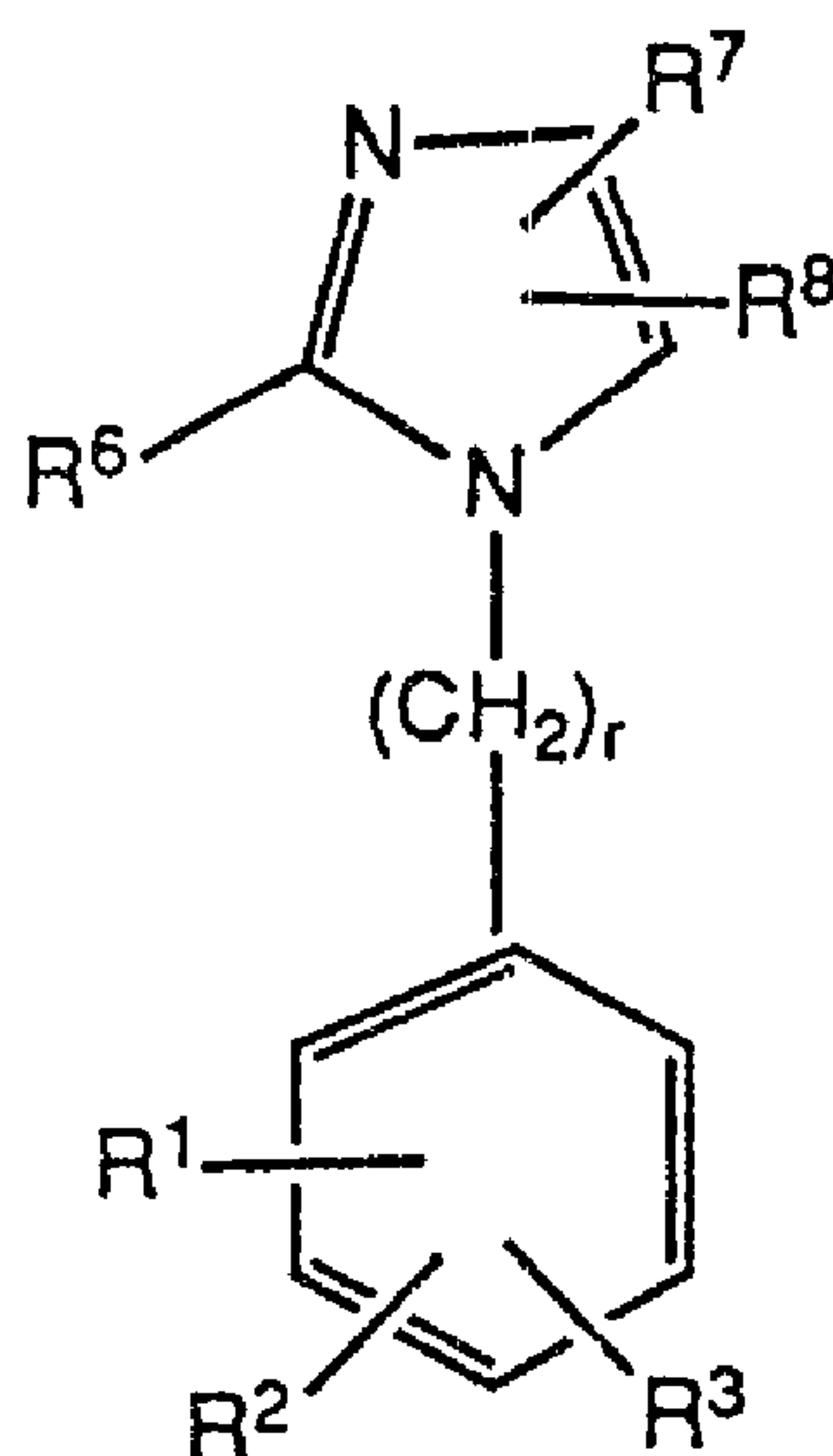
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(54) Titre : TRAITEMENT DES TROUBLES DU SYSTEME NERVEUX CENTRAL A L'AIDE D'ANTAGONISTES DE TYPE
IMIDAZOLE DU RECEPTEUR DE L'ANGIOTENSINE II

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



(I)

(57) Abrégé/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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(21) International Application Number: PCT/US91/00879 (22) International Filing Date: 14 February 1991 (14.02.91) (30) Priority data: 497,063 20 March 1990 (20.03.90) US (71) Applicant: E.I. DU PONT DE NEMOURS AND COMPANY [US/US]; 1007 Market Street, Wilmington, DE 19898 (US). (72) Inventors: CHIU, Andrew, Tak-Chau ; 9 St. David's Court, Landenberg, PA 19350 (US). DE NOBLE, Victor, John ; 1200 Camp Woods Court, Newark, DE 19711 (US). DUNCIA, John, Jonas, Vytautas ; 35-B Martine Court, Newark, DE 19711 (US). WONG, Pancras, Chor, Bun ; 3227 Whiteman Road, Wilmington, DE 19808 (US).		(74) Agents: KERR, Don, M. et al.; E.I. du Pont de Nemours and Company, Legal/Patent Records Center, 1007 Market Street, Wilmington, DE 19898 (US). (81) Designated States: AT (European patent), BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent). Published <i>With international search report.</i>
(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.		

TITLE

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

5

BACKGROUND OF THE INVENTION

Angiotensin II (All), 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
10 the release and subsequent action of other neurotransmitters (Unger et al. (1988) Circulation 77 (suppl I):40-54). Specific receptors for All with high affinity have been identified and localized in different regions of the CNS (Mann (1982) Exp. Brain Res. 4 (suppl):242). Stimulation of All receptors in the
15 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
20 hormone, oxytocin, luteinizing hormone, and prolactin, and other effects (Scholken et al. (1982) Experientia 38:469). The CNS effects of All could lead to hypertension and other cardiovascular diseases through inhibition of the baroreceptor reflex, increase in salt consumption, volume expansion, and
25 increased peripheral resistance. Besides the cardiovascular system, All 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 All in the CNS can be classified
30 into three groups which may share, at least in part, overlapping mechanisms of action. The first major function of All 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
35 increase, adrenocorticotrophic hormone (ACTH) release, and

aldosterone release (Unger et al. (1988) Circulation 77 (suppl 1):40-54, and references cited therein). This CNS function of All is closely related to the role of All in hypertension.

5 A second function of All 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).

10 A third possible CNS function of All is a synaptic function. All 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 All is limited. Published results suggest that increased All activity in brain maintains an inhibitory control on cholinergic neurons resulting in impaired cognitive performance.

15 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 All in mediating retention of a passive avoidance (PA) response in rats. These authors demonstrated that rats injected with All into the dorsal neostriatum, a brain area that has a high concentration of All as well as precursors and metabolic enzymes for All biosynthesis, showed a disruption in retention of a PA response. The authors

20 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 All in the dorsal neostriatum results in a cognitive impairment which is most likely a result of All modulation of neuronal activity that is necessary for

25 consolidation of newly acquired information.

30 A different approach for investigating the behavioral effects of All in the CNS was taken by Koller et al. Neuroscience Letters (1975) 14:71-75. These authors injected

35 renin into the lateral ventricle of the brain (IVT) and measured

increases in All in cerebrospinal fluid (CSF); All increased from 40 to about 5000 fmol per mL. This increase in All was accompanied by a disruption of avoidance learning. These results suggested that renin-stimulated biosynthesis of All 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 All 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 All or renin, a stimulator of endogenous All 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.

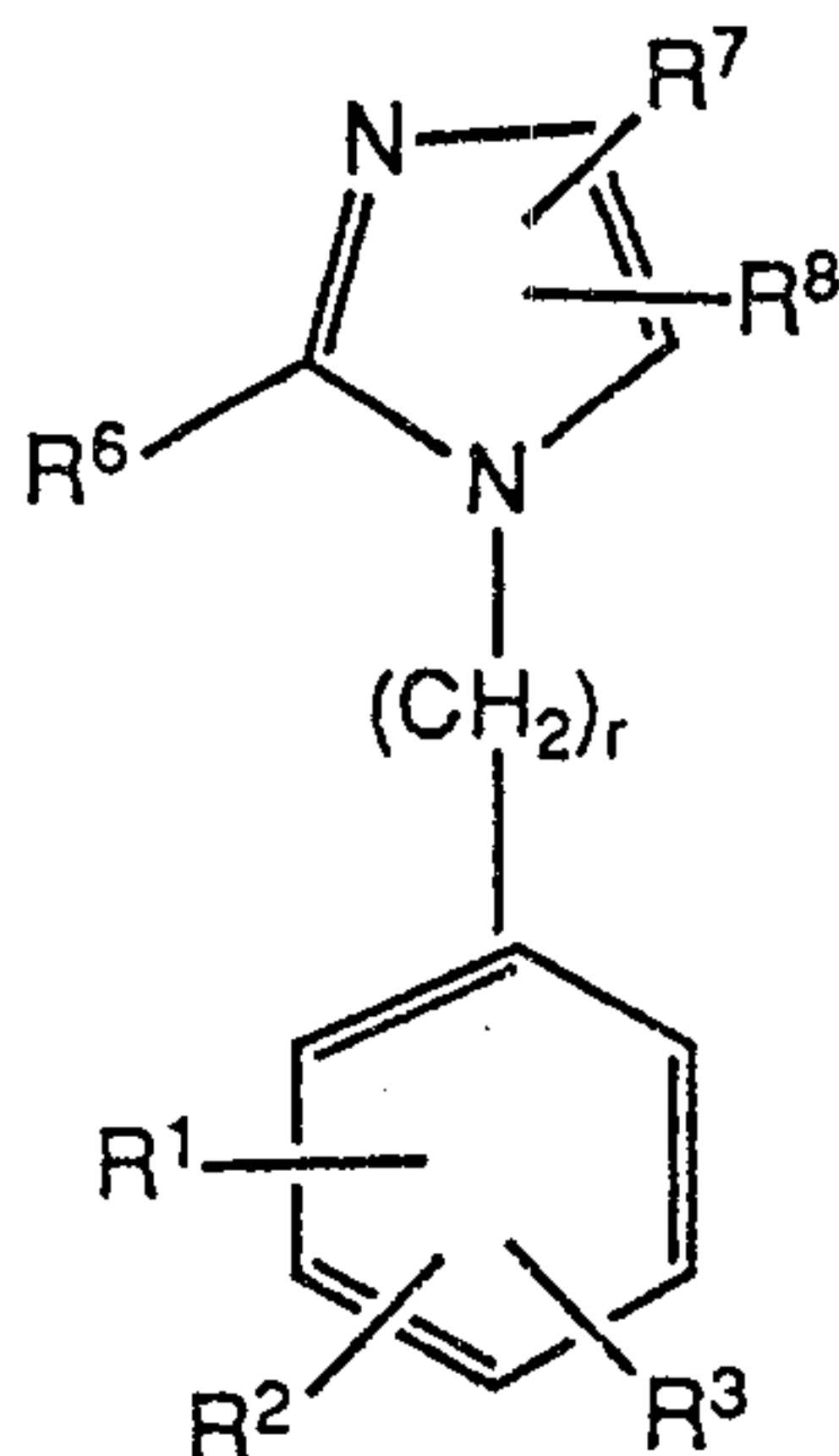
The ACE inhibitor SQ 29852 has also been reported to provide protective effects on memory of previously learned tasks and to ameliorate, at least in part, an anticholinergic effect on performance (European Patent Application EP 288,907 to Squibb, published 11/2/88).

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

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

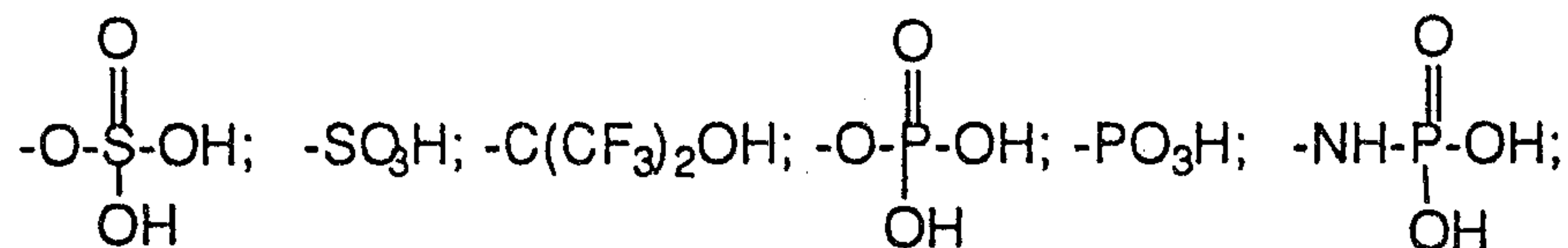
SUMMARY OF INVENTION

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 A11 in a mammal comprising administering to the mammal a pharmaceutical composition comprising a compound having the formula (I):



(I)

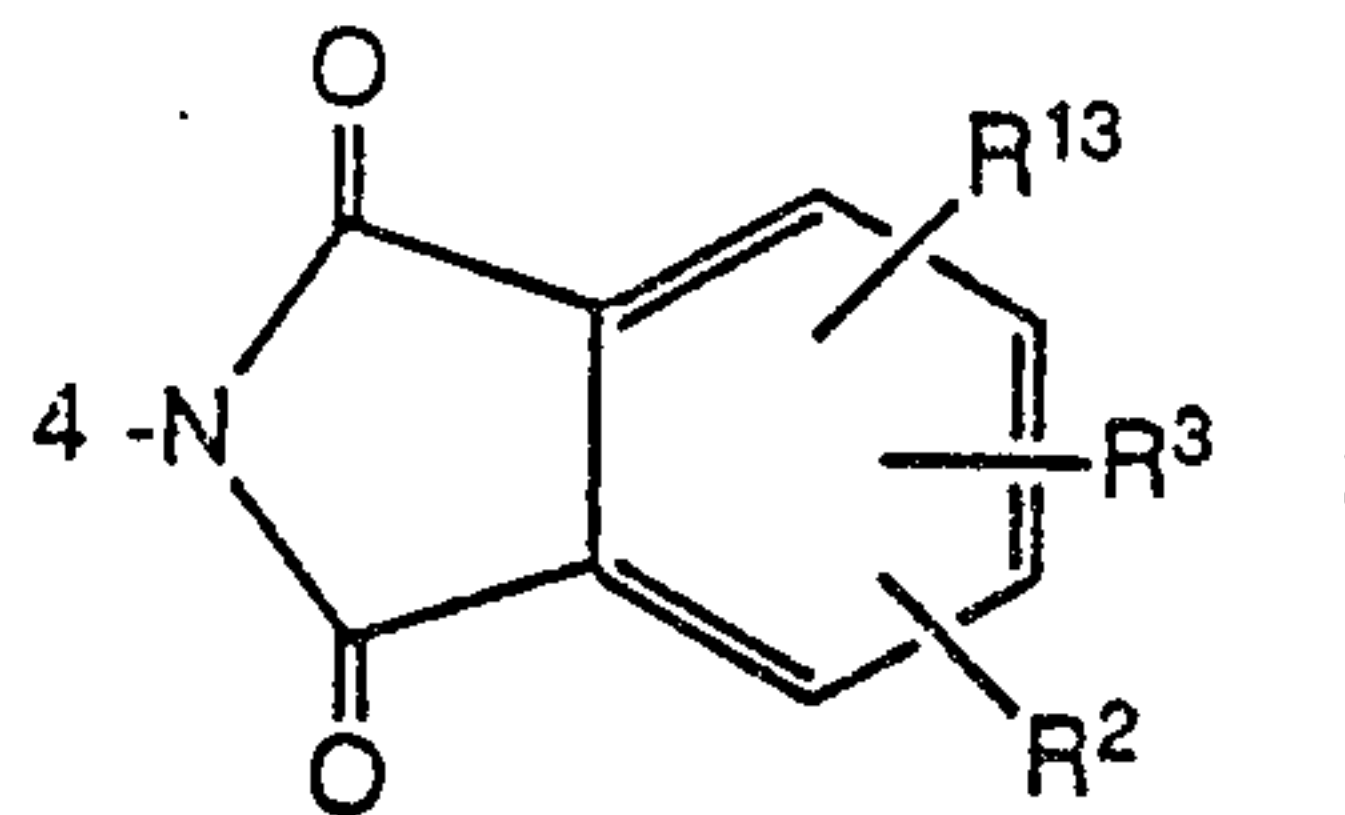
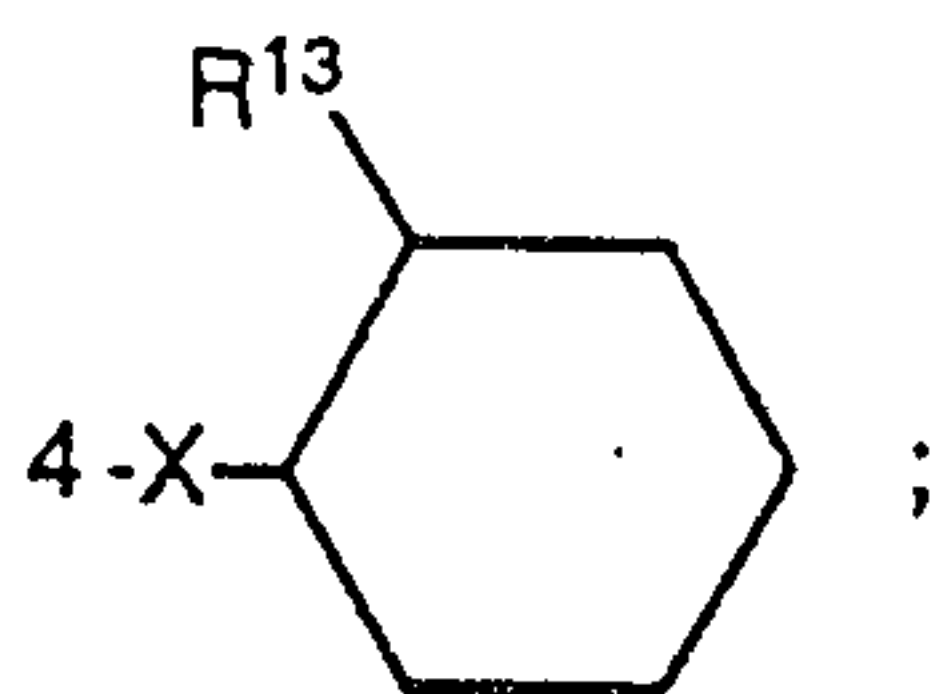
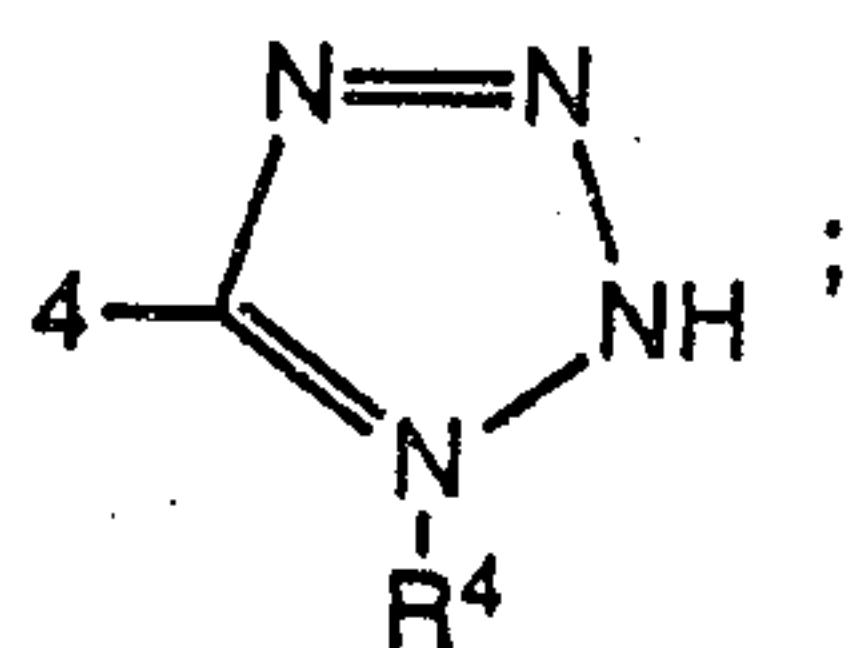
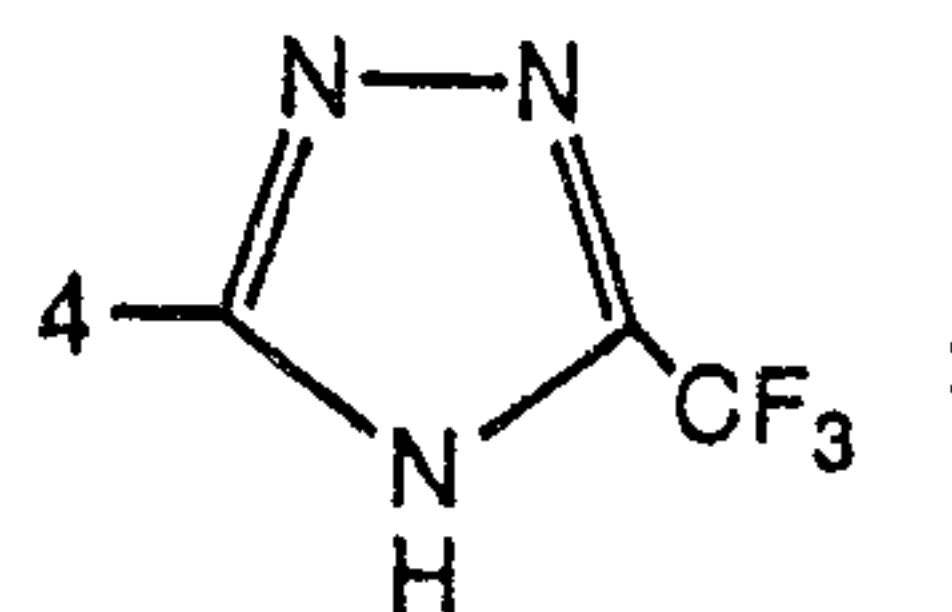
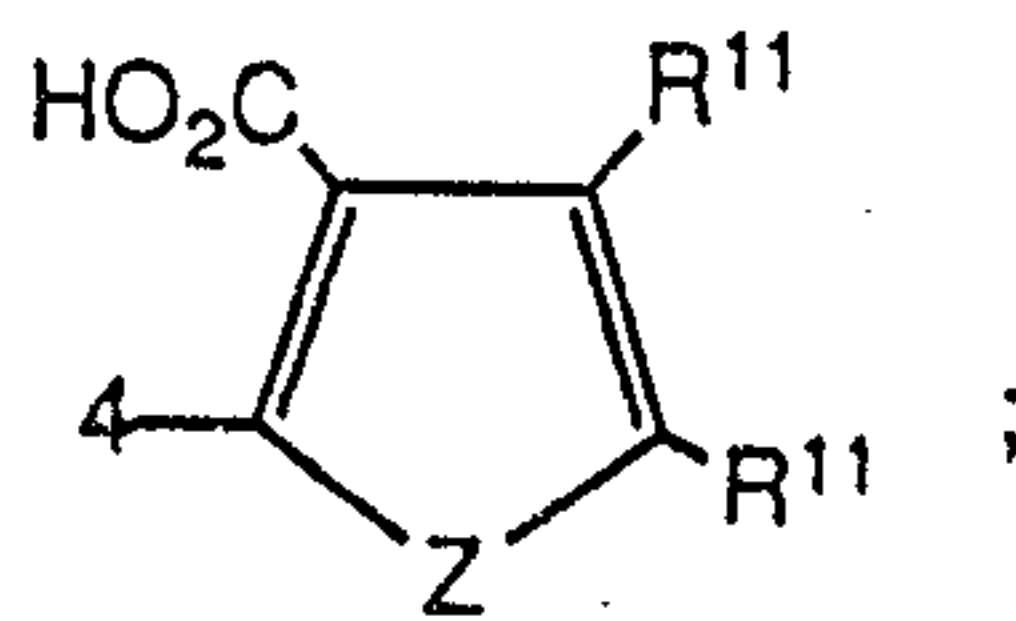
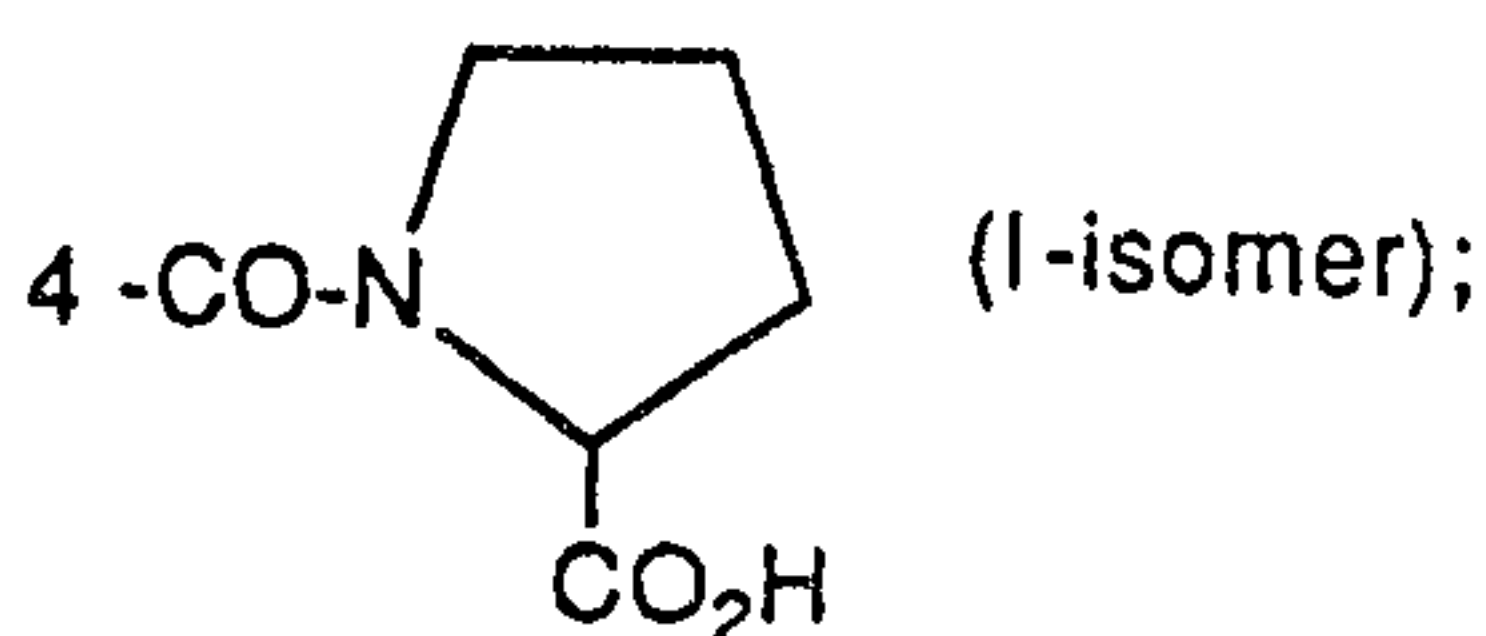
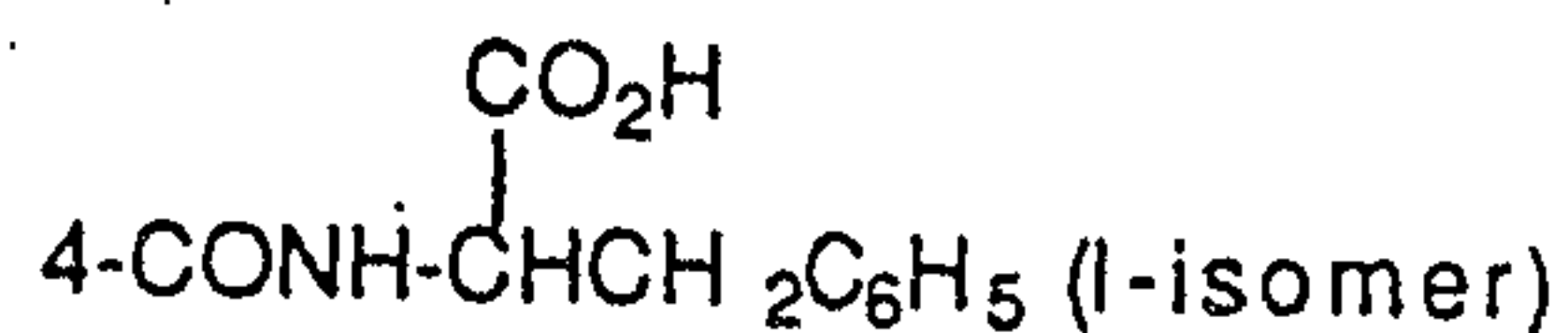
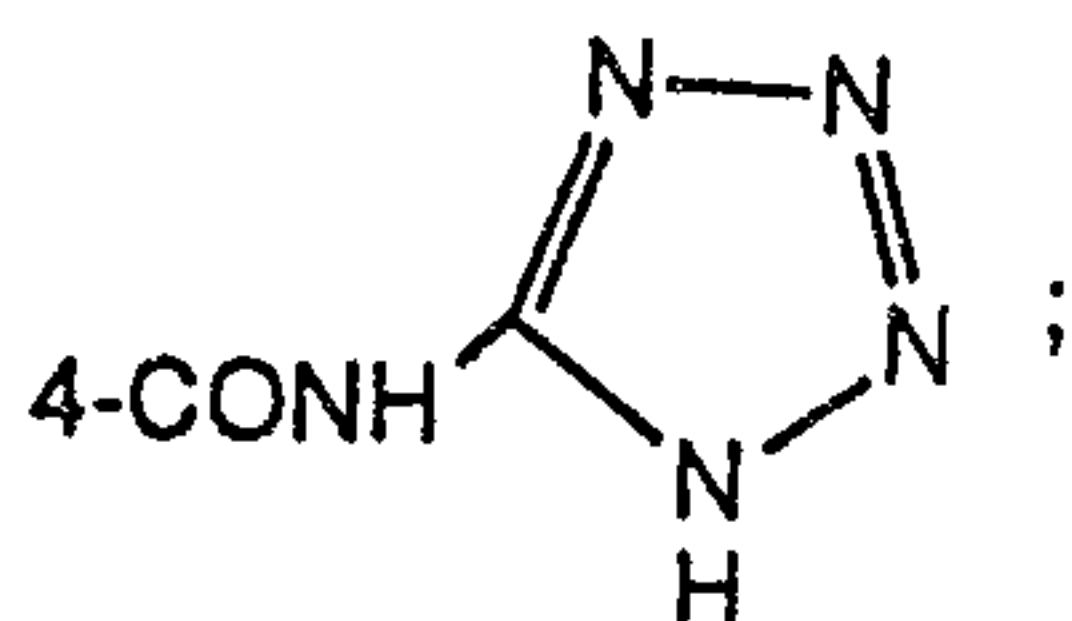
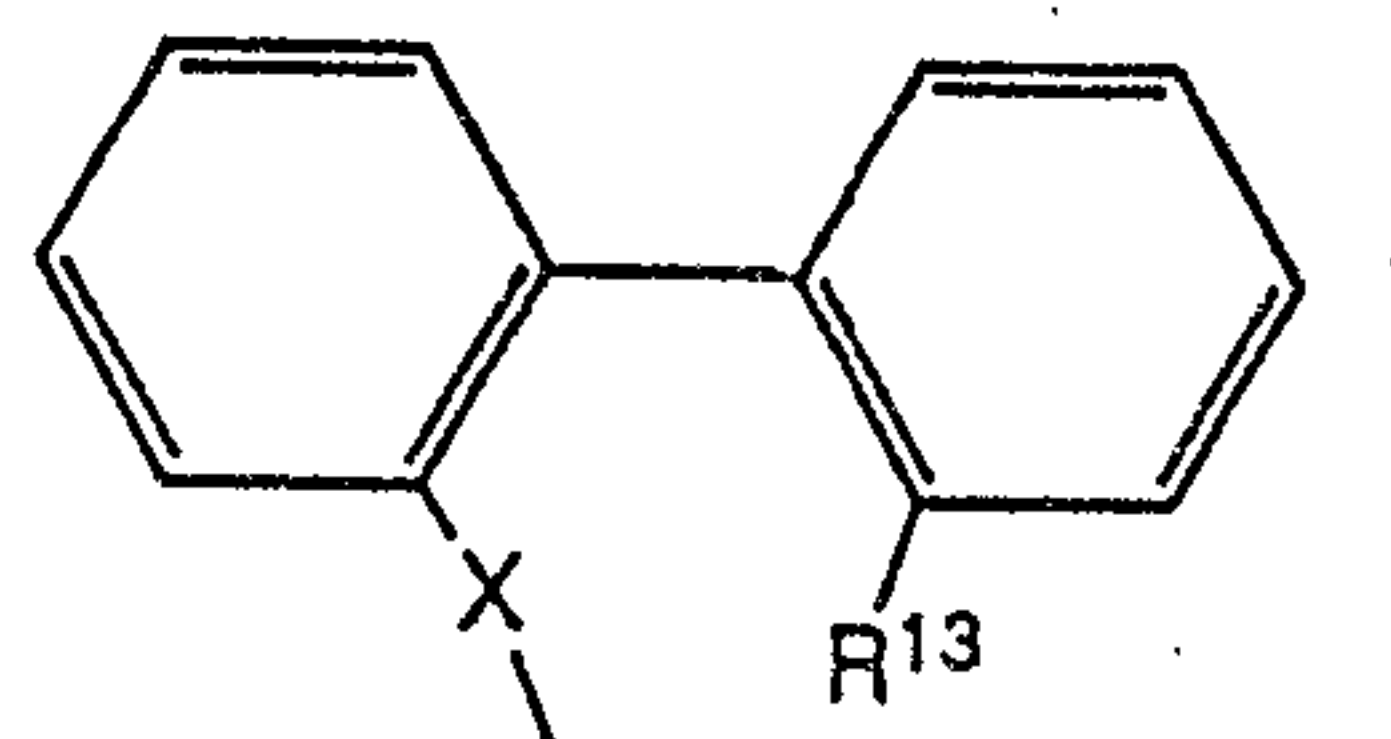
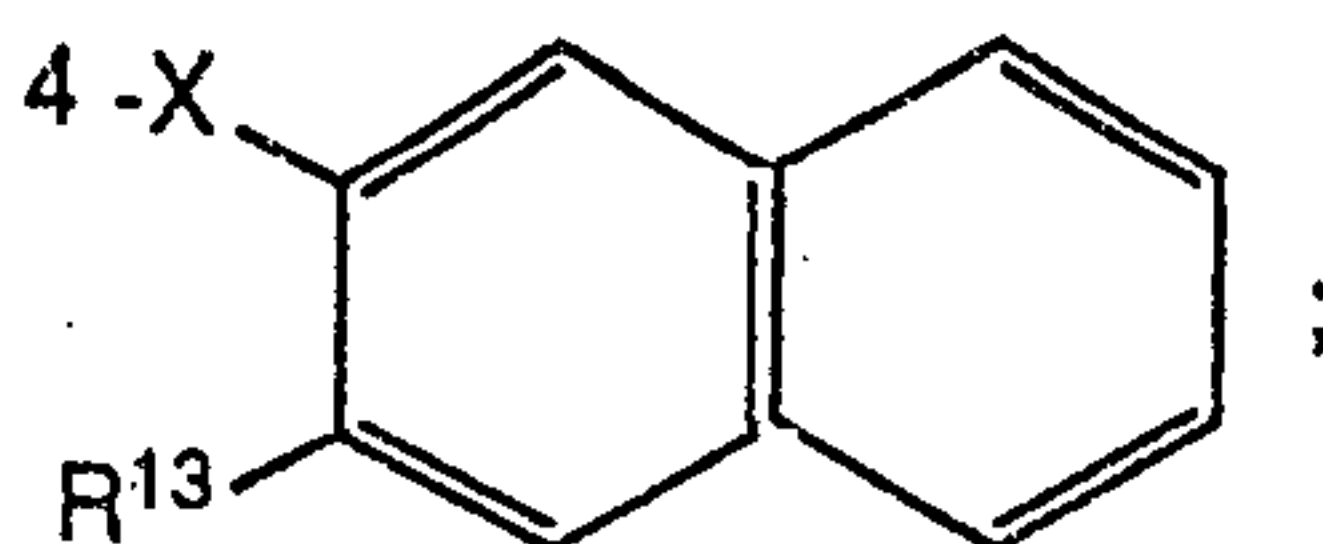
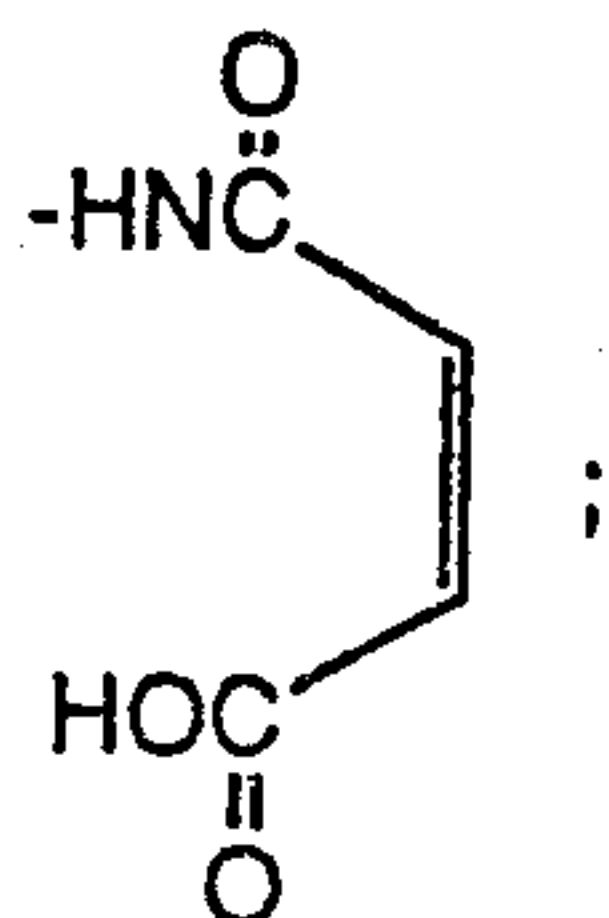
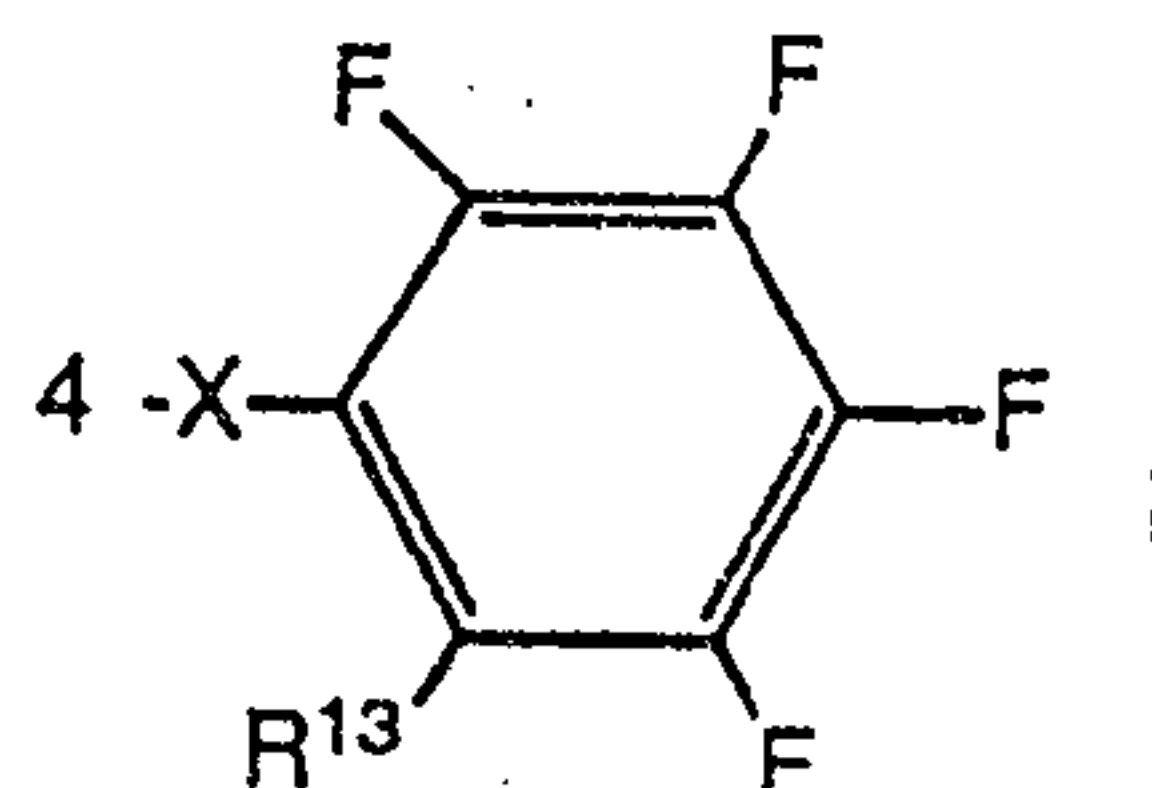
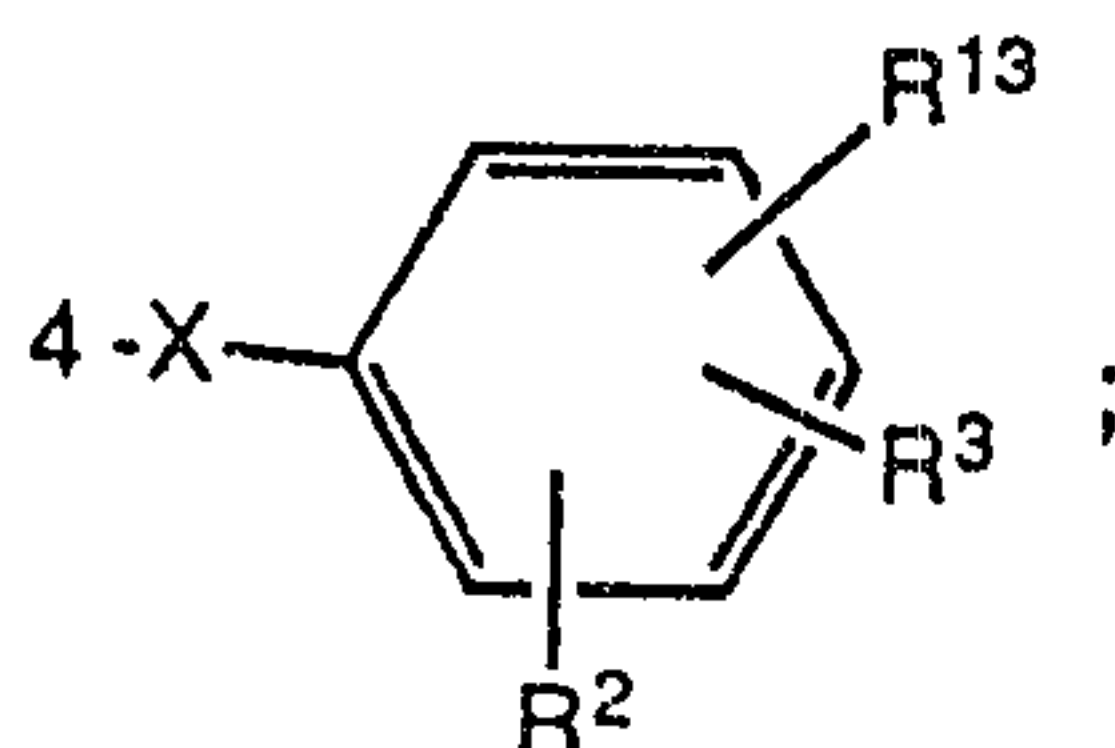
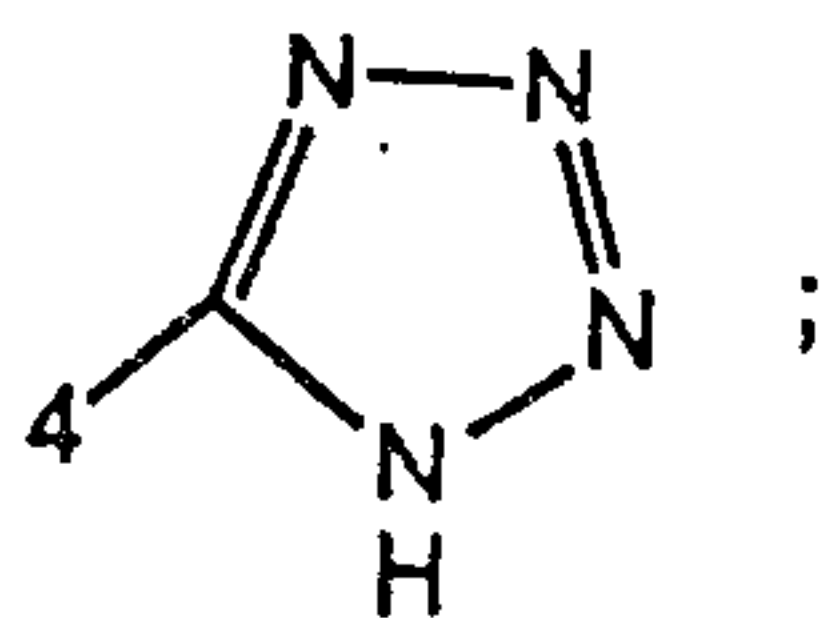
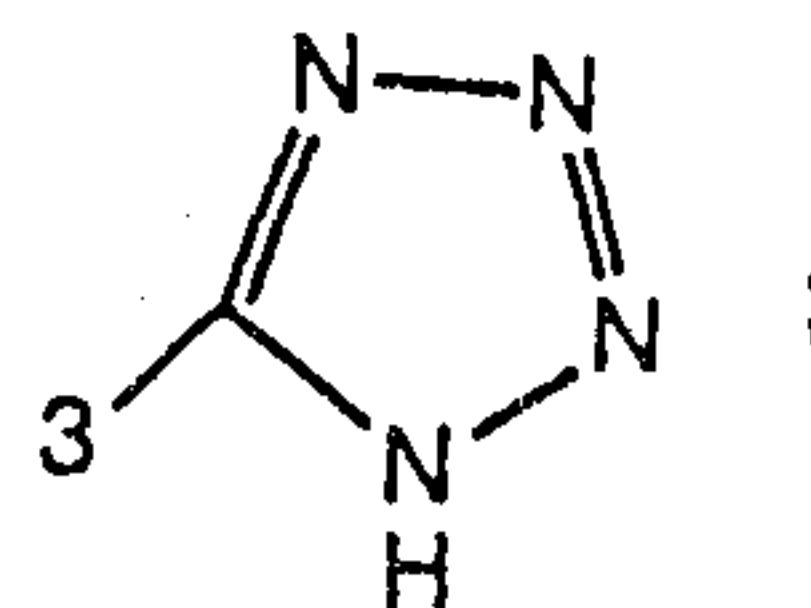
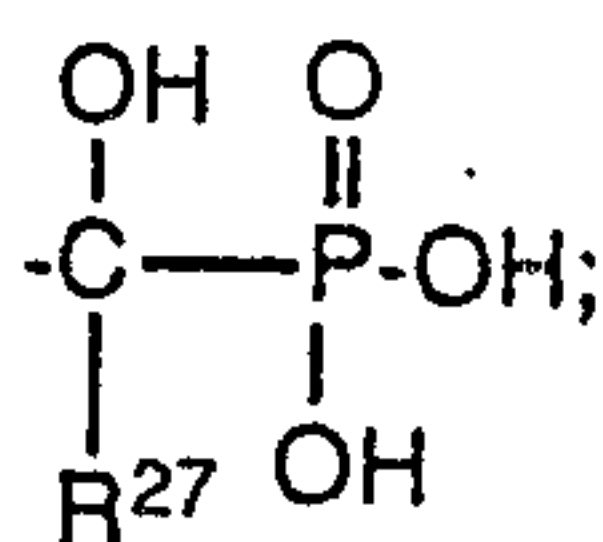
10 wherein

 R^1 is 4-CO₂H; 4-CO₂R⁹;

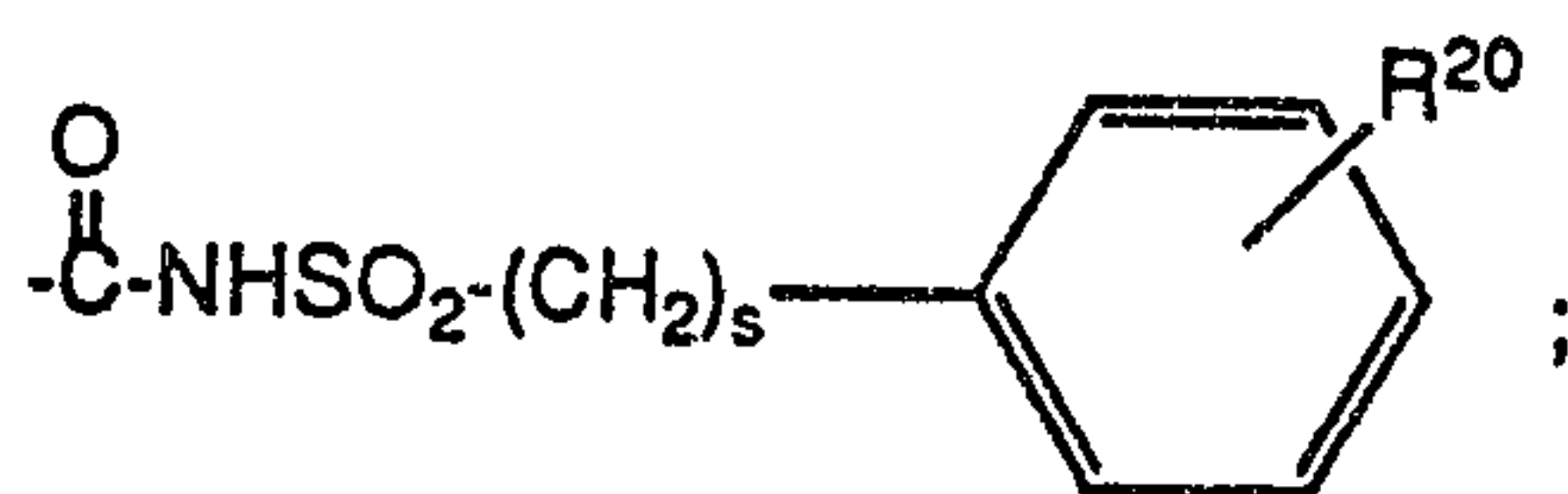
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4-NHSO₂CH₃; -4-NHSO₂CF₃; -CONHOR¹²;

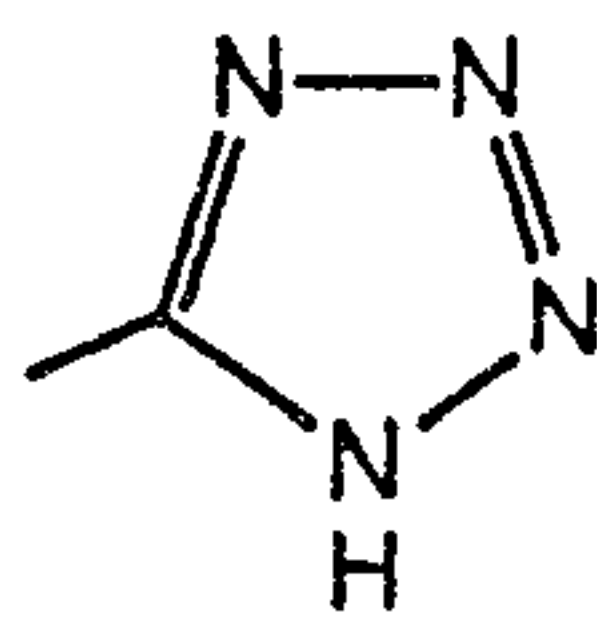
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or



5 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;

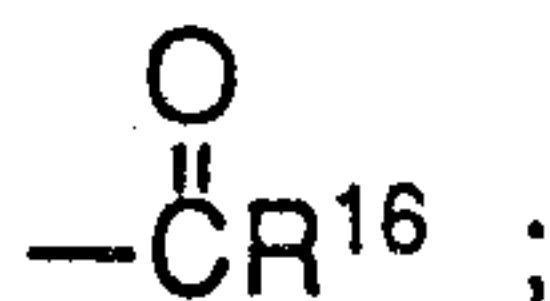
R³ is H; Cl, Br, I or F; alkyl of 1 to 4 carbon atoms or alkoxy of 1 to 4 carbon atoms;

R⁴ is CN, NO₂ or CO₂R¹¹;

5 R⁵ 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;

R⁶ 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 CO₂R¹⁴; cycloalkyl of 3 to 8 carbon atoms, cycloalkylalkyl of 4 to 10 carbon atoms; cycloalkylalkenyl or cycloalkylalkynyl of 5 to 10 carbon atoms; (CH₂)_sZ(CH₂)_mR⁵ optionally substituted with F or CO₂R¹⁴; 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;

15 R⁷ is H, F, Cl, Br, I, NO₂, C_vF_{2v+1}, where v = 1-6; C₆F₅; CN;



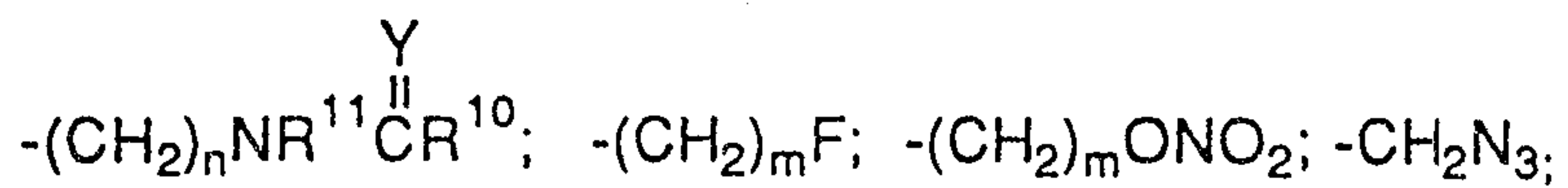
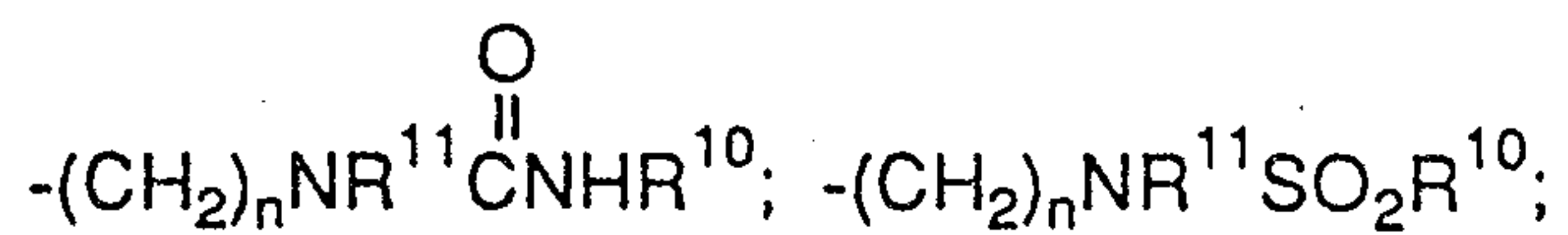
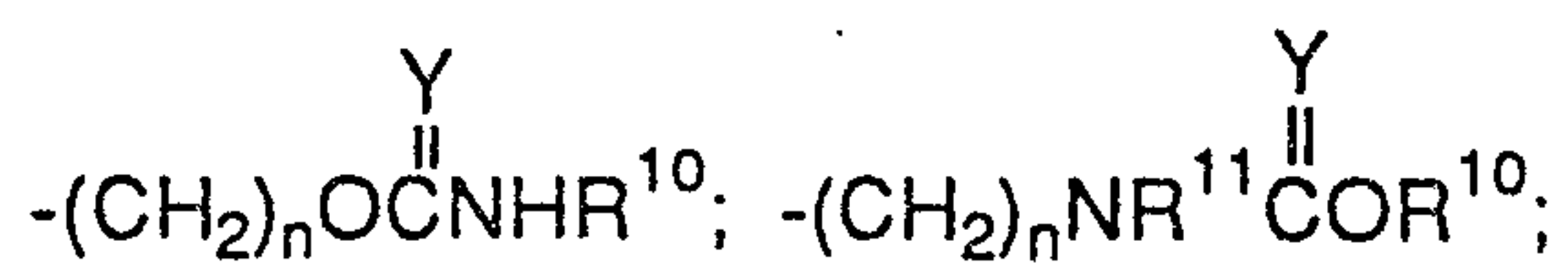
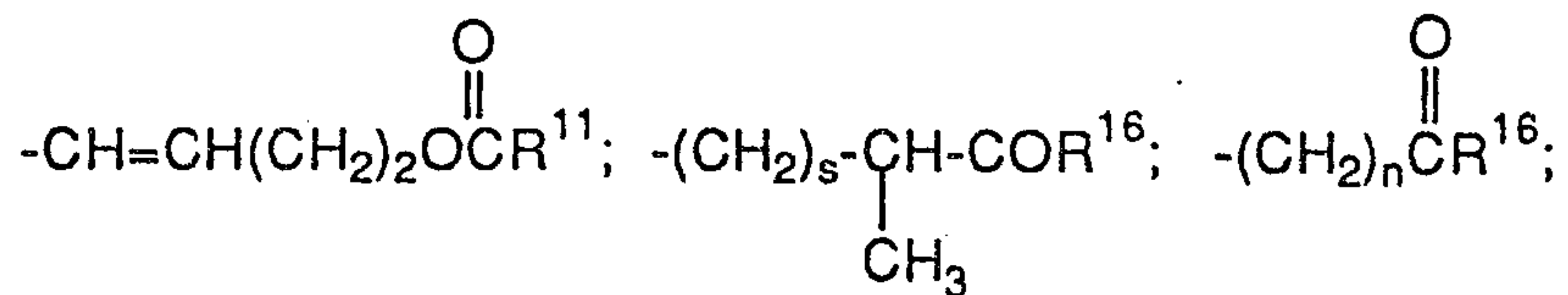
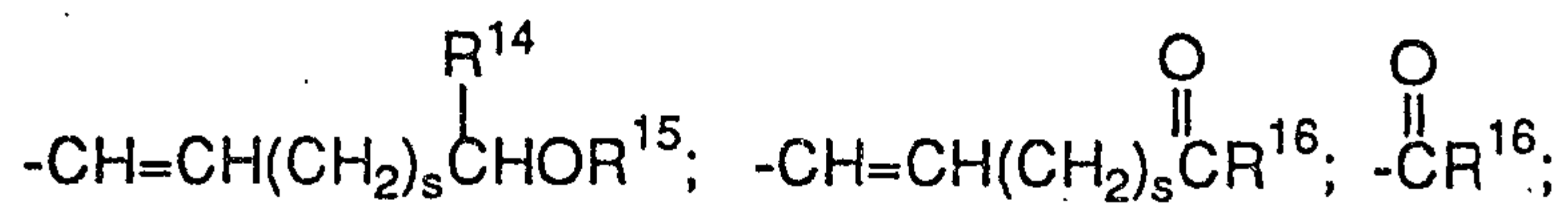
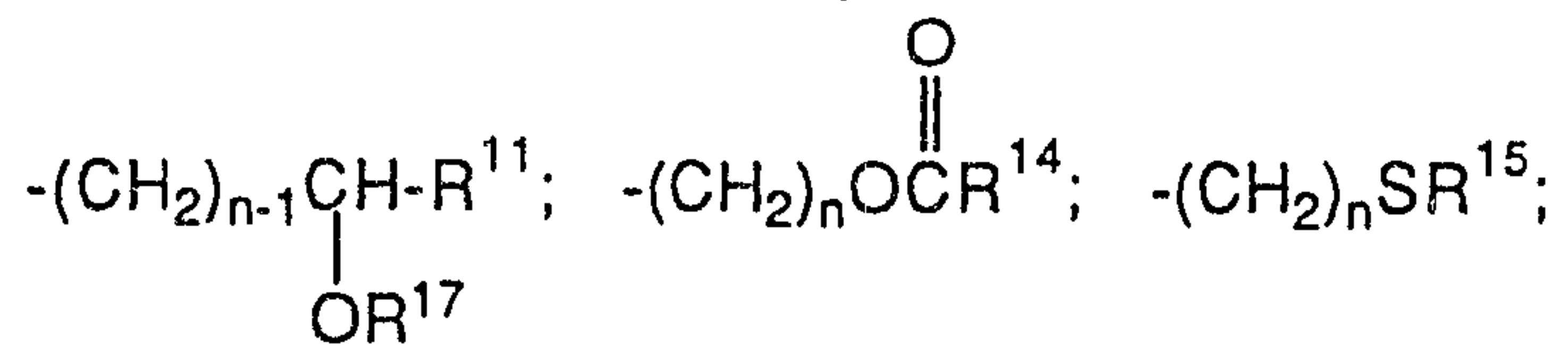
straight or branched alkyl of 1 to 6 carbon atoms; phenyl or phenylalkyl, where alkyl is 1 to 3 carbon atoms; or substituted phenyl or substituted phenylalkyl, where alkyl is 1 to 3 carbon atoms, substituted with one or two substituents selected from alkyl of 1 to 4 carbon atoms, F, Cl, Br, OH, OCH₃, CF₃, 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-biphenyl; o-, m- or p-phenoxyphenyl; substituted phenylalkynyl, heteroaryl, biphenyl or phenoxyphenyl as defined above substituted on

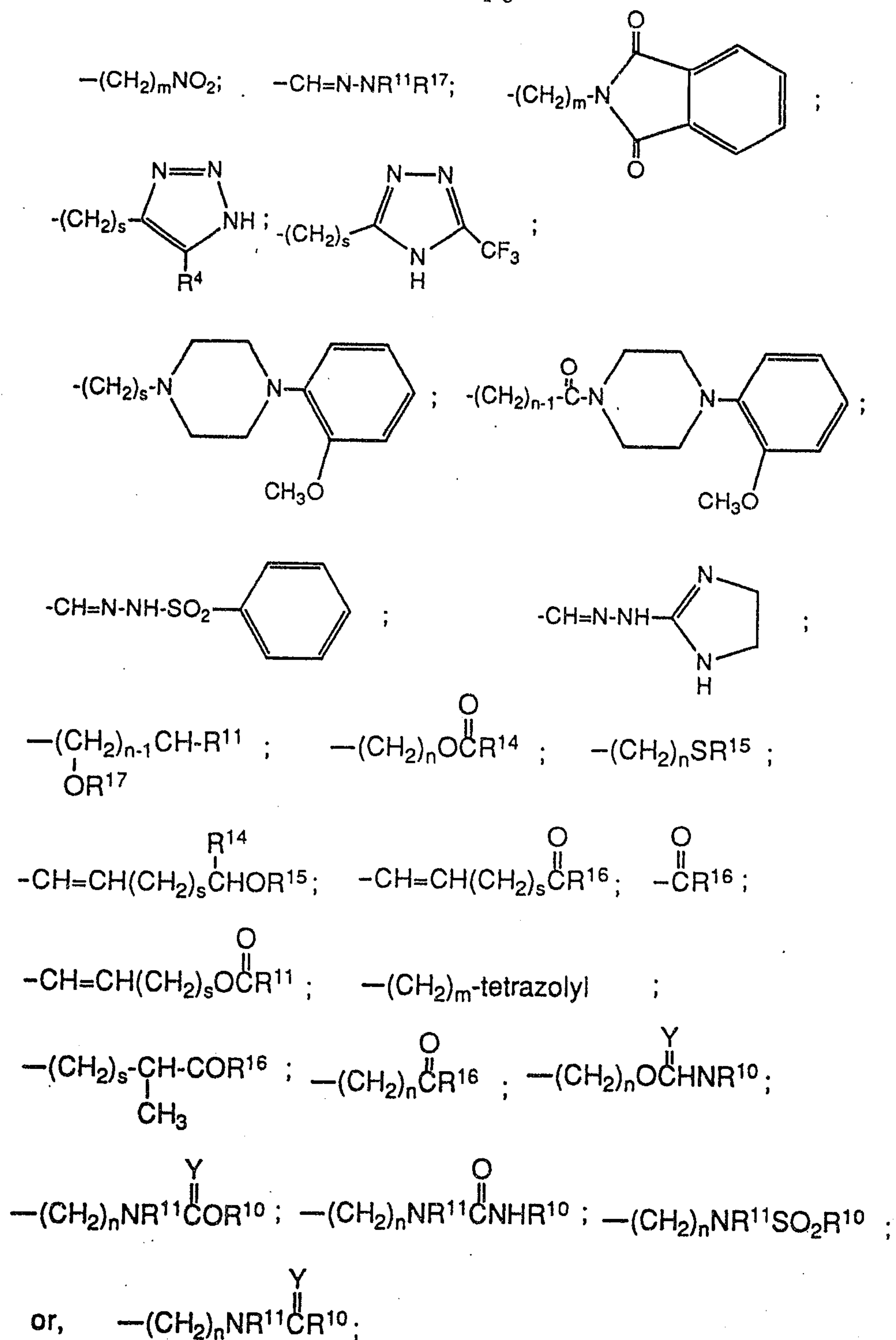
- ring carbon with 1 or 2 substituents selected from halogen, alkoxy of 1-5 carbon atoms, alkyl of 1-5 carbon atoms, -NO₂, -CN, -CF₃, -COR¹⁶, -CH₂OR¹⁷, -NHCOR¹⁷, CONR¹⁸R¹⁹, S(O)_rR¹⁷, and SO₂NR¹⁸R¹⁹; pyrrolyl, pyrazolyl or imidazolyl
- 5 as defined above substituted on ring nitrogen with alkyl of 1-5 carbon atoms or benzyl; or substituted alkyl, alkenyl, or alkynyl of 1 to 10 carbon atoms substituted with a substituted or unsubstituted heteroaryl, biphenyl or phenoxyphenyl group as defined above; 1- or 2- naphthyl; 5- or 6-naphthoquinonyl;
- 10 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-quinoliny; 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
- 15 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 substituents selected from
- 20 halogen, alkoxy of 1-5 carbon atoms, alkyl of 1-5 carbon atoms, -NO₂, -CN, -CF₃, -COR¹⁶, -CH₂OR¹⁷, -NHCOR¹⁷, CONR¹⁸R¹⁹, S(O)_rR¹⁷, and SO₂NR¹⁸R¹⁹; 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
- 25 substituted with a substituted or unsubstituted polycyclic aryl group as defined above;

R⁸ 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

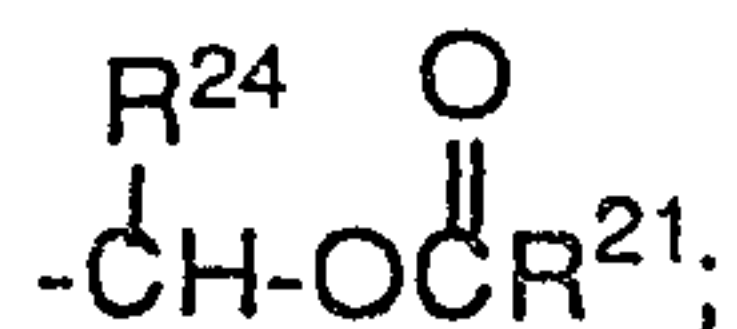
30 atoms; -(CH₂)_m-imidazol-1-yl; -(CH₂)_m-1,2,3-triazolyl optionally substituted with one or two groups selected from CO₂CH₃ or alkyl of 1 to 4 carbon atoms; -(CH₂)_s-tetrazolyl;

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R⁹ is;

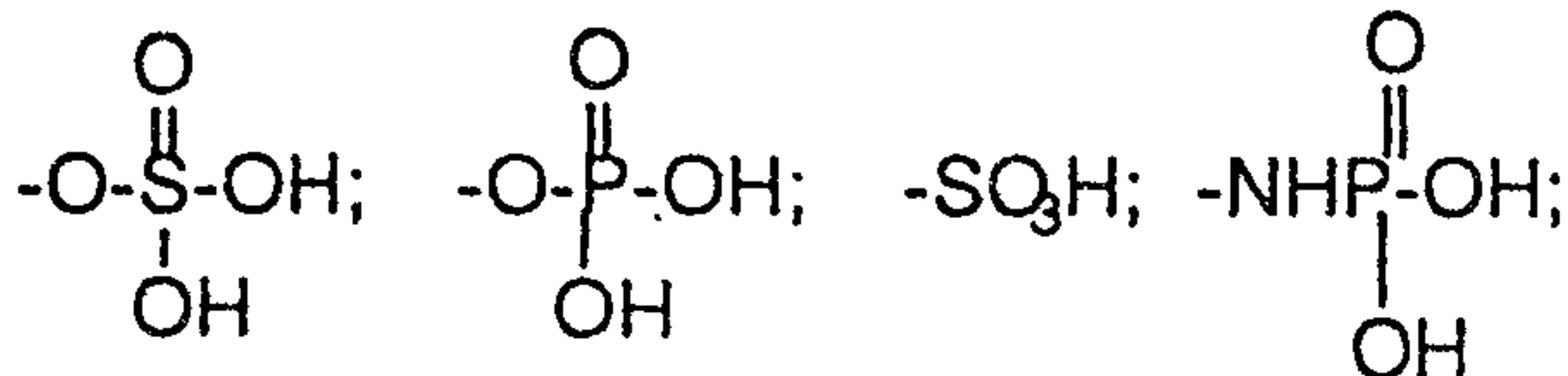


R¹⁰ is alkyl of 1 to 6 carbon atoms or perfluoroalkyl of 1 to 6 carbon atoms, 1-adamantyl, 1-naphthyl, 1-(1-naphthyl)ethyl, or (CH₂)_pC₆H₅;

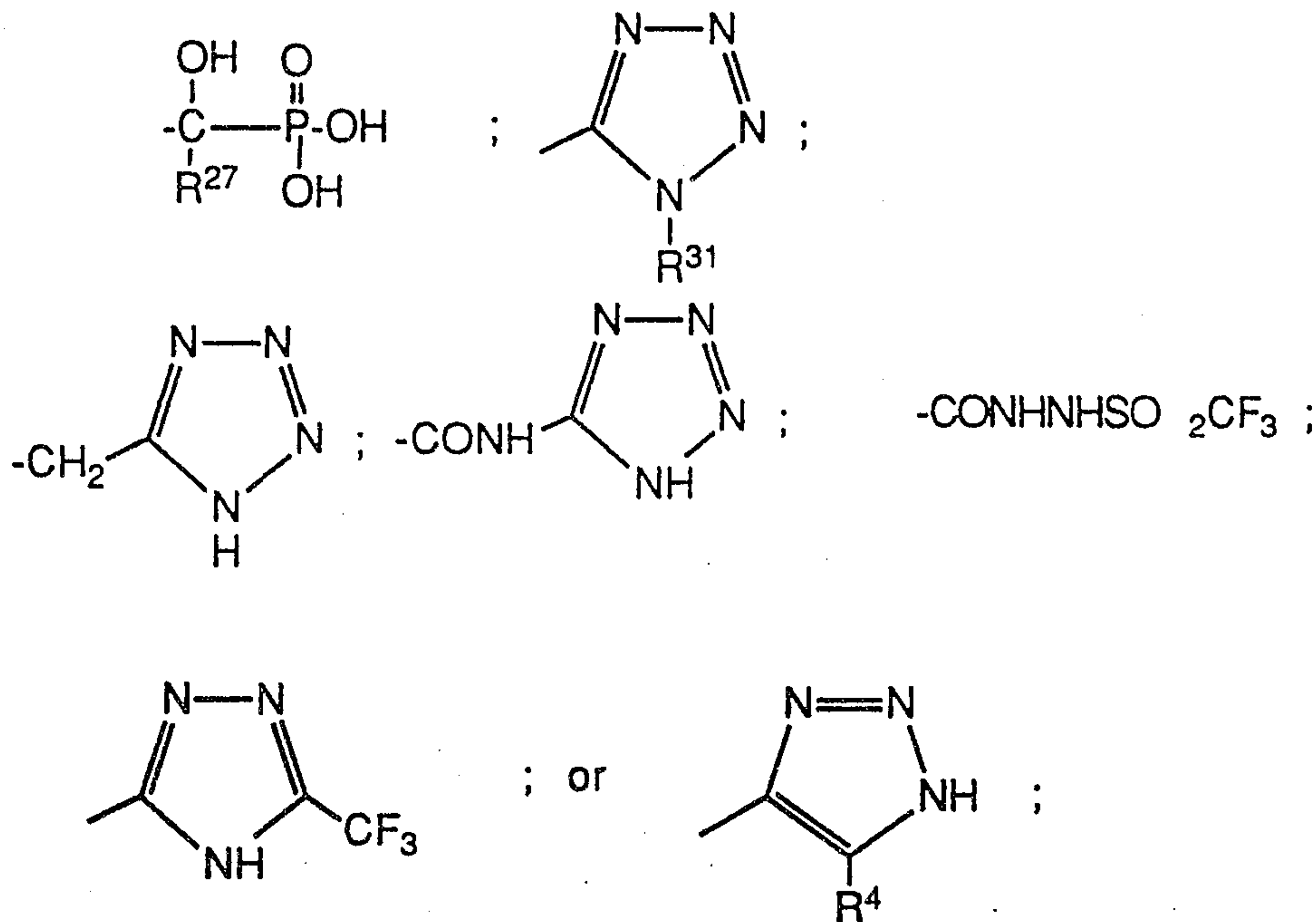
R¹¹ is H, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, phenyl or benzyl;

R¹² is H, methyl or benzyl;

R¹³ is -CO₂H; -CO₂R⁹; -CH₂CO₂H, -CH₂CO₂R⁹;



-PO₃H; -C(CF₃)₂OH; -NH₂SO₂CH₃; -NH₂SO₂CF₃; -NHCOCF₃;
-CONHOR¹²; -SO₂NH₂;



R¹⁴ is H, alkyl or perfluoroalkyl of 1 to 8 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, phenyl or benzyl;

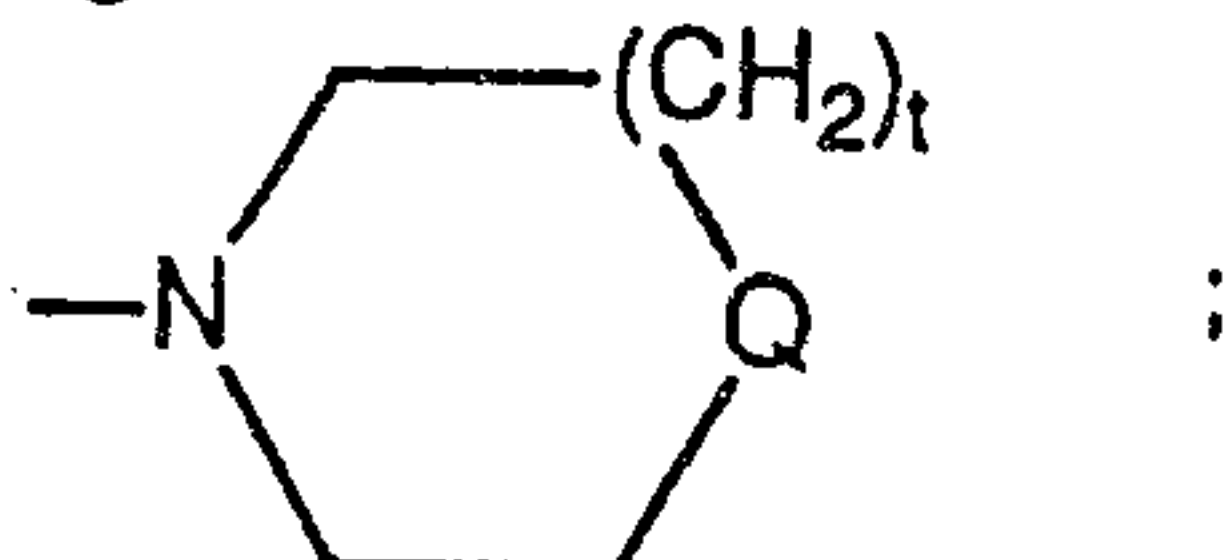
R¹⁵ is H, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3

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

R¹⁶ is H, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, (CH₂)_pC₆H₅, OR¹⁷, or NR¹⁸R¹⁹;

5 R¹⁷ is H, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, phenyl or benzyl;

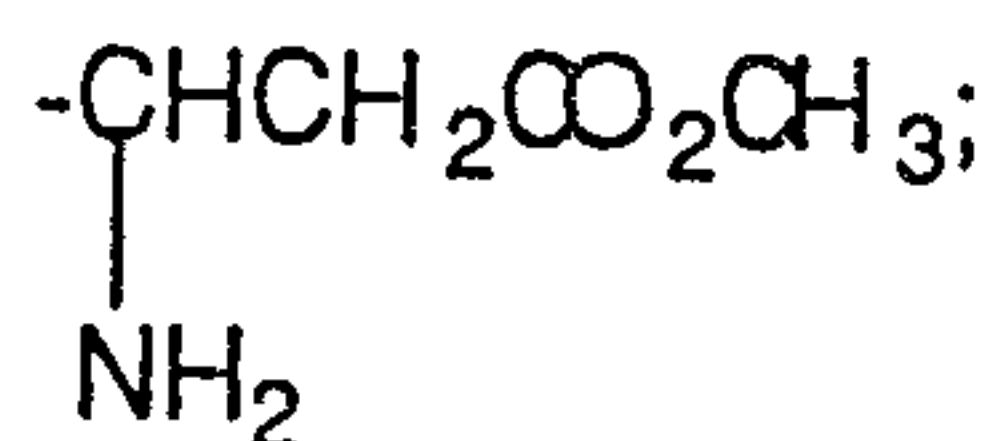
R¹⁸ and R¹⁹ independently are H, alkyl of 1 to 4 carbon atoms, phenyl, benzyl, α-methylbenzyl, or taken together with the nitrogen form a ring of the formula



Q is NR²⁰, O or CH₂;

R²⁰ is H, alkyl of 1-4 carbon atoms, or phenyl;

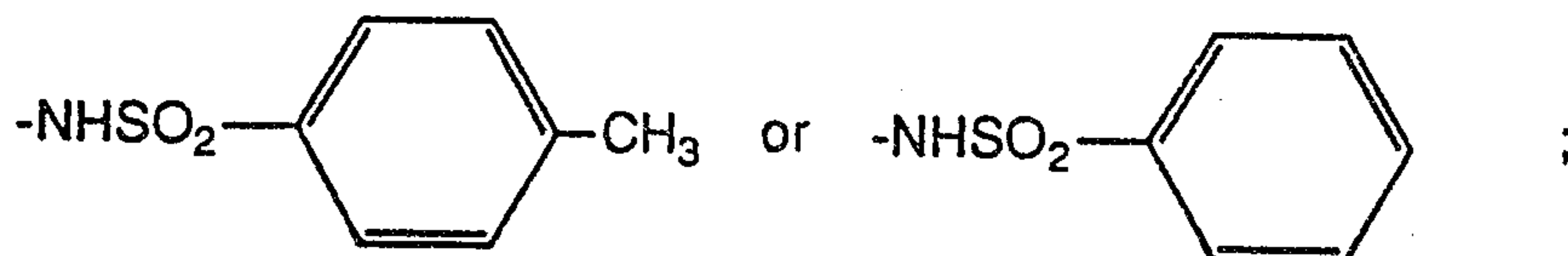
R²¹ is alkyl of 1 to 6 carbon atoms, -NR²²R²³, or



R22 and R23 independently are H, alkyl of 1 to 6 carbon atoms, benzyl, or are taken together as (CH₂)_u where u is 3-6;

R²⁴ is H, CH₃ or -C₆H₅;

R²⁵ is NR²⁷R²⁸, OR²⁸, NHCONH₂, NHCSNH₂,



25 R²⁶ is hydrogen, alkyl with from 1 to 6 carbon atoms, benzyl, or allyl;

R27 and R28 are independently hydrogen, alkyl with from 1 to 5 carbon atoms, or phenyl;

R²⁹ and R³⁰ are independently alkyl of 1-4 carbon atoms or taken together are -(CH₂)_q-;

30 R³¹ is H, alkyl of 1 to 4 carbon atoms, -CH₂CH=CH₂ or

13

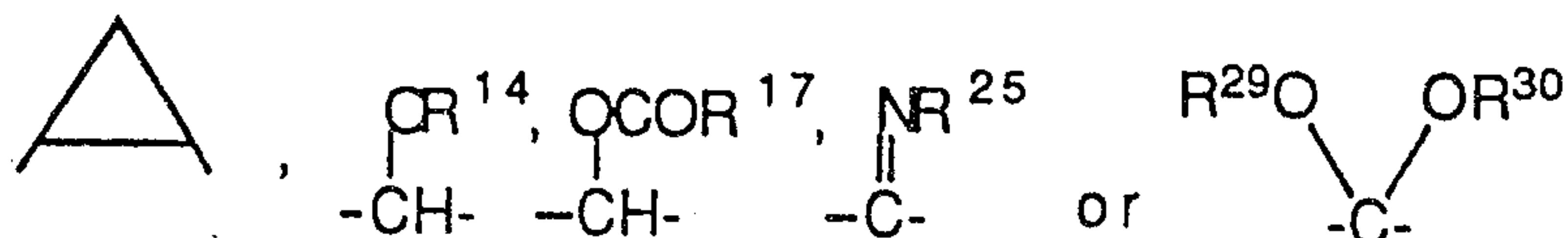
-CH₂C₆H₄R³²;R³² is H, NO₂, NH₂, OH or OCH₃;X is a carbon-carbon single bond, -CO-, -CH₂-, -O-, -S-,
-NH-,

5



-OCH₂-, -CH₂O-, -SCH₂-, -CH₂S-, NHC(R²⁷)(R²⁸), -NR²³SO₂-,
-SO₂NR²³-, -C(R²⁷)(R²⁸)NH-, -CH=CH-, -CF=CF-, -CH=CF-,
-CF=CH-, -CH₂CH₂-, -CF₂CF₂-,

10



Y is O or S;

Z is O, NR¹¹, or S;

15

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;

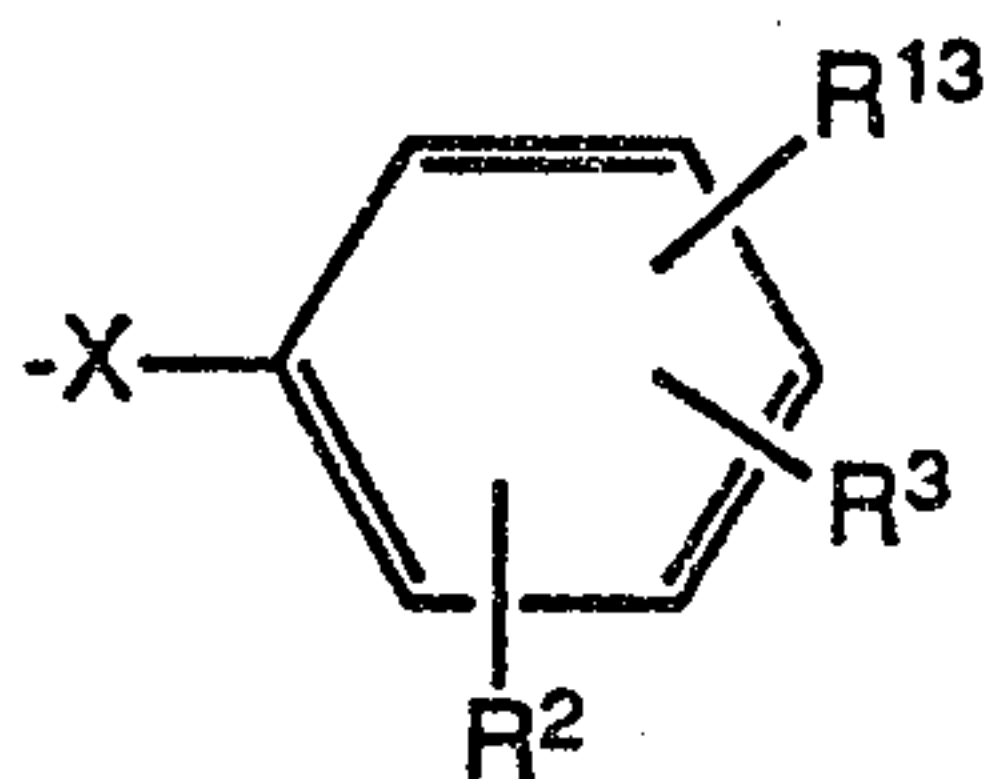
20

s is 0 to 5;

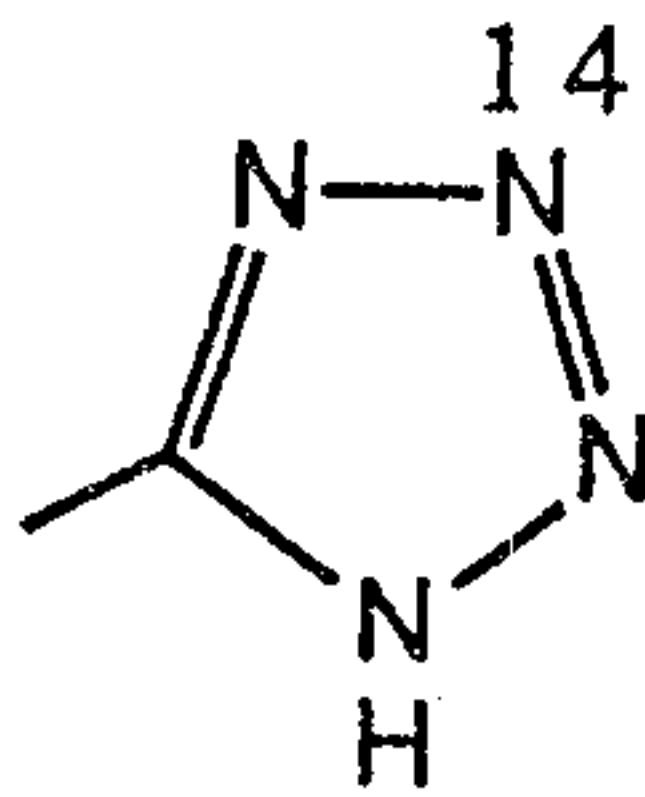
t is 0 or 1;

and pharmaceutically acceptable salts of these compounds;
provided that:

25

(1) the R¹ group is not in the ortho position;(2) when R¹ is

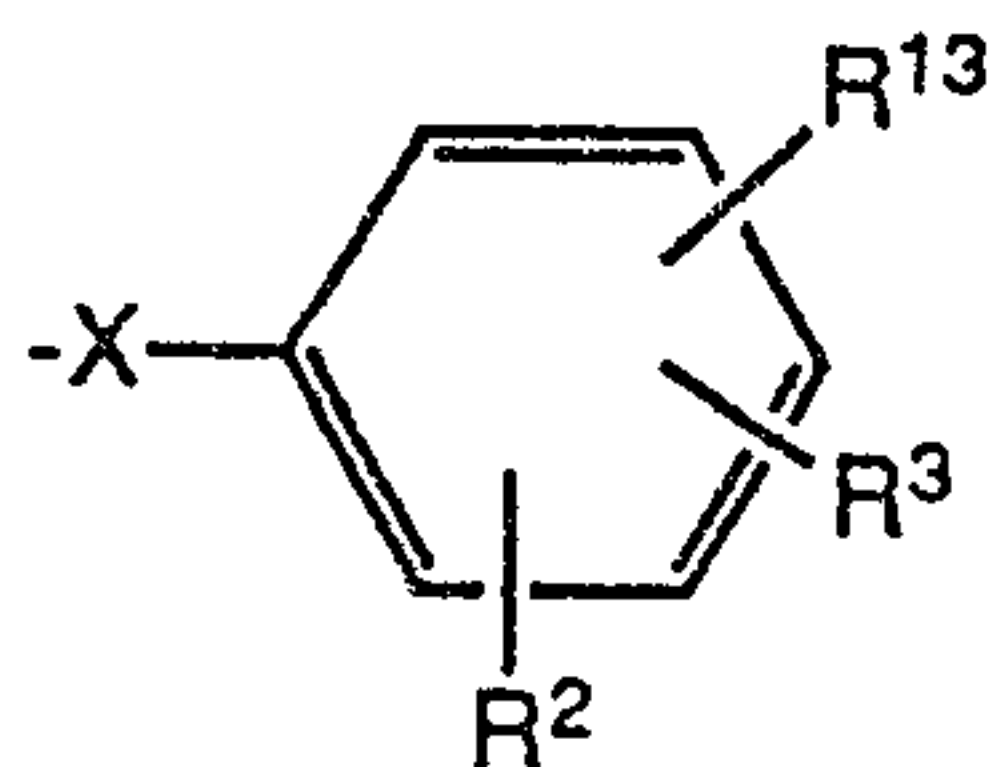
X is a single bond, and R¹³ is CO₂H, or



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

5 ortho;

(3) when R^1 is

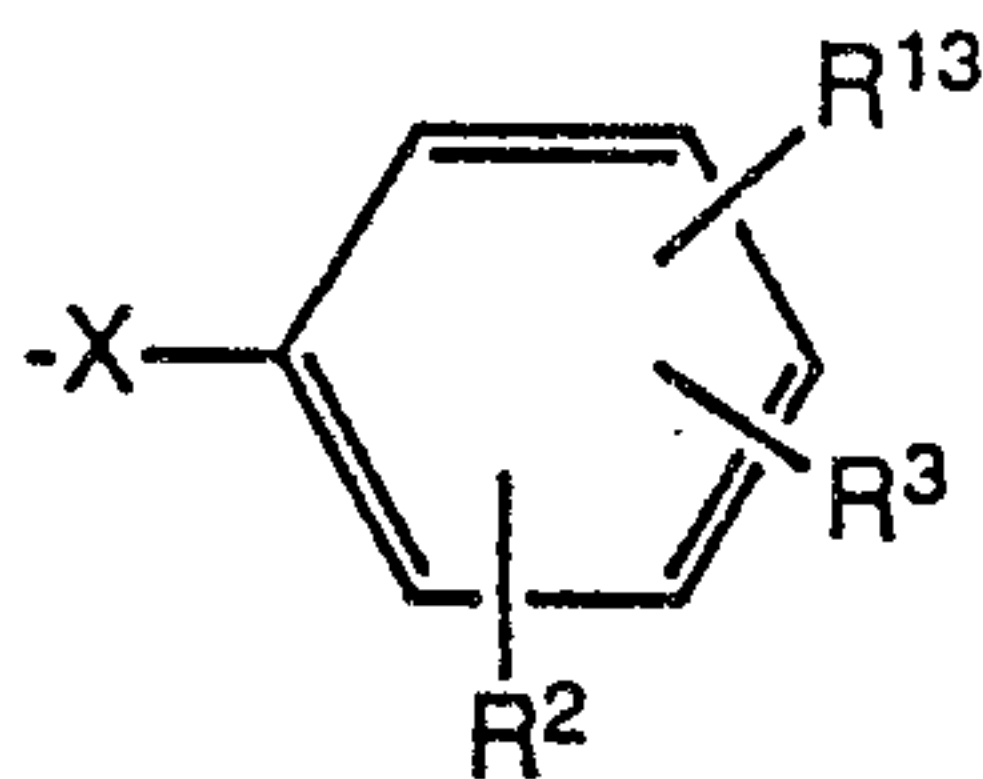


and X is other than a single bond, then R^{13} must be ortho except when $X = \text{NR}^{23}\text{CO}$ and R^{13} is NHSO_2CF_3 or NHSO_2CH_3 , then R^{13} must be ortho or meta;

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

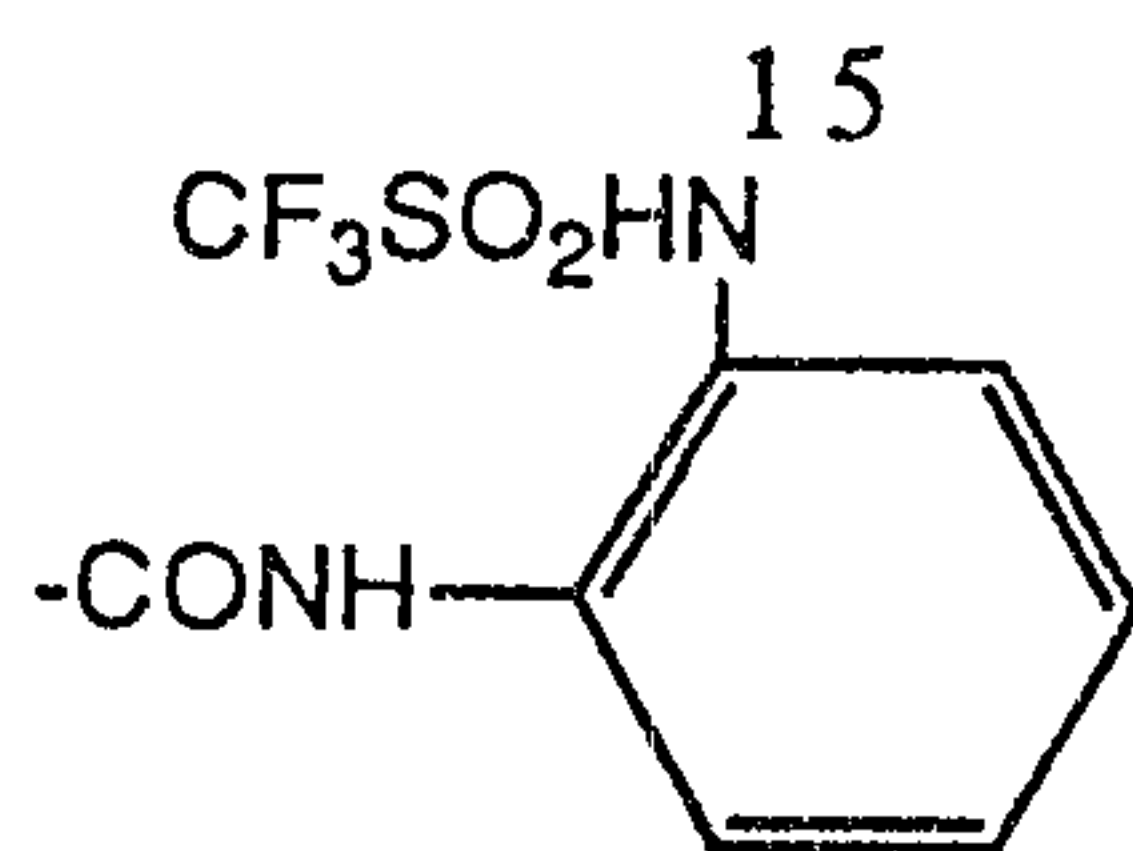
(5) when R^1 is 4- CO_2H or a salt thereof, the substituent on the 4-position of the imidazole cannot be CH_2OH , $\text{CH}_2\text{OCOCH}_3$, or $\text{CH}_2\text{CO}_2\text{H}$;

(6) when R^1 is



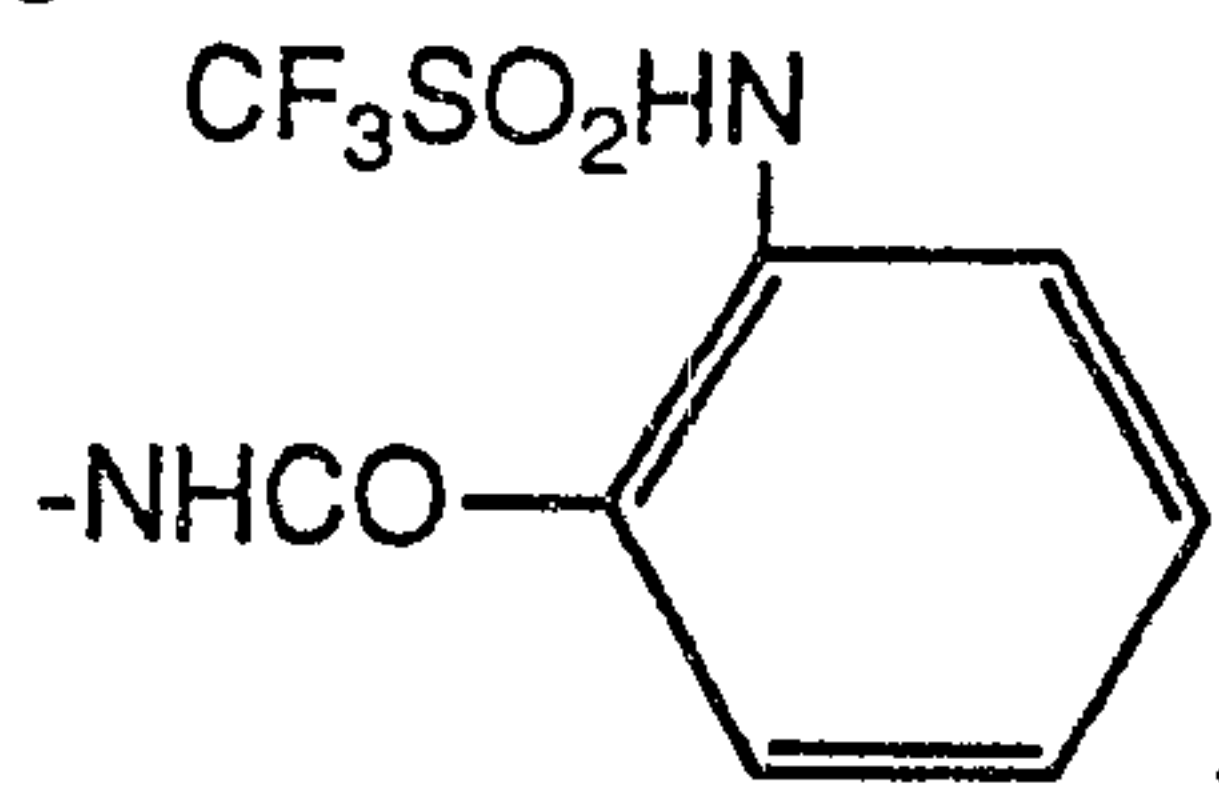
20 X is $-\text{OCH}_2-$, and R^{13} is 2- CO_2H , and R^7 is H then R^6 is not $\text{C}_2\text{H}_5\text{S}$;

(7) when R^1 is



and R⁶ is n-hexyl, then R⁷ and R⁸ are not both hydrogen;

(8) when R¹ is



5

R⁶ is not methoxybenzyl;

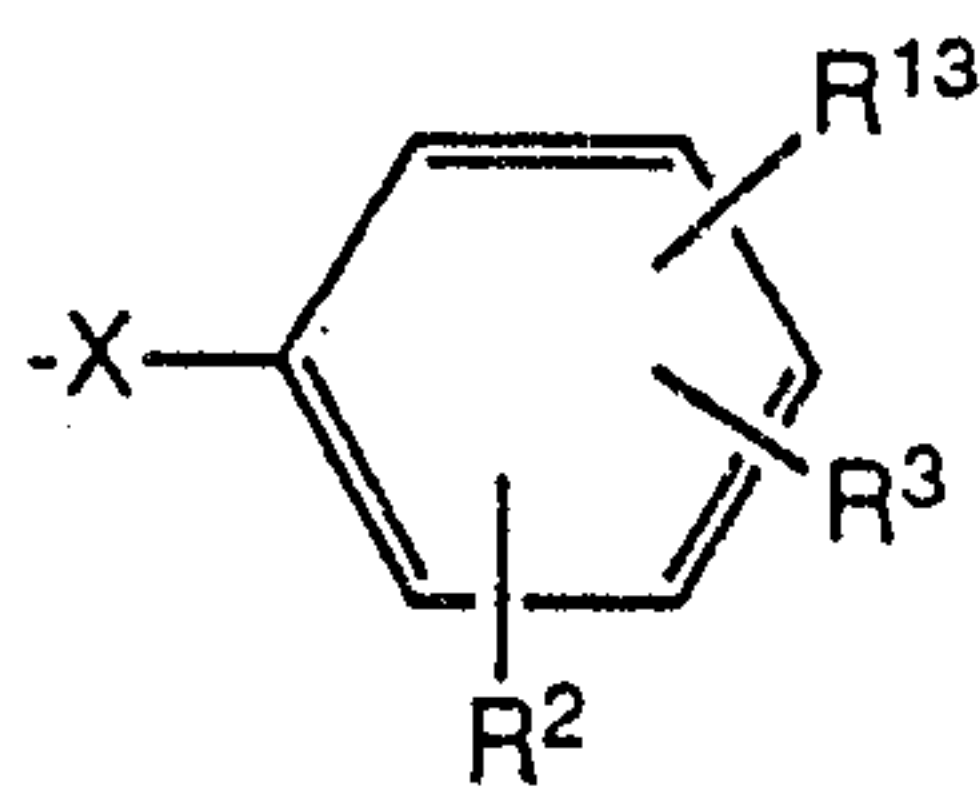
(9) the R⁶ group is not -F-CHCH₂CH₂CH₃ or CH₂OH;

(10) when r=0, R¹ is

10

X is -NH-C=O, R¹³ is 2-NHSO₂CF₃, and R⁶ is n-propyl, then R⁷ and R⁸ are not -CO₂CH₃;

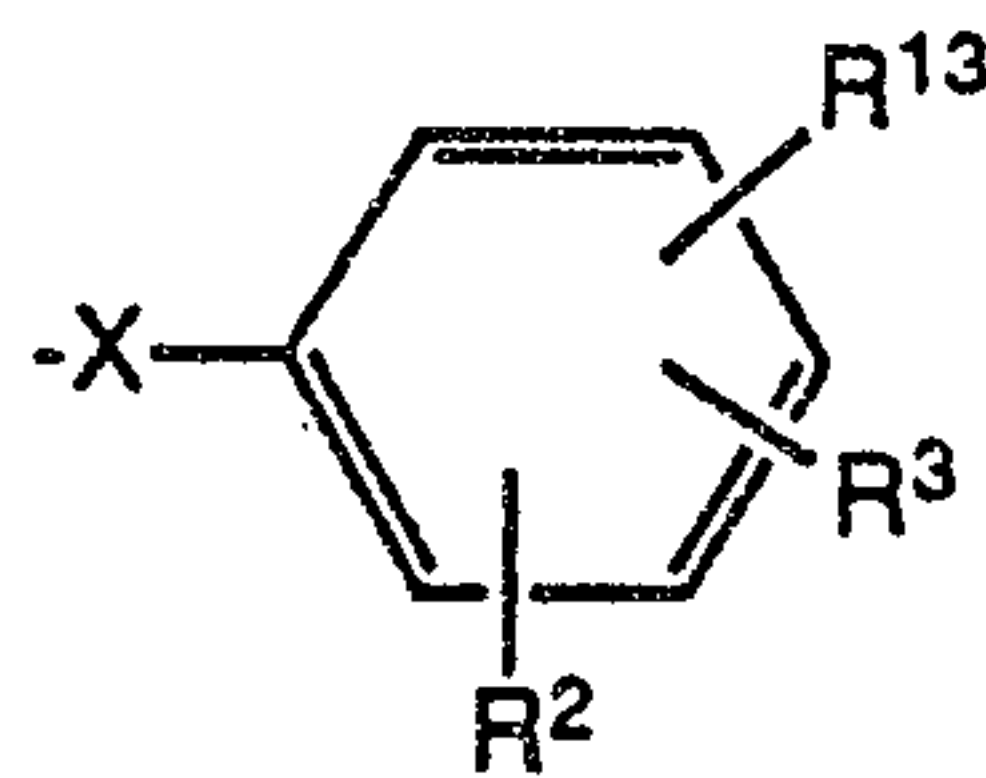
(11) when r=0, R¹ is



15

X is NH-C=O, R¹³ is 2-COOH, and R⁶ is n-propyl, then R⁷ and R⁸ are not -CO₂CH₃;

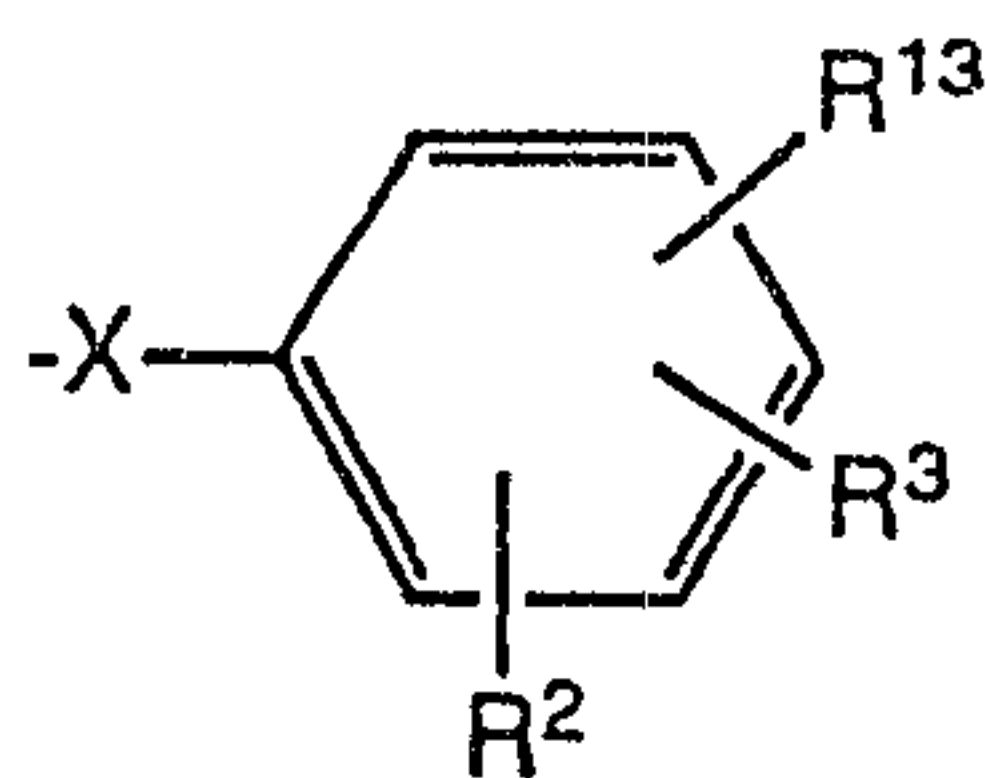
(12) when r=1, R¹=



20

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

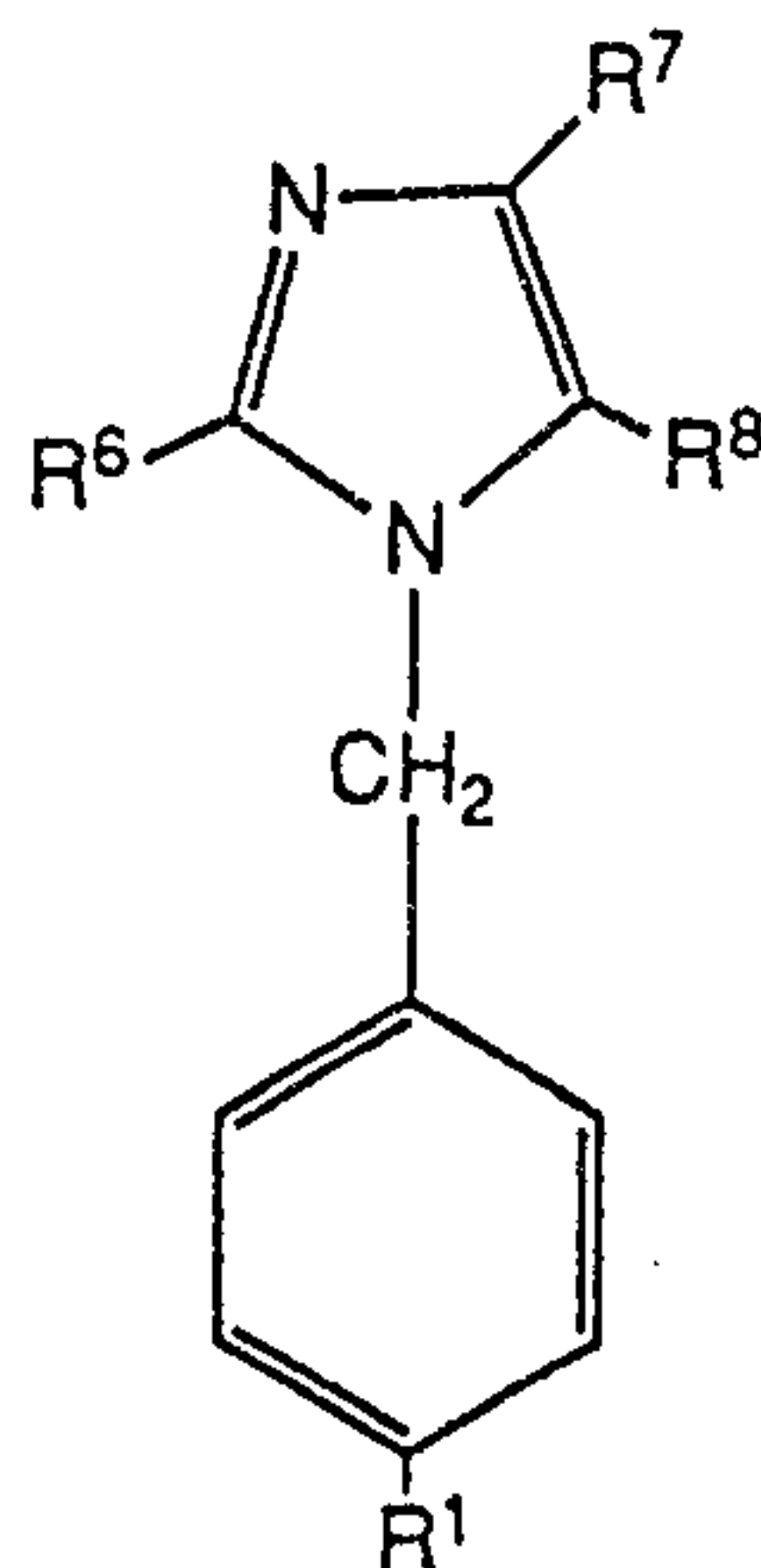
(13) when $r=1$, $R^1=$



5

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):

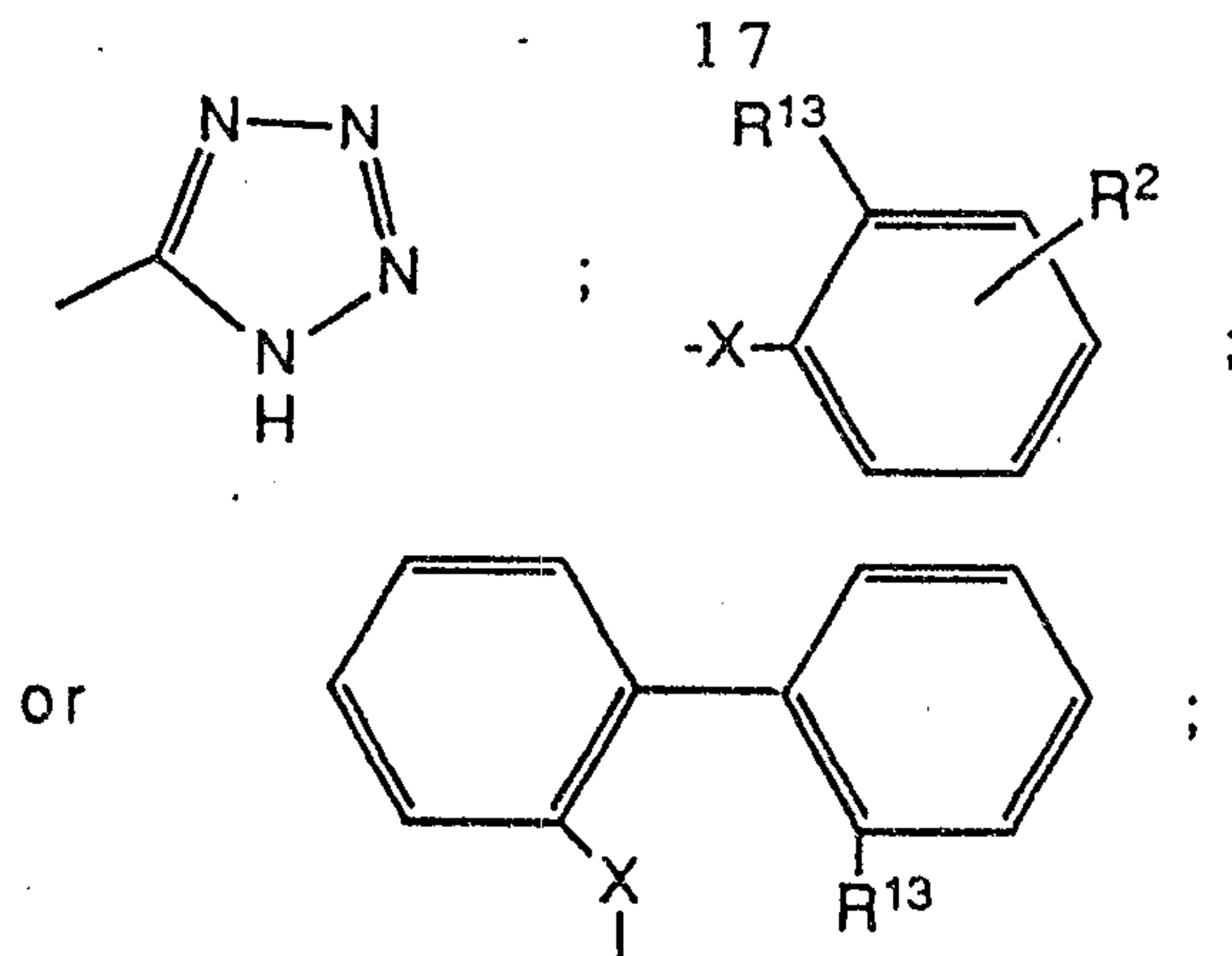


10

(II)

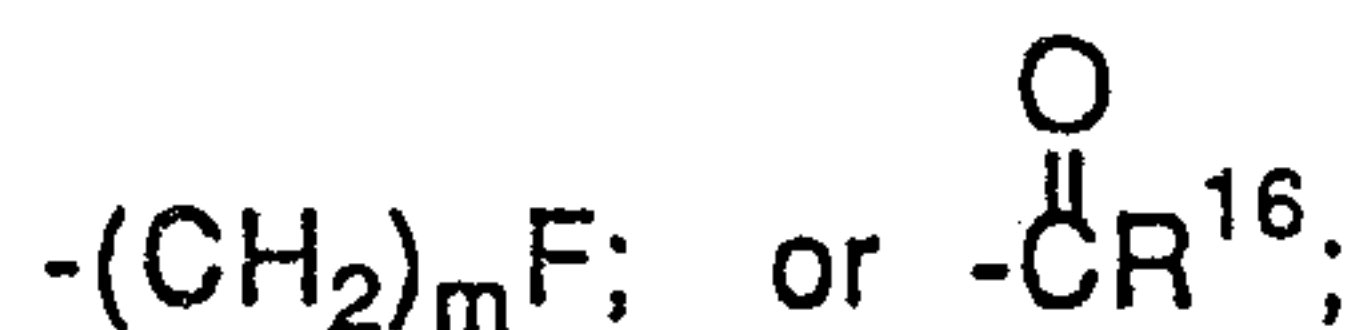
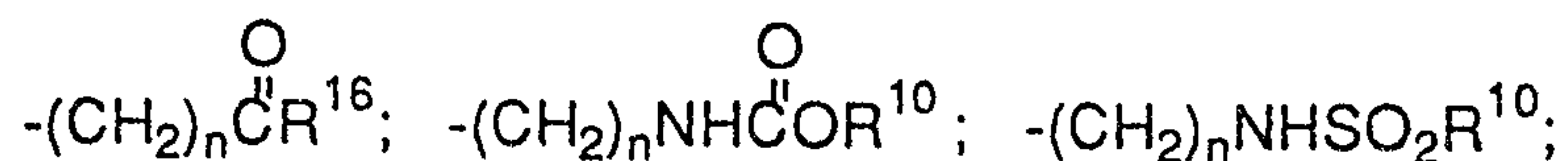
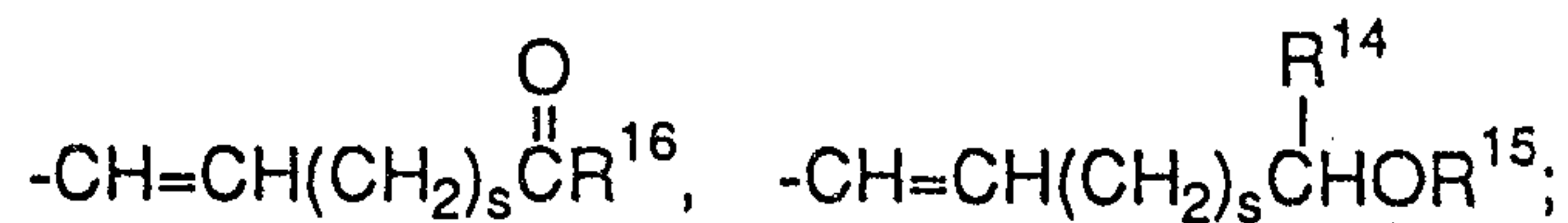
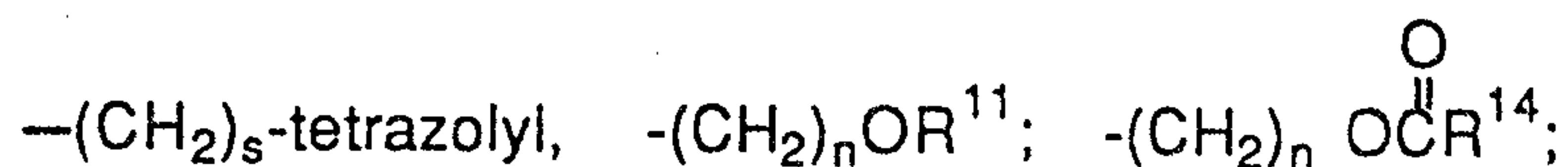
wherein

R^1 is -CO₂H; -NH₂SO₂CF₃;



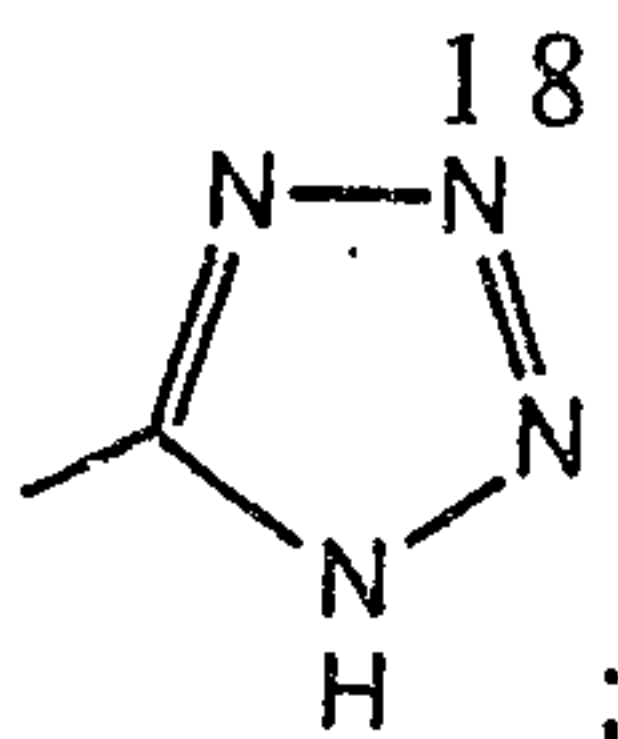
R^6 is alkyl of 3 to 10 carbon atoms, alkenyl of 3 to 10 carbon atoms, alkynyl of 3 to 10 carbon atoms, cycloalkyl of 3 to 8 carbon atoms, benzyl substituted on the phenyl ring with up to two groups selected from alkoxy of 1 to 4 carbon atoms, halogen, alkyl of 1 to 4 carbon atoms, and nitro;

R^8 is



10 phenylalkenyl wherein the aliphatic portion is 2 to 4 carbon atoms; $-(CH_2)_m\text{-imidazol-1-yl}$; or $-(CH_2)_m\text{-1,2,3-triazolyl}$ optionally substituted with one or two groups selected from $-\text{CO}_2\text{CH}_3$ or alkyl of 1 to 4 carbon atoms;

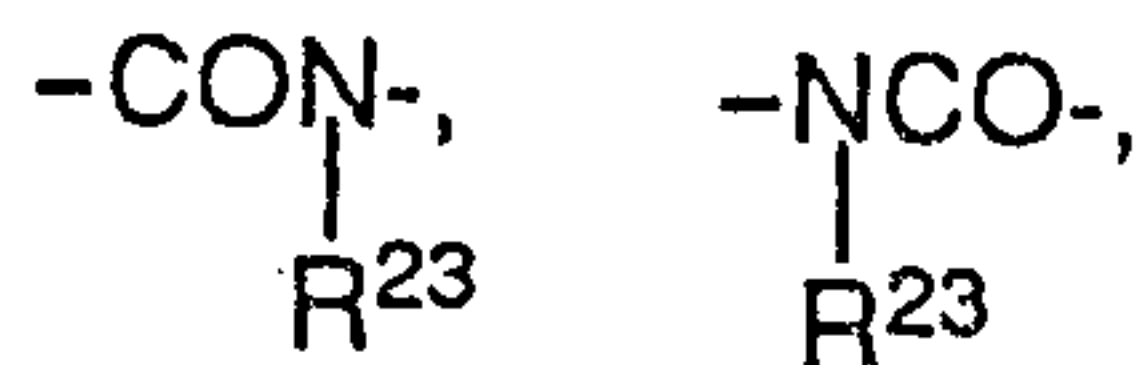
15 R^{13} is $-\text{CO}_2\text{H}$, $-\text{CO}_2R^9$, NHSO_2CF_3 ; SO_3H ; or



R¹⁶ is H, alkyl of 1 to 5 carbon atoms, OR¹⁷, or NR¹⁸R¹⁹;

X is carbon-carbon single bond, -CO-, CH₂CH₂-,

5



-OCH₂-, -CH₂O-, -O-, -SCH₂-, -CH₂S-, -NH-CH₂-, -CH₂NH- or -CH=CH-; and pharmaceutically acceptable salts of these compounds;

10

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

R² is H, alkyl of 1 to 4 carbon atoms, halogen, or alkoxy of 1 to 4 carbon atoms;

15

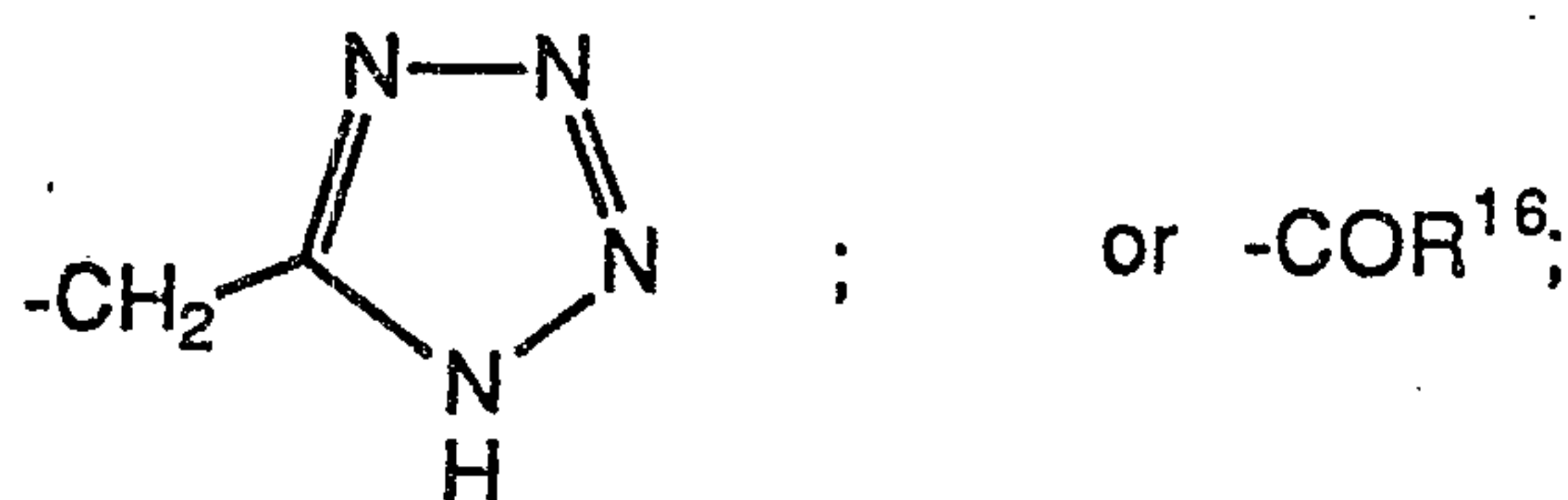
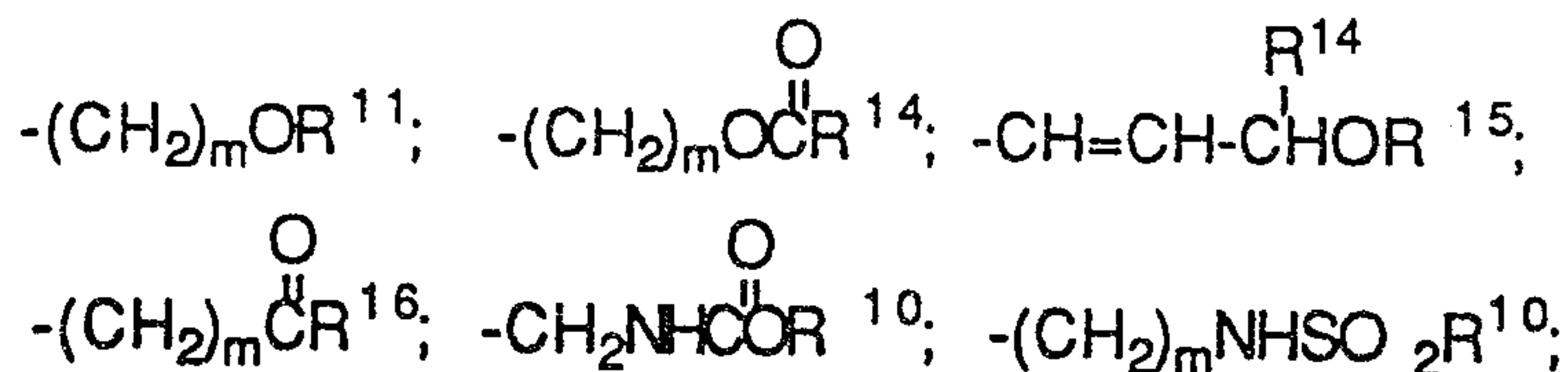
R⁶ is alkyl, alkenyl or alkynyl of 3 to 7 carbon atoms;

R⁷ is heteroaryl selected from 2- and 3-thienyl, 2- and 3-furyl, 2-, 3-, and 4-pyridyl, p-biphenyl; H, Cl, Br, I;

C_vF_{2v+1}, where v=1-3; $\overset{\text{O}}{\parallel}\text{C-R}^{16}$; straight or branched chain alkyl of 1 to 6 carbon atoms; or phenyl;

20

R⁸ is



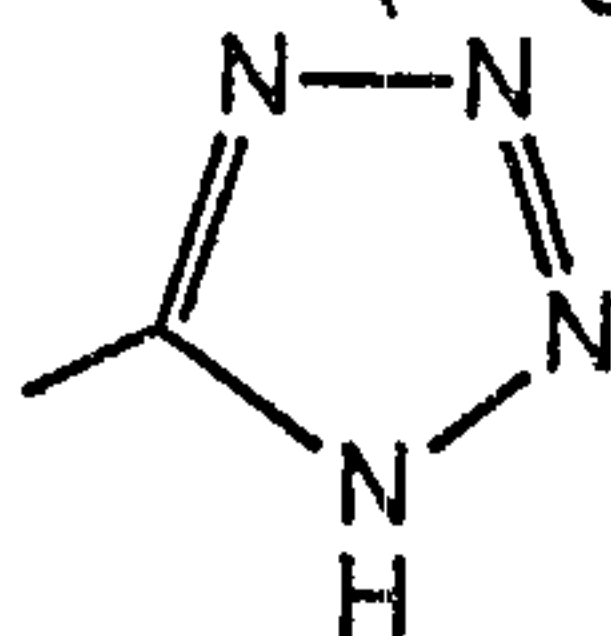
or -COR¹⁶;

R¹⁰ is CF₃, alkyl of 1 to 6 carbon atoms or phenyl;

R¹¹ is H, or alkyl of 1 to 4 carbon atoms;

19

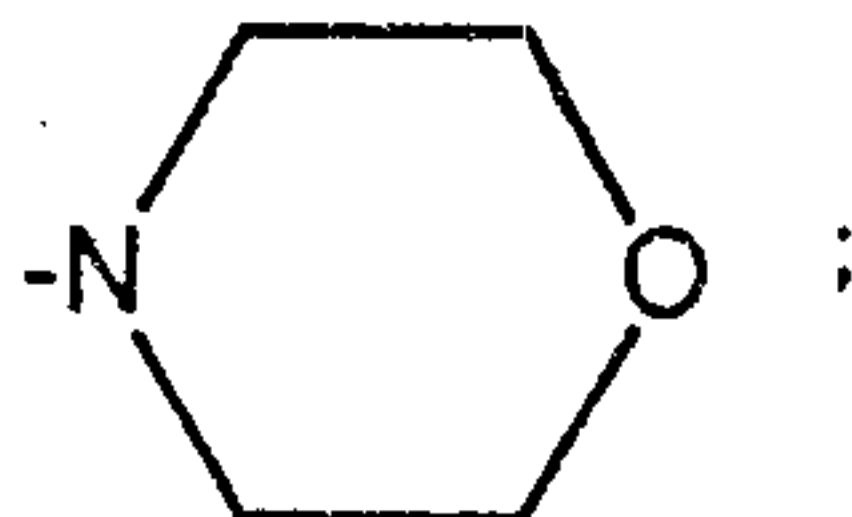
R¹³ is CO₂H; CO₂CH₂OCOC(CH₃)₃; NHSO₂CF₃;



R¹⁴ is H, or alkyl of 1 to 4 carbon atoms;

5 R¹⁵ is H, alkyl of 1 to 4 carbon atoms, or acyl of 1 to 4 carbon atoms;

R¹⁶ is H, alkyl of 1 to 5 carbon atoms; OR¹⁷; or

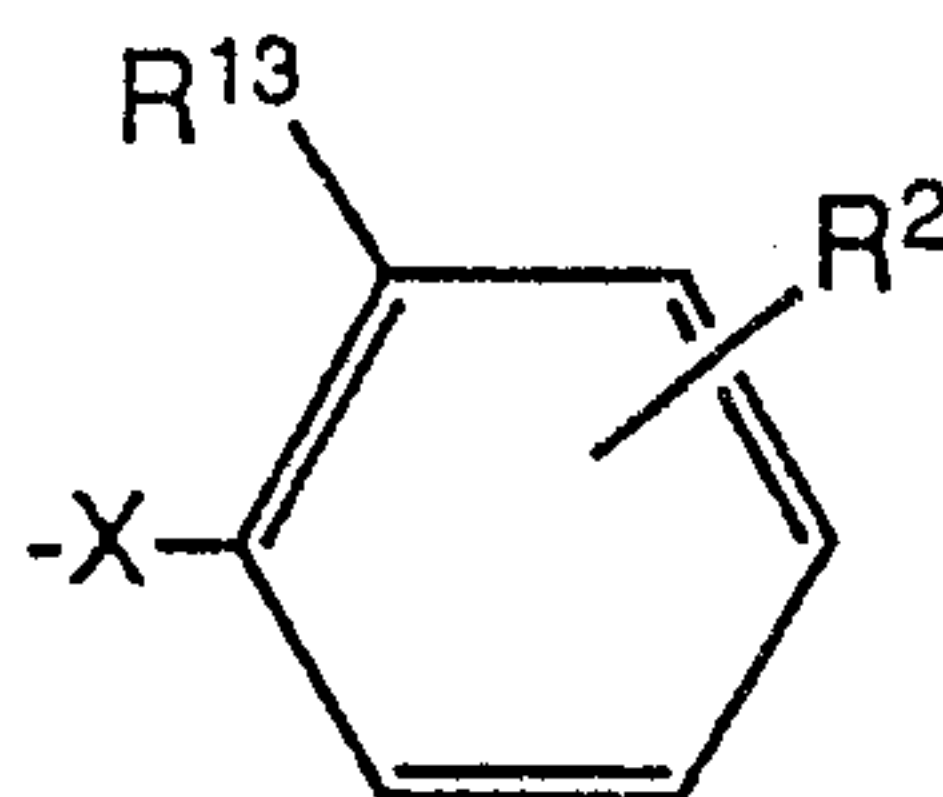


10 m is 1 to 5;

X = single bond, -O-, -CO-, -NHCO-, or -OCH₂-; and pharmaceutically acceptable salts.

More preferred in the method of the invention are compounds of Formula II, wherein R¹ is

15



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

20 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.
- 25 • 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-(hydroxymethyl)-imidazole.
 - 2-Butyl-4-trifluoromethyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxylic 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. Preferred 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, R¹, R² and R³ can each be CONHOR¹². R¹² need not be the same substituent in each of R¹, R² and R³ 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
5 Patent Application EPA 0 324 377, published 7/19/89, (page 17, line 5 through page 212, line 32), United States Patent Number 5,254,546
(page 16, line 21 through page 133, line 35),
and United States Patent Number 5,210,079
10 (page 16, line 21 through page 153, line 15).

Two distinct angiotensin II (All) receptor subtypes have been discovered and characterized by means of the
15 discriminatory effect of dithiothreitol (DTT) and by two structurally dissimilar nonpeptide All 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-
20 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
25 EPA 0 245 637).

Using radioligand-receptor binding techniques, DuP 753 was found to be highly specific for an All receptor site, designated All receptor subtype-1 or All-1, displaying an inhibitory constant IC₅₀ value of about 1.2×10^{-8} M in rat
30 adrenal cortex. This type of All receptor was particularly sensitive to inactivation by DTT. EXP655 exhibited very low affinity for the All-1 site (IC₅₀ value of about 3.0×10^{-4} M), but was highly selective for a distinct All receptor site, designated All receptor subtype-2 or All-2, exhibiting an
35 inhibitory constant IC₅₀ value of about 1.0×10^{-7} M in rat

adrenal cortex. In contrast to the All-1 receptor, the All-2 receptor was resistant to DTT inactivation. Moreover, DuP 753 had very low affinity for the All-2 receptor (IC₅₀ of about 1.4 x 10⁻⁴ M).

- 5 The rat adrenal medulla contains a relatively high density of All receptors which are predominately the All-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 All
10 receptor subtypes.

 The compounds of Formula (I) above (which includes DuP 753) block the All-1 receptor subtype. Compounds of Formula (I) above wherein R⁷ or R⁸ at the 4-position on the imidazole ring is phenyl, phenylalkyl, phenylalkenyl, phenylalkynyl,
15 substituted phenyl, substituted phenylalkyl, substituted phenylalkenyl or substituted phenylalkynyl, block both the All-1 and the All-2 receptor subtypes. For example, Compounds A and B identified below show affinity for both All-1 and All-2 receptors in the tests described in the Chiu et al. paper.

- 20 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
25 obtained in the tests for receptor specificity are summarized in Table I:

Table 1
Antagonist Specificity Exhibited by All Receptor Subtypes
IC₅₀ (M)

5	Compound	IC ₅₀ (M)	
		All-1	All-2
	All	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}
10	Compound A	2.2×10^{-8}	2.4×10^{-6}
	Compound B	2.9×10^{-7}	4.3×10^{-6}

15 All-1 site binding was determined using adrenal cortex microsomes in the presence of 10^{-5} M EXP655. All-2 site binding was determined using adrenal medulla microsomes in the presence of 10^{-5} M DuP 753. IC₅₀ was determined by displacement of [¹²⁵I]All from the receptor by the indicated compound.

20 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 All receptors which are predominately the All-2 subtype. EXP655 displaced the [¹²⁵I]All binding in rat brain membranes in a concentration-
 25 dependent manner yielding IC₅₀ value of 3.2×10^{-7} M. In contrast, DuP 753 displaced the binding of All inefficiently, with an IC₅₀ value of 1.5×10^{-4} M.

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

Despite a high density of All-2 binding sites in the brain, All-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 All-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 All-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 $22 \pm 1^\circ \text{C}$ with relative humidity of $50 \pm 10 \%$.

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 $\mu\text{g}/5\mu\text{L}$ (Sigma Chemicals), and EXP655 at 0.1-100 $\mu\text{g}/5\mu\text{L}$ 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 All-1 receptor antagonists, Compounds C and D, when co-administered with renin protected against the amnesia (Tables 3 and 4). EXP655, an All-2-specific antagonist, was much less effective in preventing the amnesia (Table 5).

27

TABLE 2Renin-induced Disruption of Passive
Avoidance Retention

<u>[renin], (ug/5uL IVT)</u>	<u>Median Retention Latency, (sec)</u>
0	300
0.1	254
0.5	117
1.0	27
3.0	56.5
5.0	17

5

TABLE 3Compound C Blocks
Renin-induced Disruption
of Passive Avoidance Retention

<u>[renin], (ug/5uL IVT)</u>	<u>[Example 5], (ug/5uL IVT)</u>	<u>Median Retention Latency, (sec)</u>
0	0	300
1.0	0	48
1.0	10	264
1.0	30	300
1.0	100	34.5

10

TABLE 4Compound D Blocks
Renin-induced Disruption
of Passive Avoidance Retention

<u>[renin], (ug/5uL IVT)</u>	<u>[Example 6], (ug/5uL IVT)</u>	<u>Median Retention Latency, (sec)</u>
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

<u>[renin],</u> <u>(ug/5uL IVT)</u>	<u>[Example 2],</u> <u>(ug/5uL IVT)</u>	<u>Median Retention</u> <u>Latency, (sec)</u>
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

5

DOSAGE FORMS

The compounds of this invention can be administered for the treatment of All-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.

5 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
10 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.
15 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.
20 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
25 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
30 (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
35 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

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

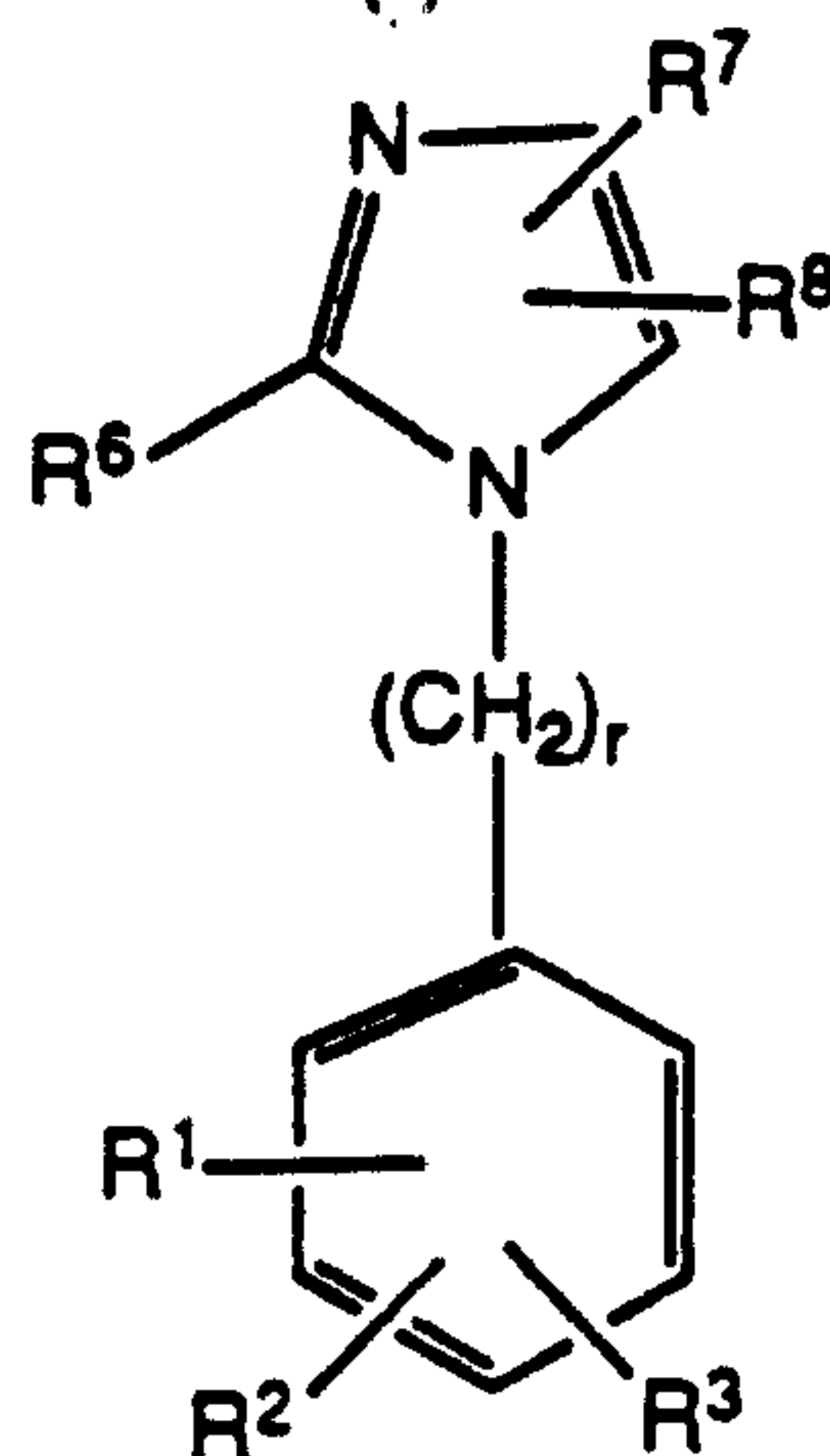
Suspension:

- 5 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.
- 10 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
- 15 both drugs.

CLAIMS:

1. The use, for treating a central nervous system (CNS)
 5 disorder mediated by Angiotensin II in a mammal of a

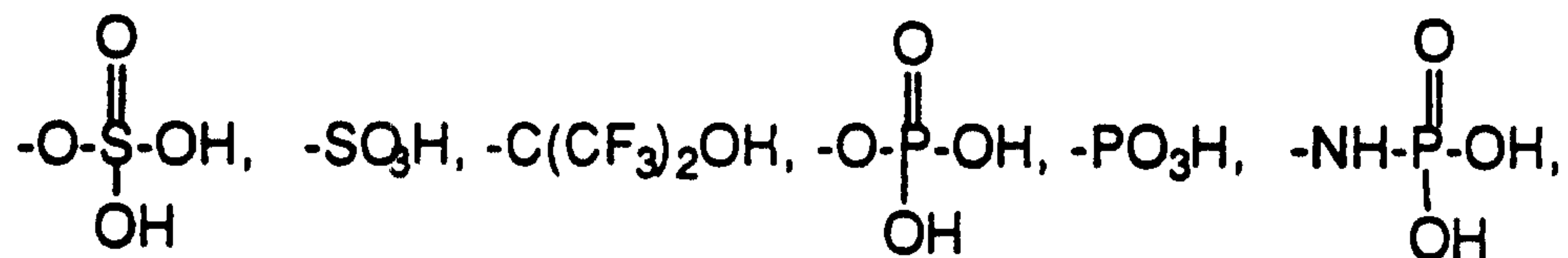
compound having the formula (I):



(I)

wherein

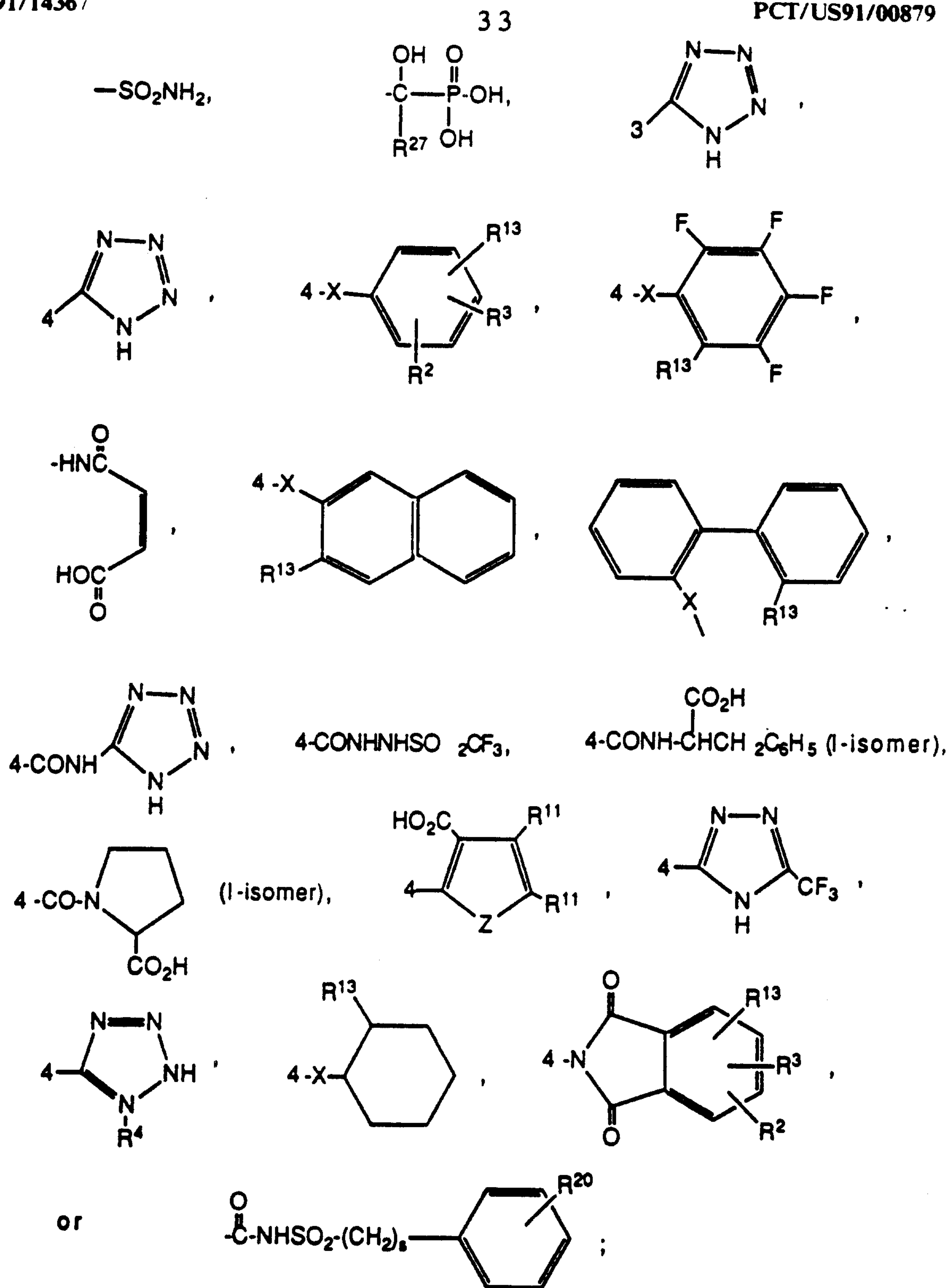
10 R^1 is 4-CO₂H; 4-CO₂R⁹;



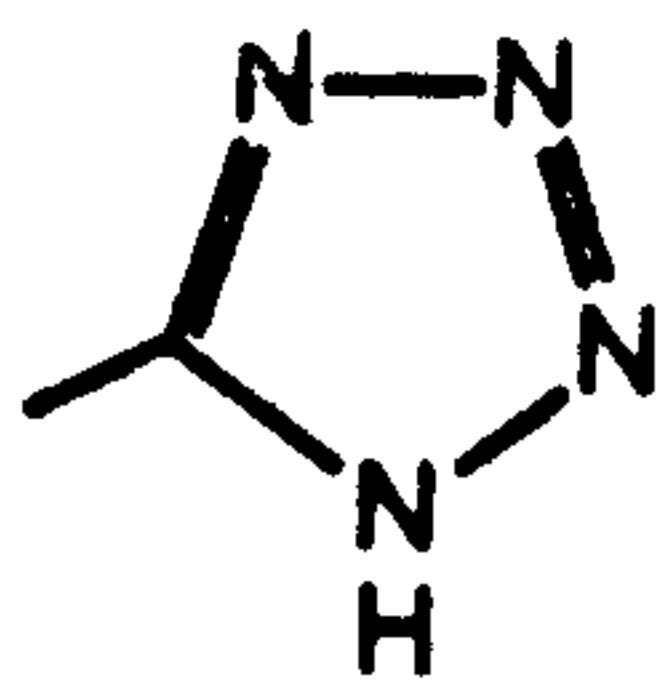
15 4-NHSO₂CH₃, -4-NHSO₂CF₃, -CONHOR¹²,

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R² is H, Cl, Br, I, F, NO₂, CN, alkyl of 1 to 4 carbon atoms, acyloxy of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, 5 CO₂H, CO₂R⁹, NHSO₂CH₃, NHSO₂CF₃, CONHOR¹², SO₂NH₂.



, aryl, or furyl,

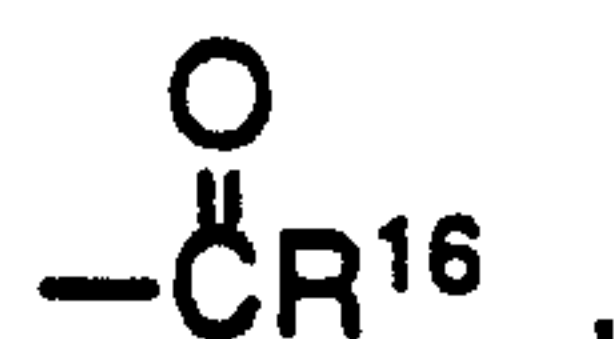
R^3 is H, Cl, Br, I or F, alkyl of 1 to 4 carbon atoms or alkoxy of 1 to 4 carbon atoms;

R^4 is CN, NO₂ or CO₂R¹¹;

5 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 CO₂R¹⁴, cycloalkyl of 3 to 8 carbon atoms, cycloalkylalkyl of 4 to 10 carbon atoms, cycloalkylalkenyl or cycloalkylalkynyl of 5 to 10 carbon atoms, (CH₂)_sZ(CH₂)_mR⁵ optionally substituted with F or CO₂R¹⁴, 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;

15 R^7 is H, F, Cl, Br, I, NO₂, C_vF_{2v+1} where v = 1-6, C₆F₅, CN,



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, OCH₃, CF₃, 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-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, 2-, 4- or 5-imidazolyl, o-, m- or p-biphenyl, o-, m- or p-phenoxyphenyl, substituted phenylalkynyl, heteroaryl, m- or p-biphenyl or o-, m- or p-phenoxyphenyl substituted on

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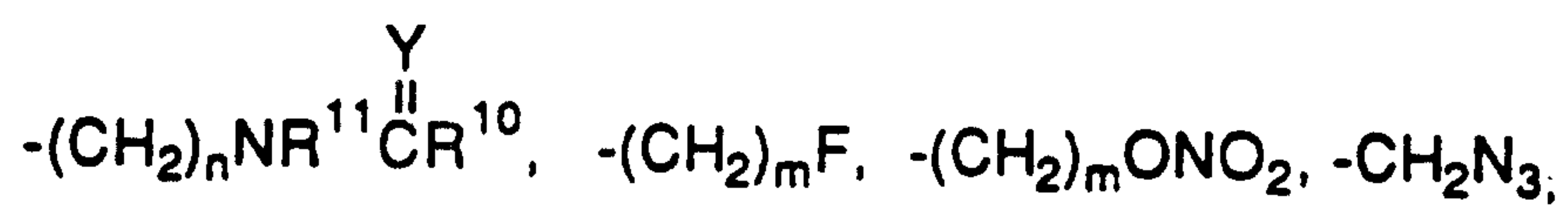
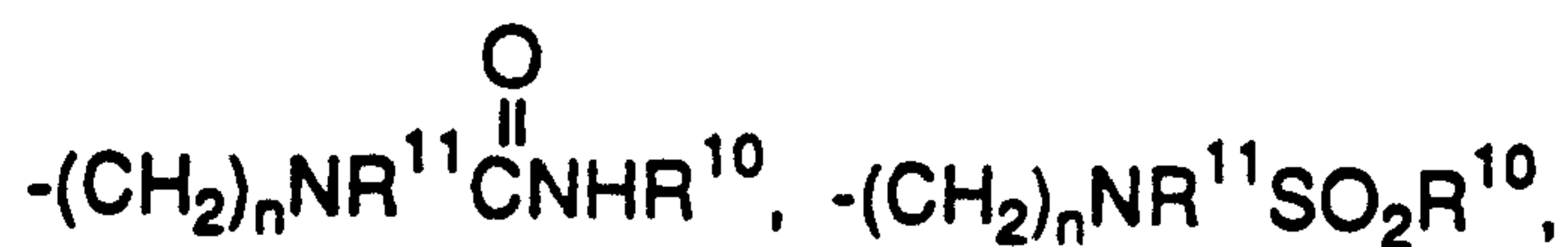
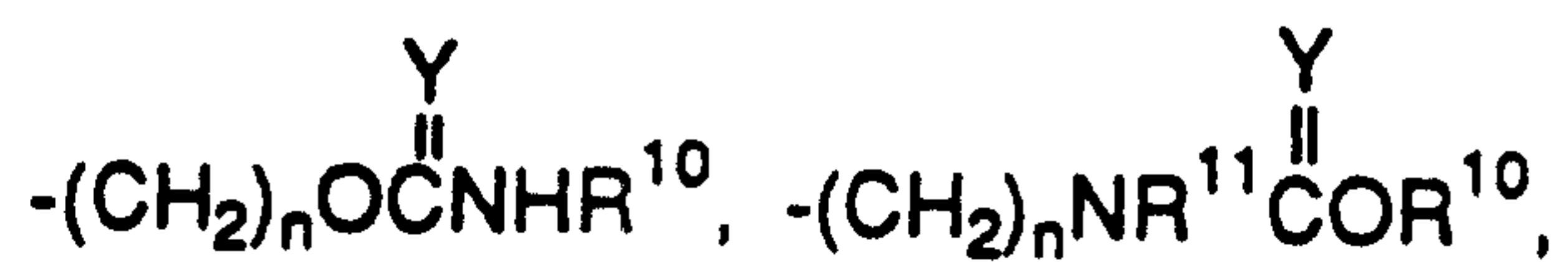
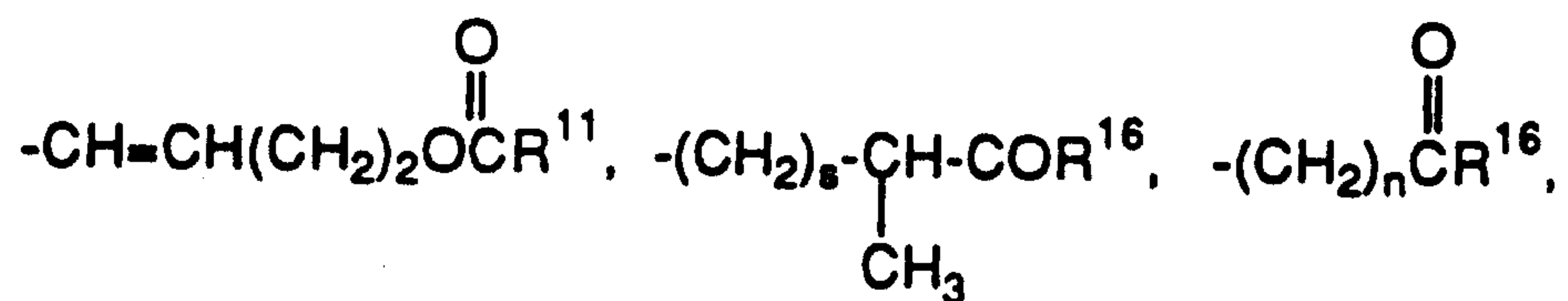
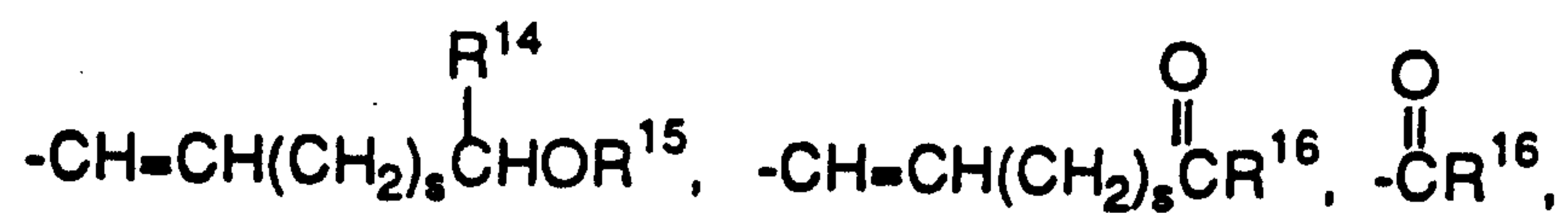
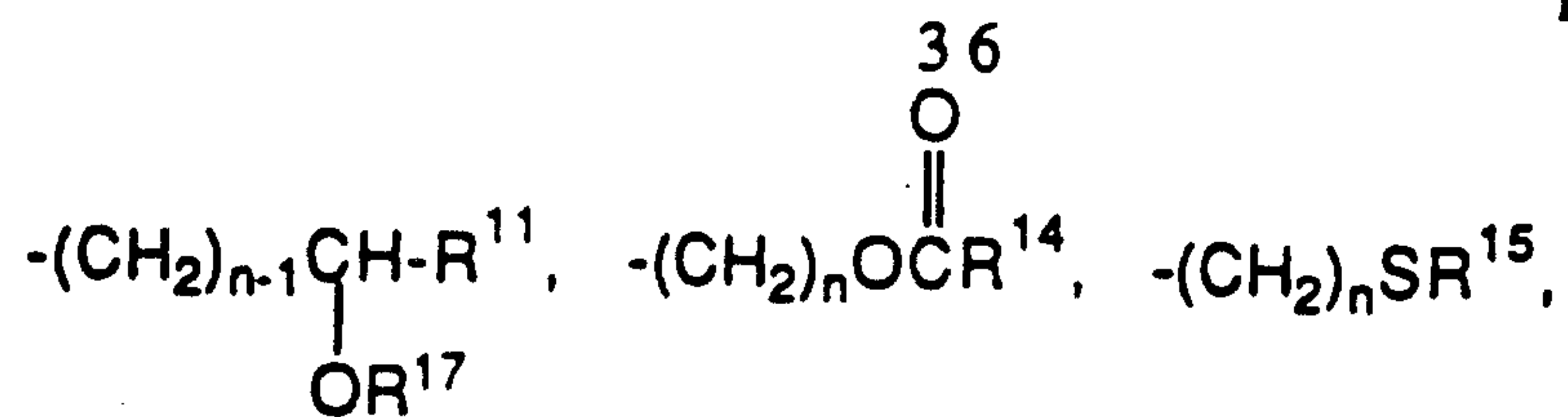
35

- ring carbon with 1 or 2 substituents selected from halogen, alkoxy of 1-5 carbon atoms, alkyl of 1-5 carbon atoms, -NO₂, -CN, -CF₃, -COR¹⁶, -CH₂OR¹⁷, -NHCOR¹⁷, CONR¹⁸R¹⁹, S(O)_rR¹⁷, or SO₂NR¹⁸R¹⁹, 2- or 3- pyrrolyl, 3-, 4- or 5- pyrazolyl or
- 5 2-, 4- or 5- imidazolyl substituted on ring nitrogen with alkyl of 1-5 carbon atoms or benzyl, substituted alkyl, alkenyl, or alkynyl of 1 to 10 carbon atoms substituted with a substituted or unsubstituted heteroaryl, m- or p- biphenyl or o-, m- or p-phenoxyphenyl group 1- or 2- naphthyl, 5- or 6-naphthoquinonyl,
- 10 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-quinoliny; 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
- 15 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-benzothieryl, 1-, 2-, 3- or 4-dibenzofuryl, 1-, 2-, 3- or 4-dibenzothieryl, 1-, 2-, 3- or 4-fluoenyl; any of the foregoing polycyclic aryl groups substituted with 1 or 2 substituents selected from
- 20 halogen, alkoxy of 1-5 carbon atoms, alkyl of 1-5 carbon atoms, -NO₂, -CN, -CF₃, -COR¹⁶, -CH₂OR¹⁷, -NHCOR¹⁷, CONR¹⁸R¹⁹, S(O)_rR¹⁷, or SO₂NR¹⁸R¹⁹; substituted alkyl of 1 to 10 carbon atoms, alkenyl or alkynyl of 2 to 10 carbon atoms substituted with any of the foregoing polycyclic aryl groups or the
- 25 anhydride of 4, 5-dicarboxyl-1- or 2-naphthyl;

- R⁸ is H, CN, alkyl of 1 to 10 carbon atoms, alkenyl of 3 to 10 carbon atoms, the same groups substituted with F,
- 30 phenylalkenyl wherein the aliphatic portion is 2 to 6 carbon atoms, -(CH₂)_m-imidazol-1-yl, -(CH₂)_m-1,2,3-triazolyl optionally substituted with one or two groups selected from CO₂CH₃ and alkyl of 1 to 4 carbon atoms, -(CH₂)_s-tetrazolyl,

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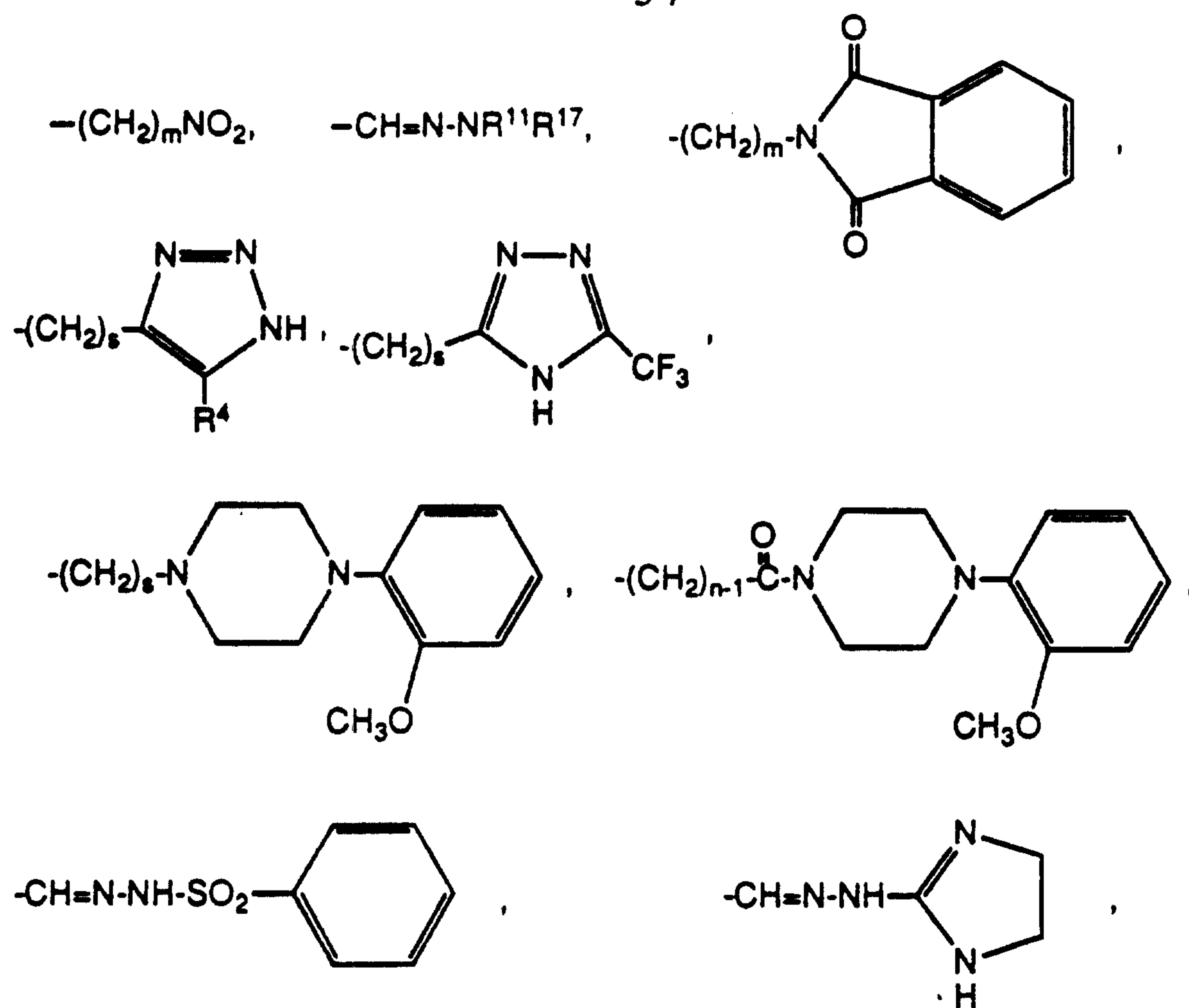
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or $-(CH_2)_m$ -tetrazolyl ;

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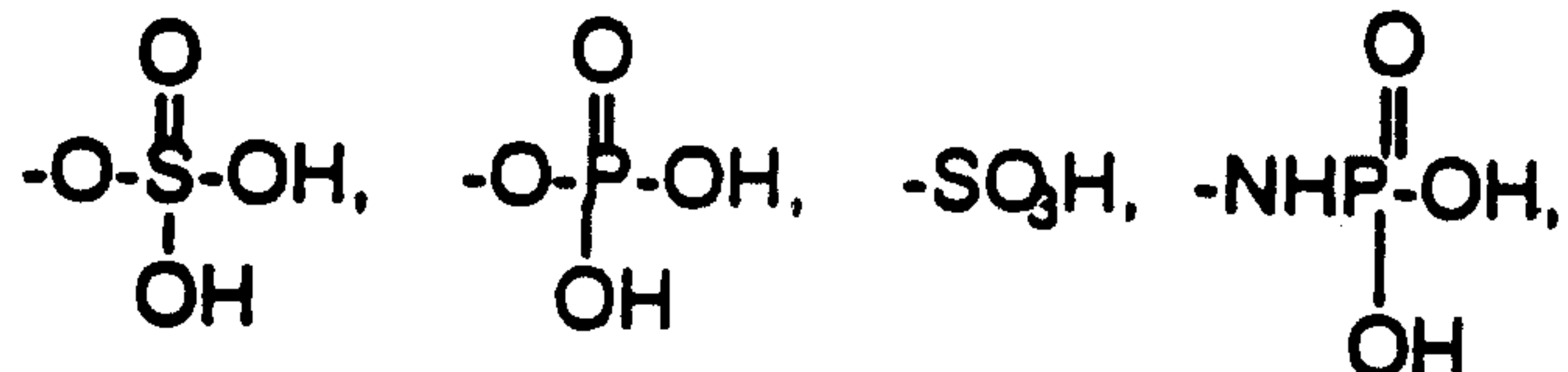
R^9 is $-\overset{\overset{R^{24}}{|}}{CH}-\overset{\overset{O}{||}}{C}R^{21}$;

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

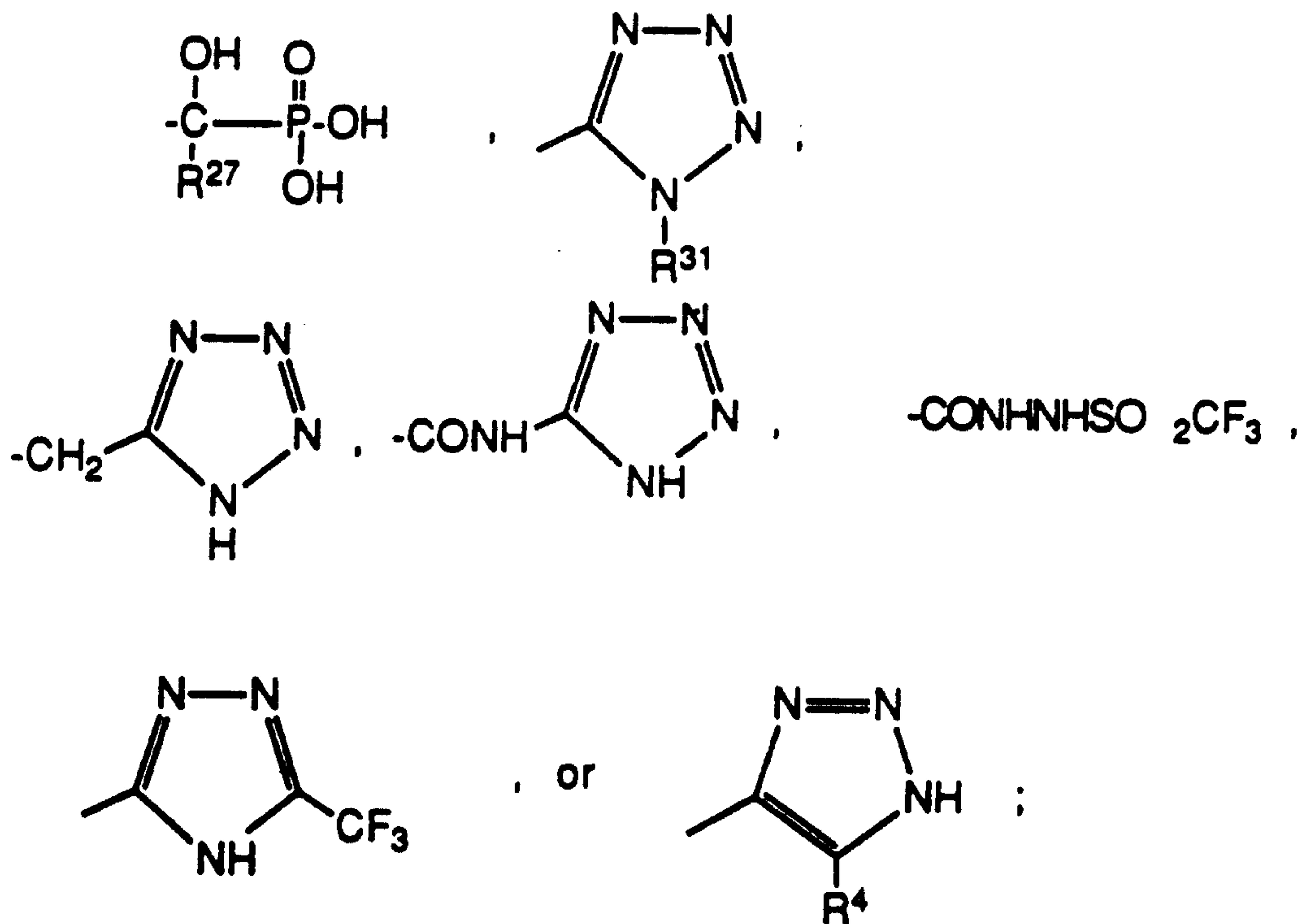
5 R^{11} is H, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, phenyl or benzyl;

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

R^{13} is $-CO_2H$, $-CO_2R^9$, $-CH_2CO_2H$, $-CH_2CO_2R^9$, $CO_2CH_2OCOC(CH_2)_3$,



10 $-PO_3H$, $-C(CF_3)_2OH$, $-NHSO_2CH_3$, $-NHSO_2CF_3$, $-NHCOCF_3$, $-CONHOR^{12}$, $-SO_2NH_2$,



15 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

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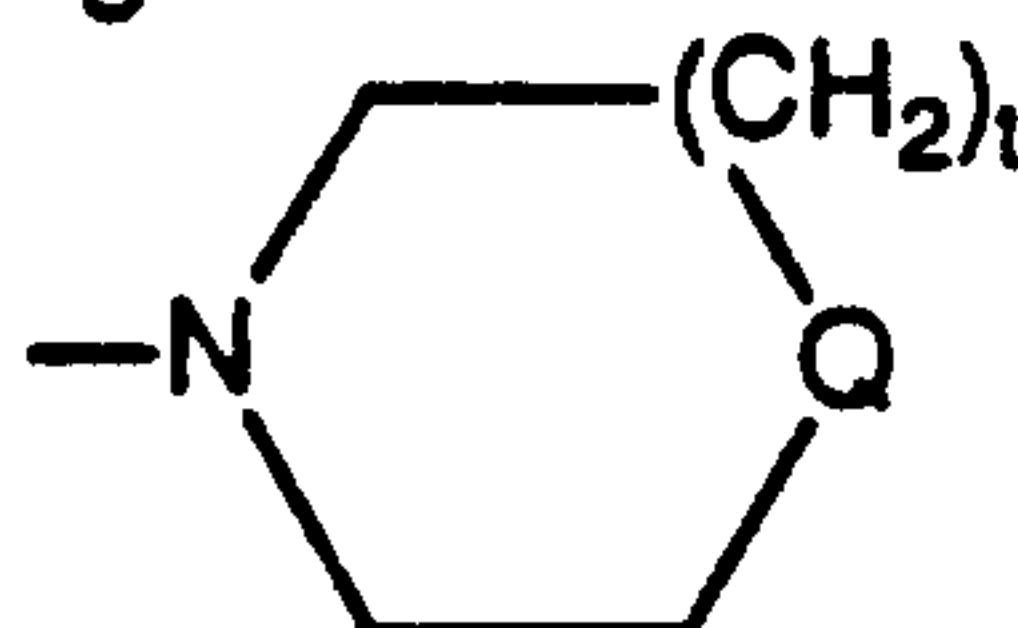
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to 6 carbon atoms, phenyl, benzyl, acyl of 1 to 4 carbon atoms, or phenacyl;

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 $NR^{18}R^{19}$;

5 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, α -methylbenzyl, or taken together with the nitrogen form a ring of the formula

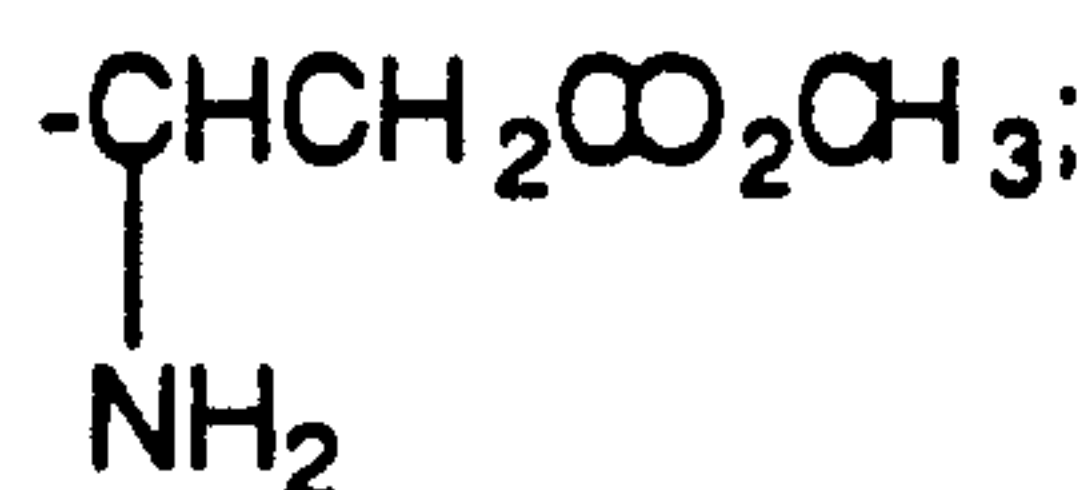


10

where 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

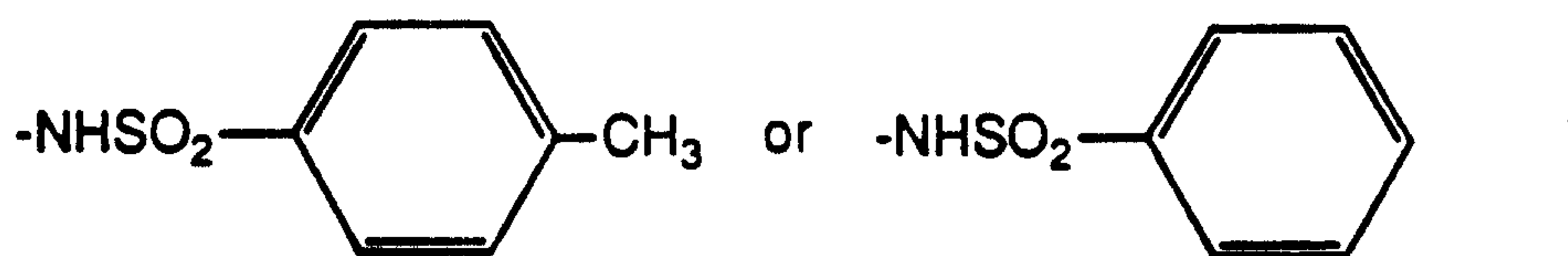


15

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 $-C_6H_5$;

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



25 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 $-(CH_2)_q-$;

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

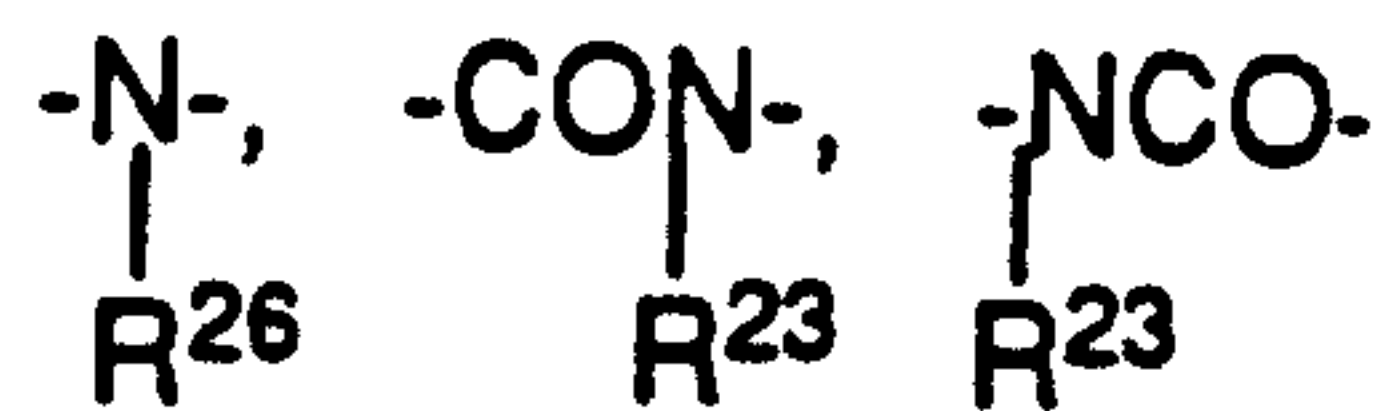
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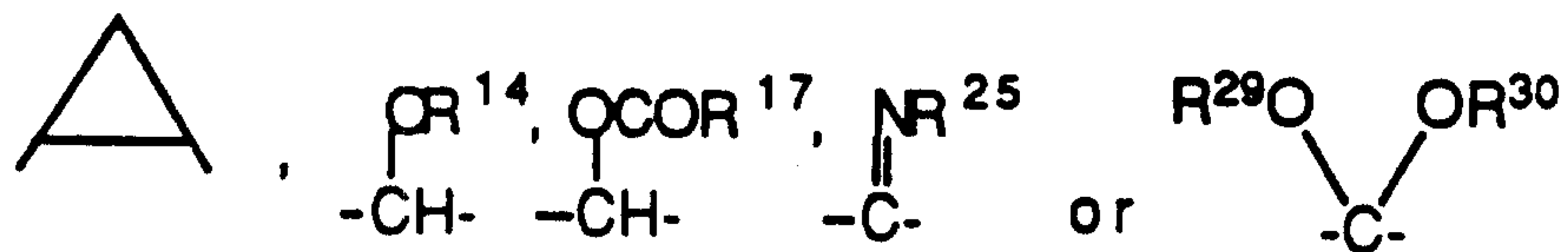
-CH₂C₆H₄R³²;R³² is H, NO₂, NH₂, OH or OCH₃;X is a carbon-carbon single bond, -CO-, -CH₂-, -O-, -S-,
-NH-,

5



-OCH₂-, -CH₂O-, -SCH₂-, -CH₂S-, NHC(R²⁷)(R²⁸), -NR²³SO₂-,
-SO₂NR²³-, -C(R²⁷)(R²⁸)NH-, -CH=CH-, -CF=CF-, -CH=CF-,
-CF=CH-, -CH₂CH₂-, -CF₂CF₂-,

10



Y is O or S;

Z is O, NR¹¹, or S;

15

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;

20

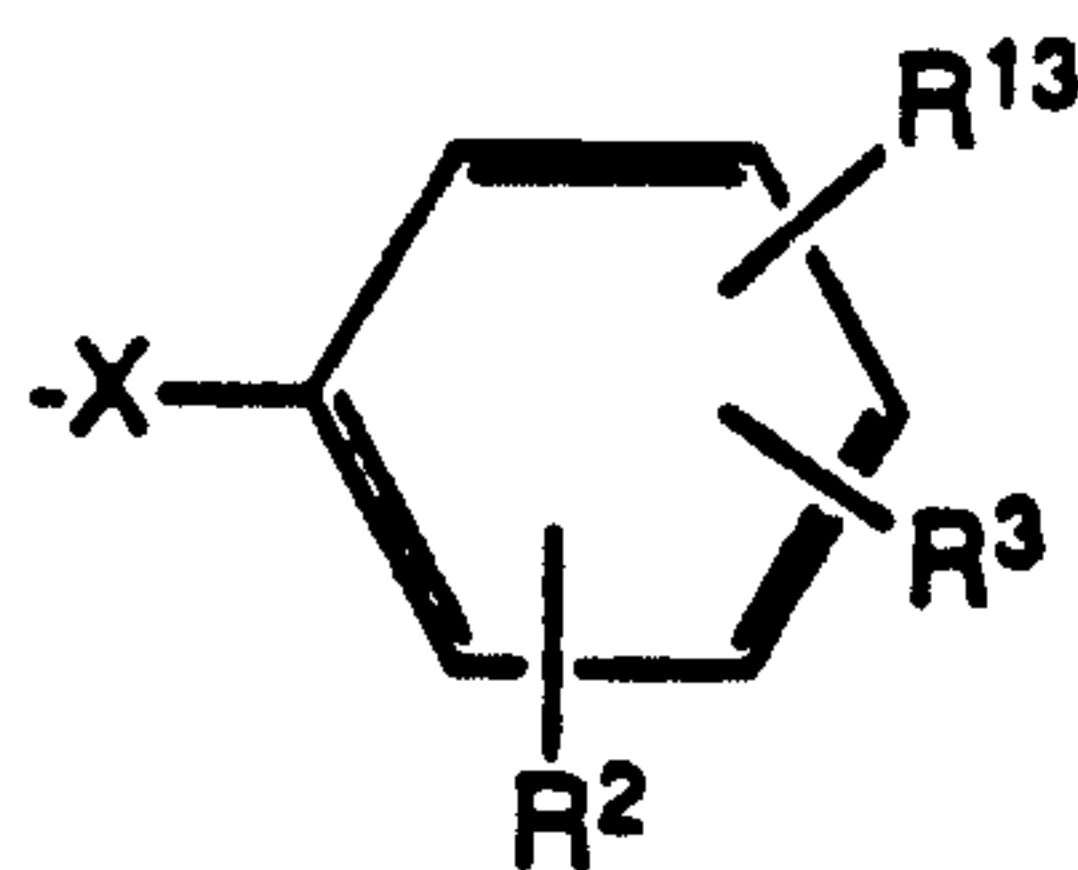
s is 0 to 5;

t is 0 or 1;

or a pharmaceutically acceptable salt thereof; provided that:

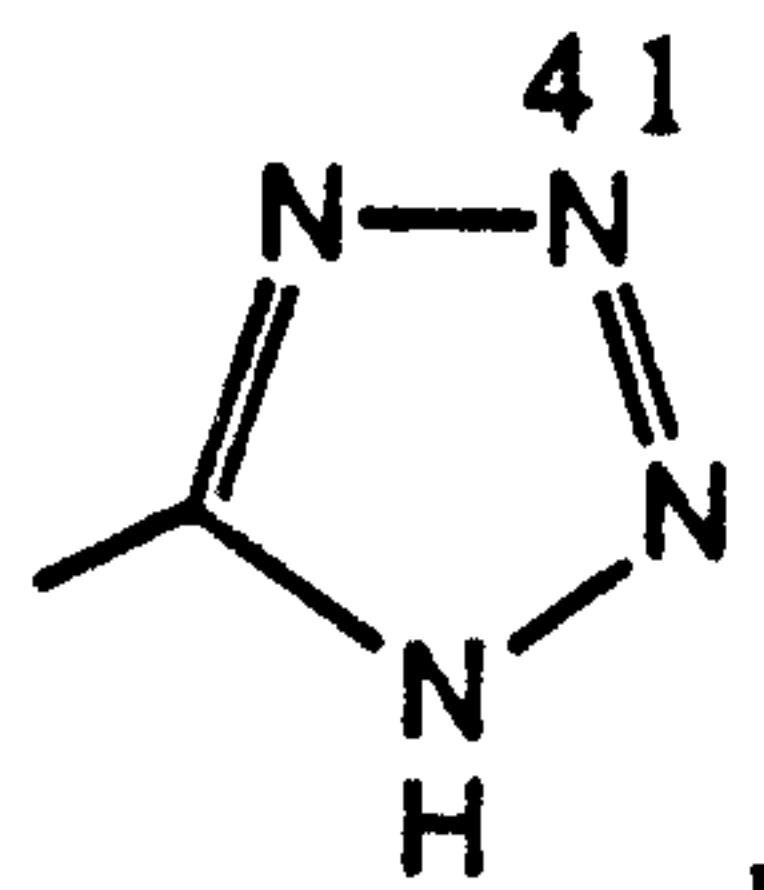
(1) the R¹ group is not in the ortho position;(2) when R¹ is

25

X is a single bond, and R¹³ is CO₂H, or

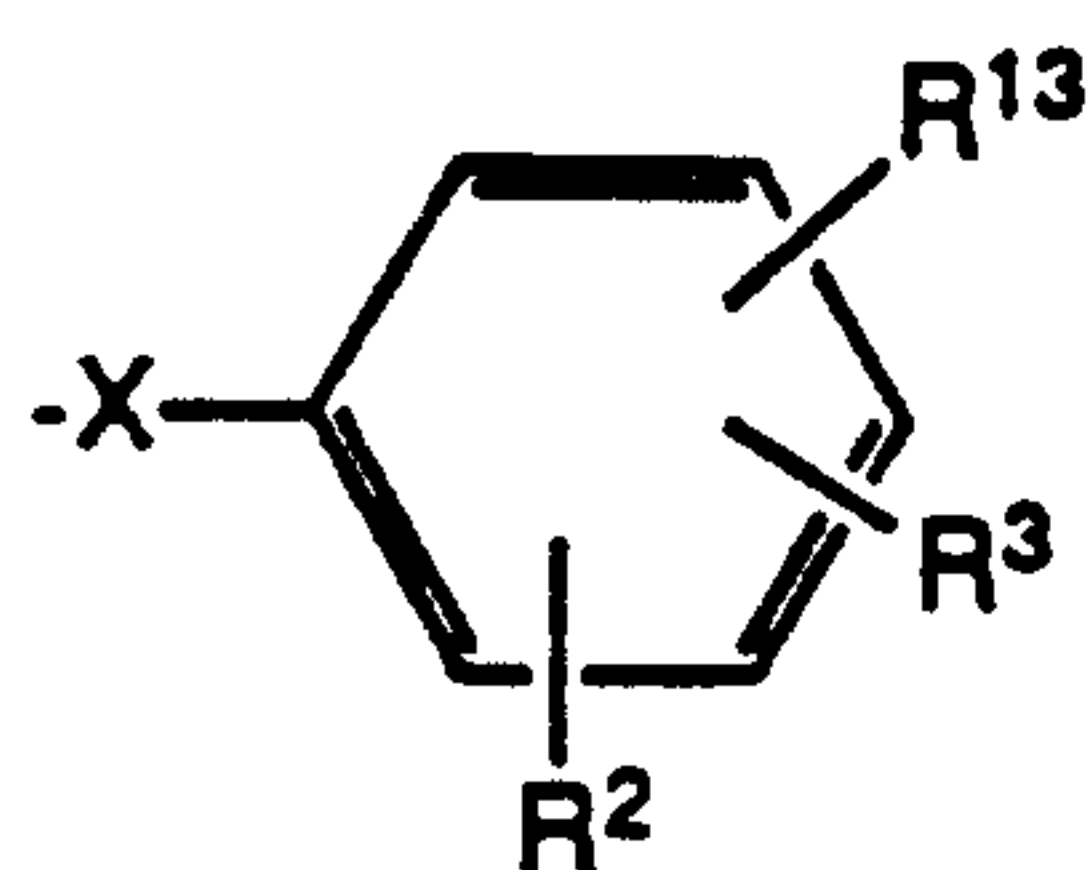
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then R^{13} must be in the ortho or meta position; or when R^1 and X are as above and R^{13} is NHSO_2CF_3 or NHSO_2CH_3 , R^{13} must be
 5 ortho;

(3) when R^1 is

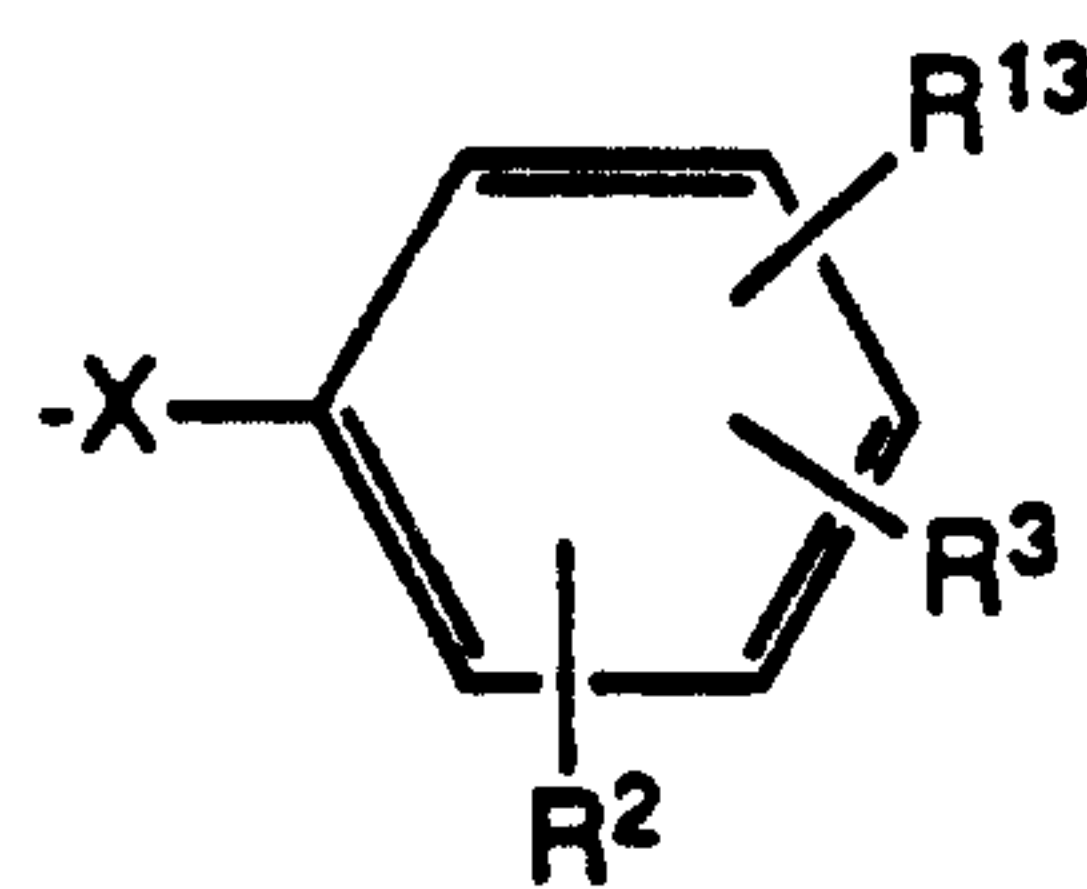


and X is other than a single bond, then R^{13} must be ortho
 10 except when $X = \text{NR}^{23}\text{CO}$ and R^{13} is NHSO_2CF_3 or NHSO_2CH_3 ,
 then R^{13} must be ortho or meta;

(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
 15 substituent on the 4-position of the imidazole cannot be
 CH_2OH , $\text{CH}_2\text{OCOCH}_3$, or $\text{CH}_2\text{CO}_2\text{H}$;

(6) when R^1 is

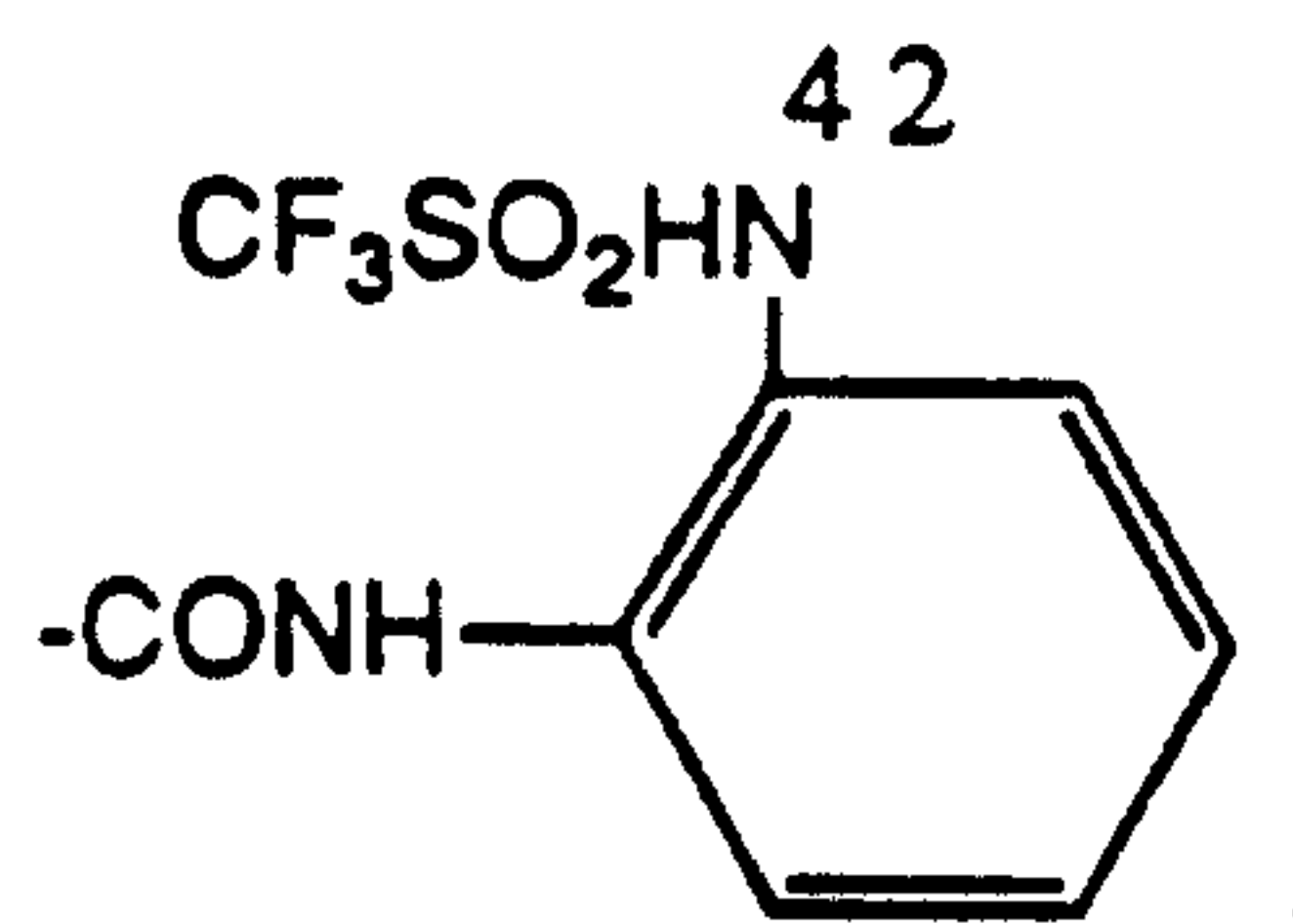


20 X is $-\text{OCH}_2-$, and R^{13} is 2- CO_2H , and R^7 is H then R^6 is not
 $\text{C}_2\text{H}_5\text{S}$;

(7) when R^1 is

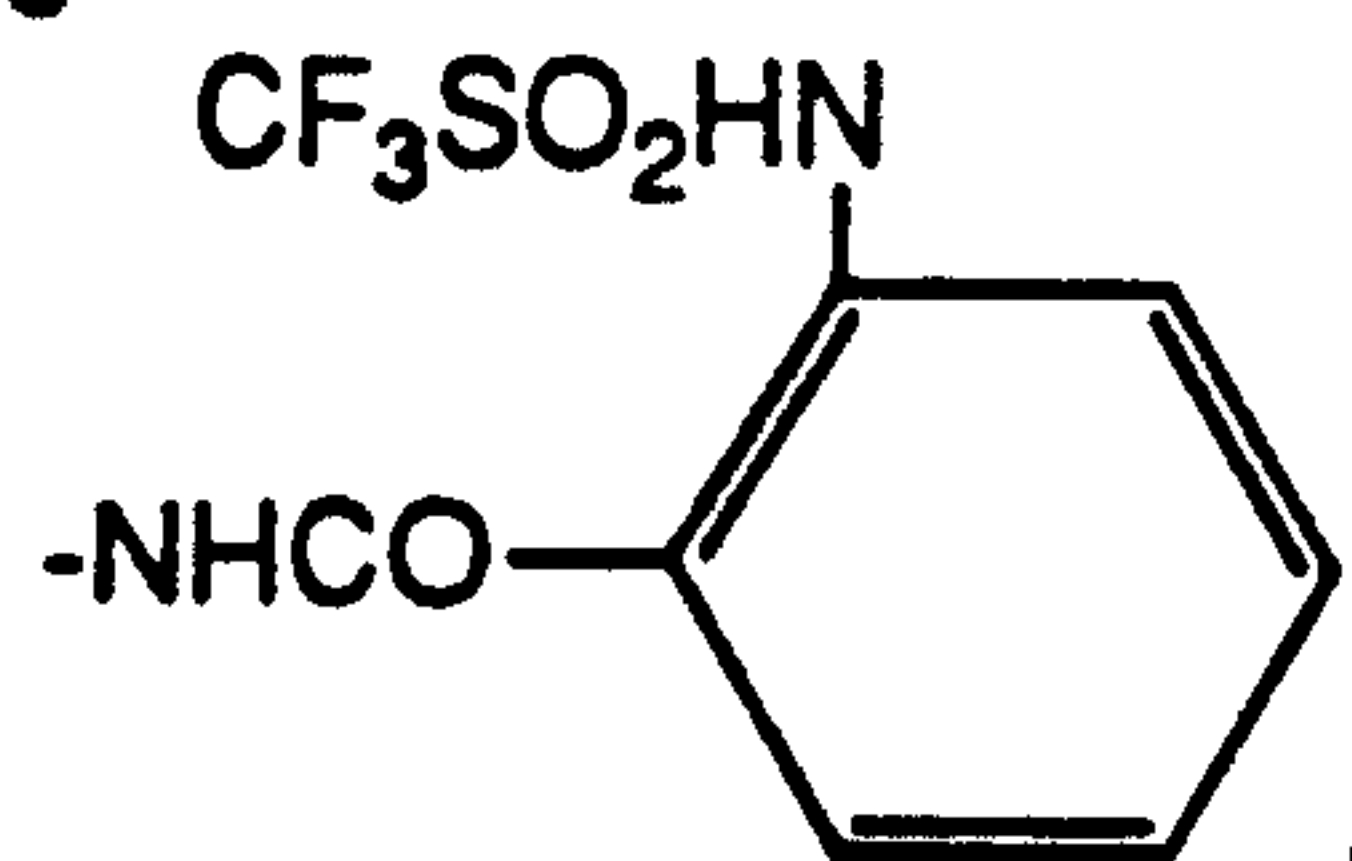
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and R^6 is n-hexyl, then R^7 and R^8 are not both hydrogen;

(8) when R^1 is

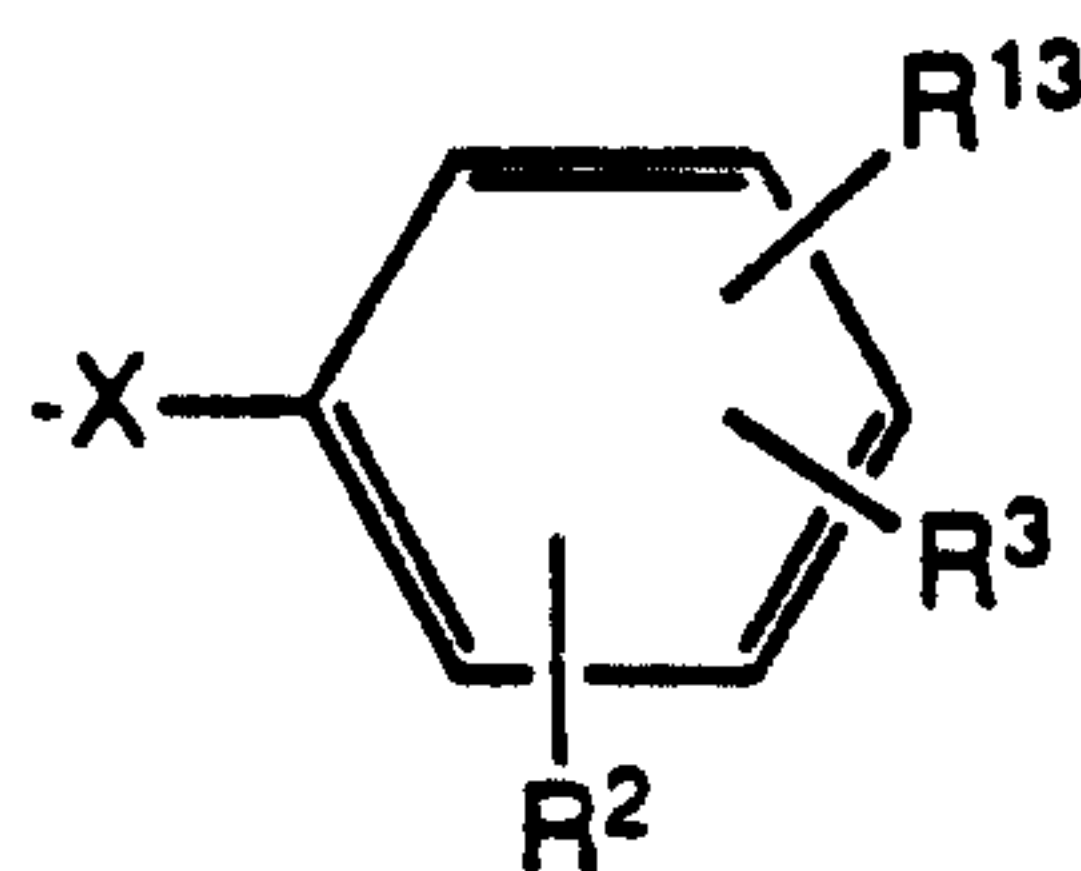


5

R^6 is not methoxybenzyl;

(9) the R^6 group is not $-\text{F}-\text{CHCH}_2\text{CH}_2\text{CH}_3$ or CH_2OH ;

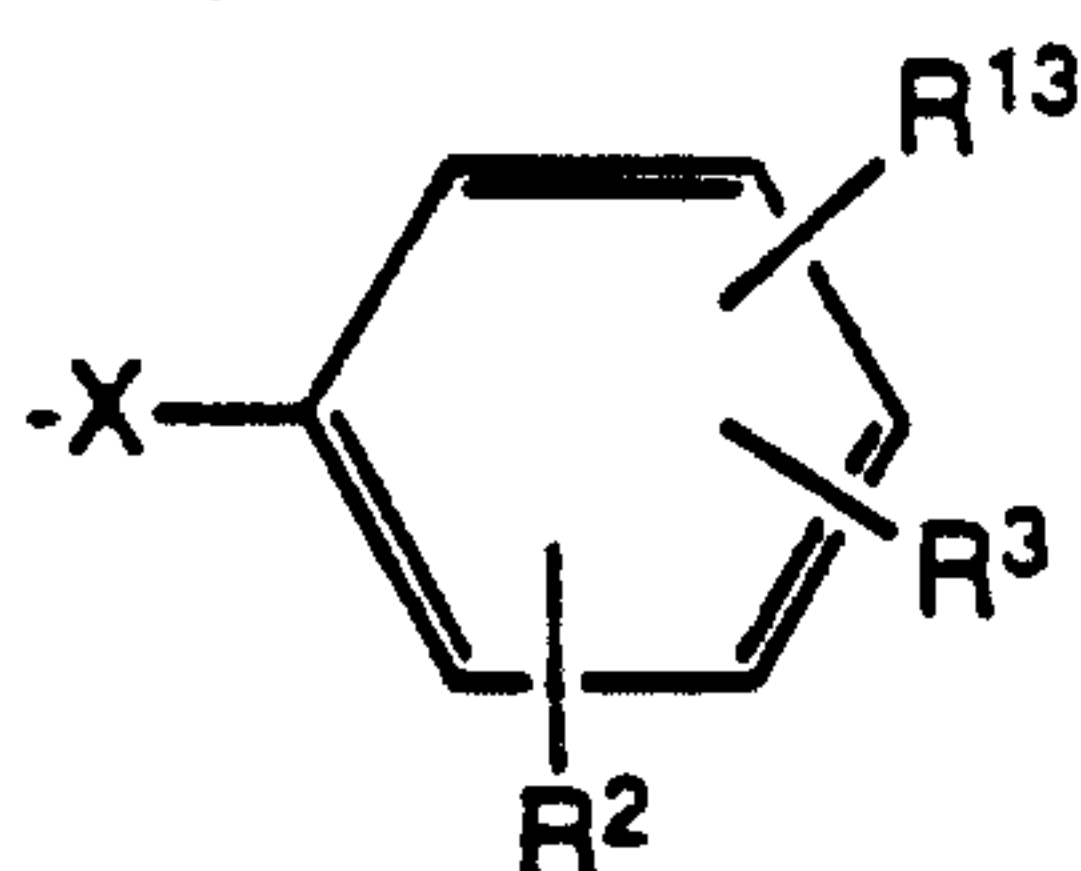
(10) when $r=0$, R^1 is



10

X is $-\text{NH}-\text{C}=\text{O}$, R^{13} is 2- NHSO_2CF_3 , and R^6 is n-propyl, then R^7 and R^8 are not $-\text{CO}_2\text{CH}_3$;

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



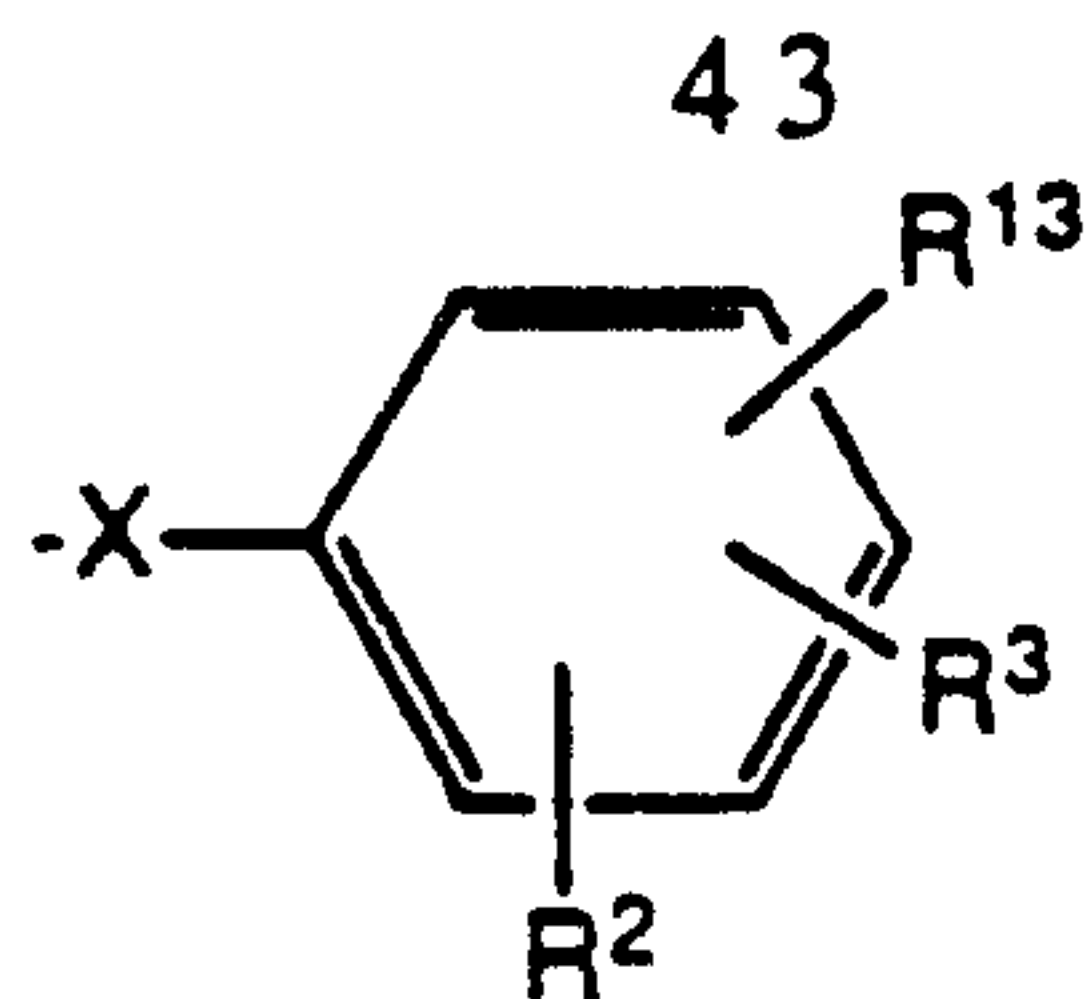
15

X is $\text{NH}-\text{C}=\text{O}$, R^{13} is 2- COOH , and R^6 is n-propyl, then R^7 and R^8 are not $-\text{CO}_2\text{CH}_3$;

(12) when $r=1$, $\text{R}^1=$

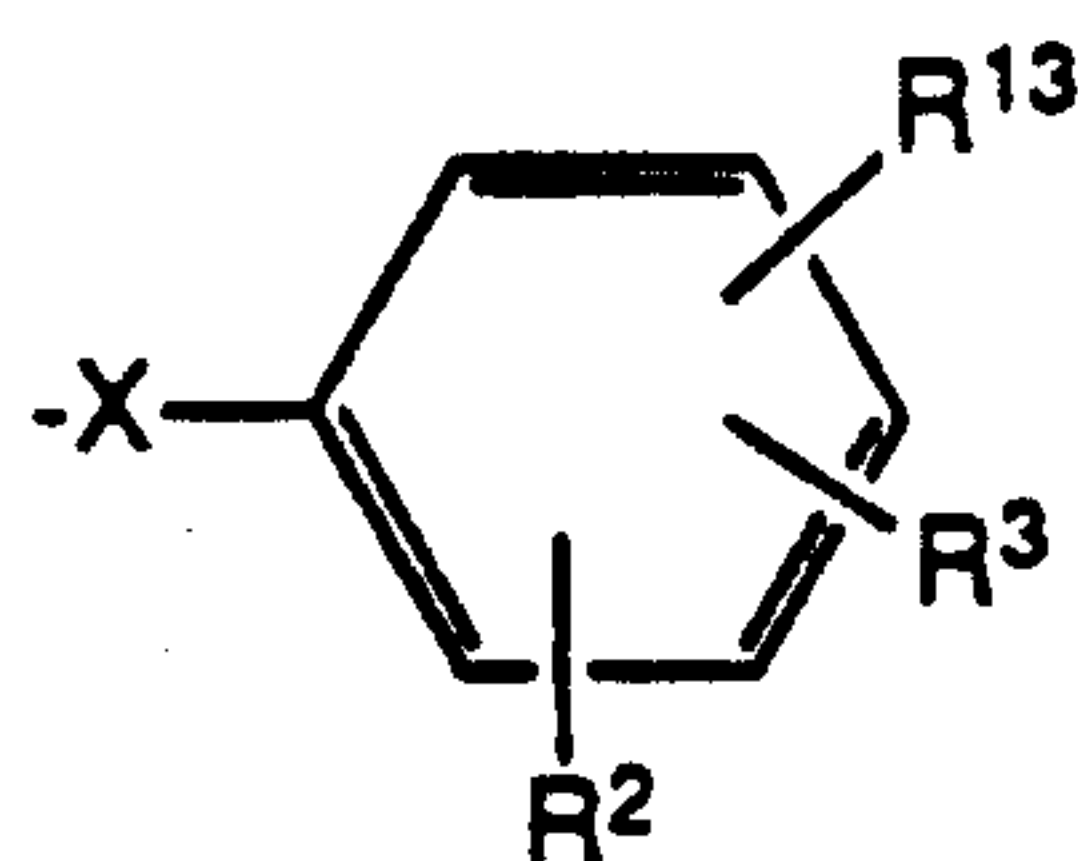
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X is a single bond, R^7 is Cl, and R^8 is $-CHO$, then R^{13} is not 3-(tetrazol-5-yl);

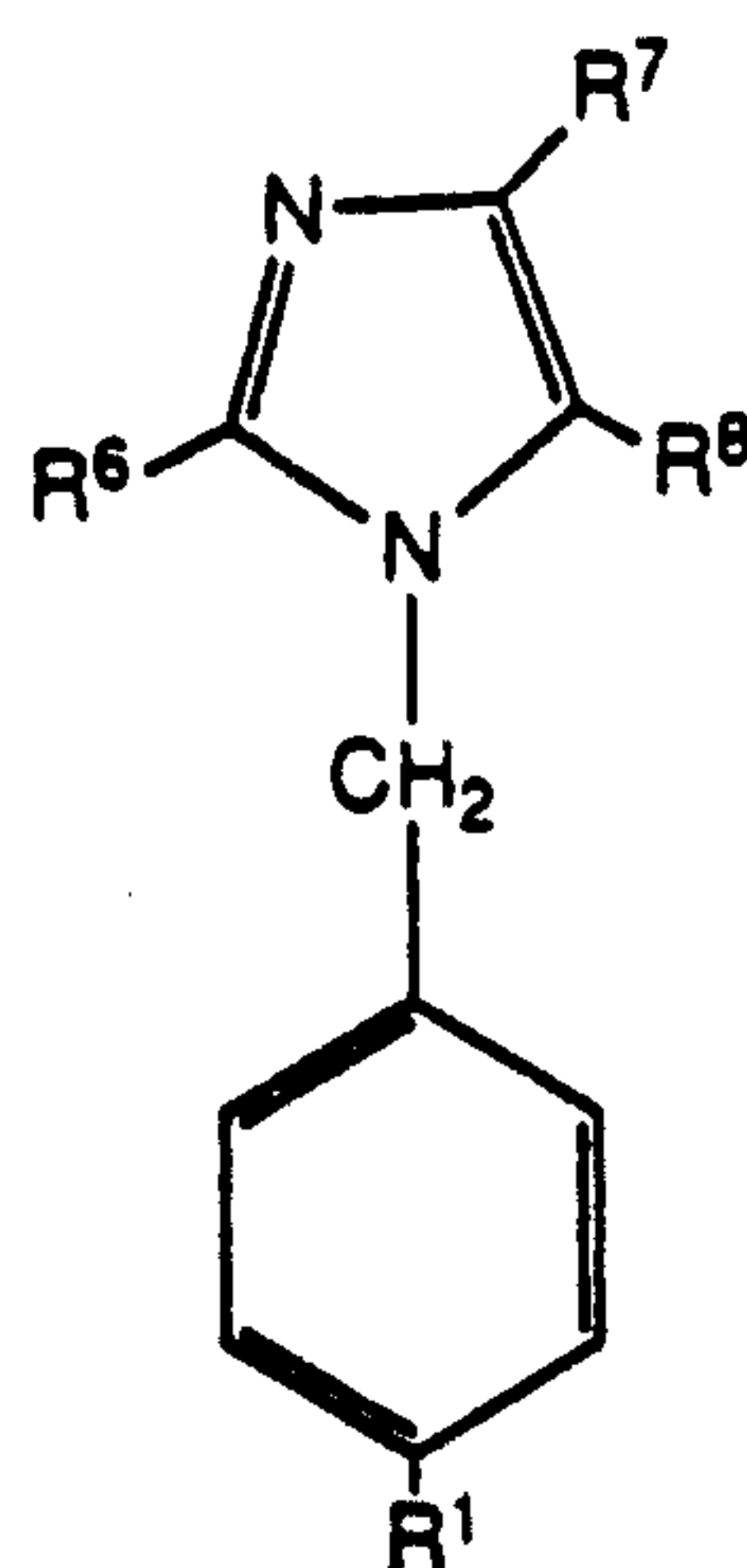
5 (13) when $r=1$, $R^1=$



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

10

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



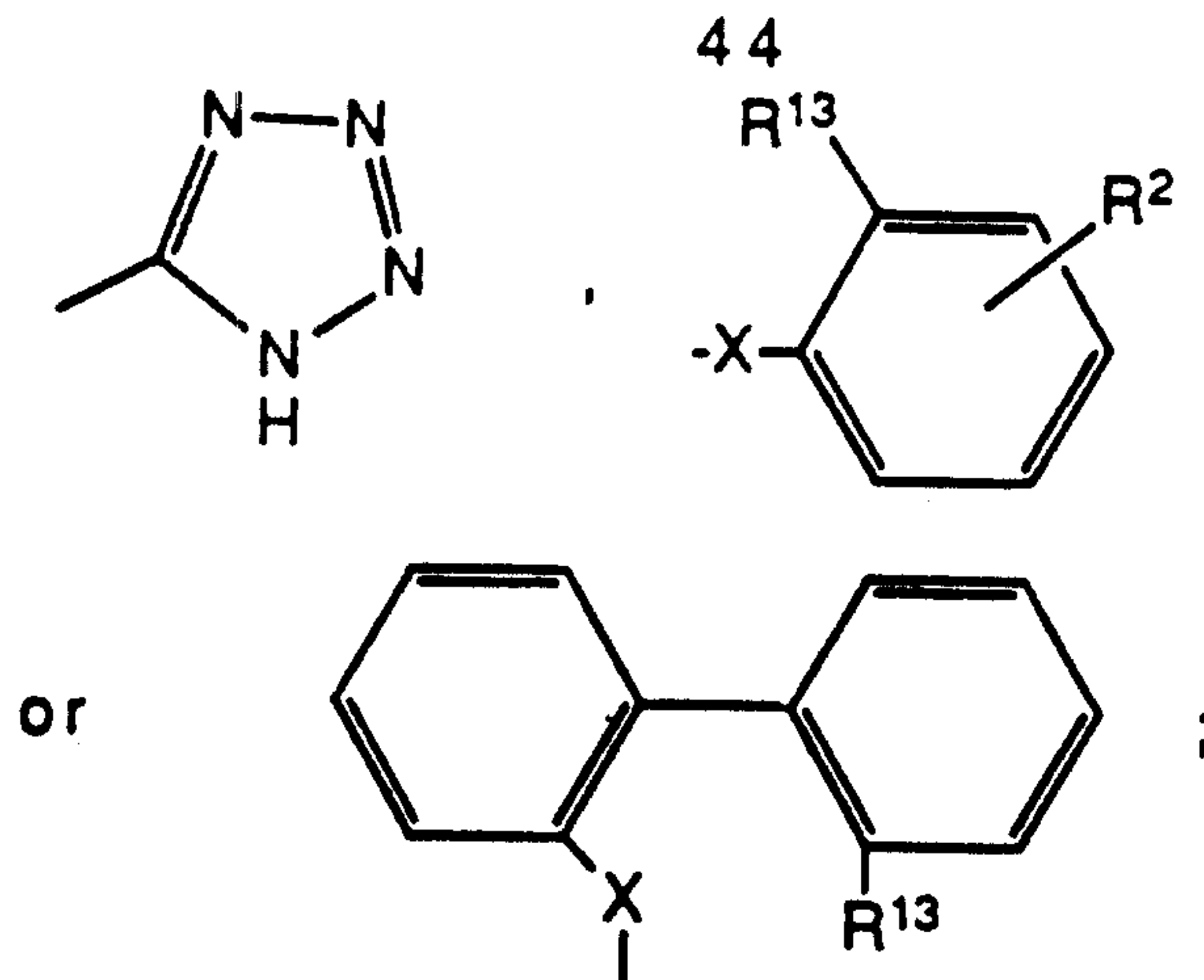
(II)

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wherein R^1 is $-CO_2H$, $-NHSO_2CF_3$.

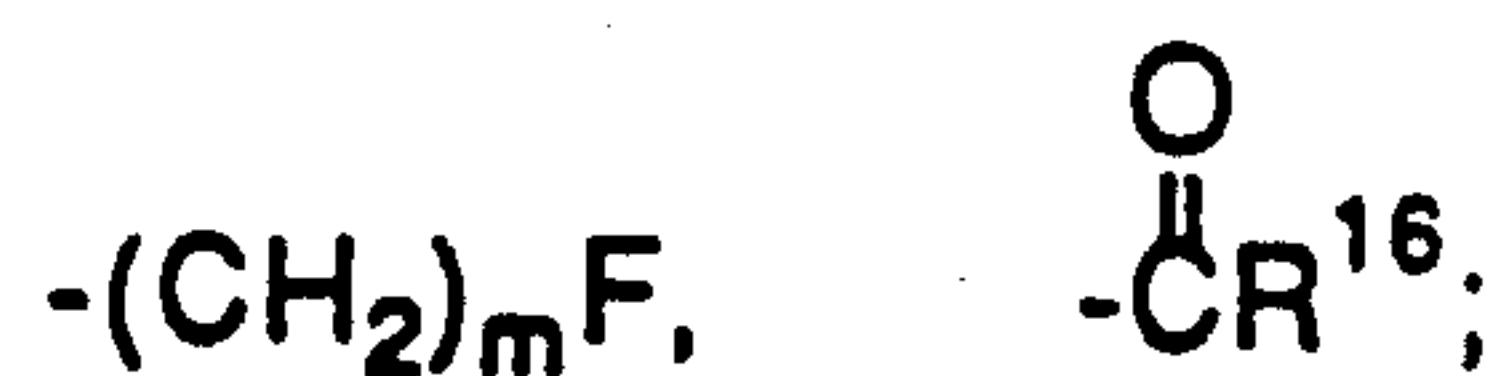
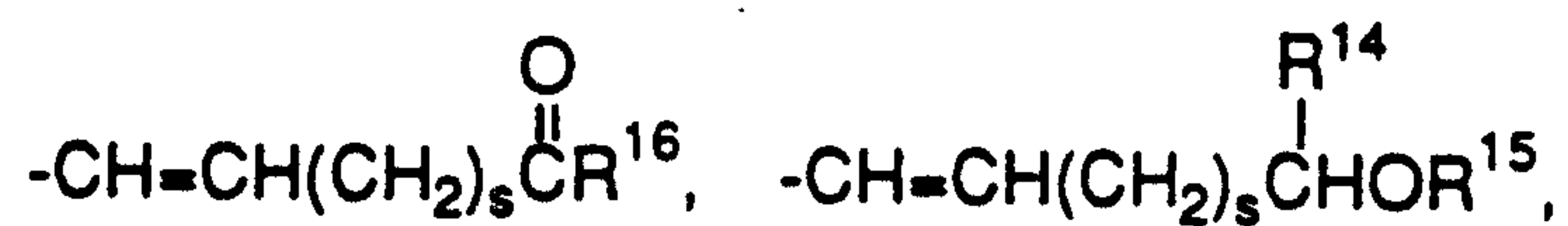
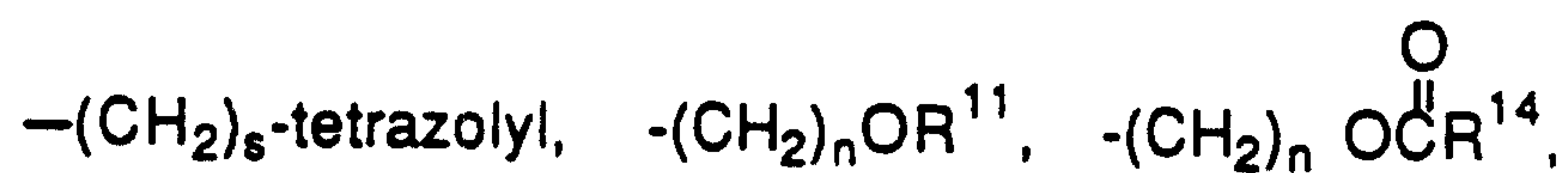
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R^6 is alkyl of 3 to 10 carbon atoms, alkenyl of 3 to 10 carbon atoms, alkynyl of 3 to 10 carbon atoms, cycloalkyl of 3 to 8 carbon atoms, benzyl substituted on the phenyl ring with up to two groups selected from alkoxy of 1 to 4 carbon atoms, halogen,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

R^8 is

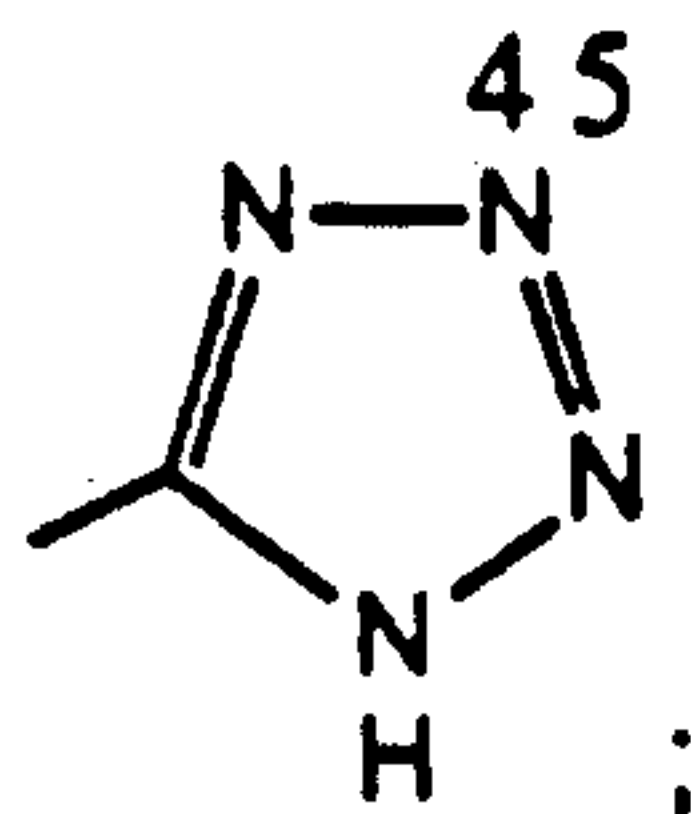


10 phenylalkenyl wherein the aliphatic portion is 2 to 4 carbon atoms, $-(CH_2)_m\text{-imidazol-1-yl}$, or $-(CH_2)_m\text{-1,2,3-triazolyl}$ optionally substituted with one or two groups selected from $-\text{CO}_2\text{CH}_3$ or alkyl of 1 to 4 carbon atoms;

15 R^{13} is $-\text{CO}_2\text{H}$, $-\text{CO}_2R^9$, $\text{NH}\text{SO}_2\text{CF}_3$, SO_3H , or

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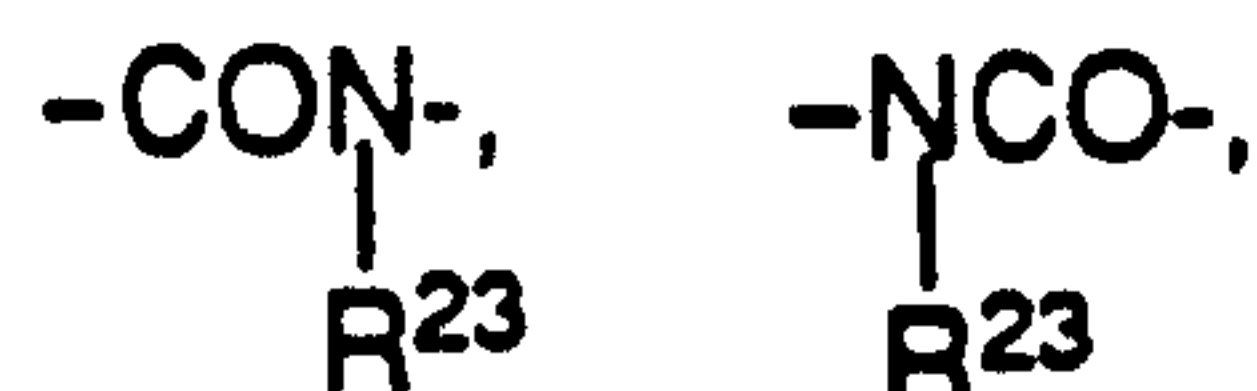
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R¹⁶ is H, alkyl of 1 to 5 carbon atoms, OR¹⁷, or NR¹⁸R¹⁹;

X is carbon-carbon single bond, -CO-, CH₂CH₂-,

5



-OCH₂-, -CH₂O-, -O-, -SCH₂-, -CH₂S-, -NH-CH₂-, -CH₂NH-
-CH=CH-, or a pharmaceutically acceptable salt thereof.

10

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

R² is H, alkyl of 1 to 4 carbon atoms, halogen;

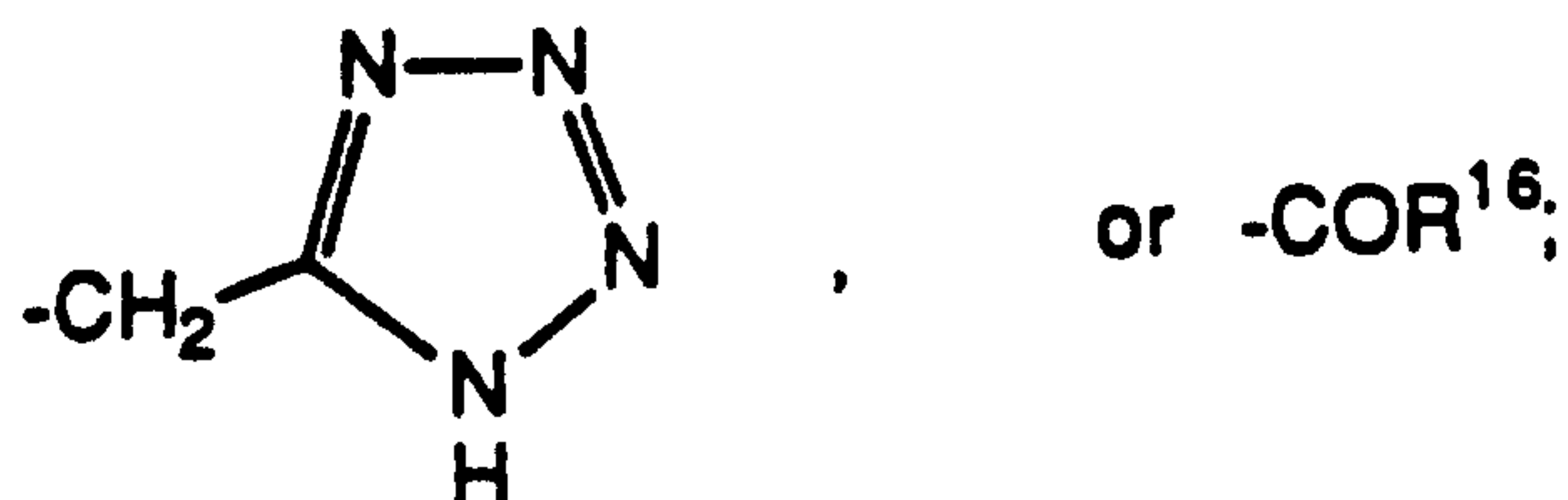
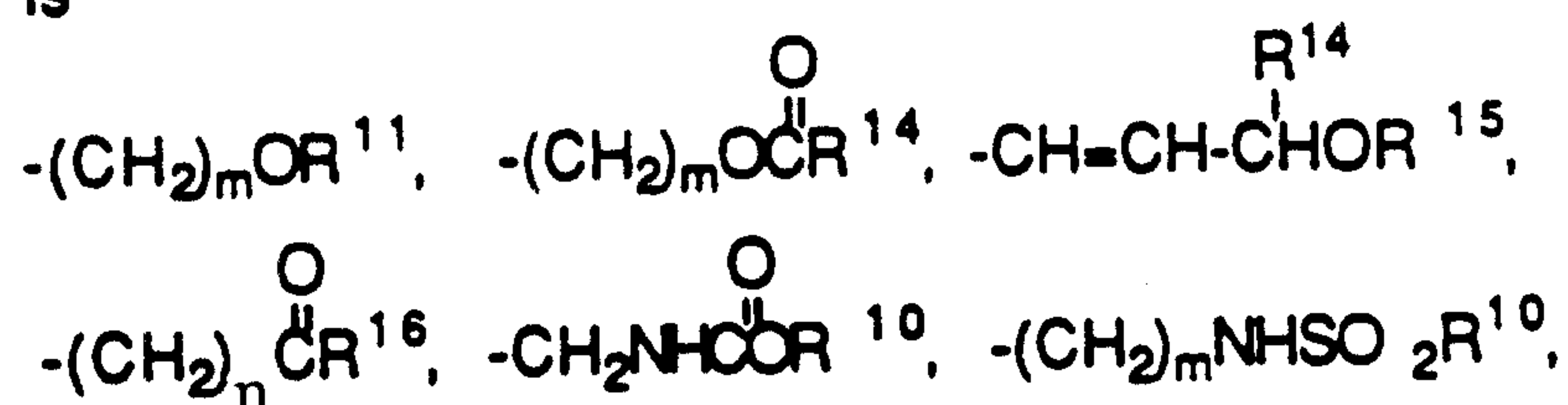
15 or alkoxy of 1 to 4 carbon atoms;

R⁶ is alkyl, alkenyl or alkynyl of 3 to 7 carbon atoms;

R⁷ is heteroaryl selected from 2- and 3-thienyl, 2- and 3-furyl, 2-, 3-, and 4-pyridyl, and p-biphenyl, H, Cl, Br, I,

20 C_vF_{2v+1} where v=1-3, $\text{--}\overset{\text{O}}{\underset{\text{||}}{\text{C}}}\text{R}^{16}$, straight or branched chain alkyl of 1 to 6 carbon atoms, and phenyl;

R⁸ is



or -COR¹⁶;

R¹⁰ is CF₃, alkyl of 1 to 6 carbon atoms or phenyl;

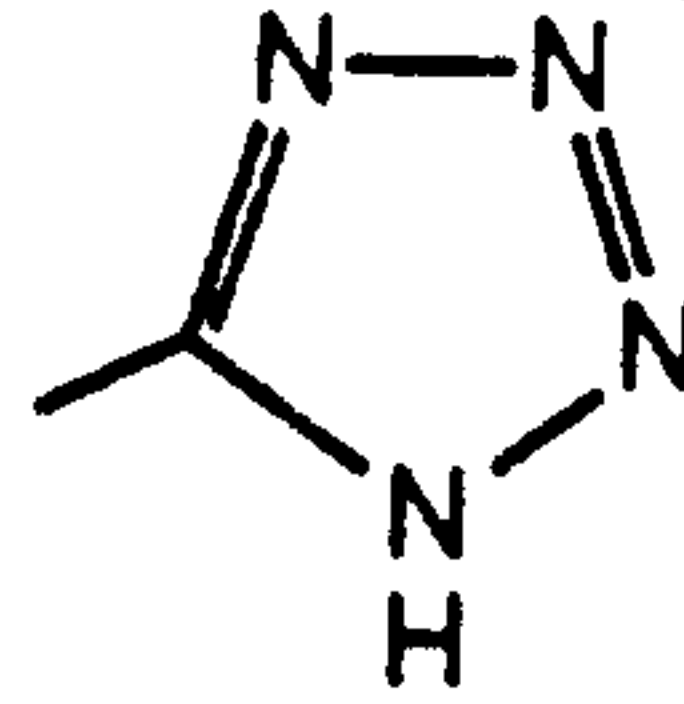
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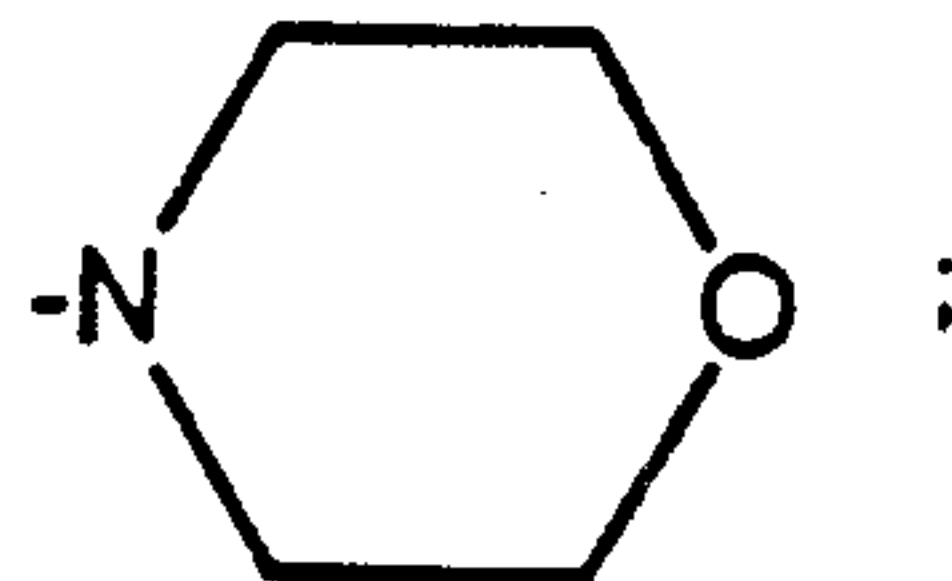
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R¹¹ is H, or alkyl of 1 to 4 carbon atoms;
 R¹³ is CO₂H; CO₂CH₂OCOC(CH₃)₃; NHSO₂CF₃,

or



- 5 R¹⁴ is H, or alkyl of 1 to 4 carbon atoms;
 R¹⁵ is H, alkyl of 1 to 4 carbon atoms, or acyl of 1 to 4 carbon atoms;
 R¹⁶ is H, alkyl of 1 to 5 carbon atoms; OR¹⁷; or

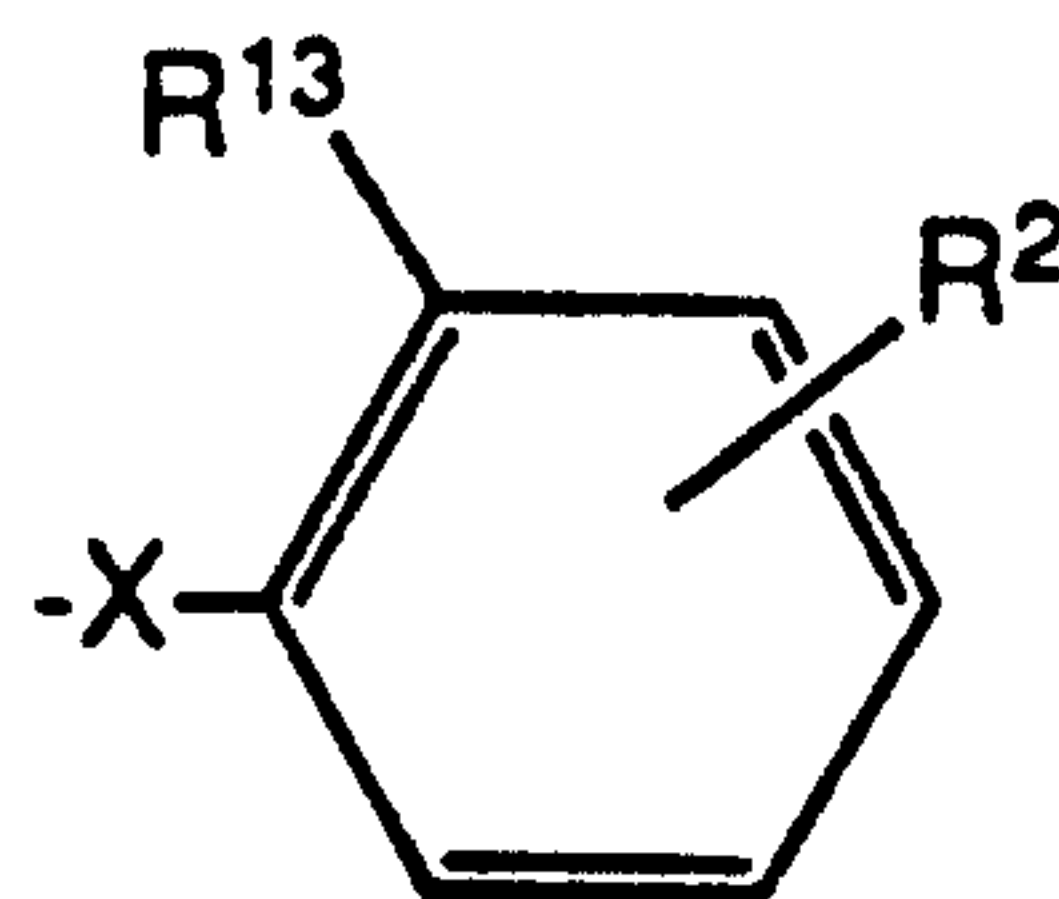


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m is 1 to 5;
 X is a single bond, -O-, -CO-, -NHCO-, or -OCH₂-; or
 a pharmaceutically acceptable salt thereof.

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4. The use of claim 3 wherein the compound
 of formula II is a compound wherein R¹ is



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

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

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

13. The use 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
5 pharmaceutically acceptable salt thereof.

14. The use 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
10 pharmaceutically acceptable salt thereof.

15. The use 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
15 pharmaceutically acceptable salt thereof.

16. The use 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
20 pharmaceutically acceptable salt thereof.

17. The use 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
25 pharmaceutically acceptable salt thereof.

18. The use 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
30 pharmaceutically acceptable salt thereof.

19. The use 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
35 pharmaceutically acceptable salt thereof.

20. The use 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 The use 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-(hydroxymethyl)imidazole or a pharmaceutically acceptable salt thereof.

22. The use 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-carboxylic acid or a pharmaceutically acceptable salt thereof.

23. The use 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. The use 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.

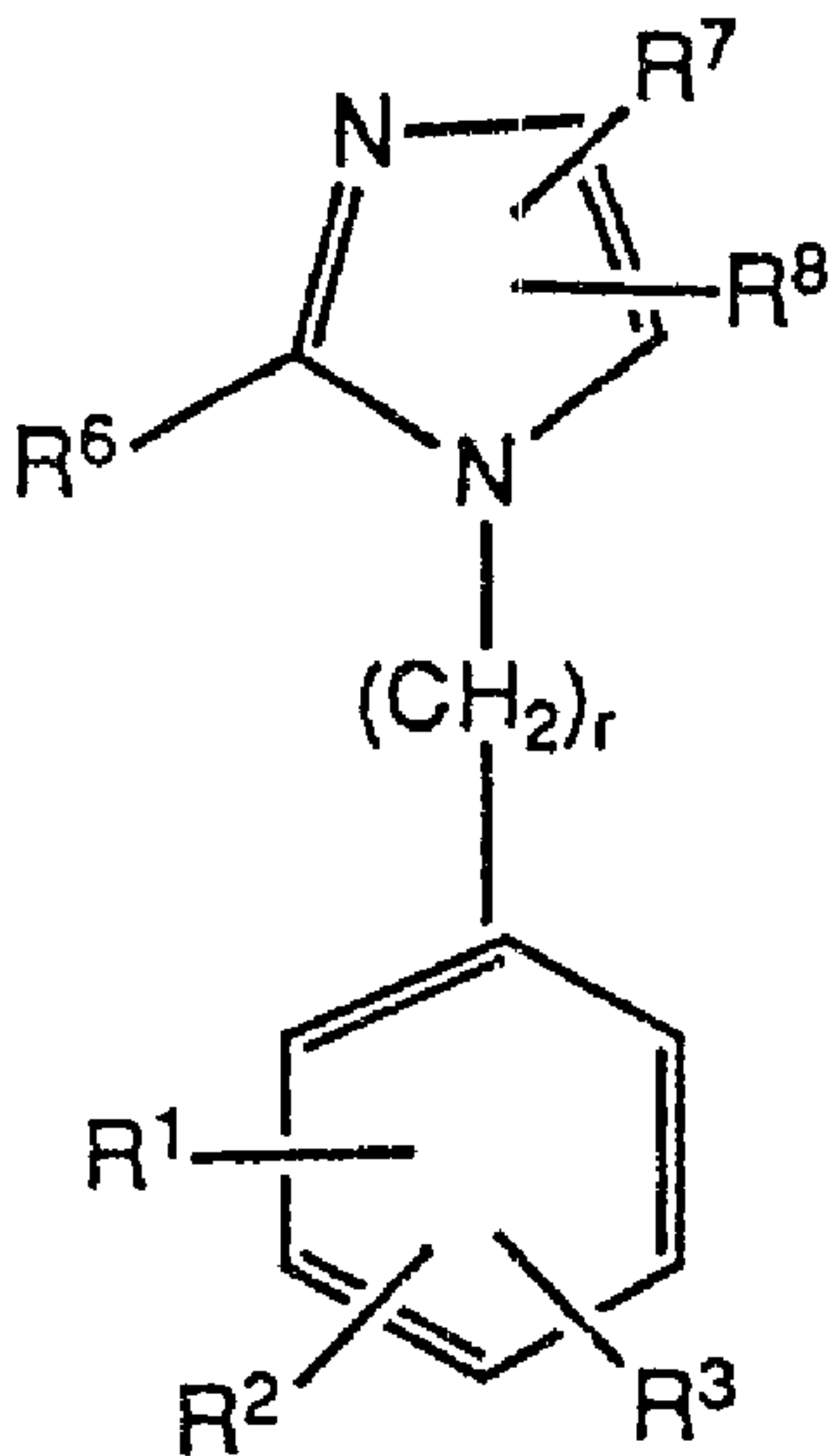
25. The use of claim 4 wherein the compound of formula II is 2-Propyl-4-pentafluoroethyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxylic acid or a pharmaceutically acceptable salt thereof.

26. The use 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. The use of claim 4 wherein the compound of formula II is 1-[(2'-(1H-Tetrazol-5-yl)biphenyl-4-yl)methyl]-4-phenyl-2-propylimidazole-5-carboxaldehyde.

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28. The use of claim 4 wherein the compound of formula II is 1-[(2'-Carboxybiphenyl-4-yl)methyl]-4-phenyl-2-propylimidazole-5-carboxaldehyde.



(I)