32,170-01

Title: TRICYCLIC DIAZEPINE VASOPRESSIN ANTAGONISTS AND OXYTOCIN ANTAGONISTS

1. Field of the Invention

This invention relates to new tricyclic non-peptide vasopressin antagonists which are useful in treating conditions where decreased vasopressin levels are desired, such as in congestive heart failure, in disease conditions with excess renal water reabsorption and conditions with increased vascular resistance and coronary vasoconstriction.

2. Background of the Invention

Vasopressin is released from the posterior pituitary either in response to increased plasma osmolarity detected by brain osmoreceptors or decreased blood volume and blood pressure sensed by low-pressure volume receptors and arterial baroreceptors. The hormone exerts its actions through two well defined receptor subtypes: vascular V_1 and renal epithelial V_2 receptors. Vasopressin-induced antidiuresis, mediated by renal epithelial V_2 receptors, helps to maintain normal plasma osmolarity, blood volume and blood pressure.

Vasopressin is involved in some cases of congestive heart failure where peripheral resistance is increased. V_1 antagonists may decrease systemic vascular resistance, increase cardiac output and prevent vasopressin induced coronary vasoconstriction. Thus, in conditions with vasopressin induced increases in total peripheral resistance and altered local blood flow, V_1-antagonists may be therapeutic agents.

The blockade of V_2 receptors may be useful in treating diseases characterized by excess renal reabsorption of free water. Antidiuresis is regulated by the hypothalamic release of vasopressin (antidiuretic hormone) which binds to specific receptors on renal collecting tubule cells. This binding stimulates adenylyl cyclase and promotes the cAMP-mediated incorporation of water pores into the luminal surface of these cells. V_2 antagonists may correct the fluid retention in congestive heart failure, liver cirrhosis, nephrotic syndrome, central nervous injuries, lung disease and hyponatremia.

Elevated vasopressin levels occur in congestive heart failure which is more common in older patients with chronic heart failure. In patients with hyponatremic congestive heart failure and elevated vasopressin levels, a V_2 antagonist may be beneficial in promoting free water excretion by antagonizing the action of antiduretic hormone. On the basis of the biochemical and pharmacological effects of the hormones antagonists of vasopressin are expected to be therapeutically useful in the treatment and/or prevention of hypertension, cardiac insufficiency, coronary vasospasm, cardiac ischemia, renal vasospasm, liver cirrhosis, congestive heart failure, nephrotic syndrome, brain edema, cerebral ischemia, cerebral hemorrhage-stroke, thrombosis-bleeding, abnormal states of water retention.

The following prior art references describe peptide vasopressin antagonists; M. Manning et al., J. Med. Chem., 35, 382(1992); M. Manning et al., J. Med. Chem., 35, 3895(1992); H. Gavras and B. Lammek, U.S. Patent 5,070,187 (1991); M. Manning and W.H. Sawyer, U.S. Patent 5,055,448(1991); F.E. Ali, U.S. Patent 4,766,108(1988); R.R. Ruffolo et al., Drug News and Perspective, 4(4), 217, (May)(1991). P.D. Williams et al., have reported on potent hexapeptide oxytocin

antagonists [J. Med. Chem., 35, 3905(1992)] which also exhibit weak vasopressin antagonist activity in binding to V_1 and V_2 receptors. Peptide vasopressin antagonists suffer from a lack or oral activity and many of these peptides are not selective antagonists since they also exhibit partial agonist activity.

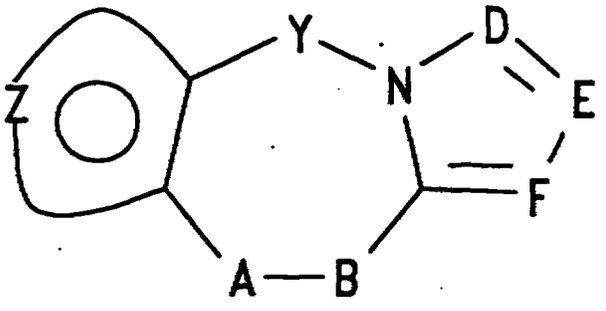
Non-peptide vasopressin antagonists have recently been disclosed, Y. Yamamura et al., Science, 252, 579(1991); Y. Yamamura et al., Br. J. Pharmacol., 105, 787(1992), Ogawa et al., (Otsuka Pharm Co., LTD.) EP 0514667-A1; JP 04154765-A; EPO 382185-A2; and W09105549. Carbostyril derivatives and pharmaceutical compositions containing the same are disclosed by Ogawa et al., (Otsuka Pharm. Co.) in EP 470514A. Non-peptide oxytocin and vasopressin antagonist have been disclosed by Merck and Co.; M.G. Bock and P.D. Williams, EP 0533242A; M.G. Bock et al., EP 0533244A; J.M. Erb, D.F. Verber, P.D. Williams, EP0533240A; K. Gilbert et al., EP 0533243A.

Premature birth can cause infant health problems and mortality and a key mediator in the mechanism of labor is the peptide hormone oxytocin. On the basis of the pharmacological action of oxytocin, antagonists of this hormone are useful in the prevention of preterm labor, B.E. Evans et al., J. Med. Chem., 35, 3919(1992), J. Med. Chem., 36, 3993(1993) and references therein. The compounds of this invention are antagonists of the peptide hormone oxytocin and are useful in the control of premature birth.

The present invention relates to novel tricyclic derivatives which exhibit antagonist activity at V_1 and/or V_2 receptors and exhibit in vivo vasopressin antagonist activity. The compounds also exhibit antagonists activity of oxytocin receptors.

SUMMARY OF THE INVENTION

This invention relates to new compounds selected from those of the general formula I:



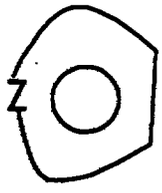
wherein Y is a moiety selected from; $-(CH_2)_n-$ wherein n is an integer from 0 to 2,

$$\text{—}\overset{|}{\text{C}}\text{H lower alkyl } (C_1\text{-}C_3) \quad \text{and} \quad \text{—}\overset{\overset{O}{\|}}{\text{C}}\text{—} \ ;$$

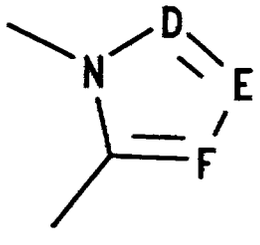
A-B is a moiety selected from

$$-(CH_2)_m\overset{|}{\underset{R^3}{N}}- \qquad \text{and} \qquad -\overset{|}{\underset{R^3}{N}}-(CH_2)_m-$$

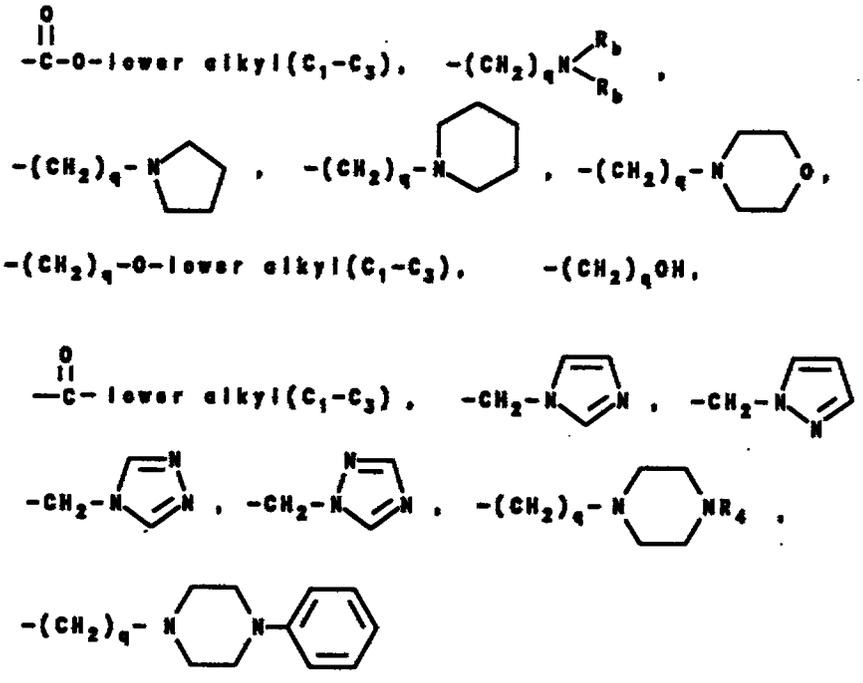
wherein m is an integer from 1 to 2 provided that when Y is $-(CH_2)_n-$ and n is 2, m may also be zero and when n is zero, m may also be three, provided also that when Y is $-(CH_2)_n-$ and n is 2, m may not be two;
and the moiety:



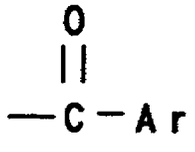
represents: (1) fused phenyl or fused substituted phenyl optionally substituted by one or two substituents selected from (C_1-C_3)lower alkyl, halogen, amino, (C_1-C_3)lower alkoxy or (C_1-C_3)lower alkylamino; (2) a 5-membered aromatic (unsaturated) heterocyclic ring having one heteroatom selected from O, N or S; (3) a 6-membered aromatic (unsaturated) heterocyclic ring having one nitrogen atom; (4) a 5 or 6-membered aromatic (unsaturated) heterocyclic ring having two nitrogen atoms; (5) a 5-membered aromatic (unsaturated) heterocyclic ring having one nitrogen atom together with either one oxygen or one sulfur atom; wherein the 5 or 6-membered heterocyclic rings are optionally substituted by (C_1-C_3)lower alkyl, halogen or (C_1-C_3)-lower alkoxy;
the moiety:



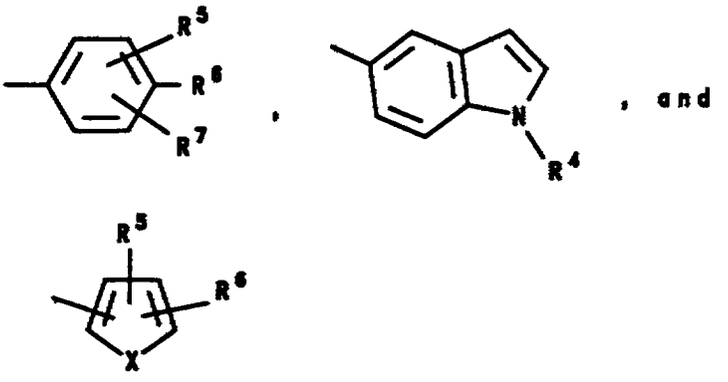
is a five membered aromatic(unsaturated) fused nitrogen containing heterocyclic ring wherein D, E and F are selected from carbon or nitrogen and wherein the carbon atoms may be optionally substituted by a substituent selected from halogen, (C_1-C_3)lower alkyl, hydroxy, $-COCl_3$, $-COCF_3$,



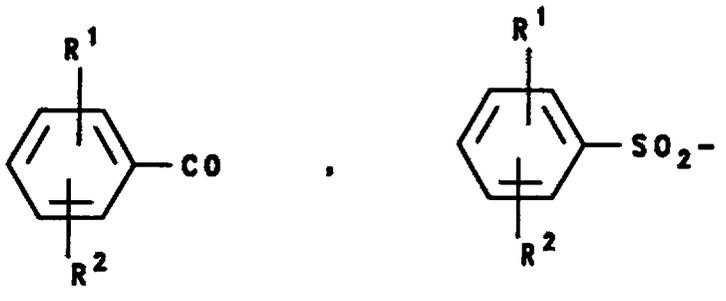
-CHO, amino, (C_1-C_3)lower alkoxy, (C_1-C_3)lower alkylamino, CONH-lower alkyl(C_1-C_3), and -CON[lower alkyl(C_1-C_3)]$_2$; q is one or two; R_b is independently selected from hydrogen, $-CH_3$ or $-C_2H_5$;
R^3 is a moiety of the formula:



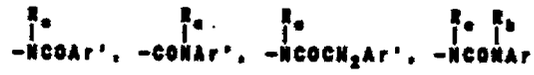
wherein Ar is a moiety selected from the group consisting of

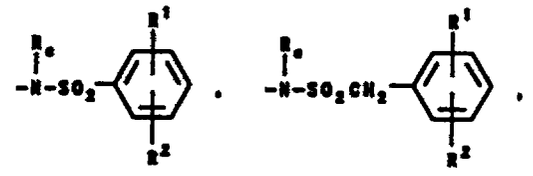


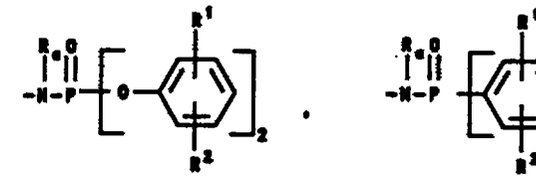
wherein X is selected from O, S, NH, NCH_3 and $NCOCH_3$; R^4 is selected from hydrogen, lower alkyl(C_1-C_3), -CO-lower alkyl(C_1-C_3),

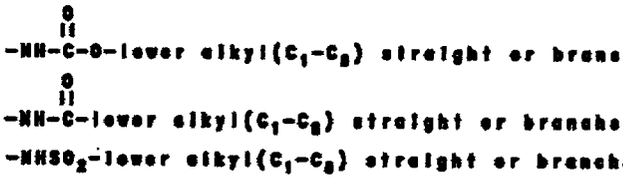


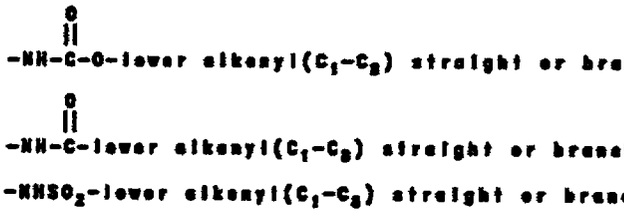
$-SO_2$lower alkyl(C_1-C_3); R^1 and R^2 are selected from hydrogen, (C_1-C_3)lower alkyl, (C_1-C_3)lower alkoxy and halogen; R^5 is selected from hydrogen, (C_1-C_3)lower alkyl, (C_1-C_3)lower alkoxy and halogen;
R^6 is selected from (a) moieties of the formulae:



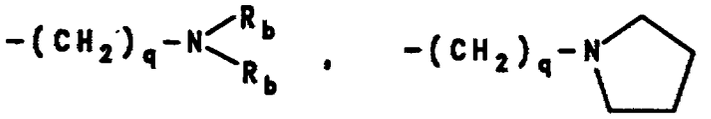


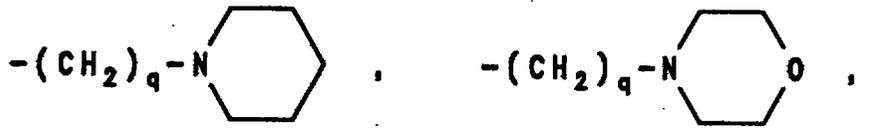






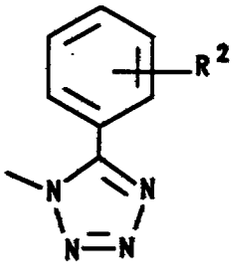
wherein cycloalkyl is defined as C_3-C_6 cycloalkyl, cyclohexenyl or cyclopentenyl; Ra is independently selected from hydrogen, $-CH_3$, $-C_2H_5$,





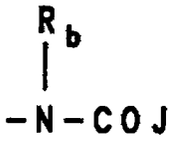
$-(CH_2)_q$-O-lower alkyl(C_1-C_3) and $-CH_2CH_2OH$, q is one or two, and R_1, R_2 and R_b are as hereinbefore defined;

(b) a moiety of the formula:

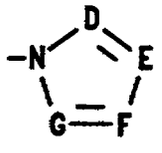


wherein R^2 is as hereinbefore defined;

(c) a moiety of the formula:



wherein J is R_a, lower alkyl(C_1-C_8) branched or unbranched, lower alkenyl(C_1-C_8) branched or unbranched, O-lower alkyl(C_1-C_8) branched or unbranched, -O-lower alkenyl(C_1-C_8) branched or unbranched, tetrahydrofuran, tetrahydrothiophene, or $-CH_2-K$ wherein K is (C_1-C_3) lower alkoxy, halogen, tetrahydrofuran, tetrahydrothiophene or the heterocyclic ring moiety:

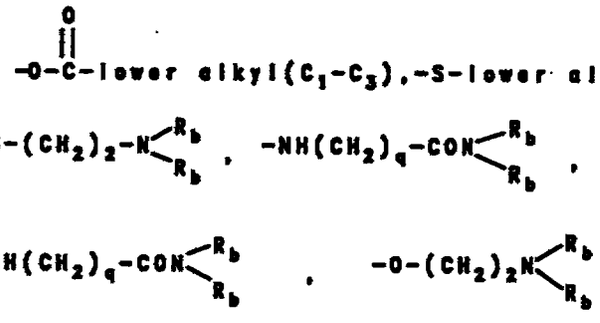


wherein D, E, F and G are selected from carbon or nitrogen and wherein the carbon atoms may be optionally substituted with halogen, (C_1-C_3)lower alkyl, hydroxy, -CO-lower alkyl(C_1-C_3), CHO, (C_1-C_3)lower alkoxy, $-CO_2$-lower alkyl(C_1-C_3), and R_a and R_b are as hereinbefore defined;

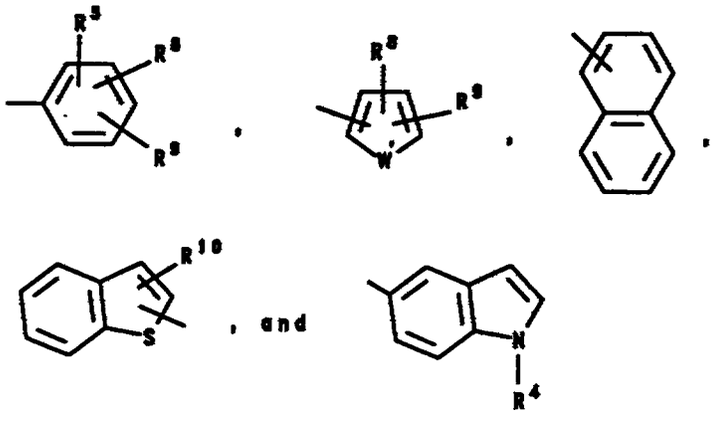
(d) a moiety of the formula:



wherein R_a is selected from halogen, (C_1-C_3) lower alkyl, -O-lower alkyl(C_1-C_3), OH,

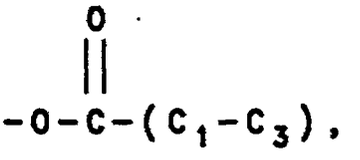


wherein R_a and R_b are as hereinbefore defined and Ar' is selected from moieties of the formula:



wherein W' is selected from O, S, NH, N-lower alkyl-(C_1-C_3), NHCO-lower alkyl(C_1-C_3), and NSO_2lower alkyl-(C_1-C_3);

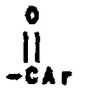
R^7 is selected from hydrogen, lower alkyl(C_1-C_3), halogen, O-lower alkyl(C_1-C_3) and CF_3;
R^8 and R^9 are independently selected from hydrogen, lower alkyl(C_1-C_3), -S-lower alkyl(C_1-C_3), halogen, -NH-lower alkyl(C_1-C_3), $-OCF_3$, -OH, -CN, $-S-CF_3$, $-NO_2$, $-NH_2$, O-lower alkyl(C_1-C_3),



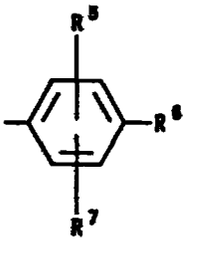
and CF_3 and;
R^{10} is selected from hydrogen, halogen and lower alkyl-(C_1-C_3), and the pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

Within the group of the compounds defined by Formula I, certain subgroups of compounds are broadly preferred. Broadly preferred are those compounds wherein R_3 is the moiety:

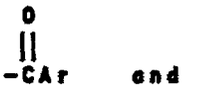


and Ar is selected from the moiety

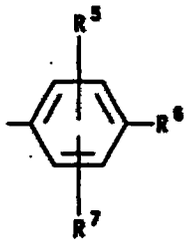


wherein R^5, R^6 and R^7 are as hereinbefore defined.

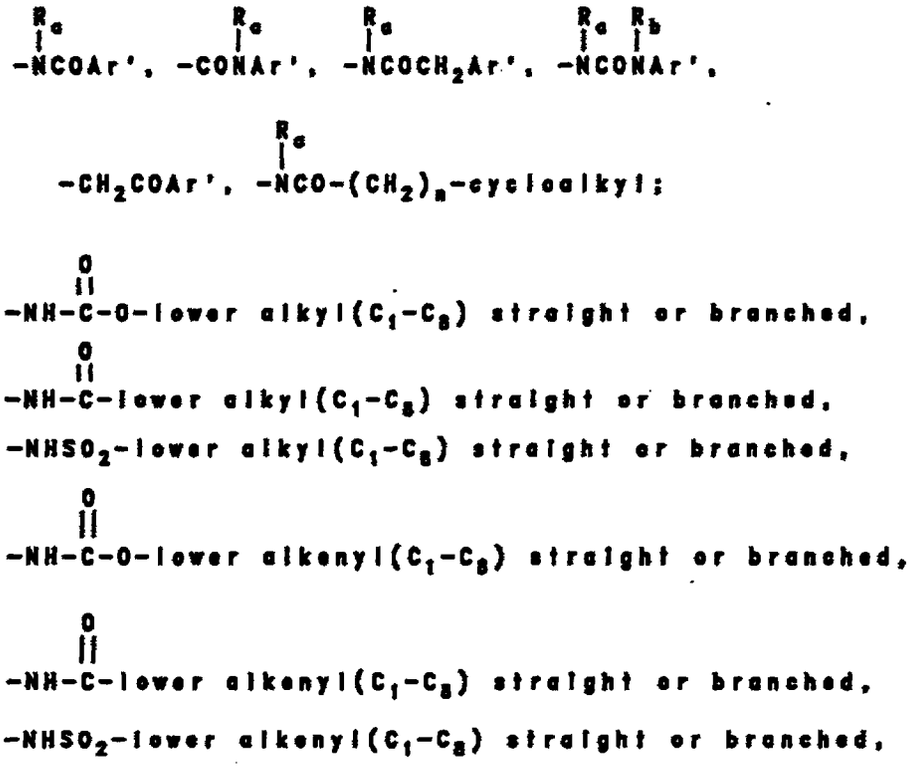
Especially preferred are compounds wherein R^3 is the moiety



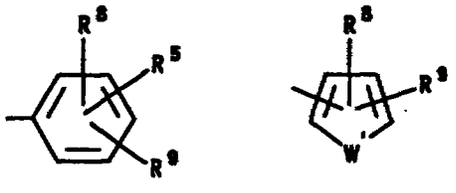
Ar is selected from the moiety



R^6 is



wherein cycloalkyl is defined as C_3-C_6 cycloalkyl, cyclohexenyl or cyclopentenyl;
R_a and R_b are as hereinbefore defined;
and Ar' is selected from the moieties:



wherein R^8, R^9 and W' are as hereinbefore defined.

Also especially preferred are compounds wherein Y in Formula I is $-(CH_2)_n-$ and n is zero or one; A-B is

$$-(CH_2)_m-\overset{|}{N}-R^3 \quad \text{or} \quad R^3-\overset{|}{N}-(CH_2)_m-$$

and R^4, R^5, R^6, R^7, R^8, R^9 and R^{10} are as hereinbefore defined; and m is an integer from 1-2.

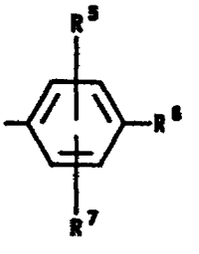
The most preferred of the compounds of Formula I are those wherein Y is $-(CH_2)_n-$ and n is one; A-B is

$$-CH_2-\overset{|}{N}-R^3 \quad \text{or} \quad R^3-\overset{|}{N}-CH_2-$$

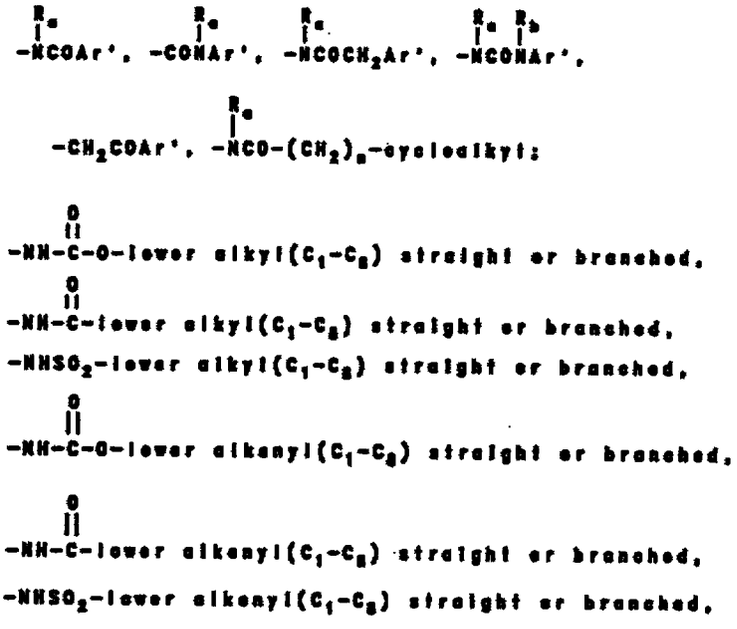
R_3 is the moiety

$$-C(=O)Ar$$

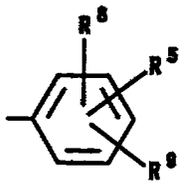
Ar is the moiety



R^6 is



$-(CH_2)_n$-cycloalkyl wherein cycloalkyl is defined as C_3-C_6 cycloalkyl, cyclohexenyl or cyclopentenyl; R_a and R_b are as hereinbefore defined;
and Ar' is

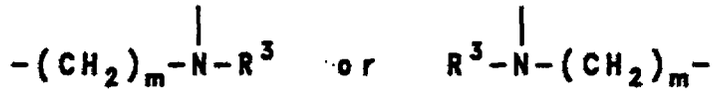


wherein R^5, R^8 and R^9 are as previously defined.

The most highly broadly preferred of the compounds of Formula I are those wherein Y is $-(CH_2)_n-$ and n is zero or one; wherein the moiety



is a fused phenyl, substituted phenyl, thiophene, furan, pyrrole or pyridine ring;
A-B is

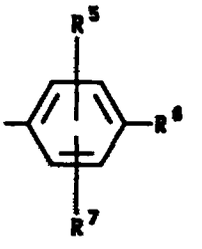


m is one when n is one and m is two when n is zero; D, E, F, R^1, R^2, R^4, R^5, R^7, R^8, R^9, R^{10}, are as previously defined;

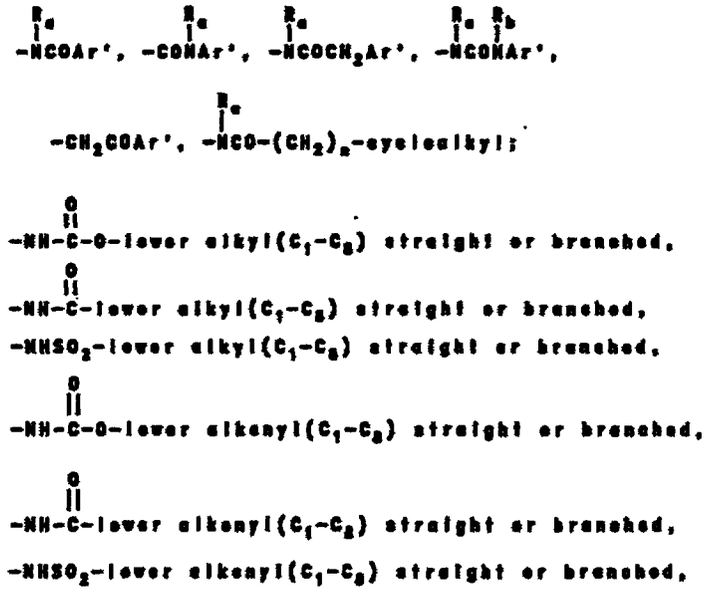
R_3 is the moiety



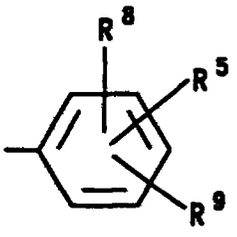
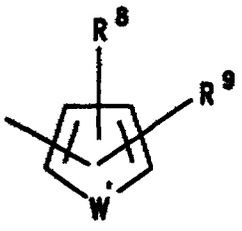
wherein Ar is



and R_6 is selected from the group

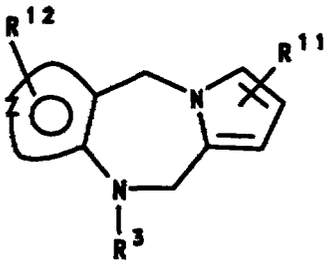
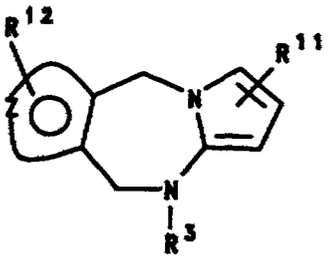


where Ar' is selected from the group

and W', R_a, R_b and cycloalkyl are as previously described.

More particularly preferred are compounds of the formulae:


and


wherein the moiety:

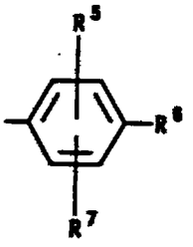


is selected from a phenyl, thiophene, furan, pyrrole or pyridine ring;

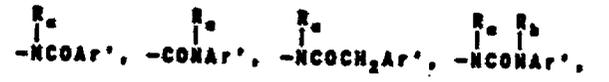
R^3 is the moiety:

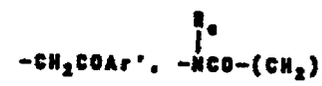


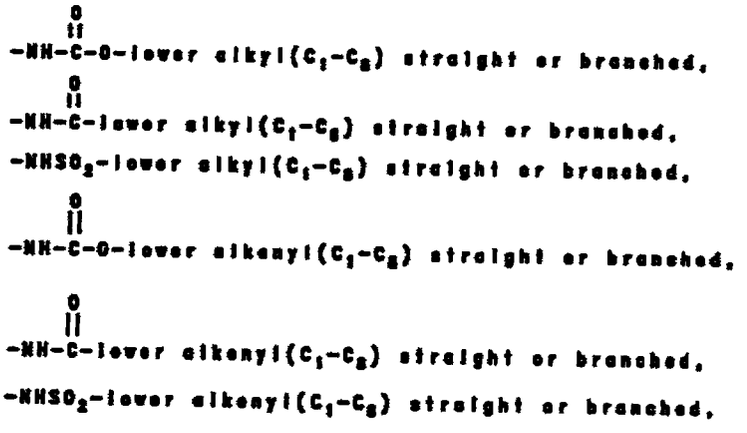
wherein Ar is the moiety:



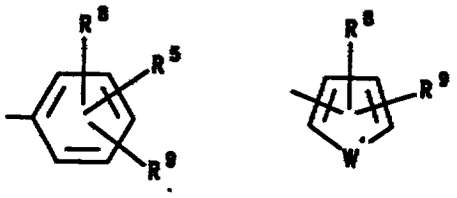
R^6 is





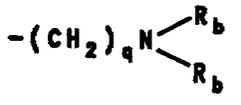


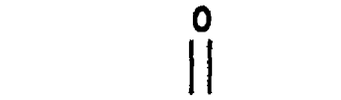
and Ar' is selected from the moieties:



wherein R_a, R_b, R^5, R^7, R^8, R^9, cycloalkyl and W' are as hereinbefore described;

R^{11} is selected from hydrogen, halogen, (C_1-C_3) lower alkyl, hydroxy,

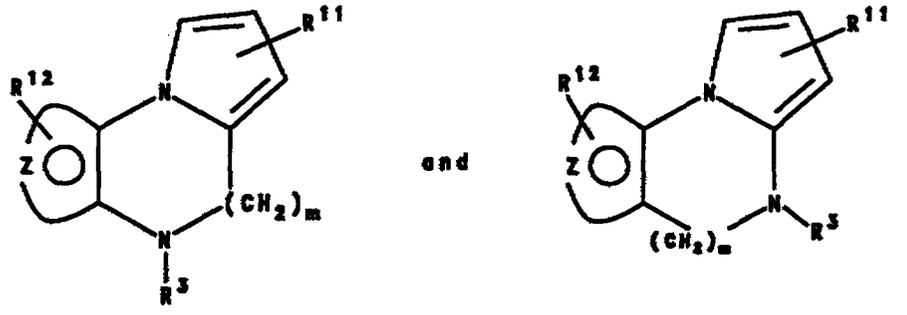




$-C-$lower alkyl(C_1-C_3),

-CHO, and (C_1-C_3)lower alkoxy; and R^{12} is selected from hydrogen, (C_1-C_3)lower alkyl, halogen and (C_1-C_3)lower alkoxy.

Also particularly preferred are compounds of the formulae:



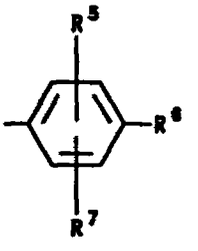
wherein m is one or two;
the moiety:



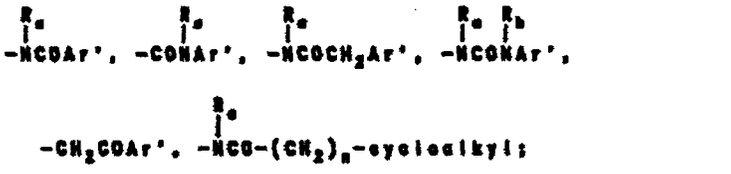
is selected from a phenyl, thiophene, furan, pyrrole or pyridine ring;
R^3 is the moiety:



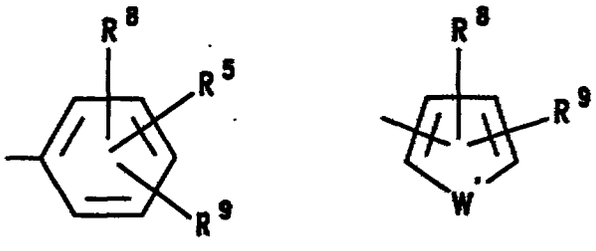
wherein Ar is the moiety:



R^6 is



$(CH_2)_n$ cycloalkyl; Ar' is selected from the moieties:

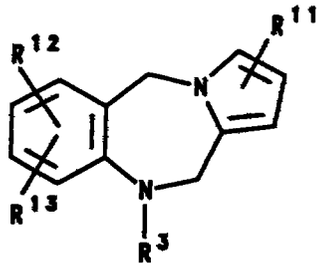
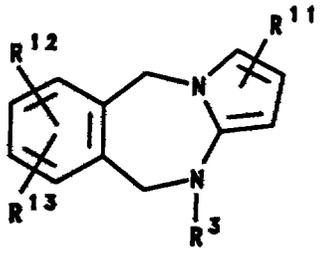


wherein R_a, R_b, R^5, R^6, R^8, R^9, cycloalkyl and W' are as hereinbefore defined;
R^{11} is selected from hydrogen, halogen, (C_1-C_3) lower alkyl, hydroxy,



-CHO, and (C_1-C_3)lower alkoxy; and
R^{12} is selected from hydrogen, (C_1-C_3)lower alkyl, halogen and (C_1-C_3)lower alkoxy.

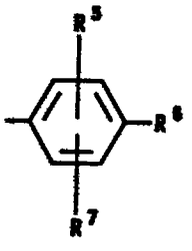
More particularly preferred are compounds of the formulae:


and


R^3 is the moiety:



wherein Ar is the moiety:



R^6 is

$-NCOAr'$, $-CONAr'$, $-NCOCH_2Ar'$, $-NCONAr'$,

$-CH_2COAr'$, $-NCO-(CH_2)_n$-cycloalkyl;

$-NH-C(=O)-O$-lower alkyl(C_1-C_8) straight or branched,

$-NH-C(=O)$-lower alkyl(C_1-C_8) straight or branched,

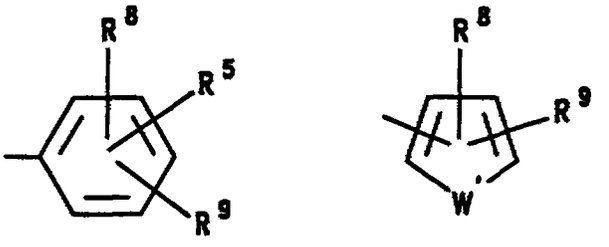
$-NHSO_2$-lower alkyl(C_1-C_8) straight or branched,

$-NH-C(=O)-O$-lower alkenyl(C_1-C_8) straight or branched,

$-NH-C(=O)$-lower alkenyl(C_1-C_8) straight or branched,

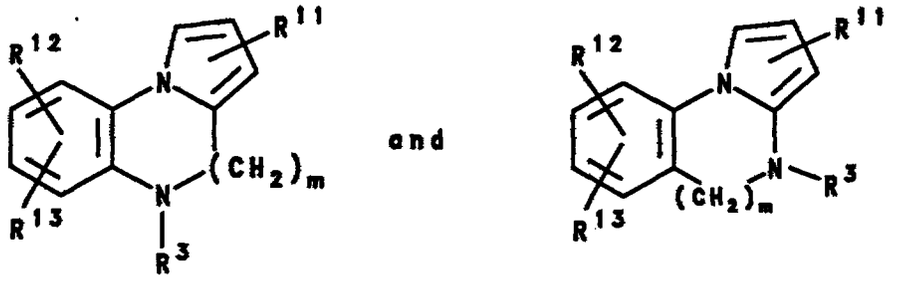
$-NHSO_2$-lower alkenyl(C_1-C_8) straight or branched,

wherein cycloalkyl is defined as C_3-C_6 cycloalkyl, cyclohexenyl or cyclopentenyl; R_b is hydrogen; R_a is independently selected from hydrogen, $-CH_3$, $-C_2H_5$ or $-(CH_2)_qN(CH_3)_2$; Ar' is selected from the moieties:

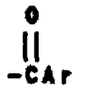


wherein q, R_a, R_b, R^5, R^7, R^8, R^9, R^{11} and W' are as hereinbefore described;
R^{12} and R^{13} are independently selected from hydrogen, (C_1-C_3) lower alkyl, halogen, amino, (C_1-C_3) lower alkoxy or (C_1-C_3) lower alkylamino.

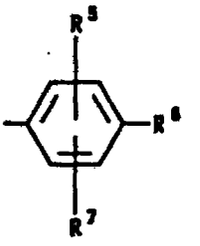
Also particularly preferred are compounds of the formulae:



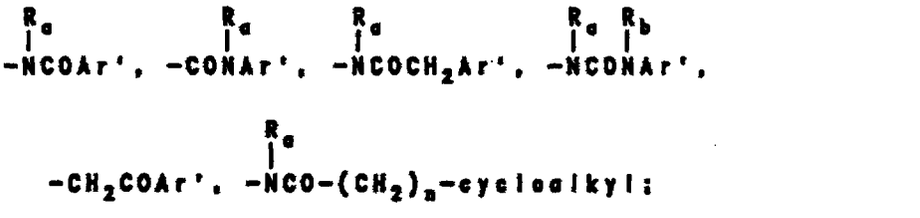
wherein m is one or two;
R^3 is the moiety:



wherein Ar is the moiety:



R^6 is



wherein cycloalkyl is defined as C_3-C_6 cycloalkyl, cyclohexenyl or cyclopentenyl; R_b is hydrogen; R_a is independently selected from hydrogen, $-CH_3$, $-C_2H_5$ or $-(CH_2)_qN(CH_3)_2$; and Ar' is selected from the moieties:

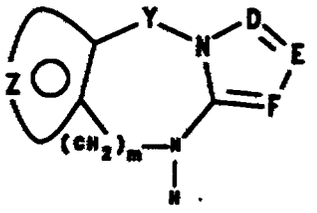


wherein q, R^5, R^7, R^8, R^9, R^{11} and W' are as hereinbefore defined;
R^{12} and R^{13} are independently selected from hydrogen, (C_1-C_3) lower alkyl, halogen, amino, (C_1-C_3)lower alkoxy or (C_1-C_3)lower alkylamino.

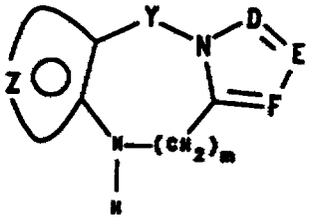
Compounds of this invention may be prepared as shown in Scheme I by reaction of tricyclic derivatives of Formula 3a and 3b with a substituted or unsubstituted 4-nitrobenzoyl chloride 4 to give the intermediates 5a and 5b. Reduction of the nitro group in intermediates 5a and 5b gives the 4-aminobenzoyl derivatives 6a and 6b. The reduction of the nitro group in intermediates 5a and 5b may be carried out under catalytic reduction conditions (hydrogen-Pd/C; Pd/C- hydrazine-ethanol) or under chemical reduction conditions ($SnCl_2$-ethanol; Zn-acetic acid; $TiCl_3$) and related reduction conditions known in the art for converting a nitro group to an amino group. The conditions for conversion of the nitro group to the amino group are chosen on the basis of compatability with the preservation of other functional groups in the molecule.

Reaction of compounds of Formula 6a and 6b with aroyl chloride or related activated aryl carboxylic acids in solvents such as chloroform, dichloromethane, dioxane, tetrahydrofuran, toluene and the like in the presence of a tertiary base such as triethylamine and diisopropylethylamine or pyridine and the like, affords the compounds 8a and 8b which are vasopressin antagonists.

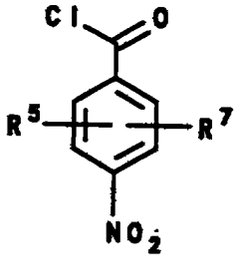
Scheme 1



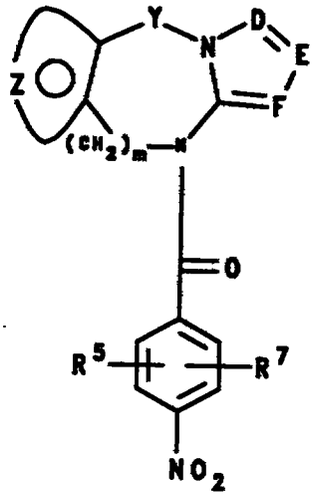
3a



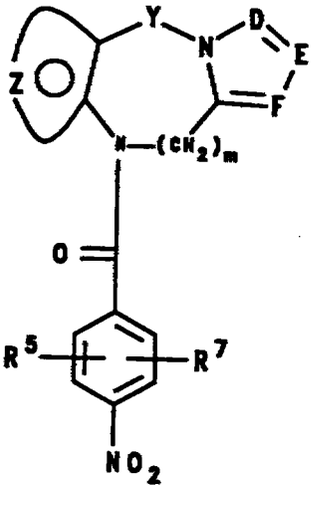
3b



4

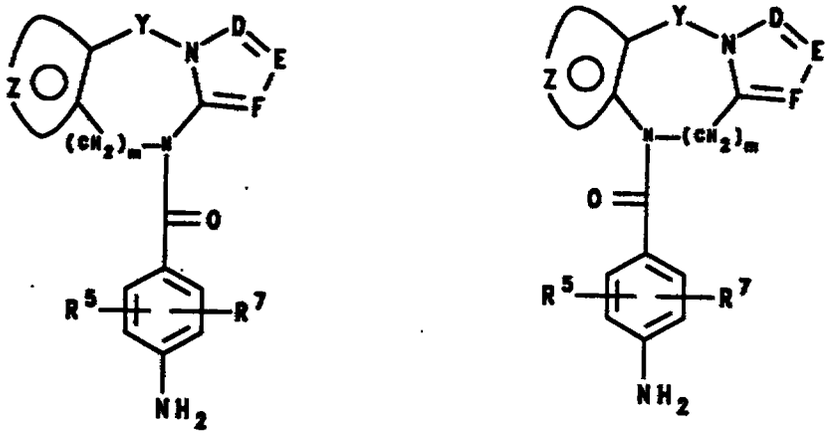


5a



5b

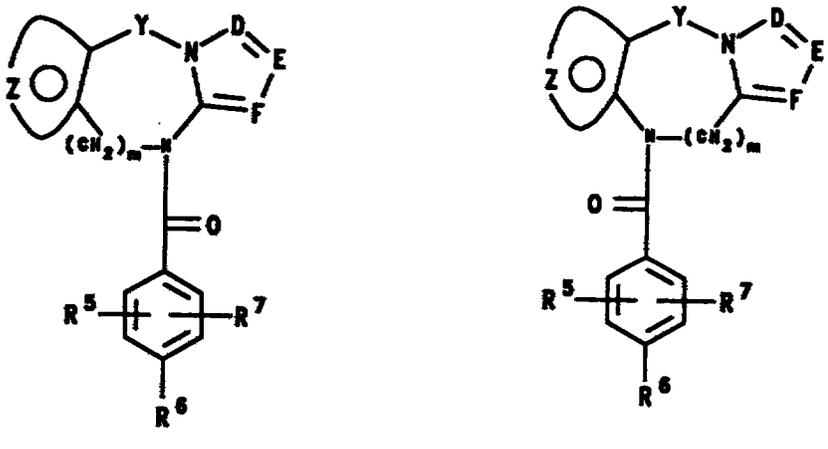
Scheme 1 (Cont'd)



6a 6b

Ar'COCl
Ar'CH_2COCl
cycloalkyl$(CH_2)_n$COCl
Ar'NCOCl
|
R_b

7



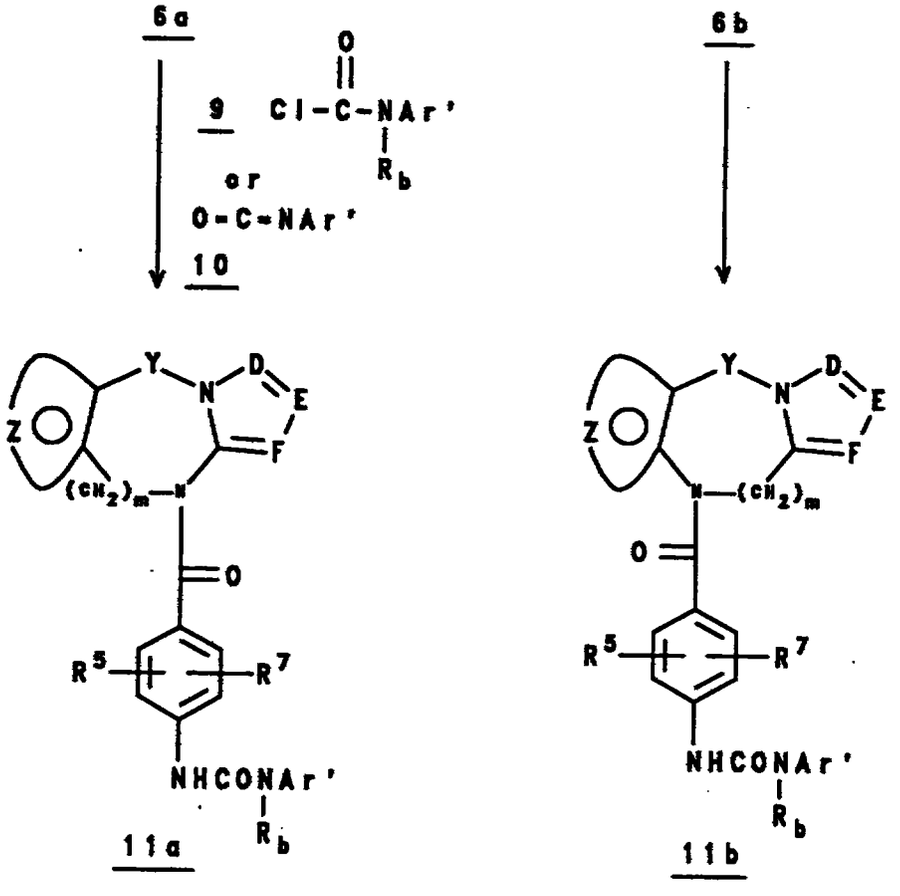
8a 8b

R^6 - NHCOAr'; -NHCOCH_2Ar';
-NHCO$(CH_2)_n$cycloalkyl; -NHCON-Ar'
|
R_b

Reaction of tricyclic derivatives of Formula 6a and 6b with either a carbamoyl derivative 9 or a isocyanate derivative 10 gives compounds (Scheme 2) of Formula 11a and 11b which are vasopressin antagonists of Formula I wherein R^6 is

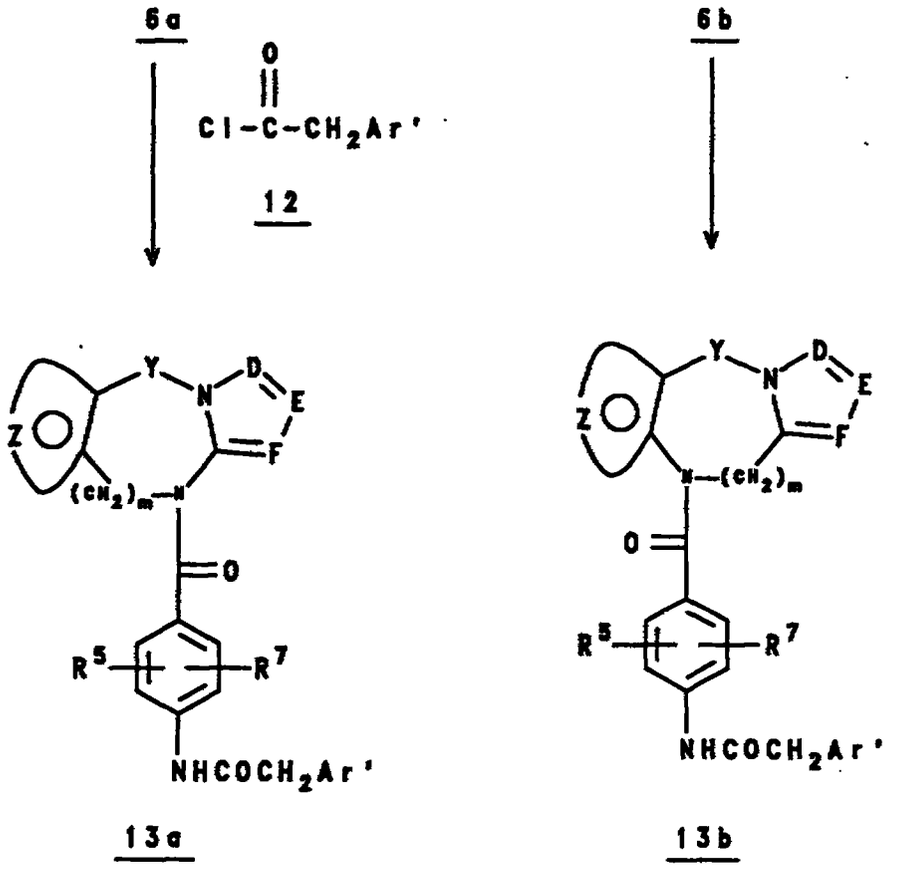


Scheme 2

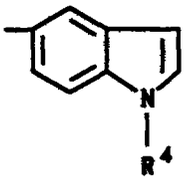


Reaction of tricyclic derivatives of Formula 6a and 6b with arylacetic acids, activated as the acid chlorides 12, anhydrides, mixed anhydrides or activated with known activating reagents, gives compounds 13a and 13b (Scheme 3).

Scheme 3

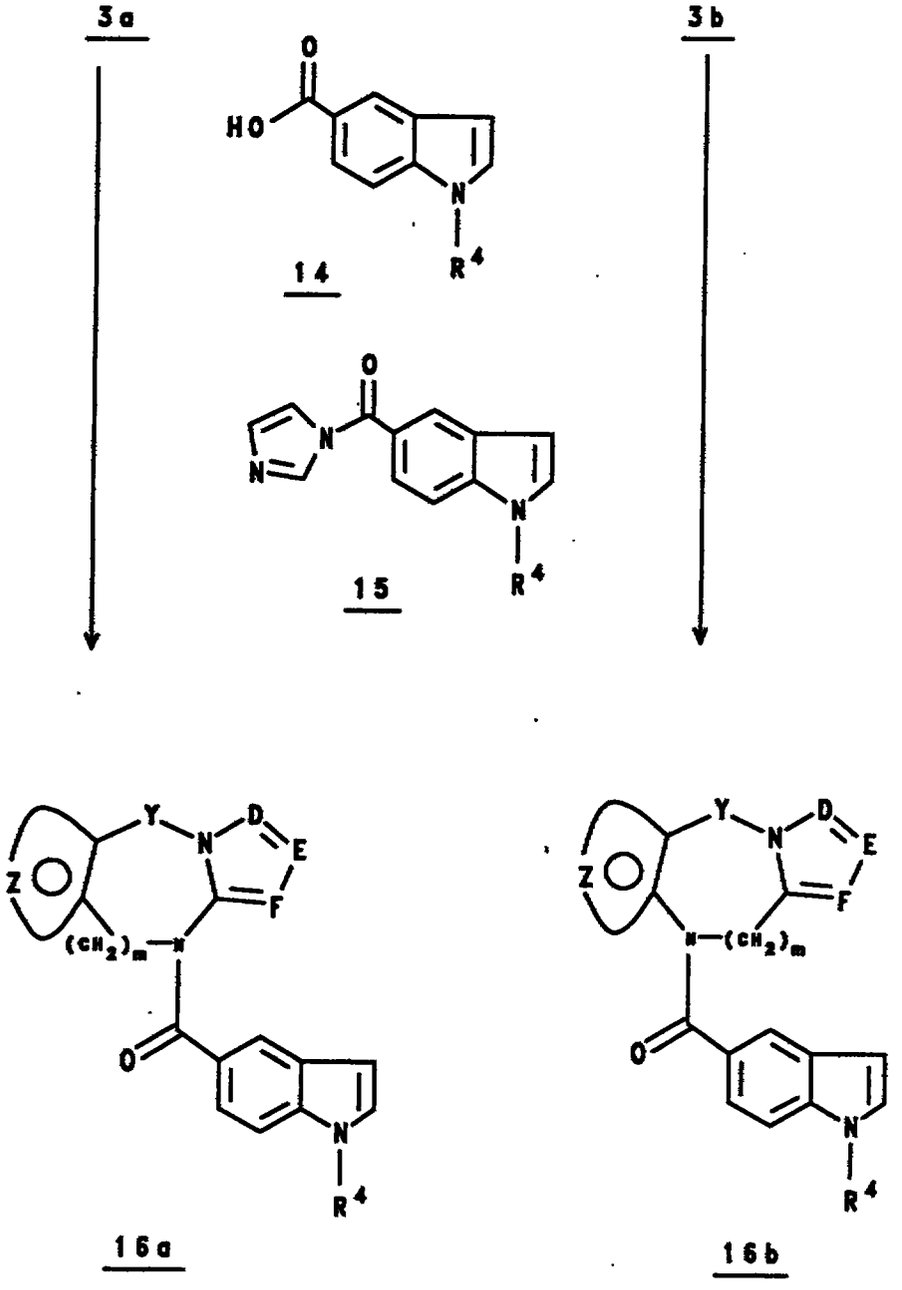


The compounds of Formula I wherein Y, A-B, Z, R^1, R^2 and R^3 are as defined and the Ar moiety of R^3 (-COAr) is

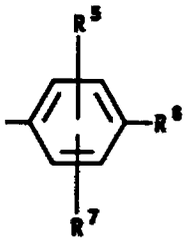


may be prepared, as shown in Scheme 4, by reacting an activated ester of the indole-5-carboxylic acids 14 with tricyclic derivatives 3a and 3b. The indole-5-carboxylic acids 14 may be activated by preparing the anhydride, a mixed anhydride or reacting with diethyl cyanophosphonate, N,N-carbonyldiimidazole or related peptide coupling reagents. As an example, the derivative 15 may be prepared by the acid 14 and N,N-carbonyldiimidazole in tetrahydrofuran; the solvent is removed and the derivative reacted with 3a or 3b at 100°C to 120°C without a solvent. Alternatively, 3a and 3b may be reacted with 15 in a solvent such as toluene or xylene at reflux temperatures. The activating reagent for the indole acids 14 is chosen on the basis of its compatibility with the R^4 group and its reactivity with the tricyclic derivatives 3a and 3b to give the vasopressin antagonists 16a and 16b.

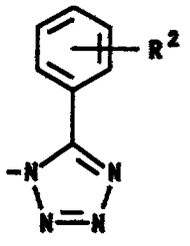
Scheme 4



The compounds of Formula I wherein Y, A-B, Z, R^1, R^2 and R^3 are as defined and the Ar moiety of R^3 (-COAr) is

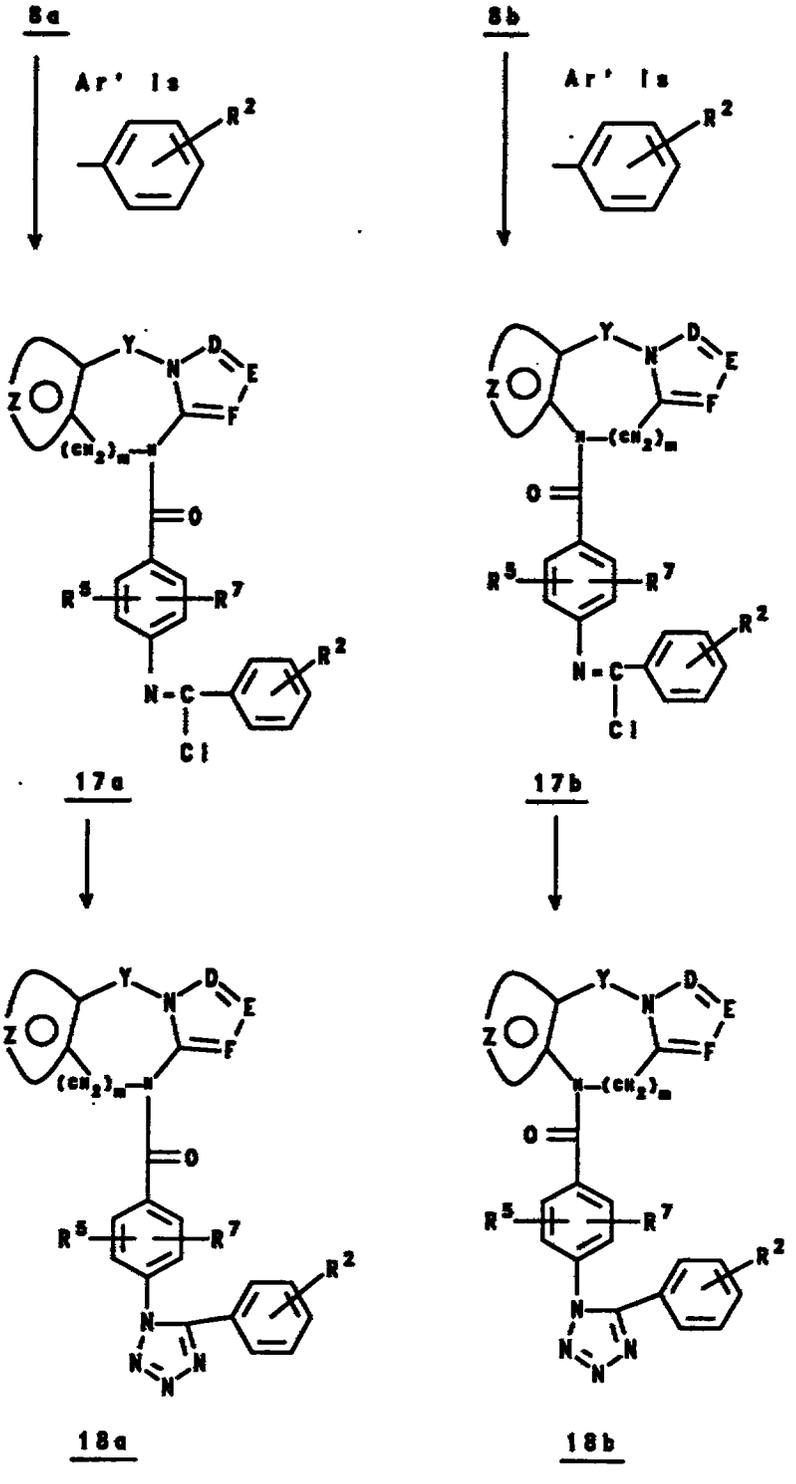


wherein R^6 is



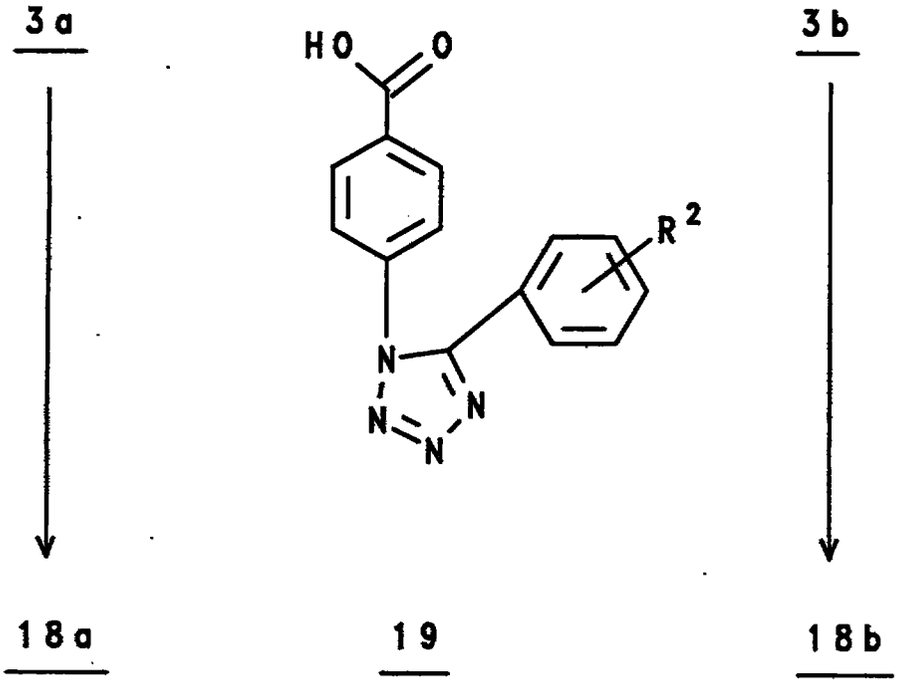
may be prepared as shown in Scheme 5 by first converting derivatives 8a and 8b into the intermediates 17a and 17b and then reacting these intermediates with sodium or lithium azide to give the products 18a and 18b.

Scheme 5



Alternatively, the products 18a and 18b may be prepared by coupling tetrazole derivatives of the Formula 19 with tricyclic derivatives 3a and 3b (Scheme 6). The tetrazole carboxylic acids are activated for coupling to the tricyclic compounds 3a and 3b by reaction with peptide coupling reagents, by conversion to the acid chlorides, anhydrides or mixed anhydrides.

Scheme 6



As an alternative method for synthesis of compounds of this invention as depicted in Formula I wherein Y, A-B, D, E, F and Z are as previously described and R^3 is

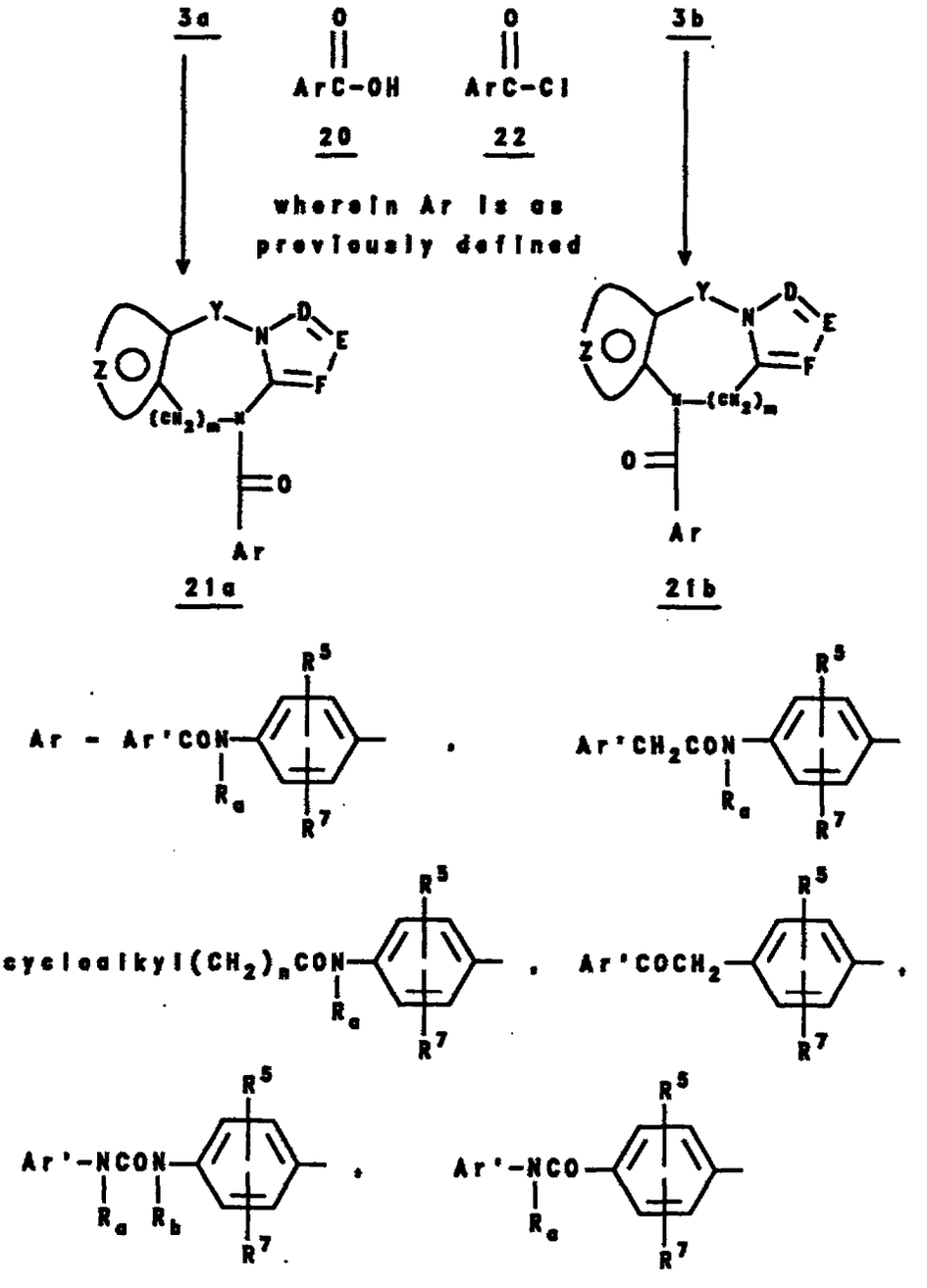


is the coupling of aryl carboxylic acids 20 with the tricyclic derivatives 3a and 3b to give 21a and 21b.

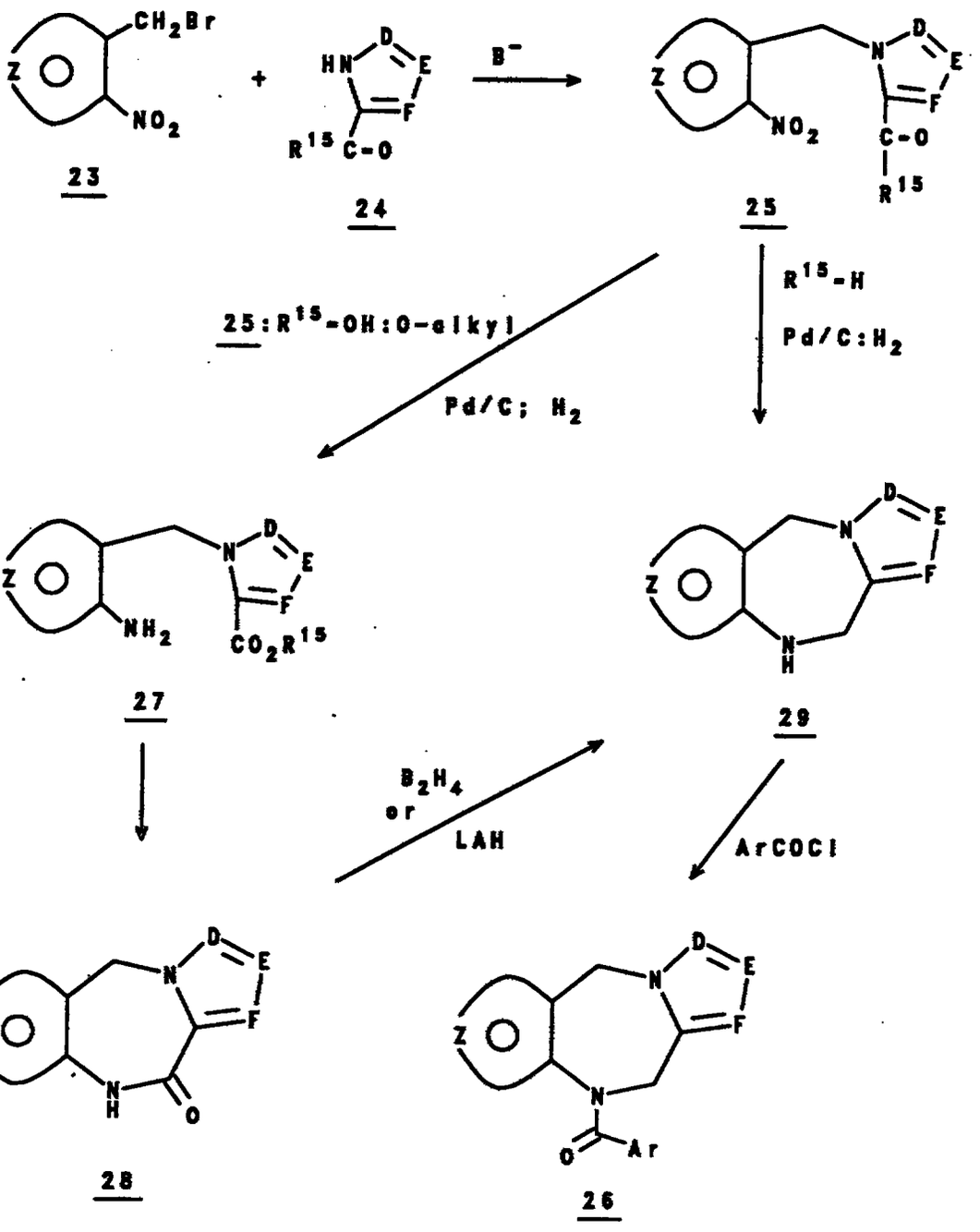
The aryl carboxylic acids are activated for coupling by conversion to an acid chloride, bromide or anhydride or by first reacting with an activating reagent such as N,N-dicyclocarbodiimide, diethyl cyanophosphonate and related "peptide type" activating reagents. The method of activating the acids 20 for coupling to the tricyclic derivatives 3a and 3b is chosen on the basis of compatibility with other substituent groups in the molecule. The method of choice is the conversion of the aryl carboxylic acids 20 to the corresponding aroyl chloride. The aryl acid chlorides 22 may be prepared by standard procedures known in the art, such as reaction with thionyl chloride, oxalyl chloride and the like. The coupling reaction is carried out in solvents such as halogenated hydrocarbons, toluene, xylene, tetrahydrofuran dioxane in the presence of pyridine or tertiary bases such as triethylamine and the like (Scheme 7). Alternatively, the aroyl chlorides 22, prepared from the aryl carboxylic acids 20, may be reacted with derivatives 3a and 3b in pyridine with or without 4-(dimethylamino)pyridine.

In general, when the aryl carboxylic acids 20 are activated with N,N-carbonyldiimidazole and other "peptide type" activating reagents, higher temperatures are required than when the aroyl chlorides are used. The reaction may be carried out in a higher boiling solvent xylene or without a solvent (100°C to 150°C).

Scheme 7


3a
3b
ArC-OH
ArC-Cl
20
22
wherein Ar is as previously defined
21a
21b
Ar - Ar'CON
Ar'CH2CON
cycloalkyl(CH2)nCON
Ar'COCH2
Ar'-NCON
Ar'-NCO

Scheme 8


CH2Br
NO2
23
HN
D
E
F
R15C-O
24
B-
NO2
C-O
R15
25
25:R15-OH:O-alkyl
Pd/C; H2
R15-H
Pd/C:H2
NH2
CO2R15
27
29
B2H4
or
LAH
ArCOCl
O
28
Ar
26

The starting materials 3a and 3b in the foregoing Schemes 1-7 may be prepared as follows. In accordance with Scheme 8, alkylation of heterocycles of structural type 24 with an alkylating moiety such as 23 gives intermediates 25. The heterocycle 24 may contain an α-carboxaldehyde function or an α-carboxylic and/or ester function as shown in Scheme 8. Where the intermediate 25 (R^{15}=H) contains an α-carboxaldehyde group, hydrogenation with palladium-on-carbon gives reduction and ring closure in one step to give 29.

In derivatives 25 where R^{15} is an α-carboxylic and/or an α-carboxylic ester function, the intermediate amino acid derivative 27 is first isolated and then ring closed. The ring closure of derivatives 27 may be carried out by heating or by activation of the acid function (27:R^{15}=H) for ring closure. The cyclic lactams 28 are conveniently reduced with diborane or lithium aluminum hydride to give intermediates 29. Reaction of tricyclic derivatives 29 with aroyl chlorides (ArCOCl), where Ar is as hereinbefore defined, gives diazepines 26.

Tricyclic derivatives of structural type 36 may be prepared as shown in Scheme 9. Formylation of 32 under known conditions in the literature, such as Vilsmeier formylation, gives intermediates 35 which on reduction and ring closure affords tricyclics 37.

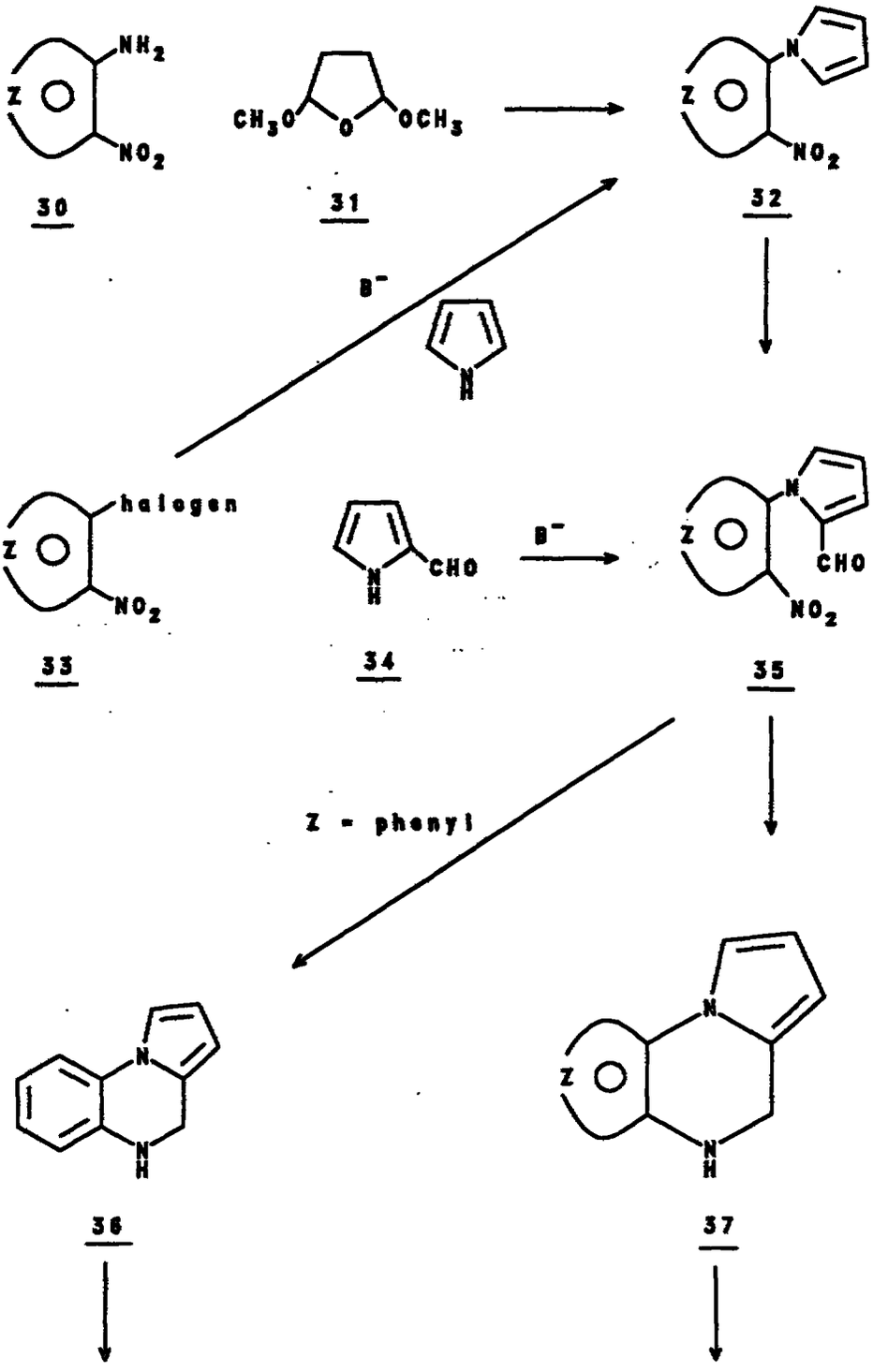
Where Z is a fused substituted or unsubstituted phenyl group, the procedure gives pyrrolo[1,2-a] quinoxalines 36. These derivatives 36 and 37 may be reacted with aroyl chlorides (ArCOCl) wherein Ar is as previously defined or with a substituted or unsubstituted 4-nitrobenzoyl chloride or with a nitrogen protecting group, such as benzyloxycarbonyl chloride to give compounds 38 and 39. The compounds 38 and 39 may be reacted with chlorine, bromine or halogenating reagents such as N-chlorosuccinimide, N-bromosuccinimide and the like to give compounds 40 and 41 wherein

R^{17} is a halogen atom. The derivatives 38 and 39 may be formylated and acetylated to give products 40 and 41 wherein R^{17} is a CHO or a $-COCH_3$ group. Halogenation, formylation and acetylation of derivatives 36 gives 1-substituted pyrrolo[1,2-a]quinoxalines. The derivatives 38, 39, 40 and 41 wherein R^{16} is a substituted or unsubstituted 4-nitrobenzoyl group are reduced to give the 4-aminobenzoyl derivatives 42d and 43d which are reacted with reagents Ar'COCl, $Ar'CH_2COCl$ or

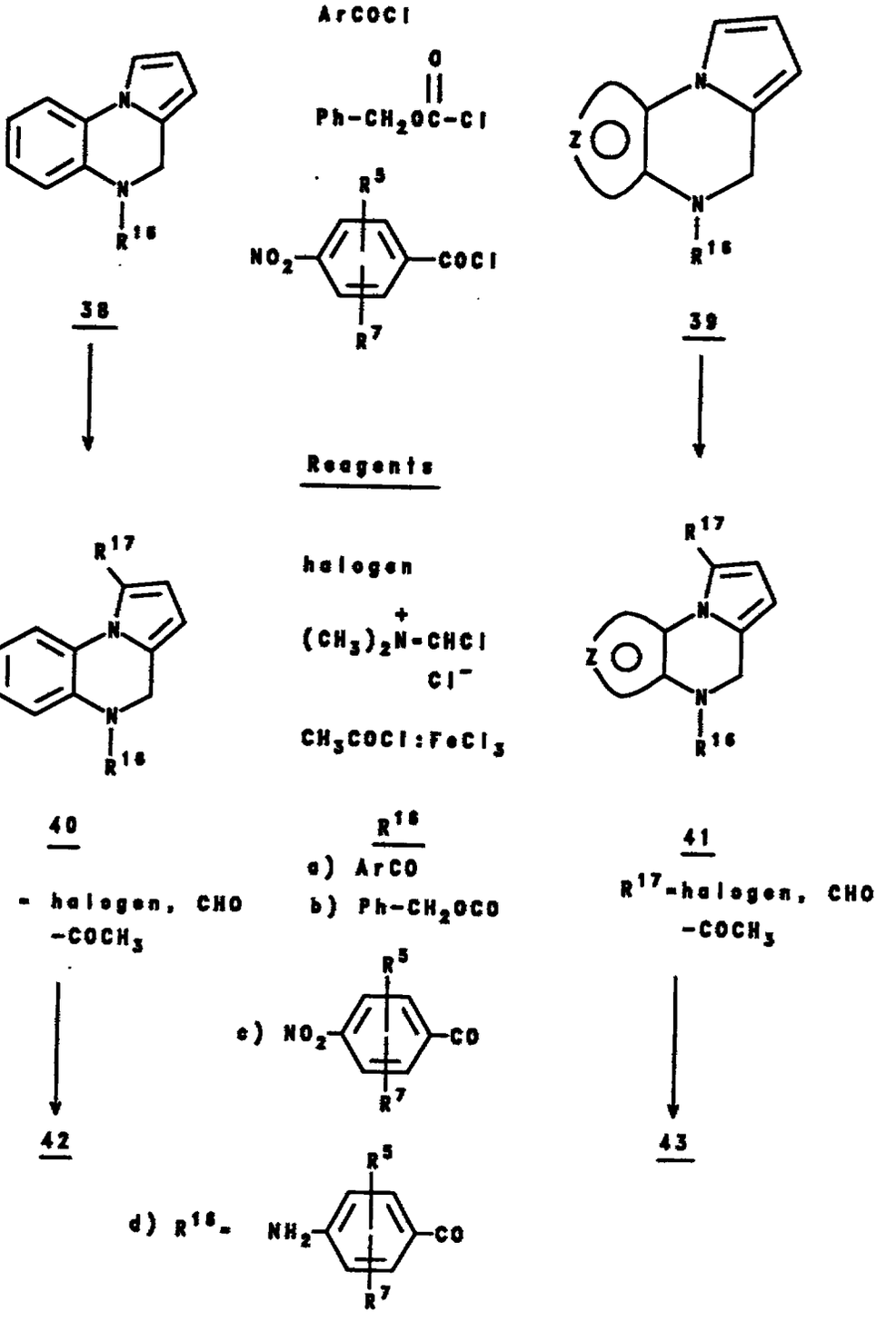
$$Ar'-\underset{\displaystyle R_b}{\overset{\displaystyle |}{N}}COCl;$$

wherein Ar' and R_b are as previously hereinbefore defined, to give tricyclic diazepines 44 and 45.

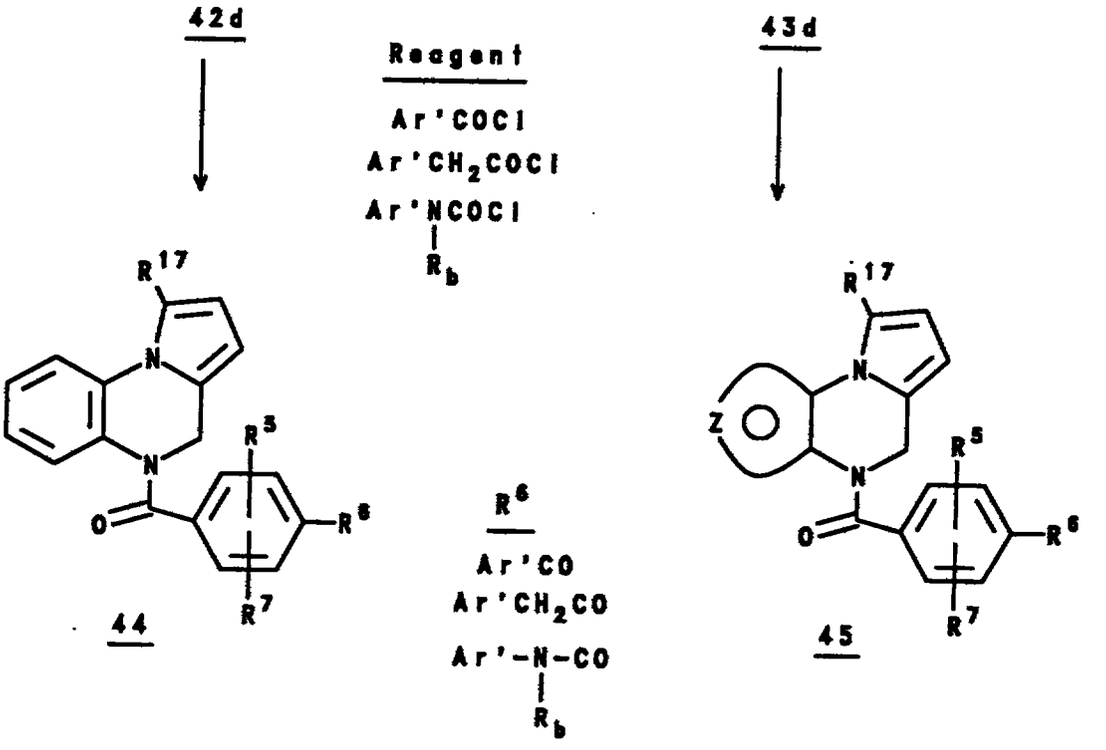
Scheme 9


NH2
NO2
Z
CH3O
OCH3
O
N
30
31
32
B⁻
halogen
CHO
33
34
35
Z = phenyl
36
37

Scheme 9 (cont'd)



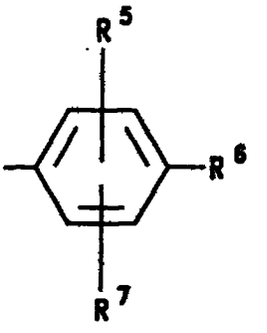
Scheme 9 (cont'd)



The compounds of this invention wherein R^3 is the moiety:



and the Ar group is the moiety:



and R^6 is a

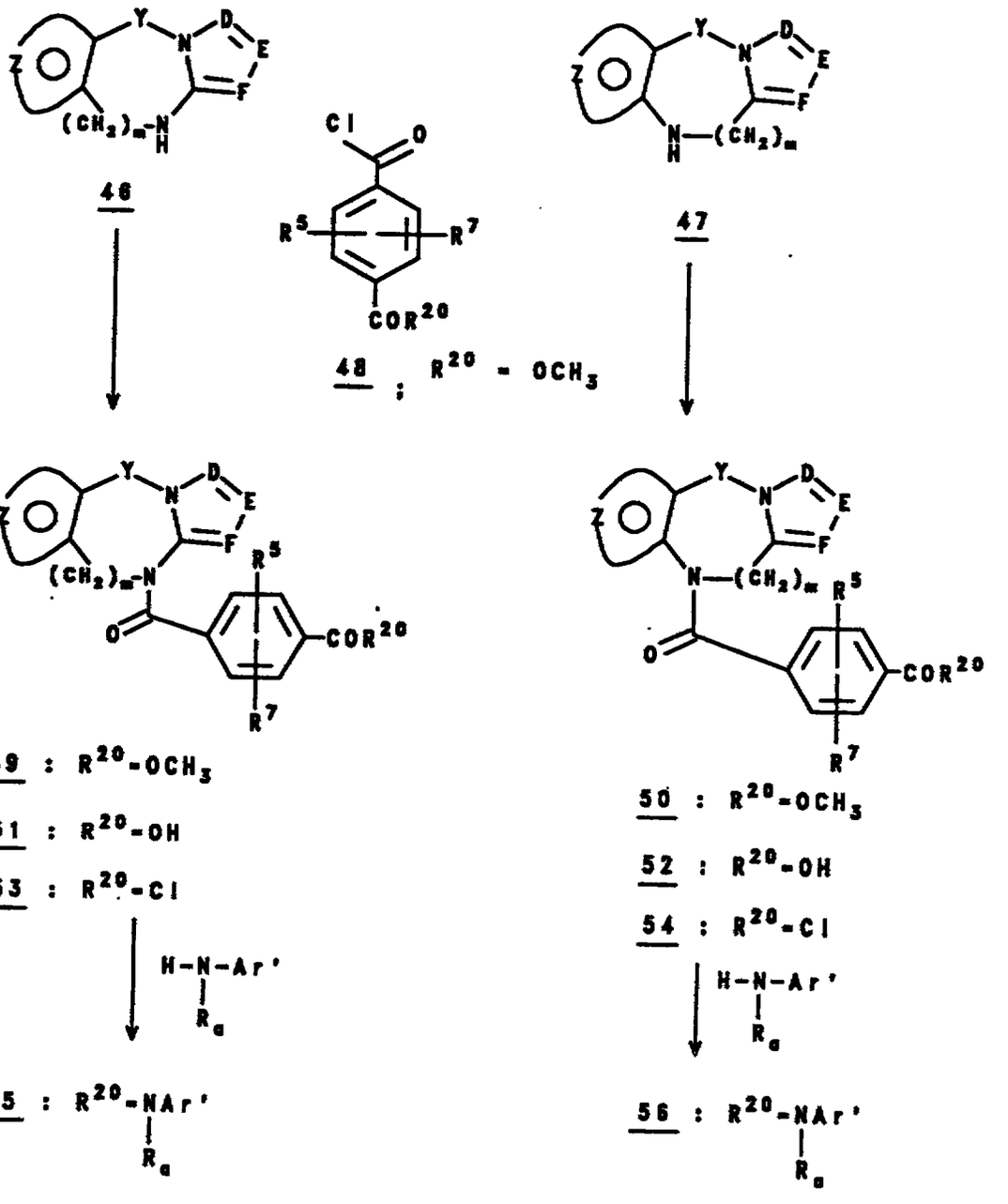


group, wherein R_a, R^5, R^7 and Ar' are as previously hereinbefore defined, are synthesized as shown in Scheme 10. The tricyclic derivatives 46 and 47 are reacted with the mono methyl terephthaloyl chloride 48 to give the aroylated methyl ester compounds 49 and 50. Hydrolysis of the methyl esters 49 and 50 gives the acids 51 and 52 which are activated for coupling by conversion to an activated ester or converted to the acid chlorides 53 and 54. Reaction of the acid chlorides 53 and 54 with the amines,



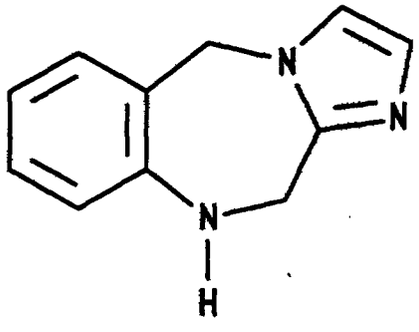
wherein R_a and Ar' are as hereinbefore defined gives the derivatives 55 and 56.

Scheme 10

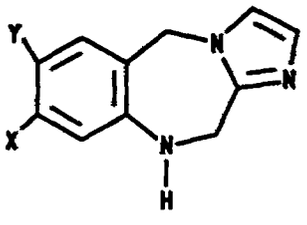

46
47
48 ; R20 = OCH3
49 : R20-OCH3
51 : R20-OH
53 : R20-Cl
H-N-Ar'
Ra
55 : R20-NAr'
Ra
50 : R20-OCH3
52 : R20-OH
54 : R20-Cl
H-N-Ar'
Ra
56 : R20-NAr'
Ra

Preparation of some tricyclic diazepines useful for starting materials for the synthesis of compounds of this invention are shown in Schemes 8 and 9. Other tricyclic diazepines are prepared by literature procedures or by methods known in the art or by procedures reported for the synthesis of specific known tricyclic diazepines. These diazepine ring systems discussed below when subjected to reaction conditions shown in Schemes 1, 2, 3, 4, 5, 6, 7, 9 and 10 give the compounds of this invention.

The tricyclic diazepine ring system, 10,11-dihydro-5H-imidazo[2,1-c][1,4]benzodiazepine,

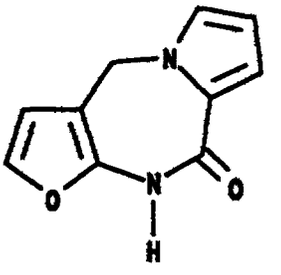


is reported by G. Stefancich, R. Silvestri and M. Artico, J. Het. Chem. 30, 529(1993); ring substitution on the same ring system is reported by G. Stefancich, M. Artico, F. Carelli, R. Silvestri, G. deFeo, G. Mazzanti, I. Durando, M. Palmery, IL Farmaco, Ed. Sc., 40, 429(1985).

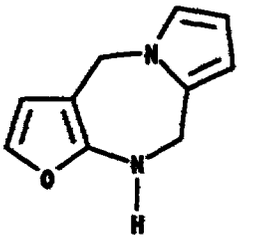


X = H, $-OCH_3$, $-OCH_2C_6H_5$; Y=H, Cl, $-OCH_3$; X,Y = $O-CH_2-O$-

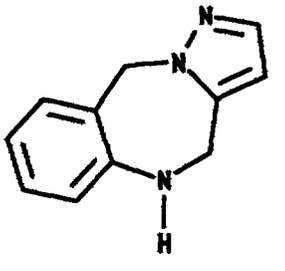
The synthesis of 9,10-dihydro-4H-furo[2,3-e]-pyrrolo[1,2-a][1,4]diazepin-9-one



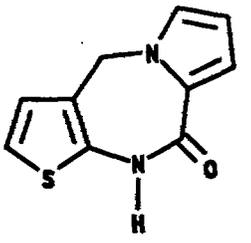
is reported by F. Povazunec, B. Decroix and J. Morel, J. Het. Chem. 29, 1507(1992) and is reduced to give the tricyclic heterocycle 9,10-dihydro-4H-furo[2,3-e]-pyrrolo[1,2-a][1,4]diazepine.



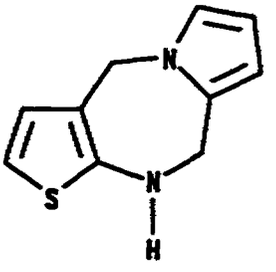
The tricyclic 5,10-dihydro-4H-pyrazolo[5,1-c][1,4]-benzodiazepine ring system is reported by L. Cecchi and G. Filacchioni, J. Het. Chem., 20, 871(1983);



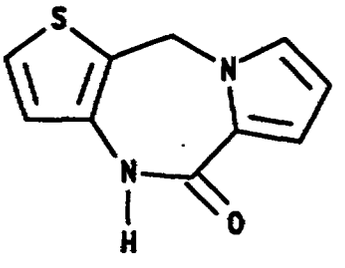
The synthesis of 9-oxo-9,10-dihydro-4H-pyrrolo[1,2-a]-thieno[2,3-e][1,4]diazepine is reported by A. Daich and B. Decroix, Bull. Soc. Chim. Fr 129, 360(1992);



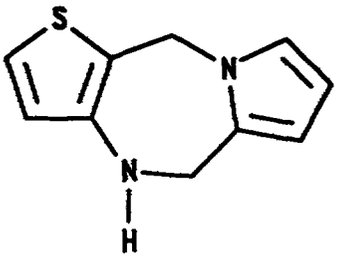
and is reduced with boron-dimethylsulfide to give 9,10-dihydro-4H-pyrrolo[1,2-a]thieno[2,3-e][1,4]diazepine.



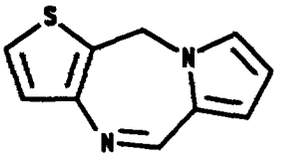
Also reported by A. Daich and B. Decroix is 5-oxo-4,5-dihydropyrrolo[1,2-a]thieno[3,2-e][1,4]diazepine



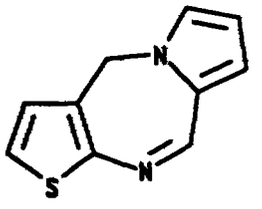
which is also reduced to give 4,10-dihydro-5H-pyrrolo-[1,2-a]thieno[3,2-e][1,4]diazepine



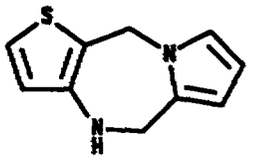
Reported by B. Decroix and J. Morel, J. Het. Chem., 28, 81(1991) are pyrrolo[1,2-a]thieno[3,2-e][1,4]diazepine;



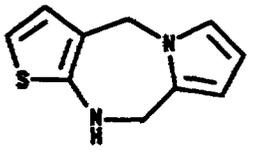
and



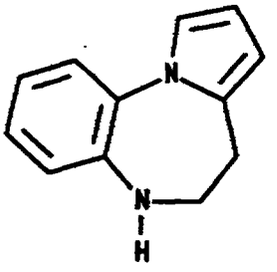
and pyrrolo[1,2-a]thieno[2,3-e][1,4]diazepine. Reduction by hydrogen-Pd/c or chemical reduction with reagents such as sodium cyanoborohydride and acetic acid gives the dihydro tricyclic heterocycles



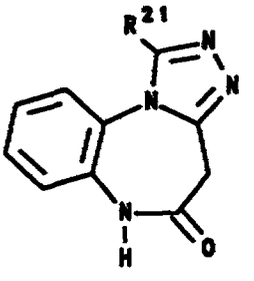
and

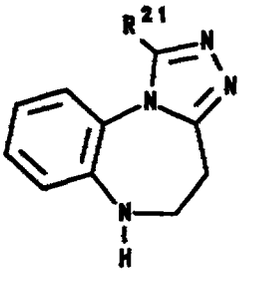


The synthesis of the tricyclic 1,5-benzodiazepine ring system, 6,7-dihydro-5H-pyrrolo[1,2-a][1,5]benzodiazepine, has been reported by F. Chimenti, S. Vomero, R. Giuliano and M. Artico, IL Farmaco, Ed. Sc., 32, 339(1977). Annelated 1,5-benzodiazepines containing five membered rings have been reviewed by A. Chimirri, R. Gitto, S. Grasso, A.M. Monforte, G. Romeo and M. Zappala, Heterocycles, 36, No. 3, 604(1993), and the ring system 6,7-dihydro-5H-pyrrolo[1,2-a][1,5]benzodiazepine is described.



The preparation of 5,6-dihydro-4H-[1,2,4]-triazolo[4,3-a][1,5]benzodiazepin-5-ones from 1,2-dihydro-3H-4-dimethylamino-1,5-benzodiazepin-2-ones has been described by M. DiBroccio, G. Roma, G. Grossi, M. Ghia, and F. Mattioli Eur. J. Med. Chem; 26, 489(1991). Reduction of 5,6-dihydro-4H-[1,2,4]triazolo[4,3-a]-[1,5]benzodiazepin-5-ones with diborane or lithium hydride gives the tricyclic 5,6-dihydro derivatives.





R^{21} = H, CH_3

The compounds of this invention and their preparation can be understood further by the following examples, but should not constitute a limitation thereof.

Example 1

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2,3-difluorobenzamide

To a stirred solution of 0.350 g of 2,3-difluorobenzoyl chloride in 5 ml of methylene chloride is added 0.346 ml of triethylamine. After stirring for 3 minutes, 0.500 g of 10,11-dihydro-10-(4-aminobenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine is added and stirring continued for 72 hours. The reaction mixture is filtered and the solid washed with methylene chloride. The solid is saved. The combined filtrate is washed with water, 2N citric acid, 1M $NaHCO_3$, and brine. The reaction mixture is dried with Na_2SO_4, filtered and evaporated in vacuo to give 100 mg of a solid. The two solids are combined and dried to afford 790 mg of the desired product as a solid, m.p. 252-258°C.

Example 2

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2-methoxybenzamide

To a stirred solution of 0.362 g of 2-methoxybenzoyl chloride 5 ml of methylene chloride is added 0.346 g of triethylamine at 0° C. After stirring for 3 minutes, 0.500 g of 10,11-dihydro-10-(4-aminobenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine is added and stirring continued for 18 hours at room temperature. The reaction mixture is diluted with 45 ml of methylene chloride and washed with water, 2N citric acid, 1M $NaHCO_3$, and brine. The reaction mixture is dried with Na_2SO_4, filtered through hydrous magnesium silicate and evaporated in vacuo to give a solid which is purified by crystallization from ethyl acetate to give 0.430 g of the desired product as a crystalline solid, m.p. 185-188°C.

Example 3

2-Methyl-N-[4-(5H-pyrrolo[2,1-c][1,4]-benzodiazepin-10(11H)-ylcarbonyl)-phenyl]benzamide

To a mixture of 1.93 g of 4-[(2-methylbenzoyl)amino]benzoyl chloride in 15 ml of methylene chloride, cooled to 0° C is added 1.13 ml of triethylamine. After stirring for 3 minutes, a mixture of 1.0 g of 10,11-dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine in 5 ml of methylene chloride is added. The cooling bath is removed and after about 30 minutes a complete solution is obtained. The reaction mixture is allowed to stir at room temperature for 48 hours and the volatiles are concentrated in vacuo to a residue. The residue is dissolved in 100 ml of ethyl acetate and washed with water, 2N citric acid, aqueous $NaHCO_3$ and brine. The solution is dried with Na_2SO_4 and the volatiles concentrated in vacuo to give 3.0 g of a residue. A 300 mg sample of the residue is purified by thick layer chromatography using 10% ethyl acetate-methylene chloride to give 160 mg of the desired product. The remainder of the crude material is purified by flash chromatography using 10% ethyl acetate in methylene chloride to give the desired product as a residue which is crystallized from ethyl acetate to give 800 mg of the desired product as white crystals, m.p. 212-215°C.

Example 4

N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin--10(11H)-ylcarbonyl)phenyl]-2,5-dichlorobenzamide

To a solution of 414.5 mg of 2,5-dichlorobenzoyl chloride in 5 ml of methylene chloride is added 276 µl of triethylamine. After stirring at 0° C for 3 minutes 400 mg of the 10,11-dihydro-10-(4-aminobenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine is added. The bath is removed and the reaction mixture stirred at room temperature for 3 hours. The volatiles are concentrated in vacuo to give a residue which is

dissolved in ethyl acetate and washed with water, 2N citric acid, 1M $NaHCO_3$ and brine. The organic layer is dried with Na_2SO_4 and concentrated in vacuo to a residue which is purified by thick layer chromatography by elution with 1:1 ethyl acetate-hexanes to give a residue. The residue is crystallized from ethyl acetate to give 220 mg of the desired product as white crystals, m.p. 218-220°C.

Example 5

N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin--10(11H)-ylcarbonyl)phenyl]-3-methyl-2-thiophene-carboxamide

To a solution of 318 mg of 3-methyl-2-thiophenecarbonyl chloride in 5 ml of methylene chloride at 0°C is added 346 µl of triethylamine. After stirring for 3 minutes, 500 mg of the 10,11-dihydro-10-(4-aminobenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine is added. The bath is removed and the reaction mixture stirred at room temperature for 18 hours. The volatiles are concentrated in vacuo to give a residue which crystallizes from ethyl acetate to afford 800 mg of solid. The solid is dissolved in methylene chloride washed with water, 2N citric acid, 1M $NaHCO_3$ and brine. The organic layer is filtered through hydrous magnesium silicate, dried with Na_2SO_4 and concentrated in vacuo to give a residue which crystallizes from ethyl acetate to afford 400 mg of the desired product as a white solid, m.p. 232-235°C.

Example 6

N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin--10(11H)-ylcarbonyl)phenyl]-2,4-dichlorobenzamide

To a solution of 415 mg of 2,4-dichlorobenzoyl chloride in 5 ml of methylene chloride at 0° C is added 346 µl of triethylamine. After stirring for 3 minutes, 500 mg of 10,11-dihydro-10-(4-aminobenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine is added. The bath is removed and the reaction mixture stirred at room temperature for 18 hours. The volatiles are concentrated in vacuo to give a residue which is dissolved in ethyl acetate, washed with water, 2N citric acid, 1M $NaHCO_3$ and brine. The organic layer is dried with Na_2SO_4, filtered and concentrated in vacuo to give a residue which is crystallized from ethyl acetate to give 420 mg of the desired product as a crystalline solid, m.p., 210-212°C.

Example 7

N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin--10(11H)-ylcarbonyl)phenyl]-2-chlorobenzamide

To a solution of 347 mg of 2-chlorobenzoyl chloride in 5 ml of methylene chloride at 0° C is added 346 µl of triethylamine. After stirring for 3 minutes, 500 mg of 10,11-dihydro-10-(4-aminobenzoyl)-5H-pyrrolo-[2,1-c][1,4]benzodiazepine is added. The bath is removed and the reaction mixture stirred at room temperature for 18 hours. The volatiles are concentrated in vacuo to give a residue which is dissolved in methylene chloride, washed with water, 2N citric acid, 1M $NaHCO_3$ and brine. The organic layer is dried with Na_2SO_4, filtered and concentrated in vacuo to give a residue which is crystallized from methylene chloride to give 525 mg of the desired product as a white crystalline solid, m.p. 228-230°C.

Example 8

N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2-fluorobenzamide

To a solution of 314 mg of 2-fluorobenzoyl chloride in 5 ml of methylene chloride at 0° C is added 346 µl of triethylamine. After stirring for 3 minutes, 500 mg of 10,11-dihydro-10-(4-aminobenzoyl)-5H-pyrrolo-[2,1-c][1,4]benzodiazepine is added. The bath is removed and the reaction mixture stirred at room temperature for 18 hours. The volatiles are concentrated in vacuo to give a residue which is dissolved in methylene chloride, washed with water, 2N citric acid, 1M $NaHCO_3$ and brine. The organic layer is dried with Na_2SO_4, filtered and concentrated in vacuo to give 620 mg of the desired product as a crystalline solid, m.p. 257-260°C.

Example 9

2-Chloro-N-[4-(5H-pyrrolo[2,1-c][1,4]-benzodiazepin-10(11H)-ylcarbonyl)phenyl]-benzeneacetamide

A mixture of 0.273 g of 2-chlorophenylacetic acid is stirred at room temperature for 2 hours. The volatiles are evaporated in vacuo to a residue which is distilled with toluene several times. The residue is dissolved in 10 ml of methylene chloride containing 0.26 ml of triethylamine and while stirring 0.485 g of 10,11-dihydro-10-(4-aminobenzoyl)-5H-pyrrolo[2,1-c][1,-4]benzodiazepine added. The reaction mixture is stirred at room temperature for 18 hours. The volatiles are removed and the residue dissolved in ethyl acetate which is washed with water, 1N HCl, 1M $NaHCO_3$ and brine. The organic layer is dried and evaporated to a residue which is purified by flash chromatography using 1:1 ethyl acetate-hexane to give the desired product as a yellow solid, m.p. 99-103°C.

Example 10

1-(2-Nitrophenyl)-1H-pyrrole-2-carboxaldehyde

To a solution of 3.76 g of 1-(2-nitrophenyl)-pyrrole in 20 ml of N,N-dimethylformamide at 0°C is added dropwise with stirring 3 ml of phosphorus oxychloride. Stirring is continued for 30 minutes and the reaction mixture is heated at 90° C for 1 hour. After cooling to room temperature the mixture is treated with crushed ice and the pH adjusted to 12 with 2N sodium hydroxide. The resulting suspension is filtered, washed with water and dried to give 5.81 g of the desired product as a light yellow solid m.p. 119°-122°C.

Example 11

4,5-Dihydro-pyrrolo-[1,2-a]-quinoxaline

To a solution of 1.0 g of 1-(2-nitrophenyl)-1H-pyrrole-2-carboxaldehyde in 40 ml of ethyl alcohol and 40 ml of ethyl acetate, under argon, is added 40 mg of 10% Pd/C. The mixture is hydrogenated at 40 psi for 2 hours and filtered through diatomaceous earth. The filtrate is concentrated in vacuo to a residue which is dissolved in ether and treated with hexanes to give 0.35 g of the desired product as a beige solid m.p. 108°-110°C.

Example 12

4-[(2-Methylbenzoyl)amino]benzoic acid

A mixture of 43.42 g of ethyl 4-aminobenzoate and 40.8 g of 2-methylbenzoyl chloride in 150 ml of dichloromethane is cooled in an ice bath and 26.56 g of triethylamine is added dropwise. After the addition, the solution is stirred at room temperature overnight. The mixture is poured into water and the organic layer separted. The organic layer is washed with water, 1N HCl, 1M $NaHCO_3$ and dried over Na_2SO_4. The solvent is removed and the solid slurried with ethyl acetate and filtered to give 57 g of ethyl 4-[(2-methylbenzoyl)-amino]benzoate as crystals, m.p. 110-115°C. A mixture of 50.7 g of the preceding compound in 280 ml of ethyl

alcohol and 55 ml of 10N NaOH is refluxed for 5 minutes. The mixture is cooled to room temperature, diluted with 200 ml of water and acidified with concentrated hydrochloric acid (pH 1-2). The mixture is filtered and the solid washed with water and dried to give 51 g of the desired product as white crystals, m.p. 270-275°C.

Example 13

4-[(2-Methylbenzoyl)amino]benzoyl chloride

A mixture of 10.3 g of 4-[(2-methylbenzoyl)-amino] benzoic acid and 32 ml of thionyl chloride is refluxed for 1.5 hours. The solution is concentrated in vacuo. Toluene is added and the solvent removed in vacuo. Toluene is added and the mixture chilled and filtered to give the desired product as a yellow solid, 135-141°C.

Example 14

2-Methyl-N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]benzamide

A mixture of 0.51 g of 4-[(2-methylbenzoyl)-amino]benzoyl chloride and 0.36 g of 1,1'-carbonyldiimidazole in 6 ml of tetrahydrofuran is stirred at room temperature for 1 hour. To the reaction mixture is added 0.17 g of 4,5-dihydropyrrolo-[1,2-a]-quinoxaline followed by heating at reflux for 60 hours. The volatiles are concentrated in vacuo to a residue which is dissolved in ethyl acetate. The organic layer is washed with 1N HCl, 1M $NaHCO_3$, brine, dried with Na_2SO_4 and filtered through hydrous magnesium silicate. The volatiles are concentrated in vacuo to a residue which is chromatographed by elution with 1:2 ethyl acetate-hexanes to give 0.14 g of the desired product as a white solid, m.p. 206-207°C.;
MASS SPEC (CI) 408(MH^+).

Table I

The following Examples are prepared using the conditions of Example 14 with the appropriately substituted aroyl chloride

Example No.	Compound
15	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-2-chlorobenzamide
16	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-2,5-dichlorobenzamide
17	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-2,4-dichlorobenzamide, m.p. 200°-202°C
18	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-2-chloro-4-methylbenzamide
19	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-2-methyl-4-chlorobenzamide
20	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-2,4-dimethylbenzamide
21	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-2,3-dimethylbenzamide, m.p. 216°-220°C

Table I (cont'd)

Example No.	Compound
22	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-2-methoxybenzamide
23	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-2-trifluoromethoxybenzamide
24	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-2,4-dimethoxybenzamide
25	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-2,6-dimethoxybenzamide
26	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]benzamide
27	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-2,6-dichlorobenzamide
28	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-2,6-dimethylbenzamide
29	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-2-(methylthio)benzamide
30	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-2-methyl-3-thiophenecarboxamide

Table I (cont'd)

Example No.	Compound
31	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-3-methyl-2-thiophenecarboxamide
32	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-2-methyl-3-furanecarboxamide
33	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-3-methyl-2-furanecarboxamide
34	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]benzeneacetamide
35	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-2-chlorobenzene-acetamide
36	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-2-methylbenzene-acetamide (yellow foam); Anal. Calc'd for $C_{27}H_{23}N_3O_2$: C, 76.9; H,5.5; N, 10.0; Found: C, 75.6; H,6.0; N,9.4
37	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-2-methyl-3-thiopheneacetamide

Example 38

N-(2-Nitrobenzoyl)pyrrole-2-carboxaldehyde

To an ice bath cooled solution of 5.6 g of 2-pyrrolecarboxaldehyde in 40 ml of tetrahydrofuran is added 2.4 g of 60% sodium hydride in mineral oil. The

temperature elevates to 40° C. After stirring for 20 minutes a solution of 11.0 g of 2-nitrobenzoyl chloride in 20 ml of tetrahydrofuran is added dropwise over 20 minutes. After stirring in the cold for 45 minutes, the reaction mixture is poured into ice water and ether then filtered. The cake is washed with additional ether. The two phase filtrate is separate and the ether layer dried and concentrated in vacuo to give 10 g of a residue as a dark syrup which is scratched with ethanol to give crystals which are collected by filtration, washed with ether and then dried to afford 3.2 g of solid, m.p. 95-99° C.

Example 39

10,11-Dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one

A mixture of 1.5 g of N-(2-nitrobenzoyl)-pyrrole-2-carboxaldehyde in 50 ml of ethyl acetate, 2 drops of concentrated HCl and 0.3 g of 10% Pd/C is shaken in a Parr apparatus under hydrogen pressure for 1.75 hours. The mixture is filtered, 0.4 g of 10% Pd/C added and the mixture shaken in a Parr apparatus under hydrogen pressure for 2 hours. The reaction mixture is filtered through diatomaceous earth and the filtrate concentrated in vacuo to give 1.0 g of a yellow oil. The residue is purified on thick layer chromatography plates by elution with 4:1 ethyl acetate:hexane to give 107 mg of the desired product as an oily solid.

Example 40

2-Methyl-N-[4-[(5-oxo-5H-pyrrolo[2,1-c]-[1,4]benzodiazepin-10(11H)-yl)carbonyl]phenyl]-benzamide

To a stirred solution of 107 mg of 10,11-dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one in 3 ml of methylene chloride containing 0.084 ml of triethylamine is added 165 mg of 4-[(2-methylbenzoyl)amino]benzoyl chloride and stirring continued for 6 hours. The volatiles are removed in vacuo to a

residue which is purified on thick layer chromatography plates with 7:3 hexane-ethyl acetate to afford the desired product as a foam.

Example 41

N-[4-(3-Chloro-5H-pyrrolo[2,1-c][1,4]benzodiazepine-10(11H)ylcarbonyl)phenyl]-2-methylbenzamide

To an ice-water cooled suspension of 211 mg of 2-methyl-N-[4-(5H-pyrrolo[2,1-c][1,4]-benzodiazepin-10(11H)-ylcarbonyl)-phenyl]benzamide in 5 ml of tetrahydrofuran is added 67 mg of N-chlorosuccinimide followed by continued stirring in the cold for 10 minutes. The bath is removed and stirring continued for 2.25 hours. The reaction mixture is added to ice-water and extracted with ether. The organic layer is dried and concentrated in vacuo to give a foam which is crystallized from ethyl acetate-hexane to give 157 mg of the desired product as an orange-pink solid, m.p. 185-187°C.

Example 42

2-Methyl-N-[4-(1-chloropyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]benzamide

To an ice-water cooled suspension of 5 mmol of 2-methyl-N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)-phenyl]benzamide in 5 ml of tetrahydrofuran is added 5.5 mmol of N-chlorosuccinimide followed by continued stirring in the cold for 10 minutes. The bath is removed and stirring continued for 2.25 hours. The reaction mixture is added to ice-water and extracted with ether. The organic layer is dried and concentrated in vacuo to give the desired product as a solid.

Table II

The following Examples are prepared using the conditions of Example 42.

Example No.	Compound
43	2-chloro-N-[4-(1-chloropyrrolo-[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-benzamide
44	2,4-dichloro-N-[4-(1-chloro-pyrrolo-[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-benzamide
45	2,5-dichloro-N-[4-(1-chloro-pyrrolo-[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-benzamide
46	2,3-dimethyl-N-[4-(1-chloro-pyrrolo-[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-benzamide
47	2,4-dimethyl-N-[4-(1-chloro-pyrrolo-[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-benzamide

Table II (cont'd)

Example No.	Compound
48	2,5-dimethyl-N-[4-(1-chloro-pyrrolo-[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-benzamide

Example 49

3-Chloro-10,11-dihydro-10-(4-nitrobenzoyl-5H-pyrrolo[2,1-c][1,4]-benzodiazepine

To an ice-water cooled solution of 250 mg of 10,11-dihydro-10(4-nitrobenzoyl)-5H-pyrrolo[2,1-c]-[1,4]benzodiazepine in 6 ml of tetrahydrofuran is added 100 mg of N-chlorosuccinimide. The reaction mixture is stirred in the cold for 30 minutes and at room temperature for 2 hours. The reaction mixture is poured into ice water, stirred for 5 minutes and extracted with ether. The organic layer is dried and concentrated in vacuo to give 0.2 g of a yellow foam. Trituration with ethyl alcohol gives 66 mg of the desired product as a yellow solid, m.p. 119-125°C.

Example 50

3-Chloro-10,11-dihydro-10-(4-aminobenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine

A mixture of 1 mmol of 3-chloro-10,11-dihydro-10-(4-nitroaminobenzoyl)-5H-pyrrolo[2,1-c][1,4]-benzodiazepine, 2.5 mmol of anhydrous hydrazine, 50 mg of palladium on carbon and 10 ml of ethyl alcohol is refluxed for 1.5 hours. The mixture is filtered through diatomaceous earth and the filtrate concentrated to dryness to give the desired product as a solid.

Example 51

N-[4-(3-Chloro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)ylcarbonyl)phenyl]-2-methylbenzamide

A mixture of 1 mmol of 3-chloro-10,11-dihydro-10-(4-aminobenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine, 2 mmol of triethylamine, and 1.1 mmol of 2-methylbenzoylchloride in 8 ml of dichloromethane is stirred at room temperature overnight. The mixture is washed with water, and 1M $NaHCO_3$ and dried(Na_2SO_4). The solvent is removed in vacuo to give a solid which is recrystallized from dichloromethane-hexane to give crystals, 185-187° C.

Table III

The following Examples are prepared using the conditions of Example 51 with the appropriately substituted aroyl chloride

Example No.	Compound
52	N-[4-(3-Chloro-5H-pyrrolo[2,1-c]-[1,4]benzodiazepin-10(11H)yl-carbonyl)phenyl]-2-chlorobenzamide
53	N-[4-(3-Chloro-5H-pyrrolo[2,1-c]-[1,4]benzodiazepin-10(11H)yl-carbonyl)phenyl]-2,5-dichloro-benzamide
54	N-[4-(3-Chloro-5H-pyrrolo[2,1-c]-[1,4]benzodiazepin-10(11H)yl-carbonyl)phenyl]-2,4-dichloro-benzamide (solid foam), Anal. Calc'd for $C_{26}H_{18}Cl_3N_3O_2$: C,61.1; H,3.6; N,8.2; Cl, 20.8; Found: C,60.0; H,3.5; N,7.7; Cl, 20.3

Table III

Example No.	Compound
55	N-[4-(3-Chloro-5H-pyrrolo[2,1-c]-[1,4]benzodiazepin-10(11H)yl-carbonyl)phenyl]-2-fluoro-benzamide
56	N-[4-(3-Chloro-5H-pyrrolo[2,1-c]-[1,4]benzodiazepin-10(11H)yl-carbonyl)phenyl]-2-chloro-4-methylbenzamide
57	N-[4-(3-Chloro-5H-pyrrolo[2,1-c]-[1,4]benzodiazepin-10(11H)yl-carbonyl)phenyl]-2-methyl-4-chlorobenzamide
58	N-[4-(3-Chloro-5H-pyrrolo[2,1-c]-[1,4]benzodiazepin-10(11H)yl-carbonyl)phenyl]-2,4-dimethyl-benzamide
59	N-[4-(3-Chloro-5H-pyrrolo[2,1-c]-[1,4]benzodiazepin-10(11H)yl-carbonyl)phenyl]-2,3-dimethyl-benzamide
60	N-[4-(3-Chloro-5H-pyrrolo[2,1-c]-[1,4]benzodiazepin-10(11H)yl-carbonyl)phenyl]-2-methoxy-benzamide
61	N-[4-(3-Chloro-5H-pyrrolo[2,1-c]-[1,4]benzodiazepin-10(11H)yl-carbonyl)phenyl]-2-trifluoro-methoxybenzamide

Table III (cont'd)

Example No.	Compound
62	N-[4-(3-Chloro-5H-pyrrolo[2,1-c]-[1,4]benzodiazepin-10(11H)yl-carbonyl)phenyl]-2,4-dimethoxy-benzamide
63	N-[4-(3-Chloro-5H-pyrrolo[2,1-c]-[1,4]benzodiazepin-10(11H)yl-carbonyl)phenyl]-2,6-dimethoxy-benzamide
64	N-[4-(3-Chloro-5H-pyrrolo[2,1-c]-[1,4]benzodiazepin-10(11H)yl-carbonyl)phenyl]benzamide
65	N-[4-(3-Chloro-5H-pyrrolo[2,1-c]-[1,4]benzodiazepin-10(11H)yl-carbonyl)phenyl]-2,6-dichloro-benzamide
66	N-[4-(3-Chloro-5H-pyrrolo[2,1-c]-[1,4]benzodiazepin-10(11H)yl-carbonyl)phenyl]-2,6-dimethyl-benzamide
67	N-[4-(3-Chloro-5H-pyrrolo[2,1-c]-[1,4]benzodiazepin-10(11H)yl-carbonyl)phenyl]-2-methylthio-benzamide
68	N-[4-(3-Chloro-5H-pyrrolo[2,1-c]-[1,4]benzodiazepin-10(11H)yl-carbonyl)phenyl]-2-methyl-3-thiophenecarboxamide

Table III (cont'd)

Example No.	Compound
69	N-[4-(3-Chloro-5H-pyrrolo[2,1-c]-[1,4]benzodiazepin-10(11H)yl-carbonyl)phenyl]-3-methyl-2-thiophenecarboxamide
70	N-[4-(3-Chloro-5H-pyrrolo[2,1-c]-[1,4]benzodiazepin-10(11H)yl-carbonyl)phenyl]-2-methyl-3-furanecarboxamide
71	N-[4-(3-Chloro-5H-pyrrolo[2,1-c]-[1,4]benzodiazepin-10(11H)yl-carbonyl)phenyl]-3-methyl-2-furanecarboxamide
72	N-[4-(3-Chloro-5H-pyrrolo[2,1-c]-[1,4]benzodiazepin-10(11H)yl-carbonyl)phenyl]phenylacetamide
73	N-[4-(3-Chloro-5H-pyrrolo[2,1-c]-[1,4]benzodiazepin-10(11H)yl-carbonyl)phenyl]-2-chlorophenyl-acetamide
74	N-[4-(3-Chloro-5H-pyrrolo[2,1-c]-[1,4]benzodiazepin-10(11H)yl-carbonyl)phenyl]-2-methylbenzene-acetamide
75	N-[4-(3-Chloro-5H-pyrrolo[2,1-c]-[1,4]benzodiazepin-10(11H)yl-carbonyl)phenyl]-2-methyl-3-thiopheneacetamide

Table III (cont'd)

Example No.	Compound
76	N-[4-(3-Chloro-5H-pyrrolo[2,1-c]-[1,4]benzodiazepin-10(11H)yl-carbonyl)phenyl]-2-methyl-3-furanacetamide

Example 77

1-(2-Nitrobenzyl)-2-pyrrolecarboxaldehyde

To 5.56 g of 60% sodium hydride in mineral oil, washed three times with hexane, is added 300 ml of N,N-dimethylformamide under argon. The reaction mixture is cooled in an ice-bath and 13.2 g of pyrrole-2-carboxaldehyde is added slowly. The reaction mixture becomes a complete solution and is stirred for an additional 10 minutes. While stirring, 30.0 g of 2 - nitrobenzyl bromide is added slowly. After complete addition, the reaction mixture is stirred for 30 minutes, the ice bath is removed and the reaction mixture stirred at room temperature for 24 hours. The N,N-dimethylformamide is concentrated in vacuo to give a residue which is stirred with ice water for 1 hour. The resulting solid is collected, air dried, then vacuum dried to give 30.64 g of the desired product as a tan solid, m.p. 128-132°C.

Example 78

10,11-dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine

A mixture of 30.6 g of 1-(2-nitrobenzyl)-2-pyrrolecarboxaldehyde and 3.06 g of 10% Pd/C in 400 ml of ethyl acetate and 400 ml of ethyl alcohol is hydrogenated over 18 hours. The reaction mixture is filtered through diatomaceous earth and the filtrate is treated with activated carbon and filtered through diatomaceous earth. The filtrate is concentrated in vacuo to give a residue which is dissolved in methylene chloride containing ethyl alcohol. The solution is passed through a pad of silica gel and the pad washed

with a 7:1 hexane-ethyl acetate solution to give 16.31 g of the desired product as solid, m.p. 145-148°C.

Example 79

10,11-Dihydro-10(4-nitrobenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine

To a solution of 3.3 g of 10,11-dihydro-5H-yrrolo[2,1-c][1,4]benzodiazepine in 50 ml of methylene chloride under argon is added 5.0 ml of triethylamine followed by ice bath cooling. A solution of 4.0 g of 4-nitrobenzoyl chloride in 20 ml of methylene chloride is added dropwise. Following complete addition, the ice bath is removed and the reaction mixture stirred at room temperature for 2 hours. The volatiles are removed in vacuo to give a residue which is dissolved in ethyl acetate. The solution is washed with water, 1N HCl, $NaHCO_3$, brine, dried with Na_2SO_4 and filtered. The filtrate is concentrated in vacuo to a solid which is dissolved in methylene chloride, passed through silica gel and the pad washed with ethyl acetate. The combined filtrate is concentrated in vacuo to give 5.3 g of the desired product as a yellow solid, m.p. 188-190°C.

Example 80

10,11-Dihydro-10-(4-aminobenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine

A mixture of 2.00g of 10,11-dihydro-10(4-itrobenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine in 15 ml of ethyl alcohol and 15 ml of ethyl acetate containing 0.2 g of 10% Pd/C is hydrogenated for 5 hours. The reaction mixture is filtered through a pad of diatomaceous earth. The filtrate is concentrated in vacuo to a solid which is dissolved in methylene chloride, passed through silica gel and the pad washed with 3:1 ethyl acetate-hexane. The filtrate is concentrated in vacuo to give 1.5 g of the desired product as a yellow solid, m.p. 166-168°C.

Example 81

10,11-Dihydro-10-(4-aminobenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine

To a solution of 21.58 g of 10,11-dihydro-10-(4-nitrobenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine in 325 ml of ethyl alcohol is added 2.15 g of 10% Pd/C and 5.16 g of hydrazine followed by stirring and heating under reflux for 15 hours. The room temperature reaction mixture is filtered through diatomaceous earth. The filtrate is concentrated in vacuo to a solid which is dissolved in methylene chloride and passed through a pad of hydrous magnesium silicate. The filtrate is concentrated in vacuo to give 19.2 g of the desired product as a tan solid. The solid is purified by flash chromatography using 7:1 ethyl acetate-hexane to give 17.97 g of the desired product, m.p. 166-168°C.

Example 82

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-3-chlorobenzo[b]thiophene-2-carboxamide

To a stirred solution of 0.440 g of 3-chlorobenzo[b]thiophen-2-carbonyl chloride in 10 ml of methylene chloride is added 0.33 ml of triethylamine. After stirring for 15 minutes, 0.485 g of 10,11-dihydro-10-(4-aminobenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine is added and stirring continued for 18 hours. The reaction mixture is washed with water, 1N HCl, $NaHCO_3$, and brine. The reaction mixture is dried with Na_2SO_4, filtered and evaporated in vacuo to give a solid which is purified by flash chromatography using 1:1 ethyl acetate-hexane to give 0.49 g of solid, m.p. 220-222°C.

Example 83

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2,3-dimethylbenzamide

To a stirred solution of 0.320 g of 2,3-dimethylbenzoyl chloride in 10 ml of methylene chloride is added 0.33 ml of triethylamine. After stirring for 15 minutes, 0.485 g of 10,11-dihydro-10-(4-aminobenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine is added and stirring continued for 5 hours. The reaction mixture is washed with water, 1N HCl, $NaHCO_3$, and brine. The reaction mixture is dried with Na_2SO_4, filtered and evaporated in vacuo to give a solid which is purified by flash chromatography using 1:1 ethyl acetate-hexane to give 0.39 g of solid, m.p. 168°-170°C.

Example 84

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2-ethoxybenzamide

To a stirred solution of 0.362 g of 2-ethoxybenzoyl chloride 5 ml of methylene chloride is added 0.346 g of triethylamine at 0°C. After stirring for 3 minutes, 0.500 g of 10,11-dihydro-10-(4-aminobenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine is added and stirring continued for 72 hours at room temperature. The reaction mixture is diluted with 45 ml of methylene chloride and washed with water, 2N citric acid, $NaHCO_3$, and brine. The reaction mixture is dried with Na_2SO_4, filtered and evaporated in vacuo to give a solid which is purified by flash chromatography using 1:1 ethyl acetate-hexane to give 0.890 g of solid which is crystallized from ethyl acetate to give 0.540 g of the desired product as a white solid, m.p. 160-176°C.

Example 85

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2-(methylthio)benzamide

To a stirred solution of 0.364 g of 2-(methylthio)benzoyl chloride 5 ml of methylene

chloride is added 0.346 g of triethylamine at 0° C. After stirring for 3 minutes, 0.500 g of 10,11-dihydro-10-(4-aminobenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine is added and stirring continued for 72 hours at room temperature. The reaction mixture is diluted with 45 ml of methylene chloride and washed with water, 2N citric acid, $NaHCO_3$, and brine. The reaction mixture is dried with Na_2SO_4, filtered and evaporated in vacuo to give a solid which is purified by flash chromatography using 1:1 ethyl acetate-hexane to give a solid which is crystallized from ethyl alcohol to give 0.480 g of the desired product as a white solid, m.p. 171-174°C.

Example 86

3-Methylbenzo[b]thiophene-2-acetyl chloride

A mixture of 2.0 g of 3-methylbenzo[b]thiophene-2-acetic acid and 19.4 ml of thionyl chloride is heated at reflux for 1 hour. The volatiles are evaporated in vacuo to give a residue which is concentrated from toluene three times and dried under vacuum to give 2.25 g of the desired product as a residue.

Example 87

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-3-methylbenzo[b]thiophene-2-acetamide

To a stirred solution of 0.445 g of 3-methylbenzo[b]thiophene-2-acetyl chloride in 5 ml of methylene chloride is added 0.346 g of triethylamine at 0° C. After stirring for 3 minutes, 0.500 g of 10,11-dihydro-10-(4-aminobenzoyl)-5H-pyrrolo[2,1-c]-[1,4]benzodiazepine is added and stirring continued for 72 hours at room temperature. An additional 0.445 g of 3-methylbenzo[b]thiophene-2-acetyl chloride, 0.346 g of triethylamine and 30 mg of dimethylaminopyridine is added and stirring continued for an additional 18 hours. The reaction mixture is diluted with 45 ml of methylene chloride and washed with water, 2N citric

acid, 1M $NaHCO_3$, and brine. The reaction mixture is dried with Na_2SO_4, filtered and evaporated in vacuo to give a solid which is purified by flash chromatography using 1:1 ethyl acetate-hexane to give 0.320 g of the desired product as a yellow foam.

Example 88

4-Chloro-2-methoxybenzoyl chloride

A solution of 2.0 g of 4-chloro-o-anisic acid in 22 ml of thionyl chloride is heated at reflux for 1 hour. The volatiles are evaporated in vacuo to give a residue which is is concentrated from toluene three times and dried under vacuum to give 2.0 g of the desired product as a residue.

Example 89

N-[4-(5H-Pyrrolo[2,1-c][1,4]-benzodiazepin-10(11H)ylcarbonyl)phenyl]-4-chloro-2-methoxybenzamide

To a stirred solution of 0.406 g of 4-chloro-2-methoxybenzoyl chloride in 5 ml of methylene chloride is added 0.346 g of triethylamine at 0°C. After stirring for 3 minutes, 0.500 g of 10,11-dihydro-10-(4-aminobenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine is added and stirring continued for 18 hours at room temperature. An additional 0.406 g of 4-chloro-2-methoxybenzoyl chloride and 0.346 g of triethylamine is added and stirring is continued for 2 hours. The reaction mixture is diluted with 45 ml of methylene chloride and washed with water, 2N citric acid, 1M $NaHCO_3$, and brine. The reaction mixture is dried with Na_2SO_4, filtered and evaporated in vacuo to give a residue which is purified by flash chromatography using 1:1 ethyl acetate-hexane to give a solid which is crystallized from ethyl acetate to give 0.320 g of the desired product as a white crystals, m.p. 222-224°C.

Example 90

2-(Trifluoromethyl)benzoyl chloride

A solution of 2.0 g of o-trifluoromethylbenzoic acid in 21 ml of thionyl chloride is heated at reflux for 1 hour. The volatiles are evaporated in vacuo to give a residue which is concentrated from toluene three times and dried under vacuum to give 2.1 g of the desired product as a residue.

Example 91

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2-(trifluoromethyl)benzamide

To a stirred solution of 0.413 g of 2-trifluoromethylbenzoyl chloride in 5 ml of methylene chloride is added 0.346 g of triethylamine at 0° C. After stirring for 3 minutes, 0.500 g of 10,11-dihydro-10-(4-aminobenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine is added and stirring continued for 18 hours at room temperature. The reaction mixture is diluted with 50 ml of ethyl acetate and washed with water, 2N citric acid, $NaHCO_3$, and brine. The reaction mixture is dried with Na_2SO_4, filtered and evaporated in vacuo to give a solid which is crystallized from ethyl acetate to afford 0.5 g of a solid which is dissolved in methylene chloride and passed through a pad of hydrous magnesium silicate. The filtrate is evaporated in vacuo to give a solid which is crystallized from ethyl acetate to afford 0.210 g of the desired product as a white crystals, m.p. 226-228°C.

Example 92

2-Methylphenylacetyl chloride

A solution of 2.0 g of o-tolylacetic acid in 27 ml of thionyl chloride is heated at reflux for 1 hour. The volatiles are evaporated in vacuo to give a residue which is concentrated from toluene three times and dried under vacuum to give 2.1 g of the desired product as a light brown oil.

Example 93

N-[4(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2-methylbenzeneacetamide

To a stirred solution of 0.334 g of 2-methylphenylacetyl chloride 5 ml of methylene chloride is added 0.346 g of triethylamine at 0°C. After stirring for 3 minutes, 0.500 g of 10,11-dihydro-10-(4-aminobenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine is added and stirring continued for 72 hours at room temperature. The reaction mixture is diluted with 45 ml of methylene chloride and washed with water, 2N citric acid, $NaHCO_3$, and brine. The reaction mixture is dried with Na_2SO_4, filtered through a pad of hydrous magnesium silicate and evaporated in vacuo to give a solid which is purified by flash chromatography using 1:1 ethyl acetate-hexane to give a solid which is crystallized from ethyl acetate to give 0.385 g of the desired product as white crystals, m.p. 198-200°C.

Example 94

10,11-Dihydro-10-(3-methyl-4-nitro-benzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine

A mixture of 1.81 g of 3-methyl-4-nitrobenzoic acid and 1.25 g of thionyl chloride in 75 ml of chloroform is heated at reflux under argon for 48 hours. The volatiles are removed in vacuo to a residue which is evaporated with toluene several times in vacuo. The residue is partially dissolved in methylene chloride and filtered free of solids and the filtrate evaporated in vacuo to give 1.47 g of the desired acid chloride. A 1.36 g sample of the acid chloride, 0.90 g of N,N-diisopropylethylamine and 1.25 g of 10,11-dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine in 25 ml of methylene chloride is allowed to stand at room temperature for 8 hours. Water is added to the reaction mixture, the organic layer is separated and dried over Na_2SO_4, filtered and hexane added to the filtrate at

the boil to give 1.4 g of the desired product as crystals, m.p. 246-248°C.

Example 95

10,11-Dihydro-10-(4-amino-3-methylbenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine

A mixture of 1.22 g 10,11-dihydro-10-(3-methyl-4-nitro-benzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine, 0.2 g of 10% Pd/C and 0.35 g of anhydrous hydrazine in 50 ml of absolute ethyl alcohol is heated on a steam bath for 1 hour. The reaction mixture is filtered hot through diatomaceous earth and evaporated in vacuo to a residue. The residue is crystallized from methylene chloride-hexane to give 0.95 g of the desired product as crystals, m.p. 232-234°C.

Example 96

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2-methylphenyl]-2-methylbenzamide

A solution of 0.83 g of 10,11-dihydro-10-(4-amino-3-methylbenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine, 0.5 g of N,N-diisopropylethylamine and 0.6 g of 2-methylbenzoyl chloride in 50 ml of methylene chloride is stirred at room temperature for 18 hours. The reaction mixture is washed with water, the organic layer dried with Na_2SO_4 and passed through a pad of hydrous magnesium silicate. Hexane is added at the boil to give 0.75 g of a solid which is crystallized from methylene chloride-hexane to give 0.61 g of the desired product, m.p. 125-130°C.

Table IV

The following Examples are prepared using the conditions of Example 96 with the appropriately substituted aroyl chloride

Example No.	Compound
97	N-[4-(5H-pyrrolo[2,1-c][1,4]-benzodiazepin-10(11H)-yl-carbonyl)-2-methylphenyl]-2-chlorobenzamide
98	N-[4-(5H-pyrrolo[2,1-c][1,4]-benzodiazepin-10(11H)-yl-carbonyl)-2-methylphenyl]-2,-5-dichlorobenzamide
99	N-[4-(5H-pyrrolo[2,1-c][1,4]-benzodiazepin-10(11H)-yl-carbonyl)-2-methylphenyl]-2,4-dichlorobenzamide, m.p. 213°-215°C
100	N-[4-(5H-pyrrolo[2,1-c][1,4]-benzodiazepin-10(11H)-yl-carbonyl)-2-methylphenyl]-2-chloro-4-methylbenzamide
101	N-[4-(5H-pyrrolo[2,1-c][1,4]-benzodiazepin-10(11H)-yl-carbonyl)-2-methylphenyl]-2-methyl-4-chlorobenzamide
1[illegible]	N-[4-(5H-pyrrolo[2,1-c][1,4]-benzodiazepin-10(11H)-yl-carbonyl)-2-methylphenyl]-2,3-dimethylbenzamide

Table IV

Example No.	Compound
103	N-[4-(5H-pyrrolo[2,1-c][1,4]-benzodiazepin-10(11H)-yl-carbonyl)-2-methylphenyl]-2-methoxybenzamide
104	N-[4-(5H-pyrrolo[2,1-c][1,4]-benzodiazepin-10(11H)-yl-carbonyl)-2-methylphenyl]-2-trifluoromethoxybenzamide
105	N-[4-(5H-pyrrolo[2,1-c][1,4]-benzodiazepin-10(11H)-yl-carbonyl)-2-methylphenyl]-2,-4-dimethoxybenzamide
106	N-[4-(5H-pyrrolo[2,1-c][1,4]-benzodiazepin-10(11H)-yl-carbonyl)-2-methylphenyl]-benzamide
107	N-[4-(5H-pyrrolo[2,1-c][1,4]-benzodiazepin-10(11H)-yl-carbonyl)-2-methylphenyl]-2-methylthiobenzamide
108	N-[4-(5H-pyrrolo[2,1-c][1,4]-benzodiazepin-10(11H)-yl-carbonyl)-2-methylphenyl]-2,6-dichlorobenzamide

Table IV (cont'd)

Example No.	Compound
109	N-[4-(5H-pyrrolo[2,1-c][1,4]-benzodiazepin-10(11H)-yl-carbonyl)-2-methylphenyl]-2-methyl-3-thiophenecarboxamide
110	N-[4-(5H-pyrrolo[2,1-c][1,4]-benzodiazepin-10(11H)-yl-carbonyl)-2-methylphenyl]-2-methyl-3-thiophenecarboxamide
111	N-[4-(5H-pyrrolo[2,1-c][1,4]-benzodiazepin-10(11H)-yl-carbonyl)-2-methylphenyl]-2-methyl-3-furancarboxamide
112	N-[4-(5H-pyrrolo[2,1-c][1,4]-benzodiazepin-10(11H)-yl-carbonyl)-2-methylphenyl]-3-methyl-2-furancarboxamide
113	N-[4-(5H-pyrrolo[2,1-c][1,4]-benzodiazepin-10(11H)-yl-carbonyl)-2-methylphenyl]-phenylacetamide
114	N-[4-(5H-pyrrolo[2,1-c][1,4]-benzodiazepin-10(11H)-yl-carbonyl)-2-methylphenyl]-2-chlorophenylacetamide

Table IV (cont'd)

Example No.	Compound
115	N-[4-(5H-pyrrolo[2,1-c][1,4]-benzodiazepin-10(11H)-yl-carbonyl)-2-methylphenyl]-2-methylphenylacetamide

Example 116

10,11-Dihydro-10-[4-[[[(2-methylphenyl]amino]-carbonyl]amino]benzoyl]-5H-pyrrolo[2,1-c]-[1,4]benzodiazepine

A mixture of 0.93 g 10,11-dihydro-10-(4-amino-3-methylbenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine and 0.37 g of o-tolyl isocyanate in 50 ml of tetrahydrofuran is heated at reflux under argon for 24 hours. The volatiles are evaporated in vacuo to a residue which is dissolved in methylene chloride and passed through a pad of hydrous magnesium silicate. Hexane is added to the filtrate at the boil to give 0.68 g of the desired product as crystals, m.p. 155-158°C.

Example 117

N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-1H-indole-5-carboxamide

To a solution of 319 mg of indole-5-carboxylic acid in 5 ml of tetrahydrofuran is added 418.4 mg of 1,1'-carbonyldiimidazole under argon with ice-bath cooling. The cooling bath is removed and the reaction mixture stirred at room temperature for 2 hours. The volatiles are evaporated in vacuo to a residue which is dissolved in 3 ml of xylene followed by 500 mg of 10,11-dihydro-10-(4-aminobenzoyl)-5H-pyrrolo[2,1-c]-[1,4]benzodiazepine and heating at 120° C for 18 hours. The volatiles are evaporated in vacuo to a residue which is partitioned between 40 ml of ethyl acetate and water. The organic layer is dried over Na_2SO_4 and the

volatiles evaporated in vacuo to a residue which is purified by chromatography on preparative plates by elution with 1:1 ethyl acetate-hexane to give 140 mg of the desired product as an orange solid, m.p. 130-170°C.

Example 118

1-(o-Nitrobenzyl)-imidazole-2-carboxaldehyde

A 2.0 g portion of sodium hydride (60% in oil) is washed with pentane two times. To the residue is added 110 ml of N,N-dimethylformamide under argon. With stirring and external cooling, 4.80 g of 2-imidazolecarboxaldehyde is added and the cooling bath removed. Slight external heating results in a yellow solution. The reaction mixture is chilled in ice and 10.8 g of 2-nitrobenzyl bromide is added. The reaction mixture is stirred at 0° C for 18 hours. The volatiles are removed in vacuo to a residue which is stirred with ice water, filtered and the cake washed well with water and suction dried to give 10.9 g of the desired product as a solid, m.p. 141-144° C. MH+ 232.

Example 119

10,11-Dihydro-5H-imidazo[2,1-c][1,4]benzodiazepine

A 5.0 g sample of 1-(o-nitrobenzyl)-imidazole-2-carboxaldehyde is dissolved in 150 ml of hot ethyl alcohol, cooled to room temperature and filtered. To the filtrate is added 0.5 g of 10% Pd/C and the mixture hydrogenated at 48 psi for 4 hours. An additional 0.5 g of 10% Pd/C is added and hydrogenation continued for 25 hours at 65 psi. The mixture is filtered through diatomaceous earth and the cake washed with ethyl acetate. The filtrate is evaporated in vacuo to a residue which is dissolved in methylene chloride, treated with activated carbon, filtered through diatomaceous earth and hexanes added to the filtrate at the boil to give 1.86 g of the desired product as a crystalline solid, m.p. 164-170°C.

Example 120

10,11-Dihydro-5H-imidazo[2,1-c][1,4]benzodiazepine

To a suspension of 4 mmol of lithium aluminum hydride in 20 ml of anhydrous tetrahydrofuran is added a 1 mmol solution of 10,11-dihydro-11-oxo-5H-imidazo-[2,1-c][1,4]benzodiazepine and the mixture is refluxed for 24 hours and cooled at 0° C. To the mixture is added dropwise 0.12 ml of water and 6 ml of 1N sodium hydroxide. The mixture is extracted with ethyl acetate and the solvent removed to give the desired product as a solid. Recrystallization from methylene chloride-hexane gives crystals, m.p. 164-170°C.

Example 121

N-[4-(5H-imidazo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2-methylbenzamide

To a mixture of 1.37 g (5 mmol) of 4-[(2-methylbenzoyl)amino]benzoyl chloride in 15 ml of methylene chloride, cooled to 0° C is added 1.5 ml of triethylamine. After stirring for 3 minutes, 5 mmol of 10,11-dihydro-5H-imidazo[2,1-c][1,4]benzodiazepine in 5 ml of methylene chloride is added. The cooling bath is removed and after about 30 minutes a complete solution is obtained. The reaction mixture is allowed to stir at room temperature for 1 hour and the volatiles are concentrated in vacuo. The residue is dissolved in 100 ml of ethyl acetate and washed with water, 2N citric acid, and brine. The solution is dried with Na_2SO_4 and the volatiles concentrated in vacuo to give the desired product as a solid.

Example 122

10,11-Dihydro-10-(4-nitrobenzoyl)-5H-imidazo[2,1-c]-[1,4]benzodiazepine

To a solution of 10 mmol of 10,11-dihydro-5H-imidazo[2,1-c][1,4]benzodiazepine in 50 ml of methylene chloride under argon is added 15 mmol of triethylamine followed by ice bath cooling. A solution of 10 mmol of 4-nitrobenzoyl chloride in 10 ml of methylene chloride is added dropwise. Following complete addition, the ice bath is removed and the reaction mixture stirred at room temperature for 2 hours. The volatiles are removed in vacuo to give a residue which is dissolved in ethyl acetate. The solution is washed with water, and brine. The organic layer is dried with Na_2SO_4, filtered and evaporated in vacuo to give a solid which is purified by flash chromatography to give desired product as a solid.

Example 123

10,11-Dihydro-10-(4-aminobenzoyl)-5H-imidazo[2,1-c]-[1,4]benzodiazepine

A mixture of 5 mmol of 10,11-dihydro-10-(4-nitrobenzoyl)-5H-imidazo[2,1-c][1,4]benzodiazepine in 10 ml of ethyl alcohol and 10 ml of ethyl acetate containing 0.2 g of 10% Pd/C is hydrogenated for 5 hours in a Parr hydrogenator at 35 psi of hydrogen. The reaction mixture is filtered through a pad of diatomaceous earth. The filtrate is concentrated in vacuo to a solid which is purified by flash chromatography to give the desired product.

Example 124

10,11-Dihydro-10-(4-aminobenzoyl)-5H-imidazo[2,1-c]-[1,4]benzodiazepine

To a solution of 5 mmol of 10,11-dihydro-10-(4-nitrobenzoyl)-5H-imidazo[2,1-c][1,4]benzodiazepine in 100 ml of ethyl alcohol is added 0.5 g of 10% Pd/C and 10 mmol of hydrazine followed by stirring and heating under reflux for 3 hours. The reaction mixture is filtered through diatomaceous earth. The filtrate is concentrated in vacuo to a residue which is dissolved in methylene chloride and passed through a pad of hydrous magnesium silicate. The filtrate is concentrated in vacuo to give the desired product which is purified by flash chromatography to give the desired product as a solid.

Example 125

N-[4-(5H-Imidazo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2-methylbenzamide

To a stirred solution of 1 mmol of 2-methylbenzoyl chloride in 10 ml of methylene chloride is added 1.5 mmol of triethylamine. After stirring for 15 minutes, 1 mmol of 10,11-dihydro-10-(4-aminobenzoyl)-5H-imidazo[2,1-c][1,4]benzodiazepine is added and the mixture stirred for 5 hours. The reaction mixture is washed with water, and brine. The reaction mixture is dried with Na_2SO_4, filtered and evaporated in vacuo to give a solid which is purified by flash chromatography to give the desired product as a solid.

Table V

The following Examples are prepared using the conditions of Example 125 with the appropriately substituted aroyl chloride

Example No.	Compound
126	N-[4-(5H-imidazo[2,1-c][1,4]-benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2-chlorobenzamide
127	N-[4-(5H-imidazo[2,1-c][1,4]-benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2,5-dichlorobenzamide
128	N-[4-(5H-imidazo[2,1-c][1,4]-benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2,4-dichlorobenzamide
129	N-[4-(5H-imidazo[2,1-c][1,4]-benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2-fluorobenzamide
130	N-[4-(5H-imidazo[2,1-c][1,4]-benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2-chloro-4-methylbenzamide
131	N-[4-(5H-imidazo[2,1-c][1,4]-benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2-methyl-4-chlorobenzamide

Table V (cont'd)

Example No.	Compound
132	N-[4-(5H-imidazo[2,1-c][1,4]-benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2,4-dimethylbenzamide
133	N-[4-(5H-imidazo[2,1-c][1,4]-benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2,3-dimethylbenzamide
134	N-[4-(5H-imidazo[2,1-c][1,4]-benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2-methoxybenzamide
135	N-[4-(5H-imidazo[2,1-c][1,4]-benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2-trifluoromethoxybenzamide
136	N-[4-(5H-imidazo[2,1-c][1,4]-benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2,-4-dimethoxybenzamide
137	N-[4-(5H-imidazo[2,1-c][1,4]-benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2,-6-dimethoxybenzamide

Table V (cont'd)

Example No.	Compound
138	N-[4-(5H-imidazo[2,1-c][1,4]-benzodiazepin-10(11H)-ylcarbonyl)phenyl]-benzamide
139	N-[4-(5H-imidazo[2,1-c][1,4]-benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2,-6-dichlorobenzamide
140	N-[4-(5H-imidazo[2,1-c][1,4]-benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2,-6-dimethylbenzamide
141	N-[4-(5H-imidazo[2,1-c][1,4]-benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2,-methylthiobenzamide
142	N-[4-(5H-imidazo[2,1-c][1,4]-benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2,-methyl-3-thiophenecarboxamide
143	N-[4-(5H-imidazo[2,1-c][1,4]-benzodiazepin-10(11H)-ylcarbonyl)phenyl]-3,-methyl-2-thiophenecarboxamide

Table V (cont'd)

Example No.	Compound
144	N-[4-(5H-imidazo[2,1-c][1,4]-benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2,-methyl-3-furanecarboxamide
145	N-[4-(5H-imidazo[2,1-c][1,4]-benzodiazepin-10(11H)-ylcarbonyl)phenyl]-3,-methyl-2-furanecarboxamide
146	N-[4-(5H-imidazo[2,1-c][1,4]-benzodiazepin-10(11H)-ylcarbonyl)phenyl]-phenylacetamide
147	N-[4-(5H-imidazo[2,1-c][1,4]-benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2-chlorophenylacetamide
148	N-[4-(5H-imidazo[2,1-c][1,4]-benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2-methylphenylacetamide
149	N-[4-(5H-imidazo[2,1-c][1,4]-benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2-methyl-3-thiopheneacetamide

Table V (cont'd)

Example No.	Compound
150	N-[4-(5H-imidazo[2,1-c][1,4]-benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2-methyl-3-furanacetamide

Example 151

N-[4-(7-Chloro-5H-imidazo[2,1-c][1,4]benzodiazepin--10(11H)-ylcarbonyl]phenyl]-2-methylbenzamide

As described for Example 125 a mixture of 1 mmol of 7-chloro-10,11-dihydro-5H-imidazo[2,1-c][1,4]-benzodiazepine, 1.1 mmol of 4-[(2-methylbenzoyl)amino]-benzoyl chloride and 1.5 mmol of triethylamine in 10 ml of dichloromethane is stirred at room temperature for 3 hours and worked up to give the desired product as a solid.

Example 152

N-[4-(7-Methoxy-5H-imidazo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl]phenyl]-2-methylbenzamide

As described for Example 125 a mixture of 1.0 mmol of 7-methoxy-10,11-dihydro-5H-imidazo[2,1-c][1,4]-benzodiazepine, 1.1 mmol of 4-[(2-methylbenzoyl)amino]-benzoyl chloride and 1.5 mmol of triethylamine in 10 ml of dichloromethane is stirred for 3 hours at room temperature and worked up to give the product as a solid.

Example 153

N-[4-(7,8-Methylenedioxy-5H-imidazo[2,1-c][1,4]-benzodiazepin-10(11H)-ylcarbonyl]phenyl]-2-methylbenzamide

As described for Example 125 a mixture of 1.0 mmol of 7,8-methylenedioxy-10,11-dihydro-5H-imidazo-[2,1-c][1,4]benzodiazepine, 1.1 mmol of 4-[(2-methyl-benzoyl)amino]benzoyl chloride and 1.5 mmol of

triethylamine in 10 ml of dichloromethane is stirred at room temperature for 3 hours and worked up to give the desired product as a solid.

Example 154

4,5-Dihydro-5-(4-nitrobenzoyl)pyrrolo[1,2-a]quinoxaline

To a solution of 5 mmol of 4,5-dihydro-pyrrolo-[1,2-a]quinoxaline in 50 ml of methylene chloride under argon is added 10 mmol of triethylamine followed by ice bath cooling. A solution of 5 mmol of 4-nitrobenzoyl chloride in 10 ml of methylene chloride is added dropwise. Following complete addition, the ice bath is removed and the reaction mixture stirred at room temperature for 2 hours. The volatiles are removed *in vacuo* to give a residue which is dissolved in ethyl acetate. The solution is washed with water, 1N HCl, $NaHCO_3$, and brine. The reaction mixture is dried with Na_2SO_4, filtered and evaporated *in vacuo* to give a solid which is purified by flash chromatography to give the desired product (from ethyl acetate) as a solid, m.p. 174-178°C.

Example 155

4,5-Dihydro-5(4-aminobenzoyl)pyrrolo[1,2-a]quinoxaline

A mixture of 1 mmol of 4,5-dihydro-5-(4-nitrobenzoyl)pyrrolo[1,2-a]quinoxaline in 10 ml of ethyl alcohol and 10 ml of ethyl acetate containing 0.2 g of 10% Pd/C is hydrogenated for 5 hours. The reaction mixture is filtered through a pad of diatomaceous earth. The filtrate is concentrated *in vacuo* to a solid which is purified by flash chromatography to give the desired product, m.p. 225-228°C.

Example 156

4,5-Dihydro-5(4-aminobenzoyl)pyrrolo[1,2-a]quinoxaline

To a solution of 1 mmol of 4,5-dihydro-5-(4-nitrobenzoyl)pyrrolo[1,2-a]quinoxaline in 20 ml of ethyl alcohol is added 0.2 g of 10% Pd/C and 2.5 mmol of hydrazine followed by stirring and heating under reflux for 2 hours. The hot reaction mixture is filtered through diatomaceous earth and the filter cake washed with hot chloroform and the filtrate concentrated *in vacuo*. The residue is triturated with ethyl acetate and the mixture filtered to give the desired product as crystals, m.p. 225°-228°C.

Example 157

N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-yl-carbonyl)phenyl]-2-methylbenzamide

To a stirred solution of 1.5 mmol of 2-methylbenzoyl chloride in 10 ml of methylene chloride is added 3 mmol of triethylamine. After stirring for 15 minutes, 1.5 mmol of 4,5-dihydro-5-(4-aminobenzoyl)-pyrrolo[1,2-a]quinoxaline is added and the mixture stirred for 5 hours. The reaction mixture is washed with water, 1N HCl, $NaHCO_3$, and brine. The reaction mixture is dried with Na_2SO_4, filtered and evaporated *in vacuo* to give a solid which is purified by flash chromatography to give the desired product as a solid, m.p. 206-207°C.

Table VI

The following Examples are prepared using the conditions of Example 157 with the appropriately substituted aroyl chloride

Example No.	Compound
158	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)ylcarbonyl)phenyl]-2-chlorobenzamide
159	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl]phenyl-2,5-dichloro-benzamide
160	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-2,4-dichloro-benzamide, m.p. 200°-202°C
161	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-2-chloro-4-methyl-benzamide
162	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-2-methyl-4-chloro-benzamide
163	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-2,4-dimethyl-benzamide

Table VI (cont'd)

Example No.	Compound
164	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-2,3-dimethylbenzamide, m.p. 216°-220°C
165	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-2-methoxybenzamide
166	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-2-trifluoromethoxybenzamide
167	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-2,4-dimethoxybenzamide
168	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-2,6-dimethoxybenzamide
169	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]benzamide
170	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-2,6-dichlorobenzamide
171	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-2,6-dimethylbenzamide

Table VI (cont'd)

Example No.	Compound
172	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-2-(methylthio)-benzamide
173	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-2-methyl-3-thiophenecarboxamide
174	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-3-methyl-2-thiophenecarboxamide
175	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-2-methyl-3-furanecarboxamide
176	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-3-methyl-2-furanecarboxamide
177	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]benzeneacetamide
178	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-2-chlorobenzene acetamide
179	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-2-methylbenzene acetamide, yellow foam

Table VI (cont'd)

Example No.	Compound
180	N-[4-(pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)phenyl]-2-methyl-3-thiopheneacetamide

Example 181

9,10-Dihydro-4H-furo[2,3-e]pyrrolo[1,2-a][1,4]diazepine

To a suspension of 4 mmol of lithium aluminum hydride in 25 ml of anhydrous tetrahydrofuran is added 1 mmol of 9,10-dihydro-4H-furo[2,3-e]pyrrolo[1,2-a]-[1,4]diazepin-9-one. The mixture is refluxed for 12 hours and allowed to stand overnight. To the mixture is added dropwise 0.12 ml of water and then 6 ml of 1N sodium hydroxide. The mixture is extracted with ethyl acetate and the extract dried(Na_2SO_4). The volatiles are removed in vacuo to give the desired product as a solid.

Example 182

9,10-Dihydro-4H-furo[2,3-e]pyrrolo[1,2-a][1,4]diazepine

A solution of 1 mmol of 4H-furo[2,3-e]-pyrrolo[1,2-a][1,4]diazepine and 0.2 g of 10% Pd/C in 10 ml of 10 ml of ethanol is hydrogenated for 18 hours. The reaction mixture is filtered through diatomaceous earth and the filtrate is evaporated in vacuo to give the desired product as a solid.

Example 183

N-[4-(4H-Furo[2,3-e]pyrrolo[1,2-a][1,4]diazepin-10-(9H)-ylcarbonyl)phenyl]-2-methylbenzamide

To a mixture of 1.1 mmol of 4-[(2-methyl-benzoyl)amino]benzoyl chloride in 10 ml of methylene chloride, cooled to 0° C is added 1.5 mmol of triethylamine. To the mixture is added 1 mmol of 9,10-dihydro-4H-furo[2,3-e]pyrrolo[1,2-a][1,4]diazepine

and the mixture stirred at toom temperature for 2 hours. The reaction mixture is concentrated in vacuo and the residue is dissolved in 100 ml of ethyl acetate and washed with water, 2N citric acid, aqueous $NaHCO_3$ and brine. The solution is dried with Na_2SO_4 and the volatiles concentrated in vacuo to give a solid which is purified by flash chromatography to give the desired product.

Example 184

9,10-Dihydro-10-(4-nitrobenzoyl)-4H-furo[2,3-e] pyrrolo[1,2-a][1,4]diazepine

To a solution of 1.0 mmol of 9,10-dihydro-4H-furo[2,3-e]pyrrolo[1,2-a][1,4]diazepine in 10 ml of methylene chloride under argon is added 1.5 mmol of triethylamine followed by ice bath cooling. A solution of 1.1 mmol of 4-nitrobenzoyl chloride in 5 ml of methylene chloride is added dropwise. Following complete addition, the ice bath is removed and the reaction mixture is stirred at room temperature for 2 hours. The volatiles are removed in vacuo to give a residue which is dissolved in ethyl acetate. The solution is washed with water, 1N HCl, $NaHCO_3$, and brine. The reaction mixture is dried with Na_2SO_4, filtered and evaporated in vacuo to give a solid which is purified by flash chromatography on silica gel to give desired product as a solid.

Example 185

9,10-Dihydro-10-(4-aminobenzoyl)-4H-furo[2,3-e] pyrrolo[1,2-a][1,4]diazepine

A mixture of 1 mmol of 9,10-dihydro-10-(4-nitrobenzoyl)-4H-furo[2,3-e]pyrrolo[1,2-a][1,4]diazepine in 10 ml of ethyl alcohol and 10 ml of ethyl acetate containing 0.2 g of 10% Pd/C is hydrogenated for 5 hours. The reaction mixture is filtered through a pad of diatomaceous earth. The filtrate is concentrated in vacuo to a solid which is purified by

flash chromatography on silica gel to give the desired product.

Example 186

9,10-Dihydro-10-(4-aminobenzoyl)-4H-furo[2,3-e] pyrrolo[1,2-a][1,4]diazepine

To a solution of 1 mmol of 9,10-dihydro-10-(4-nitrobenzoyl)-4H-furo[2,3-e]pyrrolo[1,2-a][1,4]-diazepine in 20 ml of ethyl alcohol is added 0.2 g of 10% Pd/C and 2.5 mmol of hydrazine followed by stirring and heating under reflux for 3 hours. The room temperature reaction mixture is filtered through diatomaceous earth and the filtrate concentrated in vacuo. The residue is dissolved in methylene chloride and passed through a thin pad of hydrous magnesium silicate. The filtrate is concentrated in vacuo to give the desired product which is purified by flash chromatography on silica gel to give the desired product as a solid.

Example 187

N-[4-(4H-Furo[2,3-e]pyrrolo[1,2-a][1,4]-diazepin-10(9H)-ylcarbonyl)phenyl]-2-methyl benzamide

To a stirred solution of 1.1 mmol of 2-methyl-benzoyl chloride in 10 ml of methylene chloride is added 1.5 mmol of triethylamine. To the mixture is added 1.1 mmol of 9,10-dihydro-10-(4-aminobenzoyl)-4H-furo-[2,3-e]pyrrolo[1,2-a][1,4]diazepine and the mixture is stirred for 5 hours. The reaction mixture is washed with water, 1N citric acid, $NaHCO_3$, and brine. The reaction mixture is dried with Na_2SO_4, filtered and evaporated in vacuo to give a solid which is purified by flash chromatography on silica gel with ethyl acetate-hexane as solvent to give the desired product as a solid.

Table VII

The following Examples are prepared using the conditions of Example 187 with the appropriately substituted aroyl chloride.

Example No.	Compound
188	N-[4-(4H-Furo[2,3-e]pyrrolo[1,2-a]-[1,4]diazepin-10(9H)-ylcarbonyl)-phenyl]-2-chlorobenzamide
189	N-[4-(4H-Furo[2,3-e]pyrrolo[1,2-a]-[1,4]diazepin-10(9H)-ylcarbonyl)-phenyl]-2,5-dichlorobenzamide
190	N-[4-(4H-Furo[2,3-e]pyrrolo[1,2-a]-[1,4]diazepin-10(9H)-ylcarbonyl)-phenyl]-2,4-dichlorobenzamide
191	N-[4-(4H-Furo[2,3-e]pyrrolo[1,2-a]-[1,4]diazepin-10(9H)-ylcarbonyl)-phenyl]-2-chloro-4-methylbenzamide
192	N-[4-(4H-Furo[2,3-e]pyrrolo[1,2-a]-[1,4]diazepin-10(9H)-ylcarbonyl)-phenyl]-2-methyl-4-chlorobenzamide
193	N-[4-(4H-Furo[2,3-e]pyrrolo[1,2-a]-[1,4]diazepin-10(9H)-ylcarbonyl)-phenyl]-2,4-dimethylbenzamide

Table VII (cont'd)

Example No.	Compound
194	N-[4-(4H-Furo[2,3-e]pyrrolo[1,2-a]-[1,4]diazepin-10(9H)-ylcarbonyl)-phenyl]-2,3-dimethylbenzamide
195	N-[4-(4H-Furo[2,3-e]pyrrolo[1,2-a]-[1,4]diazepin-10(9H)-ylcarbonyl)-phenyl]-2-methoxybenzamide
196	N-[4-(4H-Furo[2,3-e]pyrrolo[1,2-a]-[1,4]diazepin-10(9H)-ylcarbonyl)-phenyl]-2-trifluoromethoxybenzamide
197	N-[4-(4H-Furo[2,3-e]pyrrolo[1,2-a]-[1,4]diazepin-10(9H)-ylcarbonyl)-phenyl]-2,4-dimethoxybenzamide
198	N-[4-(4H-Furo[2,3-e]pyrrolo[1,2-a]-[1,4]diazepin-10(9H)-ylcarbonyl)-phenyl]-2-methoxy-4-chlorobenzamide
199	N-[4-(4H-Furo[2,3-e]pyrrolo[1,2-a]-[1,4]diazepin-10(9H)-ylcarbonyl)-phenyl]-2,6-dichlorobenzamide
200	N-[4-(4H-Furo[2,3-e]pyrrolo[1,2-a]-[1,4]diazepin-10(9H)-ylcarbonyl)-phenyl]-2-methylthiobenzamide

Table VII (cont'd)

Example No.	Compound
201	N-[4-(4H-Furo[2,3-e]pyrrolo[1,2-a]-[1,4]diazepin-10(9H)-ylcarbonyl)-phenyl]-2-methyl-3-thiophene-carboxamide
202	N-[4-(4H-Furo[2,3-e]pyrrolo[1,2-a]-[1,4]diazepin-10(9H)-ylcarbonyl)-phenyl]-3-methyl-2-thiophene-carboxamide
203	N-[4-(4H-Furo[2,3-e]pyrrolo[1,2-a]-[1,4]diazepin-10(9H)-ylcarbonyl)-phenyl]-2-methyl-3-furane-carboxamide
204	N-[4-(4H-Furo[2,3-e]pyrrolo[1,2-a]-[1,4]diazepin-10(9H)-ylcarbonyl)-phenyl]-3-methyl-2-furane-carboxamide
205	N-[4-(4H-Furo[2,3-e]pyrrolo[1,2-a]-[1,4]diazepin-10(9H)-ylcarbonyl)-phenyl]-2-chlorobenzeneacetamide
206	N-[4-(4H-Furo[2,3-e]pyrrolo[1,2-a]-[1,4]diazepin-10(9H)-ylcarbonyl)-phenyl]-2-methylbenzeneacetamide

Table VII (cont'd)

Example No.	Compound
207	N-[4-(4H-Furo[2,3-e]pyrrolo[1,2-a]-[1,4]diazepin-10(9H)-ylcarbonyl)-phenyl]-2-methyl-3-thiophene-acetamide
208	N-[4-(4H-Furo[2,3-e]pyrrolo[1,2-a]-[1,4]diazepin-10(9H)-ylcarbonyl)-phenyl]-cyclohexanecarboxamide
209	N-[4-(4H-Furo[2,3-e]pyrrolo[1,2-a]-[1,4]diazepin-10(9H)-ylcarbonyl)-phenyl]-cyclohexylacetamide

Example 210

N-[4-(4H-Pyrazolo[5,1-c][1,4]benzo-diazepin-5(10H)-ylcarbonyl)phenyl]-2-methylbenzamide

To a mixture of 1.37 g of 4-[(2-methyl-benzoyl)amino]benzoyl chloride in 15 ml of methylene chloride, cooled to 0° C is added 1.5 ml of triethylamine. To the mixture is added 5 mmol of 5,10-dihydro-4H-pyrazolo[5,1-c][1,4]benzodiazepine. The reaction mixture is allowed to stir at room temperature for 48 hours and the volatiles are removed in vacuo to give a residue. The residue is dissolved in 100 ml of ethyl acetate and washed with water, 2N citric acid, aqueous $NaHCO_3$ and brine. The solution is dried with Na_2SO_4 and the solvent removed in vacuo. The residue is purified by flash chromatography on silica gel with ethyl acetate-hexane to give the desired product, m.p. 142°-146°C.

Example 211

5,10-Dihydro-5-(4-nitrobenzoyl)-4H-pyrazolo-[5,1-c]-[1,4]benzodiazepine

To a solution of 10 mmol of 5,10-dihydro-4H-pyrazolo[5,1-c][1,4]benzodiazepine in 50 ml of methylene chloride under argon is added 15 mmol of triethylamine followed by ice bath cooling. A solution of 11 mmol of 4-nitrobenzoyl chloride in 10 ml of methylene chloride is added dropwise. Following complete addition, the ice bath is removed and the reaction mixture stirred at room temperature for 2 hours. The volatiles are removed in vacuo to give a residue which is dissolved in ethyl acetate. The solution is washed with water, $NaHCO_3$, and brine. The reaction mixture is dried with Na_2SO_4, filtered and evaporated in vacuo to give a solid which is purified by flash chromatography on silica gel to give desired product as a solid, m.p. 227°-229°C.

Example 212

5,10-Dihydro-5-(4-aminobenzoyl)-4H-pyrazolo-[5,1-c]-[1,4]benzodiazepine

A mixture of 5 mmol of 5,10-dihydro-5-(4-nitrobenzoyl)-4H-pyrazolo-[5,1-c][1,4]benzodiazepine in 25 ml of ethyl alcohol and 10 ml of ethyl acetate containing 0.2 g of 10% Pd/C is hydrogenated for 5 hours. The reaction mixture is filtered through a pad of diatomaceous earth. The filtrate is concentrated in vacuo to a solid which is purified by flash chromatography on silica gel to give the desired product as a tan solid.

Example 213

5,10-Dihydro-5-(4-aminobenzoyl)-4H-pyrazolo-[5,1-c]-[1,4]benzodiazepine

To a solution of 5 mmol of 5,10-dihydro-5-(4-nitrobenzoyl)-4H-pyrazolo-[5,1-c][1,4]benzodiazepine in 25 ml of ethyl alcohol is added 0.3 g of 10% Pd/C and 15 mmol of hydrazine. The mixture is heated under

reflux for 3 hours, and the mixture is filtered through diatomaceous earth. The filtrate is concentrated in vacuo to a residue which is dissolved in methylene chloride and passed through a thin pad of hydrous magnesium silicate. The filtrate is concentrated in vacuo to give the desired product which is purified by flash chromatography on silica gel to give the desired product as a solid, exact mass by mass spectrometry: 305.1402(M+H).

Example 214

N-[4-(4H-Pyrazolo[5,1-c][1,4]benzodiazepin-5(10H)-ylcarbonyl)phenyl]-2-methylbenzamide

To a stirred solution of 3 mmol of 2-methylbenzoyl chloride in 10 ml of methylene chloride is added 5 mmol of triethylamine and 3 mmol of 5,10-dihydro-5-(4-aminobenzoyl)-4H-pyrazolo-[5,1-c][1,4]benzodiazepine. The mixture is stirred at room temperature for 5 hours and is then washed with water, $NaHCO_3$, and brine. The organic layer is dried with Na_2SO_4, filtered and evaporated in vacuo to give a solid which is purified by flash chromatography on silica gel to give the desired product as a solid, m.p. 142°-146°C.

Table VIII

The following Examples are prepared using the conditions of Example 214 with the appropriately substituted aroyl chloride.

Example No.	Compound
215	N-[4-(4H-Pyrazolo[5,1-c][1,4]benzodiazepin-5(10H)-ylcarbonyl)phenyl]-2-methoxybenzeneacetamide, m.p. 185-188°C
216	N-[4-(4H-Pyrazolo[5,1-c][1,4]benzodiazepin-5(10H)-ylcarbonyl)phenyl}-2,5-dichlorobenzamide
217	N-[4-(4H-Pyrazolo[5,1-c][1,4]benzodiazepin-5(10H)-ylcarbonyl)phenyl]-2,4-dichlorobenzamide, colorless foam; exact mass by mass spectrometry:479.0896(M+H)
218	N-[4-(4H-Pyrazolo[5,1-c][1,4]benzodiazepin-5(10H)-ylcarbonyl)phenyl]-2-chloro-4-methylbenzamide
219	N-[4-(4H-Pyrazolo[5,1-c][1,4]benzodiazepin-5(10H)-ylcarbonyl)phenyl]-2-methyl-4-chlorobenzamide
220	N-[4-(4H-Pyrazolo[5,1-c][1,4]benzodiazepin-5(10H)-ylcarbonyl)phenyl]-2,4-dimethylbenzamide

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Table VIII (cont'd)

Example No.	Compound
221	N-[4-(4H-Pyrazolo[5,1-c][1,4]benzodiazepin-5(10H)-ylcarbonyl)phenyl]-2,3-dimethylbenzamide
222	N-[4-(4H-Pyrazolo[5,1-c][1,4]benzodiazepin-5(10H)-ylcarbonyl)phenyl]-2-methoxybenzamide
223	N-[4-(4H-Pyrazolo[5,1-c][1,4]benzodiazepin-5(10H)-ylcarbonyl)phenyl]-2-trifluoromethoxybenzamide
224	N-[4-(4H-Pyrazolo[5,1-c][1,4]benzodiazepin-5(10H)-ylcarbonyl)phenyl]-2,4-dimethoxybenzamide
225	N-[4-(4H-Pyrazolo[5,1-c][1,4]benzodiazepin-5(10H)-ylcarbonyl)phenyl]-2,6-dimethoxybenzamide
226	N-[4-(4H-Pyrazolo[5,1-c][1,4]benzodiazepin-5(10H)-ylcarbonyl)phenyl]-benzamide
227	N-[4-(4H-Pyrazolo[5,1-c][1,4]benzodiazepin-5(10H)-ylcarbonyl)phenyl]-2,6-dichlorobenzamide

Table VIII (cont'd)

Example No.	Compound
228	N-[4-(4H-Pyrazolo[5,1-c][1,4]benzodiazepin-5(10H)-ylcarbonyl)phenyl]-2,6-dimethylbenzamide
229	N-[4-(4H-Pyrazolo[5,1-c][1,4]benzodiazepin-5(10H)-ylcarbonyl)phenyl]-2-methylthiobenzamide
230	N-[4-(4H-Pyrazolo[5,1-c][1,4]benzodiazepin-5(10H)-ylcarbonyl)phenyl]-2-methyl-3-thiophenecarboxamide
231	N-[4-(4H-Pyrazolo[5,1-c][1,4]benzodiazepin-5(10H)-ylcarbonyl)phenyl]-3-methyl-2-thiophenecarboxamide
232	N-[4-(4H-Pyrazolo[5,1-c][1,4]benzodiazepin-5(10H)-ylcarbonyl)phenyl]-2-methyl-3-furanecarboxamide
233	N-[4-(4H-Pyrazolo[5,1-c][1,4]benzodiazepin-5(10H)-ylcarbonyl)phenyl]-3-methyl-2-furanecarboxamide
234	N-[4-(4H-Pyrazolo[5,1-c][1,4]benzodiazepin-5(10H)-ylcarbonyl)phenyl]-3-cyclohexenecarboxamide
235	N-[4-(4H-Pyrazolo[5,1-c][1,4]benzodiazepin-5(10H)-ylcarbonyl)phenyl]-2-chlorobenzeneacetamide

Table VIII (cont'd)

Example No.	Compound
236	N-[4-(4H-Pyrazolo[5,1-c][1,4]benzodiazepin-5(10H)-ylcarbonyl)phenyl]-2-methylbenzeneacetamide
237	N-[4-(4H-Pyrazolo[5,1-c][1,4]benzodiazepin-5(10H)-ylcarbonyl)phenyl]-2-methyl-3-thiopheneacetamide

Example 238

9,10-Dihydro-4H-pyrrolo[1,2-a]thieno[2,3-e][1,4]diazepine

To a mixture of 7.0 g of 9-oxo-9,10-dihydro-4H-pyrrolo[1,2-a]thieno[2,3-e][1,4]diazepin in 25 ml of anhydrous tetrahydrofuran is added 9 ml of 10 molar boron-dimethylsulfide in tetrahydrofuran. The mixture is refluxed for 6 hours. The solution is cooled to room temperature and 25 ml of methanol added dropwise. The volatiles are removed under vacuum. To the residue is added 100 ml of 2 N NaOH. The mixture is refluxed 5 hours and filtered. The solid is extracted with dichloromethane and the extract is washed with 2 N citric acid, water and dried (Na_2SO_4). The solvent is removed in vacuo to give the desired product as a solid.

Example 239

N-[4-(4H-Pyrazolo[1,2-a]thieno[2,3-a][1,4]-diazepin-10(9H)-ylcarbonyl)phenyl]-2-methylbenzamide

To a mixture of 1.37 g (5mmol) of 4-[(2-methylbenzoyl)amino]benzoyl chloride in 15 ml of methylene chloride, cooled to 0° C is added 1.5 ml of triethylamine. To the mixture is added 5 mmol of 9,10-dihydro-4H-pyrazolo[1,2-a]thieno[2,3-e][1,4]diazepine. The cooling bath is removed and the reaction

mixture is allowed to stir at room temperature for 48 hours. The volatiles are removed in vacuo to give a residue. The residue is dissolved in 100 ml of ethyl acetate and washed with water, 2N citric acid, aqueous $NaHCO_3$ and brine. The solution is dried with Na_2SO_4 and the solvent removed in vacuo to give a solid. The solid is purified by flash chromatography on silica gel to give the desired product.

Example 240

9,10-Dihydro-10-(4-nitrobenzoyl)-4H-pyrrolo-[1,2-a]thieno[2,3-e][1,4]diazepine

To a solution of 10 mmol of 9,10-dihydro-4H-pyrrolo[1,2-a]thieno[2,3-e][1,4]diazepine in 50 ml of methylene chloride under argon is added 15 mmol of triethylamine followed by ice bath cooling. A solution of 11 mmol of 4-nitrobenzoyl chloride in 10 ml of methylene chloride is added dropwise. Following complete addition, the ice bath is removed and the reaction mixture stirred at room temperature for 2 hours. The volatiles are removed in vacuo to give a residue which is dissolved in ethyl acetate. The solution is washed with water, 1N HCl, $NaHCO_3$, and brine. The organic layer is dried with Na_2SO_4, filtered and evaporated in vacuo to give a solid which is purified by flash chromatography on silica gel to give desired product as a solid.

Example 241

9,10-Dihydro-10-(4-aminobenzoyl)-4H-pyrrolo-[1,2-a]thieno[2,3-e][1,4]diazepine

A mixture of 2 g of 9,10-dihydro-10-(4-nitrobenzoyl)-4H-pyrrolo-[1,2-a]thieno[2,3-e][1,4]-diazepine in 20 ml of ethyl alcohol and 20 ml of ethyl acetate containing 0.2 g of 10% Pd/C is hydrogenated for 5 hours. The reaction mixture is filtered through a pad of diatomaceous earth. The filtrate is concentrated in vacuo to a solid which is purified by flash chromatography to give the desired product.

Example 242

9,10-Dihydro-10-(4-aminobenzoyl)-4H-pyrrolo-[1,2-a]thieno[2,3-e][1,4]diazepine

To a solution of 5 mmol of 9,10-dihydro-10-(4-nitrobenzoyl)-4H-pyrrolo-[1,2-a]thieno[2,3-e][1,4]-diazepine in 25 ml of ethyl alcohol is added 0.13 g of 10% Pd/C and 15 mmol of hydrazine followed by stirring and heating under reflux for 3 hours. The cooled reaction mixture is filtered through diatomaceous earth. The filtrate is concentrated in vacuo to a residue which is dissolved in methylene chloride and passed through a pad of hydrous magnesium silicate. The filtrate is concentrated in vacuo to give the desired product which is purified by flash chromatography on silica gel to give the desired product as a solid.

Example 243

N-[4-(4H-Pyrrolo[1,2-a]thieno[2,3-e][1,4]diazepin-10(9H)-ylcarbonyl)phenyl]-2-methylbenzamide

To a stirred solution of 5 mmol of 2-methylbenzoyl chloride in 10 ml of methylene chloride is added 7 mmol of triethylamine and 5 mmol of 9,10-dihydro-10-(4-aminobenzoyl)-4H-pyrrolo-[1,2-a]thieno[2,3-e]-[1,4]diazepine and the mixture stirred for 5 hours. The reaction mixture is washed with water, 2N citric acid, $NaHCO_3$, and brine. The organic layer is dried with Na_2SO_4, filtered and evaporated in vacuo to give a solid which is purified by flash chromatography on silica gel to give the desired product as a solid.

Table IX

The following Examples are prepared using the conditions of Example 243 with the appropriately substituted aroyl chloride.

Example No.	Compound
244	N-[4-(4H-pyrrolo[1,2-a]thieno-[2,3-e][1,4]diazepin-10(9H)-yl carbonyl)phenyl]-2-chloro-benzamide
245	N-[4-(4H-pyrrolo[1,2-a]thieno-[2,3-e][1,4]diazepin-10(9H)-yl carbonyl)phenyl]-2,5-dichloro-benzamide
246	N-[4-(4H-pyrrolo[1,2-a]thieno-[2,3-e][1,4]diazepin-10(9H)-yl carbonyl)phenyl]-2,4-dichloro-benzamide
247	N-[4-(4H-pyrrolo[1,2-a]thieno-[2,3-e][1,4]diazepin-10(9H)-yl carbonyl)phenyl]-2-chloro-4-methylbenzamide
248	N-[4-(4H-pyrrolo[1,2-a]thieno-[2,3-e][1,4]diazepin-10(9H)-yl carbonyl)phenyl]-2-methyl-4-chlorobenzamide
249	N-[4-(4H-pyrrolo[1,2-a]thieno-[2,3-e][1,4]diazepin-10(9H)-yl carbonyl)phenyl]-2,4-dimethylbenzamide

Table IX (cont'd)

Example No.	Compound
250	N-[4-(4H-pyrrolo[1,2-a]thieno-[2,3-e][1,4]diazepin-10(9H)-yl carbonyl)phenyl]-2,3-dimethylbenzamide
251	N-[4-(4H-pyrrolo[1,2-a]thieno-[2,3-e][1,4]diazepin-10(9H)-yl carbonyl)phenyl]-2-methoxy-benzamide
252	N-[4-(4H-pyrrolo[1,2-a]thieno-[2,3-e][1,4]diazepin-10(9H)-yl carbonyl)phenyl]-2-trifluoromethoxybenzamide
253	N-[4-(4H-pyrrolo[1,2-a]thieno-[2,3-e][1,4]diazepin-10(9H)-yl carbonyl)phenyl]-2,4-dimethoxybenzamide
254	N-[4-(4H-pyrrolo[1,2-a]thieno-[2,3-e][1,4]diazepin-10(9H)-yl carbonyl)phenyl]-2,6-dimethoxybenzamide
255	N-[4-(4H-pyrrolo[1,2-a]thieno-[2,3-e][1,4]diazepin-10(9H)-yl carbonyl)phenyl]-2,6-dichlorobenzamide

Table IX (cont'd)

Example No.	Compound
256	N-[4-(4H-pyrrolo[1,2-a]thieno-[2,3-e][1,4]diazepin-10(9H)-yl carbonyl)phenyl]-2,6-dimethylbenzamide
257	N-[4-(4H-pyrrolo[1,2-a]thieno-[2,3-e][1,4]diazepin-10(9H)-yl carbonyl)phenyl]-2-methoxy-4-chlorobenzamide
258	N-[4-(4H-pyrrolo[1,2-a]thieno-[2,3-e][1,4]diazepin-10(9H)-yl carbonyl)phenyl]-2-methoxybenzeneacetamide
259	N-[4-(4H-pyrrolo[1,2-a]thieno-[2,3-e][1,4]diazepin-10(9H)-yl carbonyl)phenyl]-2-(methylthio)-benzamide
260	N-[4-(4H-pyrrolo[1,2-a]thieno-[2,3-e][1,4]diazepin-10(9H)-yl carbonyl)phenyl]-2-methyl-3-thiophenecarboxamide
261	N-[4-(4H-pyrrolo[1,2-a]thieno-[2,3-e][1,4]diazepin-10(9H)-yl carbonyl)phenyl]-3-methyl-2-thiophenecarboxamide
262	N-[4-(4H-pyrrolo[1,2-a]thieno-[2,3-e][1,4]diazepin-10(9H)-yl carbonyl)phenyl]-3-methyl-2-furancarboxamide

Table IX (cont'd)

Example No.	Compound
263	N-[4-(4H-pyrrolo[1,2-a]thieno-[2,3-e][1,4]diazepin-10(9H)-yl carbonyl)phenyl]-3-chlorophenylacetamide
264	N-[4-(4H-pyrrolo[1,2-a]thieno-[2,3-e][1,4]diazepin-10(9H)-yl carbonyl)phenyl]-2-methylbenzeneacetamide
265	N-[4-(4H-pyrrolo[1,2-a]thieno-[2,3-e][1,4]diazepin-10(9H)-yl carbonyl)phenyl]-2-methyl-3-thiopheneacetamide

Example 266

4,10-Dihydro-5H-pyrrolo[1,2-a]thieno[3,2-e][1,4] diazepine

To a suspension of 7.0 g of 5-oxo-4,5-dihydropyrrolo[1,2-a]thieno[3,2-e][1,4]diazepine in 25 ml of anhydrous tetrahydrofuran is added 9 ml of 10 M borane-dimethylsulfide in tetrahydrofuran. The mixture is refluxed for 6 hours. The solution is cooled to room temperature and 25 ml of methanol added dropwise. The volatiles are removed under vacuum. To the residue is added 100 ml of 2 N NaOH. The mixture is refluxed 5 hours and filtered. The solid is extracted with dichloromethane and the extract is washed with 2 N citric acid, water and dried (Na_2SO_4). The solvent is removed to give a solid.

Example 267

N-[4-(5H-Pyrazolo[1,2-a]thieno[3,2-e][1,4]-diazepin-4(10H)-ylcarbonyl)phenyl]-2-methylbenzamide

To a mixture of 5.5 mmol of 4-[(2-methylbenzoyl)amino]benzoyl chloride in 20 ml of methylene chloride, cooled to 0° C is added 7.5 mmol of triethylamine and 5 mmol of 4,10-dihydro-5H-pyrazolo-[1,2-a]thieno[3,2-e][1,4]diazepine. The cooling bath is removed and the reaction mixture is allowed to stir at room temperature for 48 hours. The volatiles are removed in vacuo to give a residue. The residue is dissolved in 100 ml of ethyl acetate and the solution washed with water, 2N citric acid, aqueous $NaHCO_3$ and brine. The solution is dried with Na_2SO_4 and the solvent concentrated in vacuo to give a solid. The solid is purified by flash chromatography on silica gel to give the desired product as a solid and foam, m.p. 162°-188°C, Anal. Calc'd for $C_{25}H_{21}N_3O_2S$: C,70.2; H,5.0 N,9.8; S,7.5 Found: C,69.5, H,5.2 N,9.6; S,7.0.

Example 268

4,10-Dihydro-4-(4-nitrobenzoyl)-5H-pyrrolo-[1,2-a]thieno[3,2-e][1,4]diazepine

To a solution of 3 mmol of 4,10-dihydro-5H-pyrrolo[1,2-a]thieno[3,2-e][1,4]diazepine in 10 ml of methylene chloride under argon is added 5 mmol of triethylamine followed by ice bath cooling. A solution of 3.3 mmol of 4-nitrobenzoyl chloride in 3 ml of methylene chloride is added dropwise. Following complete addition, the ice bath is removed and the reaction mixture stirred at room temperature for 2 hours. The volatiles are removed in vacuo to give a residue which is dissolved in ethyl acetate. The solution is washed with water, 2 N citric acid, $NaHCO_3$, and brine. The reaction mixture is dried with Na_2SO_4, filtered and evaporated in vacuo to give a solid which

is purified by flash chromatography on silica gel to give desired product as a solid.

Example 269

4,10-Dihydro-4-(4-aminobenzoyl)-5H-pyrrolo-[1,2-a]thieno[3,2-e][1,4]diazepine

A mixture of 5 mmol of 4,10-dihydro-4-(4-nitrobenzoyl)-5H-pyrrolo-[1,2-a]thieno[3,2-e][1,4]-diazepine in 25 ml of ethyl alcohol and 25 ml of ethyl acetate containing 0.2 g of 10% Pd/C is hydrogenated for 5 hours. The reaction mixture is filtered through a pad of diatomaceous earth. The filtrate is concentrated in vacuo to a solid which is purified by flash chromatography on silica gel to give the desired product.

Example 270

4,10-Dihydro-4-(4-aminobenzoyl)-5H-pyrrolo-[1,2-a]thieno[3,2-e][1,4]diazepine

To a mixture of 5 mmol of 4,10-dihydro-4-(4-nitrobenzoyl)-5H-pyrrolo-[1,2-a]thieno[3,2-e][1,4]-diazepine in 25 ml of ethyl alcohol is added 0.3 g of 10% Pd/C and 15 mmol of hydrazine followed by stirring and heating under reflux for 3 hours. The cooled reaction mixture is filtered through diatomaceous earth. The filtrate is concentrated in vacuo to a residue which is dissolved in methylene chloride and passed through a pad of hydrous magnesium silicate. The filtrate is concentrated in vacuo to give the desired product which is purified by flash chromatography on silica gel to give the desired product as a solid.

Example 271

N-[4-(5H-Pyrrolo[1,2-a]thieno[3,2-e][1,4]diazepin-4(10H)-ylcarbonyl)phenyl]-2-methylbenzamide

To a stirred solution of 3 mmol of 2-methyl-benzoyl chloride in 10 ml of methylene chloride is added 5 mmol of triethylamine and 3 mmol of 4,10-dihydro-4-(4-aminobenzoyl)-5H-pyrrolo-[1,2-a]thieno[3,2-e]-

[1,4]diazepine. The mixture is stirred for 5 hours. The reaction mixture is washed with water, 2N citric acid, $NaHCO_3$, and brine. The reaction mixture is dried with Na_2SO_4, filtered and evaporated in vacuo to give a solid which is purified by flash chromatography on silica gel to give the desired product as a solid, m.p. 162°-188°C (amorphous)

Table X

The following Examples are prepared using the conditions of Example 271 with the appropriately substituted aroyl chloride.

Example No.	Compound
272	N-[4-(5H-pyrrolo[1,2-a]thieno-[3,2-e][1,4]diazepin-4(10H)-yl carbonyl)phenyl]-2-chloro-benzamide
273	N-[4-(5H-pyrrolo[1,2-a]thieno-[3,2-e][1,4]diazepin-4(10H)-yl carbonyl)phenyl]-2,5-dichloro-benzamide
274	N-[4-(5H-pyrrolo[1,2-a]thieno-[3,2-e][1,4]diazepin-4(10H)-yl carbonyl)phenyl]-2,4-dichloro-benzamide (solid foam), m.p. 105-190°C; Anal Calc'd for $C_{24}H_{17}N_3Cl_2O_2S$: C,59.8; H,3.6; N,8.7; S,6.6, Cl, 14.7 Found: C,59.6; H,3.8; N,8.1; S,5.5; Cl,14.0
275	N-[4-(5H-pyrrolo[1,2-a]thieno-[3,2-e][1,4]diazepin-4(10H)-yl carbonyl)phenyl]-2-chloro-4-methylbenzamide

Table X (cont'd)

Example No.	Compound
276	N-[4-(5H-pyrrolo[1,2-a]thieno-[3,2-e][1,4]diazepin-4(10H)-yl carbonyl)phenyl]-2-methyl-4-chlorobenzamide
277	N-[4-(5H-pyrrolo[1,2-a]thieno-[3,2-e][1,4]diazepin-4(10H)-yl carbonyl)phenyl]-2,4-dimethyl-benzamide
278	N-[4-(5H-pyrrolo[1,2-a]thieno-[3,2-e][1,4]diazepin-4(10H)-yl carbonyl)phenyl]-2,3-dimethyl-benzamide
279	N-[4-(5H-pyrrolo[1,2-a]thieno-[3,2-e][1,4]diazepin-4(10H)-yl carbonyl)phenyl]-2-methoxy-benzamide
280	N-[4-(5H-pyrrolo[1,2-a]thieno-[3,2-e][1,4]diazepin-4(10H)-yl carbonyl)phenyl]-2-trifluoro-methoxybenzamide
281	N-[4-(5H-pyrrolo[1,2-a]thieno-[3,2-e][1,4]diazepin-4(10H)-yl carbonyl)phenyl]-2,4-dimethoxybenzamide
282	N-[4-(5H-pyrrolo[1,2-a]thieno-[3,2-e][1,4]diazepin-4(10H)-yl carbonyl)phenyl]-2,6-dimethoxybenzamide

Table X (cont'd)

Example No.	Compound
283	N-[4-(5H-pyrrolo[1,2-a]thieno-[3,2-e][1,4]diazepin-4(10H)-yl carbonyl)phenyl]-2,6-dichlorobenzamide
284	N-[4-(5H-pyrrolo[1,2-a]thieno-[3,2-e][1,4]diazepin-4(10H)-yl carbonyl)phenyl]-2,6-dimethylbenzamide
285	N-[4-(5H-pyrrolo[1,2-a]thieno-[3,2-e][1,4]diazepin-4(10H)-yl carbonyl)phenyl]-2-methylthio-benzamide
286	N-[4-(5H-pyrrolo[1,2-a]thieno-[3,2-e][1,4]diazepin-4(10H)-yl carbonyl)phenyl]-2-methyl-3-thiophenecarboxamide
287	N-[4-(5H-pyrrolo[1,2-a]thieno-[3,2-e][1,4]diazepin-4(10H)-yl carbonyl)phenyl]-3-methyl-2-thiophenecarboxamide
288	N-[4-(5H-pyrrolo[1,2-a]thieno-[3,2-e][1,4]diazepin-4(10H)-yl carbonyl)phenyl]-3-methyl-2-furancarboxamide

Table X (cont'd)

Example No.	Compound
289	N-[4-(5H-pyrrolo[1,2-a]thieno-[3,2-e][1,4]diazepin-4(10H)-yl carbonyl)phenyl]-3-chloro-benzeneacetamide
290	N-[4-(5H-pyrrolo[1,2-a]thieno-[3,2-e][1,4]diazepin-4(10H)-yl carbonyl)phenyl]-2-methoxy-benzeneacetamide
291	N-[4-(5H-pyrrolo[1,2-a]thieno-[3,2-e][1,4]diazepin-4(10H)-yl carbonyl)phenyl]-2-methoxy-4-chlorobenzamide
292	N-[4-(5H-pyrrolo[1,2-a]thieno-[3,2-e][1,4]diazepin-4(10H)-yl carbonyl)phenyl]-2-methylbenzene-acetamide
293	N-[4-(5H-pyrrolo[1,2-a]thieno-[3,2-e][1,4]diazepin-4(10H)-yl carbonyl)phenyl]-2-methyl-3-thiopheneacetamide

Example 294

6,7-Dihydro-5-(4-nitrobenzoyl)-5H-pyrrolo[1,2-a]-[1,5]benzodiazepine

To a solution of 10 mmol of 6,7-dihydro-5H-pyrrolo[1,2-a][1,5]benzodiazepine in 30 ml of methylene chloride under argon is added 15 mmol of triethylamine followed by ice bath cooling. A solution of 11 mmol of 4-nitrobenzoyl chloride in 10 ml of methylene chloride is added dropwise. Following complete addition, the ice bath is removed and the reaction mixture stirred at

room temperature for 2 hours. The volatiles are removed *in vacuo* to give a residue which is dissolved in ethyl acetate. The solution is washed with water, 2N citric acid, $NaHCO_3$, and brine. The reaction mixture is dried with Na_2SO_4, filtered and evaporated *in vacuo* to give a solid which is purified by flash chromatography on silica gel to give the desired product as a solid.

Example 295

6,7-Dihydro-5-(4-aminobenzoyl)-5H-pyrrolo[1,2-a]-[1,5]benzodiazepine

A mixture of 2.0 g of 6,7-dihydro-5-(4-nitrobenzoyl)-5H-pyrrolo[1,2-a][1,5]benzodiazepine, 20 ml of ethyl alcohol and 20 ml of ethyl acetate containing 0.2 g of 10% Pd/C is hydrogenated for 5 hours. The reaction mixture is filtered through a pad of diatomaceous earth. The filtrate is concentrated *in vacuo* to a solid which is purified by flash chromatography on silica gel to give the desired product.

Example 296

6,7-Dihydro-5-(4-aminobenzoyl)-5H-pyrrolo[1,2-a]-[1,5]benzodiazepine

To a solution of 5 mmol of 6,7-dihydro-5-(4-nitrobenzoyl)-5H-pyrrolo[1,2-a][1,5]benzodiazepine in 25 ml of ethyl alcohol is added 0.3 g of 10% Pd/C and 15 mmol of hydrazine followed by stirring and heating under reflux for 3 hours. The reaction mixture is filtered through diatomaceous earth. The filtrate is concentrated *in vacuo* to a residue which is dissolved in methylene chloride and passed through a pad of hydrous magnesium silicate. The filtrate is concentrated *in vacuo* to give the desired product which is purified by flash chromatography on silica gel to give the desired product as a solid.

Example 297

N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a][1,5]benzodiazepin--5-yl)carbonyl]phenyl]-2-methylbenzamide

To a mixture of 1.37 g (5 mmol) of 4-[(2-methylbenzoyl)amino]benzoyl chloride in 10 ml of methylene chloride, cooled to 0° C is added 7 mmol of triethylamine and 5 mmol of 6,7-dihydro-5H-pyrrolo-[1,2-a][1,5]benzodiazepine. The cooling bath is removed and the reaction mixture is allowed to stir at room temperature for 48 hours. The volatiles are removed in vacuo to give a residue. The residue is dissolved in 100 ml of ethyl acetate and washed with water, 2N citric acid, aqueous $NaHCO_3$ and brine. The solution is dried with Na_2SO_4 and the solvent removed in vacuo to give a solid. The solid is triturated with ether-hexane to give the desired product, mass spectrum (CI):422(M+H).

Example 298

N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a][1,5]benzodiazepin--5-yl)carbonyl)phenyl]-2-methyl-benzamide

To a stirred solution of 5 mmol of 2-methyl-benzoyl chloride in 10 ml of methylene chloride is added 7 mmol of triethylamine and 5 mmol of 6,7-dihydro-5-(4-aminobenzoyl)-5H-pyrrolo[1,2-a]-[1,5]benzodiazepine. The reaction mixture is washed with water, 2M citric acid, $NaHCO_3$, and brine. The organic layer is dried with Na_2SO_4, filtered and evaporated in vacuo to give a solid which is purified by flash chromatography on silica gel to give the desired product as a solid; mass spectrum (CI):422(M+H).

Table XI

The following Examples are prepared using the conditions of Example 298 with the appropriately substituted aroyl chloride.

Example No.	Compound
299	N-[4-[(6,7-dihydro-5H-pyrrolo [1,2-a][1,5]benzodiazepin-5-yl) carbonyl]phenyl]-2-chlorobenzamide
300	N-[4-[(6,7-dihydro-5H-pyrrolo [1,2-a][1,5]benzodiazepin-5-yl) carbonyl]phenyl]-2,5-dichlorobenzamide
301	N-[4-[(6,7-dihydro-5H-pyrrolo [1,2-a][1,5]benzodiazepin-5-yl) carbonyl]phenyl]-2,4-dichlorobenzamide
302	N-[4-[(6,7-dihydro-5H-pyrrolo [1,2-a][1,5]benzodiazepin-5-yl) carbonyl]phenyl]-2-chloro-4-methylbenzamide
303	N-[4-[(6,7-dihydro-5H-pyrrolo [1,2-a][1,5]benzodiazepin-5-yl) carbonyl]phenyl]-2-methyl-4-chlorobenzamide

Table XI (cont'd)

Example No.	Compound
304	N-[4-[(6,7-dihydro-5H-pyrrolo [1,2-a][1,5]benzodiazepin-5-yl) carbonyl]phenyl]-2,4-dimethylbenzamide
305	N-[4-[(6,7-dihydro-5H-pyrrolo [1,2-a][1,5]benzodiazepin-5-yl) carbonyl]phenyl]-2,3-dimethylbenzamide
306	N-[4-[(6,7-dihydro-5H-pyrrolo [1,2-a][1,5]benzodiazepin-5-yl) carbonyl]phenyl]-2-methoxybenzamide
307	N-[4-[(6,7-dihydro-5H-pyrrolo [1,2-a][1,5]benzodiazepin-5-yl) carbonyl]phenyl]-2-trifluoromethoxybenzamide
308	N-[4-[(6,7-dihydro-5H-pyrrolo [1,2-a][1,5]benzodiazepin-5-yl) carbonyl]phenyl]-2,4-dimethoxybenzamide
309	N-[4-[(6,7-dihydro-5H-pyrrolo [1,2-a][1,5]benzodiazepin-5-yl) carbonyl]phenyl]-2,6-dimethoxybenzamide

Table XI (cont'd)

Example No.	Compound
310	N-[4-[(6,7-dihydro-5H-pyrrolo [1,2-a][1,5]benzodiazepin-5-yl) carbonyl]phenyl]-2,6-dichlorobenzamide
311	N-[4-[(6,7-dihydro-5H-pyrrolo [1,2-a][1,5]benzodiazepin-5-yl) carbonyl]phenyl]-2,6-dimethylbenzamide
312	N-[4-[(6,7-dihydro-5H-pyrrolo [1,2-a][1,5]benzodiazepin-5-yl) carbonyl]phenyl]-2-methylthiobenzamide
313	N-[4-[(6,7-dihydro-5H-pyrrolo [1,2-a][1,5]benzodiazepin-5-yl) carbonyl]phenyl]-2-methyl-3-thiophenecarboxamide
314	N-[4-[(6,7-dihydro-5H-pyrrolo [1,2-a][1,5]benzodiazepin-5-yl) carbonyl]phenyl]-3-methyl-2-thiophenecarboxamide
315	N-[4-[(6,7-dihydro-5H-pyrrolo [1,2-a][1,5]benzodiazepin-5-yl) carbonyl]phenyl]-2-methyl-3-furanecarboxamide

Table XI (cont'd)

Example No.	Compound
316	N-[4-[(6,7-dihydro-5H-pyrrolo [1,2-a][1,5]benzodiazepin-5-yl) carbonyl]phenyl]-3-methyl-2-furanecarboxamide
317	N-[4-[(6,7-dihydro-5H-pyrrolo [1,2-a][1,5]benzodiazepin-5-yl) carbonyl]phenyl]benzeneacetamide
318	N-[4-[(6,7-dihydro-5H-pyrrolo [1,2-a][1,5]benzodiazepin-5-yl) carbonyl]phenyl]-2-chlorobenzene-acetamide
319	N-[4-[(6,7-dihydro-5H-pyrrolo [1,2-a][1,5]benzodiazepin-5-yl) carbonyl]phenyl]-2-methylbenzene-acetamide
320	N-[4-[(6,7-dihydro-5H-pyrrolo [1,2-a][1,5]benzodiazepin-5-yl) carbonyl]phenyl]-2-methyl-3-thiopheneacetamide

Example 321

5,6-Dihydro-4H-[1,2,4]triazolo[4,3-a][1,5]benzodiazepine

A mixture of 7.0 g of 5,6-dihydro-4H-[1,2,4]-triazolo-[4,3-a][1,5]benzodiazepin-5-one in 25 ml of tetrahydrofuran is added 9 ml of 10 M borane-dimethylsulfide in tetrahydrofuran. The mixture is refluxed for 6 hours, cooled to room temperature and 25 ml of methanol added dropwise. The volatiles are removed under vacuum and to the residue is added 100 ml

of 2N sodium hydroxide. The mixture is refluxed for 5 hours, chilled and extracted with dichloromethane. The extract is washed with 2N citric acid, water and dried (Na_2SO_4). The solvent is removed under vacuum to give a solid. The solid is purified by chromatography on silica gel to give the desired product.

Example 322

N-[4-(4H-[1,2,4]triazolo[4,3-a][1,5]benzodiazepin-6(5H)-ylcarbonyl)phenyl]-2-methylbenzamide

To a mixture of 5 mmol of 5,6-dihydro-4H-[1,2,4]triazolo[4,3-a][1,5]benzodiazepine in 20 ml of dichloromethane is added 5.5 mmol of 4-[(2-methylbenzoyl)amino]benzoyl chloride and then 7.5 mmol of triethylamine. The mixture is stirred at room temperature for 8 hours and then washed with water, aqueous $NaHCO_3$ and brine. The solution is dried (Na_2SO_4) and the solvent removed in vacuo to give a solid. The solid is purified by chromatography on silica gel with ethyl acetate-hexane as solvent to give the desired product as a glass.

Example 323

5,6-Dihydro-6-(4-nitrobenzoyl)-4H-[1,2,4]triazolo-[4,3-a][1,5]benzodiazepine

To a mixture of 3 mmol of 5,6-dihydro-4H-[1,2,4]-triazolo[4,3-a][1,5]benzodiazepine in 10 ml of dichloromethane under argon is added 5 mmol of triethylamine. To the mixture is added dropwise 3.3 mmol of 4-nitrobenzoyl chloride in 3 ml of dichloromethane. The mixture is stirred at room temperature 3 hours and then washed with water, aqueous $NaHCO_3$ and brine. The organic layer is dried (Na_2SO_4) and the solvent removed under vacuum. The residue is purified by chromatography on silica gel to give the desired product as a solid.

Example 324

5,6-Dihydro-6-(aminobenzoyl)-4H-[1,2,4]triazolo-[4,3-a][1,4]benzodiazepine

To a mixture of 5 mmol of 5,6-dihydro-6-(4-nitrobenzoyl)-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine in 25 ml of ethanol is added 0.3 g of 10% Pd/C and 15 mmol of hydrazine. The mixture is refluxed for 3 hours, cooled and filtered through diatomaceous earth. The filtrate is concentrated in vacuo and the residue purified by chromatography on silica gel to give the desired product as a solid.

Table XII

The following Examples are prepared using the conditions of Example 322 with the appropriately substituted aroyl chloride

Example No.	Compound
325	N-[4-(4H-[1,2,4]triazolo[4,3-a][1,5] benzodiazepin-6(5H)-ylcarbonyl)phenyl] 2-chlorobenzamide
326	N-[4-(4H-[1,2,4]triazolo[4,3-a][1,5] benzodiazepin-6(5H)-ylcarbonyl)phenyl] 2,5-dichlorobenzamide
327	N-[4-(4H-[1,2,4]triazolo[4,3-a][1,5] benzodiazepin-6(5H)-ylcarbonyl)phenyl] 2,4-dichlorobenzamide
328	N-[4-(4H-[1,2,4]triazolo[4,3-a][1,5] benzodiazepin-6(5H)-ylcarbonyl)phenyl] 2,3-difluorobenzamide

Table XII

Example No.	Compound
329	N-[4-(4H-[1,2,4]triazolo[4,3-a][1,5] benzodiazepin-6(5H)-ylcarbonyl)phenyl] 2-chloro-4-methylbenzamide
330	N-[4-(4H-[1,2,4]triazolo[4,3-a][1,5] benzodiazepin-6(5H)-ylcarbonyl)phenyl] 2-methyl-4-chlorobenzamide
331	N-[4-(4H-[1,2,4]triazolo[4,3-a][1,5] benzodiazepin-6(5H)-ylcarbonyl)phenyl] 2,4-dimethylbenzamide
332	N-[4-(4H-[1,2,4]triazolo[4,3-a][1,5] benzodiazepin-6(5H)-ylcarbonyl)phenyl] 2,3-dimethylbenzamide
333	N-[4-(4H-[1,2,4]triazolo[4,3-a][1,5] benzodiazepin-6(5H)-ylcarbonyl)phenyl] 2-methoxybenzamide
334	N-[4-(4H-[1,2,4]triazolo[4,3-a][1,5] benzodiazepin-6(5H)-ylcarbonyl)phenyl] 2-trifluoromethoxybenzamide
335	N-[4-(4H-[1,2,4]triazolo[4,3-a][1,5] benzodiazepin-6(5H)-ylcarbonyl)phenyl] 2,3-dichlorobenzamide
336	N-[4-(4H-[1,2,4]triazolo[4,3-a][1,5] benzodiazepin-6(5H)-ylcarbonyl)phenyl] 2,4-dimethoxybenzamide

Table XII (cont'd)

Example No.	Compound
337	N-[4-(4H-[1,2,4]triazolo[4,3-a][1,5] benzodiazepin-6(5H)-ylcarbonyl)phenyl] 2,6-dimethoxybenzamide
338	N-[4-(4H-[1,2,4]triazolo[4,3-a][1,5] benzodiazepin-6(5H)-ylcarbonyl)phenyl] 2-methoxy-4-chlorobenzamide
339	N-[4-(4H-[1,2,4]triazolo[4,3-a][1,5] benzodiazepin-6(5H)-ylcarbonyl)phenyl] 2-trifluoromethylbenzamide
340	N-[4-(4H-[1,2,4]triazolo[4,3-a][1,5] benzodiazepin-6(5H)-ylcarbonyl)phenyl] 2,6-dichlorobenzamide
341	N-[4-(4H-[1,2,4]triazolo[4,3-a][1,5] benzodiazepin-6(5H)-ylcarbonyl)phenyl] 2,6-dimethylbenzamide
342	N-[4-(4H-[1,2,4]triazolo[4,3-a][1,5] benzodiazepin-6(5H)-ylcarbonyl)phenyl] 2-methylthiobenzamide
343	N-[4-(4H-[1,2,4]triazolo[4,3-a][1,5] benzodiazepin-6(5H)-ylcarbonyl)phenyl] 2-methyl-3-thiophenecarboxamide
344	N-[4-(4H-[1,2,4]triazolo[4,3-a][1,5] benzodiazepin-6(5H)-ylcarbonyl)phenyl] 3-methyl-2-thiophenecarboxamide

Table XII (cont'd)

Example No.	Compound
345	N-[4-(4H-[1,2,4]triazolo[4,3-a][1,5] benzodiazepin-6(5H)-ylcarbonyl)phenyl] 2-methyl-3-furanecarboxamide
346	N-[4-(4H-[1,2,4]triazolo[4,3-a][1,5] benzodiazepin-6(5H)-ylcarbonyl)phenyl] 2-methyl-3-furanecarboxamide
347	N-[4-(4H-[1,2,4]triazolo[4,3-a][1,5] benzodiazepin-6(5H)-ylcarbonyl)phenyl] 3-methyl-2-furanecarboxamide
348	N-[4-(4H-[1,2,4]triazolo[4,3-a][1,5] benzodiazepin-6(5H)-ylcarbonyl)phenyl] 2-methoxybenzeneacetamide
349	N-[4-(4H-[1,2,4]triazolo[4,3-a][1,5] benzodiazepin-6(5H)-ylcarbonyl)phenyl] 2-methylbenzeneacetamide
350	N-[4-(4H-[1,2,4]triazolo[4,3-a][1,5] benzodiazepin-6(5H)-ylcarbonyl)phenyl] 2-chlorobenzeneacetamide
351	N-[4-(4H-[1,2,4]triazolo[4,3-a][1,5] benzodiazepin-6(5H)-ylcarbonyl)phenyl] 2-methyl-3-thiopheneacetamide

Example 352

N-[4-(1-Methyl-4H-[1,2,4]triazolo[4,3-a][1,5] benzodiazepin-6(5H)-ylcarbonyl)phenyl]-2-methyl benzamide

To a mixture of 5 mmol of 5,6-dihydro-1-methyl-4H-[1,2,4]triazolo[4,3-a][1,5]benzodiazepine in 20 ml of dichloromethane is added 5.5 mmol of

4-[(2-methylbenzoyl)amino]benzoyl chloride and 7.5 mmol of triethylamine. The mixture is stirred at room temperature for 8 hours and then washed with water, aqueous $NaHCO_3$ and brine. The organic layer is dried (Na_2SO_4) and the solvent removed in vacuo to give a solid. The solid is purified by chromatography on silica gel with ethyl acetate-hexane as solvent to give the desired product.

Example 353

N-[4-(1-Methyl-4H-[1,2,4]triazolo[4,3-a][1,5]benzodiazepin-6(5H)-ylcarbonyl)phenyl]-2,4 dichlorobenzamide

To a mixture of 5 mmol of 5,6-dihydro-1-methyl-4H-[1,2,4]triazolo[4,3-a][1,5]benzodiazepine in 20 ml of dichloromethane is added 5.5 mmol of 4-[(2,4-dichlorobenzoyl)amino]benzoyl chloride and 7.5 mmol of triethylamine. The mixture is stirred at room temperature for 8 hours and then washed with water, aqueous $NaHCO_3$ and brine. The organic layer is dried (Na_2SO_4) and the solvent removed in vacuo to give a solid. The solid is purified by chromatography on silica gel to give the desired product as a solid.

Example 354

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11)-ylcarbonyl)phenyl]-3-cyclohexenecarboxamide

A mixture of 0.50 g of 10,11-dihydro-10(4-aminobenzoyl-5H-pyrrolo[2,1-c][1,4]benzodiazepine, 0.286 g of 3-cyclohexenecarbonyl chloride and 346 µl of triethylamine in 5 ml of dichloromethane is stirred at room temperature 16 hours. The mixture is diluted with 50 ml of dichloromethane and the solution washed with 20 ml of water, 2N citric acid, 1N $NaHCO_3$, brine and dried (Na_2SO_4). The solution is filtered through a thin pad of hydrous magnesium silicate and the filtrate evaporated in vacuo. The residue is chromatographed on thick layer silica gel plates to give a solid which is

crystallized from ethyl acetate to give 0.34 g of crystals, m.p. 216-218°C.

Example 355

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11) ylcarbonyl)phenyl]-5-methyl-2-thiophenecarboxamide

To a solution of 0.318 g of 5-methyl-2-thiophenecarbonyl chloride in 5 ml of dichloromethane cooled to 0° C is added 0.50 g of 10,11-dihydro-10-(4-aminobenzoyl-5H-pyrrolo[2,1-c][1,4]benzodiazepine and 346 µl of triethylamine. The mixture is stirred at room temperature 16 hours and diluted with 50 ml of dichloromethane. The solution is washed with 20 ml each of water, 2N citric acid. 1M $NaHCO_3$, brine and dried (Na_2SO_4). The solution is filtered through a thin pad of hydrous magnesium silicate and the filtrate evaporated in vacuo to give a solid. The solid is crystallized from ethyl acetate to give 0.53 g of crystals, m.p. 235-238°C.

Example 356

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11) ylcarbonyl)phenyl]-cyclohexylacetamide

To a solution of 0.318 g of cyclohexylacetyl chloride in 5 ml of dichloromethane cooled to 0° C is added 0.50 g of 10,11-dihydro-10-(4-aminobenzoyl-5H-pyrrolo[2,1-c][1,4]benzodiazepine and 346 µl of triethylamine. The mixture is stirred at room temperature 16 hours and diluted with 50 ml of dichloromethane. The solution is washed with 20 ml each of water, 2N citric acid. 1M $NaHCO_3$, brine and dried (Na_2SO_4). The solution is filtered through a thin pad of hydrous magnesium silicate and the filtrate evaporated in vacuo to give a solid. The solid is crystallized from ethyl acetate to give 0.52 g of crystals, m.p. 231-234°C.

Example 357

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11) ylcarbonyl)phenyl]-2-fluorobenzeneacetamide

To a solution of 0.342 g of 2-fluorophenylacetyl chloride in 5 ml of dichloromethane cooled to 0°C is added 0.50 g of 10,11-dihydro-10-(4-aminobenzoyl-5H-pyrrolo[2,1-c][1,4]benzodiazepine and 346 µl of triethylamine. The mixture is stirred at room temperature 16 hours and diluted with 50 ml of dichloromethane. The solution is washed with 20 ml each of water, 2N citric acid. 1M $NaHCO_3$, brine and dried (Na_2SO_4). The solution is filtered through a thin pad of hydrous magnesium silicate and the filtrate evaporated in vacuo to give a solid. The solid is crystallized from ethyl acetate to give 0.43 g of crystals, m.p. 204-207°C.

Example 358

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11) ylcarbonyl)phenyl]-cyclohexanecarboxamide

To a solution of 0.342 g of cyclohexanecarbonyl chloride in 5 ml of dichloromethane cooled to 0° C is added 0.50 g of 10,11-dihydro-10-(4-aminobenzoyl-5H-pyrrolo[2,1-c][1,4]benzodiazepine and 346 µl of triethylamine. The mixture is stirred at room temperature 16 hours and diluted with 50 ml of dichloromethane. The solution is washed with 20 ml each of water, 2N citric acid. 1M $NaHCO_3$, brine and dried (Na_2SO_4). The solution is filtered through a thin pad of hydrous magnesium silicate and the filtrate evaporated in vacuo to give a solid. The solid is crystallized from ethyl acetate to give 0.54 g of crystals, m.p. 202-204°C.

Example 359

4-[N-Methyl-N-(2-methylbenzoylamino]benzoyl chloride

A solution of 6.72 g of 4-[N-methyl-N-(2-methylbenzoyl)amino]benzoic acid in 20 ml of thionyl chloride is refluxed for one hour. The volatiles are

removed in vacuo. Toluene is added to the residue and then the toluene removed in vacuo (repeated several times) to give the 7.3 g of product as a brown oil.

Example 360

4-[N-Methyl-N-(2-methylbenzoyl)amino]benzoic acid

A sample of 1.51 g of sodium hydride (60% in oil) is washed with hexane under argon to remove the oil. To the washed sodium hydride is added 5 ml of N,N-dimethylformamide. To this mixture is added dropwise a solution of 8.69 g of ethyl 4-[(2-methylbenzoyl)amino]benzoate in 20 ml of N,N-dimethylformamide. The mixture is stirred at room temperature for 0.5 hour and then 5.23 g of methyl iodide is added. The mixture is stirred at room temperature for 16 hours. The mixture is diluted with water and extracted with dichloromethane. The extract is dried (Na_2SO_4), concentrated to reduce the volume and the solution filtered through a thin pad of hydrous magnesium silicate. The filtrate is concentrated in vacuo to give 11 g of an oil (1:1 mixture of product and N,N-dimethylformamide). The preceding product, ethyl 4-[N-methyl-N-(2-methylbenzoyl)amino]benzoate, (11 g) is dissolved in 30 ml of methanol and 25 ml of 2N NaOH added. The mixture is refluxed for 2 hours and the solvent removed. The residue is extracted with ether (discard) and the remaining residue dissolved in 50 ml of water. The basic solution is acidified with 2N citric acid and the solid filtered off and washed with water. The product is air dried to give 6.72 g of crystals, m.p. 187-190°C.

As described for Example 360 but substituting the appropriate ethyl 4-[(N-aroyl)amino]benzoate, the following compounds are prepared.

Example 361

4-[N-Methyl-N-(2-chlorobenzoyl)amino]benzoic acid

Example 362

4-[N-Methyl-N-(2,5-dichlorobenzoyl)amino]benzoic acid

Example 363

4-[N-Methyl-N-(2,4-dichlorobenzoyl)amino]benzoic acid

Example 364

4-[N-Methyl-N-(2-chloro-4-methylbenzoyl)amino]-benzoic acid

Example 365

4-[N-Methyl-N-(2-methyl-4-chlorobenzoyl)amino]-benzoic acid

Example 366

4-[N-Methyl-N-(2,4-dimethylbenzoyl)amino]benzoic acid

Example 367

4-[N-Methyl-N-(2,3-dimethylbenzoyl)amino]benzoic acid

Example 368

4-[N-Methyl-N-(2-methoxybenzoyl)amino]benzoic acid

Example 369

4-[N-Methyl-N-(2-trifluoromethoxybenzoyl)amino]-benzoic acid

Example 370

4-[N-Methyl-N-(2,4-dimethoxybenzoyl)amino]-benzoic acid

Example 371

4-[N-Methyl-N-(2-methoxy-4-chlorobenzoyl)amino]-benzoic acid

Example 372

4-[N-Methyl-N-(2-methylthiobenzoyl)amino]-benzoic acid

Example 373

4-[N-Methyl-N-(2-methylthiophen-3-ylcarbonyl)amino]-benzoic acid

Example 374

4-[N-Methyl-N-(3-methylthiophene-2-ylcarbonyl)amino]-benzoic acid

Example 375

4-[N-Methyl-N-(2-methylfuran-3-ylcarbonyl)amino]-benzoic acid

Example 376

4-[N-Methyl-N-(3-methylfuran-2-ylcarbonyl)amino]-benzoic acid

Example 377

4-[N-Methyl-N-(phenylacetyl)amino] benzoic acid

Example 378

4-[N-Methyl-N-(2-chlorophenylacetyl)amino] benzoic acid

Example 379

4-[N-Methyl-N-(2-methoxyphenylacetyl)amino]-benzoic acid

Example 380

4-[N-Methyl-N-(2-methylphenylacetyl)amino]-benzoic acid

Example 381

4-[N-Methyl-N-(cyclohexylcarbonyl)amino]-benzoic acid

Example 382

4-[N-Methyl-N-(3-cyclohexenecarbonyl)amino]-benzoic acid

Example 383

4-[N-Methyl-N-(cyclohexylacetyl)amino]-benzoic acid

Example 384

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-N-methyl-2-methylbenzamide

A mixture of 0.27 g of 10,11-dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine, 0.518 g of 4-[N-methyl-N-(2-methylbenzoyl)amino]benzoyl chloride, 0.182 g of triethylamine and 7 ml of tetrahydrofuran is stirred at room temperature for 3 hours. To the mixture is added 0.29 g of 4-[N-methyl-N-(2-methyl-benzoyl) amino]benzoyl chloride and 0.10 g of triethylamine in 2 ml of dichloromethane and the mixture stirred for 2 days. The mixture is poured into water and extracted with dichloromethane. The extract is washed with water, 1N HCl, 1N $NaHCO_3$, brine and

dried (Na_2SO_4). The solution is filtered through a thin pad of hydrous magnesium silicate. The filtrate is evaporated *in vacuo* and the residue crystallized from dichloromethane-hexane to give 0.38 g of crystals, m.p. 168-170°C.

As described for Example 384, but substituting the appropriate aroyl chloride, the following compounds are prepared.

Example 385

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-N-methyl-2-chlorobenzamide

Example 386

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-N-methyl-2,5-dichlorobenzamide

Example 387

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-N-methyl-2-chloro-4-methylbenzamide

Example 388

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-N-methyl-2-methyl-4-chlorobenzamide

Example 389

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-N-methyl-2,4-dimethylbenzamide

Example 390

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-N-methyl-2,3-dimethylbenzamide

Example 391

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-N-methyl-2-methoxybenzamide

Example 392

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-N-methyl-2-trifluoromethoxybenzamide

Example 393

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-N-methyl-2,4-dimethoxybenzamide

Example 394

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-N-methyl-2-methoxy-4-chlorobenzamide

Example 395

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-N-methyl-2-methylthiobenzamide

Example 396

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-N-methyl-2-methyl-3-thiophene-carboxamide

Example 397

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-N-methyl-3-methyl-2-thiophene-carboxamide

Example 398

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-N-methyl-2-methyl-3-furane-carboxamide

Example 399

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-N-methylbenzeneacetamide

Example 400

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-N-methyl-2-chlorobenzeneacetamide

Example 401

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-N-methyl-2-methoxybenzeneacetamide

Example 402

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-N-methyl-2-methylbenzeneacetamide

Example 403

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-N-methyl-2-methyl-3-thiophene-acetamide

Example 404

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-N-methylcyclohexanecarboxamide

Example 405

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-N-methylcyclohexylacetamide

Example 406

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-N-methyl-3-cyclohexenecarboxamide

Example 407

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2-methylphenyl]-2,4-dichlorobenzamide

A mixture of 0.40 g of 10,11-dihydro-10-(3-methyl-4-aminobenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine, 0.40 g of 2,4-dichlorobenzoyl chloride and 0.75 g of diisopropylethylamine in 50 ml of dichloromethane is stirred at room temperature for 16 hours. The mixture is washed with water, dried ($MgSO_4$) and the solution passed through a thin pad of hydrous magnesium silicate. The filtrate is concentrated and hexane added to give crystals. Recrystallization from di-

chloromethane-hexane gives 0.52 g of crystals, m.p. 213-215°C.

Example 408

1-(2-Nitrophenyl)-1H-pyrrole-2-carboxaldehyde

A sample of 4.7 g of sodium hydride (60% in oil) is washed with hexane (under argon). To the sodium hydride is added 200 ml of dry N,N-dimethylformamide and the mixture is chilled to 0°C. To the mixture is added 10.11 g of pyrrole-2-carboxaldehyde in small portions. The mixture is stirred 10 minutes and 15.0 g of 1-fluoro-2-nitrobenzene added dropwise. After the addition, the mixture is stirred at room temperature 16 hours and the mixture concentrated (65°C) under high vacuum. To the residue is added 400 ml of dichloromethane and the mixture washed with 150 ml each of H_2O, brine and dried (Na_2SO_4). The solvent is removed in vacuo to give a yellow solid. Crystallization from ethyl acetate-hexane (9:1) gives 17.0 g of light yellow crystals, m.p. 119°-122°C.

Example 409

4,10-Dihydro-5H-pyrrolo[1,2-a]thieno[3,2-e][1,4]-diazepine

To an ice cooled mixture of 2.1 g of pyrrole-2-carboxylic acid and 3.2 g of methyl 3-aminothiophene-2-carboxylate in 40 ml of dry dichloromethane is added 4 g of N,N-dicyclohexylcarbodiimide. The mixture is stirred at room temperature for 3 hours and filtered. The filter cake is washed with dichloromethane and then extracted twice with 60 ml of acetone. The acetone extract is concentrated to dryness to give 0.8 g of solid, m.p. 214-218°C. To a suspension of the preceding compound (1.19 g) in 20 ml of dry tetrahydrofuran is added 0.2 g of sodium hydride (60% in oil). After the hydrogen evolution, the mixture is stirred and refluxed for 4.5 hours, cooled and poured into ice-water. The precipitated solid is filtered and the

solid triturated with petroleum ether (bp 30-60°C) to give 0.75 g of 4,10-dihydro-4,10-dioxo-5H-pyrrolo-[1,2-a]thieno[3,2-e][1,4]diazepine as a solid, m.p. 280-290°C. The preceding compound (0.362 g) is added to an ice-water cooled solution of 1 M diborane in tetrahydrofuran. The mixture is stirred at room temperature for 65 hours. The solution is concentrated to dryness and ice-water added to the residue. The mixture is acidified with dilute HCl, stirred and then basified with solid $NaHCO_3$. The mixture is filtered to give 0.223 g of a solid (foam) m.p. 80-85°C.

Example 410

10,11-Dihydro-5H-1,2,4-triazolo[3,4-c][1,4]-benzodiazepine

A mixture of 2.2 g of 2-cyanoaniline, 2.0 g of methyl bromoacetate and 1.3 g of potassium carbonate in 12 ml of dry N,N-dimethylformamide is heated at 150-155°C for 40 minutes. The cooled mixture is poured into ice-water and the mixture filtered to give 2 g of methyl [N-(2-cyanophenyl)amino]acetate as a yellow solid, m.p. 70-78°C. The preceding compound (2.0 g) is added to a solution of 0.5 g of sodium methoxide in 50 ml of methanol. The mixture is shaken under an atmosphere of hydrogen with the catalyst Raney-Ni for 19 hours. The mixture is filtered through diatomaceous earth and the filtrate evaporated. Water is added to the residue and the mixture filtered to give 2,3,4,5-tetrahydro-1H-1,4-benzodiazepin-3-one as a yellow solid, m.p. 167-170°C.

A mixture of the preceding compound (1.6 g) and 0.84 g of phosphorus pentasulfide in 10 ml of dry (dried over KOH) pyridine is stirred and heated at 80-85°C for 15 minutes. The mixture is poured into water and stirred for 30 minutes. Filtration gives 1.0 g of 1,2,4,5-tetrahydro-3H-1,4-benzodiazepin-3-thione as yellow solid, m.p. 150-153°C.

The preceding compound (0.5 g) and 0.5 g of N-formylhydrazine in 6 ml of dry n-butanol is refluxed for 16 hours and the solvent removed. The gummy residue is triturated with cold water and the mixture filtered. The solid is triturated with acetone to give 0.19 g of yellow solid, m.p. 232-237°C.

Example 411

4,5-Dihydro-6H-[1,2,4]triazolo[4,3-a][1,5]-benzodiazepine

A mixture of 2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-thione (0.8 g) and 0.80 g of N-formylhydrazine in 8 ml of n-butanol is stirred and refluxed for 18 hours and the solvent removed under vacuum. Ice water is added to the residual solid and the mixture filtered to give 0.312 g of a gray solid, m.p. 162-165°C.

Example 412

4,5-Dihydro-6H-imidazo[1,2-a][1,5]benzodiazepine

A mixture of 30 g of acrylic acid, 33 g of o-phenylenediamine is heated on a steam bath for 1.5 hours and the cooled black mixture triturated with ice-water. The aqueous phase is decanted and ice and aqueous ammonium hydroxide added to the residue. The mixture is extracted with dichloromethane and the extract concentrated to dryness. The residue is triturated with carbon tetrachloride and filtered. The oily solid is triturated with a small amount of ethanol to give 9.7 g of a solid. Trituration of the solid with ethyl acetate gives 2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-one as an impure solid, m.p. 75-107°C.

A mixture of the preceding compound (11.3 g) and 5.9 g of phosphorus pentasulfide in 70 ml of dry pyridine is stirred and heated at approximately 80°C for 20 minutes. The mixture is poured into water and the mixture stirred for 30 minutes. Filtration gives

8.6 g of 2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-thione as a solid, m.p. 154-157°C.

A mixture of the preceding compound (0.70 g), 1.0 g of aminoacetaldehyde dimethyl acetal and 15 mg of 4-methylbenzenesulfonic acid monohydrate in 6 ml of dry n-butanol is refluxed for 4 hours and the solvent removed under vacuum. The residue is heated (refluxed) with 10 ml of 3 N hydrochloric acid for 55 minutes. Ice is added to the cooled mixture and the mixture made basic with solid $NaHCO_3$. The mixture is extracted with dichloromethane and the extract dried (Na_2SO_4). The solvent is removed to give an orange syrup which solidified on standing. The oily solid is triturated with acetone to give a light yellow solid (0.185 g) m.p. 119-122°C.

Example 413

1-(2-Nitrophenyl)-2-pyrroleacetic acid, ethyl ester

To a stirred mixture of 1.88 g of 1-(2-nitrophenyl)pyrrole, 4.80 g of ethyl iodoacetate and 2.22 g of $FeSO_4.7H_2O$ in 40 ml of dimethyl sulfoxide is added dropwise 10 ml of 30% hydrogen peroxide while keeping the reaction mixture at room temperature with a cold water bath. The mixture is stirred at room temperature for one day. An additional 2.4 g of ethyl iodoacetate, 1.1 g of $FeSO_4.7H_2O$ and 5 ml of 30% hydrogen peroxide is added and the mixture stirred at room temperature for 1 day. The mixture is diluted with water and extracted with diethyl ether. The organic extract is washed with water, brine and dried (Na_2SO_4). The solvent is removed and the residue (2.12 g) chromatographed on silica gel with ethyl acetate-hexane (1:4) as solvent to give 0.30 g of product as a brown gum.

Example 414

6,7-Dihydro-5H-pyrrolo[1,2-a][1,5]benzodiazepin-6-one

To a solution of 0.8 mmol of 1-(2-nitrophenyl)-2-pyrroleacetic acid, ethyl ester in 3 ml of

ethanol is added stannus chloride dihydrate ($SnCl_2.2H_2O$) in 2 ml of concentrated hydrochloric acid (with cooling in water bath). The mixture is stirred at room temperature for 5 hours and chilled in an ice bath. To the mixture is added slowly saturated sodium carbonate solution. The solid which precipitates is filtered and the solid washed with water and then extracted with ethyl acetate. The ethyl acetate extract is dried (Na_2SO_4) and the solvent removed to give 0.16 g of solid which is triturated with ether to give 0.11 g of product as an off-white solid.

Example 415

6,7-Dihydro-5H-pyrrolo[1,2-a][1,5]benzodiazepine

To a solution of 0.070 g of 6,7-dihydro-5H-pyrrolo[1,2-a][1,5]benzodiazepin-6-one in 2 ml of tetrahydrofuran is added 0.45 ml of a 2.0 M solution of diborane-dimethylsulfide in tetrahydrofuran. The mixture is refluxed for 3 hours, poured into water and make basic with 2 N NaOH. The tetrahydrofuran is removed under vacuum and the residual aqueous mixture extracted with diethyl ether. The extract is washed with brine, dried (Na_2SO_4) and the solvent removed to give 0.065 g of a colorless oil; one spot by thin layer chromatography (silica gel) with ethyl acetate-hexane (1:2) as solvent (Rf 0.81).

Example 416

10,11-Dihydro-10-(2-chloro-4-aminobenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine

A mixture of 5.0 g of 10,11-dihydro-10-(2-chloronitrobenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine, 15.4 g of stannus chloride and 170 ml of ethanol is heated at 70-80°C for 1 hour. The mixture is chilled (ice bath) and made basic with 1 M $NaHCO_3$ solution (350 ml) and then stirred at room temperature for 1 hour. The mixture is brought to pH 5 with acetic acid and extracted with 500 ml of ethyl acetate and

with 300 ml of ethyl acetate. The combined extract is washed with 250 ml of brine and dried (Na_2SO_4). The solution is filtered through a thin pad of hydrous magnesium silicate and the filter pad washed with ethyl acetate. The filtrate is concentrated to dryness and the residue dissolved in 200 ml of hot chloroform-methanol (1:1) and the solution filtered through a thin pad of hydrous magnesium silicate. The filtrate is concentrated under vacuum to give 4.36 g (after drying under vacuum at 60°C overnight) of product as a white solid. A sample is recrystallized from chloroform-methanol to give white crystals, m.p. 210-212°C.

Example 417

4-[(5-Fluoro-2-methylbenzoyl)amino]benzoic acid

A mixture of 0.60 g of ethyl 4-[(5-fluoro-2-methylbenzoyl)amino]benzoate 0.60 ml of 10 N NaOH, 25 ml of water and 50 ml of absolute ethyl alcohol is heated on a steam bath for 1 hour, cooled and acidified with acetic acid. The resulting solid is filtered and dried in vacuo at 60-80°C to give 0.47 g of the desired product as a solid, m.p. 272-275°C.

The following Examples are prepared using the conditions of Example 417.

Example No.	Compound
418	4-[(3-fluoro-2-methylbenzoyl)amino]-benzoic acid, m.p. 309-311°C
419	4-[(5-fluoro-2-methylbenzoyl)amino]-2-chlorobenzoic acid, m.p. 247-249°C
420	4-[3-fluoro-2-methylbenzoyl)amino]-2-chlorobenzoic acid, m.p. 260-263°C
421	4-[[4-fluoro-3-(trifluoromethyl)]benzoyl]amino]-2-chlorobenzoic acid

Example No.	Compound
422	4-[[2-fluoro-3-(trifluoromethyl)]benzoyl]amino]-2-chlorobenzoic acid
423	4-[(2,5-difluorobenzoyl)amino]-2-chlorobenzoic acid
424	4-[(2,5-dichlorobenzoyl)amino]-2-chlorobenzoic acid
425	4-[(2,3-dimethylbenzoyl)amino]-2-chlorobenzoic acid
426	4-[(2,3-dichlorobenzoyl)amino]-2-chlorobenzoic acid
427	4-[(2,5-dimethylbenzoyl)amino]-2-chlorobenzoic acid
428	4-[2,3-difluorobenzoyl)amino]-2-chlorobenzoic acid

Example 429

4-[(2,4-Dichlorobenzoyl)amino]-2-chlorobenzoic acid

To a stirred mixture of 5.19 g of 2-chloro-4-aminobenzoic acid in 150 ml of methylene chloride is added 7.86 g of N,N-diisopropylethylamine and 12.67 g of 2,4-dichlorobenzylchloride and stirring continued for 18 hours. Water is added to the filtrate and the organic layer dried with Na_2SO_4 and concentrated in vacuo to give 13.68 g of the desired product, m.p. 171-175°C.

The following Examples are prepared using the conditions of Example 429.

Example No.	Compound
430	4-[(2-methylbenzoyl)amino]-2-chlorobenzoic acid, m.p. 196-199°C
431	4-[(2-methylbenzoyl)amino]-3,5-dimethylbenzoic acid, m.p. 286-289°C
432	4-[(2,4-dichlorobenzoyl)amino]-3,5-dimethylbenzoic acid, m.p. 209-212°C
433	4-[(2-methylbenzoyl)amino]-3-chlorobenzoic acid, m.p. 199-202°C
434	4-[(2,5-dichlorobenzoyl)amino]-2-chlorobenzoic acid
435	4-[(3-fluoro-2-methylbenzoyl)amino]-3-chlorobenzoic acid, m.p. 225-227°C
436	4-[(5-fluoro-2-methylbenzoyl)amino]-3-chlorobenzoic acid, m.p. 182-185°C
437	4-[(2,3-dimethylbenzoyl)amino]-3-chlorobenzoic acid
438	4-[(2,3-dichlorobenzoyl)amino]-3-chlorobenzoic acid
439	4-[(2,5-dimethylbenzoyl)amino]-3-chlorobenzoic acid
440	4-[[4-fluoro-2-(trifluoromethyl)benzoyl]amino]-3-chlorobenzoic acid
441	4-[[3-fluorobenzoyl]amino]-2-chlorobenzoic acid, m.p. 249-252°C

Example No.	Compound
442	4-[[2-(trifluoromethyl)benzoyl]amino]-3-chlorobenzoic acid

Example 443

Ethyl 10,11-dihydro-10-(2-chloro-4-nitrobenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine-3-carboxylate

To 25 ml of absolute ethanol is added 0.12 g of sodium metal with stirring followed by 0.68 g of 10,11-dihydro-10-(2-chloro-4-nitrobenzoyl)-[3-(trichloroacetyl)]-5H-pyrrolo[2,1-c][1,4]benzodiazepine.

Stirring is continued for 18 hours. The volatiles are removed in vacuo to a residue which is partitioned between methylene chloride and water. The organic layer is separated, dried with Na_2SO_4 and filtrate heated on a steam bath while hexane is added to give 0.45 g of the desired product as a solid, m.p. 165-166°C.

The following Examples are prepared using the conditions of Example 443.

Example No.	Compound
444	ethyl 10,11-dihydro-10-(3-methyl-4-nitrobenzoyl)-5H-pyrrolo[2,1-c][1,4]-benzodiazepine-3-carboxylate, m.p. 200-202°C
445	ethyl 10,11-dihydro-10-(2-methyl-4-nitrobenzoyl)-5H-pyrrolo[2,1-c][1,4]-benzodiazepine-3-carboxylate
446	ethyl 10,11-dihydro-10-(2-chloro-4-nitrobenzoyl)-5H-pyrrolo[2,1-c][1,4]-benzodiazepine-3-carboxylate

Example No.	Compound
447	ethyl 10,11-dihydro-10-(3-chloro-4-nitrobenzoyl)-5H-pyrrolo[2,1-c][1,4]-benzodiazepine-3-carboxylate

Example 448

10,11-Dihydro-10-(3-methyl-4-nitrobenzoyl)-[3-trichloroacetyl)]-5H-pyrrolo[2,1-c][1,4]benzodiazepine

To a stirred solution of 3.47 g of 10,11-dihydro-10(4-nitro-3-methylbenzoyl)-5H-pyrrolo[2,1-c]-[1,4]benzodiazepine in 50 ml of methylene chloride is added 3.40 g of trichloroacetic anhydride and stirring continued for 18 hours. Water is added and the separated organic layer washed with saturated sodium bicarbonate, dried with Na_2SO_4 and passed through a short pad of hydrous magnesium silicate. Hexane is added to the filtrate at the boil to give 4.07 g of the desired product as a solid. MASS SPEC (CI) 491(MH^+).

The following Examples are prepared using the conditions of Example 448.

Example No.	Compound
449	10,11-dihydro-10-(4-nitrobenzoyl)-[3-(trichloroacetyl)]-5H-pyrazolo[2,1-c]-[1,4]benzodiazepine, m.p. 122-123°C
450	10,11-dihydro-10-(2-chloro-4-nitro-benzoyl)-[3-(trichloroacetyl)]-5H-pyrrolo[2,1-c][1,4]benzodiazepine, m.p. 149-151°C

Example 451

10,11-Dihydro-10-(4-nitrobenzoyl)-[3-(trifluoro-acetyl)]-5H-pyrrolo[2,1-c][1,4]benzodiazepine

A mixture of 0.50 g of 10,11-dihydro-10(4-nitrobenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine in 10 ml of methylene chloride is cooled in an ice bath

and 2.0 g of trifluoroacetic anhydride added. The bath is removed and the reactants stirred for 18 hrs, partitioned with saturated sodium bicarbonate and the separated organic layer dried with Na_2SO_4 then passed through a short pad of hydrous magnesium silicate. The filtrate is heated at the boil while hexane is added to give 0.40 g of the desired product, m.p. 169-170°C.

The following Examples are prepared using the conditions of Example 451.

Example No.	Compound
452	10,11-dihydro-10-(2-chloro-4-nitrobenzoyl)[3-(trifluoroacetyl)]-5H-pyrrolo[2,1-c][1,4]benzodiazepine, m.p. 151-153°C
453	10,11-dihydro-10-(3-chloro-4-nitrobenzoyl)[3-(trifluoroacetyl)]-5H-pyrrolo[2,1-c][1,4]benzodiazepine
454	10,11-dihydro-10-(2-methyl-4-nitrobenzoyl)[3-(trifluoroacetyl)]-5H-pyrrolo[2,1-c][1,4]benzodiazepine

Example 455

10,11-Dihydro-10-(3-methoxy-4-nitrobenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine

A mixture of 5.0 g of 3-methoxy-4-nitrobenzoic acid and 5.0 g of thionyl chloride is heated under argon for 1 hour. The volatiles are removed *in vacuo* to give 2.85 g of a 3-methoxy-4-nitrobenzoyl chloride as a residue which is dissolved in 50 ml of methylene chloride. To the preceding solution is added with stirring 1.75 g of N,N-diisopropylethylamine followed by 1.84 g of 10,11-dihydro-5H-pyrrolo[2,1-c]-[1,4]benzodiazepine. The reaction mixture is stirred under argon for 18 hours and diluted with saturated

sodium bicarbonate. The organic layer is dried with Na_2SO_4 and passed through a short pad of hydrous magnesium silicate. While boiling, hexane is added to the filtrate to give, upon cooling, 3.39 g of the desired product as a solid, m.p. 191-192°C.

The following Examples are prepared using the conditions of Example 455.

Example No.	Compound
456	10,11-dihydro-10-(2-methoxy-4-nitrobenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine
457	10,11-dihydro-10-(2-methyl-4-nitrobenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine
458	10,11-dihydro-10-(3-methoxy-6-chloro-4-nitrobenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine
459	10,11-dihydro-10-(3-methoxy-6-methyl-4-nitrobenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine

Example 460

10,11-Dihydro-10-(4-amino-3-methoxybenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine

A mixture of 3.24 g of 10,11-dihydro-10-(4-nitro-3-methoxybenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine, 0.35 g of 10% Pd/c and 0.60 g of anhydrous hydrazine in 100 ml of absolute ethyl alcohol and heated on a steam bath for 1 hour. The hot reaction mixture is filtered through diatomaceous earth and the filtrate evaporated *in vacuo* to a residue which is partitioned between methylene chloride and water. The organic layer is dried with Na_2SO_4 and passed through a

short pad of hydrous magnesium silicate. Hexane is added to the filtrate while heating on a steam bath to give 2 g of crystals, m.p. 184-185°C.

The following Examples are prepared using the conditions of Example 460.

Example No.	Compound
461	10,11-dihydro-10-(4-amino-2-chlorobenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine, m.p. 197-199°C
462	10,11-dihydro-10-(4-aminobenzoyl)[3-(trifluoroacetyl)]-5H-pyrrolo[2,1-c]-[1,4]benzodiazepine, m.p. 200-206°C
463	ethyl 10,11-dihydro-10-(4-amino-3-methylbenzoyl)-5H-pyrrolo[2,1-c]-[1,4]benzodiazepine-3-carboxylate, m.p. 210-211°C
464	ethyl 10,11-dihydro-10-(4-aminobenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine-3-carboxylate, m.p. 174-175°C

Example 465

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-5-fluoro-2-methylbenzamide

To a stirred solution of 500 mg of 10,11-dihydro-10-(4-aminobenzoyl)-5H-pyrrolo[2,1-c][1,4]-benzodiazepine in 3 ml of methylene chloride, cooled to 0°C, under argon, is added 346 µl of triethylamine followed by the addition of 340 mg of 2-methyl-5-fluorobenzoyl chloride in 2 ml of methylene chloride. The cooling bath is removed and stirring continued for 18 hours. After cooling to 0°C, an additional 342 mg of 2-methyl-5-fluorobenzoyl chloride in 2 ml of methylene chloride is added. The cooling bath is

removed and stirring continued for 18 hours. The volatiles are removed in vacuo to a residue which is dissolved in 50 ml of methylene chloride and washed with 20 ml each of water, 2 N citric acid, 1 M sodium bicarbonate and brine. The organic layer is dried over Na_2SO_4 and passed through a pad of hydrous magnesium silicate. The filtrate is evaporated in vacuo to a residue which is crystallized from ethyl acetate-hexane to give 295 mg of the desired product as a white solid, m.p. 170-180°C.

The following Examples are prepared using the conditions of Example 465 with the appropriately substituted aroyl chloride.

Example No.	Compound
466	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-3-fluoro-2-methylbenzamide, m.p. 194-208°C
467	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2,3-dimethylbenzamide, m.p. 168-170°C
468	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2,3-dichlorobenzamide, m.p. 219-222°C
469	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2,6-dichlorobenzamide, m.p. 174-182°C
470	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl-3-chlorophenyl]-2-methylbenzamide, m.p. 190-195°C
471	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl-3-chlorophenyl]-2,4-dichlorobenzamide, m.p. 144-160°C

Example No.	Compound
472	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl-2,6-dimethyl phenyl]-2-methylbenzamide, amorphous solid
473	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl-2,6-dimethyl phenyl]-2,4-dichlorobenzamide, amorphous solid
474	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-3-(trifluoromethyl)benzamide, amorphous solid
475	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2-chlorophenyl]-3-methylthiophene-2-carboxamide
476	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-3-chlorothiophene-2-carboxamide, solid; MASS SPEC (CI): 448(M+H)
477	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2-methoxyphenyl]-2-methylbenzamide, m.p. 184-186°C

Example No.	Compound
478	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2-methoxyphenyl]-2,4-dichlorobenzamide, m.p. 192-194°C
479	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2-methoxyphenyl]-3-fluoro-2-methylbenzamide m.p. 203-204°C
480	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2-chloro-5-nitrobenzamide, m.p. 110-160°C (amorphous solid)
267	N-(5H-pyrrolo[1,2-a]thieno[3,2-e][1,4]-diazepin-4(10H)-ylcarbonyl)phenyl]-2-methylbenzamide, m.p. 162-188°C (amorphous solid)
274	N-[4-(5H-pyrrolo[1,2-a]thieno[3,2-e]-[1,4]-diazepin-4(10H)-ylcarbonyl)-phenyl]-2,4-dichlorobenzamide, m.p. 105-190°C

Example 481

N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-3-chlorophenyl]-3-fluoro-2-methylbenzamide

To a solution of 1.50 g of 10,11-dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine in 25 ml of methylene chloride is added 1.23 g of N,N-diisopropylethylamine. While cooling in an ice bath, a solution of 3.08 g of [4-[(2-methyl-5-fluorobenzoyl)amino]-2-chlorobenzoyl chloride in 50 ml of methylene chloride is added. The

reaction mixture becomes homogeneous and is stirred at room temperature for 18 hours. Water is added and the separated organic layer washed with saturated sodium bicarbonate, dried with Na_2SO_4 and passed through a short pad of hydrous magnesium silicate two times. The methylene chloride is removed in vacuo to give 3.81 g of a glass. A sample is crystallized from ethyl acetate to give crystalline solid, m.p. 200-205°C.

Example 482

N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-3-chlorophenyl]-5-fluoro-2-methyl-benzamide

To a solution of 1.84 g of 10,11-dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine in 25 ml of methylene chloride is added 1.30 g of N,N-diisopropylethylamine. While cooling in an ice bath, a solution of 3.45 g of [4-[(2-methyl-5-fluorobenzoyl)amino]-2-chlorobenzoyl chloride in 50 ml of methylene chloride is added. The reaction mixture becomes homogeneous after 5 minutes and is stirred at room temperature for 18 hours. Water is added and the separated organic layer washed with saturated sodium bicarbonate, dried with Na_2SO_4 and passed through a short pad of hydrous magnesium silicate. The methylene chloride is removed in vacuo to give 4.60 g of the desired product as a glass. A sample is crystallized from ethyl acetate to give crystalline solid, m.p. 191-195°C.

Example 483

4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)benzoic acid

A solution of 0.92 g of 10,11-dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine, 1.19 g of monomethyl terephthaloyl chloride in 20 ml of pyridine is refluxed for 2 hours. The mixture is chilled and 1 N HCl added until the pH is 5. The mixture is filtered and washed with water to give 1.53 g of solid. Re-

crystallization from dichloromethane-hexane gives crystals, m.p. 186-188°C of methyl 4-(5H-pyrrolo-[2,1-c][1,4]benzodiazepin-10(11H)-yl-carbonyl)benzoate.

A mixture of 1.83 g of the preceding compound, 8 ml of 2 N NaOH and 14 ml of methanol is refluxed for 0.5 hour and then concentrated under vacuum. The residue is extracted with ether and the aqueous layer acifidied with 2 N citric acid. The mixture is filtered and the solid washed with water and dried (60°C under vacuum) to give 1.61 g of crystals, m.p. 210-214°C.

Example 484

N-(2-Methylphenyl)-4-(5H-pyrrolo[2,1-c][1,4]-benzodiazepin-10(11H)-ylcarbonyl)benzamide

A mixture of 0.332 g of 4-(5H-pyrrolo[2,1-c]-[1,4]benzodiazepin-10(11H)-ylcarbonyl)benzoic acid, 0.111 g of triethylamine, 0.107 g of o-toluidine, and 0.15 ml of diethylphosphoryl cyanide in 20 ml of dichloromethane is heated on a steam bath overnight. The mixture is washed with water, 1 M $NaHCO_3$, 1 N HCl, brine and dried (Na_2SO_4). The dichloromethane solution is filtered through a thin pad of hydrous magnesium silicate and the filtrate concentrated to dryness. The residue is crystallized from dichloromethane-hexane to give 0.23 g of white crystals, m.p. 228-231°C.

Example 485

N-(2,3-Dimethylphenyl)-4-(5H-pyrrolo[2,1-c][1,4]-benzodiazepin-10(11H)-ylcarbonyl)benzamide

A mixture of 0.332 g of 4-(5H-pyrrolo[2,1-c]-[1,4]benzodiazepin-10(11H)-ylcarbonyl)benzoic acid, 0.222 g of triethylamine, 0.157 g of 2,3-dimethylaniline hydrochloride, 0.15 ml of diethyl-phosphoryl cyanide in 20 ml of dichloromethane is heated on a steam bath for 3 hours. The mixture is washed with H_2O, 1 M $NaHCO_3$, H_2O, 1 N HCl, brine and

dried (Na_2SO_4). The solution is filtered through a thin pad of hydrous magnesium silicate and the filter cake washed with dichloromethane. The filtrate is concentrated to dryness under vacuum and the residue crystallized from dichloromethane-hexane to give 0.11 g of crystals, m.p. 239-240°C.

Example 486

N-[4-[(4,5-Dihydro-6H-[1,2,4]triazolo[4,3-a][1,5]-benzodiazepin-6-yl)carbonyl]phenyl]-2-methylbenzoate

A mixture of 0.246 g of [4-(2-methylbenzoyl)-amino]benzoyl chloride, 0.14 g of 4,5-dihydro-6H-[1,2,4]triazolo[4,3-a][1,5]benzodiazepine and 2 ml of pyridine is heated on a steam bath for 4.5 hours and heated (oil bath) at 110°C overnight. The mixture is chilled and poured into water. The mixture is neutralized with 1 N HCl and filtered. The solid is washed with dichloromethane and the dichloromethane filtrate evaporated under vacuum to give 0.151 g of product, MASS SPEC (FAB) 424.2(M+H).

Example 487

N-[4-(Pyrrolo[1,2-a]quinoxalin-5(4H)-ylcarbonyl)-phenyl]-2,3-dichlorobenzamide

As described for Example 157, 0.47 g of 4,5-dihydro-5-(4-aminobenzoyl)pyrrolo[1,2-a]quinoxaline, 346 µl of triethylamine and 5 ml of dichloromethane are chilled (ice bath) and 0.415 g of 2,3-dichlorobenzoyl chloride in 2 ml of dichloromethane added. After stirring overnight, an additional 346 µl of triethylamine is added and an additional 0.415 g of 2,3-dichlorobenzoyl chloride added. The mixture is stirred for 2 hours, diluted with 50 ml of dichloromethane and the solution washed with 20 ml each of H_2O, 2 N citric acid, 1 M $NaHCO_3$ and brine. The organic layer is dried (Na_2SO_4) and filtered through a thin pad of hydrous magnesium silicate and the filtrate concentrated to dryness. The residue is chromatographed on thick layer

silica gel plates with ethyl acetate-hexane (1:1) as solvent to give 0.100 g of white solid, m.p. 230-240°C.

Example 488

10-[4-[[(2-Chlorophenyl)sulfonyl]amino]benzoyl]-10,11-dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine

To a solution of 0.418 g of 2-chlorobenzenesulfonyl chloride in 5 ml of dichloromethane, cooled to 0°C is added 0.50 g of 10,11-dihydro-10-(4-aminobenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine and 0.346 µl of triethylamine. The mixture is stirred at room temperature overnight and diluted with 50 ml of dichloromethane. The mixture is washed with 20 ml each of H_2O, 2 N citric acid, 1 M $NaHCO_3$, brine and dried (Na_2SO_4). The solution is filtered through a thin pad of hydrous magnesium silicate and the filtrate concentrated to dryness. The residue is chromatographed on thick layer silica gel plates (4) with the solvent ethyl acetate-hexane (1:1) to give a solid. Crystallization from ethyl acetate gives 0.165 g of white crystals, m.p. 206-210°C.

Example 489

Methyl 4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)benzoate

To a cooled solution of 0.50 g of 10,11-dihydro-10-(4-aminobenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine and 346 µl of triethylamine in 5 ml of dichloromethane is added 0.394 g of mono methyl terephthaloyl chloride. The mixture is stirred overnight under argon and diluted with 50 ml of dichloromethane. The mixture is washed with 20 ml each of H_2O, 2 N citric acid, 1 M $NaHCO_3$, brine and dried (Na_2SO_4). The solution is filtered through a thin pad of hydrous magnesium silicate and the filter cake washed with dichloromethane. The filtrate is concentrated to dryness and the residue crystallized from ethyl acetate to give 0.50 g of white crystals, m.p. 224-228°C.

Example 490

N-[(Dimethylamino)methyl]-N-[4-(5H-pyrrolo[2,1-c]-[1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2,4-dichlorobenzamide

To a suspension under argon of 0.072 g of sodium hydride (60% in oil) in 10 ml of tetrahydrofuran is added 0.71 g of N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2,4-dichlorobenzamide and the mixture stirred at room temperature for 1 hour. To the mixture is added N,N-dimethylmethyleneammonium iodide and the mixture stirred 20 hours. The mixture is diluted with diethyl ether (30 ml), filtered and the filtrate concentrated under vacuum. The residue is triturated with hexane to give 0.76 g of white solid, m.p. 126-129°C.

Example 491

10-[4-[(Diphenylphosphinyl)amino]benzoyl]-10,11-dihydro-5H-pyrrolo-[2,1-c][1,4]benzodiazepine

A mixture of 0.10 g of 10,11-dihydro-10-(4-aminobenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine 0.060 g of triethylamine and 0.12 g of diphenylphosphinyl chloride in 2 ml of dichloromethane is stirred at room temperature for 2 hours and then 1 N NaOH is added. The mixture is extracted with ethyl acetate and the extract washed with brine and dried (Na_2SO_4). The solvent is removed and the residue triturated with ether-hexane to give 0.16 g of a white solid.

Example 492

10-[4-[Diphenoxyphosphinyl)amino]benzoyl]-10,11-dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine

To a solution of 0.10 g of 10,11-dihydro-10-(4-aminobenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine and 0.060 g of triethylamine in 2 ml of dichloromethane is added 0.14 g of diphenoxyphosphinyl chloride. The mixture is stirred at room temperature for 2 hours and

1 N NaOH added. The mixture is extracted with ethyl acetate and the extract washed with brine and dried (Na_2SO_4). The solvent is removed to give a solid. Trituration with ether-hexane gives 0.20 g of product as a white solid.

Example 493

10-[4-[[(2,5-Dichlorophenyl)sulfonyl]amino]benzoyl]-10,11-dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine

A mixture of 0.10 g of 10,11-dihydro-10-(4-aminobenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine, 0.050 g of triethylamine and 0.083 g of 2,5-dichlorobenzenesulfonyl chloride in 2 ml of dichloromethane is stirred at room temperature for 1 hour and then 4 mg of 4-(N,N-dimethylamino)pyridine is added. After another hour, 93 mg of 2,5-dichlorobenzenesulfonyl chloride is added along with 50 mg of triethylamine. The mixture is stirred at room temperature for 2 days and 1 N NaOH added. The mixture is extracted with ethyl acetate and the extract washed with 50% ammonium chloride solution, brine and dried (Na_2SO_4). The solvent is removed to give 0.30 g of solid. Trituration with ether-hexane gives 0.26 g of solid. This solid is dissolved in a mixture of 5 ml of tetrahydrofuran, 1 ml of methanol, 1 ml of 1 N NaOH and the mixture stirred for 18 hours at room temperature. The organic solvents are removed and the mixture extracted with ether acetate. The extract is washed with $NaHCO_3$, brine and dried (Na_2SO_4). The solvent is removed and the residue (0.16 g) triturated with ether to give 0.14 g of yellow solid.

Example 494

10-[4-[[(Phenylmethyl)sulfonyl]amino]benzoyl]-10,11-dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine

To a solution of 0.10 g of 10,11-dihydro-10-(4-aminobenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine and 0.060 g of triethylamine in 2 ml of dichloromethane is added 0.10 g of α-toluenesulfonyl chloride.

The mixture is stirred at room temperature for 2 hours and 1 N NaOH is added. The mixture is extracted with ethyl acetate and the extract washed with brine and dried (Na_2SO_4). The solvent is removed and the residue (0.20 g) is chromatographed on silica gel with the solvent ethyl acetate-hexane (3:2) to give 0.080 g of product as a white solid and 0.080 g of 10-[4-[[bis-(phenylmethyl)sulfonyl]amino]benzoyl]10,11-dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine as a white solid. The preceding compound in methanol, 2N NaOH is heated on a steam bath, the solvent removed and the basic aqueous residue extracted with ethyl acetate to give an additional amount of the product.

Example 495

Ethyl 4-[(2-methylbenzoyl)amino]-3-chlorobenzoate

A mixture of 8.26 g of ethyl 4-aminobenzoate, 8.26 g of N-chlorosuccinimide in 50 ml of dichloromethane is refluxed overnight. The mixture is washed with saturated $NaHCO_3$ solution and dried (Na_2SO_4). The solution is passed through a thin pad of hydrous magnesium silicate and the filter cake washed with dichloromethane. The filtrate is concentrated and hexane added. Chilling gives 7.38 g of ethyl 3-chloro-4-aminobenzoate, m.p. 82-83°C.

To the preceding compound (3.66 g), 3.0 g of diisopropylethylamine in 50 ml of dichloromethane is added 3.55 g of 2-methylbenzoyl chloride in 10 ml of dichloromethane. The mixture is stirred at room temperature overnight, washed with H_2O, $NaHCO_3$ and dried (Na_2SO_4). The solution is passed through a thin pad of hydrous magnesium silicate and the filter cake washed with dichloromethane. The filtrate is concentrated and diluted with hexane. Chilling gives 4.71 g of the product as crystals, 129-130°C.

The following Examples are prepared using the conditions of Example 495.

Example No.	Compound
496	Ethyl 4-[(2-chlorobenzoyl)amino]-3-chlorobenzoate
497	Ethyl 4-[(2,5-dichlorobenzoyl)amino]-3-chlorobenzoate
498	Ethyl 4-[(2,4-dichlorobenzoyl)amino]-3-chlorobenzoate
499	Ethyl 4-[(3,5-dichlorobenzoyl)amino]-3-chlorobenzoate
500	Ethyl 4-[(2-methyl-4-chlorobenzoyl)-amino]-3-chlorobenzoate
501	Ethyl 4-[(2,3-dimethylbenzoyl)amino]-3-chlorobenzoate
502	Ethyl 4-[(2-methoxybenzoyl)amino]-3-chlorobenzoate
503	Ethyl 4-[(2-(trifluoromethoxy)benzoyl]-amino]-3-chlorobenzoate
504	Ethyl 4-[(2-methoxy-4-chlorobenzoyl)-amino]-3-chlorobenzoate
505	Ethyl 4-[[2-(methylthio)benzoyl]amino]-3-chlorobenzoate
506	Ethyl 4-[(2-methylbenzeneacetyl]amino]-3-chlorobenzoate

Example No.	Compound
507	Ethyl 4-[[4-fluoro-2-(trifluoromethyl)-benzoyl]amino]-3-chlorobenzoate
508	Ethyl 4-[[4-fluoro-3-(trifluoromethyl)-benzoyl]amino]-3-chlorobenzoate
509	Ethyl 4-[[2-fluoro-3-(trifluoromethyl)-benzoyl]amino]-3-chlorobenzoate
510	Ethyl 4-[(3-fluoro-2-methylbenzoyl)-amino]-3-chlorobenzoate
511	Ethyl 4-[(2,3-dichlorobenzoyl)amino]-3-chlorobenzoate
512	Ethyl 4-[(4-fluoro-2-methylbenzoyl)-amino]-3-chlorobenzoate
513	Ethyl 4-[(5-fluoro-2-methylbenzoyl)-amino]-3-chlorobenzoate
514	Ethyl 4-[[2-fluoro-5-(trifluoromethyl)-benzoyl]amino]-3-chlorobenzoate
515	Ethyl 4-[[2-(trifluoromethyl)benzoyl]-amino]-3-chlorobenzoate
516	Ethyl 4-[[3-(trifluoromethyl)benzoyl]-amino]-3-chlorobenzoate

Example 517

N-[4-(4H-Pyrazolo[5,1-c][1,4]benzodiazepin-5(10H)-ylcarbonyl)phenyl]-3-fluoro-2-methylbenzamide

A solution of 2.87 g of 3-fluoro-2-methylbenzoic acid in 25 ml of thionyl chloride is refluxed

for 1.75 hour and the excess thionyl chloride removed under vacuum. To the residue is added toluene (several times) and the toluene removed under vacuum after each addition to give 3-fluoro-2-methylbenzoyl chloride.

To a solution of 0.25 g of 5,10-dihydro-5-(4-aminobenzoyl)-4H-pyrazolo[5,1-c][1,4]benzodiazepine and 0.0914 g of triethylamine in 6 ml of dichloromethane under argon is added a solution of 0.156 g of 3-fluoro-2-methylbenzoyl chloride in 1.5 ml of dichloromethane. The mixture is stirred overnight at room temperature and is washed with H_2O and saturated $NaHCO_3$. The organic layer is treated with activated carbon and filtered through magnesium sulfate. The filtrate is evaporated, ethyl acetate added and the solvent removed to give 0.38 g of white crystals, m.p. 245-250°C: Exact mass by mass spectrometry - 441.1720(M+H).

Example 518

N-[4-(4H-Pyrazolo[5,1-c][1,4]benzodiazepin-5(10H)-ylcarbonyl)-3-chlorophenyl]-5-fluoro-2-methylbenzamide

A mixture of 0.185 g of 5,10-dihydro-4H-pyrazolo[5,1-c][1,4]benzodiazepine, 0.391 g of 4-[(5-fluoro-2-methylbenzoyl)amino]-2-chlorobenzoyl chloride and 0.158 g of diisopropylethylamine in 10 ml of dichloromethane is stirred at room temperature overnight. The mixture is washed with H_2O, 1 N HCl, H_2O, 1 M $NaHCO_3$, brine and dried (Na_2SO_4). The solution is passed through a thin pad of hydrous magnesium silicate and the filter cake washed with dichloromethane. The filtrate is again passed through a thin pad of hydrous magnesium silicate. The filtrate is concentrated and the solid crystallized from ethyl acetate to give crystals, m.p. 137-140°C.

Example 519

N-[4-(4H-Pyrazolo[5,1-c][1,4]benzodiazepin-5(10H)-ylcarbonyl)-3-chlorophenyl]-2-methylbenzamide

As described for Example 518, a mixture of 0.185 g of 5,10-dihydro-4H-pyrazolo[5,1-c][1,4]benzodiazepine, 0.369 g of 4-[(2-methylbenzoyl)amino]-2-chlorobenzoyl chloride and 0.158 g of diisopropylethylamine in 10 ml of dichloromethane is stirred at room temperature to give crystals (from ethyl acetate) m.p. 241-244°C.

Example 520

N-[4-(4H-Pyrazolo[5,1-c][1,4]benzodiazepin-5(10H)-ylcarbonyl)-3-chlorophenyl]-2,4-dichlorobenzamide

As described for Example 518, a mixture of 0.185 g of 5,10-dihydro-4H-pyrazolo[5,1-c][1,4]benzodiazepine, 0.472 g of 4-[(2,4-dichlorobenzoyl)amino]-benzoyl chloride and 0.158 g of diisopropylethylamine in 10 ml of dichloromethane is stirred at room temperature overnight to give the product (0.27 g) as a pale yellow glass; anal. calc'd: C, 58.7; H, 3.4; N, 11.0; Cl, 20.8 Found C, 57.3; H, 3.3; N, 9.5; Cl, 21.3.

Example 521

5,10-Dihydro-5-(4-nitro-2-chlorobenzoyl)-4H)-pyrazolo[5,1-c][1,4]benzodiazepine

To a solution of 1.85 g of 5,10-dihydro-4H-pyrazolo[5,1-c][1,4]benzodiazepine and 1.60 g of diisopropylethylamine in 50 ml of dichloromethane, cooled in an ice bath, is added dropwise a solution of 2.64 g of 4-nitro-2-chlorobenzoyl chloride in 25 ml of dichloromethane. The mixture is stirred at room temperature overnight and poured into water. The organic layer is separated and washed with H_2O, saturated $NaHCO_3$, H_2O and dried (Na_2SO_4). The solution is passed through a thin pad of hydrous magnesium

silicate and the filtrate evaporated. The residue is crystallized from dichloromethane-hexane to give 3.0 g of crystals, m.p. 197-199°C.

Example 522

5,10-Dihydro-5-(4-amino-2-chlorobenzoyl)-4H-pyrazolo-[5,1-c][1,4]benzodiazepine

A mixture of 0.553 g of 5,10-dihydro-5-(4-nitro-2-chlorobenzoyl)-4H-pyrazolo[5,1-c][1,4]benzodiazepine, 1.70 g of stannous chloride dihydrate in 20 ml of ethanol is heated at 70-80°C for 1 hour. The mixture is chilled, made basic with 1 M $NaHCO_3$ and then stirred at room temperature for 0.5 hour. The mixture is brought to pH 5 with acetic acid and extracted (several times) with ethyl acetate. The combined extracts are dried (Na_2SO_4) and passed through a pad of hydrous magnesium silicate. The filtrate is evaporated and the residue dissolved in dichloromethane and the solution passed through a thin pad of hydrous magnesium silicate. The filtrate is evaporated in vacuo to give 0.40 g of a glass, m.p. 98-117°C; Anal. Calc'd: C, 62.9; H, 4.7; N, 16.3; Cl, 11.6. Found: C, 62.4; H, 4.3; N, 15.6; Cl, 11.7.

The following examples are prepared using the conditions of Example 465.

Example No.	Compound
523	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-3-chlorophenyl]-2-fluorobenzamide, m.p. 223-226°C
524	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-3-chlorophenyl]-2-(thiomethylbenzamide), white foam
525	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl]-3-chlorophenyl]-2,3-dimethylbenzamide, m.p. 189-192°C

Example No.	Compound
526	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl]-3-chlorophenyl]-2-chlorobenzamide, m.p. 198-203°C
527	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl]-3-chlorophenyl]-4-fluoro-2-chlorobenzamide, m.p. 139-141°C
528	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl]-3-chlorophenyl]-2-(trifluoromethyl)benzamide, white foam
529	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl]-3-chlorophenyl]-2,6-dichlorobenzamide, m.p. 246-248°C

Example 530

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2-chlorophenyl]-2-methylbenzamide

To a mixture of 1.38 g of 10,11-dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine, 1.11 g of N,N-diisopropylethylamine in 50 ml of dichloromethane is added 2.61 g of 4-[(2-methylbenzoyl)amino]-3-chlorobenzoyl chloride in 25 ml of dichloromethane. The mixture is stirred at room temperature overnight and then washed with H_2O and saturated $NaHCO_3$. The organic layer is dried (Na_2SO_4) and passed through a pad of hydrous magnesium silicate. The filtrate is concentrated, the residue (4.0 g) dissolved in dichloromethane and again filtered through a pad of hydrous magnesium silicate. The filtrate is evaporated to give the product as a glass (3.62 g). A 1.8 g sample of the glass is crystallized from ethyl acetate to give 1.4 g of crystals, m.p. 176-178°C.

The following Examples are prepared using the conditions of Example 530.

Example No.	Compound
531	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2-chlorophenyl]-2,3-dimethylbenzamide
532	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2-chlorophenyl]-2,5-dimethylbenzamide
533	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2-chlorophenyl]-2,6-dimethylbenzamide
534	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2-chlorophenyl]-2-chlorobenzamide
535	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2-chlorophenyl]-2,4-dichlorobenzamide
536	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2-chlorophenyl]-2,5-dichlorobenzamide
537	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2-chlorophenyl]-3,5-dichlorobenzamide
538	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-3-chlorophenyl]-3-fluorobenzamide, amorphous solid

Example No.	Compound
539	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2-chlorophenyl]-2-chloro-4-fluorobenzamide
540	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2-chlorophenyl]-2-methyl-4-chlorobenzamide
541	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2-chlorophenyl]-2-(methylthio)benzamide
542	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2-chlorophenyl]-2-chlorobenzeneacetamide
543	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2-chlorophenyl]-2-methylbenzeneacetamide
544	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2-chlorophenyl]-2-methylthiophene-3-carboxyamide
545	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2-chlorophenyl]-3-methylthiophene-2-carboxamide
546	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2-chlorophenyl]-3-fluoro-2-methylbenzamide, m.p. 230-231°C

Example No.	Compound
547	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2-chlorophenyl]-5-fluoro-2-methylbenzamide, m.p. 178-180°C
548	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2-chlorophenyl]-2,3-dichlorobenzamide
549	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2-chlorophenyl]-2,3-difluorobenzamide
550	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2-chlorophenyl]-4-fluoro-2-methylbenzamide
551	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2-chlorophenyl]-2-methoxybenzamide
552	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2-chlorophenyl]-2-(trifluoromethoxy)benzamide
553	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2-chlorophenyl]-2-methoxy-4-chlorobenzamide
554	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2-chlorophenyl]-2-(trifluoromethyl)benzamide

Example No.	Compound
555	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2-chlorophenyl]-3-(trifluoromethyl)benzamide
556	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2-chlorophenyl]-2,6-dichlorobenzamide
557	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2-chlorophenyl]-2,3,5-trichlorobenzamide
558	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2-chlorophenyl]-2-fluoro-5-(trifluoromethyl)benzamide
559	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2-chlorophenyl]-4-fluoro-2-(trifluoromethyl)benzamide
560	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2-chlorophenyl]-2-fluoro-3-(trifluoromethyl)benzamide
561	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2-chlorophenyl]-2,5-difluorobenzamide
562	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2,3-dichlorophenyl]-5-fluoro-2-methylbenzamide

Example No.	Compound
563	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2,3-dichlorophenyl]-2,3-dimethylbenzamide
564	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2,3-dichlorophenyl]-3-fluoro-2-methylbenzamide
565	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2,3-dichlorophenyl]-2,4-dichlorobenzamide
566	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2,3-dichlorophenyl]-2,3-dichlorobenzamide
567	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2,3-dichlorophenyl]-2-methylbenzamide
568	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2,5-dichlorophenyl]-5-fluoro-2-methylbenzamide
569	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2,5-dichlorophenyl]-2,3-dimethylbenzamide
570	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2,5-dichlorophenyl]-3-fluoro-2-methylbenzamide
571	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2,5-dichlorophenyl]-2,4-dichlorobenzamide

Example No.	Compound
572	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2,5-dichlorophenyl]-2,3-dichlorobenzamide
573	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2,5-dichlorophenyl]-2-methylbenzamide
574	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2,5-dichlorophenyl]-2,3-dichlorobenzamide
575	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2,5-dichlorophenyl]-2,5-dichlorobenzamide
576	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2,5-dichlorophenyl]-2-(methylthio)benzamide
577	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2,5-dichlorophenyl]-2-chlorobenzamide
578	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2,5-dichlorophenyl]-2-(trifluoromethyl)benzamide
579	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2,5-dichlorophenyl]-2-(trifluoromethoxy)benzamide

Example 580

2,4-Dichloro-N-[4-[(3-formyl-5H-pyrrolo[2,1-c][1,4]-benzodiazepin-10(11H)-yl)carbonyl]phenyl]benzamide

To a solution of 0.48 g of 2,4-dichloro-N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-yl)-carbonyl)phenyl]benzamide in 2 ml of N,N-dimethylformamide at 0°C is slowly added 0.3 ml of $POCl_3$. The mixture is stirred at 0°C for 30 minutes and at room temperature for 1 hour. The final mixture is quenched with ice and made alkaline with 2 N NaOH to pH 12. The resulting precipitate is collected, washed with water and dried *in vacuo* to give 0.55 g of solid. Further washing with 1:2 ether-isopropanol gives 0.50 g of white solid. MS(CI) calculated 503.0774;
found 503.0789.

Example 581

2,4-Dichloro-N-[4-[[3-(hydroxymethyl)-5H-pyrrolo-[2,1-c][1,4]benzodiazepin-10(11H)-yl]carbonyl]-phenyl]benzamide

To a suspension of 39 mg of $NaBH_4$ in 1 ml of tetrahydrofuran is added 0.42 g of 2,4-dichloro-N-[4-[(3-formyl-5H-pyrrolo[2,1-a][1,4]benzodiazepin-10(11H)-yl)carbonyl]phenyl]benzamide and the reaction mixture stirred at room temperature for 18 hours and then quenched with water. The tetrahydrofuran is evaporated *in vacuo* and the aqueous residue treated with 5 ml of 1 N NaOH and extracted with 50 ml of ethyl acetate. The organic extract is washed with brine, dried over Na_2SO_4 and evaporated to give 0.47 g of a foam. Preparative thick layer chromatography by elution with 2:1 ethyl acetate-hexane gives 0.24 g of white solid. MS(FAB): 488(MH^+-OH).

Example 582

2,4-Dichloro-N-[4-[[3-(1H-imidazol-1-ylmethyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-yl]-carbonyl]phenyl]benzamide

To a suspension of 0.28 g of N,N-dimethylglycine hydrochloride in 5 ml of tetrahydrofuran is added 0.21 g of triethylamine and 0.35 g of carbonyldiimidazole. After stirring at room temperature for 30 minutes and then heating at reflux for 18 hours, the tetrahydrofuran is evaporated in vacuo to a residue which is dissolved in ethyl acetate and washed with water, saturated $NaHCO_3$ and brine and dried over Na_2SO_4, filtered and evaporated in vacuo to a residue. The residue is washed with ether-hexanes (1:1) to give 0.17 g of white solid. MS(FAB): 556(M+H).

Example 583

α-Chloro-N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]benzeneacetamide

To a solution of 0.61 g of 10,11-dihydro-10-(4-aminobenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine in 8 ml of methylene chloride is added 0.30 g of triethylamine followed by 0.47 g of (±)-2-chloro-2-phenylacetyl chloride in 2 ml of methylene chloride. The mixture is stirred at room temperature for 1 hour and then diluted with 10 ml of 50% $NaHCO_3$. The methylene chloride is evaporated and the residue is extracted with ethyl acetate. The separated organic layer is washed with saturated $NaHCO_3$ and brine and then dried with Na_2SO_4 followed by filtering through a pad of hydrous magnesium silicate. The filtrate is evaporated to a residue which is stirred with ether-hexane to give 0.98 g of pink solid. MS(CI): 456(M+H).

Example 584

α-[[2-(Dimethylamino)ethyl]thio]-N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-phenyl]benzeneacetamide

A mixture of 0.14 g of α-chloro-N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-phenyl]benzeneacetamide, 0.47 g of 2-dimethylamino-ethanethiol hydrochloride in 2 ml of methyl alcohol, 0.30 g of triethylamine and 3 ml of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone is heated at 60°C for 48 hours. The methyl alcohol is evaporated and the residue diluted with water. The resulting suspension is filtered and the precipitate washed with water. The solid is dissolved in ethyl acetate and washed with saturated $NaHCO_3$, brine and dried with Na_2SO_4. The mixture is filtered and the filtrate evaporated *in vacuo* to a residue which is stirred with ether-hexane to give 0.15 g of beige solid. MS(CI): 525(M+H).

Example 585

α-[N-(Acetamido)amino]-N-[4-(5H-pyrrolo[2,1-c][1,4]-benzodiazepin-10(11H)-ylcarbonyl)phenyl]benzene-acetamide

A mixture of 0.14 g of α-chloro-N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-phenyl]benzeneacetamide, 0.17 g of glycinamide HCl, 0.15 g of triethylamine, 3 ml of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone and 1 ml of methyl alcohol is heated at 75°C for 2 days. The methyl alcohol is evaporated and the residue diluted with water. The resulting suspension is filtered and the precipitate washed with water. The solid is dissolved in ethyl acetate and washed with saturated $NaHCO_3$, brine and dried with Na_2SO_4. The mixture is filtered and the filtrate evaporated *in vacuo* to a residue which

is stirred with ether-hexanes to give 0.13 g of tan solid. MS(CI): 494(M+H).

Example 586

α-(Dimethylamino)-N-[4-(5H-pyrrolo[2,1-c][1,4]-benzodiazepin-10(11H)-ylcarbonyl)phenyl]benzene-acetamide

A partial solution of ??g of α-chloro-N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]benzeneacetamide in 1 ml of methanol is treated with 0.5 ml of dimethylamine and 1 ml of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone and stirring continued for 20 hours. The methanol is evaporated and the residue diluted with water. The resulting solid is washed with water, dissolved in ethyl acetate and the organic layer washed with saturated $NaHCO_3$, brine and dried with Na_2SO_4. The mixture is filtered and the filtrate evaporated *in vacuo* to give a residue which is stirred with ethyl acetate-hexane to give 0.15 g of a beige solid. MS(CI): 465(M+H).

Example 587

α-(Acetyloxy)-N-[4-(5H-pyrrolo[2,1-c][1,4]-benzodiazepin-10(11H)-ylcarbonyl)phenyl]-benzeneacetamide

To a solution of 0.30 g of 10,11-dihydro-10-(4-aminobenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine in 5 ml of methylene chloride is added 0.15 g of triethylamine followed by 0.27 g of O-acetylmandelic acid chloride. The mixture is stirred at room temperature for 1 hour and then diluted with 50% $NaHCO_3$. The methylene chloride is evaporated and the residue is extracted with ethyl acetate. The separated organic layer is washed with saturated $NaHCO_3$ and brine and then dried with Na_2SO_4 followed by filtering through a pad of hydrous magnesium silicate. The filtrate is

evaporated to a residue which is stirred with ether-hexane to give 0.54 g of beige solid. MS(CI): 480(M+H).

Example 588

(±)α-Hydroxy-N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]benzeneacetamide

A solution of 0.34 g of α-(acetyloxy)-N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]benzeneacetamide in 2 ml of 1 N NaOH and 4 ml of methyl alcohol is stirred at room temperature for 30 minutes, diluted with 2 ml of water and evaporated in vacuo. The aqueous suspension is extracted with 30 ml of ethyl acetate and the extract washed with brine, dried with Na_2SO_4 and filtered through a pad of hydrous magnesium silicate and evaporated in vacuo to a residue. The residue is stirred with ether-hexanes to give 0.26 g of cream colored solid. MS(CI): 438(M+H).

Example 589

2-Chloro-N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]acetamide

To a stirred solution of 0.91 g of 10,11-dihydro-10-(4-aminobenzoyl)-5H-pyrrolo[2,1-c][1,4]-benzodiazepine in 10 ml of methylene chloride is added 0.46 g of triethylamine and 36 mg of dimethylamino-pyridine followed by the slow addition of 0.42 g of chloroacetyl chloride in 5 ml of methylene chloride. The resulting mixture is stirred at room temperature for 3 hours then partitioned with 10 ml of 50% $NaHCO_3$ and the methylene chloride evaporated in vacuo. The remaining suspension is filtered, washed with 50% $NaHCO_3$, H_2O, EtOAc (2x2 ml), ether (2x5 ml) and dried in vacuo to give 1.14 g of beige solid. MS(CI): 380(M+H).

Example 590

N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-4-morpholineacetamide

A stirred suspension of 0.19 g of 2-chloro-N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]acetamide in 1 ml of methylene chloride is added 0.44 g of morpholine followed by 1 ml of 1,3-di- methyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone and stirring continued for 20 hours. The methylene chloride is evaporated and the residue diluted with water. The resulting suspension is filtered and the precipitate washed with water. The brown solid is dissolved in 15 ml of ethyl acetate and washed with saturated $NaHCO_3$, brine and dried with Na_2SO_4. The mixture is filtered and the filtrate evaporated in vacuo to give 0.23 g of a colorless gum which is stirred with ethyl acetate-hexanes to give 0.21 g of white solid. MS(CI): 431(M+H).

Example 591

N-[(2-Chlorophenyl)methyl]-N-[4-(5H-pyrrolo[2,1-c]-[1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-4-morpholineacetamide

A mixture of 0.11 g of N-[4-(5H-pyrrolo-[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-4-morpholineacetamide, 56 mg of O-chlorobenzyl bromide and 0.41 g of K_2CO_3 in 5 ml of acetonitrile is heated at reflux for 18 hours. An additional 30 mg of O-chlorobenzyl bromide and 0.4 mmol of sodium hydride is added followed by heating for 24 hours. The reaction mixture is diluted with water and extracted with ethyl acetate. The organic layer is dried with Na_2SO_4 and evaporated to give 0.18 g of a residue which is purified by chromatography on silica gel with 1:1 ethyl acetate-methylene chloride to give 80 mg of off white solid. MS(CI): 555(M+H).

Example 592

Ethyl 10-[4-[(2,4-dichlorobenzoyl)amino]-3-methylbenzoyl]-10,11-dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine-3-carboxylate

To a solution of 0.30 g of ethyl 10,11-dihydro-10-(4-amino-3-methylbenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine-3-carboxylate in 20 ml of methylene chloride is added 0.15 g of N,N-diisopropylethylamine and 0.24 g of 2,4-dichlorobenzoyl chloride. The reaction mixture is stirred at room temperature for 18 hours and washed with water, saturated $NaHCO_3$ and dried with Na_2SO_4. The organic layer is passed through a pad of hydrous magnesium silicate. Hexane is added to the filtrate at the boil to give 0.24 g of solid, m.p. 174-184°C.

Example 593

Methyl 10-[4-(2,4-dichlorobenzoyl)amino]benzoyl]-10,11-dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine-3-carboxylate

To 50 ml of absolute methyl alcohol is added 0.15 g of sodium metal. After complete solution, 1.0 g of N-[4-[[3-(trichloroacetyl)-5H-pyrrolo[2,1-c][1,4]-benzodiazepin-10(11H)-yl)]carbonyl]phenyl]-2,4-dichlorobenzamide is added and the reaction mixture stirred overnight at room temperature. Methylene chloride is added followed by Na_2SO_4. The organic layer is filtered through hydrous magnesium silicate. Hexane is added at the boil to the filtrate to give 0.29 g of solid.

Example 594

N-[4-[[3-(trifluoroacetyl)-5H-pyrrolo[2,1-c][1,4]-benzodiazepin-10(11H)-yl)]carbonyl]phenyl]-2-(trifluoromethyl)benzamide

To a solution of 1.0 g of N-[4-(5H-pyrrolo-[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-

2-(trifluoromethyl)benzamide in 10 ml of methylene chloride is added 1.0 ml of trifluoroacetic anhydride followed by stirring for 18 hours at room temperature. The reaction mixture is washed with saturated $NaHCO_3$, dried with Na_2SO_4, filtered and hexane added at the boil to give a solid which is crystallized from methylene chloride-hexane to give 0.89 g of solid, m.p. 248-250°C.

Example 595

N-[4-[[3-(Trifluoroacetyl)-5H-pyrrolo[2,1-c][1,4]-benzodiazepin-10(11H)-yl]carbonyl]-3-chlorophenyl]-2-methylbenzamide

To a solution of 0.30 g of N-[4-(5H-pyrrolo-[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-3-chlorophenyl]-2-methylbenzamide in 25 ml of methylene chloride is added 0.5 ml of trifluoroacetic anhydride followed by stirring at room temperature for 18 hours. The reaction mixture is washed with saturated $NaHCO_3$, dried with Na_2SO_4, filtered through hydrous magnesium silicate and hexane added to the filtrate at the boil to give 0.22 g of colorless solid. MS: M+551.

Example 596

Ethyl 10-[4-[(2,4-dichlorobenzoyl)amino]benzoyl]-10,11-dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine-3-carboxylate

To 50 ml of absolute ethyl alcohol is added 0.30 g of sodium metal, followed by the addition of 2.0 g of N-[4-[[3-(trichloroacetyl)-5H-pyrrolo[2,1-c]-[1,4]benzodiazepin-10(11H)yl]carbonyl]phenyl]-2,4-dichlorobenzamide and the mixture is stirred for 18 hours at room temperature. The volatiles are evaporated *in vacuo* to a residue which is dissolved in methylene chloride and washed with H_2O. The organic layer is dried with Na_2SO_4 and filtered through hydrous magnesium silicate. Hexane is added to the filtrate at the boil to give a solid which is crystallized from

methylene chloride-hexane to give 0.57 g of a solid. MS(M^+):548.2.

Example 597

N-[4-[[3-(Trichloroacetyl)-5H-pyrrolo[2,1-c][1,4]-benzodiazepin-10(11H)-yl]carbonyl]phenyl]-2-(trifluoromethyl)benzamide

To a stirred solution of 0.48 g of N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-phenyl]-2-(trifluoromethyl)benzamide in 20 ml of methylene chloride is added 0.40 g of trichloroacetic anhydride followed by stirring at room temperature for 18 hours. The reaction mixture is washed with water and saturated $NaHCO_3$, dried over Na_2SO_4 and passed through a pad of hydrous magnesium silicate. Hexane is added at the boil to give 0.37 g of solid, m.p. 219-221°C.

Example 598

N-[4-[[3-(Trichloroacetyl)-5H-pyrrolo[2,1-c][1,4]-benzodiazepin-10(11H)-yl]carbonyl]phenyl]-2,4-dichlorobenzamide

To a stirred solution of 4.76 g of N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2,4-dichlorobenzamide in 150 ml of methylene chloride is added 3.75 g of trichloroacetic anhydride followed by stirring for 18 hours. The reaction mixture is washed with water and saturated $NaHCO_3$, dried over Na_2SO_4 and passed through a pad of hydrous magnesium silicate. The filtrate is evaporated in vacuo to give 2.91 g of solid.

Example 599

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2,3,5-trichlorobenzamide

As described for Example 8, 0.50 g of 10,11-dihydro-10-(4-aminobenzoyl)-5H-pyrrolo[2,1-c][1,4]-benzodiazepine is reacted with 0.483 g of 2,3,5-

trichlorobenzoyl chloride to give a glass which is crystallized from ethyl acetate to give 0.686 g of crystals, m.p. 231-234°C.

Example 600

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]tetrahydrofurane-2-carboxamide

As described for Example 8, 0.500 g of 10,11-dihydro-10-(4-aminobenzoyl)-5H-pyrrolo[2,1-c][1,4]-benzodiazepine is reacted with 0.267 g of tetrahydrofurane-2-carbonyl chloride to give a glass which is crystallized from ethyl acetate to give 0.22 g of crystals, m.p. 208-214°C.

The following Examples are prepared using conditions of Example 297 with the appropriately substituted aroyl chloride.

Example No.	Compound
601	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-2,5-dichlorophenyl]-2,3-dimethylbenzamide
602	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-2,5-dichlorophenyl]-2-chlorobenzamide
603	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-2,5-dichlorophenyl]-2,4-dichlorobenzamide
604	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-2,5-dichlorophenyl]-3,5-dichlorobenzamide
605	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-2,5-dichlorophenyl]-2-methyl-4-chlorobenzamide

Example No.	Compound
606	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-3-chlorophenyl]-2-methoxybenzamide
607	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-3-chlorophenyl]-2-(trifluoromethoxy) benzamide
608	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-3-chlorophenyl]-2-(trifluoromethyl) benzamide
609	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-3-chlorophenyl]-2,4-dichlorobenzamide, amorphous white solid, m.p. 134-137°C
610	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-3-chlorophenyl]-2-(methylthio)benzamide
611	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-3-chlorophenyl]-3-fluoro-2-methyl-benzamide, amorphous white solid, m.p. 136-138°C
612	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-3-chlorophenyl]-5-fluoro-2-methyl-benzamide, amorphous solid, m.p. 132-135°C.

Example No.	Compound
613	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-3-chlorophenyl]-4-fluoro-2-methyl-benzamide
614	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-3-chlorophenyl]-4-fluoro-2-(trifluoro-methyl)benzamide
615	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-3-chlorophenyl]-2,3-dichlorobenzamide
616	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-3-chlorophenyl]-2,3-difluorobenzamide
617	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-3-chlorophenyl]-2-fluoro-5-(trifluoro-methyl)benzamide
618	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-3-chlorophenyl]-2-fluoro-3-(trifluoro-methyl)benzamide
619	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-3-chlorophenyl]-4-fluoro-2-(trifluoro-methyl)benzamide

Example No.	Compound
620	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-3-chlorophenyl]-2,5-difluorobenzamide
621	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-3-chlorophenyl]-2,3-difluorobenzamide
622	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-3-chlorophenyl]-2,5-dimethylbenzamide
623	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-3-chlorophenyl]-3-methyl-2-thiophene-carboxamide
624	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-3-chlorophenyl]-2-methyl-3-thiophene-carboxamide
625	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-3-chlorophenyl]-2-methyl-3-furane-carboxamide
626	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-3-chlorophenyl]-3-methyl-2-furane-carboxamide

Example No.	Compound
627	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-3-chlorophenyl]-2-chlorobenzeneacetamide
628	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-3-chlorophenyl]-2-methylbenzeneacetamide
629	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-3-chlorophenyl]-4-fluoro-3-(trifluoro-methyl)benzamide
630	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-2-chlorophenyl]-3-fluoro-2-methyl-benzamide
631	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-2-chlorophenyl]-2,3-dichlorobenzamide
632	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-2-chlorophenyl]-2,3-difluorobenzamide
633	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-2-chlorophenyl]-4-fluoro-2-methyl-benzamide
634	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-2-chlorophenyl]-5-fluoro-2-methyl-benzamide

Example No.	Compound
635	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-2-chlorophenyl]-2-fluoro-5-(trifluoromethyl)benzamide
636	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-2-chlorophenyl]-2-methylbenzamide
637	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-2-chlorophenyl]-2-chlorobenzamide
638	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-2-chlorophenyl]-2,3-dimethylbenzamide
639	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-2-chlorophenyl]-2,5-dimethylbenzamide
640	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-2-chlorophenyl]-2-methoxybenzamide
641	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-2-chlorophenyl]-2-(trifluoromethoxy)-benzamide
642	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-2-chlorophenyl]-2-methoxy-4-chloro-benzamide

Example No.	Compound
643	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-2-chlorophenyl]-2,6-dichlorobenzamide
644	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-2-chlorophenyl]-2-(methylthio)benzamide
645	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-2-chlorophenyl]-2-(trifluoromethyl)-benzamide
646	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-2-chlorophenyl]-3-(trifluoromethyl)-benzamide
647	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-2-chlorophenyl]-2,3,5-trichlorobenzamide
648	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-3-methoxyphenyl]-3-fluoro-2-methylbenz-amide
649	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-3-methoxyphenyl]-5-fluoro-2-methylbenz-amide

Example No.	Compound
650	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-3-methoxyphenyl]-4-fluoro-2-methylbenzamide
651	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-3-methoxyphenyl]-2,4-dichlorobenzamide
652	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-3-methoxyphenyl]-2,3-dimethylbenzamide
653	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-3-methoxyphenyl]-3-fluoro-5-(trifluoromethyl)benzamide
654	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-2-methoxyphenyl]-3-fluoro-2-methylbenzamide
655	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-2-methoxyphenyl]-5-fluoro-2-methylbenzamide
656	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-2-methoxyphenyl]-4-fluoro-2-methylbenzamide

Example No.	Compound
657	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-2-methoxyphenyl]-2,4-dichlorobenzamide
658	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-2-methoxyphenyl]-2,3-dimethylbenzamide
659	N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a]-[1,5]benzodiazepin-5-yl)carbonyl]-2-methoxyphenyl]-3-fluoro-5-(trifluoromethyl)benzamide

Example 660

N-[4-[[[3-[-[(Dimethylamino)methyl]-5H-pyrrolo[2,1-c]-[1,4]benzodiazepin-10(11H)-yl]carbonyl]phenyl]-2-methylbenzamide

To a stirred solution of 0.842 g of 2-methyl-N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-yl-carbonyl)phenyl]benzamide in 25 ml of 1:1 methanol-tetrahydrofuran is added 10 ml of 35% formaldehyde and 10 ml of 30% N,N-dimethylamine at 0°C. After 2 drops of acetic acid is added, the reaction mixture is stirred at room temperature for 16 hours. The reaction mixture is concentrated in vacuo to a residue which is dissolved in chloroform and washed with water. The organic layer is dried with Na_2SO_4 and evaporated in vacuo to a residue. The residue is chromatographed on silica gel with 10:1 ethyl acetate-methanol as eluent to give 0.800 g of the desired product, M^+H:479.

The following products are prepared by using the condition of Example 660 and by using the appropriately substituted benzamide.

Example No.	Compound
661	N-[4-[[3-(1-piperidinylmethyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-yl]carbonyl]phenyl]-2-methylbenzamide, solid; mass spectrum (M^+H) 518
662	N-[4-[[3-(4-morpholinomethyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-yl]carbonyl]phenyl]-2-methylbenzamide, solid; mass spectrum (M^+H) 521
663	N-[4-[[3-[[4-(phenylmethyl)-1-piperazinyl]methyl]-5H-pyrrolo[2,1-c][1,4]-benzodiazepin-10(11H)-yl]carbonyl]-phenyl]-2-methylbenzamide, solid; mass spectrum (M^+H) 610
664	N-[4-[[3-[(dimethylaminomethyl]-5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-yl]carbonyl]phenyl]-2,4-dichlorobenzamide, solid; mass spectrum (M^+H) 535
665	N-[4-[[3-(1-pyrrolidinylmethyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-yl]carbonyl]phenyl]-2,4-dichlorobenzamide, solid; mass spectrum (M^+H) 561
666	N-[4-[[3-(4-morpholinomethyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-yl]carbonyl]phenyl]-2,4-dichlorobenzamide, solid; mass spectrum (M^+H) 576

Example No.	Compound
667	N-[4-[[3-[(diethylamino)methyl]-5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-yl]carbonyl]phenyl]-2,4-dichlorobenzamide, solid; mass spectrum (M^+H)562
668	N-[4-[[3-[(dimethylamino)methyl]-5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-yl]carbonyl]-3-chlorophenyl]-5-fluoro-2-methylbenzamide, solid; mass spectrum (M^+H)531
669	N-[4-[[3-[(dimethylamino)methyl]-5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-yl]carbonyl]-3-chlorophenyl]-2-methylbenzamide, solid; mass spectrum (M^+H)513

Example 670

N-[4-[(3-Acetyl-5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-yl]carbonyl]phenyl]-2,4-dichlorobenzamide

A stirred solution of 0.954 g of N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-phenyl]-2,4-dichlorobenzamide in 25 ml of methylene chloride and 5 ml of acetic anhydride is heated at reflux for 24 hours. The volatiles are evaporated *in vacuo* to a residue which is purified by column chromatography on silica gel by elution with ethyl acetate-hexane (7:3) to give 0.800 g of a white solid; mass spectrum (M^+H)519.

Example 671

1-[2-Nitro-5-(ethoxycarbonyl)benzyl]-pyrrole-2-carboxaldehyde

To a stirred slurry of 2.2 g of sodium hydride (60% in oil, washed with hexane) in tetra-

hydrofuran is added at 0°C a solution of 4.5 g of pyrrole-2-carboxaldehyde in 25 ml of tetrahydrofuran. After the addition is complete, a solution of 15 g of ethyl 4-nitro-3-bromomethylbenzoate in 30 ml of dry tetrahydrofuran is slowly added under nitrogen. The reaction mixture is stirred at 20°C for 8 hours and carefully quenched with water. The reaction mixture is extracted with chloroform which is washed with water, dried with Na_2SO_4 and concentrated in vacuo to give 12 g of the desired product as a solid; mass spectrum (M^+H)349.

Example 672

1-[2-Nitro-4-(ethoxycarbonyl)benzyl]-pyrrole-2-carboxaldehyde

The conditions of Example 671 are used with ethyl 3-nitro-4-bromomethylbenzoate to give 13.0 g of the desired product as a solid; mass spectrum (M^+H)349.

Example 673

Ethyl 10,11-Dihydro-5H-pyrrolo[2,1-c][1,4]-benzodiazepine-7-carboxylate

A solution of 10.0 g of 1-[2-nitro-5-(ethoxycarbonyl)benzyl]-pyrrole-2-carboxaldehyde in 150 ml of absolute ethanol containing 1.0 g of 10% Pd/c is hydrogenated in a Parr apparatus for 16 hours under 40 psi of hydrogen. The reaction mixture is filtered through a pad of diatomaceous earth and the filtrate concentrated in vacuo to a residue of 5.5 g of the desired product as a solid; mass spectrum (M^+H)255.

Example 674

Ethyl 10,11-Dihydro-5H-pyrrolo[2,1-c][1,4]-benzodiazepine-8-carboxylate

The hydrogenation conditions of Example 673 are used with 1-[2-nitro-4-(ethoxycarbonyl)benzyl]-pyrrole-2-carboxaldehyde to give 5.0 g of the desired product as a solid; mass spectrum (M^+H)255.

Example 675

Ethyl 10,11-Dihydro-10-[4-[(2-methylbenzoyl)amino]-benzoyl]-5H-pyrrolo[2,1-c][1,4]benzodiazepine-7-carboxylate

A solution of 1.2 g of ethyl 10,11-dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine-7-carboxylate in 100 ml of methylene chloride is cooled to 0°C and 10 ml of triethylamine added followed by 1.5 g of 4-[(2-methylbenzoyl)amino)benzoyl chloride. The reaction mixture is stirred at room temperature for 18 hours and concentrated in vacuo to a residue which is partitioned between water and chloroform. The organic layer is dried over Na_2SO_4 and concentrated in vacuo to a residue. The residue is purified by column chromatography on silica gel by elution with 40% ethyl acetate-hexane to give 1.0 g of the desired product as a solid; mass spectrum (M^+H)494.

Example 676

Ethyl 10,11-Dihydro-10-[4-[(2-methylbenzoyl)amino]-benzoyl]-5H-pyrrolo[2,1-c][1,4]benzodiazepin-8-carboxylate

The conditions of Example 675 are used with ethyl 10,11-dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine-8-carboxylate to give 1.2 g of the desired product as a solid; mass spectrum (M^+H)494.

The subject compounds of the present invention are tested for biological activity as follows:

Example 677

10,11-Dihydro-10-(4-nitrobenzoyl)-5H-imidazo[2,1-c]-[1,4]benzodiazepine

A 292 mg sample of sodium hydride in oil is washed, under argon, with pentane. The residue is diluted with 17 ml of dioxane and then 1.35 g of 10,11-dihydro-5H-imidazo[2,1-c][1,4]benzodiazepine is added. The reaction mixture is warmed slightly until the hydrogen evolution ceases. To the cooled reaction

mixture is added a solution of 1.36 g of p-nitrobenzoyl chloride in 45 ml of dioxane and the mixture is stirred at room temperature for 18 hours. The solvent is evaporated in vacuo and the residue is heated with $CHCl_3$, filtered hot and the filter cake washed with hot $CHCl_3$. The combined $CHCl_3$ layers are washed with water, saturated $NaHCO_3$, treated with activated charcoal, filtered through a pad of $MgSO_4$ and the filtrate evaporated in vacuo to give 1.82 g of brown solid residue. The residue is purified by flash chromatography by elution with $CHCl_3$-MeOH to give 630 mg of the desired product as a solid. HR FABMS:(M+H)=335.3433.

Example 678

10,11-Dihydro-10-(4-aminobenzoyl)-5H-imidazo[2,1-c]-[1,4]benzodiazepine

A mixture of 0.550 g of 10,11-dihydro-10-(4-nitrobenzoyl)-5H-imidazo[2,1-c][1,4]benzodiazepine and 1.86 g of $SnCl_2.2H_2O$ in 22 ml of ethyl alcohol is refluxed for 1 hour under argon. The mixture is diluted with water and then a solution of 10% $NaHCO_3$ is added until the reaction mixture is basic. Additional ethyl alcohol is added and reaction mixture evaporated in vacuo to give a residue which is triturated with 1:1 $CHCl_3$-CH_3OH several times and filtered. The filtrates are combined, treated with activated carbon and filtered through diatomaceous earth. The filtrate is evaporated in vacuo to give 680 mg of tan crystalline solid. The solid is stirred in ethanol, water and 10% $NaHCO_3$ to pH=8, for 5 hours and extracted with $CHCl_3$ three times. The combined extracts are treated with activated carbon, filtered through $MgSO_4$ and evaporated in vacuo to give 370 mg of tan crystalline solid. CIMS(CH_4):MH^+=305.

Example 679

N-[4-(5H-Imidazo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2,4-dichlorobenzamide

A slurry of 0.330 g of 10,11-dihydro-10-(4-aminobenzoyl)-5H-imidazo[2,1-c][1,4]benzodiazepine in 15 ml of dioxane is stirred and warmed slightly to obtain a nearly complete solution. The reaction mixture is cooled to room temperature and 43 mg of sodium hydride in oil added. The mixture is warmed slightly. Gas evolution stops in a few minutes. The reaction mixture is cooled to room temperature and 153 µl of 2,4-dichlorobenzoyl chloride in 2.5 ml of dioxane added. An additional 3.5 ml of dioxane is added and the reaction mixture stirred at room temperature for 2 days. The volatiles are evaporated in vacuo to a residue which is partitioned between water and chloroform. The organic layer is separated and the aqueous phase extracted with chloroform two more times. The combined organic layers are trated with activated carbon and filtered through $MgSO_4$. The filtrate is evaporated in vacuo to a tan foam which is purified by flash chro- matography on silica gel by elution with $CHCl_3$ and 3-7% CH_3OH in chloroform to give 310 mg of tan foam.

Example 680

6,7-Dihydro-5-(2-chloro-4-nitrobenzoyl)-5H-pyrrolo-[1,2-a][1,5]benzodiazepine

To a solution of 0.28 g of 6,7-dihydro-5H-pyrrolo[1,2-a][1,5]benzodiazepine in 6 ml of methylene chloride is added 0.30 g of triethylamine followed by 0.50 g of 2-chloro-4-nitrobenzoyl chloride in 0.5 ml of methylene chloride. The reaction mixture is stirred at room temperature for 1 hour then quenched with 5 ml of saturated $NaHCO_3$. The methylene chloride is evaporated in vacuo and the residue is diluted with 5 ml of water and extracted with 20 ml of ethyl acetate. The organic

layer is separated, washed with saturated $NaHCO_3$ and brine, dried with Na_2SO_4 and evaporated in vacuo to give 0.59 g of a yellow foam which is triturated with ether-hexanes to give 0.56 g of the desired product as off-white solid. MS(CI): 368(M+H)(Cl^{35})
370(M+H)(Cl^{37})

Example 681

6,7-Dihydro-5-(4-amino-2-chlorobenzoyl)-5H-pyrrolo-[1,2-a][1,5]benzodiazepine

To a solution of 0.50 g of 6,7-dihydro-5-(2-chloro-4-nitrobenzoyl)-5H-pyrrolo[1,2-a][1,5]benzodiazepine in 10 ml of ethyl alcohol and 2 ml of tetrahydrofuran is added 2.35 g of $SnCl_2 \cdot 2H_2O$ and the mixture stirred at 55°C for 30 minutes. The solvents are evaporated in vacuo to a residue which is stirred with 20 ml of 1 N NaOH and 40 ml of ethyl acetate for 15 minutes and filtered through diatomaceous earth. The filter pad is washed with 2x10 ml of ethyl acetate and the combined extracts washed with brine, dried (Na_2SO_4) and evaporated in vacuo to give 0.47 g of solid residue which is triturated with ether-hexane to give 0.43 g of light yellow crystalline solid.
MS(CI): 338(M+H, Cl^{35})
340(M+H, Cl^{37})

Example 682

N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a][1,5]benzodiazepin-5-yl)carbonyl]-3-chlorophenyl]-3-fluoro-2-methylbenzamide

To a mixture of 0.10 g of 6,7-dihydro-5-(4-amino-2-chlorobenzoyl)-5H-pyrrolo-[1,2-a][1,5]benzodiazepine and 0.06 g of triethylamine in 6 ml of dichloromethane is added 0.08 g of 3-fluoro-2-methylbenzoyl chloride in 0.5 ml of dichloromethane. The mixture is stirred for 2 hours at room temperature and then 2 ml of 1 N NaOH added. The volatiles are evaporated under vacuum and the residue dissolved in 2 ml

of tetrahydrofuran and 1 ml of methanol. The mixture is stirred for 2 hours and evaporated and the residue diluted with 2 ml of 1 N NaOH and 5 ml of water. The mixture is extracted with ethyl acetate (15 ml) and the extract washed with brine and dried (Na_2SO_4). The solvent is removed and the residue triturated with diethyl ether-hexane to give 0.15 g of white solid: Mass Spectrum (CI)474(M+H, Cl^{35}); 476(M+H, Cl^{37}).

Example 683

N-[4-[(6,7-Dihydro-5H-pyrrolo[1,2-a][1,5]benzodiazepin-5-yl)carbonyl]-3-chlorophenyl]-2,4-dichlorobenzamide

To a mixture of 0.10 g of 6,7-dihydro-5-(4-amino-2-chlorobenzoyl)-5H-pyrrolo[1,2-a][1,5]benzodiazepine and 0.06 g of triethylamine in 6 ml of dichloromethane is added 0.10 g of 2,4-dichlorobenzoyl chloride in 0.5 ml of dichloromethane. The mixture is stirred at room temperature for 2 hours and 2 ml of 1 N NaOH is added. The volatiles are removed under vacuum and to the residue is added 2 ml of tetrahydrofuran and 1 ml of methanol. The mixture is stirred at room temperature for 2 hours and the volatiles removed. To the residue is added 2 ml of 1 N NaOH and 5 ml of H_2O. The mixture is extracted with ethyl acetate and the extract washed with brine and dried (Na_2SO_4). The solvent is removed and the solid triturated with diethyl ether-hexane to give 0.15 g of white solid, Mass Spectrum (CI): 510(M+H, Cl^{35}).

Example 684

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2-(1H-[1,2,4]-triazol-1-yl)-acetamide

To a suspension of 0.20 g of 1,2,4-triazole sodium in 1 ml of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone is added 0.10 g of 2-chloro-N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcar-

bonyl)phenyl]acetamide in 1 ml of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone followed by stirring at room temperature for 3 hours. The reaction mixture is quenched with 15 ml of water and the resulting solid is collected, washed with water and hexanes to give 70 mg of the desired product as a tan solid.
MS(CI): 413(M+H).

Example 685

N-[4-(5H-Pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2-(2-formyl-1-pyrrolo)acetamide

To a suspension of 72 mg of sodium hydride (60% in oil) in 5 ml of tetrahydrofuran is added 0.14 g of pyrrole-2-carboxaldehyde. The mixture is stirred for 1 hour at room temperature and 94 mg of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone and 0.19 g of 2-chloro-N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]acetamide added. The mixture is stirred at room temperature, water added and the tetrahydrofuran evaporated in vacuo. The resulting suspension is filtered and the precipitate washed with water and hexanes. The collected solid is purified by column chromatography on silica gel by elution with 3:2 ethyl acetate-hexanes to give 50 mg of pink solid. MS(CI): 439(M+H).

Example 686

N-[4-(3-Chloro-4H-pyrazolo[5,1-c][1,4]benzodiazepin-5-(10H)-ylcarbonyl)phenyl]-2-methyl-5-fluorobenzamide

A mixture of 356 mg of N-[4H-pyrazolo[5,1-c]-[1,4]benzodiazepin-5(10H)-ylcarbonyl)-3-chlorophenyl]-5-fluoro-2-methylbenzamide and 122 mg of N-chlorosuccinimide in 5 ml of methylene chloride is refluxed on a steam bath for 3 hours. The reaction mixture is washed with saturated $NaHCO_3$, H_2O and brine, then dried over Na_2SO_4 and passed through a pad of hydrous magnesium silicate. The filtrate is evaporated in vacuo to give 190 mg of the desired product as a solid.

The following examples are prepared using the conditions of Example 465.

Example No.	Compound
687	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2-bromobenzamide, white solid
688	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2-(acetoxy)benzamide, light yellow solid
689	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2-hydroxybenzamide, light yellow solid
690	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-1-naphthylcarboxamide, white solid
691	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-3-methylphenyl]-2-methylbenzamide, amorphous solid
692	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2-chloro-4-fluorobenzamide, white foam
693	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2-(trifluoromethyl)-4-fluorobenzamide, white solid

Example No.	Compound
694	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-3-methylphenyl]-5-fluoro-2-methylbenzamide, m.p. 180-182°C
695	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-3-methoxyphenyl]-5-fluoro-2-methylbenzamide, amorphous solid
696	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-3-chlorophenyl]-2-fluoro-4-(trifluoromethyl) benzamide, m.p. 140-154°C
697	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-3-chlorophenyl]-2-methylbenzeneacetamide, white glass
698	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-3-chlorophenyl]-2-fluoro-6-(trifluoromethyl) benzamide, white solid, m.p. 150-230°C
699	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-3-chlorophenyl]-2-fluoro-3-(trifluoromethyl) benzamide, white glass
700	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-3-chlorophenyl]-2-chloro-5-(methylthio) benzamide, white crystals, m.p. 124-134°C

Example No.	Compound
701	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-3-chlorophenyl]-2,5-dimethylbenzamide, crystalline solid, m.p. 253-255°C
702	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-3-chlorophenyl]-2-chloro-3,4-dimethoxybenzamide, yellow foam
703	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-6-chloro-3-methoxyphenyl]-2-methylbenzamide, crystals, m.p. 214-215°C
704	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-2-methoxyphenyl]-2,5-dimethylbenzamide, crystals, m.p. 174-175°C
705	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2-chloro-3,4-dimethoxybenzamide, white crystals, m.p. 242-244°C
706	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2,5-dimethylbenzamide, crystals, m.p. 158-160°C
707	N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-3-chlorophenyl]-2-(trifluoromethyl)-4-fluorobenzamide, white glass

Example 708

Methyl 4-[2-(2-chlorophenyl)-2-cyano-2-(4-morpholinyl)-ethyl]benzoate

A 0.876 g sample of 60% sodium hydride in oil is washed with hexane followed by the addition of 60 ml of dry N,N-dimethylformamide. The reaction mixture is stirred for 1 hour under argon at room temperature after the addition of 4.73 g of α-(2-chlorophenyl)-4-morpholineacetonitrile. To the reaction mixture is added 4.58 g of methyl 4-(bromomethyl)benzoate and stirring continued for 3 hours. Several drops of acetic acid is added to ice water and the reaction quenched. The pH is 3-4 and saturated $NaHCO_3$ added to adjust the pH to 6-7. Upon cooling a solid forms which is filtered, washed with water and dried to give 5.92 g of yellow solid. Crystallization from methylene chloride-hexane gives 2.10 g of the desired product as a crystalline solid, m.p. 116-118°C.

Example 709

Methyl 4-[2-(2-chlorophenyl)-2-oxoethyl]benzoate

A mixture of 1.0 g of methyl [4-(2-chlorophenyl)-2-cyano-2-(4-morpholinyl)ethyl]benzoate and 14 ml of water is heated at reflux for 20 minutes then poured over crushed ice. After stirring for 15 minutes the resulting solid is collected, washed with water and air dried to give 0.63 g of tan solid, m.p. 40-42°C.

Example 710

4-[2-(2-Chlorophenyl)-2-oxoethyl]benzoic acid

A mixture of 18.78 g of methyl 4-[2-(2-chlorophenyl)-2-oxoethyl]benzoate in 288.8 ml of CH_3OH, 72.2 ml of water and 5.2 g of NaOH is refluxed for 3 hours then acidified with 2 N citric acid. The reaction mixture is evaporated in vacuo to remove the CH_3OH. The aqueous phase is extracted with CH_2Cl_2 and acidified with 1 N HCl. The resulting solid is collected and dried under vacuum to give 17.27 g of the desired product, m.p. 168-172°C.

Example 711

3-Methoxy-4-nitrobenzoyl chloride

A stirred suspension of 1.0 g of 3-methoxy-4-nitrobenzoic acid and 1.40 ml of thionyl chloride is heated to reflux for 2 hours. The mixture is cooled to room temperature, 2 ml of iso-octane added and the mixture evaporated *in vacuo* to a solid residue. The residue is washed with iso-octane (2x2 ml), dried *in vacuo* to give 1.08 g of cream colored solid.

Example 712

10,11-Dihydro-10-(4-nitro-3-methoxybenzoyl)-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine

To a solution of 0.55 g of 10,11-dihydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine in 8 ml of methylene chloride is added 0.55 g of triethylamine followed by 0.97 g of 3-methoxy-4-nitrobenzoyl chloride. The reaction mixture is stirred at room temperature for 2 hours and then quenched with 10 ml of 1 N NaOH. The methylene chloride layer is evaporated and the resulting suspension filtered. The precipitate is washed with 1 N NaOH (2x5 ml), water (3x5 ml) and hexane (2x5 ml). The collected solid is dried *in vacuo* to give 1.13 g of off-white solid. MS(CI): 364(M+H).

Example 713

10,11-Dihydro-10-(4-amino-3-methoxybenzoyl)-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine

A mixture of 0.91 g of 10,11-dihydro-10-(4-nitro-3-methoxybenzoyl)-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine, 4.51 g of $SnCl_2.2H_2O$, 6 ml of ethyl alcohol, 6 ml of tetrahydrofuran and 16 ml of methylene chloride is stirred at 50°C for 2 hours. The solvents are evaporated *in vacuo* and the residue dissolved in 80 ml of ethyl acetate. The solution is treated with 50 ml of 1 N NaOH with stirring for 30 minutes. The resulting suspension is filtered through diatomaceous earth.

The pad is washed with ethyl acetate (3x15 ml). The combined ethyl acetate solutions are washed with brine, dried (Na_2SO_4), filtered through hydrous magnesium silicate and evaporated *in vacuo* to 0.99 g of residue which is stirred with ether-hexanes to give 0.90 g of cream colored solid. MS(CI): 334(M+H).

Example 714

10,11-Dihydro-10-[4-[(3-methylpropyloxycarbonyl)-amino]benzoyl]-5H-pyrrolo[2,1-c][1,4]benzodiazepine

To a stirred solution of 0.15 g of 10,11-dihydro-10-(4-aminobenzoyl)-5H-pyrrolo[2,1-c][1,4]-benzodiazepine in 2 ml of methylene chloride is added 0.10 g of triethylamine followed by 0.10 g of isobutylchloroformate. The reaction mixture is stirred for 3 hours and then quenched with 1 N NaOH. The organic layer is evaporated *in vacuo* to a residue which is stirred in 5 ml of tetrahydrofuran for 1 hour, then evaporated *in vacuo* to a residue. The residue is extracted with ethyl acetate-methylene chloride, washed with brine, dried (Na_2SO_4), filtered through hydrous magnesium silicate and evaporated *in vacuo* to give a residue which is stirred with ethyl acetate-methylene chloride to give 0.22 g of cream colored solid. MS(CI): 404(M+H).

Example 715

10,11-Dihydro-10-[4-(pentanoyl)aminobenzoyl)]-5H-pyrrolo[2,1-c][1,4]benzodiazepine

To a stirred solution of 0.15 g of 10,11-dihydro-10-(4-aminobenzoyl)-5H-pyrrolo[2,1-c][1,4]-benzodiazepine in 2 ml of methylene chloride is added 0.10 g of triethylamine followed by 0.09 g of valeryl chloride. The reaction mixture is stirred for 3 hours and then quenched with 4 ml of 1 N NaOH. The methylene chloride is evaporated *in vacuo* and the residue dissolved in 5 ml of tetrahydrofuran for 1 hour and evaporated *in vacuo* to a residue. The residue is extract-

ed with ethyl acetate-methylene chloride, washed with brine and the organic layer dried (Na_2SO_4), filtered through hydrous magnesium silicate, and evaporated in vacuo to give 0.23 g of a residue which is stirred with ether-hexanes to give 0.19 g of a white solid. MS(CI): 388(M+H).

Example 716

10,11-Dihydro-10-[4-[(3-methylbutanoyl)amino]-benzoyl]-5H-pyrrolo[2,1-c][1,4]benzodiazepine

To a stirred solution of 0.10 g of 10,11-dihydro-10-(4-amino-3-methoxybenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine in 1 ml of methylene chloride is added 0.06 g of triethylamine followed by 0.05 g of iso-valeryl chloride. The reaction mixture is stirred for 3 hours and then quenched with 1 N NaOH. The organic layer is evaporated in vacuo to a residue which is stirred in 5 ml of tetrahydrofuran for 1 hour, then evaporated in vacuo to a residue. The residue is extracted with ethyl acetate-methylene chloride, washed with brine, dried (Na_2SO_4), filtered through hydrous magnesium silicate and evaporated in vacuo to give 0.15 g of residue which is stirred with ether-hexane to give 0.13 g of light yellow solid. MS(CI): 418(M+H).

Example 717

10,11-Dihydro-10-[3-methoxy-4-[(butylsulfonyl)amino]-benzoyl]-5H-pyrrolo[2,1-c][1,4]benzodiazepine

To a stirred solution of 0.10 g of 10,11-dihydro-10-(4-amino-3-methoxybenzoyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepine in 2 ml of methylene chloride is added 60 mg of triethylamine followed by a solution of 56 mg of n-butylsulfonyl chloride in 0.5 ml of methylene chloride. After stirring at room temperature for 2 hours, the reaction mixture is evaporated in vacuo to a residue which is dissolved in methyl alcohol, stirred for 1 hour and evaporated in vacuo to a residue which is treated with 2 ml of NH_4Cl and extracted with 15 ml

of ethyl acetate. The organic extract is washed with saturated $NaHCO_3$, brine, dried (Na_2SO_4), filtered through hydrous magnesium silicate and the filtrate evaporated to a residue. The residue is stirred with ether-hexanes to give 0.14 g of light yellow solid. MS(CI): 454(M+H).

UTILITY TESTING

Binding Assay to Rat Hepatic V_1 Receptors

Rat liver plasma membranes expressing the vasopressin V_1 receptor subtypes are isolated by sucrose density gradient according to the method described by Lesko et al., (1973). These membranes are quickly suspended in 50.0 mM Tris.HCl buffer, pH 7.4, containing 0.2% bovine serum albumin (BSA) and 0.1 mM phenylmethylsulfonylfluoride (PMSF) and kept frozen at -70°C until used in subsequent binding experiments. For binding experiments, the following is added to the wells of a ninety-six well format microtiter plate: 100 µl of 100.0 mM Tris.HCl buffer containing 10.0 mM $MgCl_2$, 0.2% heat inactivated BSA and a mixture of protease inhibitors: leupeptin, 1.0 mg %; aprotinin, 1.0 mg %; 1,10-phenanthroline, 2.0 mg %; trypsin inhibitor, 10.0 mg % and 0.1 mM PMSF, 20.0 µl of [phenylalanyl-3,4,5,-^{3}H] vasopressin (S.A. 45.1 Ci/mmole) at 0.8 nM, and the reaction initiated by the addition of 80 µl of tissue membranes containing 20 µg of tissue protein. The plates are kept undisturbed on the bench top at room temperature for 120 min. to reach equilibrium. Non-specific samples are assayed in the presence of 0.1 µM of the unlabeled antagonist phenylalanylvasopressin, added in 20.0 µl volume.

For test compounds, these are solubilized in 50% dimethylsulfoxide (DMSO) and added in 20.0 µl volume to a final incubation volume of 200 µl. Upon completion of binding, the content of each well is filtered off, using a Brandel® cell Harvester (Gaithersburg, MD). The radioactivity trapped on the

filter disk by the ligand-receptor complex is assessed by liquid scintillation counting in a Packard LS Counter, with an efficiency of 65% for tritium. The data are analyzed for IC_{50} values by the LUNDON-2 program for competition (LUNDON SOFTWARE, OH).

Binding Assay to Rat Kidney Medullary V_2 Receptors

Medullary tissues from rat kidneys are dissected out, cut into small pieces and soaked in a 0.154 mM sodium chloride solution containing 1.0 mM EDTA with many changes of the liquid phase, until the solution is clear of blood. The tissue is homogenized in a 0.25 M sucrose solution containing 1.0 mM EDTA and 0.1 mM PMSF using a Potter-Elvehjem homogenizer with a teflon pestle. The homogenate is filtered through several layers (4 layers) of cheese cloth. The filtrate is rehomogenized using a dounce homogenizer, with a tight fitting pestle. The final homogenate is centrifuged at 1500 x g for 15 min. The nuclear pellet is discarded and the supernatant fluid recentrifuged at 40,000 x g for 30 min. The resulting pellet formed contains a dark inner part with the exterior, slightly pink. The pink outer part is suspended in a small amount of 50.0 mM Tris.HCl buffer, pH 7.4. The protein content is determined by the Lowry's method (Lowry et al., J. Biol. Chem., 1953). The membrane suspension is stored at -70°C, in 50.0 mM Tris.HCl, containing 0.2% inactivated BSA and 0.1 mM PMSF in aliquots of 1.0 ml containing 10.0 mg protein per ml of suspension until use in subsequent binding experiments.

For binding experiments, the following is added in µl volume to wells of a 96 well format of a microtiter plate: 100.0 µl of 100.0 mM Tris.HCl buffer containing 0.2% heat inactivated BSA, 10.0 mM $MgCl_2$ and a mixture of protease inhibitors: leupeptin, 1.0 mg %; aprotinin, 1.0 mg %; 1,10-phenanthroline, 2.0 mg %; trypsin inhibitor, 10.0 mg % and 0.1 mM PMSF, 20.0 µl of [^{3}H] Arginine^8, vasopressin (S.A. 75.0 Ci/mmole) at

0.8 nM and the reaction initiated by the addition of 80.0 µl of tissue membranes (200.0 µg tissue protein). The plates are left undisturbed on the bench top for 120 min to reach equilibrium. Non-specific binding is assessed in the presence of 1.0 µM of unlabeled ligand, added in 20 µl volume. For test compounds, these are solubilized in 50% dimethylsulfoxide (DMSO) and added in 20.0 µl volume to a final incubation volume of 200 µl. Upon completion of binding, the content of each well is filtered off, using a Brandel® cell Harvester (Gaithersburg, MD). The radioactivity trapped on the filter disk by the ligand-receptor complex is assessed by liquid scintillation counting in a Packard LS Counter, with an efficiency of 65% for tritium. The data are analyzed for IC_{50} values by the LUNDON-2 program for competition (LUNDON SOFTWARE, OH). The results of this test on representative compounds of this invention are shown in Table XIII.

Radioligand Binding Experiments with Human Platelet Membranes

(a) Platelet Membrane Preparation:

Frozen platelet rich plasma (PRP), (Platelet Source: Hudson Valley Blood Services, Westchester Medical Center, Valhalla, NY) are thawed to room temperature. The tubes containing the PRP are centrifuged at 16,000 x g for 10 min. at 4°C and the supernatant fluid discarded. The platelets resuspended in an equal volume of 50.0 mM Tris.HCl, pH 7.5 containing 120 mM NaCl and 20.0 mM EDTA. The suspension is recentrifuged at 16,000 x g for 10 min. This washing step is repeated one more time. The wash discarded and the lysed pellets homogenized in low ionic strength buffer of Tris.HCl, 5.0 mM, pH 7.5 containing 5.0 mM EDTA. The homogenate is centrifuged at 39,000 x g for 10 min. The resulting pellet is resuspended in Tris.HCl buffer, 70.0 mM, pH 7.5 and recentrifuged at

39,000 x g for 10 min. The final pellet is resuspended in 50.0 mM Tris.HCl buffer pH 7.4 containing 120 mM NaCl and 5.0 mM KCl to give 1.0-2.0 mg protein per ml of suspension.

(b) Binding to Vasopressin V_1 receptor subtype in Human Platelet Membranes:

In wells of a 96 well format microtiter plate, add 100 µl of 50.0 mM Tris.HCl buffer containing 0.2% BSA and a mixture of protease inhibitors (aprotinin, leupeptin etc.). Then add 20 µl of [^{3}H]Ligand (Manning or Arg^{8}Vasopressin), to give final concentrations ranging from 0.01 to 10.0 nM. Initiate the binding by adding 80.0 µl of platelet suspension (approx. 100 µg protein). Mix all reagents by pipetting the mixture up and down a few times. Non specific binding is measured in the presence of 1.0 µM of unlabeled ligand (Manning or Arg^{8}Vasopressin). Let the mixture stand undisturbed at room temperature for ninety (90) min. Upon this time, rapidly filter off the incubate under vacuum suction over GF/B filters, using a Brandel Harvester. Determine the radioactivity caught on the filter disks by the addition of liquid scintillant and counting in a liquid scintillator.

Binding to Membranes of Mouse Fibroblast Cell Line (LV-2) Transfected with the cDNA Expressing the Human V_2 Vasopressin Receptor

(a) Membrane Preparation

Flasks of 175 ml capacity, containing attached cells grown to confluence, are cleared of culture medium by aspiration. The flasks containing the attached cells are rinsed with 2x5 ml of phosphate buffered saline (PBS) and the liquid aspirated off each time. Finally, 5 ml of an enzyme free dissociation Hank's based solution (Specialty Media, Inc., Lafayette, NJ) is added and the flasks are left undisturbed for 2 min. The content of all flasks is

poured into a centrifuge tube and the cells pelleted at 300 x g for 15 min. The Hank's based solution is aspirated off and the cells homogenized with a polytron at setting #6 for 10 sec in 10.0 mM Tris.HCl buffer, pH 7.4 containing 0.25 M sucrose and 1.0 mM EDTA. The homogenate is centrifuged at 1500 x g for 10 min to remove ghost membranes. The supernatant fluid is centrifuged at 100,000 x g for 60 min to pellet the receptor protein. Upon completion, the pellet is resuspended in a small volume of 50.0 mM Tris.HCl buffer, pH 7.4. The protein content is determined by the Lowry method and the receptor membranes are suspended in 50.0 mM Tris.HCl buffer containing 0.1 mM phenylmethylsulfonylfluoride (PMSF) and 0.2% bovine serum albumin (BSA) to give 2.5 mg receptor protein per ml of suspension.

(b) Receptor Binding

For binding experiments, the following is added in μl volume to wells of a 96 well format of a microtiter plate: 100.0 μl of 100.0 mM Tris.HCl buffer containing 0.2% heat inactivated BSA, 10.0 mM $MgCl_2$ and a mixture of protease inhibitors: leupeptin, 1.0 mg%; aprotinin, 1.0 mg %; 1,10-phenanthroline, 2.0 mg %; trypsin inhibitor, 10.0 mg % and 0.1 mM PMSF., 20.0 μl of [^{3}H] Arginine^8, vasopressin (S.A. 75.0 Ci/mmole) at 0.8 nM and the reaction initiated by the addition of 80.0 μl of tissue membranes (200.0 μg tissue protein). The plates are left undisturbed on the bench top for 120 min to reach equilibrium. Non specific binding is assessed in the presence of 1.0 μM of unlabeled ligand, added in 20 μl volume. For test compounds, these are solubilized in 50% dimethylsulfoxide (DMSO) and added in 20.0 μl volume to a final incubation volume of 200 μl. Upon completion of binding, the content of each well is filtered off, using a Brandel® cell Harvester (Gaithersburg, MD). The radioactivity trapped on the filter disk by the ligand-receptor complex is assessed

by liquid scintillation counting in a Packard LS Counter, with an efficiency of 65% for tritium. The data are analyzed for IC_{50} values by the LUNDON-2 program for competition (LUNDON SOFTWARE, OH).

This Sheet Has Been Replaced

Table XIII

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

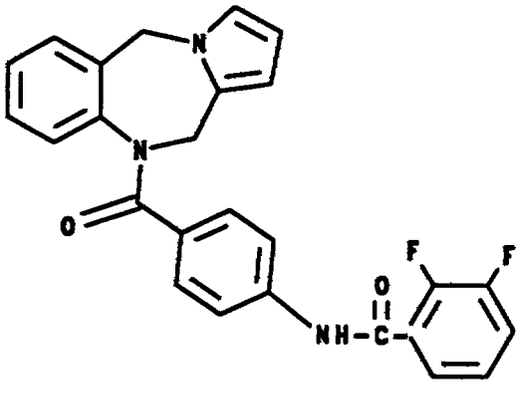
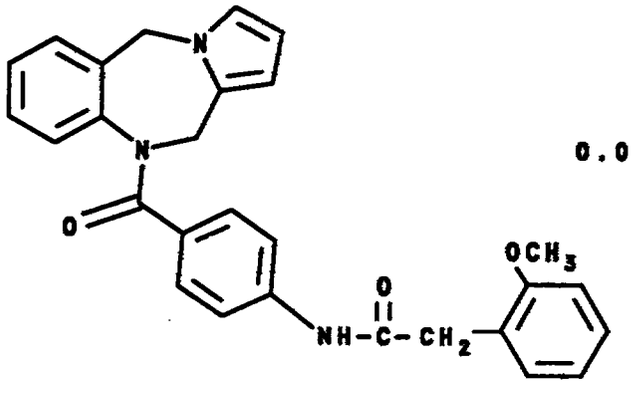
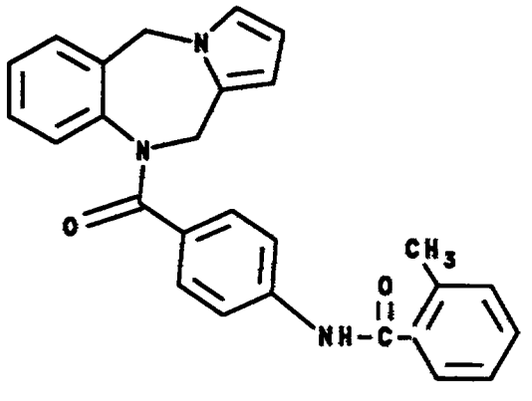
Ex.No.	Structure	V_1 $IC_{50}(\mu M)$	V_2 $IC_{50}(\mu M)$
1		0.097	0.029
215		0.016	0.022
3		0.038	0.004

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

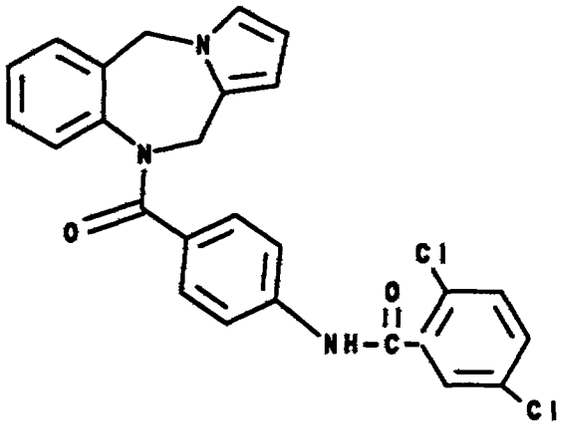
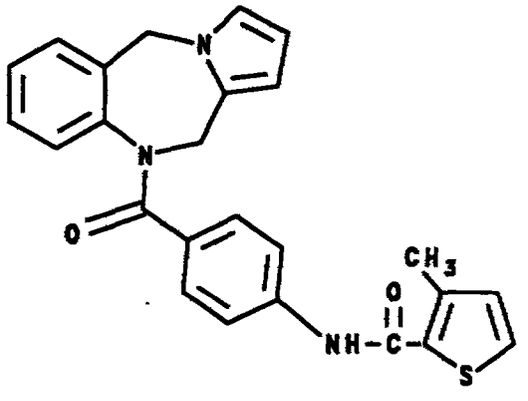
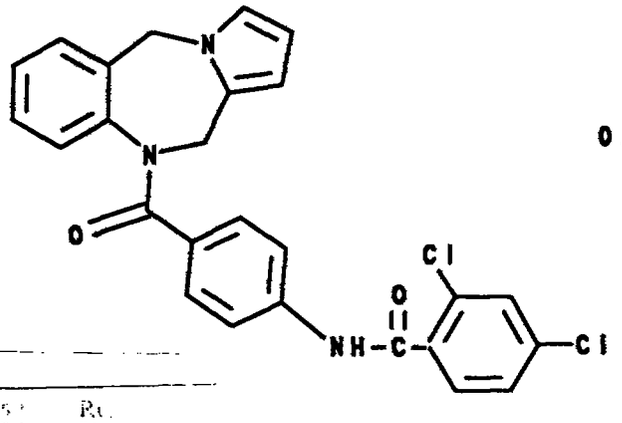
Ex.No.	Structure	V_1 $IC_{50}(\mu M)$	V_2 $IC_{50}(\mu M)$
4		0.12	0.014
5		0.015	0.025
6		0.023	0.003

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

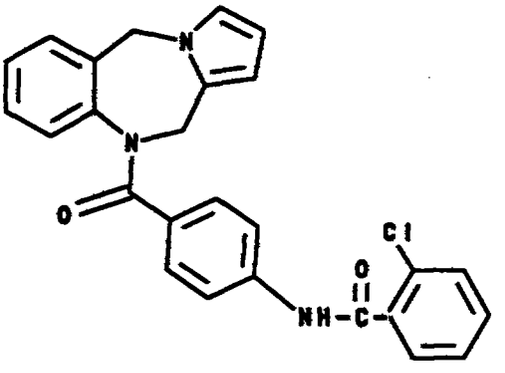
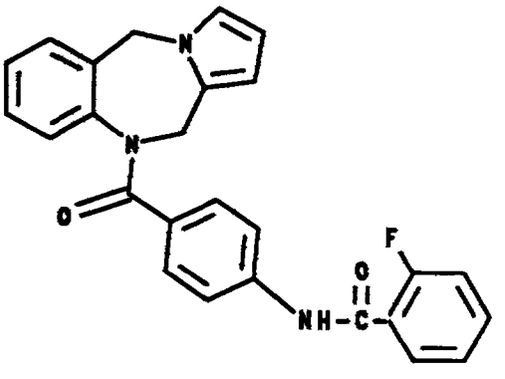
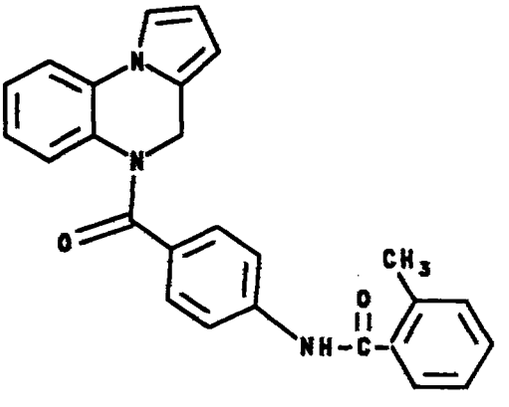
Ex.No.	Structure	V_1 $IC_{50}(\mu M)$	V_2 $IC_{50}(\mu M)$
7		0.01	0.005
8		0.056	0.035
14		0.17	0.066

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or **Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

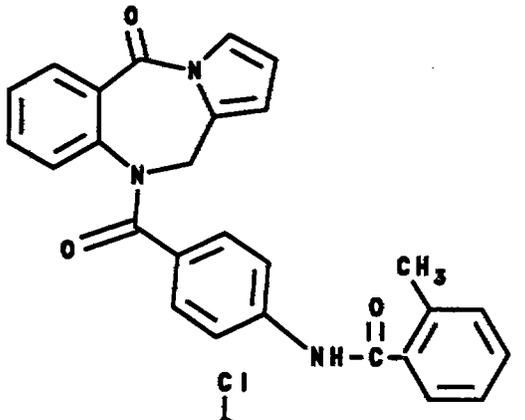
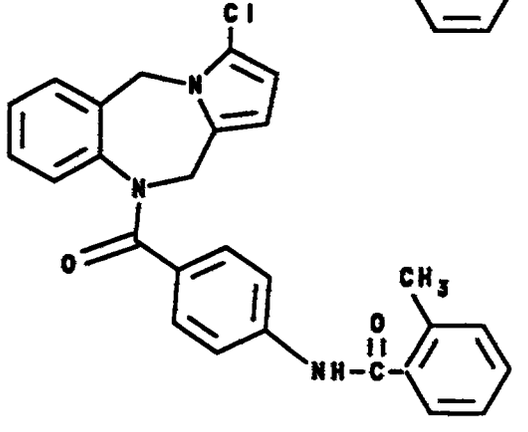
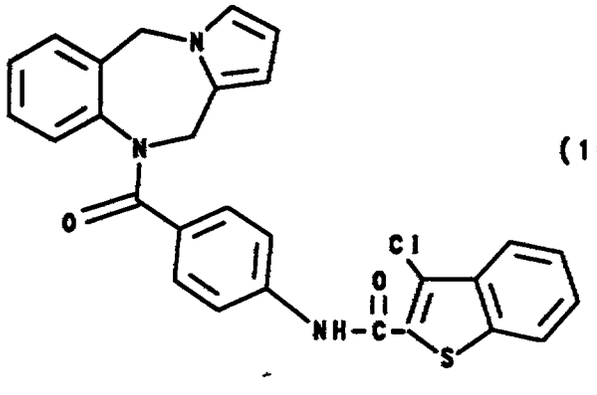
Ex.No.	Structure	V_1 $IC_{50}(\mu M)$	V_2 $IC_{50}(\mu M)$
40		2.4	0.12
41		0.037	0.017
82		(10μM)23%	(10μM)71%

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

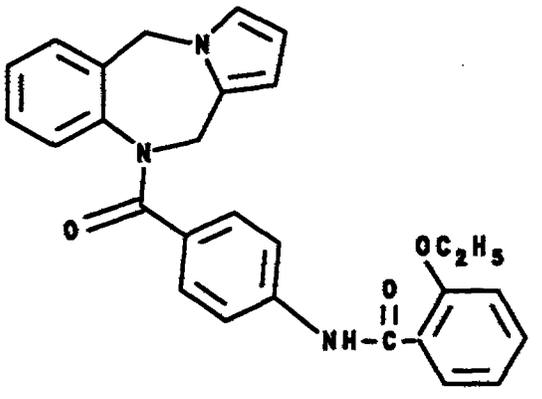
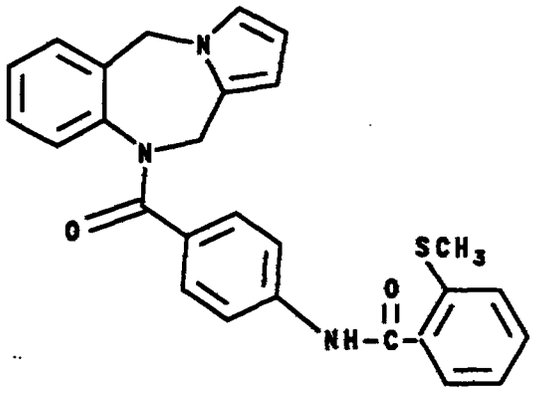
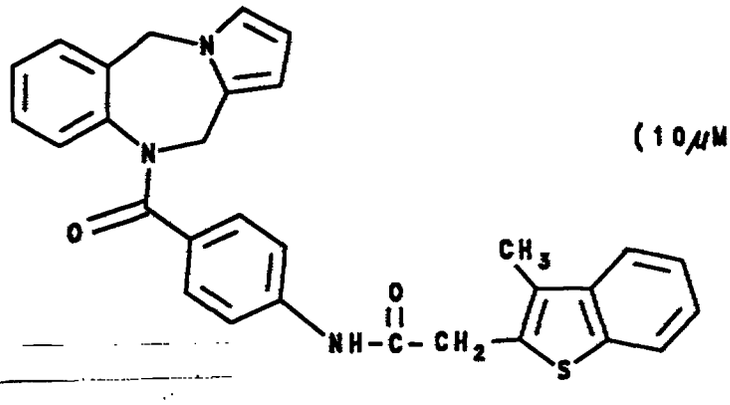
Ex.No.	Structure	V_1 $IC_{50}(\mu M)$	V_2 $IC_{50}(\mu M)$
84		0.045	0.077
85		0.009	0.013
87		(10μM)63×	(10μM)80×

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

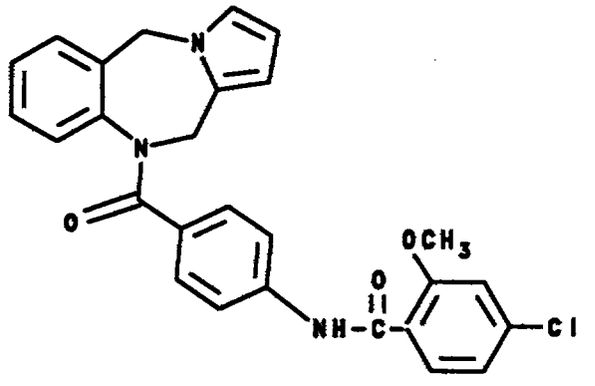
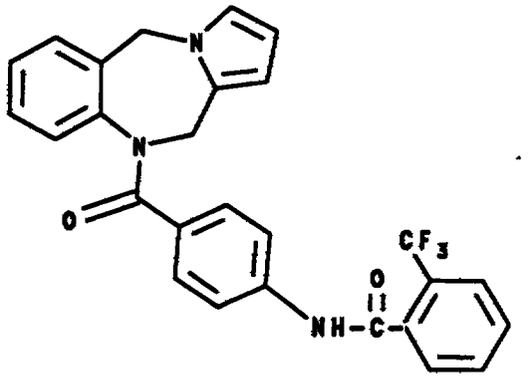
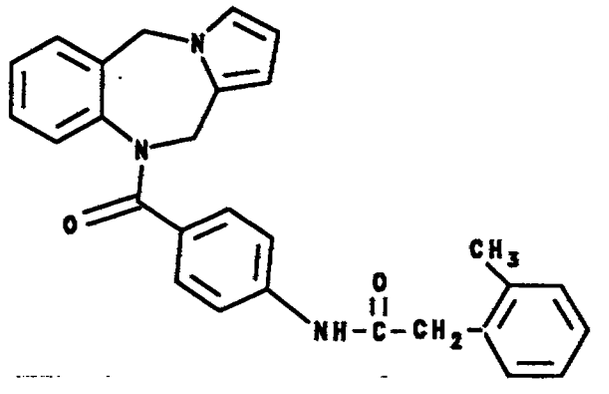
Ex.No.	Structure	V_1 $IC_{50}(\mu M)$	V_2 $IC_{50}(\mu M)$
89		0.023	0.008
91		0.028	0.022
93		0.0009	0.0007

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

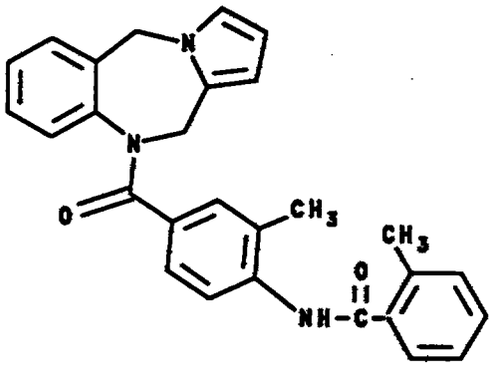
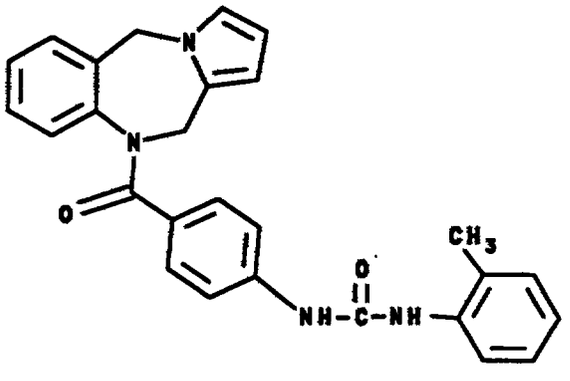
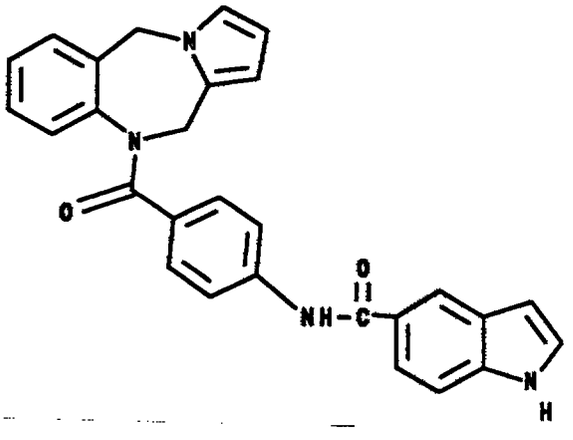
Ex.No.	Structure	V_1 IC_{50}(μM)	V_2 IC_{50}(μM)
96		0.056	0.011
116		0.28	0.085
117		2.77	0.377

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

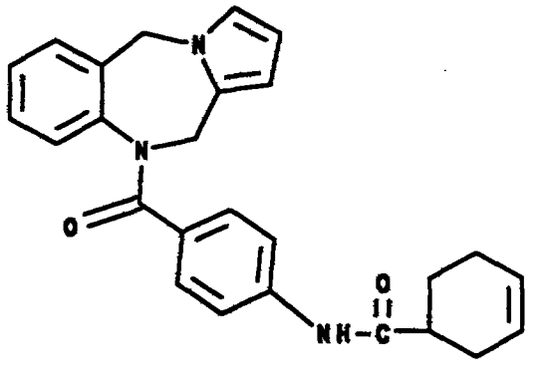
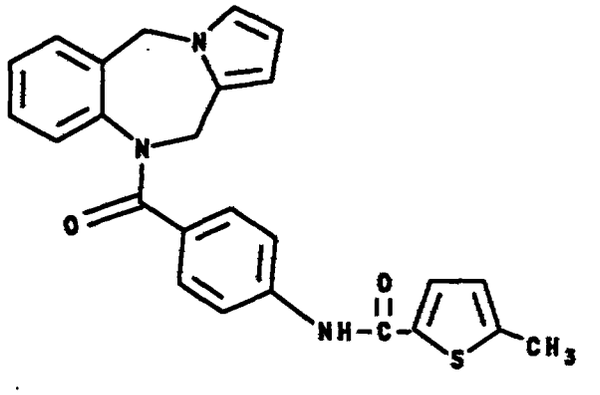
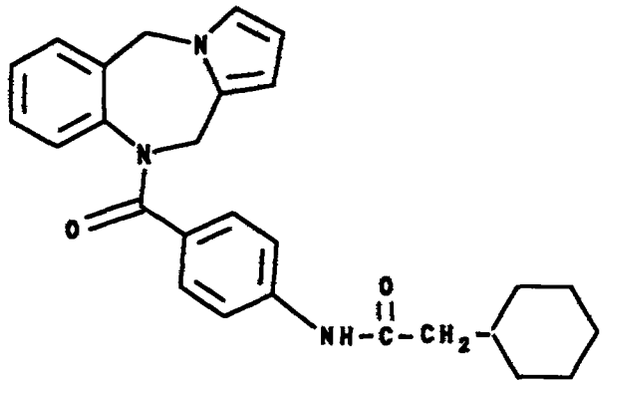
Ex.No.	Structure	V_1 $IC_{50}(\mu M)$	V_2 $IC_{50}(\mu M)$
354		0.012	0.007
355		0.165	0.35
356		0.087	0.053

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

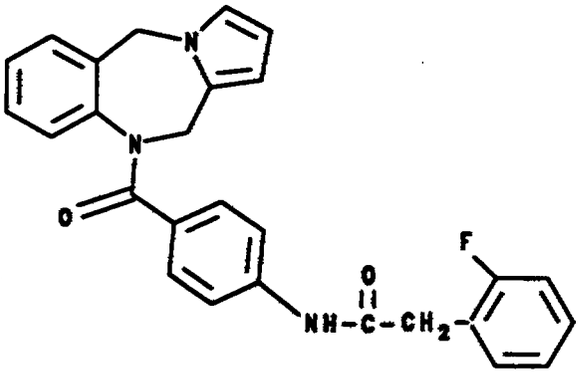
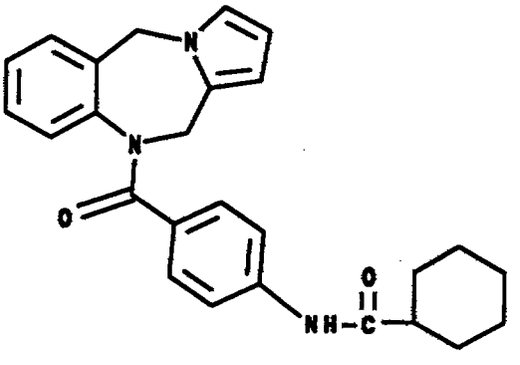
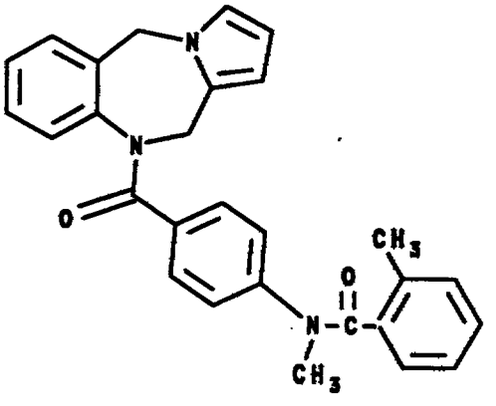
Ex.No.	Structure	V_1 $IC_{50}(\mu M)$	V_2 $IC_{50}(\mu M)$
357		0.019	0.017
358		0.011	0.016
384		0.188	0.059

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype In Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

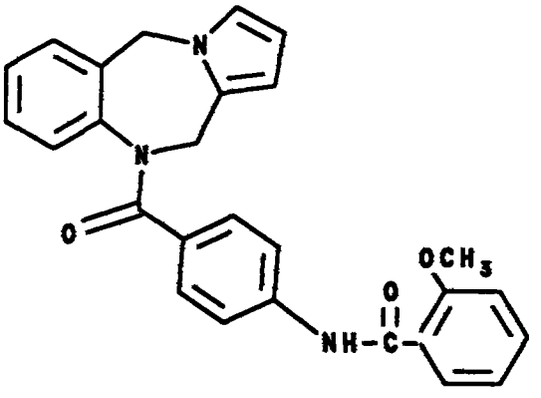
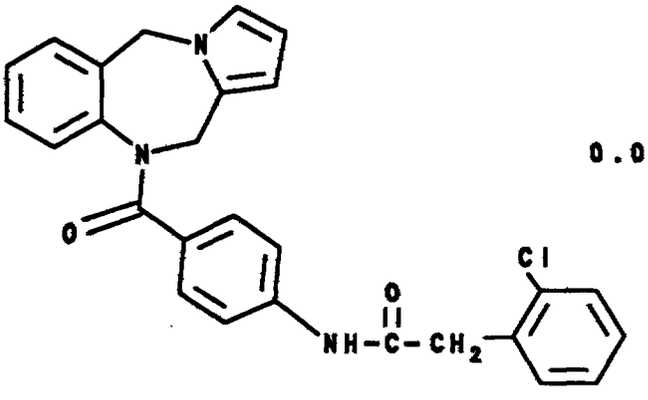
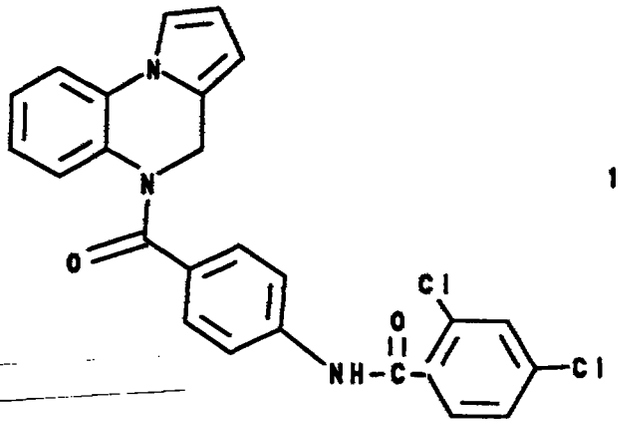
Ex.No.	Structure	V_1 $IC_{50}(\mu M)$	V_2 $IC_{50}(\mu M)$
2		0.031	0.014
9		0.007	0.004
17 160		1.2	0.11

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

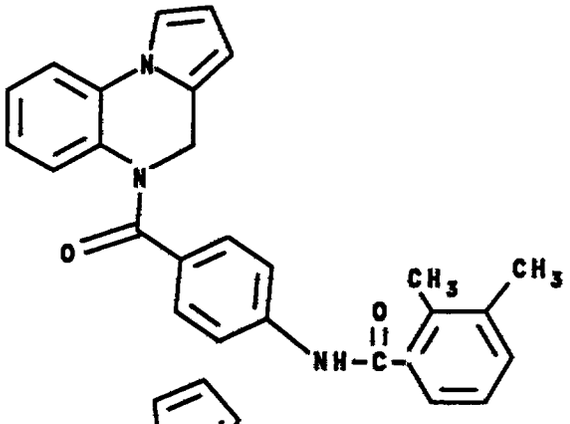
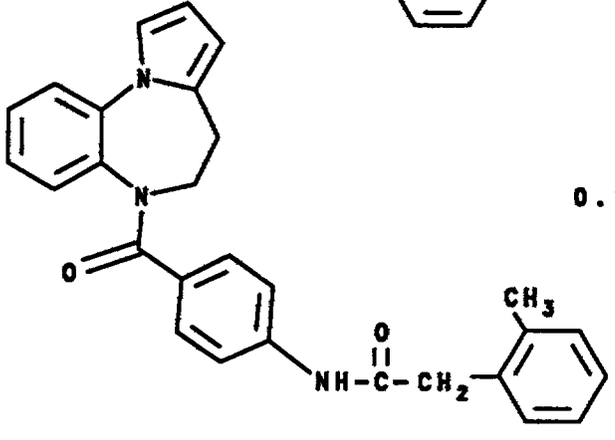
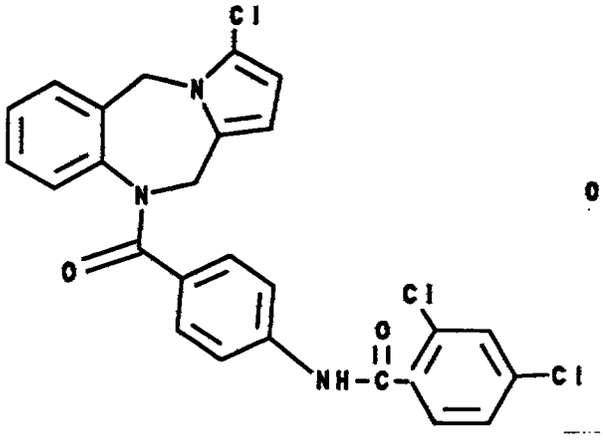
Ex.No.	Structure	V_1 $IC_{50}(\mu M)$	V_2 $IC_{50}(\mu M)$
21		0.93	0.087
36 179		0.10	0.054
54		0.31*	0.007**

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

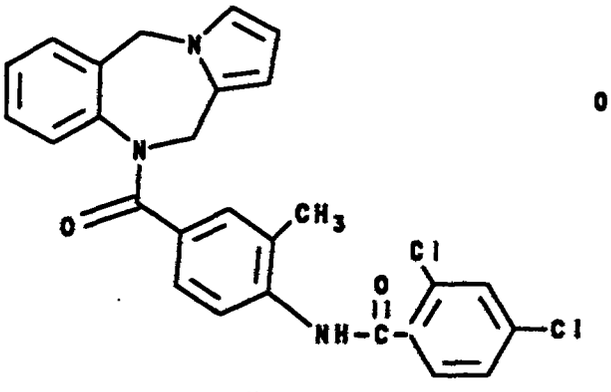
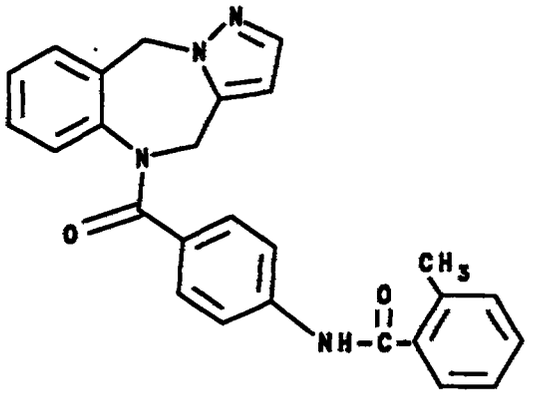
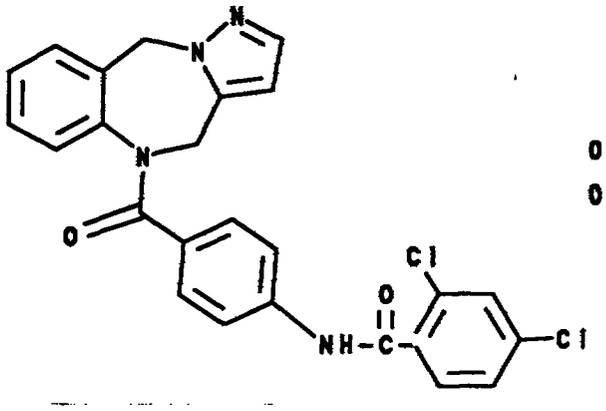
Ex.No.	Structure	V_1 $IC_{50}(\mu M)$	V_2 $IC_{50}(\mu M)$
99		0.027	0.010
210 214		0.058	0.016
217		0.068 0.19*	0.005 0.01**

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

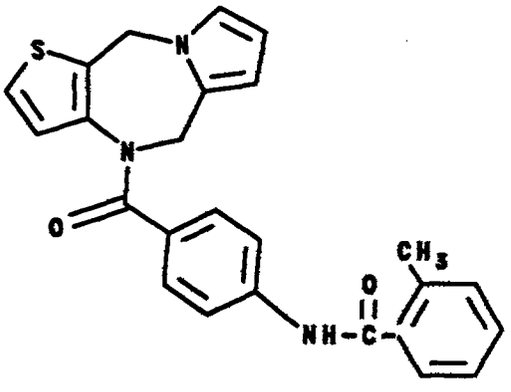
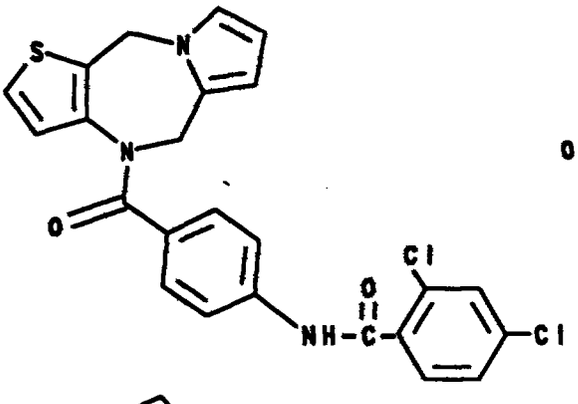
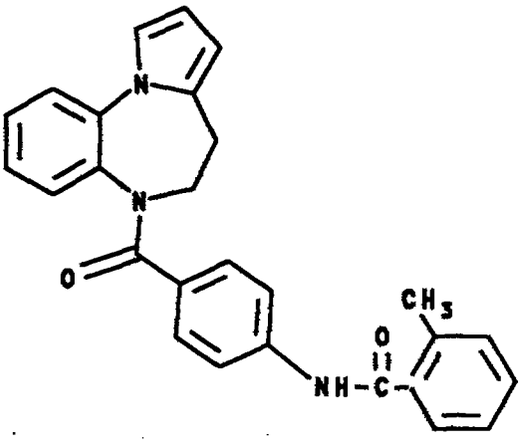
Ex.No.	Structure	V_1 $IC_{50}(\mu M)$	V_2 $IC_{50}(\mu M)$
267 271		0.22	0.028
274		0.24*	0.031**
297 298		0.27	0.033

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

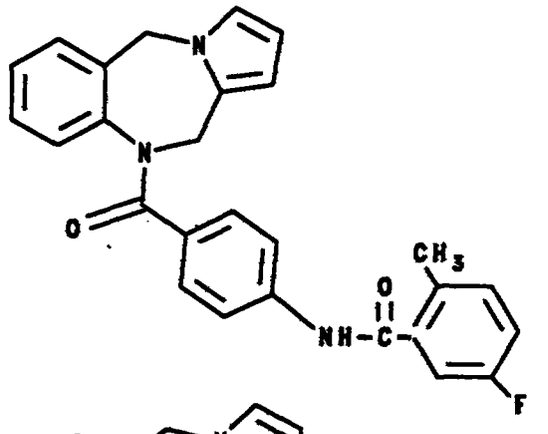
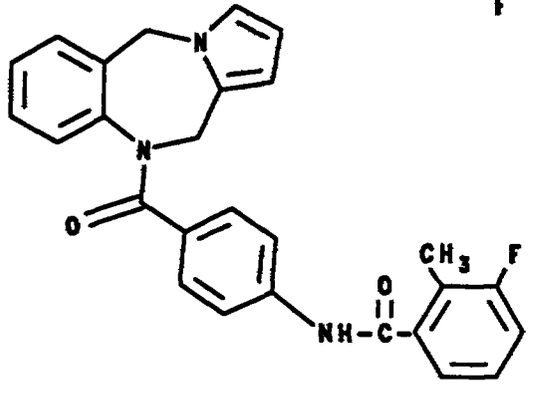
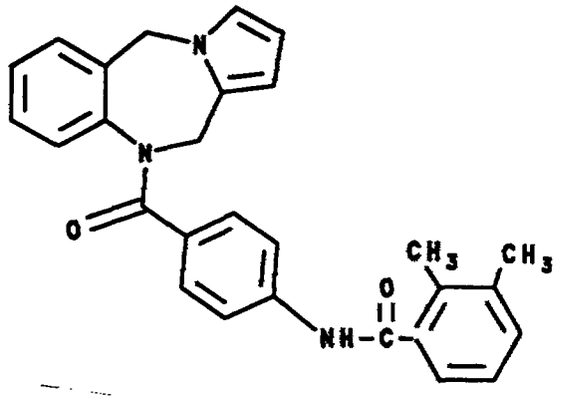
Ex.No.	Structure	V_1 $IC_{50}(\mu M)$	V_2 $IC_{50}(\mu M)$
465		0.020*	0.0015**
466		0.026	0.004
467		0.031	0.005

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

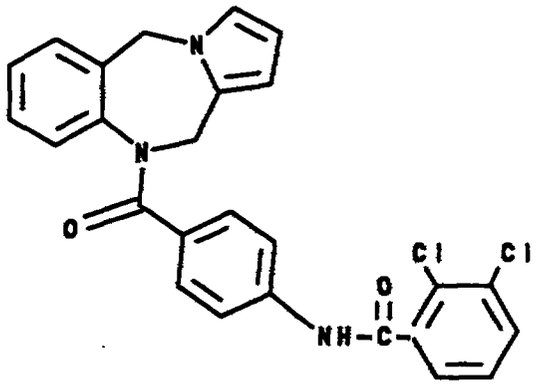
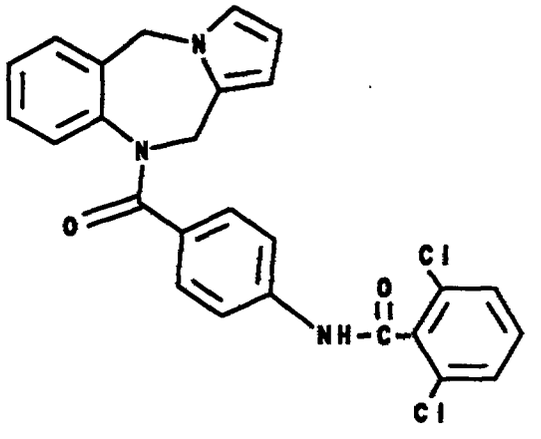
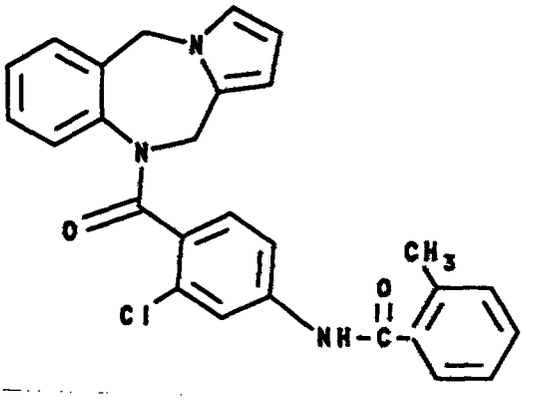
Ex.No.	Structure	V_1 $IC_{50}(\mu M)$	V_2 $IC_{50}(\mu M)$
468		0.027	0.029
469		0.094	0.015
470		0.054	0.0045

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

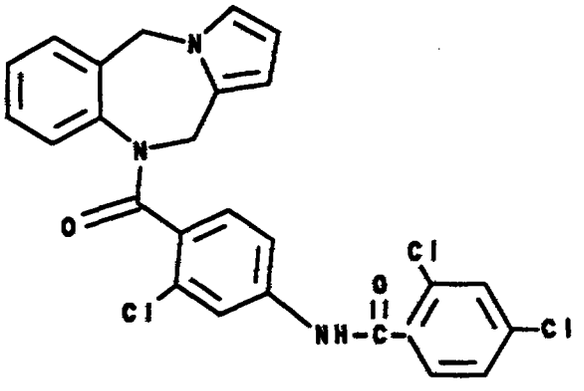
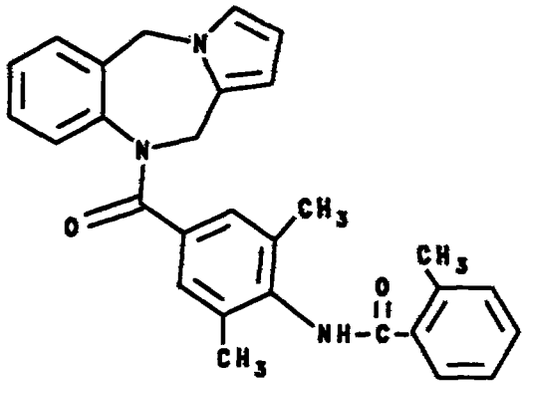
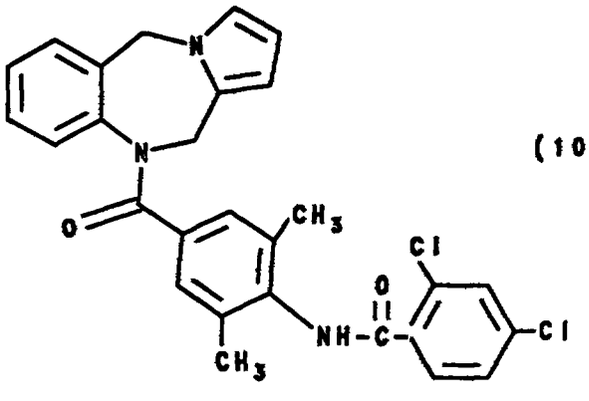
Ex.No.	Structure	V_1 $IC_{50}(\mu M)$	V_2 $IC_{50}(\mu M)$
471		0.045	0.0083
472		0.89	(10μM)22×
473		(10 μM)90×	(10 μM)56×

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

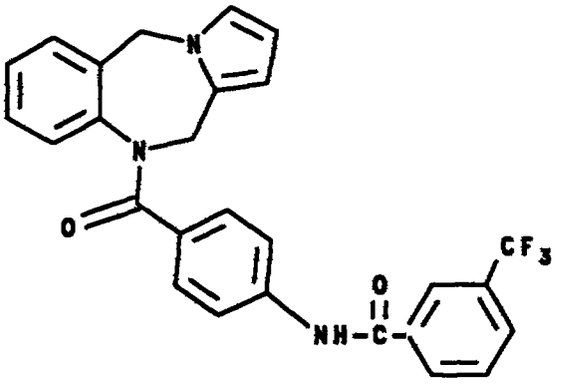
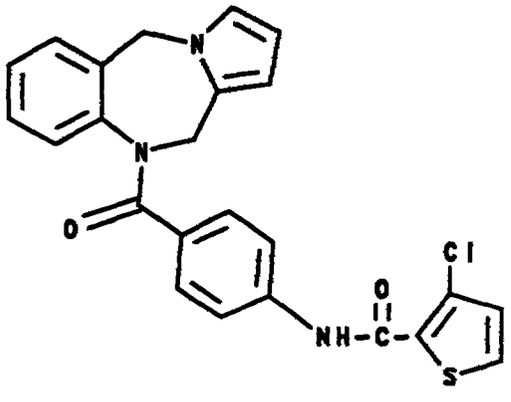
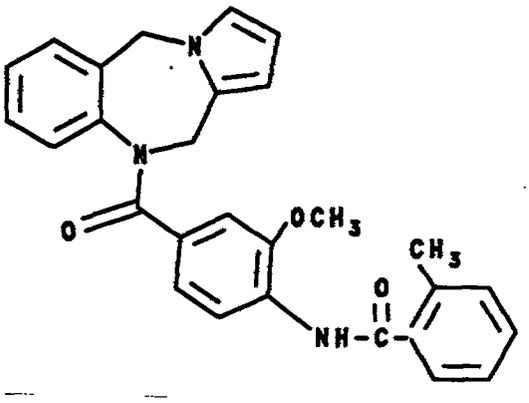
Ex.No.	Structure	V_1 $IC_{50}(\mu M)$	V_2 $IC_{50}(\mu M)$
474		0.087	0.038
476		0.084	0.069
477		0.003*	0.0032**

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

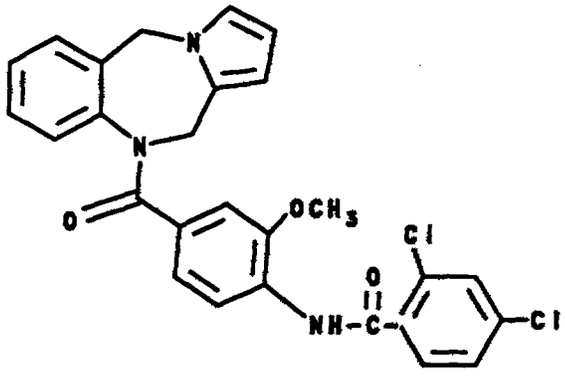
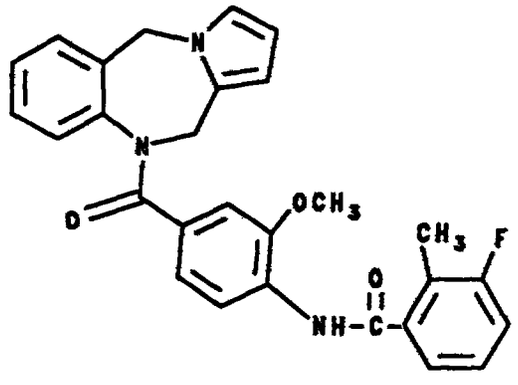
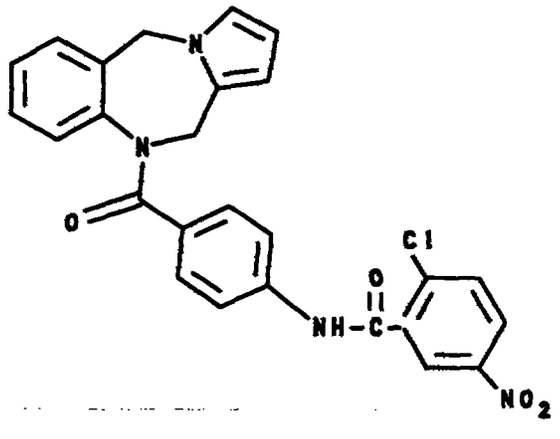
Ex.No.	Structure	V_1 $IC_{50}(\mu M)$	V_2 $IC_{50}(\mu M)$
478		0.032*	0.0019**
479		0.023*	0.008
480		0.54*	0.026**

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

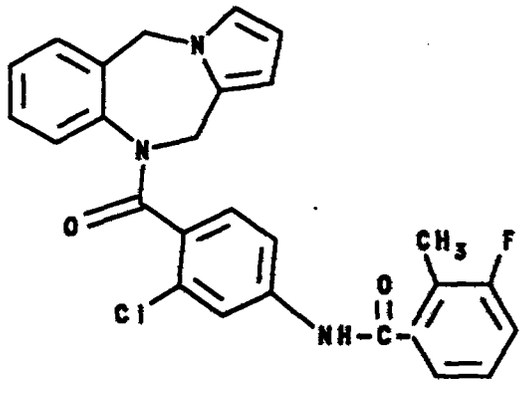
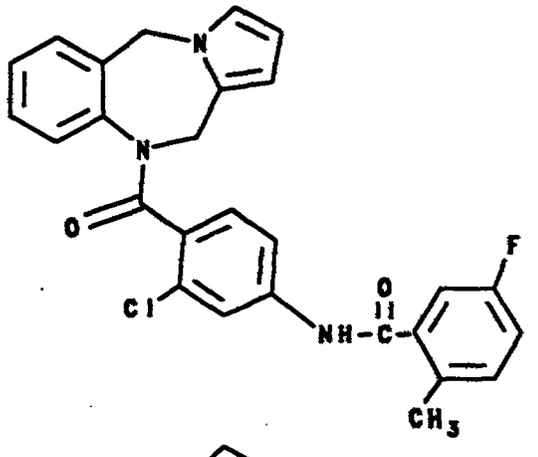
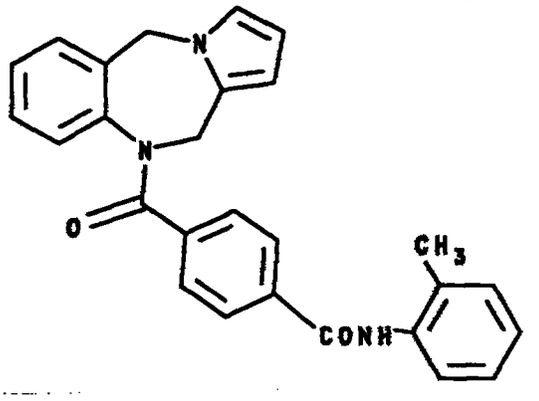
Ex.No.	Structure	V_1 IC_{50}(μM)	V_2 IC_{50}(μM)
481		1.0	0.0034
482		0.41	0.0023
484		0.097	0.025

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

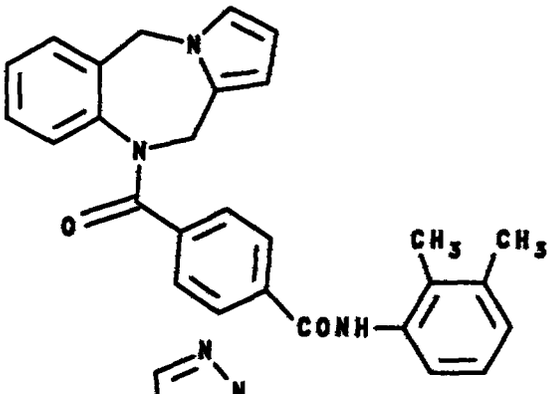
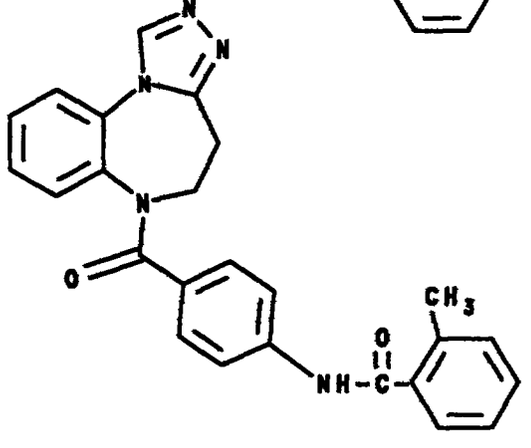
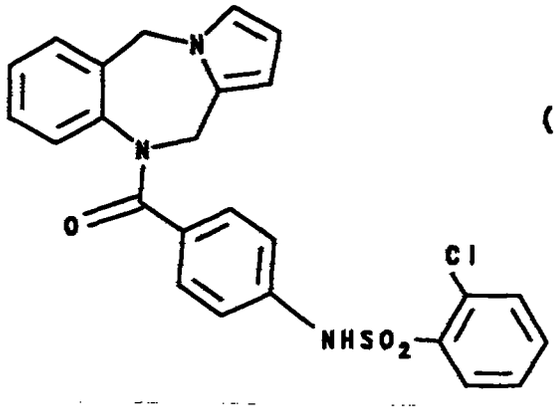
Ex.No.	Structure	V_1 $IC_{50}(\mu M)$	V_2 $IC_{50}(\mu M)$
485		0.24	0.013
486		(10μM)39%	(10μM)77%
488		(10μM)96%	(10μM)87%

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

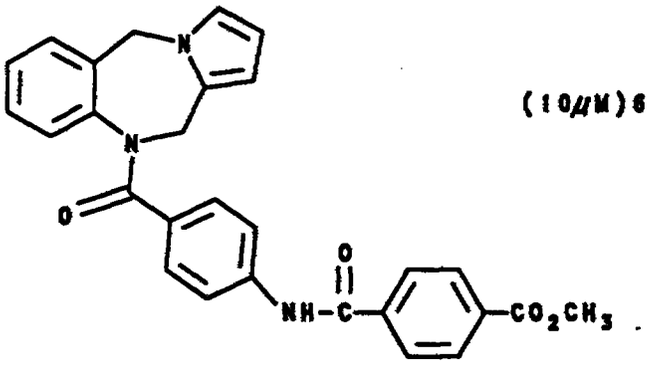
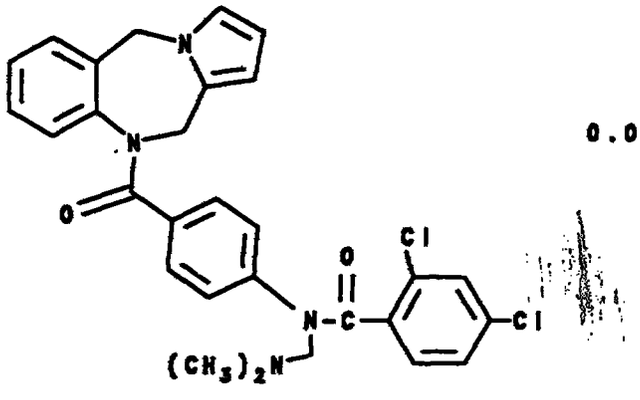
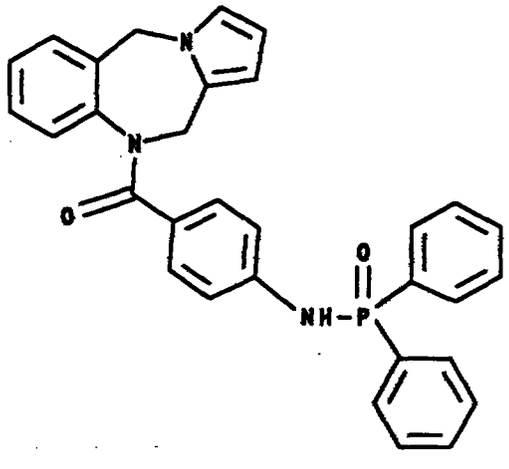
Ex.No.	Structure	V_1 $IC_{50}(\mu M)$	V_2 $IC_{50}(\mu M)$
489		(10μM)61%	(10μM)82%
490		0.014	0.005
491		(10μM)82%	(10μM)83%

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

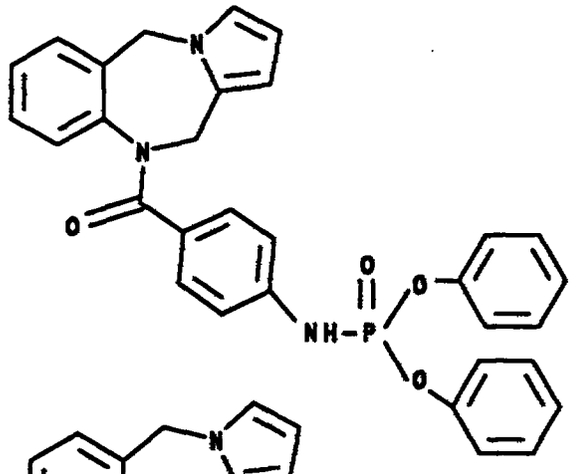
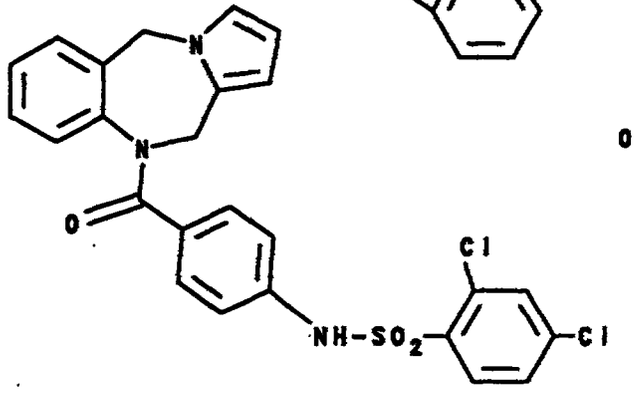
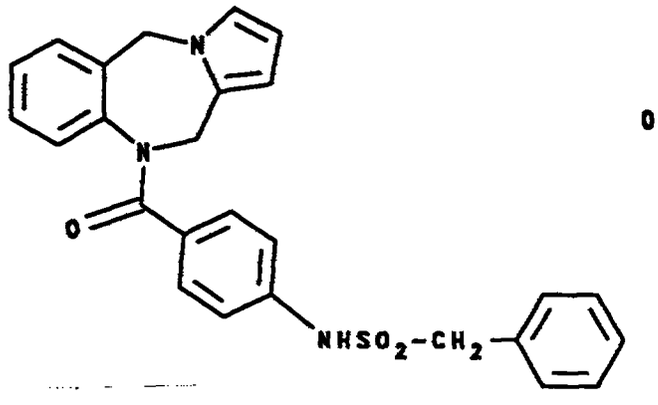
Ex.No.	Structure	V_1 $IC_{50}(\mu M)$	V_2 $IC_{50}(\mu M)$
492		0.16	3.2
493		0.14	(10μM)68*
494		0.11	5.8

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

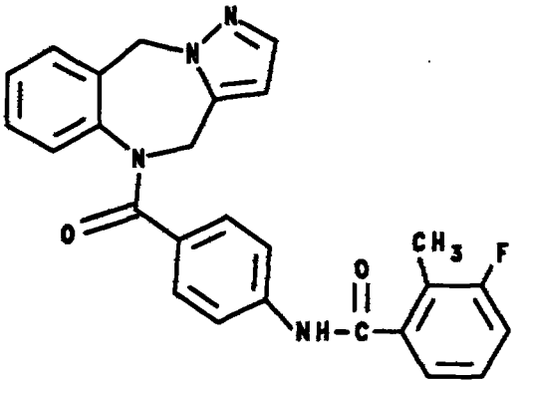
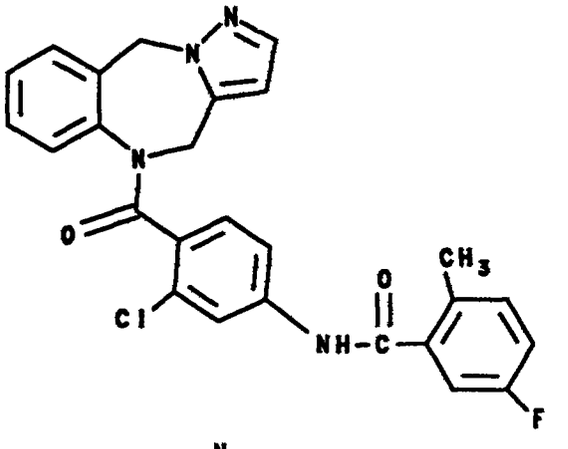
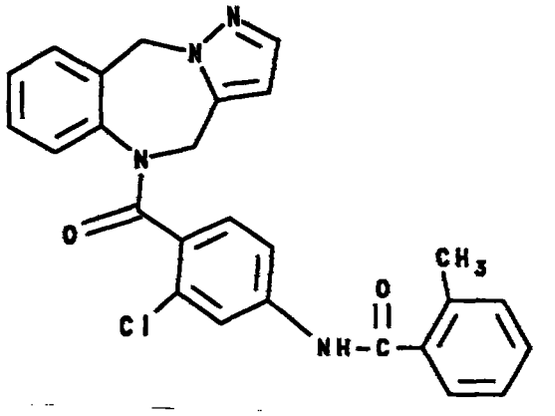
Ex.No.	Structure	V_1 $IC_{50}(\mu M)$	V_2 $IC_{50}(\mu M)$
517		0.21	0.015
518		0.22*	0.0017**
519		0.12*	0.0032**

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

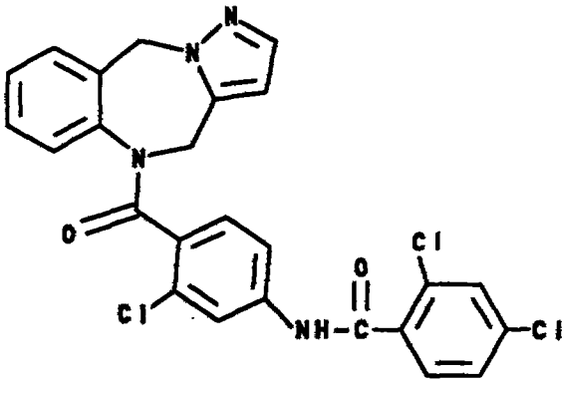
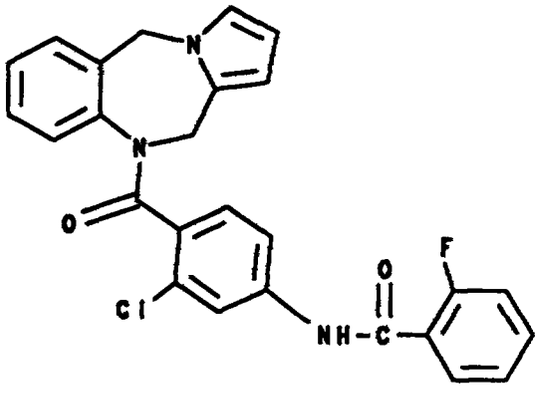
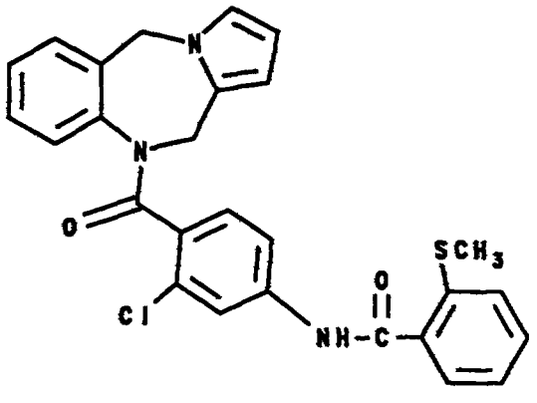
Ex.No.	Structure	V_1 $IC_{50}(\mu M)$	V_2 $IC_{50}(\mu M)$
520		0.85*	0.0044**
523		0.11*	0.0028**
524		0.17*	0.0012**

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

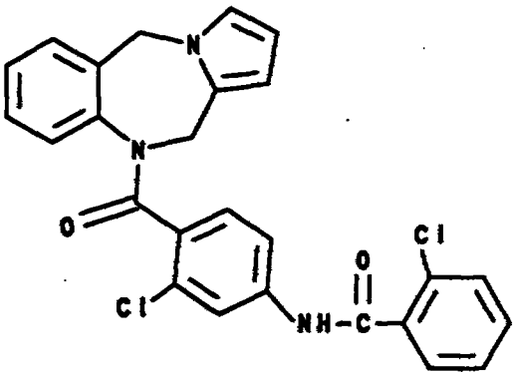
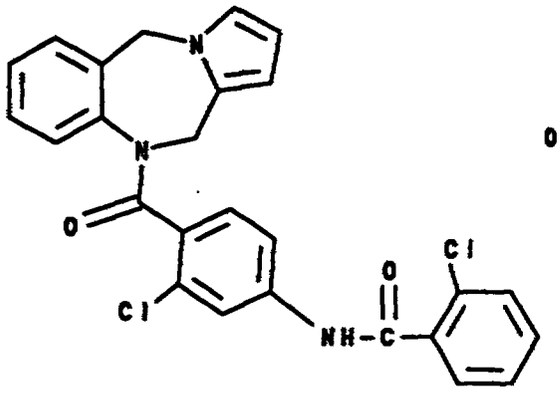
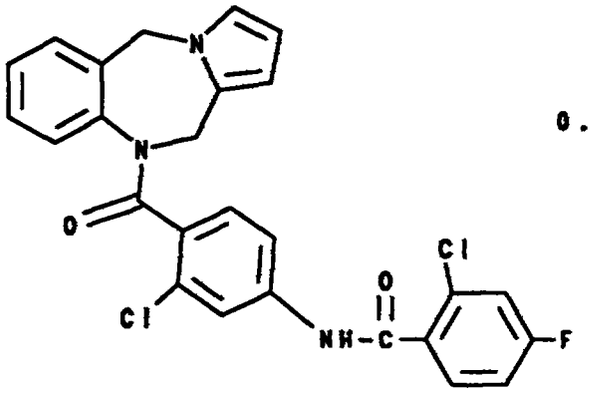
Ex.No.	Structure	V_1 IC_{50}(μM)	V_2 IC_{50}(μM)
525		0.43*	0.00042**
526		0.05*	0.0033**
527		0.026*	0.00067**

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

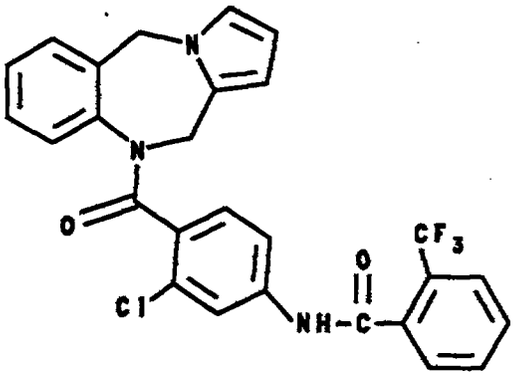
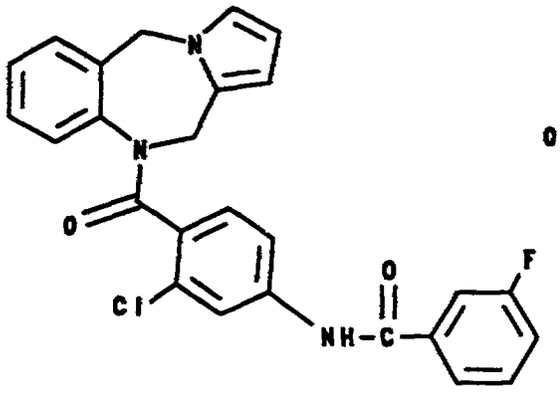
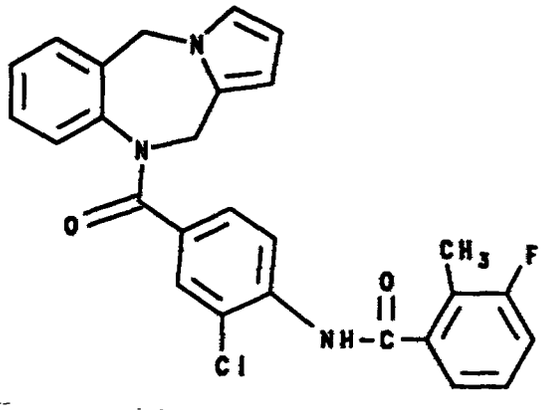
Ex.No.	Structure	V_1 $IC_{50}(\mu M)$	V_2 $IC_{50}(\mu M)$
528		0.20*	0.006**
538		0.052*	0.001**
546		0.066*	0.073**

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

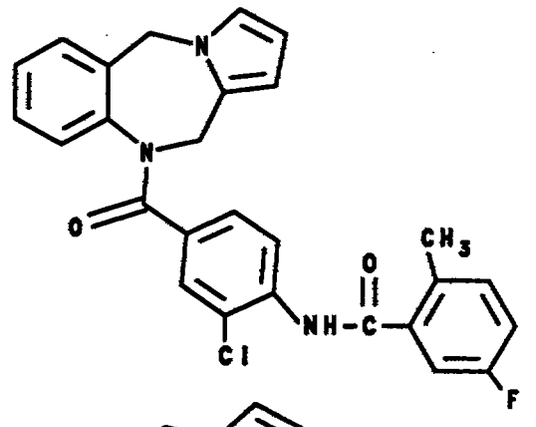
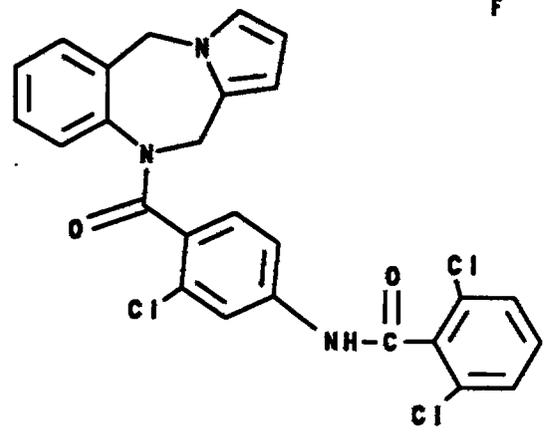
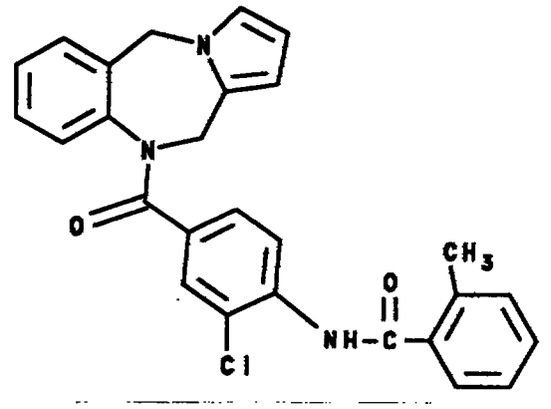
Ex.No.	Structure	V_1 $IC_{50}(\mu M)$	V_2 $IC_{50}(\mu M)$
547		0.016*	0.004**
529		0.99*	0.002**
530		0.003*	0.0037

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

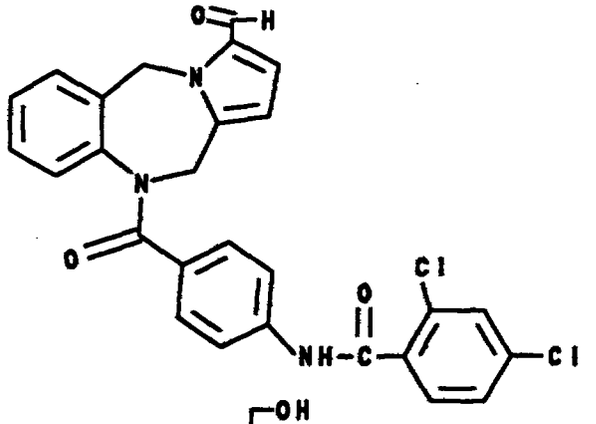
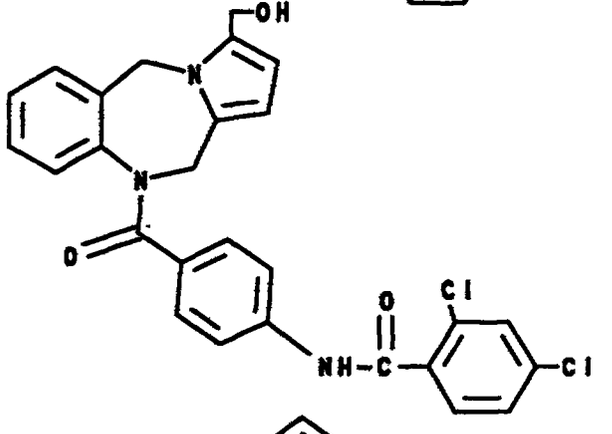
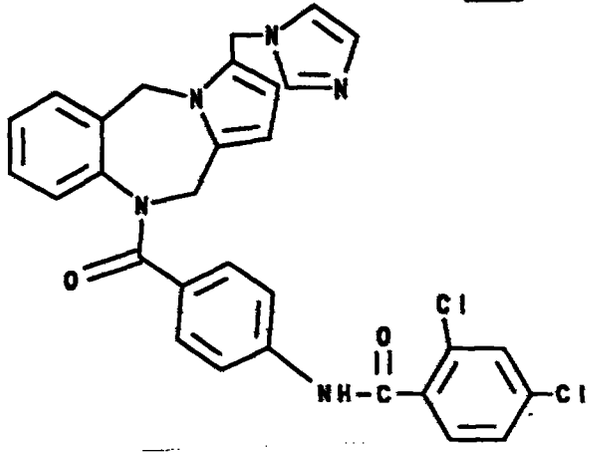
Ex.No.	Structure	V_1 $IC_{50}(\mu M)$	V_2 $IC_{50}(\mu M)$
580		0.2	0.08
581		0.021	0.0053
582		0.13	0.014

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

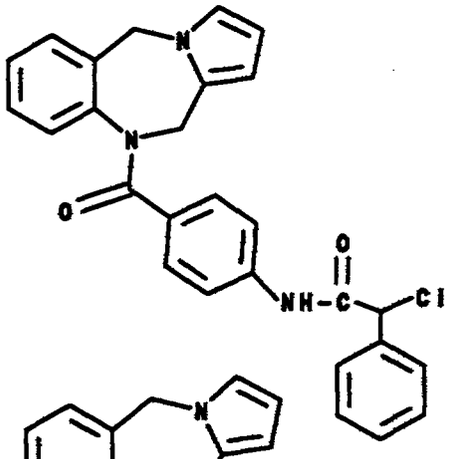
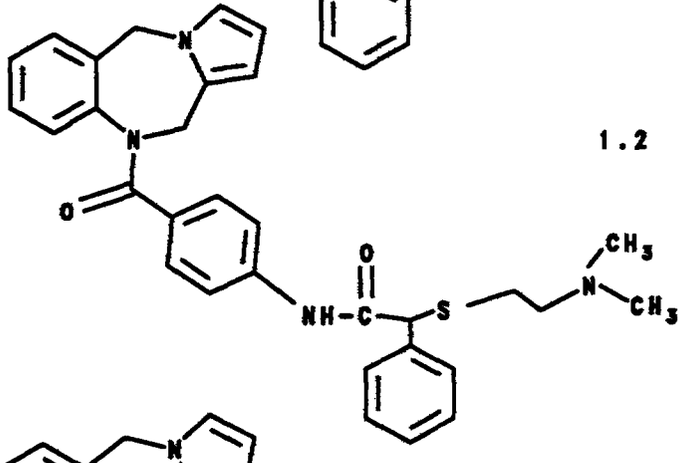
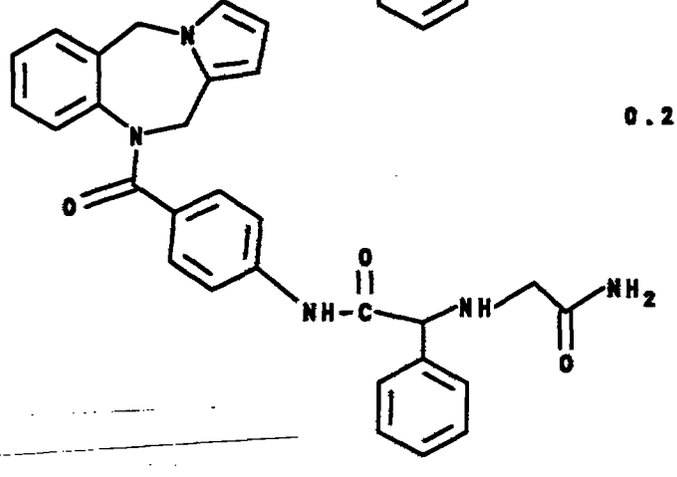
Ex.No.	Structure	V_1 $IC_{50}(\mu M)$	V_2 $IC_{50}(\mu M)$
583		0.054	0.027
584		1.2	0.48
585		0.28	0.083

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

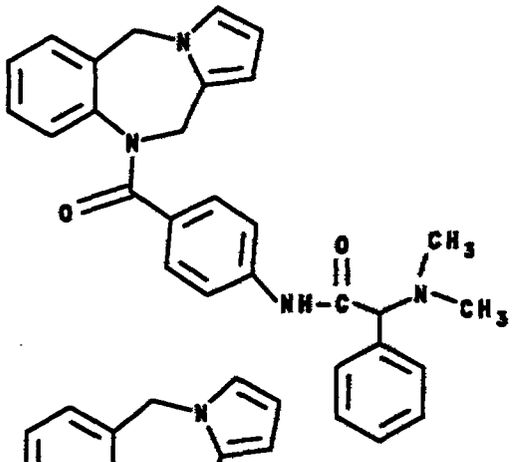
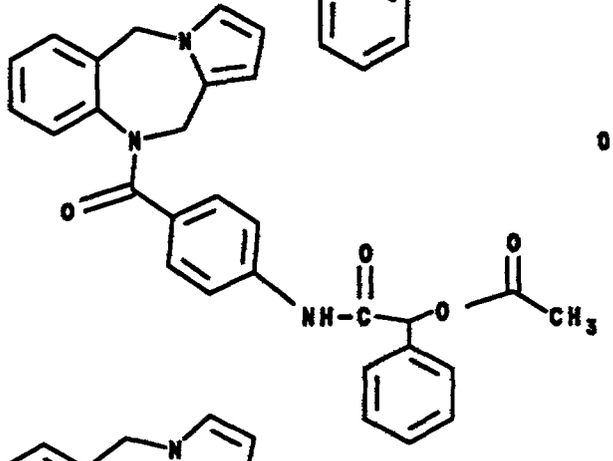
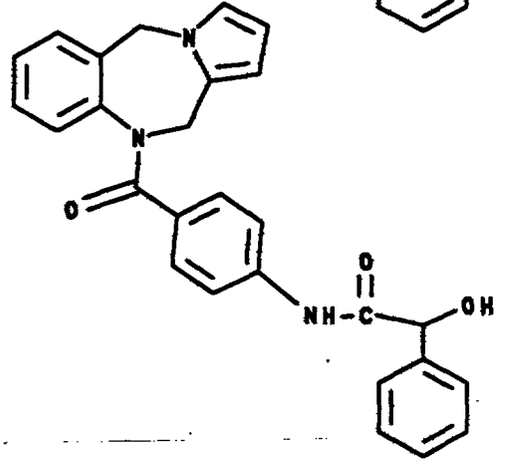
Ex.No.	Structure	V_1 $IC_{50}(\mu M)$	V_2 $IC_{50}(\mu M)$
586		0.45	0.23
587		0.087	0.022
588		0.040	0.012

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

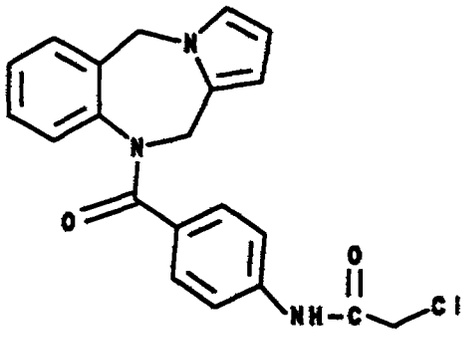
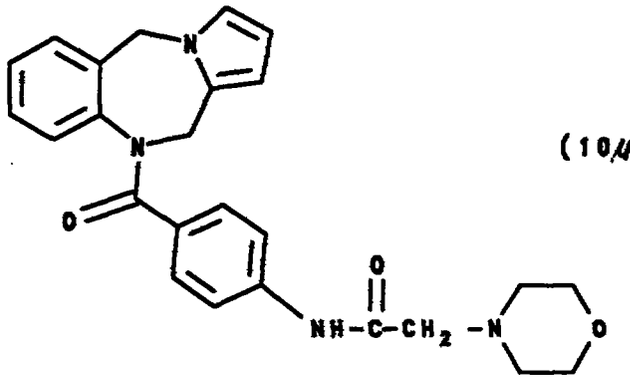
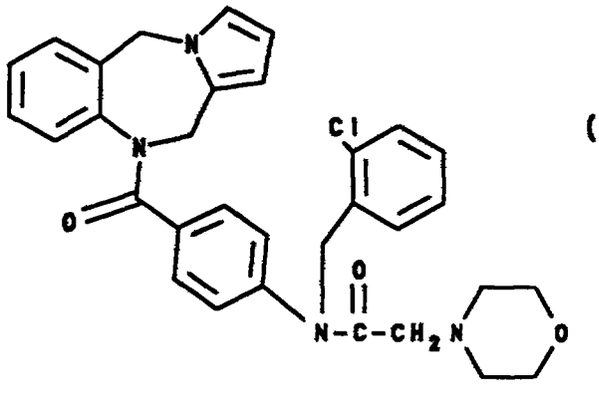
Ex.No.	Structure	V_1 $IC_{50}(\mu M)$	V_2 $IC_{50}(\mu M)$
589		(10μM)81%	(10μM)82%
590		(10μM)89%	(10μM)81%
591		(10μM)45%	(10μM)64%

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

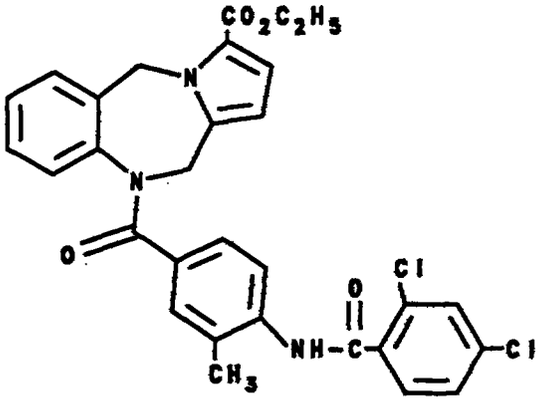
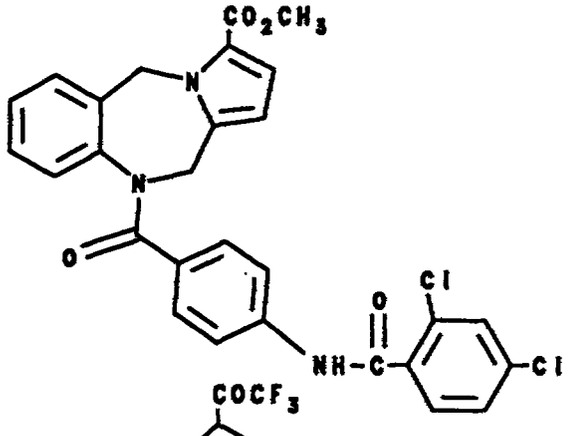
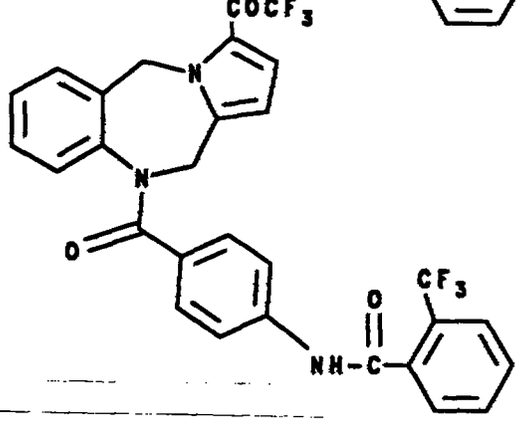
Ex.No.	Structure	V_1 $IC_{50}(\mu M)$	V_2 $IC_{50}(\mu M)$
592		3.3	0.24
593		0.21	0.042
594		(10μM)78%	(10μM)23%

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

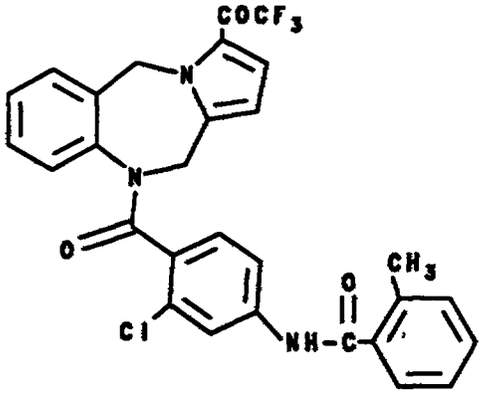
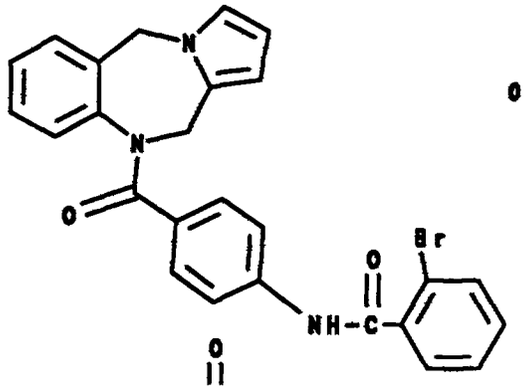
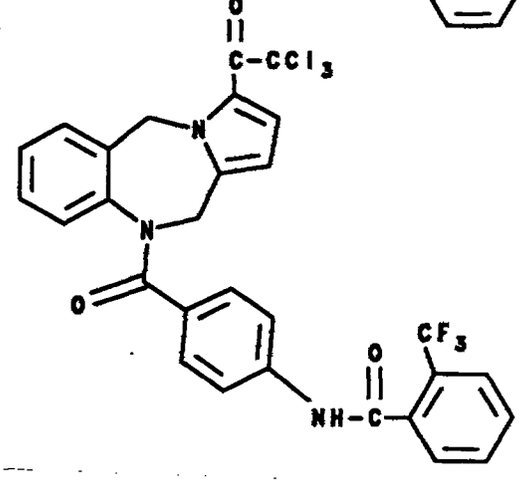
Ex.No.	Structure	V_1 $IC_{50}(\mu M)$	V_2 $IC_{50}(\mu M)$
595		(10μM)57%	(10μM)93%
687		0.002*	0.007**
597		(10μM)100%	(10μM)97%

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

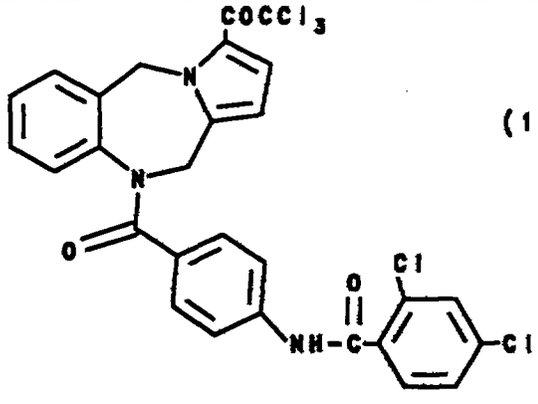
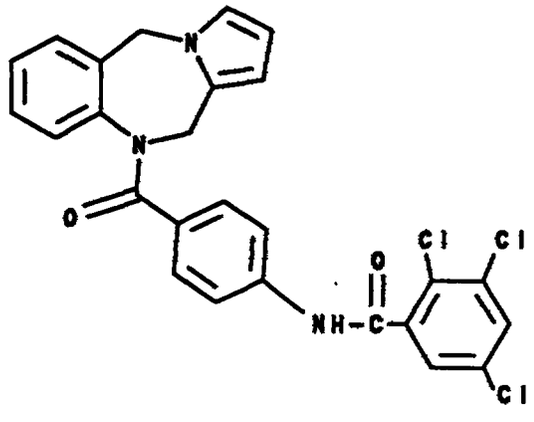
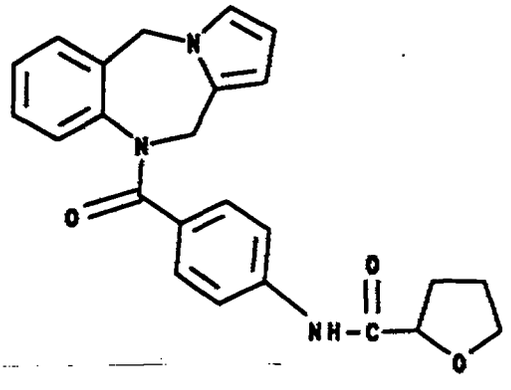
Ex.No.	Structure	V_1 $IC_{50}(\mu M)$	V_2 $IC_{50}(\mu M)$
598		(10μM)58%	(10μM)93%
599		0.046	0.014
600		0.42	0.74

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

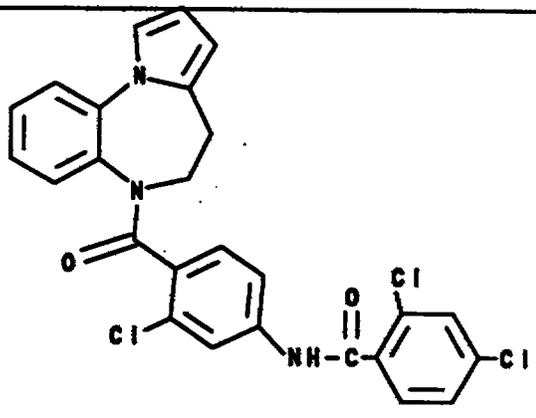
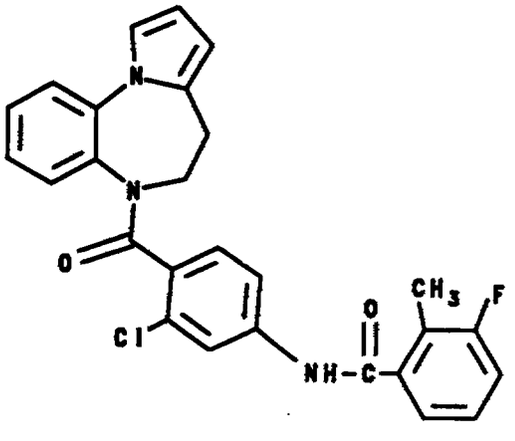
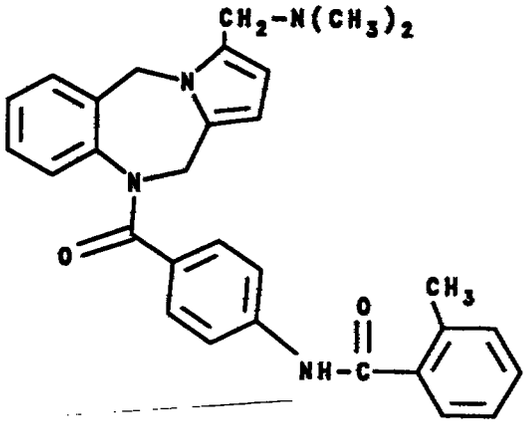
Ex.No.	Structure	V_1 $IC_{50}(\mu M)$	V_2 $IC_{50}(\mu M)$
609		2.4*	0.021**
611		0.5*	0.004**
660		0.073	0.064

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

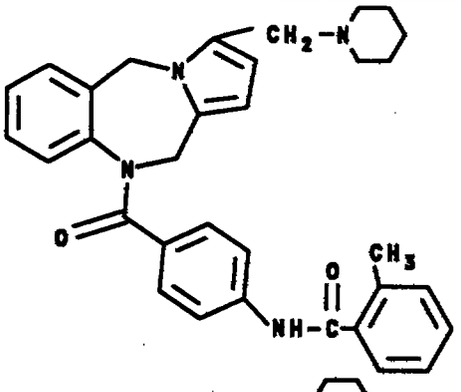
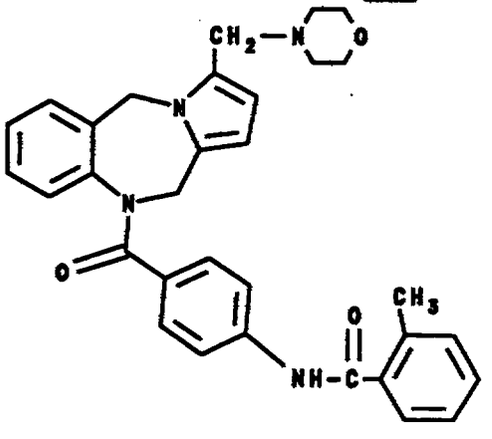
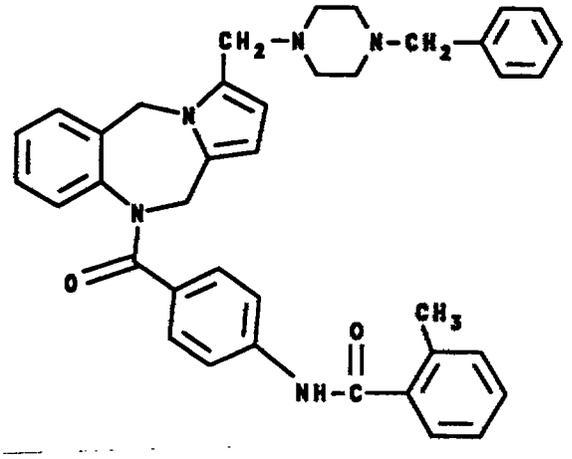
Ex.No.	Structure	V_1 $IC_{50}(\mu M)$	V_2 $IC_{50}(\mu M)$
881		0.057	0.057
882		0.04	0.035
883		0.009	0.025

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

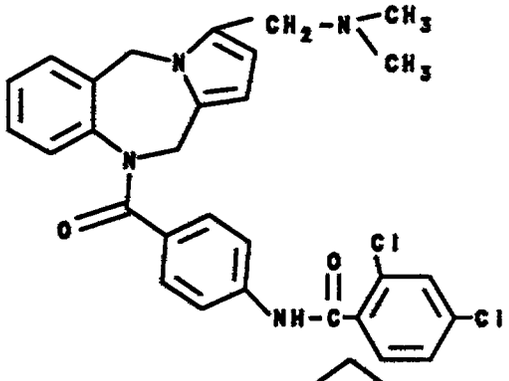
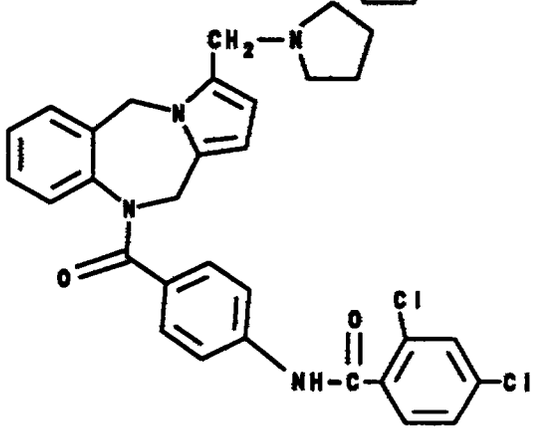
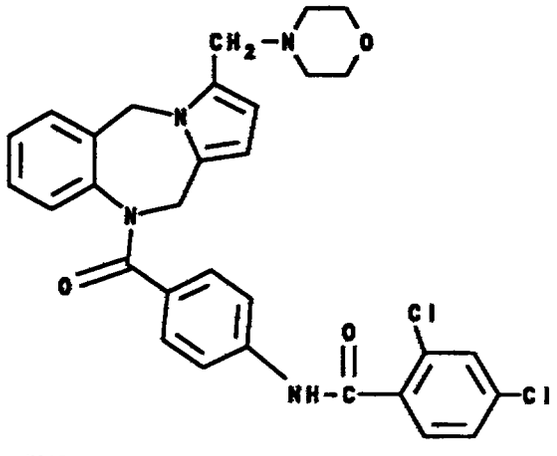
Ex.No.	Structure	V_1 IC_{50}(μM)	V_2 IC_{50}(μM)
864		0.12	0.048
865		0.056	0.039
866		0.16	0.013

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

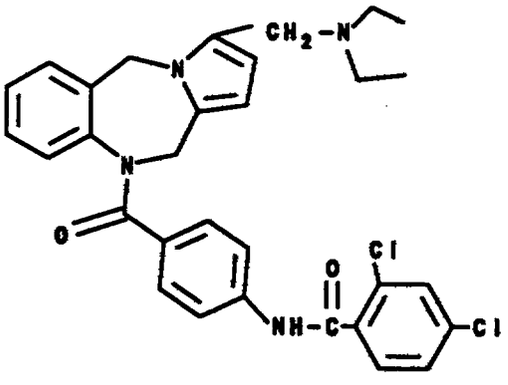
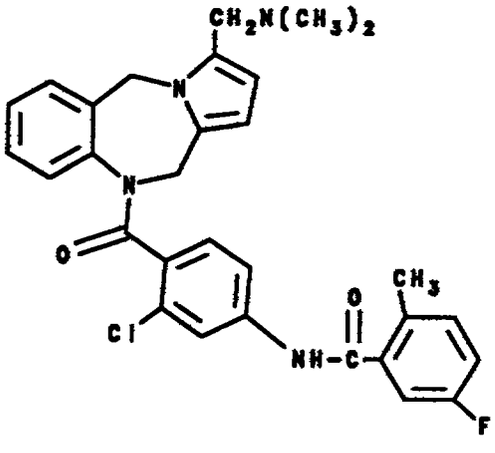
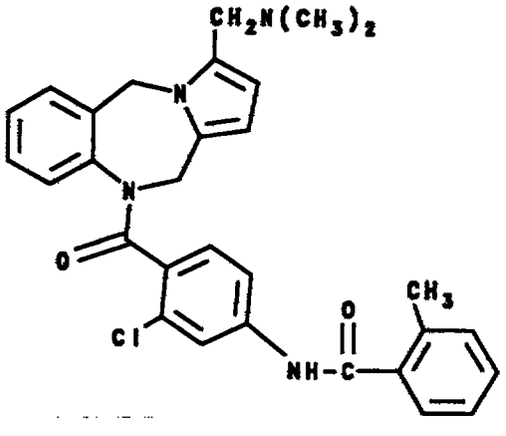
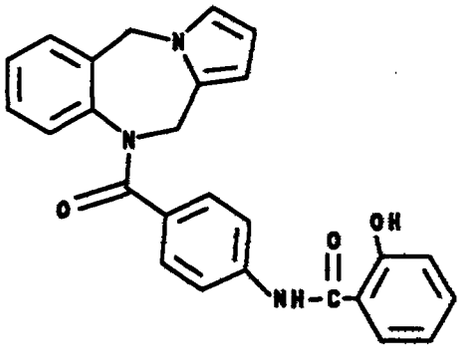
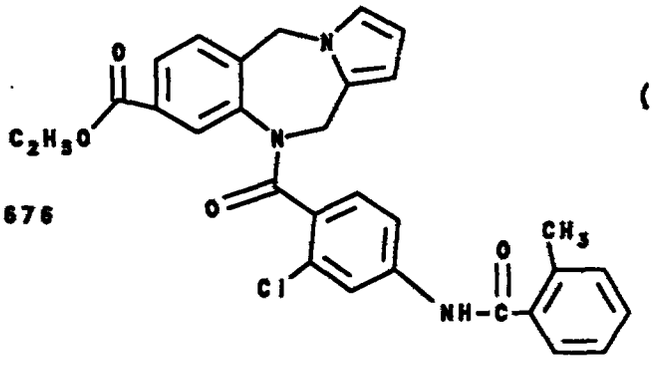
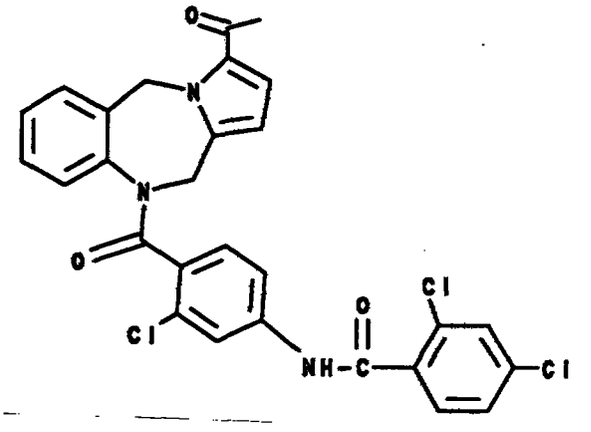
Ex.No.	Structure	V_1 $IC_{50}(\mu M)$	V_2 $IC_{50}(\mu M)$
667		0.17	0.013
668		0.17*	0.029**
669		0.071*	0.035**

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

Ex.No.	Structure	V_1 $IC_{50}(\mu M)$	V_2 $IC_{50}(\mu M)$
689		0.085*	0.54**
676		(10μM)41%	(10μM)89%
670		1.1	0.29

Replaced

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype In Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

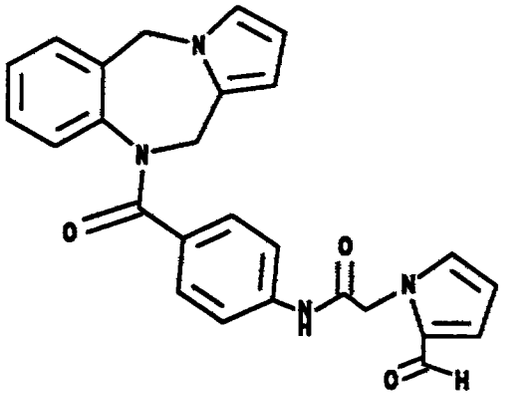
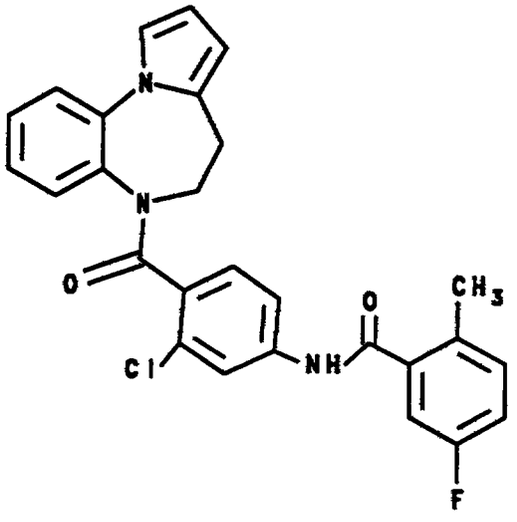
Ex.No.	Structure	V_1 $IC_{50}(\mu M)$	V_2 $IC_{50}(\mu M)$
685		0.061*	0.061**
612		1.7*	0.01**

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

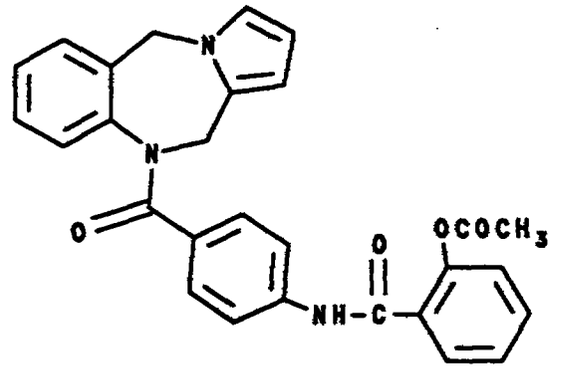
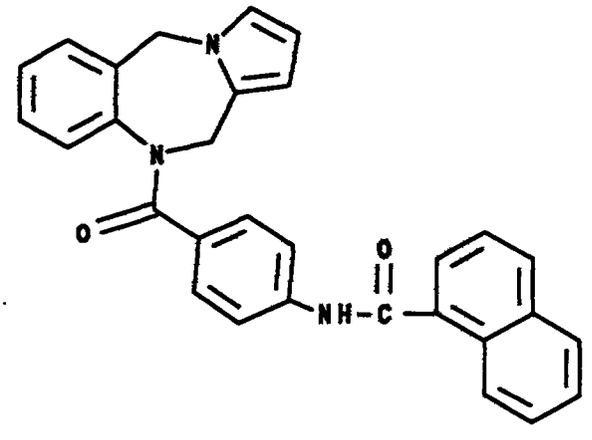
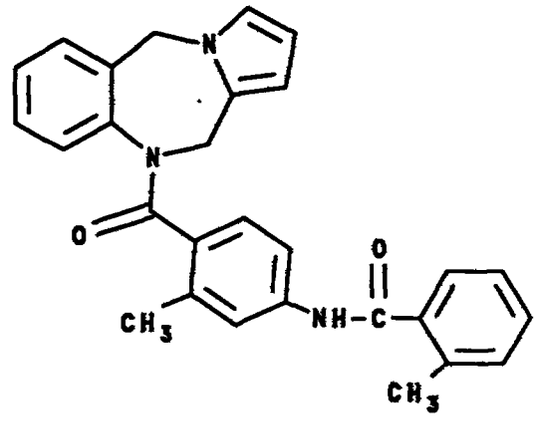
Ex.No.	Structure	V_1 $IC_{50}(\mu M)$	V_2 $IC_{50}(\mu M)$
688		0.069*	0.034**
690		0.22*	0.022**
691		0.072*	0.0029**

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

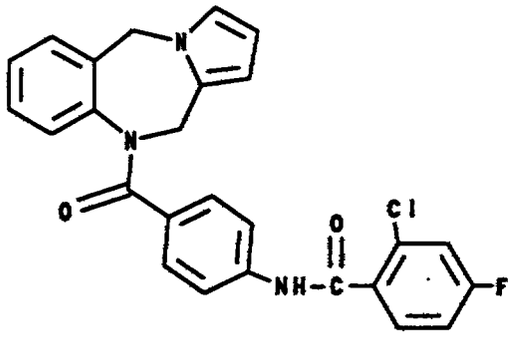
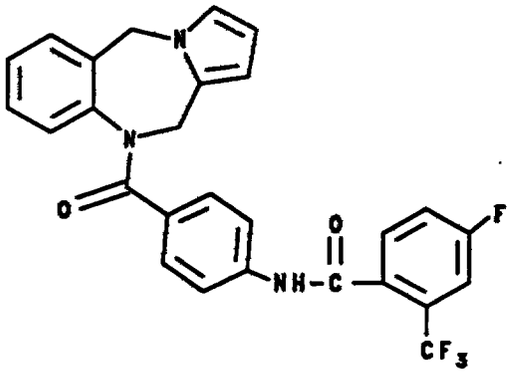
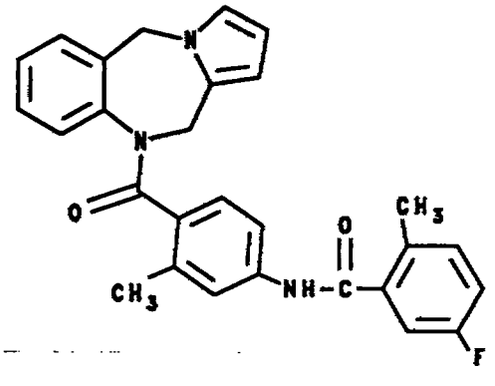
Ex.No.	Structure	V_1 IC_{50}(μM)	V_2 IC_{50}(μM)
692		0.007*	0.004**
693		0.021*	0.005**
694		0.12	0.0017**

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

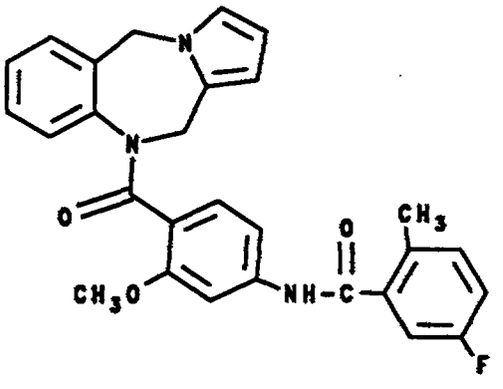
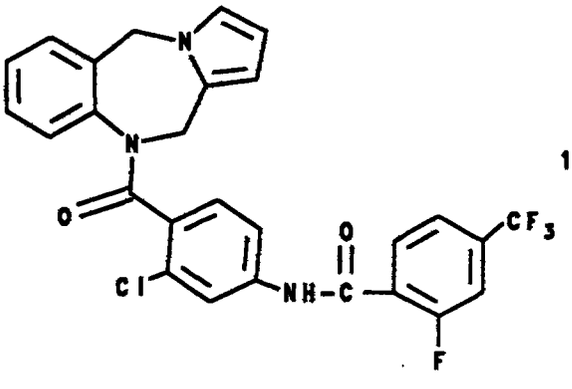
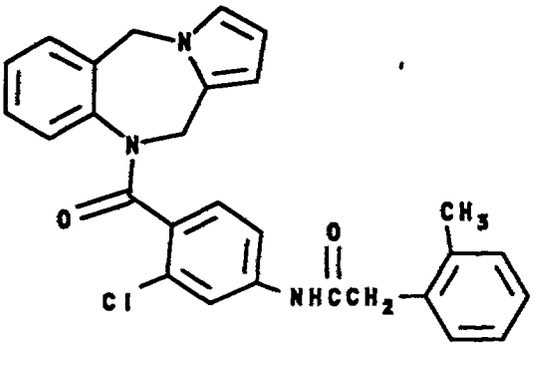
Ex.No.	Structure	V_1 $IC_{50}(\mu M)$	V_2 $IC_{50}(\mu M)$
695		0.015*	0.0018**
696		12.4*	0.065**
697		0.62*	0.003**

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

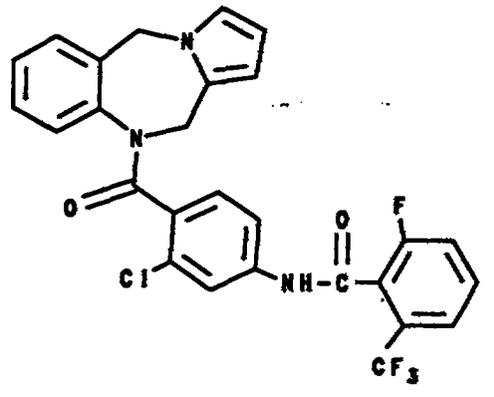
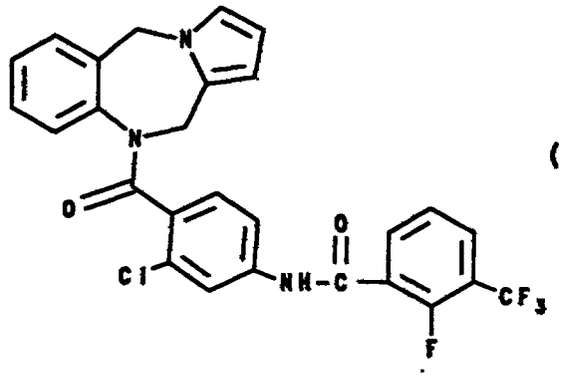
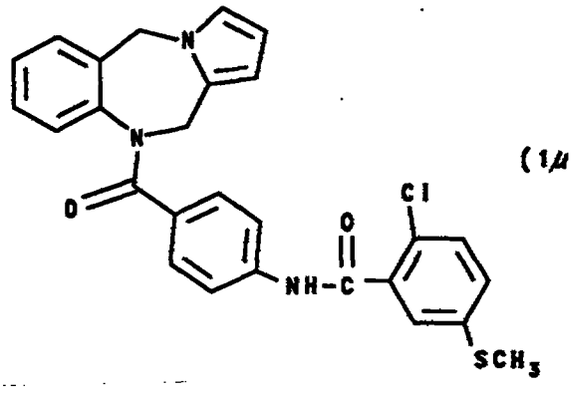
Ex.No.	Structure	V_1 $IC_{50}(\mu M)$	V_2 $IC_{50}(\mu M)$
698		1.5*	0.013**
699		(1μM)19%	(1μM)100%
700		(1μM)77%*	(10μM)100%**

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

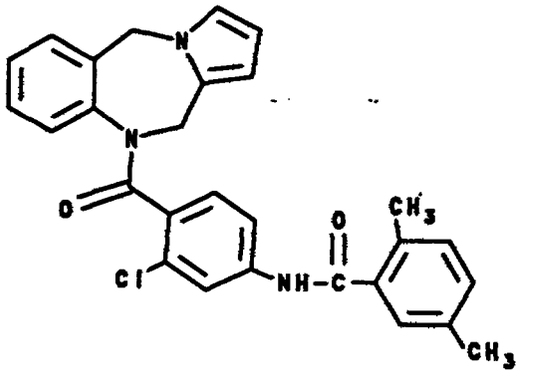
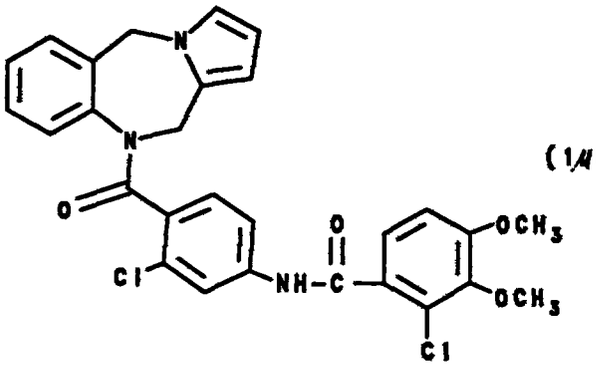
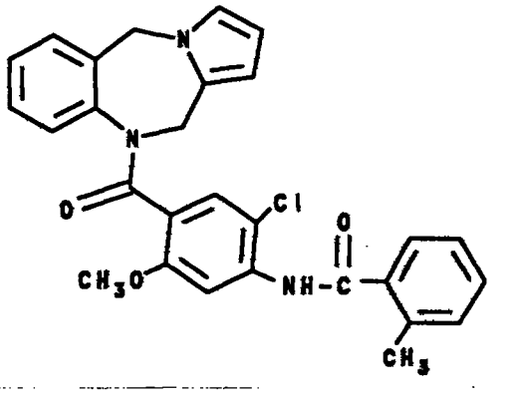
Ex.No.	Structure	V_1 $IC_{50}(\mu M)$	V_2 $IC_{50}(\mu M)$
701		0.34*	(1μM)100x
702		(1μM)9x*	(1μM)85x**
703		(1μM)35x*	(1μM)87x**

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

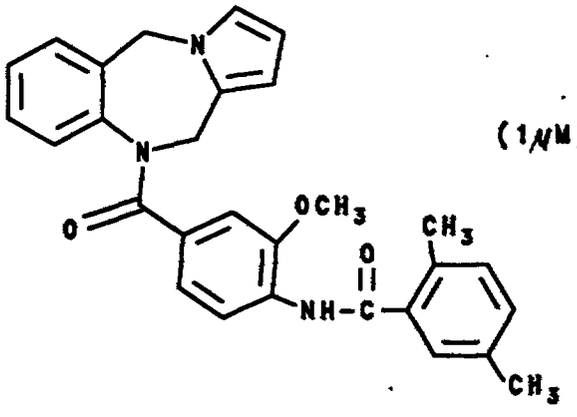
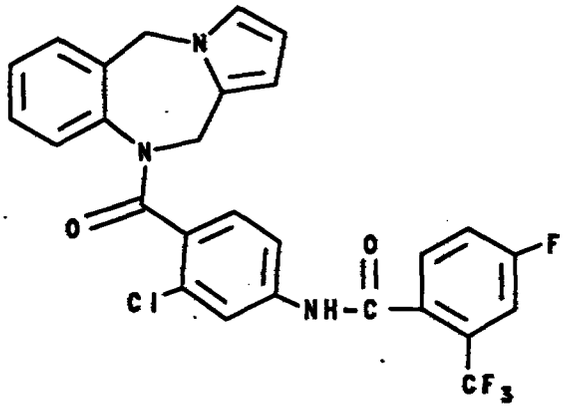
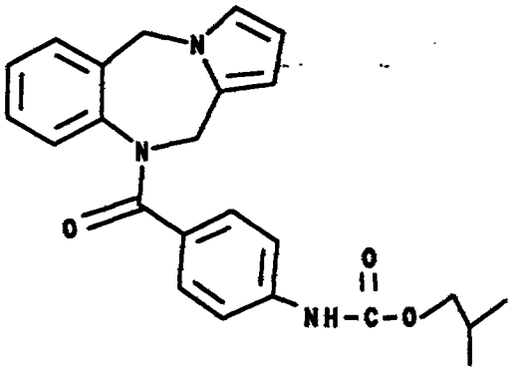
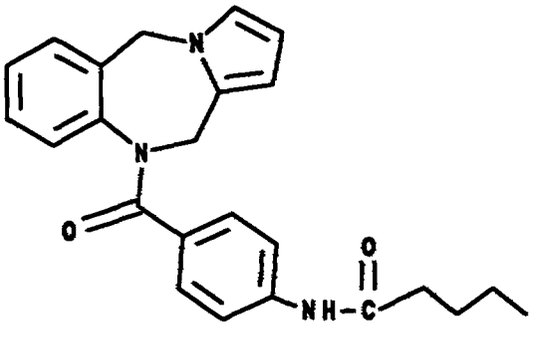
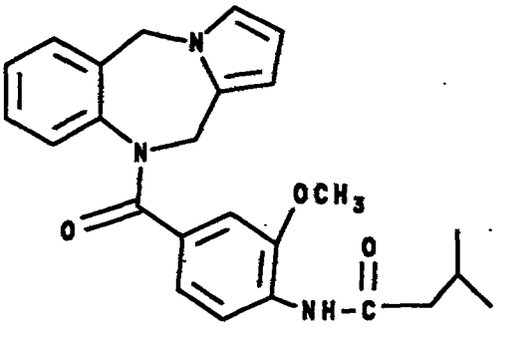
Ex.No.	Structure	V_1 $IC_{50}(\mu M)$	V_2 $IC_{50}(\mu M)$
704		(1μM)100%*	(1μM)92%**
707		0.20*	0.006**

Table XIII (cont'd)

Binding Assay to Rat Hepatic V_1 Receptors and Rat Kidney Medullary V_2 Receptors or *Binding to V_1 Receptor Subtype in Human Platelet and **Binding to Membranes of Mouse Fibroblast Cell Line(LV-2) Transfected with the cDNA Expressing the Human V_2 Receptor

Ex.No.	Structure	V_1 $IC_{50}(\mu M)$	V_2 $IC_{50}(\mu M)$
714		0.023*	0.041**
715		0.0078*	0.073**
716		0.002*	0.031**

Vasopressin V_2 Antagonist Activity in Conscious Hydrated Rats

Conscious hydrated rats are treated with compounds under study from 0.1 to 100 mg/kg orally or vehicle. Two to four rats are used for each compound. One hour later, arginine vasopressin (AVP, antidiuretic hormore, ADH) dissolved in peanut oil is administered at 0.4 μg/kg intraperitoneally. Two rats in each test would not receive arginine vasopressin but only the vehicle (peanut oil) to serve as water-loading control. Twenty minutes later each rat is given 30 mL/kg of deionized water orally by gavage and is placed individually in a metabolic cage equipped with a funnel and a graduated glass cylinder to collect urine for four hours. Urine volume is measured and osmolality analyzed by use of a Fiske One-Ten osmometer (Fiske Assoc., Norwood, MA, USA). Urinary sodium, potassium, and chloride are analyzed by use of ion-specific electrodes in a Beckman E3 (Electrolyte 3) Analyzer.

In the following results, decreased urine volume and decreased osmolality relative to AVP-control indicates activity. The results of this test on representative compounds of this invention are shown in Table XIV.

Table XIV
Vasopressin V_2 Antagonist Activity In Conscious Hydrated Rats

Ex. No.	Dose (mg/kg)	N	Urine Volume (ml/4 hrs)	Osmolality (mOsm/kg)
*		78	13.3±0.3	229±6
**		6	12.1±1	497±53
		4	12.4±0.8	361±30
***		76	2±0.2	1226±58
1	30	2	1.1	1504
215	30	2	0.7	1520
3	10	7	15.8±1	567±33
	3	8	9.6±0.9	584±56
	1	5	6.5±1	515±79
4	10	2	16.9	571
	3	4	9.5±1.2	646±115
	1	2	2	1129
5	30	2	7.7	955
	10	2	8.5	1079
6	30	5	17.9±1.3	616±87
	10	8	20.4±1.1	346±25
	3	4	15±1.6	519±30
	1	2	6	970
7	30	2	12.4	815
	10	2	9	780
8	30	2	9.1	1010
	10	2	3.4	1211

Table XIV (cont'd)
Vasopressin V_2 Antagonist Activity In
Conscious Hydrated Rats

Ex. No.	Dose (mg/kg)	N	Urine Volume (ml/4 hrs)	Osmolality (mOsm/kg)
14	10	2	5.2	836
	3	2	4.5	1000
82	30	2	1.7	1808
84	30	2	6.5	425
	10	2	4.4	416
85	30	2	12.5	383
	10	2	2	1123
87	20	2	4.3	1300
	10	2	3	1488
89	30	2	3.3	1320
91	10	2	12.5	414
	3	2	2.3	1267
93	30	2	5.1	594
96	10	4	10.3±1.3	647±63
	3	2	4.4	716

Table XIV (cont'd)
Vasopressin V_2 Antagonist Activity In
Conscious Hydrated Rats

Ex. No.	Dose (mg/kg)	N	Urine Volume (ml/4 hrs)	Osmolality (mOsm/kg)
116	30	2	8	1295
	10	2	5.5	1242
354	10	2	8.8	1010
356	10	2	5.8	1023
358	30	2	5.5	875
2	10	2	9.3	1015
9	10	2	5.8	702
99	30	2	15.2	334
467	10	2	18	365
466	10	2	14.1	522
17,160	30	2	4.1	1374
489	10	2	6.1	1194
490	10	4	71.5±1.6	487±38
590	10	2	3	1355
581	10	4	4±1.2	941±219
469	10	2	11.3	548
599	10	2	18	407
470	10	3	17	387
484	10	2	8	785
485	10	2	4	961
471	10	4	14.1±1.9	507±38
479	10	2	6	1042
482	10	4	22±0.9	372±17
54	10	2	5	1275
274	10	2	3	1177
465	10	2	21.8	361
480	10	2	8.8	827
528	10	2	11.3	647

Table XIV (cont'd)
Vasopressin V_2 Antagonist Activity In
Conscious Hydrated Rats

Ex. No.	Dose (mg/kg)	N	Urine Volume (ml/4 hrs)	Osmolality (mOsm/kg)
529	10	2	10.5	569
520	10	2	18.5	394
519	10	2	19.9	399
523	10	2	5	1218
524	10	2	10	528
525	10	2	13	557
526	10	2	17.8	455
527	10	2	19.5	430
530	10	2	6	914
518	10	2	17.5	363
668	10	2	20.7	378
609				
611				
472	10	2	4.3	1453
582	10	2	9.5	604
473	10	2	2.3	1493
474	10	2	11.5	619
594	10	4	4.9±1.2	1172±182
586	10	2	4.3	1196
584	10	2	2.5	1718
595	10	2	8.3	1474
588	10	2	9.5	687
587	10	2	9	868
210,214	10	2	15.2	451
597	10	2	5.3	1250
517	10	2	14.7	411
217	10	2	14.3	466
585	10	2	3.3	1483
476	10	2	5	1233
593	10	2	11.8	577
596	10	2	2.8	1347

Table XIV (cont'd)
Vasopressin V_2 Antagonist Activity In
Conscious Hydrated Rats

Ex. No.	Dose (mg/kg)	N	Urine Volume (ml/4 hrs)	Osmolality (mOsm/kg)
297(298)	10	2	7	796
477	10	2	5.3	701
478	10	2	3	1399
481	10	3	17.2	473
267,271				
592				

* Water-load control
** Water-load
Control+DMSO(10%)
(20%)
*** AVP-control

Vasopressin V_1 Antagonist Activity in Conscious Rats

Conscious rats are restrained in a supine position with elastic tape. The area at the base of the tail is locally anesthetized by subcutaneous infiltration with 2% procaine (0.2 ml). Using aseptic technique the ventral caudal tail artery is isolated and a cannula made of PE 10 and 20 (heat-fused) tubing is passed into the lower abdominal aorta. The cannula is secured, heparinized (1000 i.u./cc), sealed and the wound closed with one or two stitches of Dexon 4-0. The caudal vein is also cannulated in the same manner for intravenous drug administration. The duration of the surgery is approximately 5 minutes. Additional local anesthesia (2% procaine or lidocaine) is provided as needed.

The animals are placed in plastic restraining cages in an upright position. The cannula is attached to a Statham P23Db pressure transducer and pulsatile blood pressure is recorded. Increase of systolic blood pressure responses to arginine vasopressin 0.01 and 0.2 international unit (I.U.)(350 I.U.=1 mg) injections are recorded prior to any drug (compound) administration, after which each rat is dosed orally with compounds under study 0.1-100 mg/kg (10 cc/kg) or intravenously 0.1-30 mg/kg (1 cc/kg). The vasopressin injections are repeated 30,60,90,120,180,240 and 300 min. later. Percentage of antagonism by the compound is calculated using the pre-drug vasopressin vasopressor response as 100%.

The results of this test on representative compounds of this invention are shown in Table XV.

The results of this test on representative compounds of this invention in which the dose, the maximum % inhibition and the time in minutes, are shown in Table XVI.

Table XV
VASOPRESSIN (VAS) VASOPRESSOR RESPONSE

	Dose (mg/kg)	VAS Dose i.u./kg I.V.	Min Post Dose	Control Before VAS	Response After VAS	Change	Average Change	% Inhibition
CONTROL		0.01	0	155	188	33	33.5	
				156	190	34		
		0.02		153	213	60	52.5	
				165	210	45		
Ex.No.1	10 i.v.	0.01	30	161	165	4	4	88
				170	174	4		
		0.02		159	170	11	8	85
				167	172	5		
		0.01	60	157	173	16	16.5	51
				164	181	17		
		0.02		157	182	25	20	62
				178	193	15		
		0.01	90	151	176	25	21	37
				159	176	17		
		0.02		154	184	30	27	49
				165	189	24		
		0.01	120	150	173	23	22.5	33
				157	179	22		
		0.02		150	191	41	37.5	29
				162	196	34		
		0.01	180	148	177	29	29	13
				155	184	29		
		0.02		151	209	58	48	9
				165	203	38		
		0.01	240	146	176	30	27	19
				151	175	24		
		0.02		151	200	49	39.5	25
				162	192	30		
		0.01	300	146	176	30	32	4
				151	185	34		
		0.02		151	200	49	39.5	25
				162	192	30		

SPONTANEOUSLY HYPERTENSIVE RATS n=2 Body weight(s):400,480 grams

Table XV (cont'd)
VASOPRESSIN (VAS)VASOPRESSOR RESPONSE

	Dose (mg/kg)	VAS Dose i.u./kg I.V.	Min Post Dose	Control Before VAS	Response After VAS	Change	Average Change	% Inhibition
CONTROL		0.01	0	131	168	37	31	
				167	192	25		
		0.02		131	190	59	50	
				173	214	41		
Ex.No.2	10 i.v.	0.01	30	127	135	8	6.5	79
				175	180	5		
		0.02		135	144	9	8	84
				178	185	7		
		0.01	60	137	144	7	8	74
				172	181	9		
		0.02		135	145	10	13	74
				176	192	16		
		0.01	90	124	138	14	10.5	66
				173	180	7		
		0.02		132	147	15	15	70
				173	188	15		
		0.01	120	135	143	8	9.5	69
				167	178	11		
		0.02		134	150	16	15	70
				170	184	14		
		0.01	180	124	142	18	14	55
				165	175	10		
		0.02		129	150	21	22	56
				162	185	23		
		0.01	240	125	144	19	16.5	47
				164	178	14		
		0.02		133	158	25	25	50
				167	192	25		
		0.01	300	127	145	18	17.5	44
				159	176	17		
		0.02		134	170	36	31.5	37
				163	190	27		

SPONTANEOUSLY HYPERTENSIVE RATS n=2 Body weight(s):430,480 grams

Table XV (cont'd)
VASOPRESSIN (VAS) VASOPRESSOR RESPONSE

	Dose (mg/kg)	VAS Dose i.u./kg I.V.	Min Post Dose	Control Before VAS	Response After VAS	Change	Average Change	% Inhibition
CONTROL		0.01	0	175	215	40	50	
				175	235	60		
		0.02		185	240	55	55	
				200	255	55		
Ex.No.3	3 i.v.	0.01	30	180	190	10	15	70
				175	195	20		
		0.02		180	205	25	23.5	57
				185	207	22		
		0.01	60	185	190	5	12.5	75
				180	200	20		
		0.02		185	195	10	17.5	68
				185	210	25		
		0.01	90	175	185	10	17.5	65
				175	200	25		
		0.02		185	195	10	15	73
				185	205	20		
		0.01	120	170	185	15	20	60
				175	200	25		
		0.02		175	200	25	32.5	41
				185	225	40		
		0.01	180	175	195	20	30	40
				165	205	40		
		0.02		180	235	55	55	0
				185	240	55		
		0.01	240	165	195	30	40	20
				160	210	50		
		0.02		180	225	45	52.5	5
				185	245	60		

SPONTANEOUSLY HYPERTENSIVE RATS n=2 Body weight(s):340,330 grams

Table XV (CONT)
VASOPRESSIN (VAS) VASOPRESSOR RESPONSE

	Dose (mg/kg)	VAS Dose i.u./kg I.V.	Min Post Dose	Control Before VAS	Response After VAS	Change	Average Change	% Inhibition
CONTROL		0.01	0	170	215	45	53.5	
				163	225	62		
		0.02		185	225	40	52.5	
				190	255	65		
Ex.No.3	30p.o.	0.01	30	170	180	10	15	72
				155	175	20		
		0.02		175	190	15	20	62
				160	185	25		
		0.01	60	165	190	25	22.5	57
				150	170	20		
		0.02		170	190	20	22.5	57
				160	185	25		
		0.01	90	165	175	10	10	81
				160	170	10		
		0.02		165	185	20	20	62
				160	180	20		
		0.01	120	160	175	15	10	81
				165	170	5		
		0.02		165	170	5	12.5	76
				165	185	20		
		0.01	180	175	180	5	10	81
				170	185	15		
		0.02		170	185	15	17.5	67
				165	185	20		
		0.01	240	170	175	5	5	91
				160	165	5		
		0.02		165	170	5	10	81
				160	175	15		

SPONTANEOUSLY HYPERTENSIVE RATS n=2 Body weight(s):340,340 grams

Table XV (CONT)
VASOPRESSIN (VAS)VASOPRESSOR RESPONSE

	Dose (mg/kg)	VAS Dose i.u./kg I.V.	Min Post Dose	Control Before VAS	Response After VAS	Change	Average Change	% Inhibition
CONTROL		0.01	0	155	215	60	57.5	
				165	220	55		
		0.02		190	230	40	50	
				175	235	60		
Ex.No.3	10p.o.	0.01	30	150	165	15	12.5	78
				175	185	10		
		0.02		155	175	20	17.5	65
				175	190	15		
		0.01	60	150	160	10	17.5	70
				155	180	25		
		0.02		155	180	25	22.5	55
				160	180	20		
		0.01	90	145	170	20	65	81
				160	175	15		
		0.02		155	205	50	40	20
				155	185	30		
		0.01	120	150	165	15	15	74
				160	175	15		
		0.02		155	210	55	45	10
				160	195	35		
		0.01	180	145	165	20	20	65
				155	175	20		
		0.02		150	190	40	35	30
				165	195	30		
		0.01	240	145	165	20	22.5	61
				160	185	25		
		0.02		155	200	45	47.5	5
				165	215	50		

SPONTANEOUSLY HYPERTENSIVE RATS n=2 Body weight(s):340,360 grams

Table XV (CONT)
VASOPRESSIN (VAS)VASOPRESSOR RESPONSE

	Dose (mg/kg)	VAS Dose i.u./kg I.V.	Min Post Dose	Control Before VAS	Response After VAS	Change	Average Change	% Inhibition
CONTROL		0.01	0	167	209	42	35	
				170	198	28		
		0.02		170	232	62	54.5	
				177	224	47		
Ex.No. 3	10p.o.	0.01	30	116	124	8	10	71
				172	184	12		
		0.02		113	128	15	18.5	66
				168	190	22		
		0.01	60	115	122	7	10.5	70
				170	184	14		
		0.02		116	133	17	18.5	66
				168	188	20		
		0.01	90	116	122	6	6.5	81
				134	141	7		
		0.02		160	185	25	24	56
				167	190	23		
		0.01	120	162	172	10	14.5	59
				165	184	19		
		0.02		160	168	8	10.5	81
				161	174	13		
		0.01	180	162	162	0	8	77
				164	180	16		
		0.02		156	165	9	13.5	75
				163	181	18		
		0.01	240	162	168	6	8.5	76
				170	181	11		
		0.02		160	170	10	22.5	59
				175	210	35		

SPONTANEOUSLY HYPERTENSIVE RATS n=2 Body weight(s):380,360 grams

Table XV (CONT)
VASOPRESSIN (VAS)VASOPRESSOR RESPONSE

	Dose (mg/kg)	VAS Dose i.u./kg I.V.	Min Post Dose	Control Before VAS	Response After VAS	Change	Average Change	% Inhibition
CONTROL		0.01	0	147	182	35	40	
				136	181	45		
		0.02		150	213	63	54	
				146	191	45		
Ex.No. 3	10p.o.	0.01	30	147	157	10	11	73
				132	144	12		
		0.02		148	162	14	16	70
				134	152	18		
		0.01	60	143	155	12	11.5	71
				136	147	11		
		0.02		151	160	9	22.5	58
				134	170	36		
		0.01	90	142	154	12	12	70
				133	145	12		
		0.02		145	162	17	17.5	68
				130	148	18		
		0.01	120	139	154	15	12.5	69
				133	143	10		
		0.02		136	164	28	22.5	58
				127	144	17		
		0.01	180	147	160	13	15.5	61
				120	138	18		
		0.02		144	168	24	25	54
				122	148	26		
		0.01	240	145	163	18	19.5	51
				122	143	21		
		0.02		144	188	44	35.5	34
				126	153	27		
		0.01	300	146	166	20	16.5	59
				124	137	13		
		0.02		153	180	27	24	56
				134	155	21		

SPONTANEOUSLY HYPERTENSIVE RATS n=2 Body weight(s):500,390 grams

Table XV (CONT)
VASOPRESSIN (VAS)VASOPRESSOR RESPONSE

	Dose (mg/kg)	VAS Dose i.u./kg I.V.	Min Post Dose	Control Before VAS	Response After VAS	Change	Average Change	% Inhibition
CONTROL		0.01	0	146	200	54	49	
				139	183	44		
		0.02		148	205	57	51.5	
				146	192	46		
Ex.No. 3	3 i.v.	0.01	30	143	158	15	15	69
				124	139	15		
		0.02		145	166	21	22	57
				160	183	23		
		0.01	60	143	161	18	21	57
				131	155	24		
		0.02		147	185	38	29	44
				138	158	20		
		0.01	90	128	148	20	12	76
				148	152	4		
		0.02		154	188	34	28	46
				133	155	22		
		0.01	120	137	155	18	20.5	58
				148	171	23		
		0.02		138	161	23	18.5	64
				148	162	14		
		0.01	180	146	162	16	21	57
				139	165	26		
		0.02		148	179	31	28.5	45
				146	172	26		
		0.01	240	142	166	24	32	35
				132	172	40		
		0.02		126	145	19	27.5	47
				139	175	36		
		0.01	300	141	162	21	19	61
				146	163	17		
		0.02		146	179	33	30.5	41
				145	173	28		

SPONTANEOUSLY HYPERTENSIVE RATS n=2 Body weight(s):510,510 grams

Table XV (CONT)
VASOPRESSIN (VAS)VASOPRESSOR RESPONSE

	Dose (mg/kg)	VAS Dose i.u./kg I.V.	Min Post Dose	Control Before VAS	Response After VAS	Change	Average Change	% Inhibition
CONTROL		0.01	0	140	175	35	47.5	
				142	202	60		
		0.02		155	194	39	49.5	
				154	214	60		
Ex.No.4	10 p.o.	0.01	30	133	173	40	44.5	6
				139	188	49		
		0.02		154	178	24	36	27
				153	201	48		
		0.01	60	156	177	21	30.5	36
				142	182	40		
		0.02		156	182	26	44.5	10
				145	208	63		
		0.01	90	153	180	27	38.5	19
				141	191	50		
		0.02		163	199	36	52	-5
				152	220	68		
		0.01	120	164	198	34	32.5	32
				146	177	31		
		0.02		161	194	33	50.5	-2
				146	214	68		
		0.01	180	149	183	34	35.5	25
				141	178	37		
		0.02		148	185	37	44	11
				141	192	51		
		0.01	240	148	169	21	29	39
				133	170	37		
		0.02		158	184	26	26	47

SPONTANEOUSLY HYPERTENSIVE RATS n=2 Body weight(s):460,510 grams

Table XV (CONT)
VASOPRESSIN (VAS)VASOPRESSOR RESPONSE

	Dose (mg/kg)	VAS Dose i.u./kg I.V.	Min Post Dose	Control Before VAS	Response After VAS	Change	Average Change	% Inhibition
CONTROL		0.01	0	137	170	33	31.5	
				139	169	30		
		0.02		141	193	52	48	
				122	166	44		
Ex.No. 5	10i.v.	0.01	30	141	146	5	5.5	83
				120	126	6		
		0.02		143	155	12	13.5	72
				137	152	15		
		0.01	60	144	152	8	7.5	76
				123	130	7		
		0.02		144	155	11	10.5	78
				124	134	10		
		0.01	90	148	155	7	9	71
				141	152	11		
		0.02		146	155	9	8	83
				145	152	7		
		0.01	120	144	158	14	13	59
				123	135	12		
		0.02		148	164	16	15	69
				126	140	14		
		0.01	180	143	156	13	12	62
				124	135	11		
		0.02		145	164	19	19	60
				123	142	19		
		0.01	240	137	155	18	17	46
				117	133	16		
		0.02		135	160	25	23.5	51
				118	140	22		
		0.01	300	130	161	31	30	5
				112	141	29		
		0.02		139	181	42	39.5	18
				119	156	37		

SPONTANEOUSLY HYPERTENSIVE RATS n=2 Body weight(s):460,410 grams

Table XV (CONT)
VASOPRESSIN (VAS)VASOPRESSOR RESPONSE

	Dose (mg/kg)	VAS Dose i.u./kg I.V.	Min Post Dose	Control Before VAS	Response After VAS	Change	Average Change	% Inhibition
CONTROL		0.01	0	143	189	46	36.5	
				162	189	27		
		0.02		151	195	44	42	
				162	202	40		
Ex.No. 6	10i.v.	0.01	30	152	158	6	5.5	85
				157	162	5		
		0.02		144	165	21	16	62
				147	158	11		
		0.01	60	150	163	13	7.5	79
				177	179	2		
		0.02		144	170	26	23	45
				162	182	20		
		0.01	90	139	153	14	13.5	63
				155	168	13		
		0.02		145	168	23	27	36
				154	185	31		
		0.01	120	143	160	17	15	59
				154	167	13		
		0.02		143	176	33	29.5	30
				151	177	26		
		0.01	180	138	165	27	20.5	44
				152	166	14		
		0.02		148	189	41	35	17
				157	186	29		
		0.01	240	143	175	32	24	34
				163	179	16		
		0.02		151	199	48	35.5	15
				166	189	23		
		0.01	300	143	175	32	25.5	30
				165	184	19		
		0.02		152	193	41	36	14
				173	204	31		

SPONTANEOUSLY HYPERTENSIVE RATS n=2 Body weight(s):480,520 grams

Table XV (CONT)
VASOPRESSIN (VAS)VASOPRESSOR RESPONSE

	Dose (mg/kg)	VAS Dose i.u./kg I.V.	Min Post Dose	Control Before VAS	Response After VAS	Change	Average Change	% Inhibition
CONTROL		0.01	0	144	181	37	47	
				134	191	57		
		0.02		140	190	50	56	
				150	212	62		
Ex.No. 7	10i.v.	0.01	30	141	151	10	6	87
				152	154	2		
		0.02		147	162	15	7.5	87
				159	159	0		
		0.01	60	138	143	5	6	87
				148	155	7		
		0.02		136	145	9	8	86
				148	155	7		
		0.01	90	134	147	13	8.5	82
				142	146	4		
		0.02		137	149	12	12.5	78
				139	152	13		
		0.01	120	132	142	10	9.5	80
				136	145	9		
		0.02		134	150	16	13	77
				141	151	10		
		0.01	180	136	151	15	17.5	63
				138	158	20		
		0.02		136	158	22	23	59
				134	158	24		
		0.01	240	129	146	17	20.5	56
				132	156	24		
		0.02		131	157	26	30.5	46
				143	178	35		
		0.01	300	128	146	18	20	57
				136	158	22		
		0.02		134	151	17	23	59
				145	174	29		

SPONTANEOUSLY HYPERTENSIVE RATS n=2 Body weight(s):550,530 grams

Table XV (CONT)
VASOPRESSIN (VAS)VASOPRESSOR RESPONSE

	Dose (mg/kg)	VAS Dose i.u./kg I.V.	Min Post Dose	Control Before VAS	Response After VAS	Change	Average Change	% Inhibition
CONTROL		0.01	0	142	191	49	37	
				145	170	25		
		0.02		152	213	61	51.5	
				147	189	42		
Ex.No. 8	10i.v.	0.01	30	156	178	22	14.5	61
				145	152	7		
		0.02		150	176	26	23.5	54
				139	160	21		
		0.01	60	145	154	9	14.5	61
				150	170	20		
		0.02		145	162	17	21.5	58
				158	184	26		
		0.01	90	146	154	8	10	73
				160	172	12		
		0.02		142	160	18	17.5	66
				161	178	17		
		0.01	120	141	154	13	11.5	69
				156	166	10		
		0.02		139	154	15	15.5	70
				162	178	16		
		0.01	180	139	156	17	14	62
				157	168	11		
		0.02		140	172	32	28	46
				158	182	24		
		0.01	240	138	151	13	15	59
				148	165	17		
		0.02		143	178	35	29	44
				152	175	23		
		0.01	300	143	161	18	18	51
				147	165	18		
		0.02		153	183	30	28	46
				157	183	26		

SPONTANEOUSLY HYPERTENSIVE RATS n=2 Body weight(s):585,450 grams

Table XV (CONT)
VASOPRESSIN (VAS)VASOPRESSOR RESPONSE

	Dose (mg/kg)	VAS Dose i.u./kg I.V.	Min Post Dose	Control Before VAS	Response After VAS	Change	Average Change	% Inhibition
CONTROL		0.01	0	167	183	16	22	
				162	190	28		
		0.02		163	193	30	50.5	
				154	225	71		
Ex.No.41	10 i.v.	0.01	30	153	164	11	12	45
				163	176	13		
		0.02		161	194	33	23.5	53
				155	169	14		
		0.01	60	161	171	10	9	59
				159	167	8		
		0.02		156	172	16	18	64
				153	173	20		
		0.01	90	154	169	15	14	36
				166	179	13		
		0.02		151	179	28	22.5	55
				153	170	17		
		0.01	120	150	160	10	14	36
				151	169	18		
		0.02		149	163	14	16.5	67
				164	183	19		
		0.01	180	153	167	14	13.5	39
				156	169	13		
		0.02		154	172	18	21	58
				155	179	24		
		0.01	240	151	162	11	12.5	43
				151	165	14		
		0.02		156	179	23	23.5	53
				158	182	24		
		0.01	300	145	160	15	15	32
				150	165	15		
		0.02		150	180	30	27	47
				155	179	24		

SPONTANEOUSLY HYPERTENSIVE RATS n=2 Body weight(s):400,400 grams

Table XV (CONT)
VASOPRESSIN (VAS)VASOPRESSOR RESPONSE

	Dose (mg/kg)	VAS Dose i.u./kg I.V.	Min Post Dose	Control Before VAS	Response After VAS	Change	Average Change	% Inhibition
CONTROL		0.01	0	164	209	45	47.5	
				160	210	50		
		0.02		186	229	43	51.5	
				156	216	60		
Ex.No.82	10 i.v.	0.01	30	156	195	39	36	24
				152	185	33		
		0.02		165	218	53	54	-5
				159	214	55		
Ex.No.82	20 i.v.	0.01	60	162	180	18	15.5	67
				147	160	13		
		0.02		161	199	38	37	28
				151	187	36		
		0.01	90	158	181	23	23.5	51
				144	168	24		
		0.02		144	175	31	24	53
				143	160	17		
		0.01	120	157	173	16	16.5	65
				143	160	17		
		0.02		161	200	39	38.5	25
				152	190	38		
		0.01	180	149	171	22	18.5	61
				139	154	15		
		0.02		150	197	47	43.5	16
				130	170	40		
		0.01	240	144	175	31	29	39
				143	170	27		
		0.02		150	198	48	42	18
				146	182	36		
		0.01	300	152	185	33	32	33
				136	167	31		
		0.02		156	206	50	53	-3
				147	203	56		

SPONTANEOUSLY HYPERTENSIVE RATS n=2 Body weight(s):470,470 grams

Table XV (CONT)
VASOPRESSIN (VAS)VASOPRESSOR RESPONSE

	Dose (mg/kg)	VAS Dose i.u./kg I.V.	Min Post Dose	Control Before VAS	Response After VAS	Change	Average Change	% Inhibition
CONTROL		0.01	0	147	191	44	46	
				163	211	48		
		0.02		154	212	58	61	
				160	224	64		
Ex.No.84	10 i.v.	0.01	30	146	165	19	10.5	77
				172	174	2		
		0.02		152	168	16	14.5	76
				159	172	13		
		0.01	60	152	167	15	16.5	64
				154	172	18		
		0.02		158	201	43	33.5	45
				161	185	24		
		0.01	90	144	158	14	13	72
				153	165	12		
		0.02		152	173	21	26	57
				156	187	31		
		0.01	120	150	166	16	19.5	58
				143	166	23		
		0.02		150	175	25	32.5	47
				147	187	40		
		0.01	180	141	168	27	24.5	47
				149	171	22		
		0.02		148	170	22	31.5	48
				148	189	41		
		0.01	240	131	154	23	26	43
				143	172	29		
		0.02		149	186	37	37	39
				148	185	37		
		0.01	300	137	161	24	22.5	51
				151	172	21		
		0.02		148	193	45	43	30
				150	191	41		

SPONTANEOUSLY HYPERTENSIVE RATS n=2 Body weight(s):600,490 grams

Table XV (CONT)

VASOPRESSIN (VAS)VASOPRESSOR RESPONSE

	Dose (mg/kg)	VAS Dose i.u./kg I.V.	Min Post Dose	Control Before VAS	Response After VAS	Change	Average Change	% Inhibition
CONTROL		0.01	0	144	165	21	26.5	
				127	159	32		
		0.02		147	190	43	35.5	
				137	165	28		
Ex.No.85	10 i.v.	0.01	30	162	163	1	4.5	83
				119	127	8		
		0.02		156	166	10	9	75
				130	138	8		
		0.01	60	156	162	6	7	74
				124	132	8		
		0.02		156	168	12	9.5	73
				129	136	7		
		0.01	90	151	160	9	9.5	64
				125	135	10		
		0.02		143	150	7	7.5	79
				124	132	8		
		0.01	120	145	152	7	9	66
				123	134	11		
		0.02		139	147	8	6.5	82
				127	132	5		
		0.01	180	125	141	16	15.5	42
				118	133	15		
		0.02		129	147	18	19.5	45
				106	127	21		
		0.01	240	129	144	15	12	55
				107	116	9		
		0.02		135	152	17	18	49
				108	127	19		
		0.01	300	129	144	15	12	55
				107	116	9		
		0.02		135	152	17	18	49
				108	127	19		

SPONTANEOUSLY HYPERTENSIVE RATS n=2 Body weight(s):540,530 grams

Table XV (CONT)
VASOPRESSIN (VAS)VASOPRESSOR RESPONSE

	Dose (mg/kg)	VAS Dose i.u./kg I.V.	Min Post Dose	Control Before VAS	Response After VAS	Change	Average Change	% Inhibition
CONTROL		0.01	0	141	205	64	62.5	
				138	199	61		
		0.02		138	227	89	66.5	
				143	187	44		
Ex.No.87	10 i.v.	0.01	30	136	210	74	50	20
				145	171	26		
		0.02		157	227	70	57	14
				144	188	44		
Ex.No.87	20 i.v.	0.01	60	133	150	17	14.5	77
				143	155	12		
		0.02		150	191	41	32.5	51
				143	167	24		
		0.01	90	140	163	23	24.5	61
				141	167	26		
		0.02		148	197	49	33.5	50
				145	163	18		
		0.01	120	136	162	26	26	58
				146	172	26		
		0.02		152	196	44	35.5	47
				150	177	27		
		0.01	180	130	163	33	26.5	58
				139	159	20		
		0.02		148	192	44	37.5	44
				142	173	31		
		0.01	240	135	172	37	28.5	54
				132	152	20		
		0.02		136	191	55	41	38
				133	160	27		
		0.01	300	140	177	37	30	52
				128	151	23		
		0.02		138	201	63	48.5	27
				134	168	34		

SPONTANEOUSLY HYPERTENSIVE RATS n=2 Body weight(s):480,550 grams

Table XV (CONT)
VASOPRESSIN (VAS) VASOPRESSOR RESPONSE

	Dose (mg/kg)	VAS Dose i.u./kg I.V.	Min Post Dose	Control Before VAS	Response After VAS	Change	Average Change	% Inhibition
CONTROL		0.01	0	149	178	29	40	
				158	209	51		
		0.02		150	213	63	62	
				161	222	61		
Ex.No.89	10 i.v.	0.01	30	155	160	5	5	88
				160	165	5		
		0.02		160	170	10	5	92
				160	160	0		
		0.01	60	160	170	10	7.5	81
				160	165	5		
		0.02		155	170	15	10	84
				175	180	5		
		0.01	90	150	155	5	7.5	81
				160	170	10		
		0.02		150	165	15	12.5	80
				160	170	10		
		0.01	120	140	155	15	15	63
				155	170	15		
		0.02		140	170	30	27.5	56
				155	180	25		
		0.01	180	135	160	25	25	38
				155	180	25		
		0.02		140	170	30	32.5	48
				155	190	35		
		0.01	240	135	160	25	25	38
				155	180	25		
		0.02		140	170	30	35	44
				150	190	40		
		0.01	300	130	155	25	27.5	31
				150	180	30		
		0.02		135	170	35	32.5	48
				160	190	30		

SPONTANEOUSLY HYPERTENSIVE RATS n=2 Body weight(s):610,600 grams

Table XV (CONT)
VASOPRESSIN (VAS)VASOPRESSOR RESPONSE

	Dose (mg/kg)	VAS Dose i.u./kg I.V.	Min Post Dose	Control Before VAS	Response After VAS	Change	Average Change	% Inhibition
CONTROL		0.01	0	144	190	46	48.5	
				154	205	51		
		0.02		150	220	70	62.5	
				160	215	55		
Ex.No.91	10 i.v.	0.01	30	145	150	5	5	90
				150	155	5		
		0.02		150	160	10	7.5	88
				150	155	5		
		0.01	60	157	160	3	6.5	87
				155	165	10		
		0.02		150	158	8	7	89
				155	161	6		
		0.01	90	155	165	10	9	81
				152	160	8		
		0.02		150	165	15	12.5	80
				150	160	10		
		0.01	120	150	170	20	13	73
				140	146	6		
		0.02		148	165	17	17.5	72
				142	160	18		
		0.01	180	142	164	22	22	55
				143	165	22		
		0.02		149	167	18	29	54
				145	185	40		
		0.01	240	146	165	19	20	59
				129	150	21		
		0.02		147	189	42	29.5	53
				135	152	17		
		0.01	300	146	164	18	16.5	66
				146	161	15		
		0.02		144	167	23	32.5	48
				147	189	42		

SPONTANEOUSLY HYPERTENSIVE RATS n=2 Body weight(s):560,630 grams

Table XV (CONT)
VASOPRESSIN (VAS)VASOPRESSOR RESPONSE

	Dose (mg/kg)	VAS Dose i.u./kg I.V.	Min Post Dose	Control Before VAS	Response After VAS	Change	Average Change	% Inhibition
CONTROL		0.01	0	158	203	45	49.5	
				154	208	54		
		0.02		159	228	69	72	
				160	235	75		
Ex.No.93	10 i.v.	0.01	30	160	162	2	2	96
				139	141	2		
		0.02		157	162	5	4.5	94
				163	167	4		
		0.01	60	154	154	0	3	94
				163	169	6		
		0.02		161	166	5	5.5	92
				164	170	6		
		0.01	90	150	155	5	5	90
				163	168	5		
		0.02		154	162	8	7	90
				161	167	6		
		0.01	120	151	156	5	6	88
				158	165	7		
		0.02		155	160	5	7	90
				160	169	9		
		0.01	180	151	161	10	13.5	73
				151	168	17		
		0.02		151	164	13	15.5	78
				155	173	18		
		0.01	240	145	158	13	13	74
				156	169	13		
		0.02		148	166	18	17	76
				158	174	16		
		0.01	300	146	158	12	12	76
				156	168	12		
		0.02		144	162	18	18.5	74
				154	173	19		

SPONTANEOUSLY HYPERTENSIVE RATS n=2 Body weight(s):580,480 grams

Table XV (CONT)
VASOPRESSIN (VAS)VASOPRESSOR RESPONSE

	Dose (mg/kg)	VAS Dose i.u./kg I.V.	Min Post Dose	Control Before VAS	Response After VAS	Change	Average Change	% Inhibition
CONTROL		0.01	0	155	202	47	45.5	
				165	209	44		
		0.02		160	225	65	61	
				172	229	57		
Ex.No.95	10 i.v.	0.01	30	163	193	30	29.5	35
				168	197	29		
		0.02		170	225	55	56	8
				170	227	57		
Ex.No.95	20 i.v.	0.01	60	154	171	17	15	67
				156	169	13		
		0.02		160	177	17	19.5	68
				162	184	22		
		0.01	90	154	168	14	13.5	70
				167	180	13		
		0.02		158	177	19	24	61
				164	193	29		
		0.01	120	147	167	20	24	47
				161	189	28		
		0.02		153	174	21	28.5	53
				161	197	36		
		0.01	180	146	168	22	23.5	48
				156	181	25		
		0.02		154	189	35	34	44
				161	194	33		
		0.01	240	151	168	17	21.5	53
				154	180	26		
		0.02		153	189	36	34	44
				165	197	32		
		0.01	300	142	165	23	24.5	46
				151	177	26		
		0.02		148	193	45	37.5	39
				163	193	30		

SPONTANEOUSLY HYPERTENSIVE RATS n=2 Body weight(s):470,470 grams

Table XV (cont'd)
VASOPRESSIN (VAS)VASOPRESSOR RESPONSE

	Dose (mg/kg)	VAS Dose i.u./kg I.V.	Min Post Dose	Control Before VAS	Response After VAS	Change	Average Change	% Inhibition
CONTROL		0.01	0	134	163	29	32.5	
				144	180	36		
		0.02		137	193	56	57.5	
				153	212	59		
Ex.No.96	10 i.v.	0.01	30	144	157	13	11.5	65
				143	153	10		
		0.02		139	150	11	19.5	66
				148	176	28		
		0.01	60	141	149	8	7	78
				149	155	6		
		0.02		140	155	15	12.5	78
				148	158	10		
		0.01	90	133	148	15	13.5	58
				148	160	12		
		0.02		136	151	15	16	72
				146	163	17		
		0.01	120	134	148	14	13.5	58
				146	159	13		
		0.02		137	151	14	17.5	70
				148	169	21		
		0.01	180	136	153	17	15.5	52
				140	154	14		
		0.02		139	153	14	16	72
				136	154	18		
		0.01	240	133	152	19	18.5	43
				138	156	18		
		0.02		136	173	37	39.5	31
				145	187	42		
		0.01	300	138	154	16	15.5	52
				137	152	15		
				147	184	37	42	27
				138	185	47		

SPONTANEOUSLY HYPERTENSIVE RATS n=2 Body weight(s):500,440 grams

Table XV (CONT)
VASOPRESSIN (VAS)VASOPRESSOR RESPONSE

	Dose (mg/kg)	VAS Dose i.u./kg I.V.	Min Post Dose	Control Before VAS	Response After VAS	Change	Average Change	% Inhibition
CONTROL		0.01	0	158	181	23	29	
				148	183	35		
		0.02		161	198	37	48	
				151	210	59		
Ex.No.116	10i.v.	0.01	30	160	181	21	22.5	22
				162	186	24		
		0.02		160	191	31	36.5	24
				156	198	42		
		0.01	60	158	180	22	18	38
				156	170	14		
		0.02		160	197	37	33.5	30
				160	190	30		
		0.01	90	159	182	23	19	34
				157	172	15		
		0.02		163	201	38	32	33
				162	188	26		
		0.01	120	157	175	18	19.5	33
				158	179	21		
		0.02		154	203	49	40	17
				167	198	31		
		0.01	180	153	170	17	18	38
				157	176	19		
		0.02		155	201	46	40	17
				176	210	34		
		0.01	240	153	169	16	16	45
				156	172	16		
		0.02		152	188	36	38.5	20
				156	197	41		
		0.01	300	153	176	23	22	24
				127	148	21		
		0.02		154	205	51	41.5	14
				163	195	32		

SPONTANEOUSLY HYPERTENSIVE RATS n=2 Body weight(s):460,570 grams

Table XV (cont'd)
VASOPRESSIN (VAS) VASOPRESSOR RESPONSE

	Dose (mg/kg)	VAS Dose i.u./kg I.V.	Min Post Dose	Control Before VAS	Response After VAS	Change	Average Change	% Inhibition
CONTROL		0.01	0	146	184	38	36.5	
				156	191	35		
		0.02		146	210	64	56.5	
				160	209	49		
Ex.No.117	10 i.v.	0.01	30	154	195	41	36	1
				162	193	31		
		0.02		154	220	66	63	-12
				162	222	60		
	20 i.v.	0.01	60	154	182	28	36	1
				164	208	44		
		0.02		157	197	40	40	29
				173	213	40		
		0.01	90	158	174	16	22.5	38
				162	191	29		
		0.02		160	208	48	46	19
				165	209	44		
		0.01	120	151	171	20	23	37
				154	180	26		
		0.02		150	183	33	38	33
				158	201	43		
		0.01	180	141	168	27	26.5	27
				150	176	26		
		0.02		143	185	42	46	19
				151	201	50		
		0.01	240	139	168	29	25	32
				146	167	21		
		0.02		143	175	32	40.5	28
				146	195	49		
		0.01	300	137	164	27	26	29
				149	174	25		
				144	183	39	42.5	25
				149	195	46		

SPONTANEOUSLY HYPERTENSIVE RATS n=2 Body weight(s):570,460 grams

Table XV (CONT)

VASOPRESSIN (VAS)VASOPRESSOR RESPONSE

	Dose (mg/kg)	VAS Dose i.u./kg I.V.	Min Post Dose	Control Before VAS	Response After VAS	Change	Average Change	% Inhibition
CONTROL		0.01	0	135	171	36	34.5	
				121	154	33		
		0.02		138	184	46	47.5	
				156	205	49		
Ex.No.157	10i.v.	0.01	30	136	175	39	26	25
				152	165	13		
		0.02		148	199	51	38	20
				153	178	25		
		0.01	60	150	179	29	26.5	23
				135	159	24		
		0.02		160	191	31	31.5	34
				153	185	32		
		0.01	90	145	167	22	21	39
				161	181	20		
		0.02		148	185	37	40	16
				152	195	43		
		0.01	120	136	161	25	26.5	23
				138	166	28		
		0.02		140	183	43	39.5	17
				150	186	36		
		0.01	180	131	164	33	32.5	6
				132	164	32		
		0.02		137	185	48	52	-9
				140	196	56		
		0.01	240	140	167	27	28.5	17
				155	185	30		
		0.02		138	167	29	35.5	25
				143	185	42		
		0.01	300	138	162	24	25.5	26
				141	168	27		
		0.02		146	176	30	40	16
				156	206	50		

SPONTANEOUSLY HYPERTENSIVE RATS n=2 Body weight(s):400,470 grams

Table XV (CONT)
VASOPRESSIN (VAS)VASOPRESSOR RESPONSE

	Dose (mg/kg)	VAS Dose i.u./kg I.V.	Min Post Dose	Control Before VAS	Response After VAS	Change	Average Change	% Inhibition
CONTROL		0.01	0	146	191	45	41	
				161	198	37		
		0.02		157	207	50	50	
				163	213	50		
Ex.No.357	10 i.v.	0.01	30	144	159	15	16.5	60
				167	185	18		
		0.02		145	169	24	16	68
				164	172	8		
		0.01	60	156	160	4	4.5	89
				164	169	5		
		0.02		145	159	14	10.5	79
				164	171	7		
		0.01	90	142	153	11	8	80
				167	172	5		
		0.02		143	154	11	10.5	79
				168	178	10		
		0.01	120	140	151	11	8	80
				165	170	5		
		0.02		136	139	3	6	88
				165	174	9		
		0.01	180	147	154	7	9.5	77
				162	174	12		
		0.02		142	154	12	11	78
				162	172	10		
		0.01	240	145	159	14	14	66
				159	173	14		
		0.02		157	174	17	14.5	71
				160	172	12		
		0.01	300	148	164	16	16	61
				151	167	16		
		0.02		148	169	21	16	68
				158	169	11		

SPONTANEOUSLY HYPERTENSIVE RATS n=2 Body weight(s):500,460 grams

Table XV (CONT)
VASOPRESSIN (VAS)VASOPRESSOR RESPONSE

	Dose (mg/kg)	VAS Dose i.u./kg I.V.	Min Post Dose	Control Before VAS	Response After VAS	Change	Average Change	% Inhibition
CONTROL		0.01	0	139	190	51	36.5	
				159	181	22		
		0.02		155	212	57	39.5	
				166	188	22		
Ex.No.358	10 i.v.	0.01	30	147	163	16	12	67
				161	169	8		
		0.02		149	169	20	24	39
				162	190	28		
		0.01	60	145	153	8	13	64
				153	171	18		
		0.02		142	155	13	10	75
				160	167	7		
		0.01	90	142	157	25	17.5	52
				156	166	10		
		0.02		148	161	13	11	72
				161	170	9		
		0.01	120	144	153	9	8	78
				159	166	7		
		0.02		139	155	16	14	65
				155	167	12		
		0.01	180	134	158	24	17.5	52
				147	158	11		
		0.02		146	162	16	14.5	63
				154	167	13		
		0.01	240	139	153	14	12	67
				143	153	10		
		0.02		144	162	18	15.5	61
				145	158	13		
		0.01	300	137	163	26	19	48
				137	149	12		
		0.02		140	158	18	16	59
				141	155	14		

SPONTANEOUSLY HYPERTENSIVE RATS n=2 Body weight(s):520,515 grams

Table XV (CONT)
VASOPRESSIN (VAS) VASOPRESSOR RESPONSE

	Dose (mg/kg)	VAS Dose i.u./kg I.V.	Min Post Dose	Control Before VAS	Response After VAS	Change	Average Change	% Inhibition
CONTROL		0.01	0	141	165	24	23.5	
				145	168	23		
		0.02		145	182	37	37	
				153	190	37		
Ex.No.384	10 i.v.	0.01	30	145	157	12	9	62
				156	162	6		
		0.02		150	168	18	14.5	61
				158	169	11		
		0.01	60	151	160	9	9	62
				158	167	9		
		0.02		152	162	10	10.5	72
				160	171	11		
		0.01	90	154	170	16	12	49
				160	168	8		
		0.02		157	177	20	15.5	58
				162	173	11		
		0.01	120	149	159	10	10.5	55
				131	142	11		
		0.02		150	162	12	11.5	69
				164	175	11		
		0.01	180	150	162	12	11	53
				158	168	10		
		0.02		156	167	11	13.5	64
				160	176	16		
		0.01	240	145	156	11	11	53
				155	166	11		
		0.02		145	161	16	15	59
				160	174	14		
		0.01	300	148	162	14	12	49
				152	162	10		
		0.02		151	168	17	17	54
				158	175	17		

SPONTANEOUSLY HYPERTENSIVE RATS n=2 Body weight(s):455,500 grams

Table XV (CONT)
VASOPRESSIN (VAS) VASOPRESSOR RESPONSE

	Dose (mg/kg)	VAS Dose i.u./kg I.V.	Min Post Dose	Control Before VAS	Response After VAS	Change	Average Change	% Inhibition
CONTROL		0.01	0	96	135	39	36	
				151	184	33		
		0.02		131	154	23	36	
				158	207	49		
Ex.No.407	10 i.v.	0.01	30	120	131	11	9.5	74
				150	158	8		
		0.02		132	142	10	13	64
				153	169	16		
		0.01	60	112	139	27	25.5	29
				150	174	24		
		0.02		128	131	3	10	72
				154	171	17		
		0.01	90	90	114	24	19	47
				152	166	14		
		0.02		87	122	35	26.5	26
				154	172	18		
		0.01	120	120	127	7	8.5	76
				145	155	10		
		0.02		113	127	14	17	53
				147	167	20		
		0.01	180	112	124	12	11.5	68
				141	152	11		
		0.02		109	129	20	20	44
				139	159	20		
		0.01	240	114	130	16	18	50
				131	151	20		
		0.02		120	136	16	21.5	40
				142	169	27		
		0.01	300	115	130	15	20	44
				130	155	25		
		0.02		116	137	21	22.5	38
				136	160	24		

SPONTANEOUSLY HYPERTENSIVE RATS n=2 Body weight(s):470,550 grams

Table XVI

VASOPRESSIN (VAS) VASOPRESSOR RESPONSE

Ex. No.	Dose mg/kg	Max. % Inhibition	Time (min)
2	30 i.v.	74	120
9	10 i.v.	95	60
17	30 i.v.	50	60
36	30 i.v.	71	60
99	10 i.v.	76	120
210	10 i.v.	78	90
217	30 i.v.	57	90
271	10 i.v.	56	60
274	10 i.v.	59	300
465	10 i.v.	85	90
466	30 i.v.	94	94
467	10 i.v.	65	120
468	10 i.v.	68	30
469	10 i.v.	69	30
470	10 i.v.	87	180
	30 p.o.	69	180
471	30 i.v.	85	90
472	30 i.v.	36	90
474	30 i.v.	80	60
476	10 i.v.	78	30
	30 p.o.	19	180
477	10 i.v.	88	180
	30 p.o.	82	30
478	10 i.v.	76	120
479	10 i.v.	83	60
	30 p.o.	69	90
480	10 i.v.	29	300
481	30 p.o.	58	80
482	10 i.v.	40	60
484	10 i.v.	79	300
	30 p.o.	22	180
485	30 i.v.	64	60
488	30 i.v.	43	60

Table XVI (cont'd)

VASOPRESSIN (VAS) VASOPRESSOR RESPONSE

Ex. No.	Dose mg/kg	Max. % Inhibition	Time (min)
489	30 i.v.	39	120
490	10 i.v.	74	90
	10 p.o.	65	120
517	10 i.v.	81	90
525	30 i.v.	70	60
527	30 i.v.	85	180
528	30 i.v.	66	300
530	30 i.v.	89	120
581	10 i.v.	94	30
	30 p.o.	79	30
582	10 i.v.	75	180
585	10 i.v.	56	30
587	10 i.v.	75	60
588	10 i.v.	65	90
	30 p.o.	80	120
590	30 i.v.	89	120
592	30 i.v.	37	90
593	30 i.v.	67	60
594	30 i.v.	36	180
595	30 i.v.	44	90
599	30 i.v.	86	90
600	30 i.v.	78	60

Oxytocin Receptor Binding

(a) Membrane Preparation

Female Sprague-Dawley rats weighing approximately 200-250 g are injected intramuscularly (i.m.) with 0.3 mg/kg of body weight of diethylstilbestrol (DES). The rats are sacrificed 18 hours later under pentobarbital anesthesia. The uteri are dissected out, cleaned of fat and connective tissues and rinsed in 50 ml of normal saline. The tissue pooled from six rats is homogenized in 50 ml of 0.01 mM Tris.HCl, containing 0.5 mM dithiothreitol and 1.0 mM EDTA, adjusted to pH 7.4, using a polytron at setting 6 with three passes of 10 sec each. The homogenate is passed through two (2) layers of cheesecloth and the filtrate centrifuged at 1000 x g for 10 min. The clear supernatant is removed and recentrifuged at 165,000 x g for 30 min. The resulting pellet containing the oxytocin receptors is resuspended in 50.0 mM Tris.HCl containing 5.0 mM $MgCl_2$ at pH 7.4, to give a protein concentration of 2.5 mg/ml of tissue suspension. This preparation is used in subsequent binding assays with [^{3}H]Oxytocin.

(b) Radioligand Binding

Binding of 3,5-[^{3}H]Oxytocin ([^{3}H]OT) to its receptors is done in microtiter plates using [^{3}H]OT, at various concentrations, in an assay buffer of 50.0 mM Tris.HCl, pH 7.4 and containing 5.0 mM $MgCl_2$, and a mixture of protease inhibitors: BSA, 0.1 mg; aprotinin, 1.0 mg; 1,10-phenanthroline, 2.0 mg; trypsin, 10.0 mg; and PMSF, 0.3 mg per 100 ml of buffer solution. Non-specific binding is determined in the presence of 1.0 uM unlabeled OT. The binding reaction is terminated after 60 min., at 22°C, by rapid filtration through glass fiber filters using a Brandel® cell harvester (Biomedical Research and Development Laboratories, Inc., Gaithersburg, MD). Competition experiments are conducted at equilibrium using 1.0 nM [^{3}H]OT and varying the concentration of the displacing agents.

The concentrations of agent displacing 50% of [^{3}H]OT at its sites (IC_{50}) are calculated by a computer assisted LUNDON-2 program (LUNDON SOFTWARE INC., Ohio, USA).

The results of this assay on representative examples are shown in Table XVII.

Table XVII

Oxytocin

Ex. No.	Dose (μM)	% Inhibition at 10 μM	IC_{50}
3	10	90	0.36
4	10	98	0.66
6	10	92	0.35
7	10	97	0.13
17	10	31	
36	10	67	2.45
54	10	94	0.16
85	10	98	0.46
93	10	87	0.06
96	10	94	1.2
160	10	31	
164	10	67	2.45
210	10	64	4
214	10	64	4
215	10	74	0.57
217	10	87	1.2
274	10	95	1
297	10	76	4
298	10	76	4
416	10	44.6	7.4
417	10	21	
418	10	39	
419	10	28	
420	10	16	
429	10	11	
430	10	16	
431	10	18	

Table XVII (cont'd)

Oxytocin

Ex. No.	Dose (μM)	% Inhibition at 10 μM	IC_{50}
432	10	19	
433	10	12	
435	10	10	
436	10	32	
441	1	22	
443	10	70	
444	10	21	
448	10	11	
449	10	14	
450	10	22	
451	10	43	
452	10	36	
455	10	75	2.9
460	10	77	3.1
461	10	44.6	7.4
462	10	14	
463	10	55	8.5
464	10	71	2.4
465	10	93	0.033
468	10	96	0.26
469	10	96	0.265
470	2.5	92	0.22
471	10	99	0.35
472	10	0	
473	10	20	
474	10	18	
476	10	94	0.82
477	1.25	97	0.029
478	1.25	97	0.04
479	10	76	0.15
480	10	98	0.15
481	10	88	0.24
482	10	97	0.126

Table XVII (cont'd)

Oxytocin

Ex. No.	Dose (μM)	% Inhibition at 10 μM	IC_{50}
485	10	86	2.2
486	10	18	
489	10	44	
490	10	99	0.3
491	10	46	
517	10	91	0.32
519	10	97	0.48
520	10	79	2.2
524	10	84	1.8
525	10	98	0.28
526	10	97	0.47
527	10	92	0.45
528	10	90	1.17
529	10	92	0.45
530	10	99	0.31
538	10	90	0.9
546	10	91	0.99
547	5	97	0.26
580	10	79	2.96
581	10	99	0.2
582	10	96	0.675
583	10	61	4
584	10	26	
585	10	70	4.7
586	10	61	4.7
587	10	56	8
588	10	90	2
589	10	79	2.9
590	10	12	
591	10	29	
592	10	41	
593	10	82	1.1
594	10	19	

Table XVII (cont'd)

Oxytocin

Ex. No.	Dose (μM)	% Inhibition at 10 μM	IC_{50}
595	10	49	
596	10	86	4
597	10	42	
598	10	2	
599	10	92	0.35
609	10	66	2.7
664	10	95	1.4
665	10	97	1
666	10	83	2.1
667	10	89	1.6
676	10	32	

The compounds of the present invention can be used in the form of salts derived from pharmaceutically or physiologically acceptable acids or bases. These salts include but are not limited to the following: salts with inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid and, as the case may be, such organic acids as acetic acid, oxalic acid, succinic acid, and maleic acid. Other salts include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium or with organic bases. The compounds can also be used in the form of esters, carbamates and other conventional "pro-drug" forms, which, when administered in such form, convert to the active moiety in vivo.

When the compounds are employed for the above utility, they may be combined with one or more pharmaceutically acceptable carriers, for example, solvents, diluents and the like, and may be administered orally in such forms as tablets, capsules, dispersible powders, granules, or suspensions containing, for example, from about 0.05 to 5% of suspending agent, syrups containing, for example, from about 10 to 50% of sugar, and elixirs containing, for example, from about 20 to 50% ethanol, and the like, or parenterally in the form of sterile injectable solution or suspension containing from about 0.05 to 5% suspending agent in an isotonic medium. Such pharmaceutical preparations may contain, for example, from about 0.05 up to about 90% of the active ingredient in combination with the carrier, more usually between about 5% and 60% by weight.

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration and the severity of the condition being treated. However, in general, satisfactory results are obtained when the compounds of the invention are administered at a daily dosage of from about 0.5 to about 500 mg/kg of animal body weight, preferably given in divided doses two to four times a day, or in sustained release form. For most large mammals the total daily dosage is from about 1 to 100 mg, preferably from about 2 to 80 mg. Dosage forms suitable for internal use comprise from about 0.5 to 500 mg of the active compound in intimate admixture with a solid or liquid pharmaceutically acceptable carrier. This dosage regimen may be adjusted to provide the optimal therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation.

These active compounds may be administered orally as well as by intravenous, intramuscular, or

subcutaneous routes. Solid carriers include starch, lactose, dicalcium phosphate, microcrystalline cellulose, sucrose and kaolin, while liquid carriers include sterile water, polyethylene glycols, non-ionic surfactants and edible oils such as corn, peanut and sesame oils, as are appropriate to the nature of the active ingredient and the particular form of administration desired. Adjuvants customarily employed in the preparation of pharmaceutical compositions may be advantageously included, such as flavoring agents, coloring agents, preserving agents, and antioxidants, for example, vitamin E, ascorbic acid, BHT and BHA.

The preferred pharmaceutical compositions from the standpoint of ease of preparation and administration are solid compositions, particularly tablets and hard-filled or liquid-filled capsules. Oral administration of the compounds is preferred.

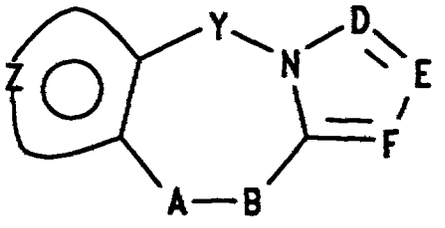
These active compounds may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparation contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion

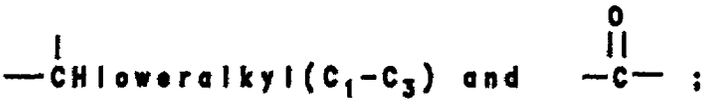
medium containing, for example, water, ethanol, polyol(e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

What is claimed is:

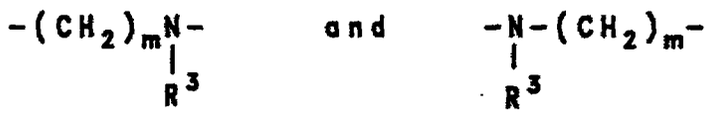
1. A compound selected from those of the formula:



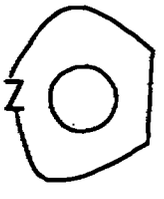
wherein Y is a moiety selected from $-(CH_2)_n-$ wherein n is an integer from 0 to 2,



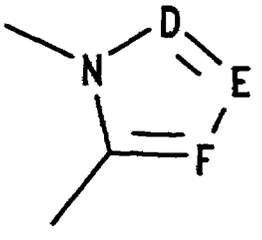
A-B is a moiety selected from



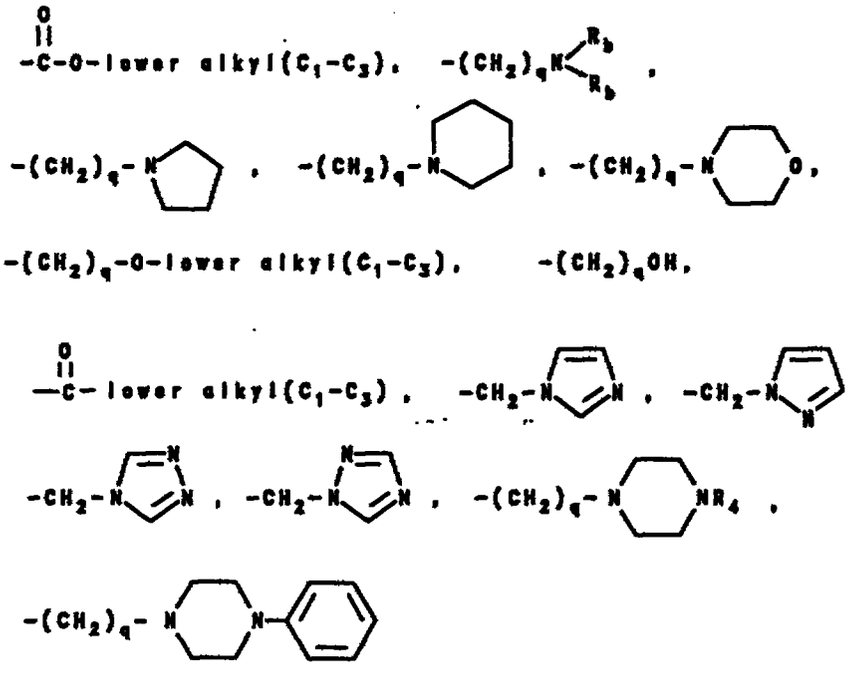
wherein m is an integer from 1 to 2 provided that when Y is $-(CH_2)_n-$ and n is 2, m may also be zero and when n is zero, m may also be three, provided also that when Y is $-(CH_2)_n-$ and n is 2, m may not be two;
the moiety



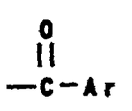
represents: (1) fused phenyl or fused substituted phenyl optionally substituted by one or two substituents selected from (C_1-C_3)lower alkyl, halogen, amino, (C_1-C_3)lower alkoxy and (C_1-C_3)lower alkylamino; (2) a 5-membered aromatic (unsaturated) heterocyclic ring having one heteroatom selected from O, N and S; (3) a 6-membered aromatic (unsaturated) heterocyclic ring having one nitrogen atom; (4) a 5 or 6-membered aromatic (unsaturated) heterocyclic ring having two nitrogen atoms; (5) a 5-membered aromatic (unsaturated) heterocyclic ring having one nitrogen atom together with either one oxygen or one sulfur atom; wherein the 5 or 6-membered heterocyclic rings are optionally substituted by (C_1-C_3)lower alkyl, halogen or (C_1-C_3)lower-alkoxy;
the moiety:



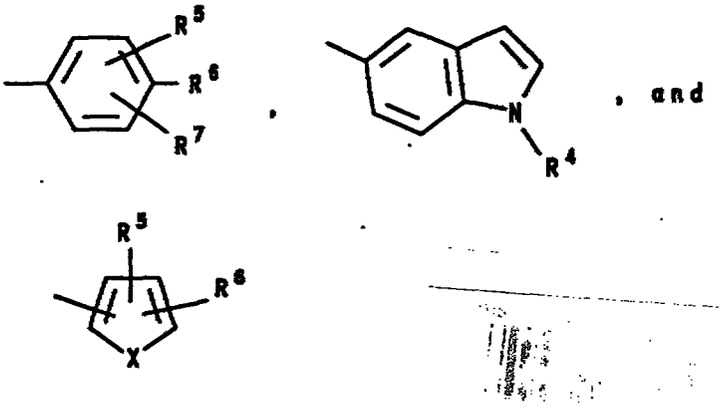
is a five membered aromatic(unsaturated) fused nitrogen containing heterocyclic ring wherein D, E and F are selected from carbon and nitrogen and wherein the carbon atoms may be optionally substituted by a substituent selected from halogen, (C_1-C_3)lower alkyl, hydroxy, $COCl_3$, $COCF_3$,



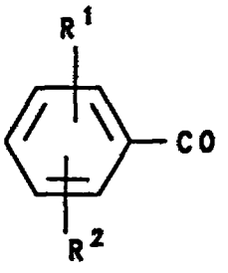
-CHO, amino, (C_1-C_3)lower alkoxy, (C_1-C_3)lower alkylamino, CONH lower alkyl(C_1-C_3) and -CON[lower alkyl(C_1-C_3)]$_2$; q is one or two; R_b is independently selected from hydrogen, $-CH_3$ or $-C_2H_5$;
R^3 is a moiety of the formula



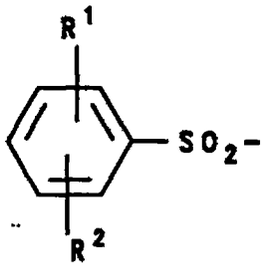
wherein Ar is a moiety selected from the group consisting of



wherein X is selected from O, S, NH, NCH_3 and $NCOCH_3$; R^4 is selected from hydrogen, lower alkyl(C_1-C_3), -CO-lower alkyl(C_1-C_3),



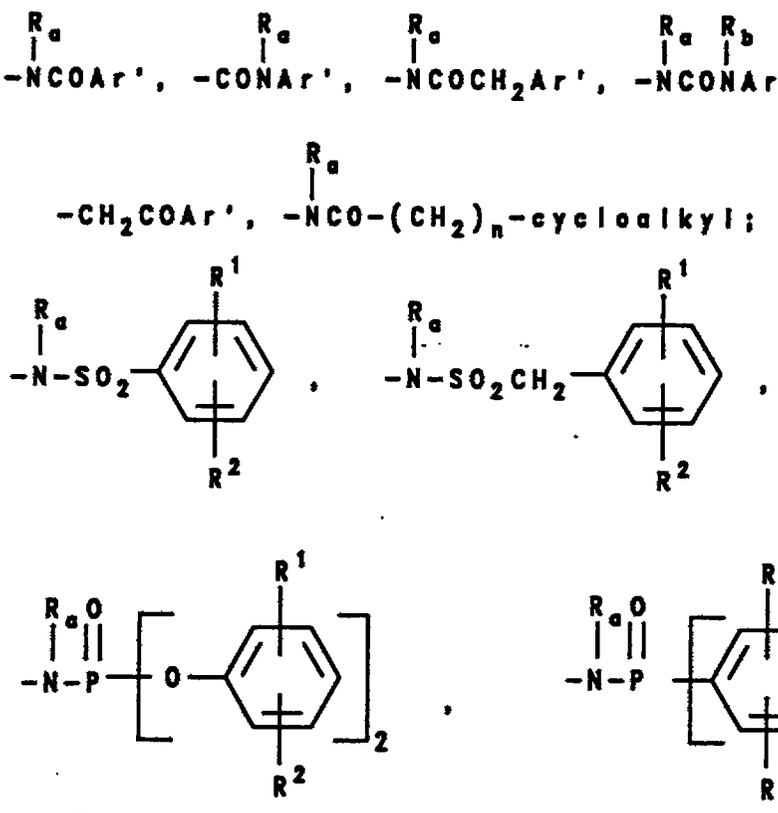
,



$-SO_2$lower alkyl(C_1-C_3); R^1 and R^2 are independently selected from hydrogen, (C_1-C_3)lower alkyl, (C_1-C_3)lower alkoxy and halogen; R^5 is selected from hydrogen, (C_1-C_3)lower alkyl, (C_1-C_3)lower alkoxy and halogen;

R^6 is selected from (a) moieties of the formula:





$-NCOAr'$, $-CONAr'$, $-NCOCH_2Ar'$, $-NCONAr'$,

$-CH_2COAr'$, $-NCO-(CH_2)_n$-cycloalkyl;

$-NH-C(=O)-O-$lower alkyl(C_1-C_8) straight or branched,

$-NH-C(=O)-$lower alkyl(C_1-C_8) straight or branched,

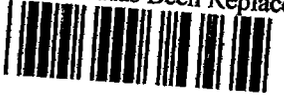
$-NHSO_2-$lower alkyl(C_1-C_8) straight or branched,

$-NH-C(=O)-O-$lower alkenyl(C_1-C_8) straight or branched,

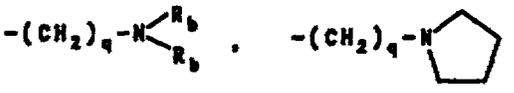
$-NH-C(=O)-$lower alkenyl(C_1-C_8) straight or branched,

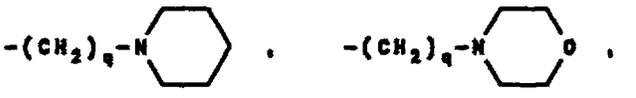
$-NHSO_2-$lower alkenyl(C_1-C_8) straight or branched,

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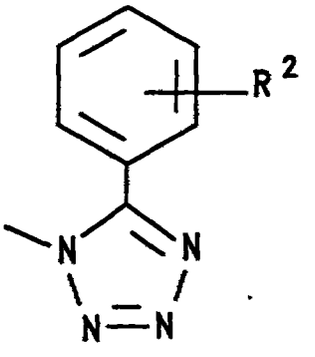


wherein cycloalkyl is defined as C_3 to C_6 cycloalkyl, cyclohexenyl or cyclopentenyl; R_a is independently selected from hydrogen, $-CH_3$, $-C_2H_5$,

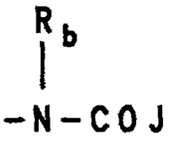




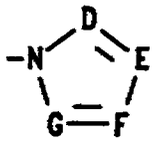
$-(CH_2)_q-O$ lower alkyl(C_1-C_3), and $-CH_2CH_2OH$; q is one or two; and R_1, R_2 and R_b are as hereinbefore defined;
(b) a moiety of the formula:



wherein R^2 is as hereinbefore defined;
(c) a moiety of the formula:



wherein J is R_a, lower alkyl(C_1-C_8) branched or unbranched, lower alkenyl(C_1-C_8) branched or unbranched, O-lower alkyl(C_1-C_8) branched or unbranched, -O-lower alkenyl(C_1-C_8) branched or unbranched, tetrahydrofuran, tetrahydrothiophene, or $-CH_2-K$ wherein K is (C_1-C_3) lower alkoxy, halogen, tetrahydrofuran, tetrahydrothiophene or the heterocyclic ring moiety:

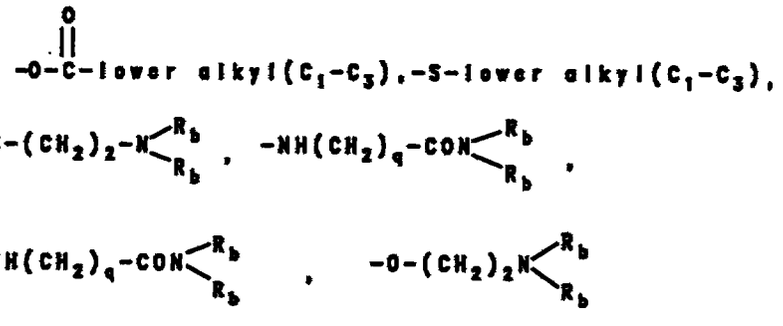


wherein D, E, F and G are selected from carbon or nitrogen and wherein the carbon atoms may be optionally substituted with halogen, (C_1-C_3)lower alkyl, hydroxy, -CO-lower alkyl(C_1-C_3), CHO, (C_1-C_3)lower alkoxy, $-CO_2$-lower alkyl(C_1-C_3), and R_a and R_b are as hereinbefore defined;

(d) a moiety of the formula:



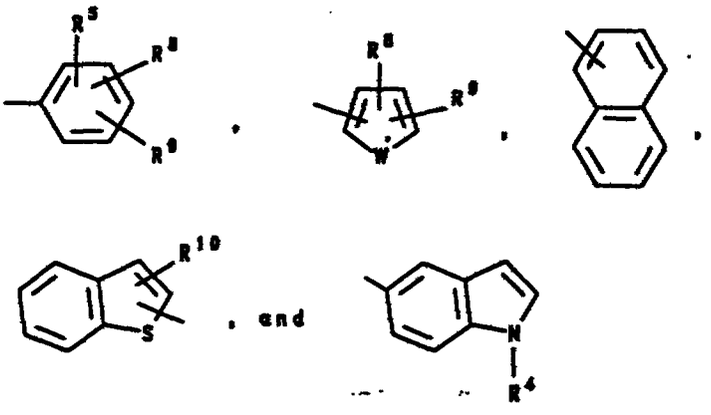
wherein R_a is selected from halogen, (C_1-C_3) lower alkyl, -O-lower alkyl(C_1-C_3), OH,



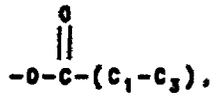
and R_a, R_b are as hereinbefore defined;

wherein Ar' is selected from moieties of the formula:

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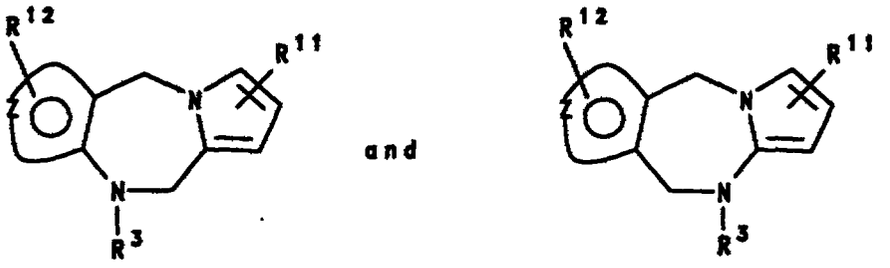


wherein W' is selected from O, S, NH, N-lower alkyl-(C_1-C_3), NHCO-lower alkyl(C_1-C_3) and NSO_2lower alkyl-(C_1-C_3);
R^7 is selected from hydrogen, lower alkyl(C_1-C_3), halogen, O-lower alkyl(C_1-C_3) and CF_3;
R^8 and R^9 are independently selected from hydrogen, lower alkyl(C_1-C_3), -S-lower alkyl(C_1-C_3), halogen, -NH-lower alkyl(C_1-C_3),-OCF_3, -OH, -CN, -S-CF_3, -NO_2, -NH_2, O-loweralkyl(C_1-C_3),

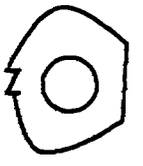


and CF_3 and;
R^{10} is selected from hydrogen, halogen and lower alkyl-(C_1-C_3), and the pharmaceutically acceptable salts, esters and pro-drug forms thereof.

2. A compound according to Claim 1 selected from those of the formulae:



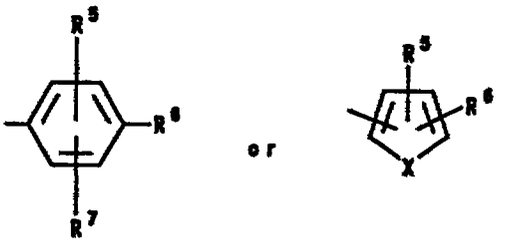
wherein the moiety



is selected from a phenyl, thiophene, furan, pyrrole or pyridine ring wherein the phenyl ring may be optionally substituted with one or two substituents selected from (C_1-C_3) lower alkyl, halogen, amino, (C_1-C_3) lower alkoxy and (C_1-C_3) lower alkylamino,
R^3 is the moiety:

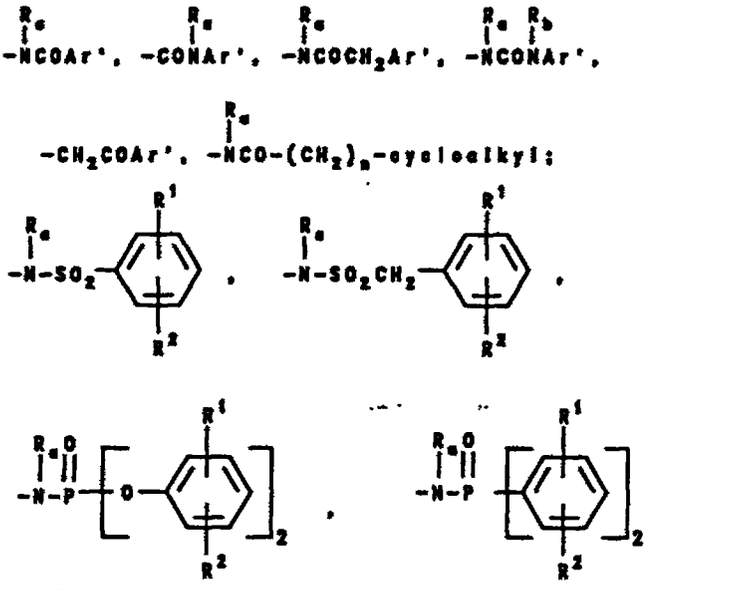


wherein Ar is the moiety:

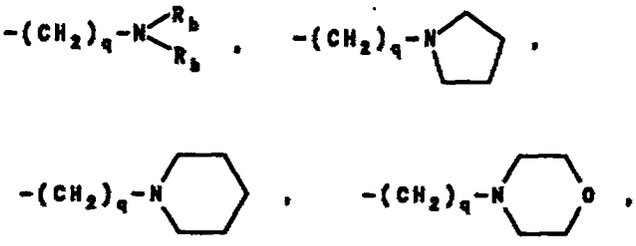


R^6 is selected from (a) moieties of the formula:

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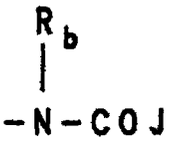
wherein cycloalkyl is defined as C_3 to C_6 cycloalkyl, cyclohexenyl or cyclopentenyl; R_a is independently selected from hydrogen, $-CH_3$, $-C_2H_5$,



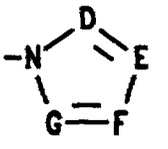
$-(CH_2)_q$-O-lower alkyl(C_1-C_3), $-CH_2CH_2OH$; q is one or two;

R_b is independently selected from hydrogen, $-CH_3$ and $-C_2H_5$;

(b) a moiety of the formula:



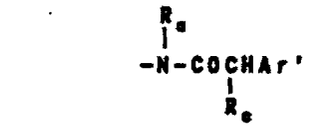
wherein J is R_a, lower alkyl(C_1-C_8) branched or unbranched, lower alkenyl(C_1-C_8) branched or unbranched, O-lower alkyl(C_1-C_8) branched or unbranched, -O-lower alkenyl(C_1-C_8) branched or unbranched, tetrahydrofuran, tetrahydrothiophene, or $-CH_2$-K wherein K is (C_1-C_3) lower alkoxy, halogen, tetrahydrofuran, tetrahydrothiophene or the heterocyclic ring moiety:



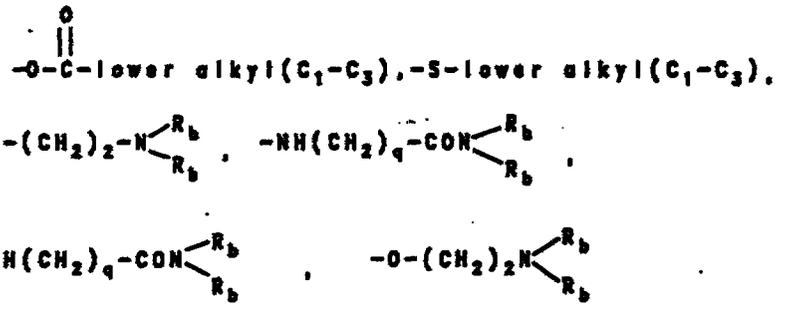
wherein D, E, F and G are selected from carbon or nitrogen and wherein the carbon atoms may be optionally substituted with halogen, (C_1-C_3)lower alkyl, hydroxy, -CO-lower alkyl(C_1-C_3), CHO, (C_1-C_3)lower alkoxy, $-CO_2$-lower alkyl(C_1-C_3), and R_a and R_b are as hereinbefore defined; R^1 and R^2 are independently selected from hydrogen, (C_1-C_3)lower alkyl, (C_1-C_3) lower alkoxy and halogen;

(c) a moiety of the formula:

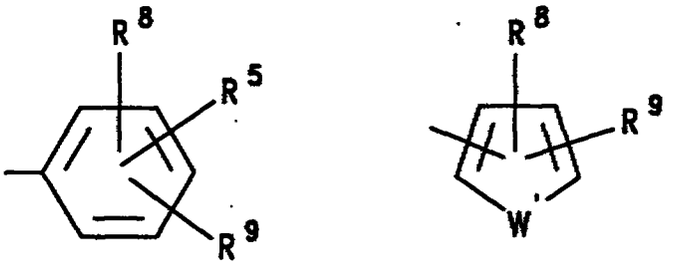
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wherein R_c is selected from halogen, (C_1-C_3) lower alkyl, -O-lower alkyl(C_1-C_3), OH,



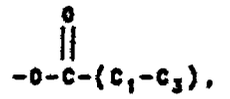
and R_a, R_b are as hereinbefore defined;
and Ar' is selected from the moieties:



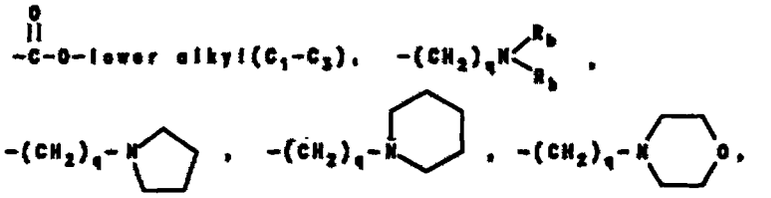
wherein X is selected from O, S, NH, NCH_3, $NCOCH_3$;
R^5 is selected from hydrogen, (C_1-C_3)lower alkyl, (C_1-C_3)lower alkoxy, and halogen;
R^7 is selected from hydrogen, lower alkyl(C_1-C_3), halogen, O-lower alkyl(C_1-C_3) and CF_3;
R^8 and R^9 are independently selected from hydrogen, lower alkyl(C_1-C_3), -S-lower alkyl(C_1-C_3), halogen, -NH-lower alkyl(C_1-C_3), $-OCF_3$, -OH, -CN, $-S-CF_3$, $-NO_2$, $-NH_2$, O-lower alkyl(C_1-C_3),

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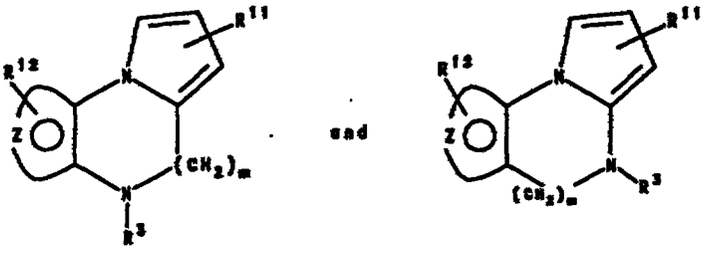


and CF_3;
R^{11} is selected from hydrogen, halogen, (C_1-C_3)lower alkyl, hydroxy, $COCl_3$, $COCF_3$,



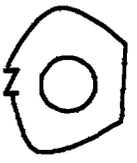
CHO, and (C_1-C_3)lower alkoxy; q is one or two;
R^{12} is selected from hydrogen, (C_1-C_3)lower alkyl, halogen and (C_1-C_3)lower alkoxy; W' is selected from O, S, NH, N-lower alkyl(C_1-C_3), NHCO-lower alkyl(C_1-C_3) and NSO_2-lower alkyl(C_1-C_3), and the pharmaceutically acceptable salts thereof.

3. A compound according to Claim 1 selected from those of the formulae:



wherein m is one or two; and

the moiety:

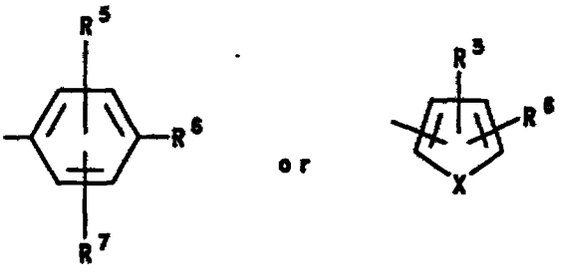


is selected from a phenyl, thiophene, furan, pyrrole and pyridine ring;

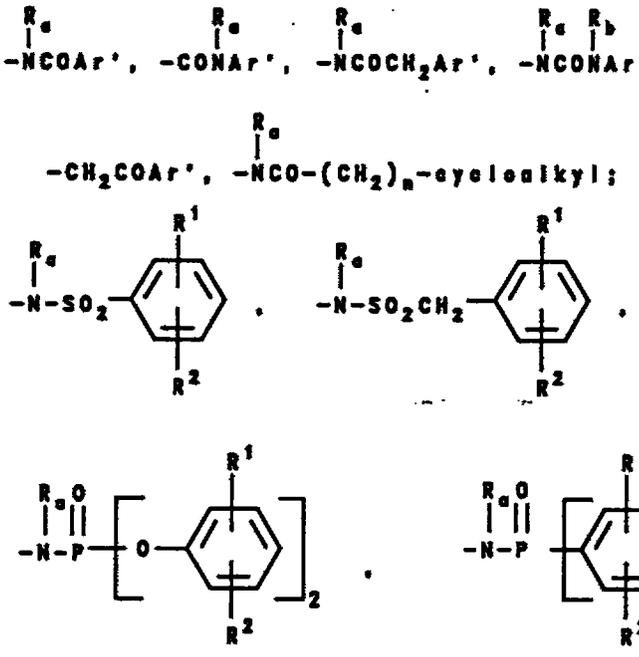
R^3 is the moiety:



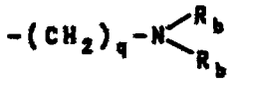
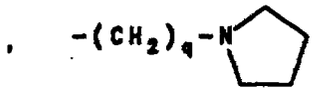
wherein Ar is the moiety:

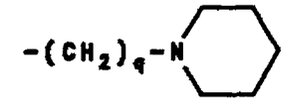
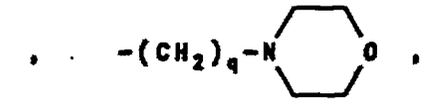


R^6 is selected from (a) moieties of the formula:



wherein cycloalkyl is defined as C_3 to C_6 cycloalkyl, cyclohexenyl or cyclopentenyl; R_a is independently selected from hydrogen, $-CH_3$, $-C_2H_5$,

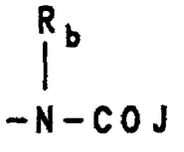



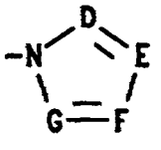
$-(CH_2)_q$-O-lower alkyl(C_1-C_3), $-CH_2CH_2OH$; q is one or two;

R_b is independently selected from hydrogen, $-CH_3$ and $-C_2H_5$;

(b) a moiety of the formula:

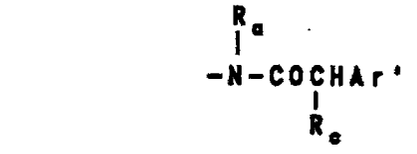


wherein J is R_a, lower alkyl(C_1-C_8) branched or unbranched, lower alkenyl(C_1-C_8) branched or unbranched, O-lower alkyl(C_1-C_8) branched or unbranched, -O-lower alkenyl(C_1-C_8) branched or unbranched, tetrahydrofuran, tetrahydrothiophene, or $-CH_2$-K wherein K is (C_1-C_3) lower alkoxy, halogen, tetrahydrofuran, tetrahydrothiophene or the heterocyclic ring moiety:

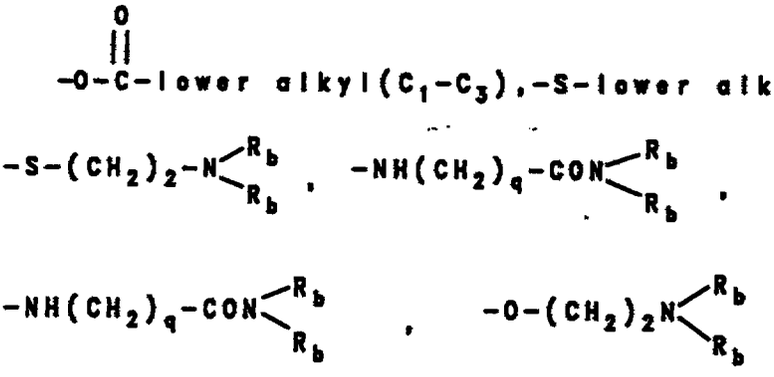


wherein D, E, F and G are selected from carbon or nitrogen and wherein the carbon atoms may be optionally substituted with halogen, (C_1-C_3)lower alkyl, hydroxy, -CO-lower alkyl(C_1-C_3), CHO, (C_1-C_3)lower alkoxy, $-CO_2$-lower alkyl(C_1-C_3), and R_a and R_b are as hereinbefore defined; R^1 and R^2 are independently selected from hydrogen, (C_1-C_3)lower alkyl, (C_1-C_3) lower alkoxy and halogen;

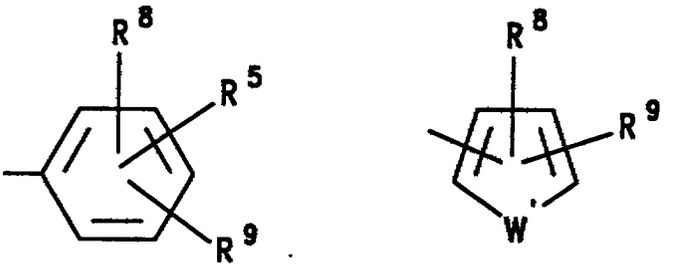
(c) a moiety of the formula:



wherein R_c is selected from halogen, (C_1-C_3) lower alkyl, -O-lower alkyl(C_1-C_3), OH,



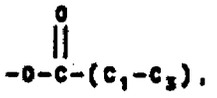
and R_a, R_b are as hereinbefore defined;
Ar' is selected from the moieties:



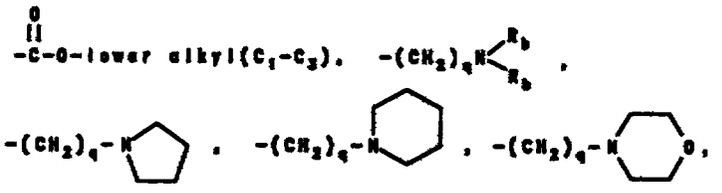
wherein X is selected from O, S, NH, NCH_3, $NCOCH_3$;
wherein R^5 is selected from hydrogen (C_1-C_3)lower alkyl, (C_1-C_3)lower alkoxy, and halogen;
R^7 is selected from hydrogen, lower alkyl(C_1-C_3), halogen, O-lower alkyl(C_1-C_3) and CF_3;
R^8 and R^9 are independently selected from hydrogen, lower alkyl(C_1-C_3), -S-lower alkyl(C_1-C_3), halogen, -NH-lower alkyl(C_1-C_3), $-OCF_3$, -OH, -CN, $-S-CF_3$, $-NO_2$, $-NH_2$, O-lower alkyl(C_1-C_3),

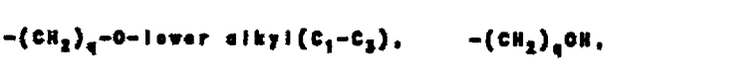
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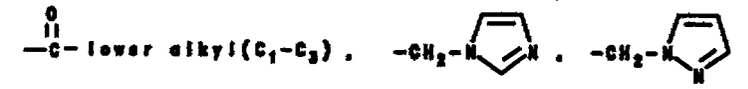


and CF_3;
R^{11} is selected from hydrogen, halogen, (C_1-C_3)lower alkyl, hydroxy, $COCl_3$, $COCF_3$,

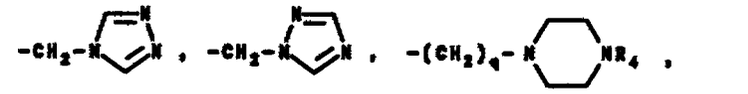








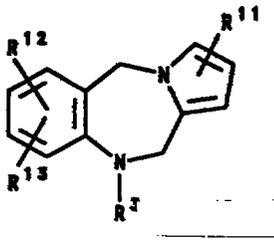




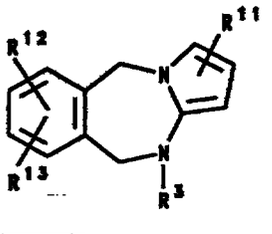


CHO, and (C_1-C_3)loweralkoxy; q is one or two;
R^{12} is selected from hydrogen, (C_1-C_3)lower alkyl, halogen and (C_1-C_3)lower alkoxy; W' is selected from O, S, NH, N-lower alkyl(C_1-C_3), NHCO-lower alkyl(C_1-C_3) or NSO_2-loweralkyl(C_1-C_3), and the pharmaceutically acceptable salts thereof.

4. A compound according to Claim 1 selected from those of the formulae:



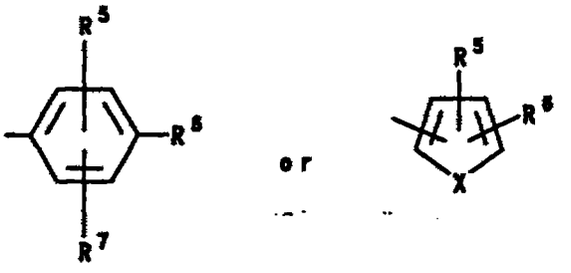
and



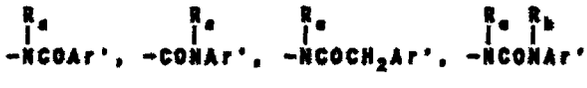
R^3 is the moiety:

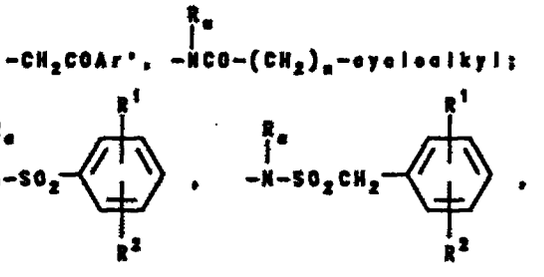


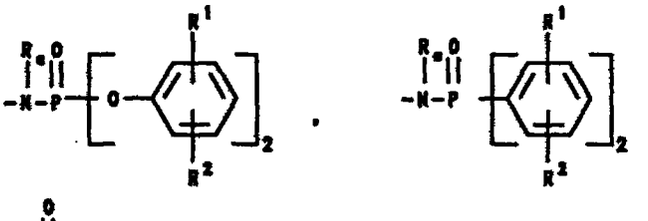
wherein Ar is the moiety:



R^6 is selected from (a) moieties of the formula:







-NH-C-O-lower alkyl(C_1-C_8) straight or branched,

-NH-C-lower alkyl(C_1-C_8) straight or branched,

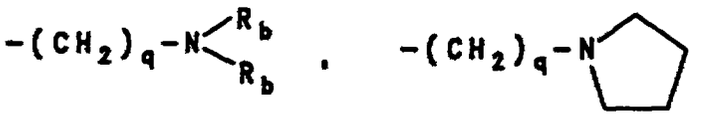
$-NHSO_2$-lower alkyl(C_1-C_8) straight or branched,

-NH-C-O-lower alkenyl(C_1-C_8) straight or branched,

-NH-C-lower alkenyl(C_1-C_8) straight or branched,

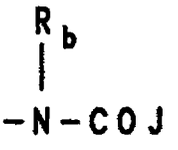
$-NHSO_2$-lower alkenyl(C_1-C_8) straight or branched,

wherein cycloalkyl is defined as C_3 to C_6 cycloalkyl, cyclohexenyl or cyclopentenyl; R_a is independently selected from hydrogen, $-CH_3$, $-C_2H_5$,

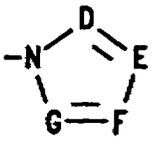




$-(CH_2)_q$-O-lower alkyl(C_1-C_3), $-CH_2CH_2OH$; q is one or two;
R_b is independently selected from hydrogen, $-CH_3$ and $-C_2H_5$;
and (b) a moiety of the formula:



wherein J is R_a, lower alkyl(C_1-C_8) branched or unbranched, lower alkenyl(C_1-C_8) branched or unbranched, O-lower alkyl(C_1-C_8) branched or unbranched, -O-lower alkenyl(C_1-C_8) branched or unbranched, tetrahydrofuran, tetrahydrothiophene, or $-CH_2$-K wherein K is (C_1-C_3) lower alkoxy, halogen, tetrahydrofuran, tetrahydrothiophene or the heterocyclic ring moiety:



wherein D, E, F and G are selected from carbon or nitrogen and wherein the carbon atoms may be optionally substituted with halogen, (C_1-C_3)lower alkyl, hydroxy, -CO-lower alkyl(C_1-C_3), CHO, (C_1-C_3)lower alkoxy, $-CO_2$-lower alkyl(C_1-C_3), and R_a and R_b are as hereinbefore defined; R^1 and R^2 are independently

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selected from hydrogen, (C_1-C_3)lower alkyl, (C_1-C_3) lower alkoxy and halogen;

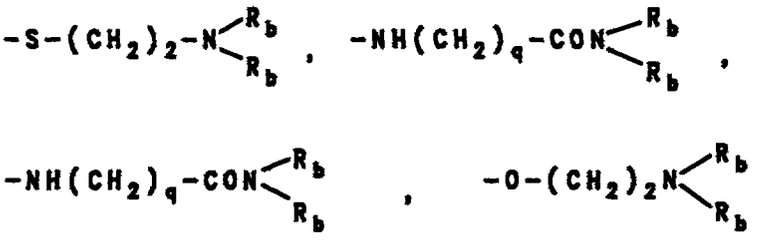
(c) a moiety of the formula:



wherein R_e is selected from halogen, (C_1-C_3) lower alkyl, -O-lower alkyl(C_1-C_3), OH,

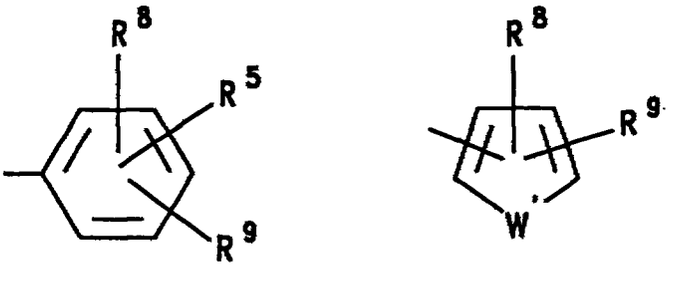


-O-C-lower alkyl(C_1-C_3), -S-lower alkyl(C_1-C_3),



and R_a, R_b are as hereinbefore defined;

and Ar' is selected from the moieties:

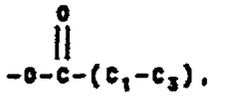


wherein X is selected from O, S, NH, NCH_3, $NCOCH_3$;

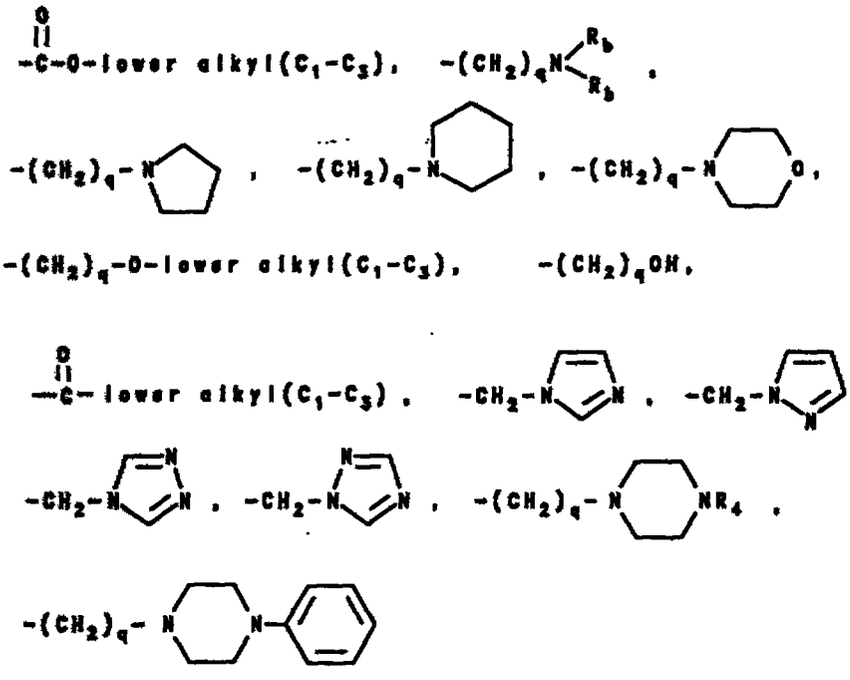
R^5 is selected from hydrogen (C_1-C_3)lower alkyl, (C_1-C_3)lower alkoxy, and halogen;

R^7 is selected from hydrogen, lower alkyl(C_1-C_3), halogen, O-lower alkyl(C_1-C_3) and CF_3;

R^8 and R^9 are independently selected from hydrogen, lower alkyl(C_1-C_3), -S-lower alkyl(C_1-C_3), halogen, -NH-lower alkyl(C_1-C_3), $-OCF_3$, -OH, -CN, $-S-CF_3$, $-NO_2$, $-NH_2$, O-lower alkyl(C_1-C_3),

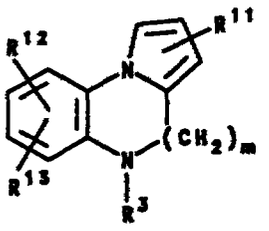


and CF_3;
R^{11} is selected from hydrogen, halogen, (C_1-C_3)lower alkyl, hydroxy, $COCl_3$, $COCF_3$,

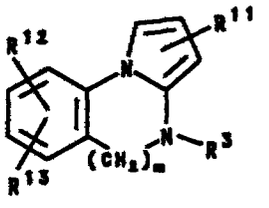


CHO, and (C_1-C_3)loweralkoxy; q is one or two; R^{12} and R^{13} are independently selected from (C_1-C_3)lower alkyl, hydrogen, halogen, amino, (C_1-C_3)lower alkoxy or (C_1-C_3)lower alkylamino; W' is selected from O, S, -NH, NH-lower alkyl(C_1-C_3), NHCO-lower alkyl(C_1-C_3) or NSO_2 lower alkyl(C_1-C_3), and the pharmaceutically acceptable salts thereof.

5. A compound according to Claim 1 selected from those of the formulae:



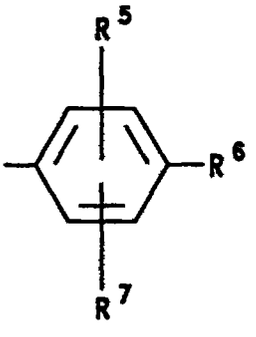
and



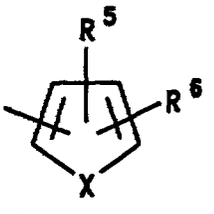
wherein m is one or two;
R^3 is the moiety:



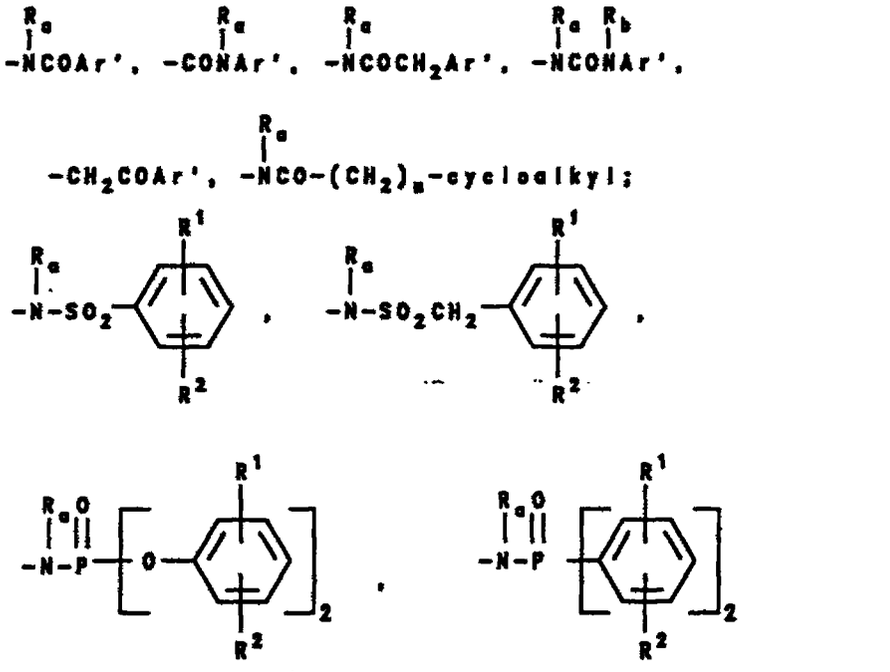
wherein Ar is the moiety:



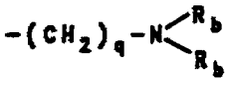
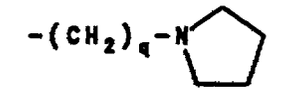
or

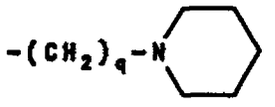
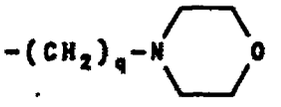


R^6 is selected from (a) moieties of the formula:



wherein cycloalkyl is defined as C_3 to C_6 cycloalkyl, cyclohexenyl or cyclopentenyl; R_a is independently selected from hydrogen, $-CH_3$, $-C_2H_5$,

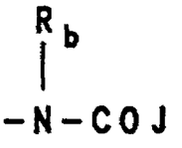



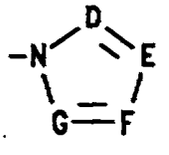
$-(CH_2)_q$-O-lower alkyl(C_1-C_3), $-CH_2CH_2OH$; q is one or two;

R_b is independently selected from hydrogen, $-CH_3$ and $-C_2H_5$;

(b) a moiety of the formula:

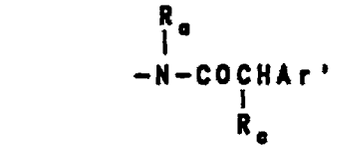


wherein J is R_a, lower alkyl(C_1-C_8) branched or unbranched, lower alkenyl(C_1-C_8) branched or unbranched, O-lower alkyl(C_1-C_8) branched or unbranched, -O-lower alkenyl(C_1-C_8) branched or unbranched, tetrahydrofuran, tetrahydrothiophene, or $-CH_2$-K wherein K is (C_1-C_3) lower alkoxy, halogen, tetrahydrofuran, tetrahydrothiophene or the heterocyclic ring moiety:

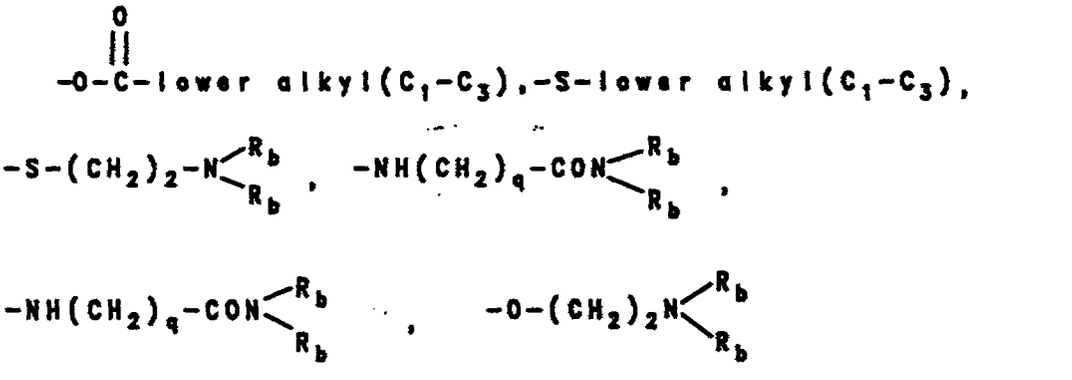


wherein D, E, F and G are selected from carbon or nitrogen and wherein the carbon atoms may be optionally substituted with halogen, (C_1-C_3)lower alkyl, hydroxy, -CO-lower alkyl(C_1-C_3), CHO, (C_1-C_3)lower alkoxy, $-CO_2$-lower alkyl(C_1-C_3), and R_a and R_b are as hereinbefore defined; R^1 and R^2 are independently selected from hydrogen, (C_1-C_3)lower alkyl, (C_1-C_3) lower alkoxy and halogen;

(c) a moiety of the formula:



wherein R_c is selected from halogen, (C_1-C_3) lower alkyl, -O-lower alkyl(C_1-C_3), OH,



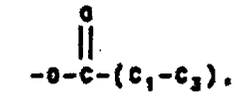
and R_a, R_b are as hereinbefore defined;
and Ar' is selected from the moieties:



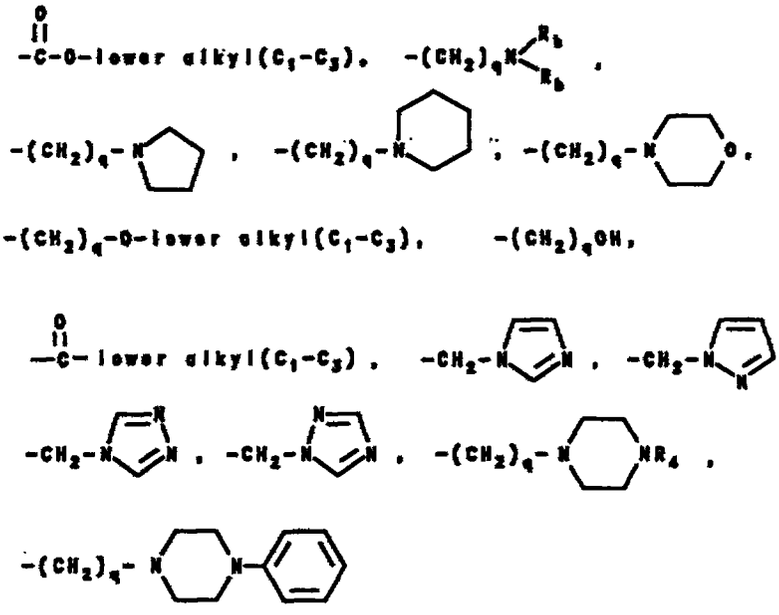
wherein X is selected from O, S, NH, NCH_3, $NCOCH_3$;
R^5 is selected from hydrogen, (C_1-C_3)lower alkyl, (C_1-C_3)lower alkoxy, and halogen;
R^7 is selected from hydrogen, lower alkyl(C_1-C_3), halogen, O-lower alkyl(C_1-C_3) and CF_3;
R^8 and R^9 are independently selected from hydrogen, lower alkyl(C_1-C_3), -S-lower alkyl(C_1-C_3), halogen, -NH-lower alkyl(C_1-C_3), $-OCF_3$, -OH, -CN, $-S-CF_3$, $-NO_2$, $-NH_2$, O-lower alkyl(C_1-C_3),

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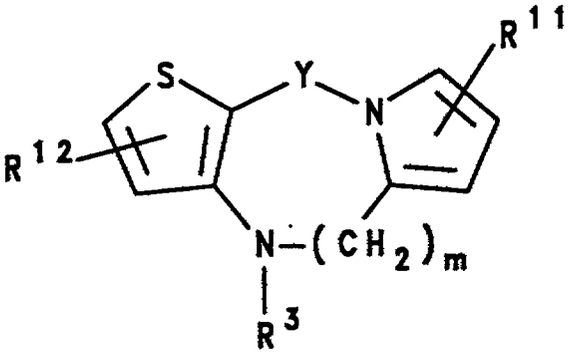


and CF_3;
R^{11} is selected from hydrogen, halogen, (C_1-C_3)lower-alkyl, hydroxy, $COCl_3$, $COCF_3$,



CHO, and (C_1-C_3)loweralkoxy; q is one or two; and W' is selected from O, S, NH, N-lower alkyl(C_1-C_3), NHCO-lower alkyl(C_1-C_3), or NSO_2-lower alkyl(C_1-C_3); R^{12} and R^{13} are independently selected from hydrogen, (C_1-C_3)lower alkyl, halogen, amino, (C_1-C_3)lower alkoxy or (C_1-C_3)lower alkylamino, and the pharmaceutically acceptable salts thereof.

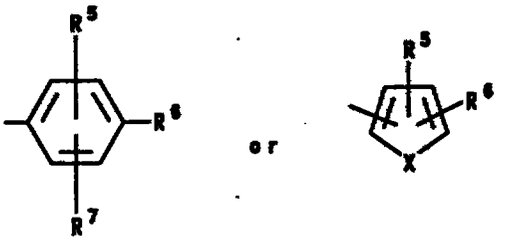
6. A compound according to Claim 1 selected from those of the formula:



wherein Y is $-(CH_2)_n-$;
n is one when m is one; and m is one or two when n is zero;
R^3 is the moiety:



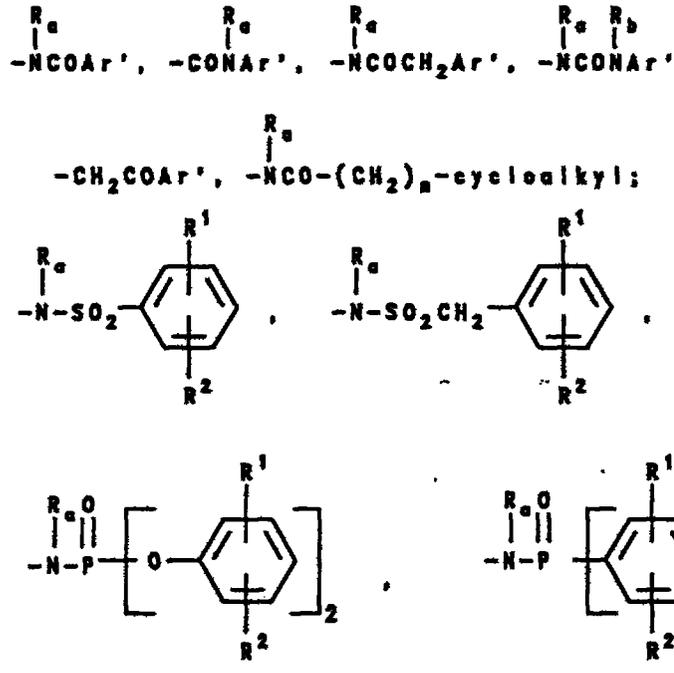
wherein Ar is the moiety:



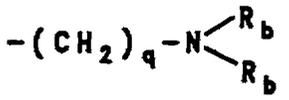
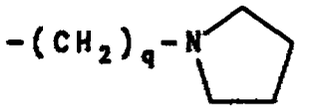
R^6 is selected from (a) moieties of the formula:

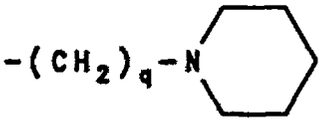
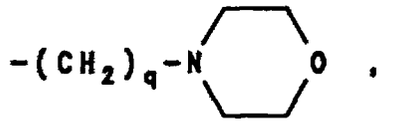
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wherein cycloalkyl is defined as C_3 to C_6 cycloalkyl, cyclohexenyl or cyclopentenyl; R_a is independently selected from hydrogen, $-CH_3$, $-C_2H_5$,

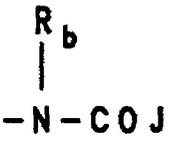



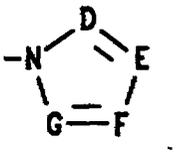
$-(CH_2)_q$-O-lower alkyl(C_1-C_3), $-CH_2CH_2OH$; q is one or two;

R_b is independently selected from hydrogen, $-CH_3$ and $-C_2H_5$;

and (b) a moiety of the formula:



wherein J is R_a, lower alkyl(C_1-C_8) branched or unbranched, lower alkenyl(C_1-C_8) branched or unbranched, O-lower alkyl(C_1-C_8) branched or unbranched, -O-lower alkenyl(C_1-C_8) branched or unbranched, tetrahydrofuran, tetrahydrothiophene, or $-CH_2$-K wherein K is (C_1-C_3) lower alkoxy, halogen, tetrahydrofuran, tetrahydrothiophene or the heterocyclic ring moiety:

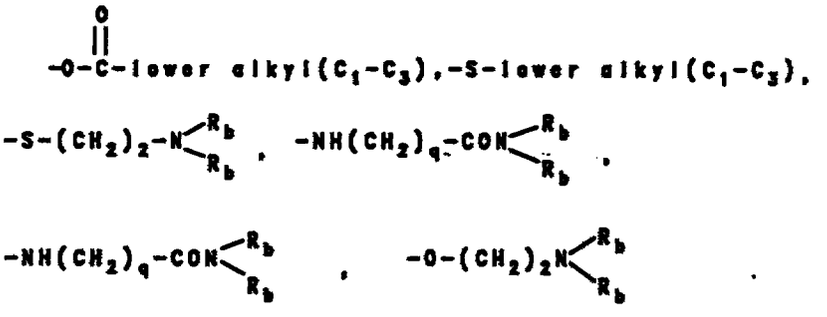


wherein D, E, F and G are selected from carbon or nitrogen and wherein the carbon atoms may be optionally substituted with halogen, (C_1-C_3)lower alkyl, hydroxy, -CO-lower alkyl(C_1-C_3), CHO, (C_1-C_3)lower alkoxy, $-CO_2$-lower alkyl(C_1-C_3), and R_a and R_b are as hereinbefore defined; R^1 and R^2 are independently selected from hydrogen, (C_1-C_3)lower alkyl, (C_1-C_3) lower alkoxy and halogen;

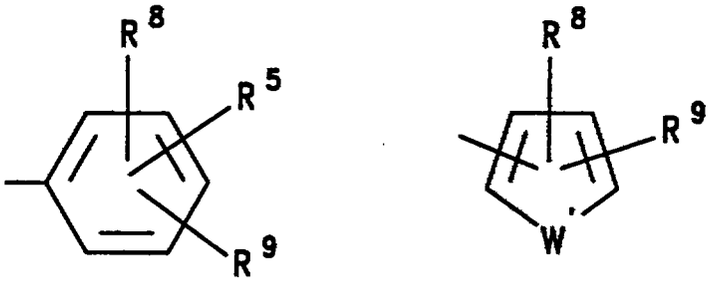
(c) a moiety of the formula:



wherein R_e is selected from halogen, (C_1-C_3) lower alkyl, -O-lower alkyl(C_1-C_3), OH,

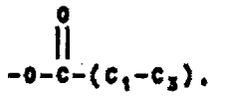


and R_a, R_b are as hereinbefore defined;
and Ar' is selected from the moieties:

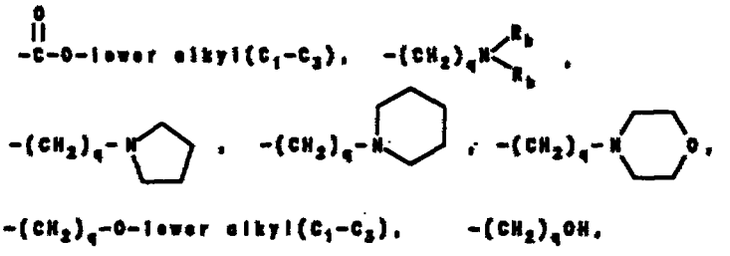


wherein X is selected from O, S, NH, NCH_3 and $NCOCH_3$;
R^5 is selected from hydrogen (C_1-C_3)lower alkyl, (C_1-C_3)lower alkoxy, and halogen;
R^7 is selected from hydrogen, lower alkyl(C_1-C_3), halogen, O-lower alkyl(C_1-C_3) and CF_3;
R^8 and R^9 are independently selected from hydrogen, lower alkyl(C_1-C_3), -S-lower alkyl(C_1-C_3), halogen, -NH-lower alkyl(C_1-C_3), $-OCF_3$, -OH, -CN, $-S-CF_3$, $-NO_2$, $-NH_2$, O-lower alkyl(C_1-C_3),

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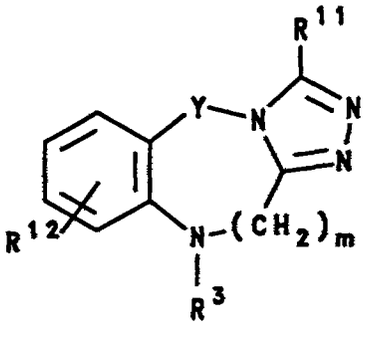


and CF_3;
R^{11} is selected from hydrogen, halogen, (C_1-C_3)lower alkyl, hydroxy, $COCl_3$, $COCF_3$,



CHO, and (C_1-C_3)lower alkoxy; q is one or two;
R^{12} is selected from (C_1-C_3)lower alkyl, hydrogen, halogen, and (C_1-C_3)lower alkoxy; W' is selected from O, S, -NH, N-lower alkyl(C_1-C_3), NHCO-lower alkyl(C_1-C_3), or NSO_2-lower alkyl(C_1-C_3), and the pharmaceutically acceptable salts thereof.

7. A compound according to Claim 1 selected from those of the formula:

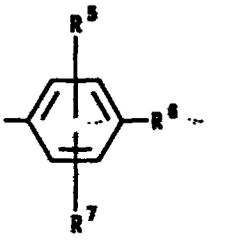


wherein Y is $-(CH_2)_n$; n is one when m is one and m is two when n is zero;

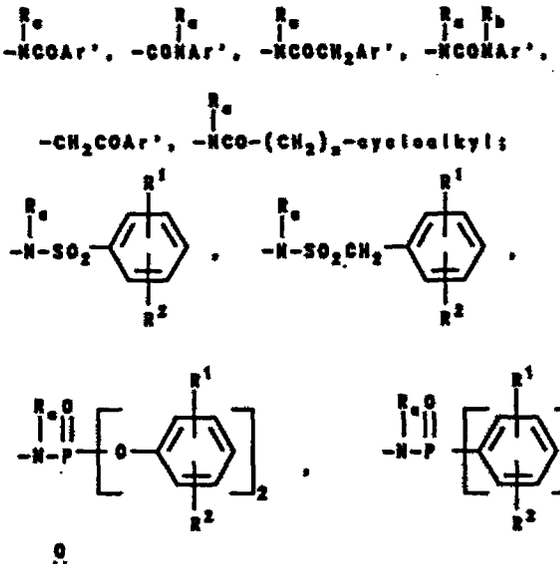
R^3 is the moiety:



wherein Ar is the moiety:



R^6 is selected from moieties of the formula:



-NHCOAr', -CONHAr', -NHCOCH$_2$Ar', -NHCONHAr',

-CH$_2$COAr', -NHCO-(CH$_2$)$_2$-cycloalkyl;

-NH-C(=O)-O-lower alkyl(C_1-C_8) straight or branched,

-NH-C(=O)-lower alkyl(C_1-C_8) straight or branched,

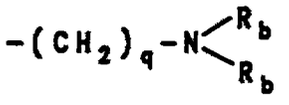
-NHSO$_2$-lower alkyl(C_1-C_8) straight or branched,

-NH-C(=O)-O-lower alkenyl(C_1-C_8) straight or branched,

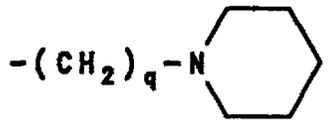
-NH-C(=O)-lower alkenyl(C_1-C_8) straight or branched,

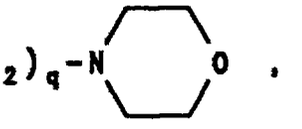
-NHSO$_2$-lower alkenyl(C_1-C_8) straight or branched,

R^1 and R^2 are independently selected from hydrogen, (C_1-C_3) lower alkyl, (C_1-C_3)lower alkoxy and halogen; wherein cycloalkyl is defined as C_3 to C_6 cycloalkyl, cyclohexenyl or cyclopentenyl; R_a is independently selected from hydrogen, $-CH_3$, $-C_2H_5$,



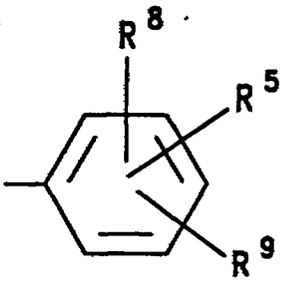


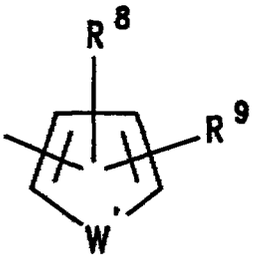




$-(CH_2)_q$-O-lower alkyl(C_1-C_3), CH_2CH_2OH; q is one or two;

R_b is independently selected from hydrogen, $-CH_3$ and $-C_2H_5$; and Ar' is selected from the moieties:

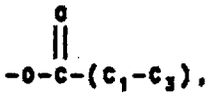




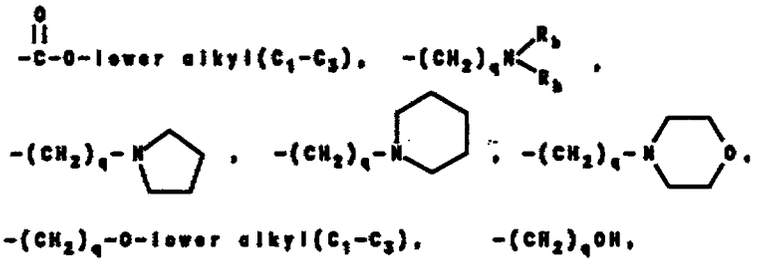
R^5 is selected from hydrogen, (C_1-C_3)lower alkyl, (C_1-C_3)lower alkoxy, and halogen;

R^7 is selected from hydrogen, lower alkyl(C_1-C_3), halogen, O-lower alkyl(C_1-C_3) and CF_3;

R^8 and R^9 are independently selected from hydrogen, lower alkyl(C_1-C_3), -S-lower alkyl(C_1-C_3), halogen, -NH-lower alkyl(C_1-C_3), $-OCF_3$, -OH, -CN, $-S-CF_3$, $-NO_2$, $-NH_2$, O-lower alkyl(C_1-C_3),

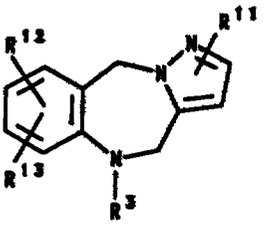
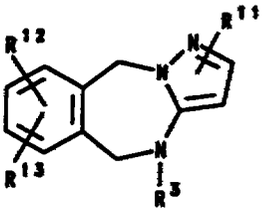


and CF_3;
R^{11} is selected from hydrogen, halogen, (C_1-C_3)lower alkyl, hydroxy, $COCl_3$, $COCF_3$,



CHO, (C_1-C_3)lower alkoxy and q is one or two;
R^{12} is selected from (C_1-C_3)lower alkyl, hydrogen, halogen, and (C_1-C_3)lower alkoxy; W' is selected from O, S, -NH, N-lower alkyl(C_1-C_3), NHCO-lower alkyl(C_1-C_3), or NSO_2-lower alkyl(C_1-C_3);
and the pharmaceutically acceptable salts thereof.

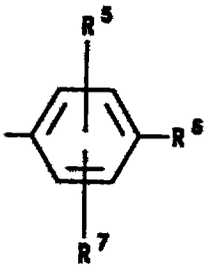
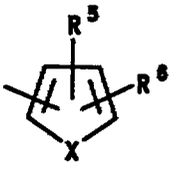
8. A compound according to Claim 1 selected from those of the formulae:


and


R^3 is the moiety:

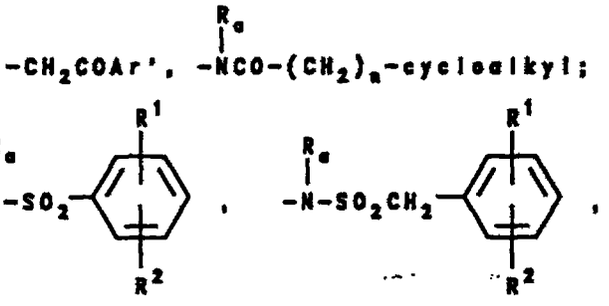


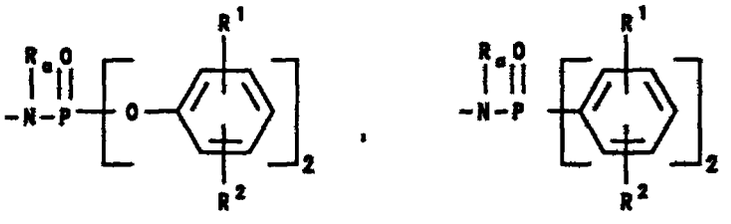
wherein Ar is the moiety:


or


R^6 is selected from (a) moieties of the formula:







$$-NH-\overset{O}{\overset{\|}{C}}-O\text{-lower alkyl}(C_1\text{-}C_8)\text{ straight or branched,}$$

$$-NH-\overset{O}{\overset{\|}{C}}\text{-lower alkyl}(C_1\text{-}C_8)\text{ straight or branched,}$$

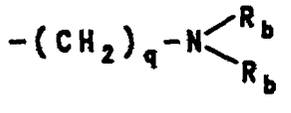
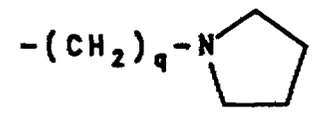
$$-NHSO_2\text{-lower alkyl}(C_1\text{-}C_8)\text{ straight or branched,}$$

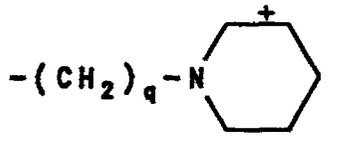
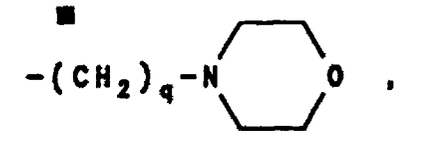
$$-NH-\overset{O}{\overset{\|}{C}}-O\text{-lower alkenyl}(C_1\text{-}C_8)\text{ straight or branched,}$$

$$-NH-\overset{O}{\overset{\|}{C}}\text{-lower alkenyl}(C_1\text{-}C_8)\text{ straight or branched,}$$

$$-NHSO_2\text{-lower alkenyl}(C_1\text{-}C_8)\text{ straight or branched,}$$

wherein cycloalkyl is defined as C_3 to C_6 cycloalkyl, cyclohexenyl or cyclopentenyl; R_a is independently selected from hydrogen, $-CH_3$, $-C_2H_5$,


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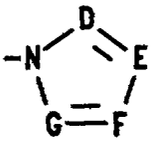
$-(CH_2)_q$-O-lower alkyl(C_1-C_3), $-CH_2CH_2OH$; q is one or two;

R_b is independently selected from hydrogen, $-CH_3$ and $-C_2H_5$;

and (b) a moiety of the formula:



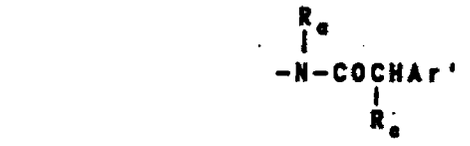
wherein J is R_a, lower alkyl(C_1-C_8) branched or unbranched, lower alkenyl(C_1-C_8) branched or unbranched, O-lower alkyl(C_1-C_8) branched or unbranched, -O-lower alkenyl(C_1-C_8) branched or unbranched, tetrahydrofuran, tetrahydrothiophene, or $-CH_2$-K wherein K is (C_1-C_3) lower alkoxy, halogen, tetrahydrofuran, tetrahydrothiophene or the heterocyclic ring moiety:



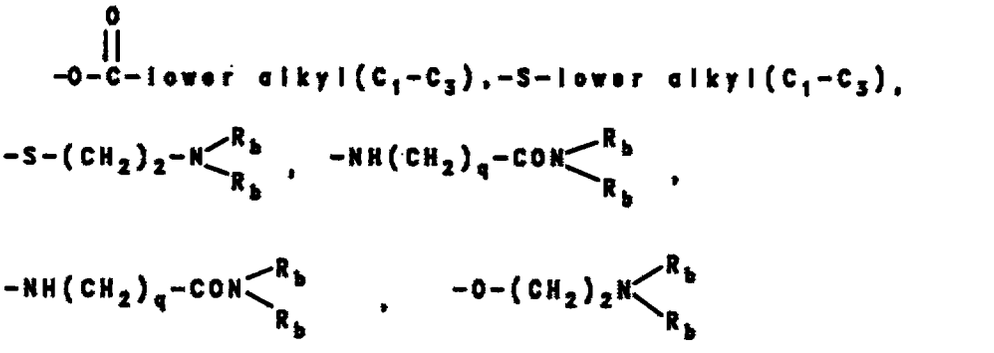
wherein D, E, F and G are selected from carbon or nitrogen and wherein the carbon atoms may be optionally substituted with halogen, (C_1-C_3)lower alkyl, hydroxy, -CO-lower alkyl(C_1-C_3), CHO, (C_1-C_3)lower alkoxy, $-CO_2$-lower alkyl(C_1-C_3), and R_a and R_b are as hereinbefore defined; R^1 and R^2 are independently selected from hydrogen, (C_1-C_3)lower alkyl, (C_1-C_3) lower alkoxy and halogen;

(c) a moiety of the formula:

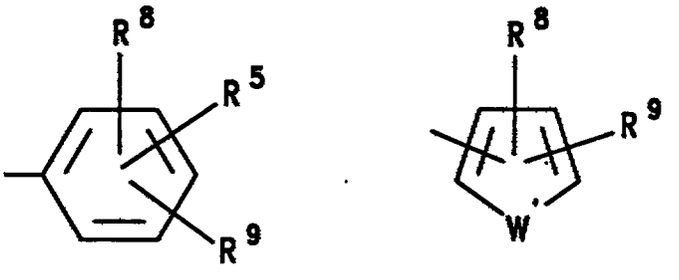




wherein R_e is selected from halogen, (C_1-C_3) lower alkyl, -O-lower alkyl(C_1-C_3), OH,



and R_a, R_b are as hereinbefore defined;
and Ar' is selected from the moieties:

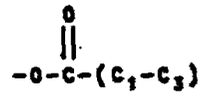


wherein X is selected from O, S, NH, NCH_3 and $NCOCH_3$;
R^5 is selected from hydrogen (C_1-C_3)lower alkyl, (C_1-C_3)lower alkoxy, and halogen;
R^7 is selected from hydrogen, lower alkyl(C_1-C_3), halogen, O-lower alkyl(C_1-C_3) and CF_3;
R^8 and R^9 are independently selected from hydrogen, lower alkyl(C_1-C_3), -S-lower alkyl(C_1-C_3), halogen, -NH-lower alkyl(C_1-C_3), $-OCF_3$, -OH, -CN, $-S-CF_3$, $-NO_2$, $-NH_2$, O-lower alkyl(C_1-C_3),

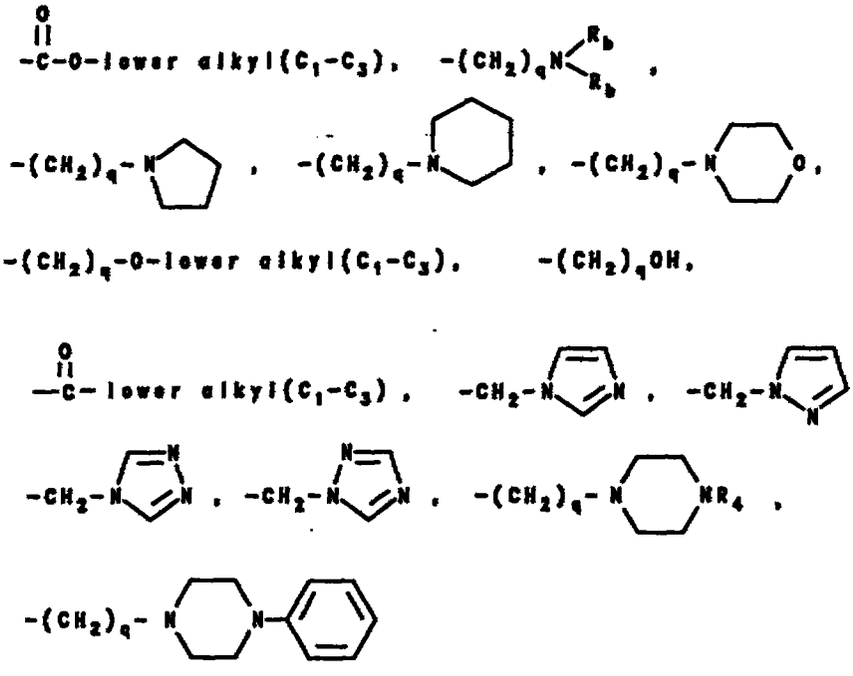
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and CF_3;
R^{11} is selected from hydrogen, halogen, (C_1-C_3)lower alkyl, hydroxy, $COCl_3$, $COCF_3$,

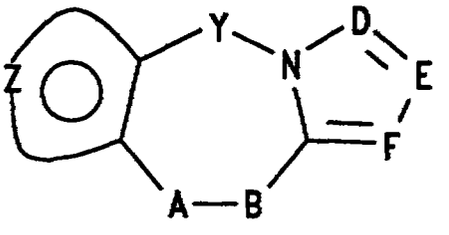


CHO, and (C_1-C_3)loweralkoxy; q is one or two; R^{12} and R^{13} are independently selected from (C_1-C_3)lower alkyl, hydrogen, halogen, amino, (C_1-C_3)lower alkoxy or (C_1-C_3)lower alkylamino; W' is selected from O, S, -NH, NH-lower alkyl(C_1-C_3), NHCO-lower alkyl(C_1-C_3) or NSO_2 lower alkyl(C_1-C_3), and the pharmaceutically acceptable salts thereof.

9. A pharmaceutical composition useful for treating diseases characterized by excess renal reabsorption of water as well as congestive heart failure, liver cirrhosis, nephrotic syndrome, central nervous system injuries, lung disease and hyponatremia in a mammal comprising a suitable pharmaceutical carrier and an effective amount of a compound of Claim 1.

10. A method of treating diseases characterized by excess renal reabsorption of water as well as congestive heart failure, liver cirrhosis, nephrotic syndrome, central nervous system injuries, lung disease and hyponatremia in a mammal comprising administering a compound of Claim 1 to said mammal in an amount effective to alleviate the condition.

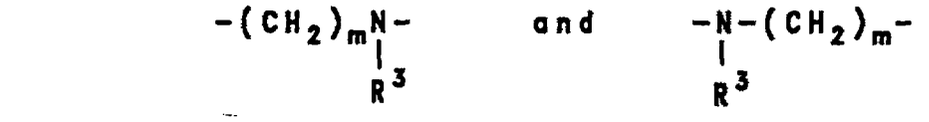
11. A process for preparing a compound of the formula:



wherein Y is a moiety selected from; $-(CH_2)_n-$ wherein n is an integer from 0 to 2,

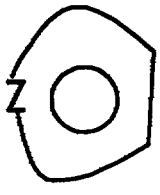


A-B is a moiety selected from

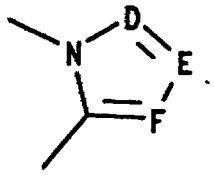


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wherein m is an integer from 1 to 2 provided that when Y is $-(CH_2)_n-$ and n is 2, m may also be zero and when n is zero, m may also be three, provided also that when Y is $-(CH_2)_n-$ and n is 2, m may not be two;
the moiety



represents: (1) fused phenyl or fused substituted phenyl optionally substituted by one or two substituents selected from (C_1-C_3)lower alkyl, halogen, amino, (C_1-C_3)lower alkoxy or (C_1-C_3)lower alkylamino; (2) a 5-membered aromatic (unsaturated) heterocyclic ring having one heteroatom selected from O, N and S; (3) a 6-membered aromatic (unsaturated) heterocyclic ring having one nitrogen atom; (4) a 5 or 6-membered aromatic (unsaturated) heterocyclic ring having two nitrogen atoms; (5) a 5-membered aromatic (unsaturated) heterocyclic ring having one nitrogen atom together with either one oxygen or one sulfur atom; wherein the 5 or 6-membered heterocyclic rings are optionally substituted by (C_1-C_3)lower alkyl, halogen or (C_1-C_3)lower-alkoxy;
the moiety:



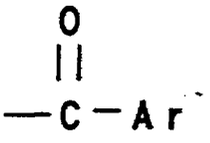
is a five membered aromatic(unsaturated) fused nitrogen containing heterocyclic ring wherein D, E and F are selected from carbon and nitrogen and wherein the carbon atoms may be optionally substituted by a substituent selected from halogen, (C_1-C_3)lower alkyl, hydroxy,



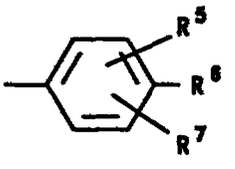


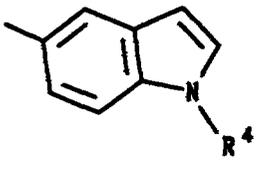
-CHO, amino, (C_1-C_3)loweralkoxy and (C_1-C_3)lower alkylamino;

R^3 is a moiety of the formula

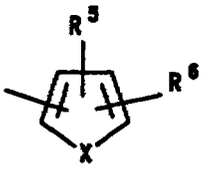


wherein Ar is a moiety selected from the group consisting of



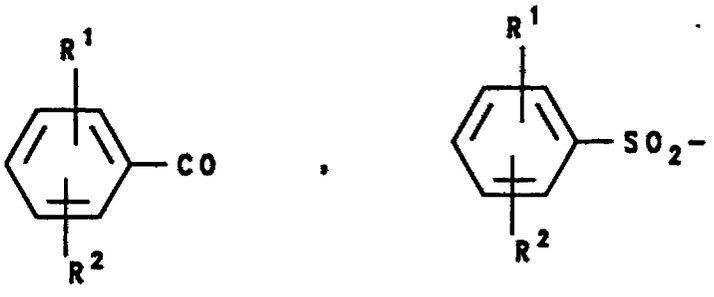


, and



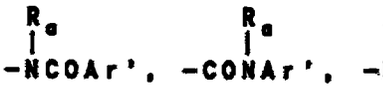
wherein X is selected from O, S, NH, NCH_3 and $NCOCH_3$;

R^4 is selected from hydrogen, lower alkyl(C_1-C_3), -CO-lower alkyl(C_1-C_3),



$-SO_2$lower alkyl(C_1-C_3); R^1 and R^2 are independently selected from hydrogen, (C_1-C_3)lower alkyl, (C_1-C_3)lower alkoxy and halogen;
R^5 is selected from hydrogen, (C_1-C_3)lower alkyl, (C_1-C_3)lower alkoxy and halogen;
R^6 is selected from (a) moieties of the formula:

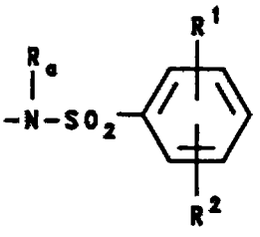




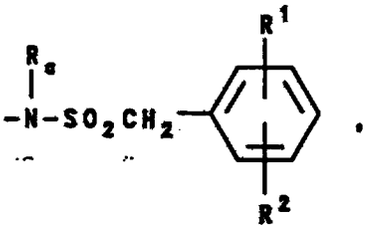
$-NCOAr'$, $-CONAr'$, $-NCOCH_2Ar'$, $-NCONAr'$,



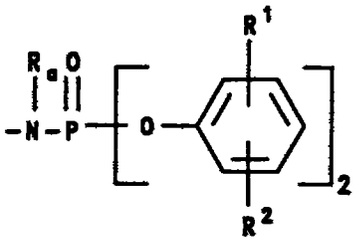
$-CH_2COAr'$, $-NCO-(CH_2)_n-$cycloalkyl;



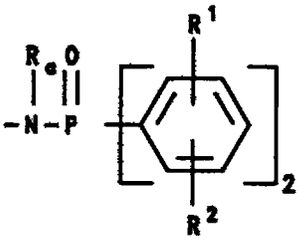
,



,



,



$-NH-\overset{O}{\overset{\|}{C}}-O-$lower alkyl($C_1$-$C_8$) straight or branched,

$-NH-\overset{O}{\overset{\|}{C}}-$lower alkyl($C_1$-$C_8$) straight or branched,

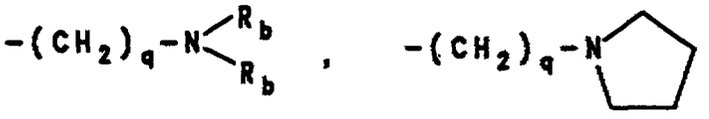
$-NHSO_2-$lower alkyl(C_1-C_8) straight or branched,

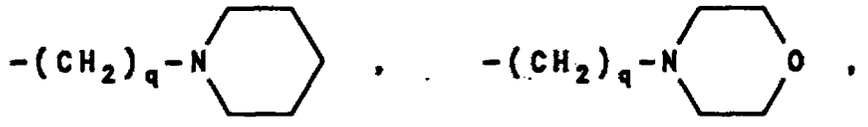
$-NH-\overset{O}{\overset{\|}{C}}-O-$lower alkenyl($C_1$-$C_8$) straight or branched,

$-NH-\overset{O}{\overset{\|}{C}}-$lower alkenyl($C_1$-$C_8$) straight or branched,

$-NHSO_2-$lower alkenyl(C_1-C_8) straight or branched,

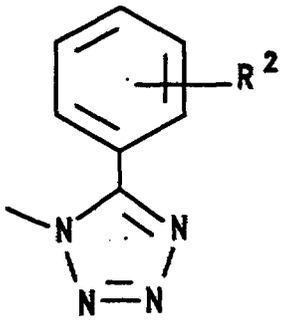
wherein cycloalkyl is defined as C_3 to C_6 cycloalkyl, cyclohexenyl or cyclopentenyl; R_a is independently selected from hydrogen, $-CH_3$, $-C_2H_5$,



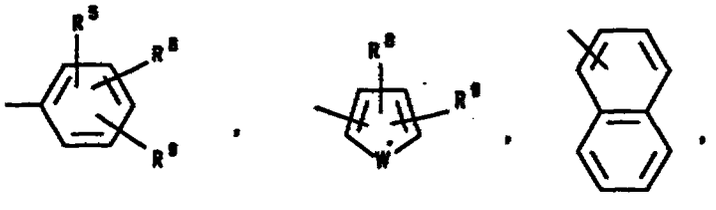


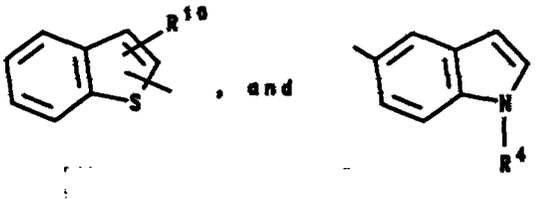
$-(CH_2)_q$-O-lower alkyl(C_1-C_3), $-CH_2CH_2OH$, q is one or two;

R_b is independently selected from hydrogen, $-CH_3$, and $-C_2H_5$; and (b) a moiety of the formula:

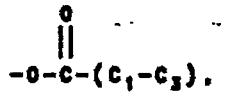


wherein Ar' is selected from moieties of the formula:

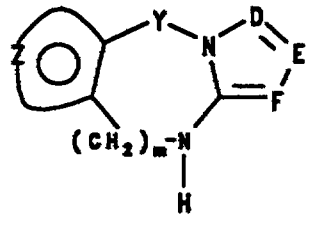




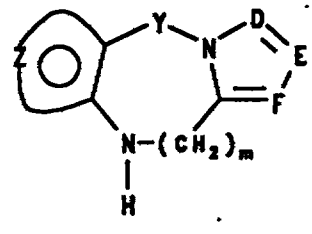
wherein W' is selected from O, S, NH, N-lower alkyl-(C_1-C_3) NHCO-lower alkyl(C_1-C_3) and NSO_2lower alkyl-(C_1-C_3);
R^7 is selected from hydrogen, lower alkyl(C_1-C_3), halogen, O-loweralkyl(C_1-C_3) and CF_3;
R^8 and R^9 are independently selected from hydrogen, lower alkyl(C_1-C_3), -S-lower alkyl(C_1-C_3), halogen, -NH-lower alkyl(C_1-C_3),-OCF_3, -OH, -CN, -S-CF_3, -NO_2, -NH_2, O-lower alkyl(C_1-C_3),



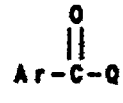
and CF_3; and
R^{10} is selected from hydrogen, halogen and lower alkyl-(C_1-C_3); which comprises reacting a compound of the formulae:



and



with a compound of the formula:



wherein Q is a halogen or an activating group, which results from conversion of an aryl carboxylic acid to a mixed anhydride or from activation with a peptide coupling reagent, to give compounds of the Formula I.

12. The compound according to Claim 1 N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)phenyl]-2,4-dichlorobenzamide.

13. The compound according to Claim 1 N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-ylcarbonyl)-3-chlorophenyl]-5-fluoro-2-methylbenzamide.

14. The compound according to Claim 1 N-[4-[[3-[(dimethylamino)methyl]-5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-yl]carbonyl]-3-chlorophenyl]-5-fluoro-2-methylbenzamide.

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