TRICYCLIC VASOPRESSIN AGONISTS

The present invention concerns novel compounds having vasopressin agonist activity, as well as methods of treatment and pharmaceutical compositions utilizing the same.

Background of the Invention

Vasopressin (antidiuretic hormone, ADH), a nine amino acid peptide hormone and neurotransmitter, is synthesized in the hypothalamus of the brain and is transported through the supraopticohypophyseal tract to the posterior pituitary where it is stored. Upon sensing an increase of plasma osmolality by brain osmoreceptors or a decrease of blood volume or blood pressure detected by the baroreceptors and volume receptors, vasopressin is released into the blood circulation and it activates vasopressin V_{1a} receptors on blood vessels to cause vasoconstriction to raise blood pressure and vasopressin V_2 receptors of the nephrons of the kidney to retain mainly water, and to a lesser degree electrolytes, to expand the blood volume (Cervoni P. and Chan P. S., Diuretic Agents, In Kirk-Othmer: Encyclopedia of Chemical Technology, 4th Ed., Wiley, Volume 8, 398-432, 1993.). The existence of vasopressin in the pituitary was known as early as 1895 (Oliver, H. and Schaefer, J. Physiol. (London) 18: 277-279, 1895). The determination of the structure and the complete synthesis of vasopressin were accomplished by duVigneaud and co-workers in 1954 (duVigneaud, V., Gish, D. T., and Katsoyannis, J. Am. Chem. Soc. 76: 4751-4752, 1954.).

Vasopressin V_{1a} receptors are mediated through the phosphatidylinositol pathway. Activation of vasopressin V_{1a} receptors causes contraction of the smooth muscle of the blood vessels so as to raise blood pressure. The actions of the vasopressin V_2 receptors are mediated through activation of the adenylate cyclase system and elevation of intracellular levels of cAMP. The activation of the vasopressin V_2 receptors by vasopressin or vasopressin-like (peptide or nonpeptide) compounds increases water permeability of the collecting ducts of the nephron and permits the reabsorption of a large quantity of free water. The end result is the formation and

excretion of a concentrated urine, with a decrease of urine volume and an increase of urinary osmolality.

Vasopressin plays a vital role in the conservation of water by concentrating the urine at the site of the collecting ducts of the kidney. The collecting ducts of the kidney are relatively impermeable to water without the presence of vasopressin at the receptors and therefore, the hypotonic fluid formed after filtering through the glomeruli, passing the proximal convoluted tubules, the loops of Henle, and the distal convoluted tubules, will be excreted as dilute urine. However, during dehydration, volume depletion or blood loss, vasopressin is released from the brain and activates the vasopressin V_2 receptors in the collecting ducts of the kidney rendering the ducts very permeable to water, and hence water is reabsorbed and a concentrated urine is excreted. In patients and animals with central or neurogenic diabetes insipidus, the synthesis of vasopressin in the brain is defective and therefore, they produce no or very little vasopressin, but their vasopressin receptors in the kidneys are normal. Because they cannot concentrate the urine, they may produce as high as 10 times the urine volume of their healthy counterparts and they are very sensitive to the action of vasopressin and vasopressin V_2 agonists. Vasopressin and desmopressin, which is a peptide analog of the natural vasopressin, are being used in patients with central diabetes insipidus. Vasopressin V_2 agonists are also useful for the treatment of nocturnal enuresis, nocturia, urinary incontinence and help provide the ability of the recipient to temporarily delay urination, whenever desirable.

Vasopressin, through activation of its V_{1a} receptors, exerts vasoconstricting effects so as to raise the blood pressure. A vasopressin V_{1a} receptor antagonist will counteract this effect. Vasopressin and vasopressin agonists release factor VIII and von Willebrand factor so they are useful for the treatment of bleeding disorders, such as hemophilia. Vasopressin and vasopressin-like agonists also release tissue-type plasminogen activator (t-PA) into the blood circulation so they are useful in dissolving blood clots such as in patients with myocardial infarction and other thromboembolic disorders (Jackson, E. K., Vasopressin and other agents affecting the renal conservation of water. In: Goodman's and Gilman's The Pharmacological Basis of Therapeutics, 9th ed., Eds. Hardman, Limbird, Molinoff, Ruddon and Gilman, McGraw-Hill, New York, pp. 715-731, 1996, Lethagen, S., Ann. Hematol., 69;

173-180 (1994), Cash, J. D. et al., Brit. J. Haematol. 27; 363-364, 1974., David, J-L., Regulatory Peptides, 45; 311-317, 1993, and Burggraaf, J., et al., Clin. Sci. 86; 497-503 (1994).

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 of 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. Albright et al. describe tricyclic diazepines as vasopressin and oxytocin antagonists in US 5,516,774 (May 14, 1996); tetrahydrobenzodiazepine derivatives as vasopressin antagonists are disclosed in JP 08081460-A (March 26, 1996); Ogawa, et al. disclose benzoheterocyclic derivatives as vasopressin and oxytocin antagonists, and as vasopressin agonists in WO 9534540-A; Albright, et al. disclose tricyclic benzazepine derivatives as vasopressin antagonists in US 5,512,563 (April 30, 1996); and Venkatesan, et al. disclose tricyclic benzazepine derivatives as vasopressin and oxytocin antagonists in US 5,521,173 (May 28, 1996).

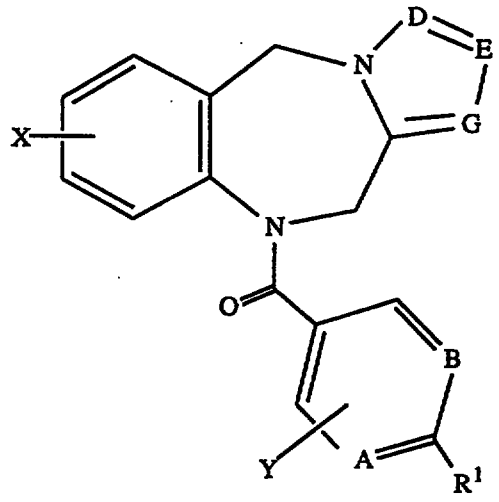
As mentioned above, desmopressin (1-desamino-8-D-arginine vasopressin) (Huguenin, Boissonnas, Helv. Chim. Acta, 49, 695 (1966)) is a vasopressin agonist. The compound is a synthetic peptide with variable bioavailability. An intranasal route is poorly tolerated and an oral formulation for nocturnal enuresis requires a 10-20 fold greater dose than by intranasal administration.

The compounds of this invention are non-peptidic and have good oral bioavailability. They are specific vasopressin V_2 agonists, and have no V_{1a} agonist

effects so they do not raise blood pressure. In contrast, the prior art compounds of Ogawa, H. et al. WO 9534540-A are vasopressin / oxytocin antagonists.

SUMMARY OF THE INVENTION

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



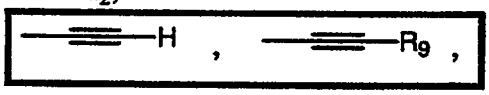
(I)

wherein:

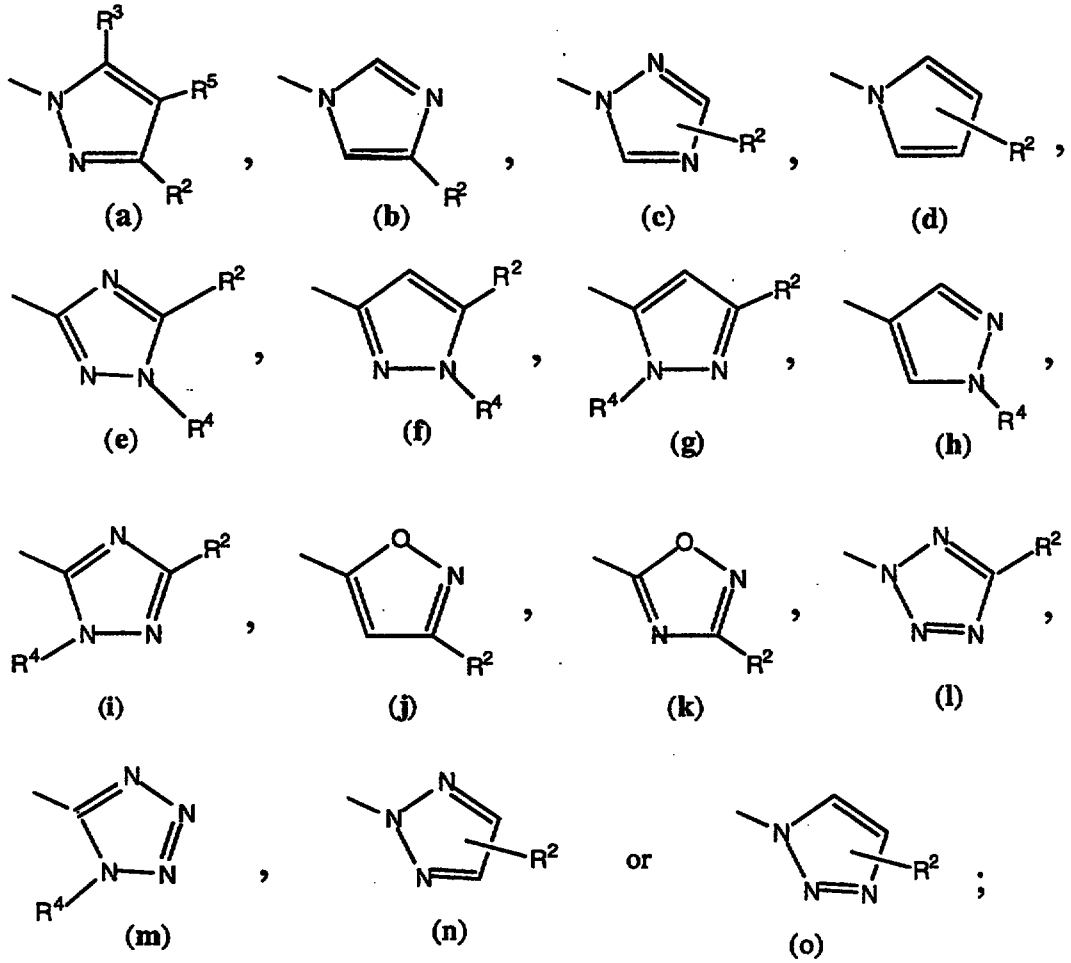
A, B, E, G are, independently, CH or nitrogen;

D is, independently, C-W or nitrogen;

R^1 is alkanoyl of 2 to 7 carbon atoms, a group selected from CN, COOH, $CONH_2$,



or a moiety selected from the group:



R^2, R^3 and R^5 are, independently, hydrogen, straight chain alkyl of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7 carbon atoms, cycloalkyl of 3 to 7 carbon atoms, or perfluoroalkyl of 1 to 6 carbons;

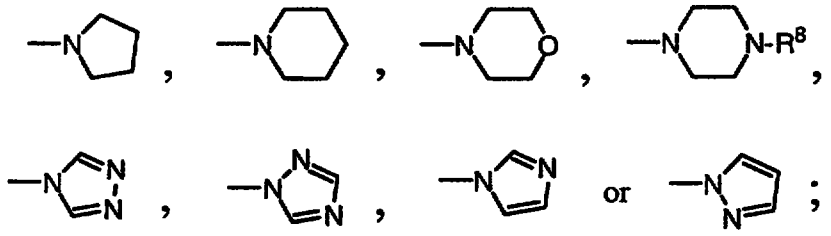
R^4 is hydrogen, straight chain alkyl of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7 carbon atoms, cycloalkyl of 3 to 7 carbon atoms, alkoxyalkyl of 2 to 7 carbon atoms, or an acyl substituent selected from the group consisting of alkanoyl of 2 to 7 carbon atoms, alkenoyl of 3 to 7 carbon atoms, cycloalkanoyl of 3 to 7 carbon atoms, aroyl, or arylalkanoyl;

X and Y are, independently, hydrogen, straight chain alkyl of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7 carbon atoms, cycloalkyl of 3 to 7 carbon atoms, perfluoroalkyl of 1 to 6 carbons, alkoxyalkyl of 2 to 7 carbon atoms, halogen

(including chlorine, bromine, fluorine, and iodine), alkoxy of 1 to 6 carbons, hydroxy, CF_3, or perfluoroalkyl of 2 to 6 carbons;

W is hydrogen, halogen (preferably chloro, bromo or iodo), alkyl, alkoxyalkyl of 2 to 7 carbons, hydroxyalkyl of 1 to 6 carbons, or $CH_2NR^6R^7$;

R^6 and R^7 are, independently, hydrogen, straight chain alkyl of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7 carbon atoms; or, taken together with the nitrogen atom of $CH_2NR^6R^7$, R^6 and R^7 form a five or six membered ring optionally containing one or more additional heteroatoms such as, but not limited to, those of the group:



R^8 is a straight chain alkyl of 1 to 6 carbon atoms

R^9 is independently hydrogen, trimethylsilyl or a straight chain alkyl of 1 to 6 carbon atoms;

or a pharmaceutically acceptable salt, ester or prodrug form thereof.

E and G are preferably CH; D is preferably N or C-W wherein W is hydrogen, alkyl, $CH_2NR^6R^7$ or a halogen, more preferably wherein W is hydrogen, methyl, CH_2NMe_2 or bromo.

R^2, R^3 and R^5 are preferably each independently, hydrogen, straight chain alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 7 carbon atoms or perfluoroalkyl of 1 to 6 carbons, more preferably hydrogen or a straight chain alkyl of 1 to 6 carbon atoms, most preferably hydrogen or methyl.

R^4 is preferably hydrogen, straight chain alkyl of 1 to 6 carbon atoms or an acyl substituent, more preferably hydrogen, methyl, ethyl, n-propyl, n-butyl, methoxymethyl, acetyl, cyclopropylcarbonyl, n-propylcarbonyl, 2-thienylcarbonyl, 2-methyl, 5-fluorophenylcarbonyl, 2-methylphenylcarbonyl, 2-chloro-4-fluorophenylcarbonyl, 2,4-difluorophenylcarbonyl or 2,4-difluorobenzylcarbonyl.

X and Y are preferably each independently hydrogen, perfluoroalkyl of 1 to 6 carbons, halogen, alkoxy of 1 to 6 carbons or hydroxy, more preferably hydrogen, trifluoromethyl, chlorine, bromine, fluorine, methoxy or hydroxy. Most preferably at least one of X and Y is hydrogen.

R^6 and R^7 are preferably both methyl.

Preferred values of R^1 include CN, CONH2, acetyl or one of the following:

- moiety a wherein R^2, R^3 and R^5 are each independently hydrogen or a straight chain alkyl of 1 to 6, more preferably where the alkyl is methyl;

- moiety a wherein two of R^2, R^3 and R^5 are hydrogen and the third is cycloalkyl of 3 to 7 carbon atoms or perfluoroalkyl of 1 to 6 carbons, more preferably where the third is cyclopropyl or trifluoromethyl;

- moiety b, c, d or i wherein R^2 is hydrogen or a straight chain alkyl of 1 to 6, more preferably where the alkyl is methyl;

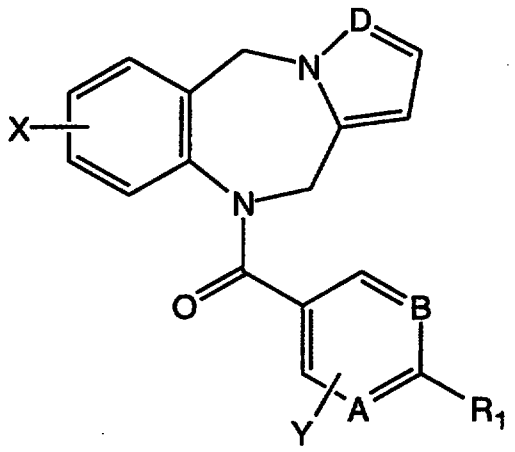
- moiety f wherein R^2 is hydrogen and/or R^4 is hydrogen, straight chain alkyl of 1 to 6 carbon atoms or an acyl substituent selected from the group consisting of alkanoyl of 2 to 7 carbon atoms, alkenoyl of 3 to 7 carbon atoms, cycloalkanoyl of 3 to 7 carbon atoms, aroyl, or arylalkanoyl; more preferably wherein R^4 is hydrogen, methyl, ethyl, n-propyl, n-butyl, methoxymethyl or acetyl, cycloproylcarbonyl, n-propylcarbonyl, 2-thienylcarbonyl, 2-methyl, 5-fluorophenylcarbonyl, 2-methylphenylcarbonyl, 2-chloro-4-fluorophenylcarbonyl, 2,4-difluorophenylcarbonyl or 2,4-difluorobenzylcarbonyl;

- moiety f or g wherein R^4 is hydrogen and/or R^2 is straight chain alkyl of 1 to 6, more preferably wherein the alkyl is methyl

- moiety k or h wherein R^2 is methyl;

- moiety m wherein R^2 is hydrogen

Among the more preferred compounds of this invention are those of the formula:

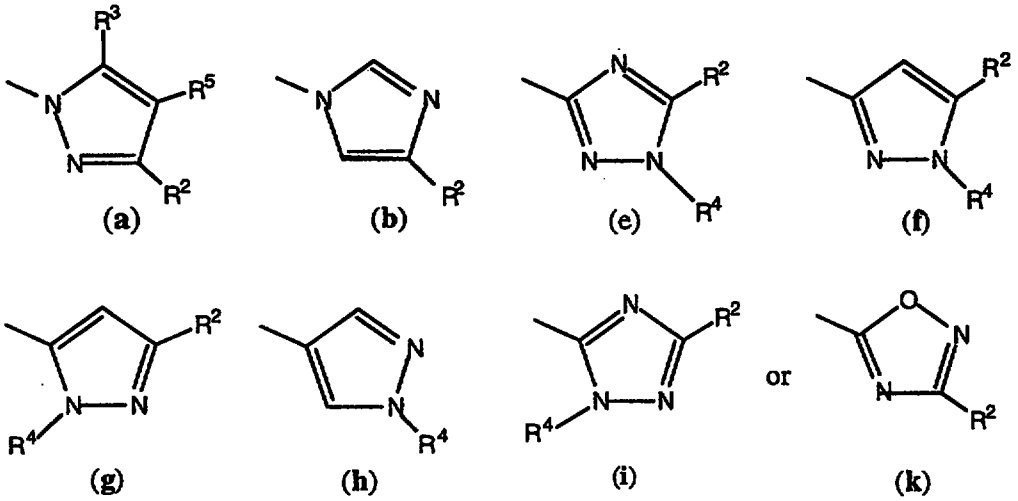


wherein:

A and B are, independently, CH or nitrogen;

D is C-W or nitrogen;

R^1 is alkanoyl of 2 to 7 carbon atoms or a group selected from



R^2, R^3 and R^5 are, independently, hydrogen, straight chain alkyl of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7 carbon atoms, cycloalkyl of 3 to 7 carbon atoms, or perfluoroalkyl of 1 to 6 carbons;

R^4, X, Y, W, R^6, R^7 and R^8 are as defined above;

or a pharmaceutically acceptable salt thereof.

When used herein the term alkyl as a moiety or part of a moiety, e.g. alkoxy, includes straight and branched chain alkyl groups e.g. methyl, ethyl, propyl, i-propy, n-butyl, s-butyl, i-butyl, t-butyl, pentyl, hexyl and heptyl groups. When used herein the term cycloalkyl includes saturated and unsaturated cyclic groups, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclpropenyl, cyclobutenes, cyclopentenes, cyclohexenes and cycloheptenes. Saturated cycloalkyls are preferred.

For the compounds defined above and referred to herein, unless otherwise noted, aroyl groups include, for example, benzoyl, naphthoyl which can be substituted independently with one or more substituents from the group of hydrogen, halogen, cyano, straight chain alkyl of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7 carbon atoms, alkoxy of 1 to 6 carbons, CF_3, or phenyl (which is itself optionally substituted). Heteroaroyl groups herein refer to a carbonyl (radical) directly bonded to a carbon atom of a five membered heterocyclic ring having one or two heteroatoms selected from nitrogen, oxygen, sulfur, for example 2-thienoyl. The heterocyclic ring

of the heteroaroyl groups may also include, but are not limited to, groups in which the heteroaryl portion is a furan, pyrrole, 2H-pyrrole, imidazole, pyrazole, isothiazole, isoxazole, thiophene, pyrazoline, imidazolidine or pyrazolidine group. The heteroaryl groups herein can be substituted independently with one or more substituents from the group of hydrogen, halogen, cyano, straight chain alkyl of 1 to 6 carbon atoms, or branched chain alkyl of 3 to 7 carbon atoms.

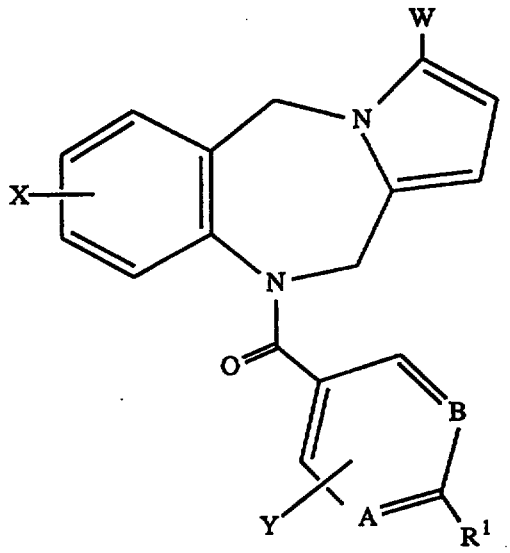
The arylalkanoyl groups herein refer to a carbonyl group or radical directly bonded to an alkyl group of 1 to 6 carbon atoms which is terminally substituted by an aryl group, for example, phenylacetic acid. The aryl group can be substituted independently with one or more substituents from the group of hydrogen, halogen, cyano, straight chain alkyl of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7 carbon atoms, alkoxy of 1 to 6 carbons, CF_3, or phenyl or substituted phenyl where the substituents are selected from halogen, cyano, straight chain alkyl of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7 carbon atoms, alkoxy of 1 to 6 carbons, CF_3.

The halogens referred to herein may be selected from fluorine, chlorine, bromine or iodine, unless otherwise specified.

It is understood by those practicing the art that the definition of the compounds of formula (I), when R^1, R^2, R^3, R^4, R^5, R^6, R^7, X, or Y contain asymmetric carbons, encompass all possible stereoisomers and mixtures thereof which possess the activity discussed below. In particular, it encompasses any optical isomers and diastereomers; as well as the racemic and resolved, enantiomerically pure R and S stereoisomers; as well as other mixtures of the R and S stereoisomers and pharmaceutically acceptable salts thereof, which possess the indicated activity. Optical isomers may be obtained in pure form by standard separation techniques. It is also understood that the definition of R^1, R^2, R^3, R^4, R^5, R^6, R^7, X, or Y of the compounds of formula (I), encompasses all possible regioisomers, and mixtures thereof which possess the activity discussed below. Such regioisomers may be obtained pure by standard separation methods known to those skilled in the art.

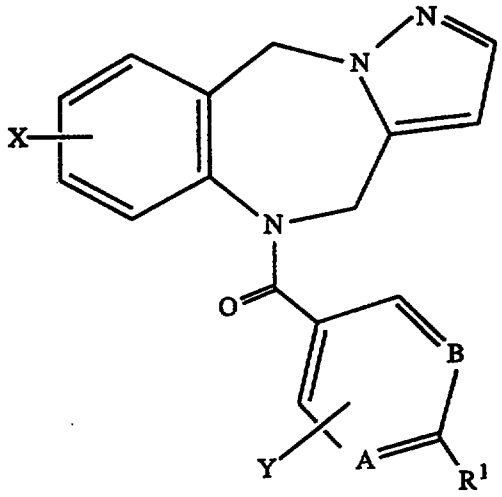
Also among the preferred groups of compounds of this invention are those in the subgroups:

a) compounds having the general formula:



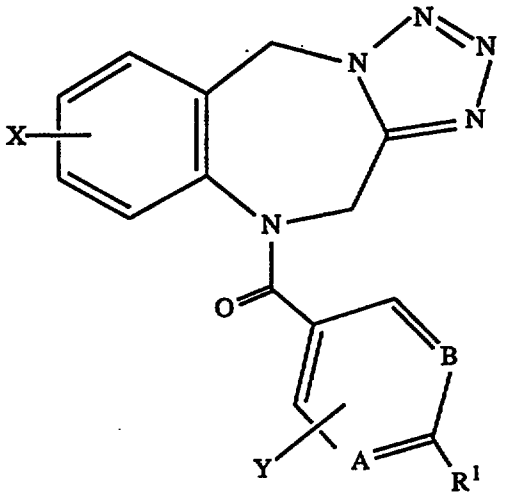
wherein A, B, W, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, X, and Y are as defined above;

b) compounds having the general formula:



wherein A, B, R^1, R^2, R^3, R^4, R^5, R^9, X, and Y, are as defined above; and

c) compounds having the general formula:

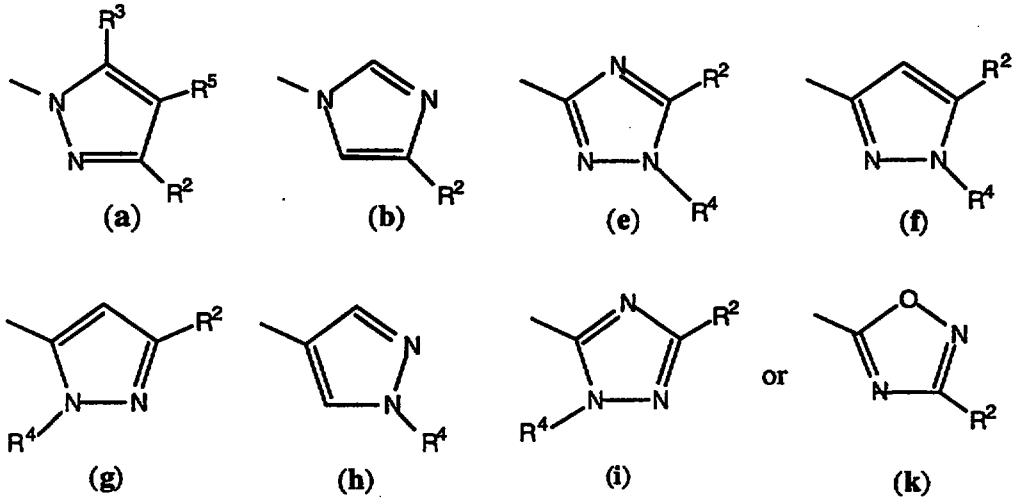


wherein A, B, R^1, R^2, R^3, R^4, R^5, R^9, X, and Y, are as defined above.

It is understood that subgroups a)-c), above, further include subgroups wherein:

A and B are, independently, CH or nitrogen;

R^1 is alkanoyl of 2 to 7 carbon atoms or a group selected from



(a) (b) (e) (f)

(g) (h) (i) or (k)

R^2, R^3 and R^5 are, independently, hydrogen, straight chain alkyl of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7 carbon atoms, cycloalkyl of 3 to 7 carbon atoms, or perfluoroalkyl of 1 to 6 carbons; and

R^4, X, Y, W, R^6, R^7 and R^8 are as defined above;

or a pharmaceutically acceptable salt thereof.

Particularly preferred among the compounds of group a), above, are those in which W is H, A and B are each CH, and R^1 is the group of alkanoyl of 2 to 7 carbon atoms or a group selected from the moieties (a), (b), (e), (f), (g), (h), (i) or (k), listed above, .

The pharmaceutically acceptable salts include those derived from such organic and inorganic acids as: lactic, citric, acetic, tartaric, succinic, maleic, malonic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methanesulfonic, and similarly known acceptable acids.

Also according to the present invention there is provided a method of treating diseases, conditions or disorders in which vasopressin agonist activity is desired, the method comprising administering to a human or other mammal in need thereof an effective amount of a compound or a pharmaceutical composition of this invention. The present methods of treatment include those for diseases, conditions or disorders which make it desirable to release factor VIII and von Willebrand factor into the circulatory system, release tissue-type plasminogen activator (t-PA) in the blood circulation, or affect the renal conservation of water and urine concentration. Such methods of treatment include, but are not limited to, treatments for diabetes insipidus, nocturnal enuresis, nocturia, urinary incontinence, or bleeding and coagulation disorders in humans or other mammals.

The methods herein include facilitation in humans or other mammals of temporary delay of urination, which may also be described as controlling or treating the inability to temporarily delay urination, whenever desirable. This method is understood to include treatments facilitating the temporary delay of urination which are separate from and not included in the treatment of the condition known as nocturnal enuresis.

The present invention accordingly provides a pharmaceutical composition useful for treating the abovementioned diseases, conditions or disorders, the pharmaceutical composition comprising one or more compounds, or a pharmaceutically acceptable salt thereof, of this invention in combination or association with a pharmaceutically acceptable carrier.

The compositions are preferably adapted for oral administration. However, they may be adapted for other modes of administration, for example, parenteral administration for patient suffering from heart failure.

In order to obtain consistency of administration, it is preferred that a composition of the invention is in the form of a unit dose. Suitable unit dose forms include tablets, capsules and powders in sachets or vials. Such unit dose forms may contain from 0.1 to 1000 mg of a compound of the invention and preferably from 2 to 50 mg. Still further preferred unit dosage forms contain 5 to 25 mg of a compound of the present invention. The compounds of the present invention can be administered orally at a dose range of about 0.01 to 100 mg/kg or preferably at a dose range of 0.1 to 10 mg/kg. Such compositions may be administered from 1 to 6 times a day, more usually from 1 to 4 times a day.

The compositions of the invention may be formulated with conventional carriers or excipients such as fillers, disintegrating agents , binders, lubricants, flavoring agents and the like. They are formulated in conventional manner, for example, in a manner similar to that use for known antihypertensive agents, diuretics and β-blocking agents.

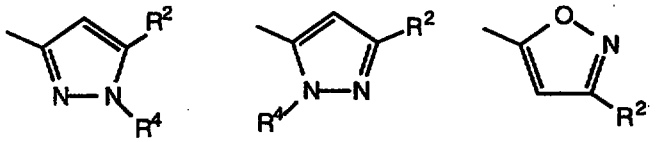
Also according to the present invention there are provided processes for producing the compounds of the present invention.

PROCESS OF THE INVENTION

The compounds of the present invention may be prepared according to one of the general processes outlined below.

As shown in Scheme I, a tricyclic benzodiazepine of formula (**1**) is treated with an appropriately substituted acetylaroyl (heteroaroyl) halide, preferably an aroyl (heteroaroyl) chloride of formula (**2**) in the presence of a base such as pyridine or a trialkylamine such as triethylamine, in an aprotic organic solvent such as dichloromethane or tetrahydrofuran at temperatures from -40°C to 50°C to yield the acylated derivative of formula (**3**). Treatment of (**3**) with a dialkylamide dialkyl acetal of formula (**4**) in an aprotic organic solvent such as dichloromethane at temperatures ranging from 0°C to the reflux temperature of the solvent yields the enone of formula

(5) according to the procedure of Lin et al., J. Het. Chem., 14, 345 (1977). Treatment of (5) with hydroxylamine or a substituted hydrazine of formula (6) in acetic acid at temperatures ranging from ambient to the reflux temperature of the solvent yields the target compounds of formula (I) wherein A, B, D, E, G, X, Y, R^2 and R^4 are as defined above, and R^1 is an heterocyclic moiety selected from the (f), (g), or (j) group of heterocycles defined above.



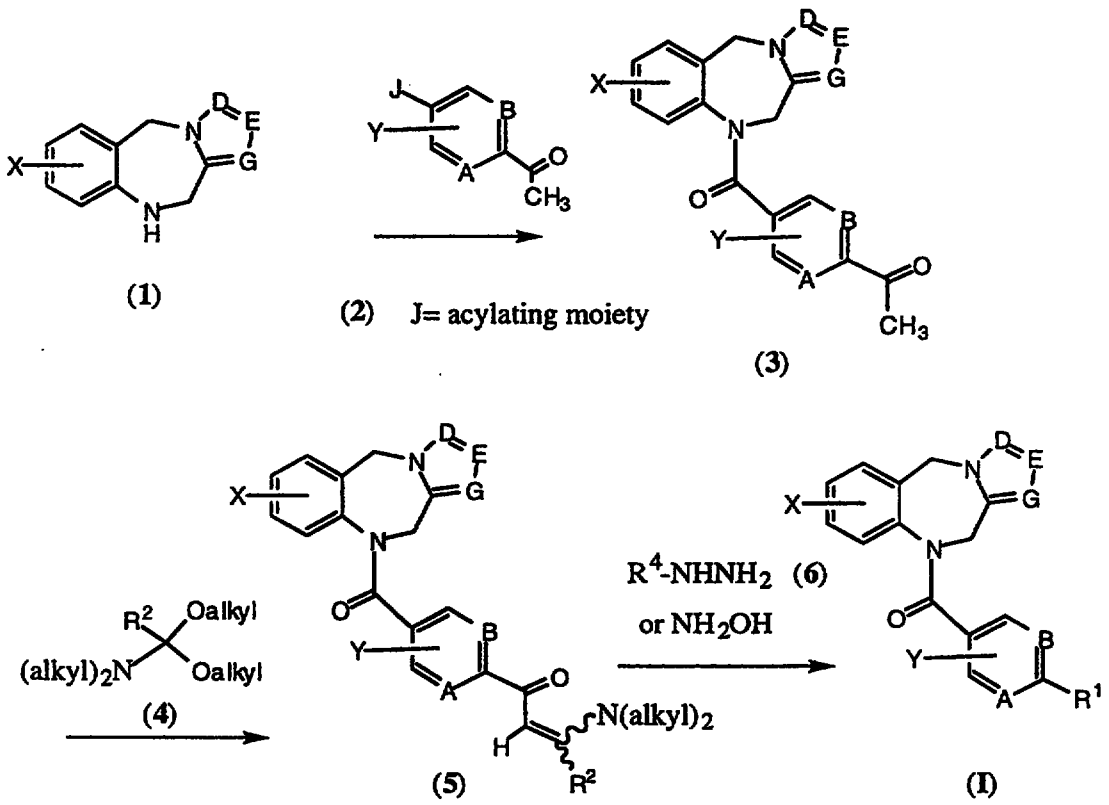
(f) (g) (j)

The preferred substituted acetylaroyl (heteroaroyl) chlorides of formula (2) of Scheme I are conveniently prepared by treating the corresponding carboxylic acids with thionyl chloride at temperatures ranging from ambient to the reflux temperature of the solvent, or with oxalyl chloride in an aprotic solvent such as dichloromethane or tetrahydrofuran in the presence of a catalytic amount of dimethylformamide at temperatures ranging from 0°C to 40°C.

The preferred dialkylamide dialkylacetals are either available commercially, or are known in the literature, or can be conveniently prepared according to procedures analogous to those in the literature. Kantlehner, W. Chem. Ber. 105, 1340 (1972).

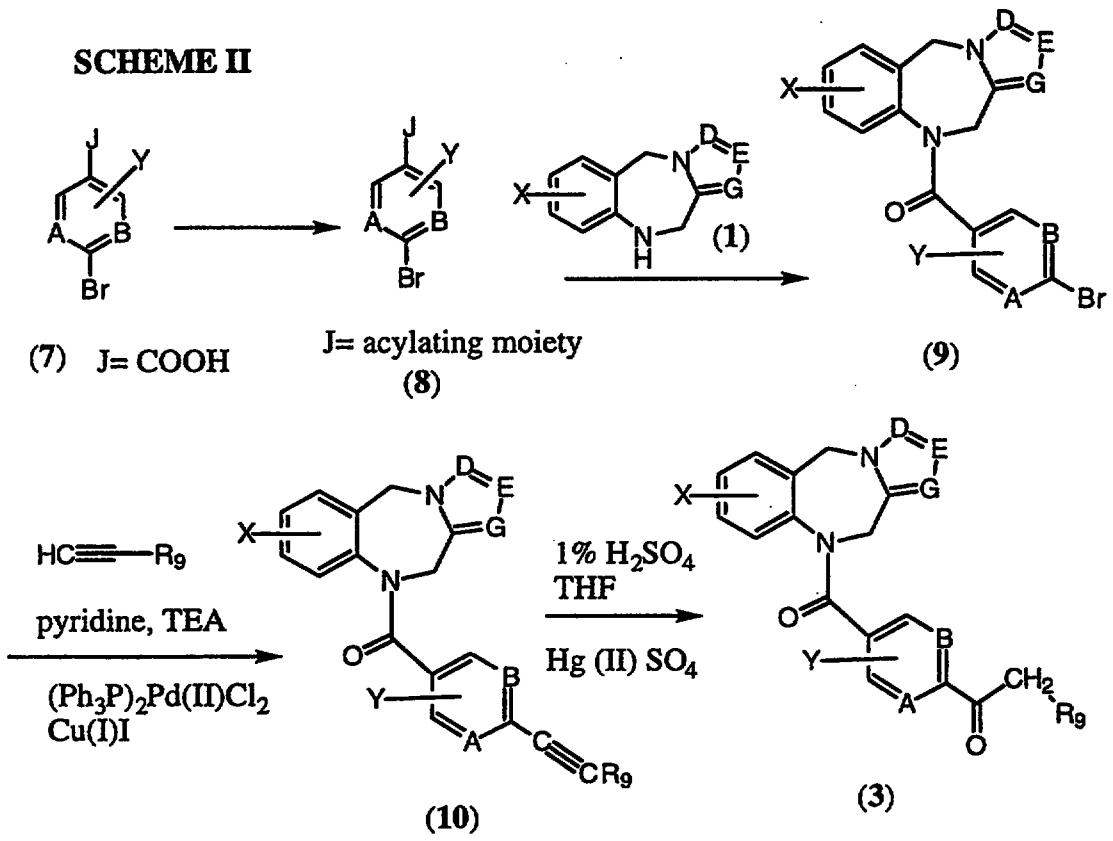
The preferred tricyclic benzodiazepines of formula (1) are a 10,11-dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine (Albright et al., U.S. Patent No. 5,536,718, issued July 16, 1996), a 10,11-dihydro-5H-pyrazole[5,1-c][1,4]benzodiazepine, Cecchi, L. et. al., J. Het. Chem., 20, 871 (1983). and 10,11-dihydro-5H-tetrazole[5,1-c][1,4]benzodiazepine, Klaubert, D.H., J. Het. Chem., 22, 333 (1985).

SCHEME I



An alternate process for the preparation of intermediates of formula (3) is illustrated in the following Scheme II.

SCHEME II



Thus, a tricyclic benzodiazepine of formula (**1**) is treated with an appropriately substituted bromo aroyl (heteroaroyl) halide, preferably an aroyl (heteroaroyl) chloride of formula (**8**) in the presence of an organic base such as pyridine or a trialkylamine such as triethylamine in an aprotic organic solvent such as dichloromethane or tetrahydrofuran at temperatures from -40°C to 50°C to yield the acylated intermediate of formula (**9**). The intermediate (**9**) is subsequently coupled with a mono substituted terminal acetylene such as trimethylsilyl or a straight chain alkyl of 1 to 6 carbon atoms, in the presence of pyridine and a catalyst such as bis(triphenylphosphine) palladium (II) chloride and copper (I) iodide in an organic base such as triethylamine as the solvent, in a sealed pressure tube at temperatures ranging from ambient to 100°C essentially according to the procedure of Martinez et al., J. Med. Chem., 35, 620 (1992). The resulting acetylene intermediate of formula (**10**) is then hydrated by treatment with 1% sulfuric acid in an aprotic organic solvent such as tetrahydrofuran saturated with mercury (II) sulfate at ambient temperature essentially according to the procedure of Reed et al., J. Org. Chem. , **52**, 3491 (1987) to provide the desired acyl compound of formula (**3**) wherein A,B, D, E, G, X, and Y, are as defined above and R^9 is hydrogen

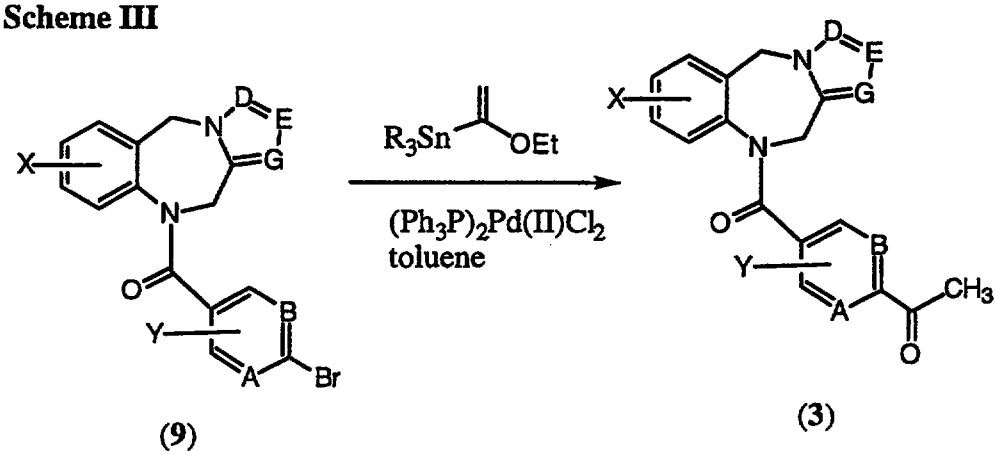
or a straight chain alkyl of 1 to 6 carbon atoms . Alternatively, compound **9** where R^9 is trimethylsilyl is treated with tetrabutylammonium fluoride in an ether solvent such as tetrahydrofuran to afford compound **(10)** where R^9 is hydrogen.

The preferred acylating agents of formula (**8**) of Scheme II are conveniently prepared by treating an appropriately substituted aryl (heteroaryl) carboxylic acid of formula (**7**) with thionyl chloride at temperatures ranging from ambient to the reflux temperature of the solvent, or with oxalyl chloride in an aprotic organic solvent such as dichloromethane or tetrahydrofuran in the presence of a catalytic amount of dimethylformamide at temperatures ranging from 0°C to 40°C.

The protected acetylene intermediates of Scheme II are either available commercially, or are known in the art, or can be readily prepared by procedures analogous to those in the art.

As shown in Scheme III, the intermediate acetyl compounds (**3**) of Scheme I can be prepared also by the Stille coupling of a bromo aryl (heteroaryl) compound of formula (**9**) of Scheme II with a (α-ethoxyvinyl)trialkyltin, preferably a (α-ethoxyvinyl)tributylltin, in the presence of a catalytic amount of bis(triphenylphosphine) palladium(II) chloride in an aprotic organic solvent such as toluene at temperatures ranging from ambient to the reflux temperature of the solvent, essentially according to the procedure of Kosugi et al., Bull. Chem. Soc. Jpn., 60, 767 (1987).

Scheme III



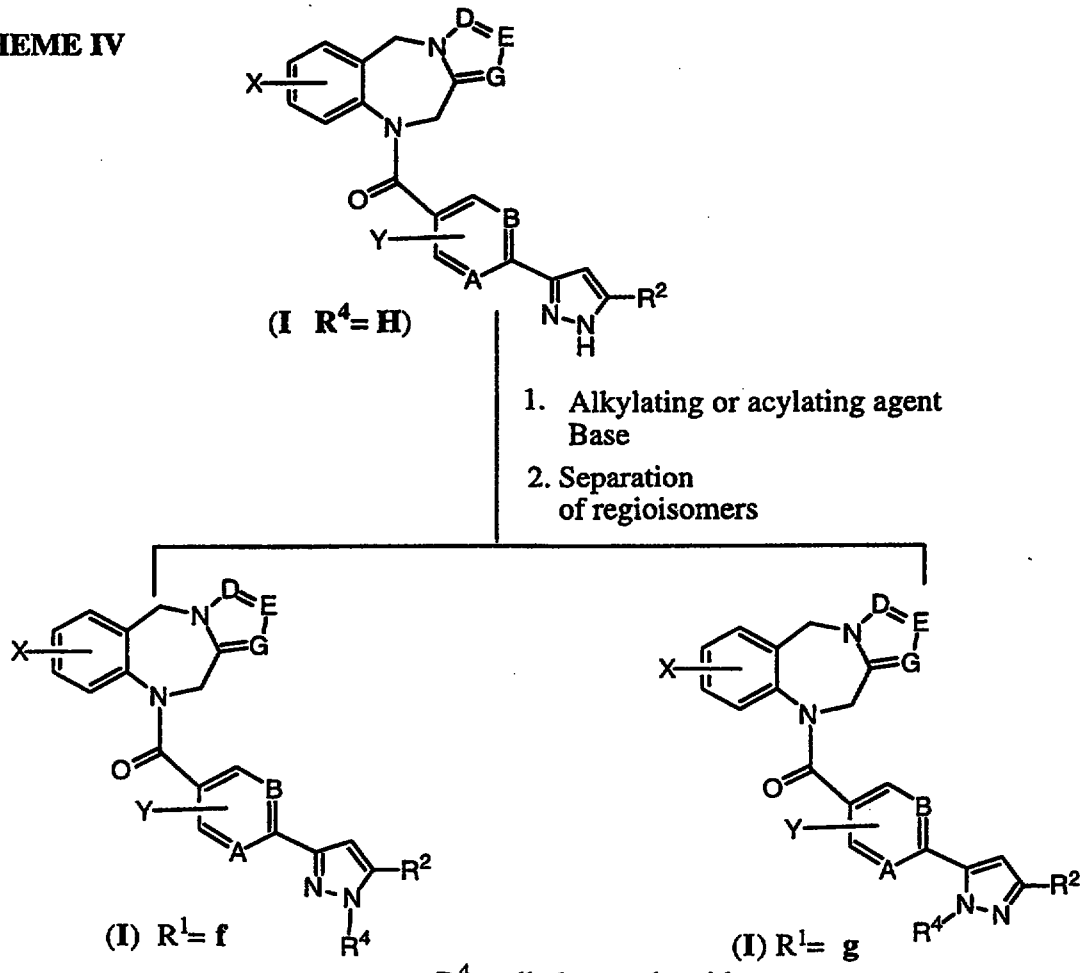
(**9**) (**3**)

The preparation of the acetyl compound (3) can also be accomplished via a palladium-catalyzed arylation of a vinyl alkyl ether such as vinyl butylether, with the aryl halide intermediate of formula (9) according to the procedure of Cabri et al., Tetrahedron Lett., 32, 1753 (1991).

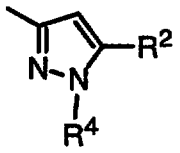
The (α-alkoxyvinyl)trialkyltin intermediates of Scheme III are either available commercially, or are known in the art, or can be readily prepared by procedures analogous to those in the art.

In the case where R^4 in Scheme I is hydrogen, the heterocyclic nitrogen can be alkylated or acylated according to the reactions outlined in Scheme IV.

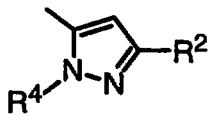
SCHEME IV



Thus, the pyrazole compound of formula (I, R^4 is H) is alkylated by treatment with a strong base such as sodium or potassium hydride and an alkylating agent such as an alkyl halide, preferably an alkyl chloride (bromide or iodide) in an aprotic organic solvent such as dimethylformamide or tetrahydrofuran at temperatures ranging from 0°C to 80°C to yield compound (**I**, R^1= (f) or (g)) wherein A, B, D, E, G, X, Y, and R^2 are as defined above, and R^4 is an alkyl or acyl moiety. Alternatively, compound (**I**) is acylated by treatment with a carboxylic acid halide, preferably a chloride, or a carboxylic acid anhydride in the presence of an amine base such as pyridine or a trialkylamine, preferably triethylamine, in an aprotic organic solvent such as dichloromethane or tetrahydrofuran with no additional solvent when pyridine is used as the base, at temperatures ranging from -40°C to ambient to yield compound (I) wherein A, B, D, E, G, X, Y and R^2 are as defined above, and R^4 is an alkyl or acyl moiety. The alkylation or acylation of a compound of formula (**I**, R^4 is H) leads to a mixture of regioisomers wherein R^2 is hydrogen and R^1 is an heterocyclic moiety selected either from the (f) or (g) group of heterocycles defined above and illustrated below, respectively.

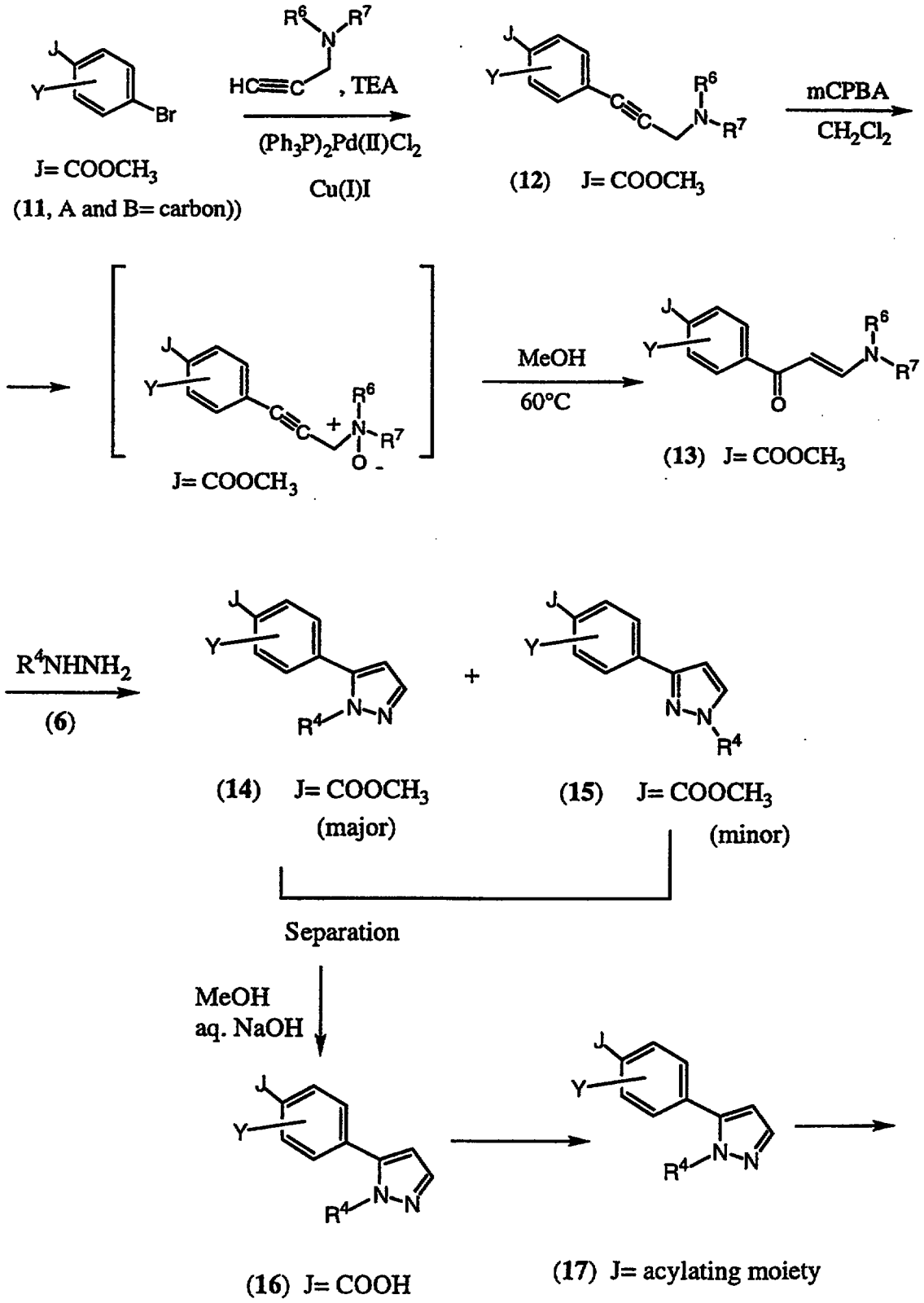


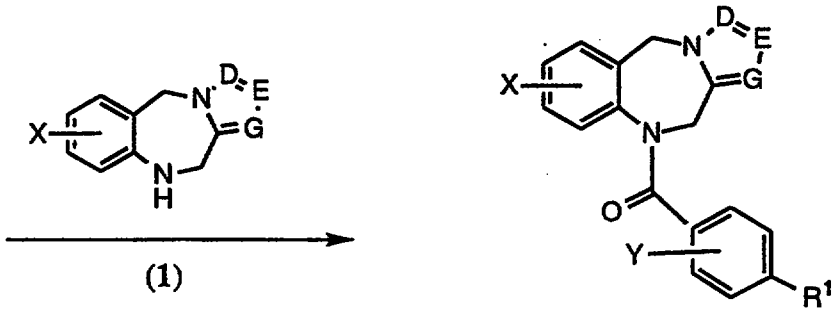
(f)



(g)

The compounds of general formula (I) of Scheme I wherein A and B are carbon, R^2 is H, and R^1 is an heterocyclic moiety selected from the (g) group of heterocycles defined above, can be prepared according to the general process outlined in Scheme V.


J= COOCH3
(11, A and B= carbon))
HC≡C , TEA
(Ph3P)2Pd(II)Cl2
Cu(I)I
(12) J= COOCH3
mCPBA
CH2Cl2
J= COOCH3
MeOH
60°C
(13) J= COOCH3
R4NHNH2
(6)
(14) J= COOCH3
(major)
(15) J= COOCH3
(minor)
Separation
MeOH
aq. NaOH
(16) J= COOH
(17) J= acylating moiety



(1) (I)

Thus, an appropriately substituted haloaryl (heteroaryl) carboxylic acid ester, preferably a bromo (or iodo) methylester of formula (**11**) is coupled with a dialkylamino propyne, preferably 1-dimethylamino propyne, in the presence of a catalyst such as bis(triphenylphosphine) palladium(II) chloride and copper(I) iodide in an organic base such as triethylamine as the solvent and at temperatures ranging from ambient to 80°C essentially according to the procedures of Alami et al., Tetrahedron Lett., 34, 6403 (1993), and of Sanogashira et al., Tetrahedron Lett., 4467 (1975) to provide the substituted acetylene intermediate of general formula (**12**). The intermediate (**12**) is subsequently converted into its N-oxide by treatment with an oxidizing agent using any of a number of standard oxidative procedures (Albini, A., Synthesis, 263 (1993) or with dioxirane reagents (Murray, R.W., Chem. Rev., 1187 (1989), in an aprotic organic solvent such as dichloromethane at temperatures below ambient. The intermediate N-oxide is not isolated but is rearranged *in situ* to an enone of general formula (**13**) by treatment with, preferably with heating, a hydroxylic solvent, including any solvent or combination of solvents composed of or containing water, any C_1-C_8 straight chain or branched chain alkyl alcohol, ethylene glycol, polyethylene glycol, 1,2-propylene diol, polypropylene glycol, glycerol, 2-methoxyethanol, 2-ethoxyethanol, 2,2,2-trifluoroethanol, benzyl alcohol, phenol, or any equivalent solvent that contains one or more free hydroxyl (-OH) substituent(s) that is known to those skilled in the art.

Solvent systems containing one or more cosolvents, along with one or more solvents may also be used for this process of rearranging the N-oxide to the desired enaminone. The cosolvents referred to herein may be defined as a diluent of the main solvent(s) and can be selected from: hydrocarbons such as pentane, hexane or heptane; aromatic hydrocarbon such as benzene, toluene or xylene; ethers such as diethyl ether,

tetrahydrofuran, dioxane or dimethoxy ethane; chlorinated hydrocarbons such as dichloromethane, chloroform, dichloroethane, or tetrachloroethane; or other common solvents such as ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, acetonitrile, dimethylsulfoxide, acetone, or the like.

The conversion of the amine N-oxide into an enaminone may be accomplished by introducing the amine N-oxide into a suitable hydroxylic solvent, preferably with stirring, at or between about room or ambient temperature and about the reflux temperature of the solvent. In other instances the introduction of the amine N-oxide to a hydroxylic solvent, preferably with stirring, may be accomplished in the presence of an acceptable catalyst, such as a palladium(II) catalyst or a copper (I) catalyst, at or between room temperature and the reflux temperature of the solvent.

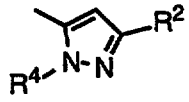
This procedure provides a novel synthesis of enaminone compounds from propargylic amines or their N-oxides in hydroxylic solvents, which influence the ultimate outcome of the reaction. This new method of enaminone synthesis provides a convenient alternative to existing methods and further extends the range of starting materials that can be converted into enaminone products.

Although the precise mechanism by which a propargylic amine N-oxide is converted into an enaminone product has not been rigorously determined, it likely resembles two known processes; the thermal [2,3]-sigmatropic rearrangement of propargylic amine N-oxides (Craig, et. al., Tetrahedron Lett., 4025, 1979; Hallstrom, et. al., Tetrahedron Lett., 667, 1980; Khuthier, A-H, et. al., J. Chem. Soc. Chem. Commun., 9, 1979) and the conversion of certain isoxazoles into enaminones (Liguori, et. al., Tetrahedron, 44, 1255, 1988).

Treatment of (**13**) with a substituted hydrazine (**6**) in acetic acid at temperatures ranging from ambient to reflux leads to a mixture of regioisomeric compounds of general formulas (**14**) and (**15**) in a variable ratio. The major isomer of formula (**14**) is separated by means of chromatography and/or crystallization and subsequently hydrolyzed to the desired carboxylic acid of formula (**16**).

The intermediate (**16**) is then converted into an acylating species, preferably an acid chloride (bromide or iodide) or a mixed anhydride of formula (**17**) by procedures analogous to those described hereinbefore. The acylating agent (**17**) is then used to

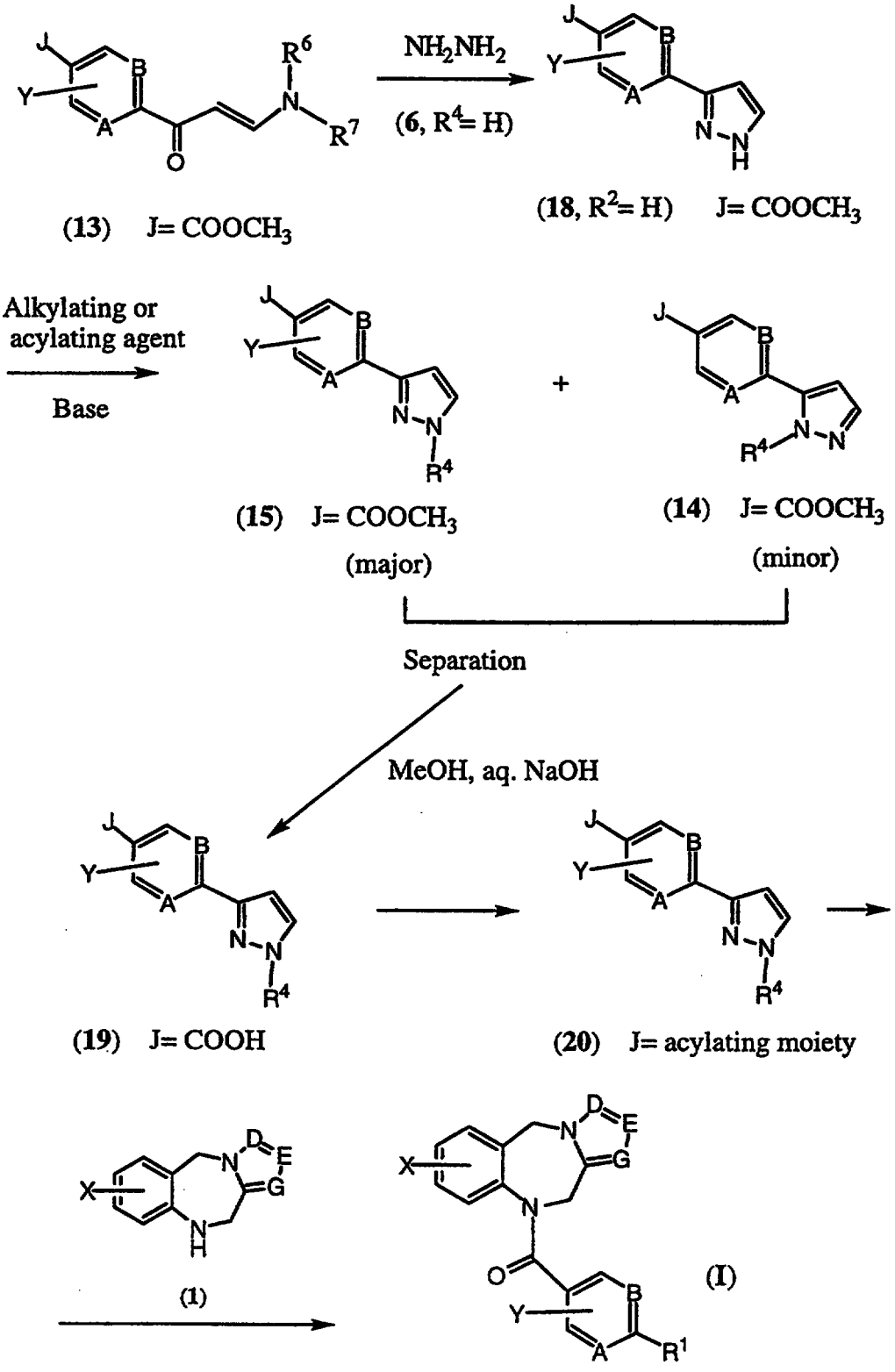
acylate a tricyclic benzodiazepine of formula (**1**) by any of the procedures described hereinbefore to yield the desired compound of formula (**I**), wherein A, B are CH and D, E, G, X, Y, and R^4 are as defined above, R^2 is hydrogen and R^1 is a heterocyclic moiety selected from the (g) group of heterocycles illustrated below.



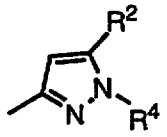
(g)

Likewise, treatment of (**13**) with an unsubstituted hydrazine (**6**, R^4 is H) in acetic acid at temperatures ranging from ambient to the reflux temperature of the solvent yields the intermediate pyrazole ester of formula (**18**). In this case the heterocyclic nitrogen can be alkylated or acylated as shown in Scheme VI to provide compounds of formula (**I**) wherein R^2 is hydrogen, and R^1 is an heterocyclic moiety selected from the (f) group of heterocycles defined above.

SCHEME VI


NH2NH2
(6, R4= H)
(13) J= COOCH3
(18, R2= H) J= COOCH3
Alkylating or acylating agent
Base
(15) J= COOCH3
(major)
(14) J= COOCH3
(minor)
Separation
MeOH, aq. NaOH
(19) J= COOH
(20) J= acylating moiety
(1)
(I)

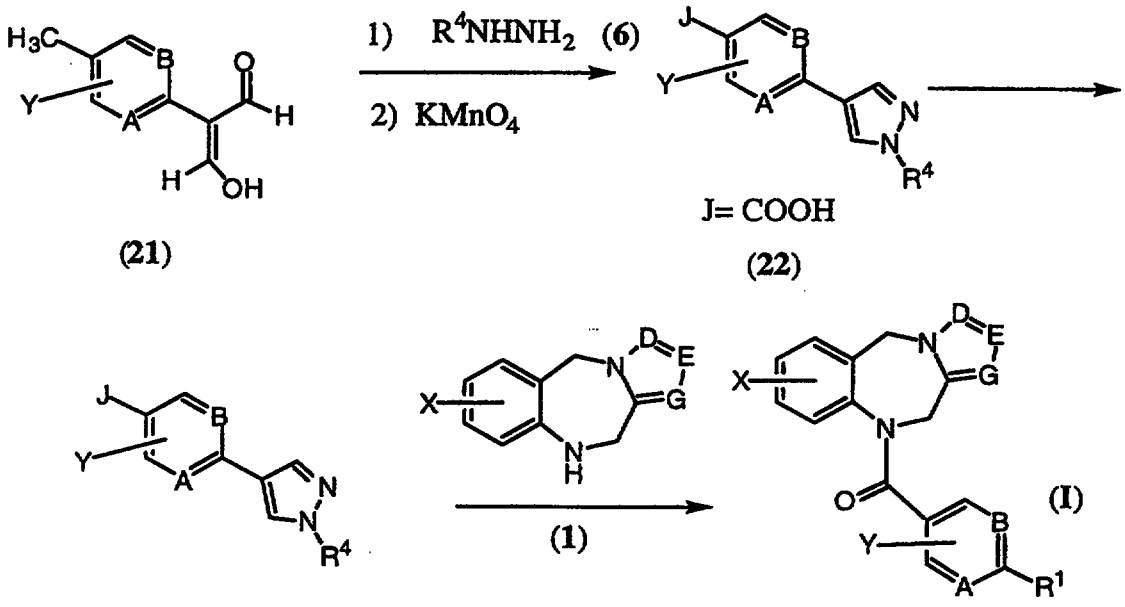
Thus, the intermediate ester of formula (**18**) is alkylated by treatment with a strong base such as sodium or potassium hydride and an alkylating agent such as an alkyl halide, preferably an alkyl chloride (bromide or iodide), in an aprotic solvent such as dimethylformamide or tetrahydrofuran at temperatures ranging from 0°C to 80°C to yield a mixture of regioisomers of formulas (**14**) and (**15**) in a variable ratio. The major regioisomer of formula (**15**) is separated by chromatography and/or crystallization and subsequently hydrolyzed to the desired carboxylic acid of formula (**19**), which is then converted into an acylating agent, preferably an acyl chloride or a mixed anhydride by procedures analogous to those described hereinbefore. The acylating species of formula (**20**) is then used to acylate a tricyclic benzodiazepine of formula (**1**) to yield the desired compound of formula (**I**), wherein A, B, D, E, G, X, Y, and R^4 are as defined above, R^2 is hydrogen, and R^1 is a heterocyclic moiety selected from the (f) group of heterocycles defined above.



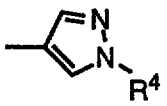
(**f**)

Compounds of general formula (**I**) wherein R^1 is an heterocyclic moiety selected from the (h) group of R^1 heterocycles defined above, can be prepared as outlined in Scheme VII.

SCHEME VII



An appropriately substituted malondialdehyde of formula (**21**) is treated first with a hydrazine in acetic acid at temperatures ranging from ambient to the reflux temperature of the solvent and the intermediate pyrazole is then oxidized with potassium permanganate in a basic aqueous solution at temperatures ranging from ambient to the reflux temperature of the solvent to yield a carboxylic acid intermediate of formula (**22**). The acid (**22**) is converted into an acylating agent, preferably an acid chloride (bromide or iodide) or a mixed anhydride by procedures analogous to those described hereinbefore. The acylating agent of formula (**23**) is finally reacted with a tricyclic benzodiazepine of formula (**1**) to yield compounds of general formula (**I**) wherein A, B, D, E, G, X, Y, and R^4 are as defined above, and R^1 is a heterocyclic moiety selected from the (h) group of heterocycles defined above.



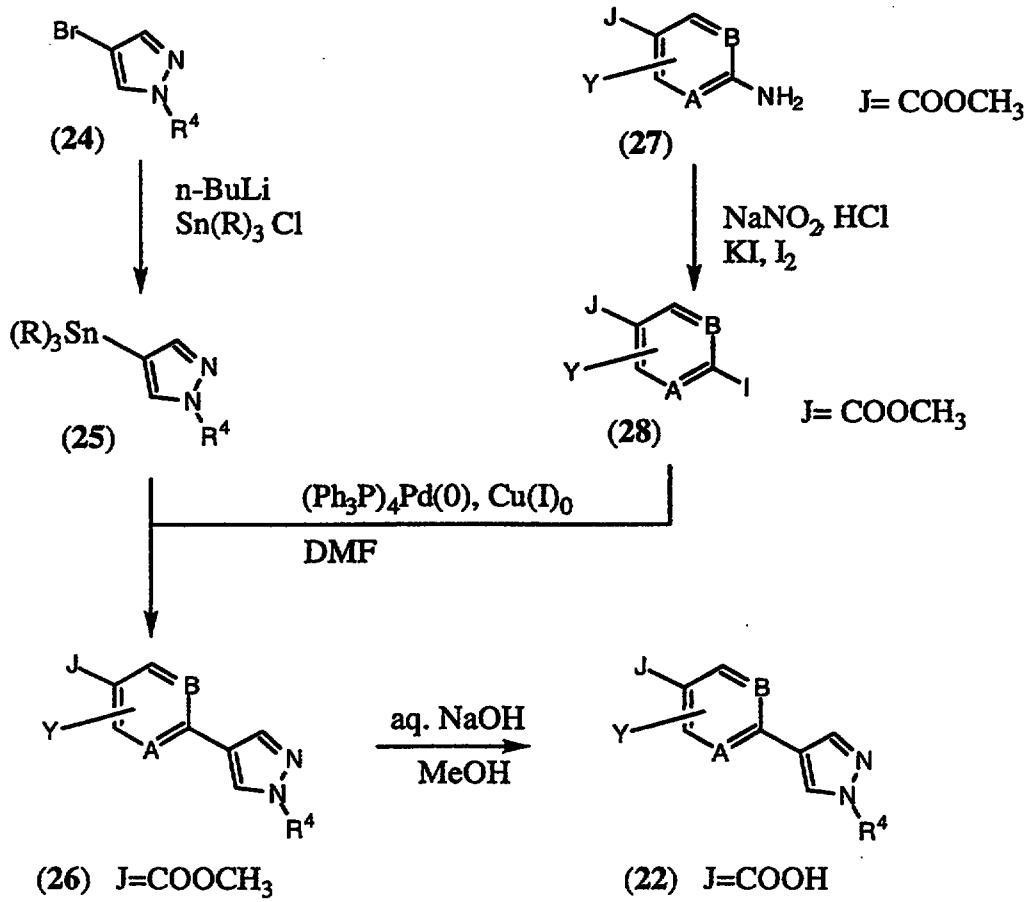
(h)

In the case where R^4 in Scheme VII is hydrogen, the heterocyclic nitrogen can be alkylated or acylated according to the procedures outlined hereinbefore.

The preferred malondialdehydes of formula (21) and the hydrazines of Scheme VII are either available commercially, or are known in the art, or can be readily prepared by procedures analogous to those in the literature for known compounds, such as those of Knorr et al., J. Org. Chem., 49, 1288 (1984) and Coppola et al., J. Het. Chem., 11, 51 (1974).

An alternative preparation of the intermediate carboxylic acids of formula (22) of Scheme VII wherein Y is as defined above and R^4 is other than hydrogen, is outlined in Scheme VIII.

SCHEME VIII



The organotin reagent of formula (25) is reacted in a Stille coupling reaction with an appropriately substituted aryl (heteroaryl) halide, preferably a bromide or iodide of formula (28) in the presence of a catalyst such as tetrakis(triphenylphosphine)-

palladium (0) and copper (I) iodide in an organic aprotic solvent such as dimethylformamide at temperatures ranging from ambient to 150°C, essentially according to procedures analogous to those found in Farina et al., J. Org. Chem., 59, 5905 (1994). Basic hydrolysis of the resulting ester of formula (**26**) with sodium or lithium hydroxide in aqueous alcohol or tetrahydrofuran at temperatures ranging from ambient to the reflux temperature of the solvent yields the desired carboxylic acids of formula (**22**).

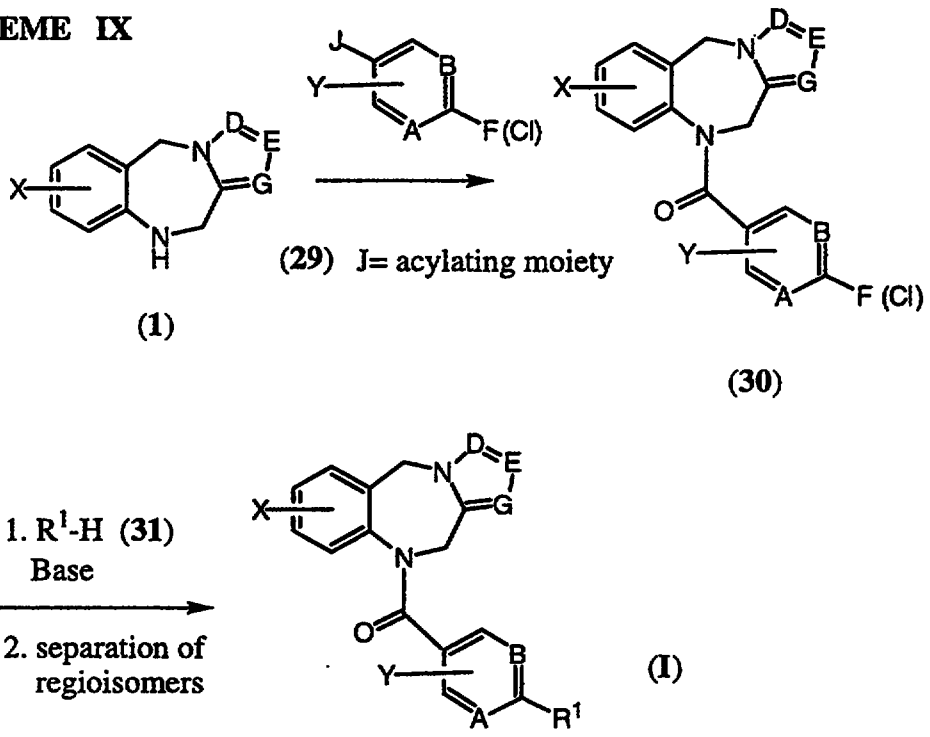
In turn, the organotin reagents of formula (**25**) wherein the R groups are preferably alkyl groups, are conveniently prepared by metallation of a 4-bromo N-alkylpyrazole of formula (**24**) with a trialkyltin halide, preferably a tributyltin chloride (or bromide) in the presence of a metallating agent such as an alkyllithium such as n-butyl lithium, sec-butyl lithium, or tert-butyllithium in an aprotic organic solvent such as diethylether at temperatures ranging from -40°C to ambient according to procedures analogous to those found in Martina et al., Synthesis, **8**, 613 (1991).

The preferred N-alkyl substituted 4-bromo pyrazoles of formula (**24**) are conveniently prepared from 4-bromo pyrazole by alkylation with an alkyl halide, preferably an alkyl chloride (bromide or iodide) in the presence of a strong base such as lithium, sodium or potassium hydride in an aprotic organic solvent such as dimethylformamide or tetrahydrofuran at temperatures ranging from 0°C to 80°C. Alternatively, alkylation of 4-bromopyrazole can be carried out with an alkylating agent mentioned above, and a strong alkaline base such as lithium, sodium or potassium hydroxide in the presence of a phase transfer catalyst (Jones, R.A. Aldrichimica ACTA, 9(3), 35, 1976) such as benzyldimethyltetradecylammonium chloride, or benzyltrimethylammonium chloride.

The preferred aryl (heteroaryl) iodides of formula (**28**) are conveniently prepared by diazotization of the corresponding substituted anilines of formula (**27**) followed by reaction of the corresponding diazonium salt with iodine and potassium iodide in aqueous acidic medium essentially according to the procedures of Street et al., J. Med. Chem., 36, 1529 (1993) and of Coffen et al., J. Org. Chem., 49, 296 (1984).

An alternative preparation of compounds of general formula (I) is outlined in Scheme IX.

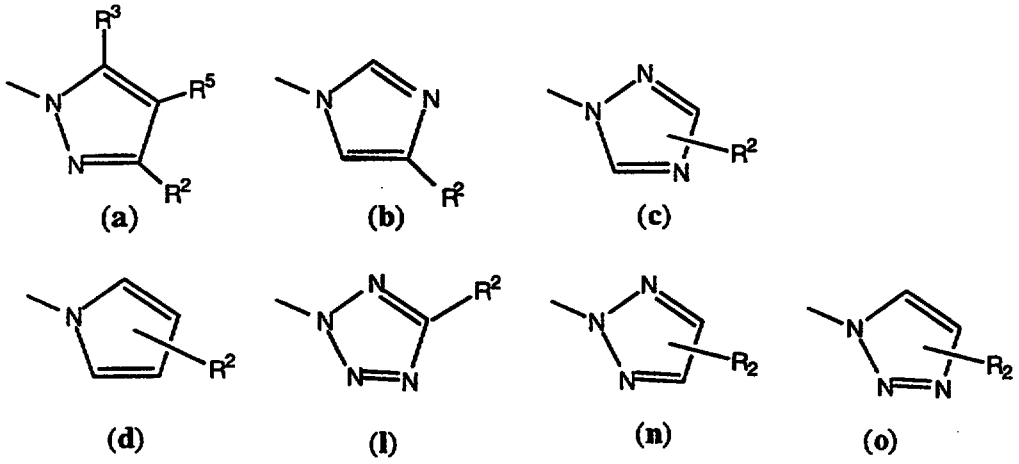
SCHEME IX



A tricyclic benzodiazepine of formula (1) is treated with an appropriately substituted haloaroyl (heteroaroyl) halide, preferably a fluoro aroyl or a fluoro (or chloro) heteroaroyl chloride of formula (29), in the presence of a base such as triethylamine or diisopropylethylamine in an aprotic organic solvent such as dichloromethane or tetrahydrofuran at temperatures from -40°C to the reflux temperature of the solvent to yield the acylated derivative (30).

Alternatively, the acylating species can be a mixed anhydride of the carboxylic acid described above, such as that prepared by reaction 2,4,6-trichlorobenzoyl chloride in a solvent such as dichloromethane according to the procedure of Inanaga et al., Bull. Chem. Soc. Jpn, 52, 1989 (1979). Treatment of said mixed anhydride of general formula (29) with the tricyclic benzodiazepine of formula (1) in a solvent such as dichloromethane and in the presence of an organic base such as 4-dimethylaminopyridine at temperatures ranging from 0°C to the reflux temperature of the solvent, yields the intermediate acylated derivative (30) of Scheme IX.

A compound of formula (**30**) is then treated with the lithium, sodium or potassium salt of an appropriately substituted heterocycle of formula (**31**) in a polar aprotic organic solvent such as dimethylformamide or tetrahydrofuran at temperatures ranging from ambient to the reflux temperature of the solvent to yield a compound of general formula (**I**), wherein A, B, D, E, G, X, Y, R^2, R^3, and R^5 are as defined above, and R^1 is a heterocyclic moiety selected from the group consisting of (a), (b), (c), (d), (l), (n) or (o) defined above.



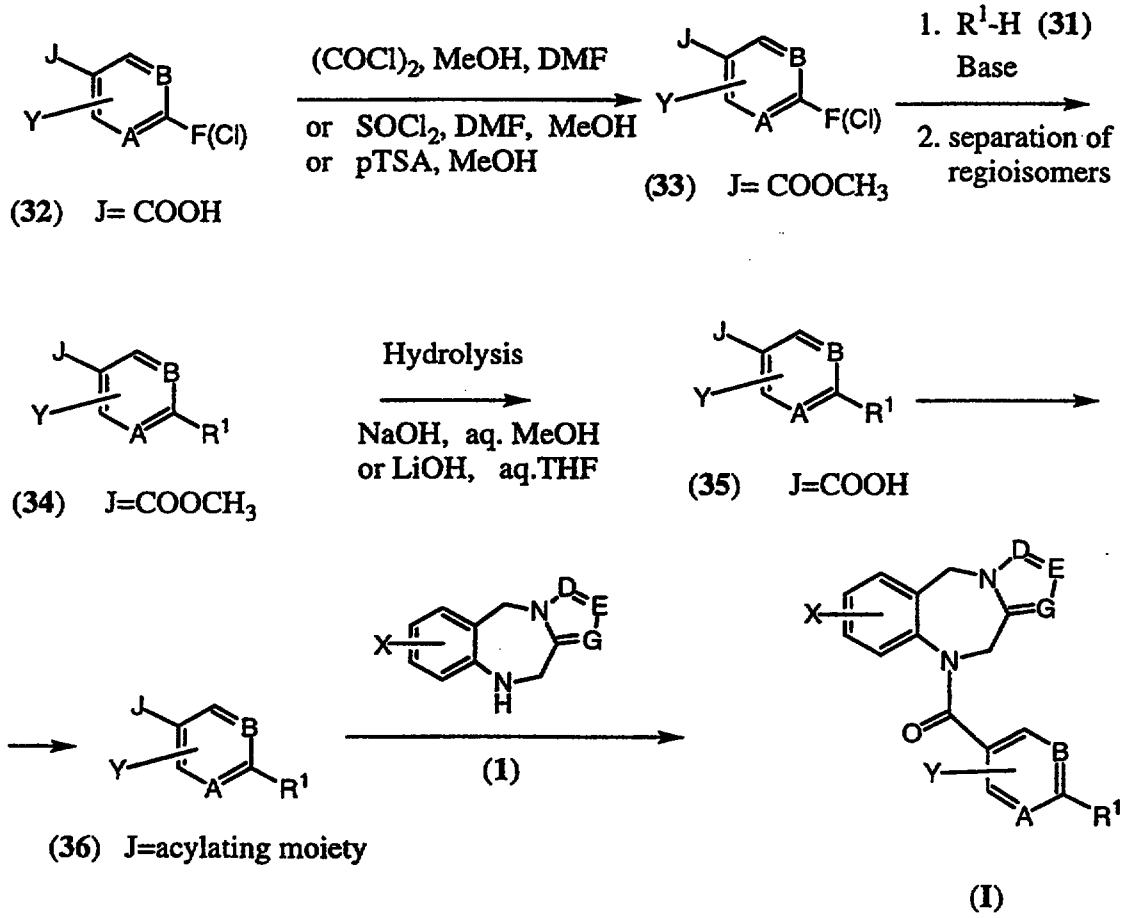
The condensation of the intermediate of formula (**30**) with the intermediate salt of formula (**31**) leads to a variable ratio of regioisomers of general formula (**I**) which are separated by means of chromatography and/or crystallization.

The preferred substituted fluoro aroyl and fluoro (or chloro) heteroaroyl chlorides of formula (**29**) are either available commercially, or are known in the art, or can be readily prepared by procedures analogous to those in the literature for the known compounds.

The lithium, sodium or potassium salts of the heterocycles of formula (**31**) are prepared by treatment of said heterocycle with a strong base such as lithium hydride, sodium hydride, potassium hydride or a metal alkoxide at temperatures ranging from -40°C to ambient in an aprotic organic solvent such as dimethylformamide or tetrahydrofuran.

Alternatively, the compounds of general formula (I) described in Scheme IX can be prepared according to the process outlined in Scheme X.

SCHEME X



Thus, an appropriately substituted fluoroaryl or fluoro (or chloro)heteroaryl carboxylic acid of formula (32) is esterified using methods known in the art such as treatment with oxalyl chloride (or thionyl chloride) in an alcohol solvent such as methanol, in the presence of a catalytic amount of dimethylformamide; or by condensation with methanol in the presence of an acid catalyst such as para-toluenesulfonic acid at temperatures ranging from ambient to reflux.

The resulting ester of formula (33) is reacted with the lithium, sodium or potassium salt of an appropriately substituted heterocycle of formula (31) in a polar

aprotic organic solvent such as dimethylformamide at temperatures ranging from ambient to 150°C, to yield an intermediate ester of formula (**34**). The condensation of (**33**) with (**31**) leads to a variable ratio of regioisomers of formula (**34**) which are separated by means of chromatography and/or crystallization.

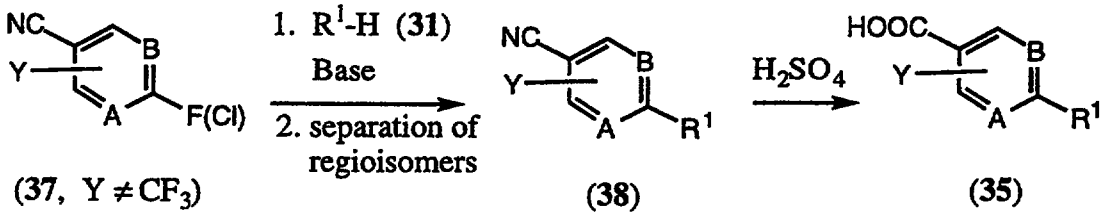
Subsequent hydrolysis of the intermediate ester of formula (**34**) with an aqueous base such as lithium, sodium or lithium hydroxide in methanol or tetrahydrofuran affords the carboxylic acid of formula (**35**).

The intermediate carboxylic acid (**35**) is then converted into an acylating agent preferably an acid chloride or a mixed anhydride of general formula (**36**) using any of the procedures described hereinbefore.

Subsequent reaction of the tricyclic benzodiazepine of formula (**1**) with the intermediate acylating agent of formula (**36**) according to any of the procedures described hereinbefore yields the desired compounds of formula (**I**) of Scheme IX.

Alternatively, the substituted carboxylic acids of formula (**35**) described in Scheme X can be prepared according to the process outlined in Scheme XI.

SCHEME XI



(37, Y ≠ CF_3) (38) (35)

Thus, a fluoro aryl or fluoro (chloro)heteroaryl nitrile of formula (**37**) is reacted with the lithium, sodium or potassium salt of a substituted heterocycle of formula (**31**) in an apolar aprotic solvent such as dimethylformamide at temperatures ranging from ambient to 150°C, to yield an intermediate of general formula (**38**).The reaction of (**37**) with (**31**) leads to a variable ratio of regioisomers of formula (**38**) which are separated by means of chromatography and/or crystallization. Hydrolysis of the intermediate

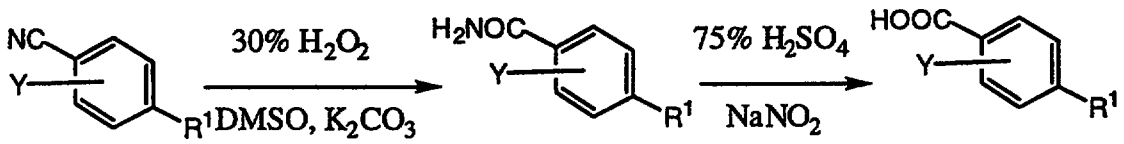
nitriles of formula (**38**, Y≠ CF_3) is preferentially carried out with an inorganic acid such as sulfuric acid at temperatures ranging from ambient to 60°C.

Alternatively, hydrolysis of the nitrile (**38**) can be carried out by heating in ethanol in the presence of a strong alkaline base such as sodium hydroxide with or without a phase transfer catalyst (Jones, R.A. Aldrichimica Acta, 9(3), 35, 1976,) such as benzyldimethyltetradecyl ammonium chloride.

The resulting carboxylic acids of formula (**35**) are then converted into the desired compounds of formula (**I**) of Scheme IX by procedures analogous to those described hereinbefore.

Alternatively, the substituted carboxylic acids of formula (**35**) of Scheme X can be prepared according to the process outlined in Scheme XII by sequential treatment of a nitrile of formula (**38**) wherein A and B are CH and where R^1 is not alkanoyl of 2 to 7 carbons, alkynyl, (b) or (d), with basic hydrogen peroxide in dimethylsulfoxide essentially according to the procedure of Katritzky et al., Synthesis, 949 (1989), followed by hydrolysis of the resulting amide of formula (**38**) preferably by treatment with dilute sulfuric acid and sodium nitrite according to the procedure of Hanes et al., Tetrahedron, 51, 7403 (1995).

SCHEME XII

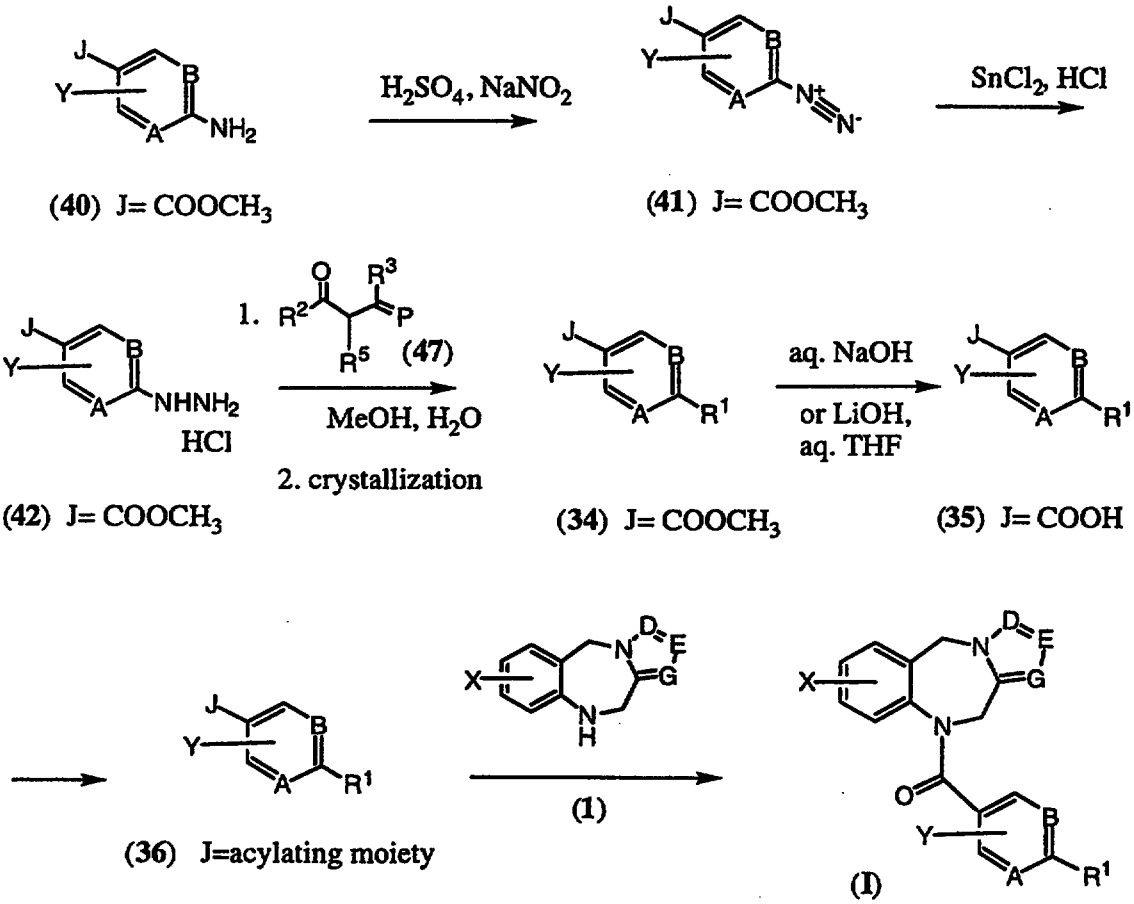


(**38**) (**39**) (**35**)

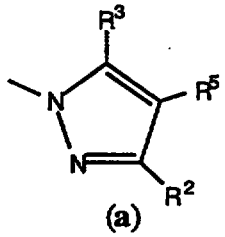
Where R^1 is not (b) or (d)

A preferred process for the preparation of the intermediate substituted carboxylic acids of formula (**35**) of Scheme X wherein R^1 is a heterocyclic moiety selected from the (a) group of R^1 heterocycles defined above, is outlined in Scheme XIII.

SCHEME XIII



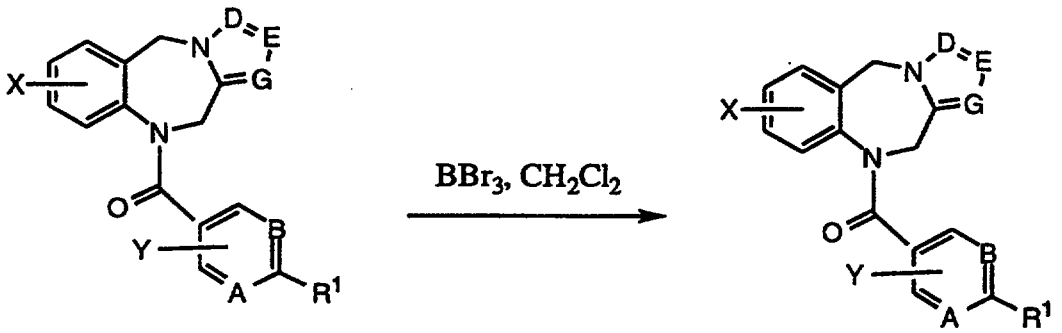
Diazotization of an appropriately substituted aniline of formula (**40**) followed by reduction of the resulting diazonium salt of formula (**41**) with tin (II) chloride in concentrated hydrochloric acid according to the procedure of Street et al., J. Med. Chem., **36**, 1529 (1993) provides the intermediate hydrazine hydrochloride salt of formula (**42**). Subsequent condensation of (**42**) with an aldehyde derivative of formula (**47**), wherein R^2 is as defined above, R^3 and R^5 is H, and P is dialkylacetal) such as acetylacetaldehyde dimethyl acetal, or a ketone of formula (**47**), wherein R^2, R^3 and R^5 are as defined above, and P is =O or $(O\text{-alkyl})_2$ in a solvent such as aqueous methanol at temperatures ranging from ambient to 100°C provides after crystallization, the desired intermediate ester of formula (**34**, R^1 is (a) and R^5 is H), which is then converted to the compound of formula (I) as outlined in Scheme X above.



(a)

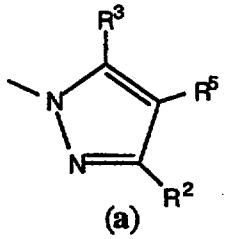
When Y is OCH_3 the compounds of general formula (I) of Scheme I can be conveniently demethylated as outlined in Scheme XIV.

SCHEME XIV



(I) Y= OCH_3 (I) Y= OH

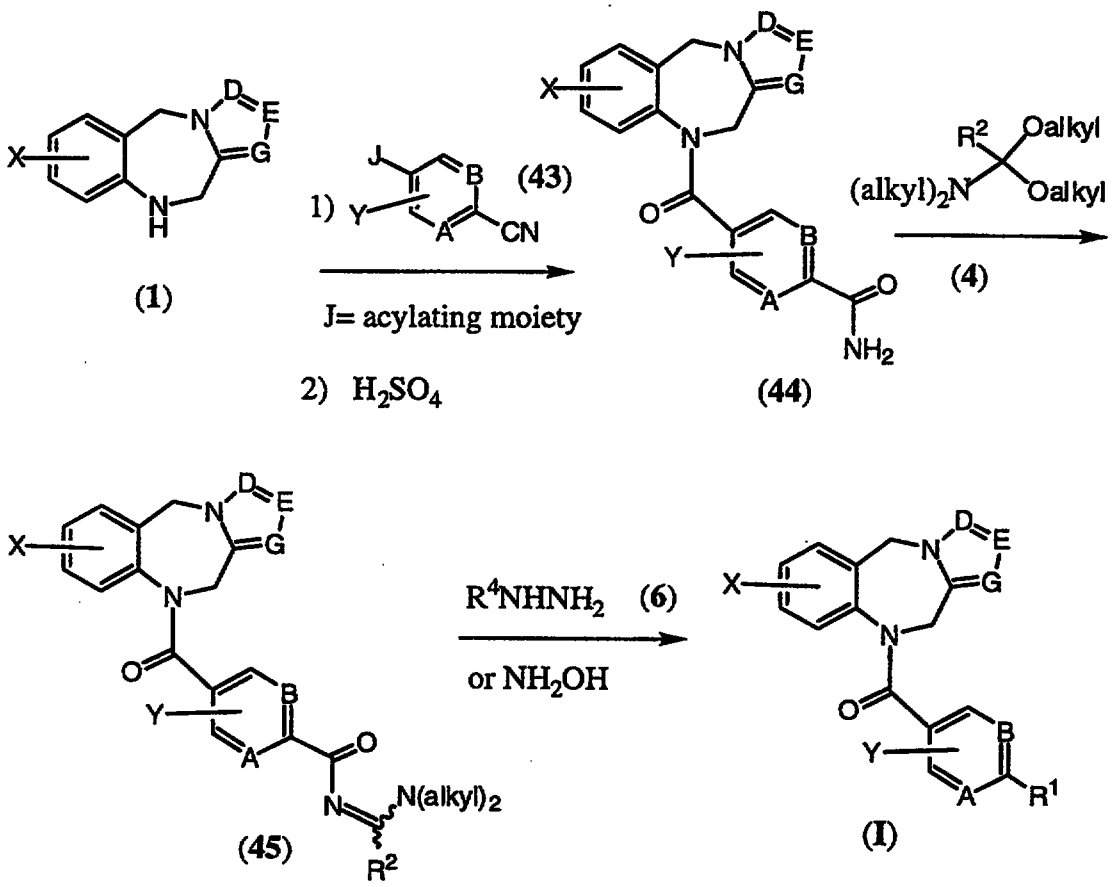
Thus, the reaction of compound (I) wherein Y is OCH_3 with boron tribromide in an organic solvent, such as dichloromethane, yields the corresponding phenol of formula (I) wherein Y is OH, and A, B, D, E, G, X, R^2 and R^3 are as defined above and R^1 is an heterocyclic moiety selected from the group (a) of heterocycles defined above and illustrated below.



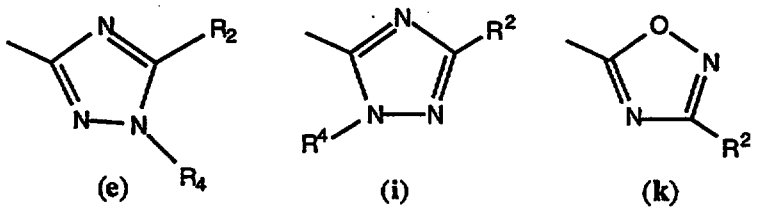
(a)

Compounds in which R^1 contains three heteroatoms are prepared according to Scheme XV.

SCHEME XV

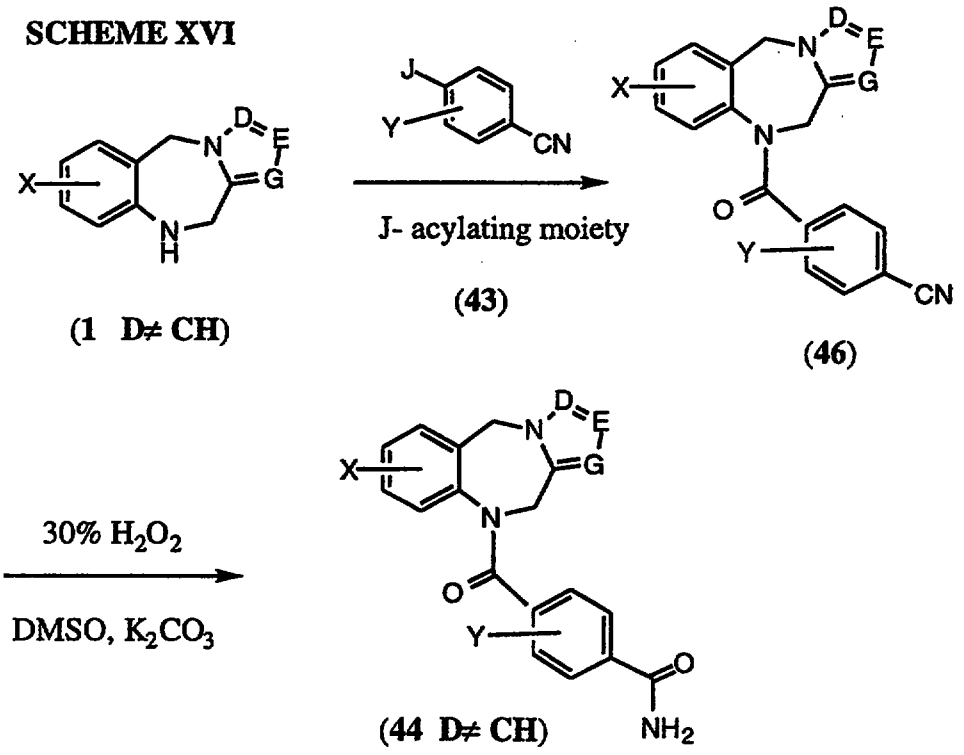


Thus, a tricyclic benzodiazepine of formula (**1**) is treated with an appropriately substituted cyano aroyl (heteroaroyl) halide, preferably an aroyl (heteroaroyl) chloride of formula (**43**) in the presence of a base in an aprotic organic solvent such as dichloromethane or tetrahydrofuran at temperatures ranging from -40°C to 80°C to yield an intermediate nitrile of formula (**46**, Scheme XVI) which in turn, is hydrolyzed to an amide intermediate of general formula (**44**) with an inorganic acid such as sulfuric acid at ambient temperature to 50 °C. Treatment of the amide (**44**) with a dialkyl amide dialkyl acetal of formula (**4**) in an aprotic organic solvent such as dichloromethane or tetrahydrofuran at temperatures ranging from 0°C to 80°C yields the intermediate of formula (**45**). Treatment of (**45**) with hydroxylamine or a hydrazine of formula (**6**) in acetic acid at temperatures ranging from ambient to reflux yields the desired target compounds of formula (**I**) wherein A, B, D, E, G, X, Y, R^2 and R^4 are as defined above, and R^1 is an heterocyclic moiety selected from the (e), (i) and (k) group of heterocycles defined above.



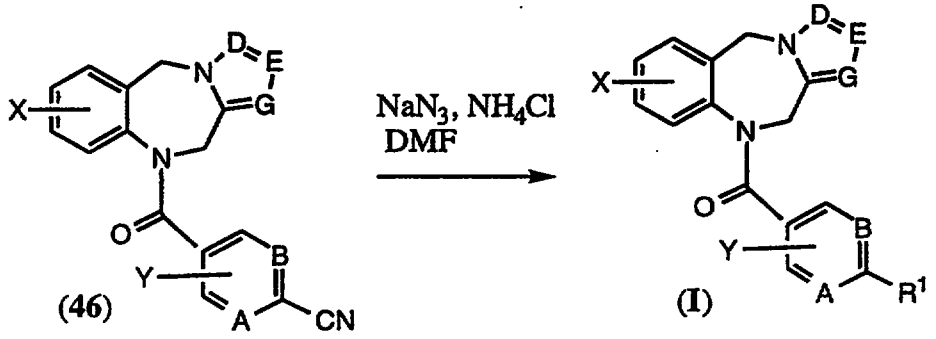
Another preferred process for the preparation of the intermediate amide of formula (44), see Scheme XV, wherein A and B are CH and D is not CH is outlined in Scheme XVI and consists of treating a nitrile of formula (46) with basic hydrogen peroxide in dimethylsulfoxide essentially according to the procedure of Katritzky et al., Synthesis, 949 (1989).

SCHEME XVI

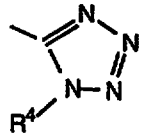


The preferred process to prepare compounds of general formula (I) in which R^1 contains four heteroatoms and R^4 is hydrogen is outlined in Scheme XVII.

SCHEME XVII



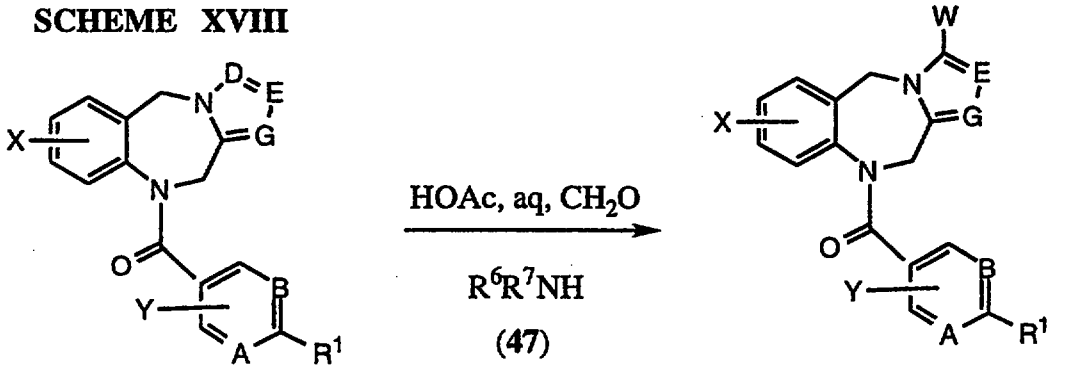
Treatment of the nitrile intermediate of formula (**46**) of Scheme XVI with sodium azide and ammonium chloride in an aprotic organic solvent such as dimethylformamide at temperatures ranging from ambient to the reflux temperature of the solvent yields the desired compounds of formula (**I**) wherein A, B, D, E, G, X, and Y, are as defined above, R^4 is hydrogen and R^1 is an heterocyclic moiety selected from the group (m) of heterocycles defined above.



(**m**)

The compounds of general formula (**I**) wherein D is CW and W is hydrogen, can undergo Mannich condensation as shown in Scheme XVIII.

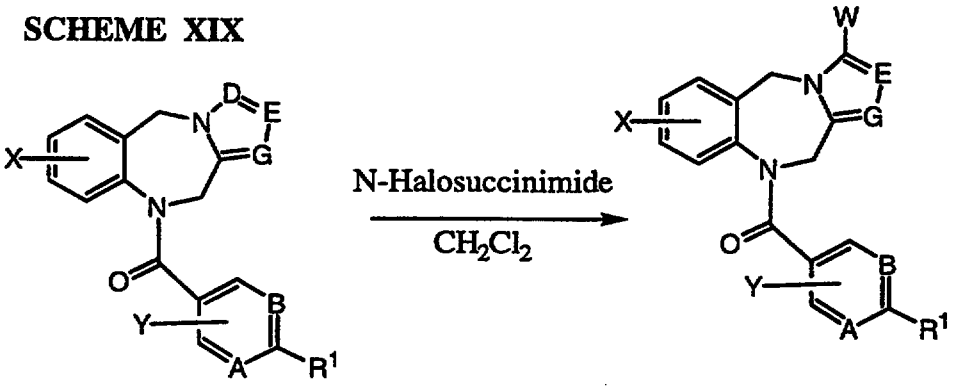
SCHEME XVIII



Thus, reaction of compounds of formula (I, D is CH) with either aqueous formaldehyde or paraformaldehyde , a substituted amine of formula (47), and glacial acetic acid in an alcohol solvent such as methanol at temperatures ranging from ambient to reflux yields the corresponding Mannich bases of general formula (I), wherein A, B, E, G, X, Y, R^2, R^3, R^5, R^6 and R^7 are as defined above; D is CW; W is a dialkylaminoalkyl residue preferably a dimethylaminomethyl residue, and R^1 is an heterocyclic moiety selected from the (a), (c), (e), (f), (g), (h), (i), (j), (k), (l), (m), (n) and (o) group of heterocycles defined above.

Likewise, the compounds of general formula (I) wherein D is CH can undergo halogenation as shown in Scheme XIX.

SCHEME XIX



(I, D= CH) (I W = halogen)

Thus, reaction of (I, D is CH) with a N-halosuccinimide such as N-chloro (bromo or iodo)succinimide in a polar aprotic organic solvent such as dichloromethane at temperatures ranging from -80°C to ambient yields the corresponding halogenated derivatives of general formula (I), wherein A, B, E, G, X, R^2, R^3 and R^5 are as defined above, D is CW, W is a halogen such as chlorine (bromine or iodine), and R^1 is an heterocyclic moiety selected from the (a), (c), (e), (f), (g), (h), (i), (j), (k), (l), (m), (n) and (o) group of heterocycles defined above.

The subject compounds of the present invention were tested for biological activity according to the following procedures.

Vasopressin V_2 Agonist Effects of Test Compounds in Normal Conscious Water-Loaded Rats:

Male or female normotensive Sprague-Dawley rats (Charles River Laboratories, Inc., Kingston, NY) of 350-500 g body weight were supplied with standard rodent diet (Purina Rodent Lab. Chow 5001) and water ad libitum. On the day of test, rats were placed individually into metabolic cages equipped with devices to separate the feces from the urine and containers for collection of urine. Test compound or reference agent was given at an oral dose of 10 mg/kg in a volume of 10 ml /kg. The vehicle used was 20% dimethylsulfoxide (DMSO) in 2.5% preboiled corn starch. Thirty minutes after dosing the test compound, rats were gavaged with water at 30 ml /kg into the stomach using a feeding needle. During the test, rats were not provided with water or food. Urine was collected for four hours after dosing of the test compound. At the end of four hours, urine volume was measured. Urinary osmolality was determined using a Fiske One-Ten Osmometer (Fiske Associates, Norwood, MA, 02062) or an Advanced CRYOMATIC Osmometer, Model 3C2 (Advanced Instruments, Norwood, MA). Determinations of Na^+, K^+ and Cl^- ion were carried out using ion specific electrodes in a Beckman SYNCHRON EL-ISE Electrolyte System analyzer. The urinary osmolality should increase proportionally. In the screening test, two rats were used for each compound. If the difference in the urine volume of the two rats was greater than 50%, a third rat was used.

Vasopressin V_2 Agonist Effects of Test Compounds in Normal Conscious Homozygous Brattleboro Rats with Central Diabetes Insipidus

Male or female homozygous Brattleboro rats (Harlan Sprague Dawley, Inc., Indianapolis, IN) of 250-350 g body weight were supplied with standard rodent diet (Purina Rodent Lab. Chow 5001) and water ad libitum. On the day of test, rats were placed individually into metabolic cages equipped with devices to separate the feces from the urine and containers for collection of urine. Test compound or reference agent was given at an oral dose of 1 to 10 mg/kg in a volume of 10 ml /kg. The vehicle used was 20% dimethylsulfoxide (DMSO) in 2.5% preboiled corn starch. During the test, rats were provided with water ad libitum. Urine was collected for six hours after

dosing of the test compound. At the end of six hours, urine volume was measured. Urinary osmolality was determined using a Fiske One-Ten Osmometer (Fiske Associates, Norwood, MA, 02062) or an Advanced CRYOMATIC Osmometer, Model 3C2 (Advanced Instruments, Norwood, MA). Determinations of Na^+, K^+ and Cl^- ion were carried out using ion specific electrodes in a Beckman SYNCHRON EL-ISE Electrolyte System analyzer. This animal model was mainly used for evaluation of potency and duration of action of the active compounds. The results of this study are shown in Table I.

Example #	Urine Volume (% decrease)[a]	Osmolality (% Increase)[b]	Rat Type [c]
2	80% (1 mg/kg)	306% (1 mg/kg)	CD
3	58%	240%	CD
4	57%	225%	CD
5	56%	231%	CD
6	58%	270%	CD
7	13%	137%	CD
9A	70%	325%	CD
9B	21%	168%	CD
11	70%	285%	CD
12	69%	330%	CD
13	50%	229%	CD
14	86%	406%	CD
15	47%	38%	CD
16	88%	400%	CD
18	52%	214%	CD
20	25% (1 mg/kg)	152% (1 mg/kg)	CD
21	49%	181%	CD
22	80%	322%	CD
24	47%	159%	CD
25	87%	979%	CD
26	54%	279%	CD
27	76%	183%	CD
28	75%	37%	CD
29	66%	305%	CD
30	81%	334%	BB
31	72%	298%	CD
32	77%	373%	CD
33	68%	362%	CD
34	76%	407%	BB
35	63%	308%	CD
36	66%	164%	BB
37	71%	370%	CD
38	66%	256%	BB
39	69%	253%	CD
40	46%	183%	CD
41	69%	240%	CD
49	74%	221%	BB
50	53%	223%	CD

Example #	Urine Volume (% decrease)[a]	Osmolality (% Increase)[b]	Rat Type [c]
51	72%		CD
52	66%	261%	CD
55	80%	164%	CD
57	77%	288%	CD
58	49%	324%	CD
59	80%	607%	CD
60	54%	165%	CD
61	59%	245%	CD
62	22%	150%	CD
63	27%	214%	CD
64	79%	349%	CD
71	84%	264%	CD
77	13%	90%	CD
78	21%	115%	CD
79	38%	123%	CD
81	82%	490%	CD
83	85%	442%	CD
84	56%	291%	CD
85	76%	436%	CD
86	5%	86%	CD
87	71%	214%	CD
88	68%	226%	CD
90	61%	413%	CD
91	22%	69%	CD
92	69%	454%	CD
95	68%	300%	CD
97	3%	106%	CD
99	43%	205%	CD
100	24%	248%	CD
101	76%	376%	CD
107	31%	125%	CD
108	30%	145%	CD
109	21%	95%	CD
115	66%	229%	CD
116	66%	256%	CD
117	68%	311%	CD
120A	66%	269%	CD
120B	67%	272%	CD
121	22%	155%	CD
123	88%	663%	CD

[a]Percent decrease in urine volume vs. control at 10 mg per kg, unless otherwise stated.
[b]Change in osmolality as percent of control at 10 mg/kg, unless otherwise stated.
[c]Rat model used: Sprague-Dawley (CD) or Brattleboro (BB).

The following examples are presented to illustrate rather than limit the scope of the invention.

EXAMPLE 1

(4-Fluoro-2-trifluoromethyl-phenyl)-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone

Oxalyl chloride (2.0 g) was added to a suspension of 4-fluoro-2-trifluoromethylbenzoic acid (2.0 g) in dichloromethane (25 ml). Two drops of dimethylformamide were added and the mixture was stirred for 18 hours at room temperature. The resultant solution was evaporated to dryness to give the crude acid chloride. This was redissolved in dichloromethane and filtered. Evaporation of this material gave a liquid which was then redissolved in hexane, filtered, and evaporated to yield the acid chloride as a pale yellow viscous liquid, which was used without further purification.

The acid chloride (2.26 g) in dichloromethane (25 ml) was added portionwise to a mixture of 10,11-dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine (1.66 g), dichloromethane (10 ml), and diisopropylethylamine (1.30 g), cooled in an ice bath. After remaining at room temperature for 18 hours, the reaction mixture was washed with water and saturated aqueous sodium bicarbonate. The dichloromethane solution was dried over anhydrous sodium sulfate and filtered through a short column of hydrous sodium magnesium silicate and further eluted with several volumes of dichloromethane. The combined organic phase was concentrated on a hot plate with the gradual addition of hexane until crystallization occurred. After cooling, the crystals were collected by filtration to yield 2.57 g of the title compound, m.p. 154-155 °C.

EXAMPLE 2

[4-(3-Methyl-pyrazol-1-yl)-2-trifluoromethyl-phenyl](5H,11H-pyrrolo[2,1-c]-[1,4]benzodiazepin-10-yl)-methanone

60% Sodium hydride in oil (0.15 g) was washed with hexane and dry dimethylformamide (25 ml) was added, followed by 3-methylpyrazole (0.25 g). After

hydrogen evolution ceased, (4-fluoro-2-trifluoromethyl-phenyl)(5H,11H-pyrrolo[2,1-c][1,4]benzodiaxepin-10-yl)-methanone (1.0 g) was added. The reaction mixture was heated in a sand bath at 110 °C for 15 hours. The reaction mixture was poured onto ice and saturated saline solution was added. The precipitate was collected by filtration. The crude reaction product was dissolved in dichloromethane and filtered through a short column of hydrous sodium magnesium silicate and further eluted with several additional volumes of dichloromethane. The combined organic phase was concentrated on a hot plate with the gradual addition of hexane. After cooling, the crystals were collected by filtration to yield 0.77 g of a crude product. Further purification by additional filtration through a short column of hydrous sodium magnesium silicate, followed by the addition of hexane, yielded the title compound as a crystalline solid (0.66 g), m.p. 194-195 °C.

EXAMPLE 3

[4-(4-Methyl-pyrazol-1-yl)-2-trifluoromethyl-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone

In the manner of Example 2, employing (4-fluoro-2-trifluoromethyl-phenyl)(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (0.8 g), 60% sodium hydride in oil (0.15 g), 4-methylpyrazole (0.20 g) and dimethylformamide (25 ml), the product (0.47 g) was obtained as a colorless amorphous solid, MS, *m/z*: 437.3 $(M+H)^+$, 873.2 $(2M+H)^+$.

EXAMPLE 4

(4-Pyrazol-1-yl-2-trifluoromethyl-phenyl)-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone

In the manner of Example 2, employing (4-fluoro-2-trifluoromethyl-phenyl)-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (1.0 g), 60% sodium hydride in oil (0.20 g), pyrazole (0.25 g) and dimethylformamide (35 ml). The product (0.62 g) was obtained as a colorless amorphous solid, MS, *m/z*: 423.2 $(M+H)^+$, 445.2 $(M+Na)^+$, 845.3 $(2M+H)^+$.

EXAMPLE 5

[4-(3-Cyclopropyl-pyrazol-1-yl)-2-trifluoromethy-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone

In the manner of Example 2, employing (4-fluoro-2-trifluoromethyl-phenyl)-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (1.42 g), 60% sodium hydride in oil (0.20 g), 3-cyclopropylpyrazole (0.43 g) and dimethylformamide (50 ml), the product (1.22 g) was obtained as a crystalline solid, m.p. 163-164 °C.

EXAMPLE 6

[4-(4-Methyl-imidazol-1-yl)-2-trifluoromethyl-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone

In the manner of Example 2, employing (4-fluoro-2-trifluoromethyl-phenyl)-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (1.0 g), 60% sodium hydride in oil (0.20 g), 4-methylimidazole (0.25 g) and dimethylformamide (25 ml), the title compound (0.66 g) was obtained as an amorphous solid. MS, *m/z*: 437.2 $(M+H)^+$, 873.2 $(2M+H)^+$.

EXAMPLE 7

(5H,11H-Pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-(4-[1,2,4]triazol-1-yl-2-trifluoromethylphenyl)-methanone

In the manner of Example 2, employing (4-fluoro-2-trifluoromethyl-phenyl)-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (1.0 g), 60% sodium hydride in oil (0.20 g), 1,2,4-triazole (0.20 g), and dimethylformamide (25 ml), the title compound (0.36 g) was obtained as a colorless amorphous solid, MS, *m/z*: 424.2 $(M+H)^+$, 847.3 $(2M+H)^+$

EXAMPLE 8

(2-Chloro-4-fluorophenyl)-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone

Oxalyl chloride (2.60 g) was added to a suspension of 2-chloro-4-fluorobenzoic acid (3.44 g) in dichloromethane (50 ml). Two drops of dimethylformamide were added and the mixture was stirred for 18 hours at room temperature. The resultant solution was evaporated to give the crude 2-chloro-4-fluorobenzoyl chloride as a viscous oil (3.72 g).

The crude 2-chloro-4-fluorobenzoyl chloride (3.68 g) in dichloromethane (25 ml) was added portionwise to a stirred, ice cooled solution of 10,11-dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine (2.76 g), diisopropylethylamine (2.47 g) and dichloromethane (50 ml). After 18 hours at room temperature, the reaction mixture was washed with water and saturated aqueous sodium bicarbonate. The dichloromethane solution was dried with anhydrous sodium sulfate and filtered through a short column of hydrous sodium magnesium silicate and further eluted with several volumes of dichloromethane. The combined organic phase was concentrated on a hot plate with the gradual addition of hexane until crystallization occurred. After cooling, the crystals were collected by filtration to yield the title compound (3.85 g), m.p. 110-112 °C.

EXAMPLE 9

[2-Chloro-4-(3-methyl-pyrazol-1-yl)-phenyl]-(5H,11H)-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (Isomer A)

and

[2-Chloro-4-(5-methyl-pyrazol-1-yl)-phenyl]-(5H,11H)-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (Isomer B)

Method 1: To 60% sodium hydride in oil (0.3 g, degreased with hexane) in dimethylformamide (25 ml) was added 3-methylpyrazole (0.55 g). When the hydrogen evolution subsided, (2-chloro-4-fluorophenyl)-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (1.70 g) was added. The reaction mixture was heated for 18 hours in a sand bath (internal temperature 125 °C). The reaction mixture was then

poured onto ice and further diluted with a saturated saline solution. The precipitated solid was recovered by filtration. The crude product was dissolved in dichloromethane, dried over anhydrous sodium sulfate, and then filtered through a short column of hydrous sodium magnesium silicate and further eluted with several volumes of dichloromethane. The combined eluate was refluxed on a hot plate with the gradual addition of hexane until an opaque solution was observed. On cooling an amorphous solid was obtained. On subjecting this material to a second column of hydrous sodium magnesium silicate and evaporation of the solvent in vacuo gave a mixture of regioisomers 9A and 9B in approximately a 9:1 ratio as an amorphous glass (1.11 g), MS, *m/z*: 403.2 $(M+H)^+$.

Method 2: To a pre-cooled, stirred suspension of hexane-washed 60% sodium hydride (3.00 g) in dry dimethylformamide (250 ml) was added dropwise under nitrogen 3-methylpyrazole (5.50 g) at 0°C. The mixture was warmed to room temperature. After gas evolution ceased, 2-chloro-4-fluorophenyl)-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (17.0 g) was added as a solid, and the mixture heated to 130°C for one hour. The reaction mixture was poured into ice water, a precipitate collected by filtration, and air-dried. The precipitate was dissolved in dichloromethane, dried over anhydrous sodium sulfate, and filtered through a short column of silica gel, eluting with ethyl acetate. The combined filtrate was evaporated in vacuo to a residual foam (18.5 g). Purification and separation of regioisomers by low pressure column chromatography on silica gel eluting with a gradient mixture of ethyl acetate-hexane (10:90 to 25:75), yielded two purified regioisomers:

Isomer A, [2-chloro-4-(3-methyl-pyrazol-1-yl)-phenyl]-(5H,11H)-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (13.5 g), as a colorless amorphous solid; MS (EI), *m/z*: 402 $(M)^+$. A sample (0.5 g) was crystallized from diethyl ether, followed by recrystallization from ethanol to yield regioisomer A (0.275 g) as a colorless, crystalline solid, m.p. 141-143 °C;

Isomer B, [2-chloro-4-(5-methyl-pyrazol-1-yl)-phenyl]-(5H,11H)-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (1.93 g) as a colorless amorphous solid. A sample was crystallized from diethyl ether, followed by recrystallization from methanol to yield regioisomer B as colorless, needles (1.4 g), m.p. 160-163 °C; MS (EI), *m/z*: 402 $(M)^+$, MS (+FAB), *m/z*: 403 $(M+H)^+$.

EXAMPLE 10

[2-Chloro-4-(3-methyl-pyrazol-1-yl)-phenyl]-(5H,11H)-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone

Step a) 2-Chloro-4-(3-methylpyrazol-1-yl)benzonitrile: To a cooled (0 °C) suspension of sodium hydride (60% in oil; 2.0 g) in dimethylformamide (50 ml) was added 3-methylpyrazole (3.39 g) in portions. After hydrogen gas evolution ceased, 2-chloro-4-fluorobenzonitrile (5.17 g) was added and the mixture was stirred at room temperature for 18 hours. The mixture was poured onto ice, diluted with brine, and the resulting precipitate was collected by filtration. The crude product was dissolved in dichloromethane, filtered through a column of anhydrous sodium magnesium silicate, and crystallized by the addition of hexane. Recrystallization from ethanol gave 4.42 g of product, m.p. 148-150 °C.

Step b) 2-Chloro-4-(3-methylpyrazol-1-yl)benzamide: A suspension of 2-chloro-4-(3-methylpyrazol-1-yl)benzonitrile (4.35 g) from step a in dimethyl sulfoxide (20 ml) containing potassium carbonate (0.40 g) was cooled in an ice bath. Hydrogen peroxide (30%, 2.4 ml) was added and the mixture was warmed to room temperature over 1 hour. The resultant precipitate was recovered by filtration and recrystallized from ethanol to yield 2.44 g of product as fine needles, m.p. 159-160 °C; MS, *m/z*: 235.9 $(M+H)^+$.

Step c) 2-Chloro-4-(3-methylpyrazol-1-yl)benzoic Acid: A solution of 2-chloro-4-(3-methylpyrazol-1-yl)benzamide (1.09 g) from step b in aqueous 75% sulfuric acid (25 ml) was cooled in an ice bath and sodium nitrite (1.73 g) was added. The mixture was warmed to room temperature over 1 h and poured onto ice. The precipitate was collected by filtration and used directly in the next reaction.

Step d) [2-Chloro-4-(3-methyl-pyrazol-1-yl)-phenyl]-(5H-10,11-dihydro-pyrrolo[2,1-c][1,4] benzodiazepin-10-yl)-methanone: A mixture of 2-chloro-4-(3-methylpyrazol-1-yl)benzoic acid (0.69 g), dichloromethane (25 ml) from step c , oxalyl chloride (1.0 g), and 1 drop of dimethylformamide was stirred at room temperature for 18 hour. The mixture was concentrated, taken up in dichloromethane (25 ml), and

added to a mixture of 10,11-dihydro-5H-pyrrolo[2,1-c][1,4]-benzodiazepine (0.51 g) in dichloromethane (25 ml) containing diisopropylethylamine (0.76 g). The mixture was stirred at room temperature for 18 h and washed with saturated aqueous sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulfate and filtered through a short column of anhydrous sodium magnesium silicate. The solution was concentrated and the resultant material was crystallized from diethyl ether to give 0.67 g of product, m.p. 137-138 °C; MS, *m/z*: 403.2 $(M+H)^+$, 805.8 $(2M+H)^+$.

EXAMPLE 11

[2-Chloro-4-(4-methyl-pyrazol-1-yl)-phenyl-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone

In the manner of Example 9's Method 1, employing (2-chloro-4-fluorophenyl)-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (1.0 g), 60% sodium hydride in oil (0.3 g, degreased with hexane), 4-methylpyrazole (0.48 g) and dimethylformamide (25 ml), the title compound (0.74 g) was obtained as an amorphous solid, MS, *m/z*: 403.2 $(M+H)^+$, 425.2 $(M+Na)^+$, 805.3 $(2M+H)^+$.

EXAMPLE 12

[2-Chloro-4-(4-methyl-imidazol-1-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone

In the manner of Example 9's Method 1, employing (2-chloro-4-fluorophenyl)-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (1.0 g), 60% sodium hydride in oil (0.3 g, degreased with hexane), 4-methylimidazole (0.48 g), and dimethylformamide (25 ml), the title compound (0.38 g) was obtained as an amorphous solid, MS, *m/z*: 403.3 $(M+H)^+$.

EXAMPLE 13

[2-Chloro-4-(3-trifluoromethyl-pyrazol-1-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone

In the manner of Example 9's Method 1, employing (2-chloro-4-fluorophenyl)-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (0.8 g), 60% sodium hydride in oil (0.25 g, degreased with hexane), 3-trifluoromethylpyrazole (0.61 g) and dimethylformamide (25 ml), the title compound was obtained as an amorphous solid, MS, *m/z*: 457.2 $(M+H)^+$.

EXAMPLE 14

[2-Chloro-4-(1,2,4-triazol-1-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone

In the manner of Example 9's Method 1, employing (2-chloro-4-fluorophenyl)-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (1.7 g), 60% sodium hydride in oil (0.5 g, degreased with hexane), 1,2,4-triazole (0.70 g) and dimethylformamide (50 ml), the title compound (0.51 g) was obtained as an amorphous solid, MS, *m/z*: 390.3 $(M+H)^+$, 779.3 $(2M+H)^+$.

EXAMPLE 15

(2-Chloro-4-pyrrol-1-yl-phenyl)-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone

In the manner of Example 9's Method 1, employing (2-chloro-4-fluorophenyl)-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (1.7 g), 60% sodium hydride in oil (0.3 g, degreased with hexane), pyrrole (0.42 g) and dimethylformamide (25 ml), the title compound (0.60 g) was obtained as an amorphous solid, MS, *m/z*: 388.2 $(M+H)^+$.

EXAMPLE 16

(2-Chloro-4-pyrazol-1-yl-phenyl)(5H,11H-Pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone

In the manner of Example 9's Method 1, employing (2-chloro-4-fluorophenyl)-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (1.0 g), 60% sodium hydride in oil (0.2 g, degreased with hexane), pyrazole (0.20 g) and dimethylformamide (25 ml), the title compound was obtained as an amorphous solid, MS, *m/z*: 389.2 $(M+H)^+$, 777.1 $(2M+H)^+$.

EXAMPLE 17

[2-Chloro-4-(1H-imidazol-1-yl)-phenyl)-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone

In the manner of Example 9's Method 1, employing (2-chloro-4-fluorophenyl)-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (2.0 g), 60% sodium hydride in oil (0.50 g, degreased with hexane), imidazole (0.50 g) and dimethylformamide (25 ml), the title compound (0.57 g) was obtained as a tan amorphous solid, MS, *m/z*: 389 $(M+H)^+$.

EXAMPLE 18

[2-Chloro-4-(3-methylpyrazol-1-yl)-phenyl]-(3-methyl-5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone

Step a) 1-(5H, 11H-Pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-2,2,2-trifluoroethanone: To an ice cooled solution of 10,11-dihydro-5H-pyrrolo[2,1-c][1,4]-benzodiazepine (5.62 g) and diisopropylethylamine (4.0 g) in dichloromethane (75 ml) was added dropwise trifluoroacetic anhydride (7.0 g) in dichloromethane. The mixture was stirred at room temperature for 18 hours, and washed with water and saturated aqueous sodium bicarbonate. The organic phase was dried over anhydrous sodium sulfate and filtered through a short column of anhydrous sodium magnesium silicate. The combined organic phase was concentrated on a hot plate with the gradual addition

of hexane until crystallization occurred. After cooling, the crystals were collected by filtration to yield 7.70 g of product as fine needles, m.p. 134-135 °C, MS *m/z*: 281 $(M+H)^+$.

Step b) 1-(3-Dimethylaminomethyl-5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-2,2,2-trifluoroethanone. A mixture of 1-(5H, 11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-2,2,2-trifluoroethanone (2.80 g),) from step a) , bis-dimethylaminomethane (2.04 g), paraformaldehyde (2.70 g) and acetic acid (1.20 g) in a mixture of tetrahydrofuran (50 ml) and methanol (50 ml) and was stirred at room temperature for 18 hours. The mixture was concentrated in vacuo , water was added, and the aqueous mixture was extracted with dichloromethane. The combined extracts were dried over anhydrous sodium sulfate and filtered through a short column of anhydrous sodium magnesium silicate. The solution was concentrated in vacuo and the residue was crystallized from hexane to yield 2.05 g of the product as a colorless solid m.p. 109-110 °C, MS *m/z*: 338.3 $(M+H)^+$.

Step c) Trimethyl-(10-trifluoroacetyl-10,11-dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-3-yl-methyl)-ammonium iodide: A mixture of 1-(3-dimethylaminomethyl-5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-2,2,2-trifluoroethanone (1.83 g) from step b) and iodomethane (1.0 g) in dichloromethane (20 ml) was stirred at room temperature for 18 hours. Diethyl ether was added and the resulting precipitate was collected by filtration to give 2.54 g of product as a colorless solid, m.p. 140-155 °C (dec).

Step d) 10,11-Dihydro-3-methyl-5H-pyrrolo[2,1-c][1,4]benzodiazepine: Sodium borohydride (2.6 g) was added in two portions to a refluxing mixture of trimethyl-(10-trifluoroacetyl-10,11-dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-3-yl-methyl)-ammonium iodide (2.60 g) from step c) in ethanol. After 4 hours, the mixture was concentrated in vacuo. Water was added to the residue and the mixture was extracted with dichloromethane. The combined extracts were dried over anhydrous sodium sulfate and filtered through a short column of anhydrous sodium magnesium silicate. The solution was concentrated in vacuo and the residue was crystallized from hexane to yield 1.14 g of product, m.p. 150-151 °C, MS *m/z*: 199.1 $(M+H)^+$.

Step e) [2-Chloro-4-(3-methylpyrazol-1-yl)-phenyl]-(3-methyl-5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl)-methanone: A mixture of 2-chloro-4-(3-methylpyrazol-1-yl)-benzoic acid (0.18 g) from step c) of Example 10, oxalyl chloride (0.18 g) and one drop of dimethylformamide in dichloromethane (10 ml), was stirred at room temperature for 18 hours. The mixture was concentrated in vacuo, and the residue was redissolved in dichloromethane and reconcentrated in vacuo to yield 2-chloro-4-(3-methyl-pyrazol-1-yl)-benzoyl chloride. A slurry of the acid chloride in dichloromethane (25 ml) was added dropwise to a solution of 10,11-dihydro-3-methyl-5H-pyrrolo[2,1-c][1,4]benzodiazepine (0.12 g) and diisopropylethylamine (0.10 g) in dichloromethane (25 ml). The mixture was stirred at room temperature for 18 h, and washed with water and saturated aqueous sodium bicarbonate. The organic phase was dried over anhydrous sodium sulfate and filtered through a short column of anhydrous sodium magnesium silicate. The solution was concentrated in vacuo and triturated with diethyl ether to yield 0.115 g of product as colorless crystals, m.p. 178-180 °C, MS *m/z*: 417.3 $(M+H)^+$, 833.3 $(2M+H)^+$.

EXAMPLE 19

(2-Chloro-4-trifluoromethyl-pyrimidin-5-yl)-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone

2-Chloro-4-(trifluoromethyl)pyrimidine-5-carbonyl chloride (2.57 g) was added gradually to an ice-cooled solution of 10,11-dihydro-5H-pyrrolo[2,1-c][1,4]-benzodiazepine, (1.84 g) and diisopropylethylamine (1.37 g) in dichloromethane (50 ml). After stirring at room temperature for 18 hours, the reaction mixture was washed with water and saturated aqueous sodium bicarbonate. The dichloromethane solution was dried over anhydrous sodium sulfate and filtered through a short column of hydrous sodium magnesium silicate and further eluted with several volumes of dichloromethane. The combined organic phase was concentrated on a hot plate with the gradual addition of hexane until crystallization occurred. After cooling, the crystals were collected by filtration to yield the title compound (3.22 g), m.p. 221-223 °C.

EXAMPLE 20

[2-(3-Methyl-pyrazol-1-yl)-4-trifluoromethyl-pyrimidin-5-yl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone

To 60% sodium hydride in oil (0.15 g, degreased with hexane) in dimethylformamide (25 ml) was added 3-methylpyrazole (0.25 g). When the hydrogen evolution subsided, (2-chloro-4-trifluoromethyl-pyrimidin-5-yl)-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (0.98 g) was added. The reaction mixture was heated for 18 hours in a sand bath (internal temperature 110 °C). The mixture was then poured onto ice and further diluted with a saturated saline solution. The precipitate was filtered, redissolved in dichloromethane and dried over anhydrous sodium sulfate. Purification was aided by filtration through a short column of hydrous sodium magnesium silicate and further elution with several volumes of dichloromethane. The combined eluate was concentrated on a hot plate with the gradual addition of hexane until crystallization occurred. After cooling, the solid was collected by filtration to yield the title compound (0.54 g) as colorless crystals, m.p. 202-204 °C.

EXAMPLE 21

[2-(4-Methyl-pyrazol-1-yl)-4-trifluoromethyl-pyrimidin-5-yl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone

In the manner of Example 9's Method 1, employing (2-chloro-4-trifluoromethyl-pyrimidin-5-yl)-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (0.98 g), 60% sodium hydride in oil (0.15 g), 4-methylpyrazole (0.42 g) and dimethylformamide (25 ml), the title compound (0.73 g) was obtained as a crystalline solid, m.p. 214-217 °C.

EXAMPLE 22

1-[4-(5H,11H-Pyrrolo[2,1-c][1,4]benzodiazepine-10-carbonyl)-phenyl]-ethanone

4-Acetylbenzoic acid (5.0 g) and thionyl chloride (10 ml) were heated on a steam bath under argon for 0.75 hour, and the volatile material was removed under reduced pressure. Toluene was added and the volatiles were removed again to give the crude acid chloride as a red-orange oil. This compound tended to solidify and was used as such for further transformations.

The acid chloride (4.56 g) in dichloromethane (25 ml) was added portionwise to an ice-cooled solution of 10,11-dihydro-5H-pyrrolo[2,1-c][1,4]-benzodiazepine (3.68 g) and diisopropylethylamine (3.25 g) in dichloromethane (100 ml). After stirring at room temperature for 18 hours, the reaction mixture was washed with water and saturated aqueous sodium bicarbonate. The dichloromethane solution was dried over anhydrous sodium sulfate and filtered through a short column of hydrous sodium magnesium silicate eluting with several volumes of dichloromethane. The combined organic phase was concentrated on a hot plate with the gradual addition of hexane until crystallization occurred. After cooling, the crystals were collected by filtration to yield the title compound (1.75 g), m.p. 135-137 °C.

EXAMPLE 23

3-Dimethylamino-1-[4-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepine-10-carbonyl)-phenyl]-2-propen-1-one

A reaction mixture of 1-[4-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepine-10-carbonyl)-phenyl]-ethanone (1.40 g), t-butoxy-bis-dimethylaminomethane (5.0 ml) and dichloromethane (10 ml) was stirred for 18 hours. The red-orange precipitate was filtered to yield the title compound (1.22 g), m.p. 203-205 °C. Additional product (0.18 g) was isolated from the reaction mixture by concentration.

EXAMPLE 24

[4-(1H-Pyrazol-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone

A reaction mixture of 3-dimethylamino-1-[4-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepine-10-carbonyl)-phenyl]-2-prop-1-one (1.0 g), anhydrous hydrazine (0.20 g), and glacial acetic acid (20 ml) was refluxed for 7 hours and evaporated to dryness. The crude residue was dissolved in dichloromethane, washed with a saturated aqueous sodium bicarbonate solution and dried over anhydrous sodium sulfate. The solution was filtered through a short column of hydrous sodium magnesium silicate, eluting with several volumes of dichloromethane. The combined organic phase was concentrated on a hot plate with the gradual addition of hexane until crystallization occurred. After cooling, the crystals were collected by filtration. The column procedure was repeated to yield the title compound (0.65 g), m.p. 219-221 °C.

EXAMPLE 25

[4-(1-Methyl-1H-pyrazolyl-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl)-methanone

To a mixture of 60% sodium hydride in oil (0.35 g, degreased with hexane) and dimethylformamide (20 ml) was added [4-(1H-pyrazol-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (0.98 g) followed in a few minutes by iodomethane (0.50 g). The reaction mixture was stirred for 18 hours at room temperature and then poured into water and extracted with dichloromethane. After drying, the organic layer was filtered through a short column of hydrous sodium magnesium silicate, eluting with several volumes of dichloromethane. The combined organic phase was concentrated on a hot plate with the gradual addition of hexane until crystallization occurred. After cooling, the crystals were collected by filtration to yield the title compound (0.70 g), m.p. 194-195 °C.

EXAMPLE 26

[4-(1-Ethyl-1H-pyrazol-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl)-methanone

In the manner of Example 25, employing [4-(1H-pyrazol-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (1.0 g), 60% sodium hydride in oil (0.27 g), dimethylformamide (25 ml), and ethyl iodide (0.87 g), the title compound (0.69 g) was obtained as a crystalline solid, m.p. 180-183 °C.

EXAMPLE 27

[4-(1-Propyl-1H-pyrazol-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl)-methanone

In the manner of Example 25, employing [4-(1H-pyrazol-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (0.98 g), 60% sodium hydride in oil (0.30 g), dimethylformamide (25 ml), and 1-iodopropane (0.60 g), the title compound (0.32 g) was obtained as a crystalline solid, m.p. 159-161 °C.

EXAMPLE 28

[4-(1-Butyl-1H-pyrazol-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl)-methanone

In the manner of Example 25, employing [4-(1H-pyrazol-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (0.98 g), 60% sodium hydride in oil (0.30 g), dimethylformamide (25 ml), and 1-iodobutane (0.60 g), the title compound (0.32 g) was obtained as a crystalline solid, m.p. 122-123 °C.

EXAMPLE 29

[4-(1-methoxymethyl-1H-pyrazol-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl)-methanone

In the manner of Example 25, employing [4-(1H-pyrazol-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (1.0 g), 60% sodium hydride in oil (0.15 g), dimethylformamide (25 ml), and iodomethyl methyl ether (0.50 g), the title compound (0.26 g) was obtained as an amorphous solid, MS, *m/z*: 399.2$(M+H)^+$, 797.2 $(2M+H)^+$.

EXAMPLE 30

1-{3-[4-(5H,11H-Pyrrolo[2,1-c][1,4]benzodiazepine-10-carbonyl)-phenyl]-pyrazol-1-yl}-ethanone

To a solution of [4-(1H-pyrazol-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (0.50 g) in dry pyridine (10 ml) was added acetic anhydride (0.20 g). After stirring at room temperature for 18 hours the reaction mixture was poured into water and the precipitate was collected by filtration. The crude product was dissolved in dichloromethane and dried over anhydrous sodium sulfate. This solution was filtered through a short column of hydrous sodium magnesium silicate, eluting with several additional volumes of dichloromethane. The eluant was concentrated on a hot plate with the gradual addition of hexane until crystallization occurred. After cooling, the crystals were collected by filtration to yield the title compound (0.46 g), m.p. 192-194 °C.

EXAMPLE 31

1-{3-[4-(5H,11H-Pyrrolo[2,1-c][1,4]benzodiazepine-10-carbonyl)-phenyl]-pyrazol-1-yl}-propan-1-one

In the manner of Example 30, employing [4-(1H-pyrazol-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (0.16 g) in dry pyridine

(10 ml) and propionic anhydride (0.10 g), the title compound (0.17 g) was obtained as a crystalline solid, m.p. 150-152 °C.

EXAMPLE 32

[4-(1-Cyclopropanecarbonyl-1H-pyrazol-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone

To a solution of [4-(1H-pyrazol-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl)-methanone (1.0 g) in dry pyridine (10 ml) was added cyclopropanecarbonyl chloride (0.44 g). After stirring at room temperature for 18 hours the reaction mixture was poured into water and the precipitate was collected by filtration. The crude product was dissolved in dichloromethane and dried over anhydrous sodium sulfate. This solution was filtered through a short column of hydrous sodium magnesium silicate, eluting with several additional volumes of dichloromethane. The eluant was concentrated on a hot plate with the gradual addition of hexane until crystallization occurred. After cooling, the crystals were collected by filtration to yield the title compound (0.88 g) was obtained as a crystalline solid, m.p. 197-199 °C.

EXAMPLE 33

1-{3-[4-(5H,11H-Pyrrolo[2,1-c][1,4]benzodiazepine-10-carbonyl)-phenyl]-pyrazol-1-yl}-butan-1-one

In the manner of Example 32, employing [4-(1H-pyrazol-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (0.71 g) in dry pyridine (10 ml) and butyryl chloride (0.32 g), the title compound (0.54 g) was obtained as a solid, m.p. 105-110 °C; MS, *m/z*: 424 $(M)^+$.

EXAMPLE 34

(5H,11H-Pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-{4-[1-(thiophene-2-carbonyl)-1H-pyrazoly-3-yl]phenyl}-methanone

In the manner of Example 32, employing [4-(1H-pyrazol-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (0.5 g) in dry pyridine (10 ml) and thiophene-2-carbonyl chloride (0.25 g), the title compound (0.41 g) was obtained as a crystalline solid, m.p. 195-197 °C; MS, *m/z*: 464 $(M)^+$.

EXAMPLE 35

{4-[1-(5-Fluoro-2-methyl-benzoyl)-1H-pyrazol-3-yl]-phenyl}-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone

In the manner of Example 32, employing [4-(1H-pyrazol-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (0.35 g) in dry pyridine (10 ml) and 2-methyl-5-fluorobenzoyl chloride (0.22 g), the title compound (0.11 g) was obtained as an amorphous pale yellow solid, MS, *m/z*: 490 $(M)^+$.

EXAMPLE 36

{4-[1-(2-Methyl-benzoyl)-1H-pyrazol-3-yl]-phenyl}-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone

In the manner of Example 32, employing [4-(1H-pyrazol-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (0.71 g) in dry pyridine (20 ml) and o-toluyl chloride (0.39 g), the title compound (0.59 g) was obtained as a crystalline solid, m.p. 170-173 °C; MS, *m/z*: 472 $(M)^+$.

EXAMPLE 37

{4-[1-(2-Chloro-4-fluoro-benzoyl)-1H-pyrazol-3-yl]-phenyl}-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl}methanone

Portionwise, 2-chloro-4-fluorobenzoyl chloride (0.82 g) was added to a solution of [4-(1H-pyrazol-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (1.0 g) and diisopropylamine (0.55g) in dichloromethane (25 ml) which was cooled in an ice bath. The reaction mixture was allowed to stir at room temperature overnight. The reaction mixture was washed with water and saturated sodium bicarbonate and dried over anhydrous sodium sulfate. The dichloromethane solution was passed through a short column of hydrous sodium magnesium silicate, eluting several additional volumes of dichloromethane. The eluent was evaporated to dryness to yield 1.06 g of the product as a solid, m.p. 150-157 °C; MS, *m/z*: 510 $(M)^+$.

EXAMPLE 38

{4-[1-(2,4-Dichloro-benzoyl)-1H-pyrazol-3-yl]-phenyl}-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone

In the manner of Example 32, employing [4-(1H-pyrazol-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (0.71 g) in dry pyridine (20 ml) and 2,4-dichlorobenzoyl chloride (0.52 g), the title compound (0.66 g) was obtained as a crystalline solid, m.p. 180-182 °C; MS, *m/z*: 528 $(M)^+$.

EXAMPLE 39

2-(2,4-Dichloro-phenyl)-1-{3-[4-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepine-10-carbonyl)-phenyl]-pyrazol-1-yl}-ethanone

In the manner of Example 32, employing [4-(1H-pyrazol-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (0.71 g) in dry pyridine (25 ml) and 2,4-dichlorophenylacetyl chloride (0.56 g), the title compound (0.20 g) was obtained as a crystalline solid, m.p. 130-140 °C, resolidifies, m.p. 180-182 °C.

EXAMPLE 40

{4-[1-(Biphenyl-2-carbonyl)-1H-pyrazol-3-yl]-phenyl}-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone

In the manner of Example 32, employing [4-(1H-pyrazol-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (0.71 g) in dry pyridine (20 ml) and 2-biphenylcarbonyl chloride (0.65 g), the title compound (0.49 g) was obtained as an amorphous solid, MS, *m/z*: 534 $(M)^+$.

EXAMPLE 41

{4-[1-(4'-Trifluoromethyl-biphenyl-2-carbonyl)-1H-pyrazol-3-yl]-phenyl}-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone

In the manner of Example 32, employing [4-(1H-pyrazol-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (0.71 g) in dry pyridine (20 ml) and 4'-trifluoromethyl-2-biphenylcarbonyl chloride (0.71 g), the title compound (0.59 g) was obtained as an amorphous solid, MS, *m/z*: 602 $(M)^+$.

EXAMPLE 42

3-Dimethylamino-1-[4-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepine-10-carbonyl)-phenyl]-2-buten-1-one

A mixture of 1-[4-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepine-10-carbonyl)-phenyl]-ethanone (2.0 g) and dimethylacetamide dimethylacetal (15 ml) was refluxed in an inert atmosphere for 15 hours and the volatiles were removed at reduced pressure. The crude solid was dissolved in dichloromethane and filtered through a short column of hydrous sodium magnesium silicate followed by several volumes of dichloromethane. The combined eluant was concentrated and hexane was gradually added until crystallization occurred. The cooled solution was filtered to recover the title compound (1.03 g) as a crystalline solid, m.p. 183-185 °C.

EXAMPLE 43

[4-(5-Methyl-1H-pyrazol-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl)-methanone

Anhydrous hydrazine (0.10 g) was added to a solution of 3-Dimethylamino-1-[4-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepine-10-carbonyl)-phenyl]-2-buten-1-one (0.50 g) in glacial acetic acid (25 ml). The reaction mixture was refluxed for 18 hours and then concentrated under vacuum. The solid was extracted with dichloromethane and washed with saturated aqueous sodium bicarbonate solution. The dichloromethane solution was dried over anhydrous sodium sulfate and filtered through a short column of hydrous sodium magnesium silicate and further eluted with several volumes of dichloromethane. The combined organic phase was concentrated on a steam bath with the gradual addition of hexane to give an opaque solution. After cooling the amorphous solid was recovered by filtration to yield the product (0.33 g), MS, *m/z*: 368 $(M)^+$.

EXAMPLE 44

4-(5H,11H-Pyrrolo[2,1-c][1,4]benzodiazepine-10-carbonyl)-benzonitrile

4-Cyanobenzoic acid (5.0 g) and thionyl chloride (5.0 ml) were heated on a steam bath for one hour, and all of the volatiles were removed at reduced pressure. Hexane was added and the crude crystalline acid chloride (5.30 g) was recovered by filtration, and used without further purification.

To a reaction mixture of 10,11-dihydro-5H-pyrrolo[2,1-c][1,4]-benzodiazepine (3.68 g), dichloromethane (100 ml), and diisopropylethylamine (2.80 g) was added 4-cyanobenzoyl chloride (2.97 g). After remaining at room temperature for 18 hours, the reaction mixture was washed with water and saturated aqueous sodium bicarbonate solution. The dichloromethane solution was dried over anhydrous sodium sulfate and filtered through a short column of hydrous sodium magnesium silicate and further eluted with several volumes of dichloromethane. The combined organic phase was concentrated on a hot plate with the gradual addition of hexane until crystallization

occurred. After cooling, the crystals were collected by filtration to yield the title compound (5.05) g, m.p. 184-186 °C.

EXAMPLE 45

4-(5H,11H-Pyrrolo[2,1-c][1,4]benzodiazepine-10-carbonyl)-benzamide

4-(5H,11H-Pyrrolo[2,1-c][1,4]benzodiazepine-10-carbonyl)-benzonitrile (0.5 g) from Example 44 was added to concentrated sulfuric acid (5 ml) and the mixture was stirred for 18 hours at room temperature to yield a bright yellow solution. The solution was poured onto ice and made basic with the addition of concentrated ammonium hydroxide. The resultant solid was filtered, dissolved in dichloromethane, and filtered through a short column of hydrous sodium magnesium silicate and further eluted with several volumes of dichloromethane. The combined organic phase was concentrated on a hot plate with the gradual addition of hexane until crystallization occurred.. After cooling, the crystals were collected by filtration to yield the title compound (5.05 g), m.p. 226-228 °C.

EXAMPLE 46

N-(Dimethylaminomethylene)-4-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepine-10-carbonyl)-benzamide

A mixture of 4-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepine-10-carbonyl)-benzamide (1.25 g) from Example 45 and dimethylformamide dimethylacetal (20 ml) was refluxed for 4 hours and the volatiles removed in vacuo to give a solid. The solid was dissolved in dichloromethane and filtered through a short column of hydrous sodium magnesium silicate and further eluted with several volumes of dichloromethane. The combined organic phase was concentrated on a steam bath with the gradual addition of hexane until crystallization occurred. After cooling, the crystals were collected by filtration to yield the title compound (1.40 g), m.p. 232-234 °C.

EXAMPLE 47

N-(1-Dimethylaminoethylene)-4-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepine-10-carbonyl)-benzamide

A mixture of 4-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepine-10-carbonyl)-benzamide (1.24 g) **from Example 45** and dimethylacetamide dimethylacetal (5.0 ml) was heated on a steam bath for 4 hours. On cooling for 18 hours a crystalline solid precipitated which was recovered by filtration. The solid was washed with hexane to yield the product (1.54 g), m.p. 210-212 °C; MS, *m/z*: 400 $(M)^+$.

EXAMPLE 48

(5H,11H-Pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-[4-(2H-[1,2,4]triazol-3-yl)-phenyl]-methanone

A mixture of N-(dimethylaminomethylene)-4-(5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepine-10-carbonyl)-benzamide (1.0 g) from Example 46, glacial acetic acid (15 ml), and anhydrous hydrazine (0.16 g) was refluxed for 15 hours and the volatiles removed in vacuo. Saturated aqueous sodium bicarbonate solution was added and the resultant solid was recovered by filtration. The solid was refluxed for 4 hours and the volatiles removed in vacuo to give a solid. The solid was dissolved in dichloromethane and filtered through a short column of hydrous sodium magnesium silicate and further eluted with several volumes of dichloromethane. The combined organic phase was concentrated on a steam bath with the gradual addition of hexane until crystallization occurred. After cooling, the crystals were collected by filtration to yield the title compound (0.39 g), m.p. 225-227 °C; MS, *m/z*: 355 $(M)^+$.

EXAMPLE 49

[4-(2-Methyl-2H-[1,2,4]triazol-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl)-methanone

In the same manner as Example 48, employing N-(dimethylaminomethylene)-4-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepine-10-carbonyl)-benzamide (1.56 g) from

Example 46 in glacial acetic acid (75 ml) and methylhydrazine (0.32 g), the title compound (0.10 g) was obtained as a solid, m.p. 155-158 °C; MS, *m/z*: 369 $(M)^+$.

EXAMPLE 50

[4-(5-Methyl-2H-[1,2,4]triazol-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl)-methanone

In the same manner as Example 48, employing N-(1-dimethylaminoethylene)-4-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepine-10-carbonyl)-benzamide (1.00 g) from Example 47 in glacial acetic acid (75 ml) and anhydrous hydrazine (0.25 g), the title compound (0.20 g) was obtained as an amorphous solid, MS, *m/z*: 369 $(M)^+$.

EXAMPLE 51

[4-(2,5-Dimethyl-2H-[1,2,4]triazol-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c]-[1,4]benzodiazepin-10-yl)-methanone

In the manner of Example 48, employing N-(1-dimethylaminoethylene)-4-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepine-10-carbonyl)-benzamide (1.18 g) from Example 47 in glacial acetic acid (75 ml) and methylhydrazine (0.30 g), the title compound (0.33 g) was obtained as a solid, m.p. 193-195 °C; MS, *m/z*: 383 $(M)^+$.

EXAMPLE 52

[4-(3-Methyl[1,2,4]oxadiazol-5-yl)-phenyl]-(5H,11H-pyrrolo-[2,1-c][1,4]-benzodiazepin-10-yl)-methanone

A solution of N-(1-dimethylaminoethylene)-4-(5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepine-10-carbonyl)-benzamide (1.15 g) from Example 47 in glacial acetic acid (50 ml) containing hydroxylamine hydrochloride (0.40 g) and potassium acetate (1.0 g) was refluxed for 2 hours. All volatiles were removed under reduced pressure and a saturated aqueous solution of sodium bicarbonate was added. The mixture was extracted with dichloromethane and the extracts were dried over anhydrous sodium sulfate. The solution was filtered through a short column of hydrous sodium

magnesium silicate and further eluted with several volumes of dichloromethane. The combined organic phase was concentrated on a steam bath with the gradual addition of hexane until crystallization occurred. After cooling, the crystals were collected by filtration to yield the title compound (0.38 g), m.p. 177-179 °C; MS, *m/z*: 371.3 $(M)^+$, 741.3 $(2M)^+$.

EXAMPLE 53

1-Methyl-4-(4-methylphenyl)-1H-pyrazole

A mixture of 2-(4-methylphenyl)-malondialdehyde (3.05 g), absolute ethanol (40 ml), and methylhydrazine (1.09 g) was stirred at room temperature for 18 hours and the volatiles removed at room temperature. Water was added and the mixture was extracted with dichloromethane. After drying over anhydrous sodium sulfate, the solution was filtered through a short column of hydrous sodium magnesium silicate and further eluted with several volumes of dichloromethane. The combined organic phase was concentrated on a steam bath with the gradual addition of hexane until crystallization occurred. After cooling, the crystals were collected by filtration to yield the title compound (2.91 g), m.p. 107-108 °C.

EXAMPLE 54

4-(1-Methyl-1H-pyrazol-4-yl)-benzoic acid

A mixture of 1-methyl-4-(4-methylphenyl)-1H-pyrazole (1.70 g), potassium permanganate (9.70 g), and 1 N sodium hydroxide (100 ml) was refluxed for 18 hours. The suspension was filtered through diatomaceous earth and cooled. The aqueous solution was extracted with dichloromethane which was discarded. The aqueous solution was acidified to pH 5.5. The resultant precipitate was difficult to filter and was thus extracted with dichloromethane. After evaporation of the solvent, the resulting solid was recrystallized from acetone to yield the title compound (0.60 g), m.p. 274-275 °C; MS *m/z*: 202 $(M)^+$.

EXAMPLE 55

[4-(1-Methyl-1H-pyrazol-4-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl)-methanone

Oxalyl chloride (0.30 g) was added to a suspension of 4-(1-methyl-1H-pyrazol-4-yl)-benzoic acid (0.46 g) in dichloromethane (25 ml). Two drops of dimethylformamide were added and the mixture was stirred for 18 hours at room temperature. The resultant solution was evaporated to dryness to yield the crude acid chloride (0.57 g), which was utilized without further purification.

The acid chloride was added to a solution of 10,11-dihydro-5H-pyrrolo[2,1-c][1,4]-benzodiazepine (0.37 g) and diisopropylethylamine (0.58 g) in dichloromethane (50 ml). After 18 hours at room temperature, the reaction mixture was washed with water and saturated aqueous sodium bicarbonate. The dichloromethane solution was dried over anhydrous sodium sulfate and filtered through a short column of hydrous sodium magnesium silicate and further eluted with several volumes of dichloromethane. The combined organic phase was concentrated on a hot plate with the gradual addition of hexane until crystallization occurred. After cooling, the crystals were collected by filtration to yield the title compound (0.38 g), m.p. 200-201 °C; MS *m/z*: 368 $(M)^+$.

EXAMPLE 56

6-(1-Methyl-1H-pyrazol-4-yl)-pyridine-3-carboxylic acid

A suspension of 6-(1-formyl-2-hydroxyvinyl)pyridine-3-carboxylic acid (1.93 g) (Eastman Chemicals) in absolute ethanol (50 ml) and methylhydrazine (0.50 g) was stirred for 18 hours at room temperature. The reaction mixture was filtered to give the product (1.30 g). The filtrate was evaporated to give a solid which was recrystallized from ethyl acetate to give an analytical sample of the title compound (0.55 g), m.p. 262-264 °C.

EXAMPLE 57

[6-(1-Methyl-1H-pyrazol-4-yl)-pyridin-3-yl]-(5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl)-methanone

A suspension of 6-(1-methyl-1H-pyrazol-4-yl)pyridine-3-carboxylic acid (0.48 g) in thionyl chloride (5.0 ml) was stirred at room temperature for 2 hours. The volatile material was removed under reduced pressure to afford 6-(1-methyl-1H-pyrazol-4-yl)pyridine-3-carbonyl chloride as a solid, which was utilized without further purification.

A solution of 10,11-dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine (0.37 g) and diisopropylethylamine (0.61 g) in dichloromethane (25 ml) was cooled to 0 °C and a solution of 6-(1-methyl-1H-pyrazol-4-yl)pyridine-3-carbonyl chloride in dichloromethane (25 ml) was added portionwise. After 18 hours at room temperature, the reaction mixture was washed with water and a saturated aqueous sodium bicarbonate solution. The dichloromethane solution was dried over anhydrous sodium sulfate and filtered through a short column of hydrous sodium magnesium silicate and further eluted with several volumes of dichloromethane. The combined organic phase was concentrated on a hot plate with the gradual addition of hexane until crystallization occurred. After cooling, the crystals were collected by filtration to yield the title compound (0.31 g), m.p. 173-175 °C; MS, *m/z*: 370.3 $(M+H)^+$.

EXAMPLE 58

[4-(Pyrazol-1-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone

To a suspension of 4-(pyrazol-1-yl)benzoic acid (1.56 g) in dichloromethane (25 ml) was added oxalyl chloride (1.04 g) and one drop of dimethylformamide. The mixture was stirred at room temperature for 18 hours to yield a clear solution. The volatile material was removed under reduced pressure to afford 4-(pyrazol-1-yl)benzoyl chloride as a pale yellow solid (1.58 g), which was utilized without further purification.

The 4-(pyrazol-1-yl)benzoyl chloride (0.75 g) was added to a solution of 10,11-dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine (0.61 g) and diisopropylethylamine (0.47 g) in dichloromethane (25 ml). After 18 hours at room temperature, the reaction mixture was washed with water and a saturated aqueous sodium bicarbonate solution. The dichloromethane solution was dried over anhydrous sodium sulfate and filtered through a short column of hydrous sodium magnesium silicate and further eluted with several volumes of dichloromethane. The combined organic phase was concentrated on a hot plate with the gradual addition of hexane until crystallization occurred. After cooling, the crystals were collected by filtration to yield the title compound (0.90 g), m.p. 179-181 °C.

EXAMPLE 59

[4-(3-Methyl-pyrazol-1-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl)-methanone

To a suspension of 4-(3-methylpyrazol-1-yl)benzoic acid (1.84 g) in dichloromethane (25 ml) was added oxalyl chloride (1.16 g) and one drop of dimethylformamide. The mixture was stirred at room temperature for 18 hours and the volatile material was removed under reduced pressure. Dichloromethane was added, the solution filtered, and the solvent evaporated under reduced pressure to yield 4-(3-methylpyrazol-1-yl)benzoyl chloride as a yellow oil (1.76 g), which was utilized without further purification.

The 4-(3-methylpyrazol-1-yl)benzoyl chloride was added to an ice-cooled solution of 10,11-dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine (0.55 g) and diisopropylethylamine (0.44 g) in dichloromethane (25 ml). After stirring at room temperature for 18 hours, the reaction mixture was washed with water and a saturated aqueous sodium bicarbonate solution. The dichloromethane solution was dried over anhydrous sodium sulfate and filtered through a short column of hydrous sodium magnesium silicate and further eluted with several volumes of dichloromethane. The combined organic phase was concentrated on a hot plate with the gradual addition of hexane until crystallization occurred. After cooling, the title compound (0.90 g) was obtained as an amorphous solid, MS, *m/z*: 369 $(M+H)^+$.

EXAMPLE 60

[4-(4-Methyl-pyrazol-1-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl)-methanone

To a suspension of 4-(4-methylpyrazol-1-yl)benzoic acid (0.75 g) in dichloromethane (15 ml) was added oxalyl chloride (0.50 g) and one drop of dimethylformamide. The mixture was stirred at room temperature for 18 hours and the volatile material was removed under reduced pressure. The residue was dissolved in hexane and filtered through diatomaceous earth. Evaporation of the solvent in vacuo yielded 4-(4-methylpyrazol-1-yl)benzoyl chloride (0.77 g), which was used without further purification.

The 4-(4-methylpyrazol-1-yl)benzoyl chloride (0.72 g) was added to an ice-cooled solution of 10,11-dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine (0.60 g) and diisopropylethylamine (0.48 g) in dichloromethane (25 ml). After stirring at room temperature for 18 hours, the reaction mixture was washed with water and saturated aqueous sodium bicarbonate. The dichloromethane solution was dried over anhydrous sodium sulfate and filtered through a short column of hydrous sodium magnesium silicate and further eluted with several volumes of dichloromethane. The combined organic phase was concentrated on a hot plate with the gradual addition of hexane until crystallization occurred. After cooling, the crystals were collected by filtration to yield the title compound (0.75 g), m.p. 179-181 °C; MS *m/z*: 369 $(M+H)^+$.

EXAMPLE 61

[4-(3,5-Dimethyl-pyrazol-1-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl)-methanone

To a suspension of 4-(3,5-dimethylpyrazol-1-yl)benzoic acid (1.34 g) in dichloromethane (25 ml) was added oxalyl chloride (1.0 g) and one drop of dimethylformamide. The mixture was stirred at room temperature for 18 hours and the volatile material was removed under reduced pressure. The residue was dissolved in hexane and filtered through diatomaceous earth. Evaporation of the solvent in vacuo

yielded 4-(3,5-dimethylpyrazol-1-yl)benzoyl chloride (0.80 g), which was used without further purification.

The 4-(3,5-dimethylpyrazol-1-yl)benzoyl chloride (0.75 g) was added to an ice-cooled solution of 10,11-dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine (0.55 g) and diisopropylethylamine (0.42 g) in dichloromethane (25 ml). After stirring at room temperature for 18 hours, the reaction mixture was washed with water and saturated aqueous sodium bicarbonate. The dichloromethane solution was dried over anhydrous sodium sulfate and filtered through a short column of hydrous sodium magnesium silicate and further eluted with several volumes of dichloromethane. The combined organic phase was concentrated on a hot plate with the gradual addition of hexane until crystallization occurred. After cooling, the title compound (0.79 g) was obtained as an amorphous solid, MS *m/z*: 383 $(M+H)^+$.

EXAMPLE 62

(5H,11H-Pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-[4-(3-trifluoromethyl-pyrazol-1-yl)-phenyl]-methanone

A suspension of 4-(3-trifluoromethylpyrazolyl-1-yl)benzoic acid (1.45 g) in thionyl chloride (5.0 ml) was heated at reflux for 3 hours. The volatile material was removed under reduced pressure, the residue dissolved in dichloromethane, and filtered through diatomaceous earth. Evaporation of the solvent in vacuo yielded 4-(3-trifluoromethylpyrazol-1-yl)benzoyl chloride (1.45 g), which was used without further purification.

To a solution of 10,11-dihydro-5H-pyrrolo[2,1-c][1,4]-benzodiazepine (0.88 g) and diisopropylethylamine (0.66 g) in dichloromethane (50 ml) was added the 4-(3-trifluoromethylpyrazol-1-yl)benzoyl chloride (1.40 g). After stirring at room temperature for 18 hours, the reaction mixture was washed with water and saturated aqueous sodium bicarbonate. The dichloromethane solution was dried over anhydrous sodium sulfate and filtered through a short column of hydrous sodium magnesium silicate and further eluted with several volumes of dichloromethane. The combined organic phase was concentrated on a hot plate with the gradual addition of hexane until crystallization occurred. After cooling, the crystals were collected by filtration to yield

the title compound (1.70 g), m.p. 166-167 °C; MS, *m/z*: 423.3 $(M+H)^+$, 845.4 $(2M+H)^+$.

EXAMPLE 63

[4-(Imidazol-1-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone

A suspension of 4-(imidazol-1-yl)benzoic acid (0.90 g) in thionyl chloride (2.0 ml) was heated on a steam bath under argon for one hour. Evaporation of the volatile material under reduced pressure afforded a residue which crystallized upon the addition of hexane to yield the 4-(imidazol-1-yl)benzoyl chloride as the hydrochloride salt (1.17 g), m.p. 242-247 °C.

To a solution of 10,11-dihydro-5H-pyrrolo[2,1-c][1,4]-benzodiazepine (0.75), diisopropylethylamine (1.20 g), and 4-dimethylaminopyridine (0.1 g) in dichloromethane (50 ml) was added 4-(imidazol-1-yl)benzoyl chloride hydrochloride (1.12 g). After stirring at room temperature for 18 hours, the reaction mixture was washed with water and saturated aqueous sodium bicarbonate. The dichloromethane solution was dried over anhydrous sodium sulfate, filtered through a short column of hydrous sodium magnesium silicate, and further eluted with several volumes of dichloromethane. The combined organic phase was concentrated on a hot plate with the gradual addition of hexane until crystallization occurred. After cooling, the crystals were collected by filtration to yield the title compound (0.57 g), m.p. 171-172 °C; MS, *m/z*: 354 $(M+H)^+$.

EXAMPLE 64

[4-(4-Methyl-imidazol-1-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl)-methanone

To a suspension of 4-(4-methylimidazol-1-yl)benzoic acid (0.80 g) in dichloromethane (25 ml) was added oxalyl chloride (0.50 g) and one drop of dimethylformamide. The mixture was stirred at room temperature for 18 hours and the

volatile material was removed under reduced pressure to yield 4-(4-methylimidazol-1-yl)benzoyl chloride (1.02 g), which was utilized without further purification.

The 4-(4-methylimidazol-1-yl)benzoyl chloride (0.99 g) was added to an ice-cooled solution of 10,11-dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine (0.64 g) and diisopropylethylamine (0.60 g) in dichloromethane (25 ml). After stirring at room temperature for 18 hours, the reaction mixture was washed with water and saturated aqueous sodium bicarbonate. The dichloromethane solution was dried over anhydrous sodium sulfate, filtered through a short column of hydrous sodium magnesium silicate, and further eluted with several volumes of dichloromethane. The combined organic phase was concentrated on a hot plate with the gradual addition of hexane until crystallization occurred. After cooling, the title compound (0.52 g) was obtained as a solid, m.p. 140-145 °C; MS, *m/z*: 369 $(M+H)^+$.

EXAMPLE 65

4-Bromo-2-chloro-benzoic acid, methyl ester

Thionyl chloride (1.64 ml) was added dropwise to a suspension of 4-bromo-2-chlorobenzoic acid (6.92 g) in methanol, and heated to 60 °C for 2 hours. The solvent was removed in vacuo, the residue redissolved in ethyl acetate, and washed sequentially with 0.5 N sodium hydroxide (2x), water, and brine. The organic phase was dried over anhydrous sodium sulfate, and the solvent removed in vacuo to afford the title compound (7.8 g). ^{1}H NMR (300 MHz), (DMSO-d_6) δ: 3.87 (s,3H), 7.68-7.9 (m, 3H).

EXAMPLE 66

2-Chloro-4-(3-dimethylamino-propyn-1-yl)benzoic acid, methyl ester

To a stirred solution of 4-bromo-2-chlorobenzoic acid, methyl ester (18.69 g) in triethylamine (110 ml), was added 1-dimethylamino-2-propyne (12.1 ml), bis(triphenylphosphine)palladium(II) chloride (1.26 g), and copper(I) iodide (0.136 g). The mixture was heated slowly to 60 °C, and the temperature maintained for one hour.

The reaction was cooled to room temperature, filtered through diatomaceous earth, and the collected solid washed with ethyl acetate. The solvent was removed in vacuo, the resulting residue redissolved in ethyl acetate, and washed with water (3x). The combined organic extract was dried over anhydrous sodium sulfate, and the solvent removed in vacuo to give a crude product. The crude product was purified by column chromatography on silica gel (225 g), eluting with 40% ethyl acetate/hexane. After removing the solvent in vacuo, the title compound was obtained as a viscous oil (17.7 g), MS (+FAB), *m/z*: 252 $(M+H)^+$.

EXAMPLE 67

2-Chloro-4-(3-dimethylamino-2-propen-1-on-1-yl)-benzoic acid, methyl ester

Gradually, 3-chloroperoxybenzoic acid (10.76 g) was added to a solution of 2-chloro-4-(3-dimethylamino-propyn-1yl)-benzoic acid, methyl ester (15.07 g in dichloromethane (40 ml), at a rate to maintain the reaction temperature at -20 °C. The mixture was stirred for 10-15 minutes. The resulting N-oxide was purified by chromatography on Activity Grade I basic alumina (215 g), eluting with 10% methanol/dichloromethane. The solvent was evaporated in vacuo between 12 to 18 °C. The resulting residue was dissolved in methanol (100 ml) and heated at 60-65 °C with stirring for 18 hours. After removing the solvent in vacuo, and the product was purified by column chromatography on silica gel (190 g), eluting with 70% ethyl acetate/hexane. Trituration with diethyl ether containing some hexane afforded the title compound as a solid (5.68 g), m.p. 92-96 °C.

EXAMPLE 68

2-Chloro-4-(1H-pyrazol-3-yl)-benzoic acid, methyl ester

To a suspension of 2-chloro-4-(3-dimethylamino-2-propen-1-on-1-yl)-benzoic acid, methyl ester (13.67g) in ethanol (53 ml) was added hydrazine monohydrochloride (7.0 g). The mixture was heated in an oil bath at 75-80 °C for one hour. The solvent was removed in vacuo. The resulting residue was dissolved in ethyl acetate, washed

with water and brine, dried over anhydrous sodium sulfate, and the solvent removed in vacuo to yield the title compound as a crude solid (12 g). A purified sample had a melting point of 130-131 °C.

EXAMPLE 69

2-Chloro-4-(1-methyl-1H-pyrazol-3-yl)-benzoic acid, methyl ester

To a suspension of hexane washed sodium hydride (3.05 g, 60% dispersion) in dimethylformamide (6 ml) under nitrogen was added a solution of 2-chloro-4-(1H-pyrazol-3yl)-benzoic acid, methyl ester (12.0 g) in dimethylformamide (30 ml) over a period of 15 minutes. The mixture was stirred at room temperature for 30 minutes. Iodomethane (9.5 ml) was added dropwise over 15 minutes. The mixture was allowed to stir at room temperature for 45 minutes. Additional iodomethane (5.16 ml) was added, and the reaction stirred another 75 minutes. The reaction was diluted with a small quantity of water, and concentrated in vacuo. The residue was diluted with water (500 ml) and extracted with a small quantity of ethyl acetate (5x). The combined organic phase was evaporated in vacuo to afford a crude product (13.48 g). The crude product was purified by column chromatography on silica gel (195 g) eluting with 15% ethyl acetate/hexane to afford the pure 1-methyl regioisomer (4.29 g), followed by a mixture of the 1-methyl and 2-methyl regioisomers (4.6 g). The mixture of isomers was triturated with hexane three times to give an additional sample of the pure 1-methyl regioisomer (2.55 g), m.p. 66.5-67 °C; MS (+FAB), *m/z*: 251 $(M+H)^+$.

EXAMPLE 70

2-Chloro-4-(1-methyl-1H-pyrazol-3-yl)-benzoic acid

To a solution of 2-chloro-4-(1-methyl-1H-pyrazol-3-yl)-benzoic acid, methyl ester (6.85 g) in methanol (32 ml) was added 2.5 N sodium hydroxide solution (15.3 ml). The reaction was heated to 50 °C for one hour. The solvent was removed in vacuo, and the residue dissolved in water (250 ml), cooled in an ice bath, and acidified with 2N hydrochloric acid (24 ml). The resulting precipitate was filtered and dried to give a colorless solid (6.3 g) m.p. 232-233 °C; MS (+FAB), *m/z*: 236 $(M+H)^+$.

EXAMPLE 71

[2-Chloro-4-(1-methyl-1H-pyrazol-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c]-[1,4]benzodiazepine-10-yl)-methanone

Well powdered 2-chloro-4-(1-methyl-1H-pyrazol-3-yl)-benzoic acid (6.3 g) and dimethylformamide (2.16 ml) were suspended under nitrogen in a mixture of tetrahydrofuran (70 ml) and dichlormethane (15 ml). A solution of oxalyl chloride (2.43 ml) in dichloromethane (5 ml) was added dropwise, and the reaction stirred for one hour. The resulting suspension of 2-chloro-4-(1-methyl-1H-pyrazol-3-yl)-benzoyl chloride was utilized without further purification.

To a suspension of 10,11-dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine (4.93 g) in dichloromethane (15 ml) was added diisopropylethylamine (7 ml). The suspension of the freshly prepared acid chloride was gradually added over 15 minutes under a positive flow of nitrogen. The slightly warm reaction mixture was stirred under nitrogen for 50 minutes. After stirring one hour, the mixture was concentrated in vacuo. The residue was dissolved in dichloromethane, washed with water, 5% sodium bicarbonate, and water. The organic phase was washed with brine, dried over anhydrous sodium sulfate, and the solvent removed in vacuo to give a crude product (10.95 g). The crude product was purified by column chromatography on silica gel (200 g), loading the column with 25% ethyl acetate/hexane. Less polar impurities were eluted with 25-30% ethyl acetate/hexane. The product was eluted with 30-40% ethyl acetate/hexane to afford a pure sample (7.42 g); which, after seeding with crystals, was triturated with diethyl ether containing some hexane for 24 hours. Filtration afforded the title compound as a crystalline solid (6.88 g), m.p. 148.5-150 °C; MS (EI), *m/z*: 402 $(M)^+$.

EXAMPLE 72

2-chloro-4-(2-methyl-1H-pyrazol-3-yl)-benzoic acid, methyl ester

The title compound was prepared in the same manner as described in Example 68, employing methyl-2-chloro-4-(3-dimethylamino-2-propene-1-one)-benzoate (0.8 g) and methylhydrazine (0.319 ml). The major 2-methyl regioisomer was isolated by

column chromatography on silica gel, ^{1}H NMR (300 MHz), (DMSO-d_6) δ: 3.87 (s, 3H), 3.89 (s, 3H), 6.58 (d, 1H), 7.5 (d, 1H) 7.62-7.93 (m, 3H).

EXAMPLE 73

2-Chloro-4-(2-methyl-1H-pyrazol-3-yl)-benzoic acid

The title compound was prepared in the same manner as described in Example 70, employing 2-chloro-4-(2-methyl-1H-pyrazol-3yl)-benzoic acid, methyl ester (0.464 g) and 2.5N sodium hydroxide (1.04 ml). ^{1}H NMR (300 MHz), (DMSO-d_6) δ: 3.89 (s, 3H), 6.56 (d, 1H), 7.49 (d, 1H), 7.59-7.90 (m, 3H)

EXAMPLE 74

[2-Chloro-4-(2-methyl-1H-pyrazol-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c] [1,4]benzodiazepine-10-yl)-methanone

The title compound was prepared in the same manner as described in Example 71, Employing 2-chloro-4-(2-methyl-1H-pyrazol-3yl)-benzoic acid (3.98 g) yielded the corresponding acid chloride, and acylation with 10,11-dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine (0.293 g) yielded the title compound as a foam, m.p. 78-79 °C; MS (EI), *m/z*: 402 $(M)^+$.

EXAMPLE 75

2-Chloro-4-cyanobenzoic acid, methyl ester

2-chloro-4-aminobenzoic acid, methyl ester (13.95 g) was suspended in a mixture of water (65 ml) and concentrated hydrochloric acid (15.7 ml). After stirring at room temperature for 10 minutes, the suspension was cooled to 0 °C. A solution of sodium nitrite (5.71 g) in water (37 ml) was gradually added over 20 minutes, maintaining a reaction temperature of 0 °C. After stirring at 0 °C for 35 minutes, the reaction mixture was partially neutralized by the addition of solid sodium carbonate (3.16 g) to afford a cold solution of the diazonium salt.

To a pre-cooled solution of copper(I) cyanide (8.4 g) and sodium cyanide (9.19 g) in water (112 ml) was gradually added the above solution of diazonium salt over a 45-50 minute period. The diazonium salt solution was maintained at 0 °C during the addition. The resulting mixture was stirred for 18 hours at room temperature. A precipitate was filtered, air-dried, dissolved in ethyl acetate (250 ml), and filtered to remove insoluble matter. The organic phase was dried over anhydrous magnesium sulfate, and the solvent removed in vacuo to afford a crude product as a brown solid (13.2 g). The crude product was purified by column chromatography on silica gel (250 g), eluting with 5-10% ethyl acetate/hexane to yield the title compound (10.9 g) as a solid, m.p. 90-92 °C; MS (EI), *m/z*: 195 $(M)^+$.

EXAMPLE 76

2-Chloro-4-cyanobenzoic acid

To a stirred solution of 2-chloro-4-cyanobenzoic acid, methyl ester (24.3 g) in methanol (150 ml) was added 2.5N sodium hydroxide (54.5 ml). After stirring at room temperature. for 45 minutes, the solvent was removed in vacuo. The residue was dissolved in water, cooled in an ice bath, and made acidic with 2N hydrochloric acid (14 ml). The resulting precipitate was filtered and dried in vacuo to yield the title compound as a solid (22.55g) m.p. 154-158 °C.

EXAMPLE 77

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

To a cooled suspension of 2-chloro-4-cyanobenzoic acid (9.1 g) in a mixture of dichloromethane (40 ml) and dimethylformamide (3.88 ml) was added dropwise a solution of oxalyl chloride (4.6 ml) in dichloromethane (10 ml) at 0 °C. The stirred reaction was allowed to warm to room temperature over a one hour period. A cloudy solution of 2-chloro-4-cyanobenzoyl chloride was utilized without further purification.

To a stirred suspension of 10,11-dihydro-5H-pyrrolo[2,1-c][1,4] benzodiazepine (7.32 g) and diisopropylethylamine (13.6 ml) in dichloromethane (35

ml) was added under nitrogen the cloudy solution of 2-chloro-4-cyanobenzoyl chloride. After one hour at room temperature, the mixture was diluted with dichloromethane and washed sequentially with water, 5% sodium bicarbonate, and 50% saturated brine, After drying over anhydrous sodium sulfate, the solvent was removed in vacuo to afford a crude product (18.0 g). Purification by column chromatography on silica gel (250 g), eluting with 20% ethyl acetate/hexane, followed by 25% ethyl acetate/hexane, yielded the title compound (13.56 g) as a straw yellow foam, MS (EI), *m/z*: 347 $(M)^+$.

EXAMPLE 78

3-Chloro-4-(5H,11H-Pyrrolo[2,1-c][1,4]benzodiazepine-10-carbonyl)-benzoic acid

To a suspension of 3-chloro-4-(5H,11H-pyrrolo-[2,1-c][1.4]-benzodiazepine-10-carbonyl)-benzonitrile (90.72 g) in ethanol was added 10 N sodium hydroxide (1.02 ml) and the mixture heated under reflux for two hours. The solvent was removed in vacuo, the residue dissolved in water, and made acidic with 2 N hydrochloric acid (4.7 ml). The resulting precipitate was extracted with ethyl acetate, and the organic phase dried over anhydrous sodium sulfate. After removing the solvent in vacuo, a foam was triturated with diethyl ether for 18 hours and filtered to give a crude product (0.69g). The crude product was purified by treatment with activated charcoal in methanol. Crystallization from methanol/ether afforded the title compound as a purified solid (0.29 g), m.p. 198-199 °C; MS (EI), *m/z*: 366 $(M)^+$.

EXAMPLE 79

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

Concentrated sulfuric acid (70 ml) was added to 3-chloro-4-(5H,11H-pyrrolo-[2,1-c][1.4]benzodiazepine-10-carbonyl)-benzonitrile (12.85 g). The mixture was stirred at 60 °C for 3 hours, followed by stirring at room temperature for 18 hours. The reaction mixture was poured over ice and neutralized at 0 °C, with 30% ammonium hydroxide (184 ml). The resulting suspension was extracted with ethyl acetate. The aqueous mixture was filtered, and reextracted with ethyl acetate. The combined organic

phase was dried over anhydrous sodium sulfate, and the solvent removed in vacuo. The residue was triturated with a mixture of diethyl ether (50-60 ml) and a small quantity of ethyl acetate. Filtration of the precipitate afforded the title compound as a crystalline solid (10.44 g), m.p. 211-212 °C; MS (EI), *m/z*: 365 $(M)^+$.

EXAMPLE 80

N-(1-Dimethylaminoethylene)-3-chloro-4-(5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepine-10-carbonyl)-benzamide

A suspension of 3-chloro-4-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepine-10-carbonyl)-benzamide (5.48 g) and dimethylacetamide dimethyl acetal (10.97 ml) was heated at 90 °C for 20 minutes. The excess reagent was removed under reduced pressure, and the title compound utilized without further purification, MS (EI), *m/z*: 434 $(M)^+$.

EXAMPLE 81

[2-Choro-4-(5-methyl-2H-[1,2,4]triazol-3-yl)phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepine-10-carbonyl)-methanone

To a solution of N-(1-dimethylaminoethylene)-3-chloro-4-(5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepine-10-carbonyl)-benzamide (3.01 g) in acetic acid (4 ml) was added a solution of anhydrous hydrazine (0.435 ml) in acetic acid (4 ml). The reaction mixture was stirred at between 85-90 °C for 45 minutes. After removing the acetic acid in vacuo, the reaction mixture was diluted with water (35-40 ml), neutralized to pH 7.0 with aqueous sodium bicarbonate, and extracted with ethyl acetate. The organic extract was washed with brine, dried over anhydrous sodium sulfate, and the solvent removed in vacuo to afford a crude product (2.68 g). Purification of the crude product by column chromatography on silica gel (45 g), eluting with 70% ethyl acetate/hexane, afforded a purified product (2.5g), which, after trituration with diethyl ether, yielded the title compound as a solid (2 g), m.p. 211-212 °C; MS (EI), *m/z*: 403 $(M)^+$.

EXAMPLE 82

N-(Dimethylaminomethylene)-3-chloro-4-(5H,11H-pyrrolo[2,1-c][1,4] benzodiazepine-10-carbonyl)-benzamide

The title compound was prepared in the same manner as described in Example 80, employing 3-chloro-4-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepine-10-carbonyl)-benzamide (1.83 g) and dimethylformamide dimethylacetal (5.3 ml), MS (EI), *m/z*::420 $(M)^+$.

EXAMPLE 83

[2-Chloro-4-(2H-1,2,4-triazol-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl)-methanone

The title compound was prepared in the same manner as described in Example 81, employing N-(dimethylaminomethylene)-3-chloro-4-(5H,11H-pyrrolo[2,1-c[1,4]benzo-diazepine-10-carbonyl)-benzamide (2.53 g) and hydrazine (0.38 ml), m.p. 174-177 °C; MS (EI), *m/z*: 389 $(M)^+$.

EXAMPLE 84

[2-Chloro-4-(2-methyl-2H-[1,2,4]triazol-3-yl)-phenyl]-(5H,11H-pyrrolo [2,1-c][1,4]benzodiazepin-10-carbonyl)-methanone

The title compound was prepared in the same manner as described in Example 48, using N-(dimethylaminomethylene)-3-chloro-4-(5H,11H-pyrrolo[2,1-c[1,4]benzodiazepin-10-carbonyl)-benzamide (0.572 g), and methylhydrazine (0.149 ml). m.p. 141-143°C. MS (EI): 403 $(M)^+$.

EXAMPLE 85

4-[(2,5-Dimethyl-2H-[1,2,4]triazol-3-yl)-2-chloro-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-carbonyl)-methanone

The title compound was prepared in the same manner as described in Example 48, using N-(1-dimethylaminoethylene)-3-chloro-4-(5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-carbonyl)-benzamide (0.51 g) and methylhydrazine (0.125 ml). m.p. 197-199°C. MS (EI): 417 $(M)^+$.

EXAMPLE 86

[2-Chloro-4-(1H-tetrazol-5-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4] benzodiazepin-10-yl)- methanone

To a solution of 3-chloro-4-(5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepine-10-carbonyl)-benzonitrile (0.348 g) in dimethylformamide (2 ml) was added sodium azide (0.078 g) and ammonium chloride (0.065 g). The mixture was heated to 100°C for 18 hours.

Most of the dimethylformamide was removed in vacuo. The residue dissolved in water (approximately 8 ml) and basified to pH 9.0 with 2.5N sodium hydroxide (0.6 ml) and extracted with ethyl acetate. The aqueous extract was acidified with 2N hydrochloric acid (1.1 ml), reextracted with ethyl acetate, dried over anhydrous sodium sulfate and the solvent removed in vacuo to give crude product (0.350g) as an oil. The oily product was triturated with diethyl ether, filtered through acid treated silica gel, and eluted with 40% ethyl acetate/hexane to give purer sample. This was further triturated with diethyl ether , and filtered to give a sample (0.88g) m.p. 218-220°C. MS (+FAB) 391 $(M+H)^+$.

EXAMPLE 87

[2-Chloro-4-(3-methyl-pyrazol-1-yl)-phenyl]-(3-dimethylaminomethyl-5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone

To a stirred solution of [2-chloro-4-(3-methyl-pyrazol-1-yl)-phenyl]-(5H,11H-pyrrolo-[2,1-c][1,4]benzodiazepin-10-yl)-methanone (1.61 g), N, N, N', N', tetramethyldiamino-methane (0.82 g), and glacial acetic acid (0.48 g) in methanol (25 ml) was added a solution of 37% aqueous formaldehyde (4 ml). The mixture was warmed to 40 °C for 10 minutes. After stirring one hour at room temperature, the reaction was concentrated in vacuo, redissolved in dichloromethane, and extracted sequentially with aqueous sodium bicarbonate and water (4x). The organic phase was dried over anhydrous sodium sulfate, and filtered through a plug of silica gel, eluted with ethyl acetate. Evaporation of the solvent in vacuo afforded an oil, which on trituration with hexane yielded 0.36 g of the title compound as a colorless powder, m.p. 100-102 °C; MS (+FAB), *m/z*: 482 $(M+Na)^+$, 460 $(M+H)^+$.

EXAMPLE 88

(3-Bromo-5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-[2-chloro-4-(3-methyl-pyrazol-1-yl)-phenyl]-methanone

To a stirred pre-cooled solution of [2-chloro-4-(3-methyl-pyrazol-1-yl)-phenyl]-(5H, 11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (1.61 g) in dichloromethane (25 ml) was added solid N-bromosuccinimide (0.712 g) over 10 minutes at -78 °C. The reaction was allowed to warm to -40 °C over thirty minutes. The mixture was diluted with dichloromethane, and extracted sequentially with saturated aqueous sodium bicarbonate (2 x 100 ml) and water (100 ml). The organic phase was dried over anhydrous sodium sulfate, filtered through a plug of silica gel, and evaporated in vacuo to a residue. Crystallization from diethyl ether yielded 1.47 g of the title compound as a colorless solid, m.p. 148-149 °C (dec); MS (EI), *m/z*: 480 $(M)^{+\cdot}$.

EXAMPLE 89

(4-Bromo-2-chlorophenyl)-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone

Dimethylformamide (1 drop) was added to a solution of 4-bromo-2-chlorobenzoic acid (2.20 g) in anhydrous tetrahydrofuran (20 ml). Oxalyl chloride (1.46 g) was added and the mixture was warmed to reflux. The resultant solution was cooled to ambient temperature before being evaporated to dryness to give crude 4-bromo-2-chlorobenzoyl chloride as a gold viscous liquid, which was used without further purification.

To a mixture of 10,11-dihydro-5H-pyrrolo[2,1-c][1,4]-benzodiazepine (1.44 g) and triethylamine (0.95 g) in dichloromethane (40 ml), cooled in an ice bath, was added dropwise a solution of 4-bromo-2-chlorobenzoyl chloride (2.42 g) in dichloromethane (20 ml). The cooling bath was removed and after stirring for 22 hours, the reaction mixture was washed sequentially with water, saturated aqueous sodium bicarbonate, 0.5 N hydrochloric acid and water. The dichloromethane solution was dried over anhydrous sodium sulfate, filtered, then evaporated in vacuo to dryness to yield an off-white foam. Purification by flash chromatography on silica gel eluting with hexane-ethyl acetate (2:1) resulted in a white foam (3.02 g), m.p. 77-80 °C, MS *m/z*: 400 $(M)^+$.

EXAMPLE 90

[2-Bromo-4-(3-methyl-pyrazol-1-yl)-phenyl]-(5H,11H)-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone

Step a) 4-Fluoro-2-bromobenzoyl chloride: Dimethylformamide (2 drops) was added to a solution of 4-fluoro-2-bromobenzoic acid (4.91 g) in anhydrous tetrahydrofuran (55 ml). Oxalyl chloride (3.41 g) was added and the mixture was warmed to reflux. The resultant solution was cooled to room temperature, evaporated in vacuo to give the crude acid chloride as a gold viscous liquid, which was used without further purification.

Step b) (4-Fluoro-2-bromophenyl)-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone: A solution of 4-fluoro-2-bromobenzoyl chloride (5.32 g) from step a), in dichloromethane (35 ml), was added dropwise to a solution of 10,11-dihydro-5H-pyrrolo[2,1-c][1,4]-benzodiazepine (3.44 g) and triethylamine (2.27 g) in dichloromethane (80 ml) and cooled in an ice bath. The cooling bath was removed and after stirring for 16 hours, the reaction mixture was washed sequentially with water, saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride. The dichloromethane solution was dried over anhydrous magnesium sulfate, filtered and evaporated in vacuo to give a pale purple foam. Purification by flash chromatography on silica gel eluting with hexane-ethyl acetate (1:1) resulted in the intermediate (4-fluoro-2-bromophenyl)-(5H,11H-pyrrolo[2,1-c] [1,4]benzodiazepin-10-yl)-methanone as a tan foam (6.91 g), MS *m/z*: 384 $(M)^+$. This material was used without further purification in the next step.

Step c) [2-Bromo-4-(3-methyl-pyrazol-1-yl)-phenyl]-(5H,11H)-pyrrolo[2,1-c] [1,4]benzodiazepin-10-yl)-methanone: A dispersion of 60% sodium hydride in oil (0.20 g) was washed with hexane, and then suspended in dimethylformamide (15 ml). To this suspension was added 3-methylpyrazole (0.41 g). When hydrogen gas evolution subsided, (4-fluoro-2-bromophenyl)-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (1.74 g) from step b) was added. The reaction mixture was heated to 130 °C for 6 hours. After the reaction mixture was cooled to room temperature, poured into a 50% saturated aqueous sodium chloride solution and extracted with ethyl acetate. The ethyl acetate solution was dried over anhydrous magnesium sulfate, filtered and evaporated in vacuo to afford a brown oil. Purification by flash chromatography on silica gel eluting with hexane-ethyl acetate (1:1) gave a colorless solid (0.75 g). Recrystallization from methanol gave an off-white crystalline solid (0.53 g), m.p. 141-142.5°C, MS *m/z*: 446 $(M)^+$.

EXAMPLE 91

(2,4-Difluoro-phenyl)-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone

Step a) 2,4-Difluorobenzoyl chloride: A suspension of 2,4-difluorobenzoic acid (3.6 g) containing a few drops of dimethylformamide in dichloromethane (40 ml) was

treated dropwise under nitrogen with oxalyl chloride (2.4 ml). After gas evolution subsided, the reaction mixture was refluxed for an additional 15 minutes. The solution was evaporated to dryness in vacuo and the residue was utilized without further purification.

Step b) (2,4-Difluorophenyl)-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone: To a solution of the crude 2,4-difluorobenzoyl chloride acid chloride of Step a in dichloromethane under nitrogen was added solid 10,11-dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine amine (2.0 g) and diisopropylethylamine (3.4 ml). The reaction mixture turned yellow-orange. After stirring at room temperature for 10 the reaction mixture was washed with water, 1 N hydrochloric acid, 1 N sodium hydroxide and brine. The organic phase was dried over anhydrous sodium sulfate and evaporated to dryness to give a brown solid. The crude product was purified by column chromatography on silica gel (Merck-60) with 20% ethyl acetate -hexane to provide 2.9 g of the title compound as a white foam.
MS (EI, *m/z*): 324 $(M)^+$.

EXAMPLE 92

[2-Fluoro-4-(3-methyl-pyrazol-1-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl)-methanone

A suspension of hexane washed 60% sodium hydride (0.31 g) in dry dimethylformamide was treated dropwise with 3-methylpyrazole (0.62 ml) under nitrogen at room temperature. Stirring was continued until the gas evolution subsided (10 minutes). In one portion (2,4-difluorophenyl)-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (2.5 g) from step b) of Example 91 was added and stirring was continued until a clear solution was attained. The mixture was heated in a preheated oil bath at 130°C for one hour. After cooling, the mixture was partitioned between water and ethyl acetate. The organic extracts were dried over anhydrous sodium sulfate and evaporated to dryness. The crude product was purified by flash column chromatography on silica gel (Merck-60) eluting with 20% ethyl acetate -hexane to yield 0.82 g of the title product as a foam which was crystallized by sonication from ethanol/hexane, m.p. 192-193 °C. MS (EI) *m/z*: 386 $(M)^+$.

EXAMPLE 93

Methyl 4-(3-methyl-pyrazol-1-yl)-2-trifluoromethyl-benzoate

Step a) Methyl 4-fluoro-2-trifluoromethylbenzoate: A suspension of 4-fluoro-2-trifluoromethylbenzoic acid (25.6 g) and a few drops of dimethylformamide in dichloromethane (250 ml) was treated dropwise under nitrogen with oxalyl chloride (11.3 ml). After gas evolution subsided, the reaction mixture was refluxed for an additional 15 minutes. The reaction was cooled and methanol (50 ml) was added. After stirring for 2 hours, the reaction was concentrated in vacuo, and the residue was partitioned between dichloromethane and water. The organic phase was washed with saturated sodium bicarbonate, dried over anhydrous sodium sulfate, and evaporated to dryness to give 18.0 g of the title compound as a golden oil. MS, (EI) *m/z*: 222 $(M)^+$.

The aqueous layer was acidified with 2 N hydrochloric acid to give a colorless solid which was collected by filtration to give 7.5 g of the starting benzoic acid.

Step b) Methyl 4-(3-methyl-pyrazol-1-yl)-2-trifluoromethyl-benzoate: A suspension of hexane washed 60% sodium hydride (3.85 g) in dry dimethylformamide (150 ml) was treated with the dropwise addition of a solution of 3-methylpyrazole (7.75 ml) in dimethylformamide (50 ml) under nitrogen at room temperature. Stirring was continued until the gas evolution subsided (10 minutes). A solution of methyl 4-fluoro-2-trifluoromethylbenzoate (17.8 g) from step a) in dimethylformamide (50 ml) was added dropwise to the clear solution. After stirring for 30 min. at room temperature the reaction was quenched with saturated ammonium chloride and extracted with ethyl acetate. The organic extracts (3x) were dried over anhydrous sodium sulfate and evaporated to dryness. The crude product was purified by flash column chromatography on silica gel (Merck 60) with a dichloromethane-hexane gradient (50% - 75%) to give 13.6 g of the title product as a colorless solid. m.p. 59-61°C MS (EI, m/z): 284 $(M)^+$.

EXAMPLE 94

4-(3-Methyl-pyrazol-1-yl)-2-trifluoromethyl-benzoic acid

Methyl 4-(3-methyl-pyrazol-1-yl)-2-trifluoromethyl-benzoate (1.19 g) from Example 93, step b) was dissolved in methanol (10 ml) and a solution of 2.5 N sodium hydroxide (3.3 ml) was added. The reaction was heated at reflux for 90 minutes, cooled to room temperature and concentrated in vacuo to dryness. The residue was partitioned between ethyl acetate and 1 N hydrochloric acid. The combined organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo to give 1.14 g of the title compound as a colorless solid. MS (FAB) *m/z*: 271 $(M+H)^+$.

EXAMPLE 95

[4-(3-Methylpyrazol-1-yl)-2-trifluoromethylphenyl]-(5H,11H-pyrazolo[5,1-c]-[1,4]benzodiazepin-10-yl)-methanone

A solution of 4-(3-methyl-pyrazol-1-yl)-2-trifluoromethylbenzoic (0.26g) from Example 94 in tetrahydrofuran (5 ml) was treated with dimethylformamide (0.020 ml) followed by oxalyl chloride (0.090 ml). The solution was stirred at room temperature until gas evolution stopped and then the solution was warmed to reflux for 10 minutes. The sample was cooled to room temperature, concentrated to a solid and the solid was dissolved in tetrahydrofuran (25 mL). this solution was added to a solution (5H-10,11-dihydropyrazolo [5,1-c][1,4]benzodiazepine (0.143 g) and triethylamine (0.150 ml) in tetrahydrofuran (20 ml). The solution was stirred overnight at room temperature. A precipitate formed. The sample was diluted with dichloromethane to dissolve the precipitate and then the sample was concentrated in vacuo to about 1/3 of the original volume. The sample was partitioned between dichloromethane and saturated aqueous ammonium chloride. The sample was extracted with dichloromethane and the organic layers were pooled, dried over anhydrous sodium sulfate, filtered and concentrated to an oil. The oil was flash chromatographed on silica gel using a gradient of 40% ethyl acetate/hexanes to 100% ethyl acetate affording the title compound as a foam (0.30 g). A portion of this material was recrystallized from acetone/ hexanes to give heavy plates m.p. 100-102°C, MS *m/z*: 437 $(M)^+$.

EXAMPLE 96

2-Chloro-4-(3-methyl-1H-pyrazol-1-yl)-benzoic acid methyl ester and 2-chloro-4-(5-methyl-1H-pyrazol-1-yl)-benzoic acid methyl ester

A suspension of hexane washed potassium hydride (0.424 g) in dimethylformamide (5 ml) was treated in one portion with 3-methyl pyrazole (0.85 ml) while stirring. After the gas evolution ceased, 2-chloro-4-fluorobenzoic acid methyl ester (2.0 g, 10.6) was added to the clear solution and heated at 130°C for 15 minutes. The reaction mixture was cooled to room temperature and partitioned between ethyl acetate and brine. The organic phase was washed with water, brine, and dried over anhydrous sodium sulfate. Removal of solvent in vacuo afforded 2.2 g of a yellow oil. (Note: 20% hydrolysis of the ester was detected by analysis of the NMR spectrum of the crude product). The desired regioisomer 2-chloro-4-(3-methyl-1H-pyrazol-1-yl)-benzoic acid methyl ester was isolated from the other isomer (described below) by flash column chromatography on silica gel (Merck 60) eluting with dichloromethane-hexane 2:1) to give 1.55 g of the title compound as a colorless solid. MS (EI *m/z*: 250/252 (M)+.

The 5-regioisomer, namely 2-chloro-4-(5-methyl-1H-pyrazol-1-yl)-benzoic acid methyl ester was isolated from the above flash column chromatography on silica gel (Merck 60) by further eluting with dichloromethane-hexane 2:1 to give 0.20 g of the product as a colorless solid. MS (EI), *m/z*: 250/252 $(M)^+$.

EXAMPLE 97

2-Chloro-4-(3-methyl-1H-pyrazol-1-yl)-benzoic acid

A solution of 2-chloro-4-(3-methyl-1H-pyrazol-1-yl)-benzoic acid methyl ester (1.42 g) from Example 96 and 6 ml of 1 M aqueous lithium hydroxide in tetrahydrofuran (20 ml) was stirred for 18 hours at room temperature. The reaction mixture was partitioned between ethyl acetate and 1 N hydrochloric acid. The organic layer was washed with water, brine and was dried over anhydrous sodium sulfate. Evaporation of the solvent in vacuo afforded 1.05 g of the title compound as a colorless solid. m.p. 192-193°C. MS (EI), *m/z*: 236/238 $(M)^+$.

EXAMPLE 98

(2,6-Dichloropyridin-3-yl)(5H,11H-Pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)- methanone

A solution of 2,6-dichloronicotinic acid (3.84 g), oxalyl chloride (2.0 g), and 1 drop of dimethylformamide in dichloromethane (25 ml), was stirred at room temperature for 18 hours. The solution was concentrated in vacuo to give 3.50 g of 2,6-dichloronicotinyl chloride which was added portionwise in dichloromethane (25 ml) to an ice cooled solution of 10,11-dihydro-5H-pyrrolo[2,1-c][1,4]-benzodiazepine (2.15 g) and diisopropylethylamine (2.03 g) in dichloromethane (50 ml). The mixture was stirred at room temperature for 18 hours and washed with saturated aqueous sodium bicarbonate. The organic phase was dried over anhydrous sodium sulfate and filtered through a short column of anhydrous sodium magnesium silicate. The combined organic phase was concentrated on a hot plate with the gradual addition of hexane until crystallization occurred. After cooling, the crystals were collected by filtration to yield 2.65 g of the title as a an amorphous solid. m.p. 115-130 °C. MS, *m/z*: 358.1 $(M+H)^+$.

EXAMPLE 99

(2-Chloro-6-pyrazol-1-yl-pyridin-3-yl)-(5H,11H-pyrrolo[2,1-c][1,4] benzodiazepin-10-yl)-methanone

To a suspension of 60% sodium hydride in oil (0.1 g) in dimethylformamide (25 ml) was added dropwise pyrazole (0.15 g). After hydrogen gas evolution ceased, (2,6-dichloropyridin-3-yl)(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (0.67 g) was added and the reaction mixture was heated in a sand bath at 110 °C for 18 hours. The mixture was poured onto ice, diluted with brine, and extracted with dichloromethane. The combined extracts were dried over anhydrous sodium sulfate and filtered through a short column of anhydrous sodium magnesium silicate. The solution was concentrated in vacuo and triturated with diethyl ether to give 0.18 g of the title compound as a colorless solid, m.p. 133-135 °C. MS *m/z*: 390.8 $(M+H)^+$, 779.1 $(2M+H)^+$.

EXAMPLE 100

[2-Chloro-6-(3-methylpyrazol-1-yl)-pyridin-3-yl]-(5H,11H-pyrrolo[2,1-c] [1,4]benzodiazepin-10-yl)-methanone

To a suspension of 60% sodium hydride in oil (0.1 g) in dimethylformamide (25 ml) was added dropwise 3-methylpyrazole (0.15 g). After hydrogen gas evolution ceased, (2,6-dichloropyridin-3-yl)(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (0.67 g) was added and the reaction mixture was heated in a sand bath at 110 °C) for 18 hours. The mixture was poured onto ice, diluted with brine, and extracted with dichloromethane. The combined extracts were dried over anhydrous sodium sulfate and filtered through a short column of anhydrous sodium magnesium silicate. The crude product was purified by preparative hplc (Dynamax c60 silica cartridge) eluting with 40% ethyl acetate in hexanes to give 0.21 g of colorless crystals, m.p. 171-172 °C. MS, *m/z*: 404.2 $(M+H)^+$, 807.1 $(2M+H)^+$.

EXAMPLE 101

[2-Chloro-6-(4-methylpyrazol-1-yl)-pyridin-3-yl](5H,11H- pyrrolo[2,1-c] [1,4]benzodiazepin-10-yl)-methanone

To a suspension of 60% sodium hydride in oil (0.1 g) in dimethylformamide (25 ml) was added dropwise 3-methylpyrazole (0.45 g). After hydrogen gas evolution ceased, (2,6-dichloropyridin-3-yl)(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone, (1.79 g) was added and the reaction mixture was heated in a sand bath at 110 °C for 18 hours. The mixture was poured onto ice, diluted with brine, and extracted with dichloromethane. The combined extracts were dried over anhydrous sodium sulfate and filtered through a short column of anhydrous sodium magnesium silicate. The crude product was purified by preparative hplc (Dynamax c60 silica cartridge) eluting with 40% ethyl acetate in hexanes to give 0.26 g of colorless crystals, m.p. 155-156 °C, MS, *m/z*: 404.2 $(M+H)^+$, 807.0 $(2M+H)^+$.

EXAMPLE 102

[2-Chloro-4-(3-methyl-1,2,4-triazol-1-yl)-phenyl](5H,11H-pyrrolo[2,1-c]-[1,4]benzodiazepin-10-yl)-methanone

To a suspension of 60% sodium hydride in oil (0.3 g) in dimethylformamide (50 ml) was added dropwise 3-methyl-1,2,4-triazole (0.45 g). After hydrogen gas evolution ceased, 2-chloro-4-fluorophenyl-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepine-10-yl)-methanone (1.70 g) was added and the reaction mixture was heated in a sand bath at 110 °C for 18 hours. The mixture was poured onto ice, diluted with brine, and extracted with dichloromethane. The combined extracts were dried over anhydrous sodium sulfate and filtered through a short column of anhydrous sodium magnesium silicate. The solution was concentrated in vacuo and the residue was triturated with diethyl ether to give 1.25 g of the title compound as colorless crystals, m.p. 191-193 °C, MS *m/z*: 404.1 $(M+H)^+$.

EXAMPLE 103

[4-(3-Methyl-1,2,4-triazol-1yl)-2-trifluoromethyl-phenyl](5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone

To a suspension of 60% sodium hydride in oil (0.3 g) in dimethylformamide (50 ml) was added dropwise 3-methyl-1,2,4-triazole (0.45 g). After hydrogen gas evolution ceased, 4-fluoro-2-trifluoromethyl-phenyl-(5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepine-10-yl)-methanone (1.76 g) was added and the reaction mixture was heated in a sand bath at 110 °C for 18 hours. The mixture was poured onto ice, diluted with brine, and extracted with dichloromethane. The combined extracts were dried over anhydrous sodium sulfate and filtered through a short column of anhydrous sodium magnesium silicate. The solution was concentrated in vacuo and the residue was triturated with diethyl ether to give 0.81 g of the title compound as colorless crystals, m.p. 148-150 °C, MS *m/z*: 438.2 $(M+H)^+$, 875.8 $(2M+H)^+$.

EXAMPLE 104

4-Hydrazino-2-methoxybenzoic acid, methyl ester, hydrochloride (1:1), hydrate (2:1)

A stirred suspension of 4-amino-2-methoxybenzoic acid, methyl ester (21.74 g) in concentrated hydrochloric acid (110 ml), which was cooled to -10 °C, was treated with a precooled solution of sodium nitrite (8.5 g) in water (45 ml) at a rate required to maintain a reaction temperature less than 0 °C. After the addition was complete, the reaction mixture was stirred at -2 °C for 10 minutes. The cloudy, orange solution was added dropwise to a vigorously stirred precooled solution of tin (II) chloride dihydrate (101 g) in concentrated hydrochloric acid (67 ml) at -10 °C. The rate of addition was controlled to maintain a reaction temperature less than -5 °C. After the addition was complete, the cream colored suspension was warmed to room temperature and a solid was filtered. The solid was washed with diethyl ether and dried over anhydrous sodium sulfate to yield 52 g of a crude product. The crude product (20 g) was partitioned between aqueous 2.5 N sodium hydroxide and dichloromethane. The organic phase was filtered through diatomaceous earth, washed with brine, and dried over anhydrous magnesium sulfate. Filtration and evaporation of the solvent in vacuo afforded a cream colored solid (7.1 g), which upon treatment with one equivalent of an anhydrous hydrogen chloride solution in diethyl ether afforded the title compound as the monohydrochloride salt, m.p. 76-79 °C, MS, *m/z*: 197 $(M+H)^+$.

EXAMPLE 105

2-Methoxy-4-(3-methyl-pyrazol-1-yl)-benzoic acid, methyl ester

To a stirred solution of 4-hydrazino-2-methoxybenzoic acid, methyl ester hydrochloride (0.88 g) from Example 104 and one drop of concentrated hydrochloric acid in a 1:1 water/methanol (10 ml) mixture was added acetylacetaldehyde dimethylacetal (0.53 g). The reaction was heated to 90 °C for 5 minutes. The reaction was concentrated in vacuo and partitioned between 1 N sodium hydroxide (10 ml) and ethyl acetate (50 ml). The organic phase was removed and washed with brine, dried over anhydrous magnesium sulfate and filtered. Evaporation of the solvent in vacuo

afforded a brown oil which was combined with a previous lot (0.54 g) and recrystallized three times from diisopropyl ether to give 2-methoxy-4-(3-methyl-pyrazol-1-yl)-benzoic acid, methyl ester (0.5 g). m.p. 167-169°C, MS, *m/z*: 246 $(M)^+$.

EXAMPLE 106

2-Methoxy-4-(3-methyl-pyrazol-1-yl)-benzoic acid

A solution of 2-methoxy-4-(3-methyl-pyrazol-1-yl)-benzoic acid methyl ester (0.5 g) from Example 105 in tetrahydrofuran (2.5 ml) was treated with 1 N lithium hydroxide (2.13 ml) at room temperature. After 14 hours the solvent was removed in vacuo and the title compound precipitated by the addition at 0 °C of 1N hydrochloric acid. After drying under vacuum 0.42g of the title compound was obtained as a solid. MS, *m/z*: 232 $(M)^+$.

EXAMPLE 107

[2-Methoxy-4-(3-methyl-pyrazol-1-yl)-phenyl](5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl) methanone

Oxalyl chloride (0.17 ml) was added to a stirred solution of 2-methoxy-4-(3-methyl-pyrazol-1-yl)-benzoic acid (0.41 g) from Example 106 and dimethylformamide (0.004 ml) in anhydrous tetrahydrofuran (10 ml). The reaction was heated at 35 °C for ten minutes. The resulting solution was evaporated in vacuo to yield the crude 2-methoxy-4-(3-methyl-pyrazol-1-yl)-benzoic acid carbonyl chloride. Following coevaporation with dichloromethane the acid chloride was dissolved in dichloromethane (10 ml) and 10,11-dihydro-5H-pyrrolo[2,1-c][1,4]-benzodiazepine (0.31 g) added. Diisopropylethylamine (0.37 ml) was added and the reaction stirred at room temperature for 2 hours. The reaction was diluted with dichloromethane and washed with water followed by 1N hydrochloric acid. The organic phase was washed with brine, dried over anhydrous magnesium sulfate and concentrated to dryness in vacuo. The solid residue was purified by flash column chromatography on silica gel eluting with hexane /ethyl acetate (2/1) to give 0.35 g of the title compound as a colorless solid, m.p. 92-94 °C.

EXAMPLE 108

(3-Dimethylaminomethyl-5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)[2-methoxy-4-(3-methyl-pyrazol-1-yl)-phenyl]-methanone

To a stirred solution of [2-methoxy-4-(3-methyl-pyrazol-1-yl)-phenyl](5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl) methanone from Example 107 (0.57 g) in warm methanol (10 ml) was added N,N,N,N'-tetramethyldiaminomethane (0.392 ml) and acetic acid (0.164 ml). Following the addition of aqueous 37% formalin solution (2.9 ml) the reaction was stirred for fifteen minutes. The mixture was concentrated in vacuo and partitioned between dichloromethane and sodium hydrogen carbonate. The organic phase was removed, washed with brine and dried over anhydrous magnesium sulfate. The solution was filtered and the solvent removed in vacuo. The residue was purified by flash column chromatography on silica eluting with chloroform/methanol (50/1) to afford a solid. Recrystallisation of the solid from acetone gave the title compound as a colorless solid, m.p. 196-198 °C.

EXAMPLE 109

[2-Hydroxy-4-(3-methyl-pyrazol-1-yl](5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl)-methanone

[2-Methoxy-4-(3-methyl-pyrazol-1-yl)-phenyl](5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl) methanone (0.82 g) from Example 107 was dissolved in dichloromethane (20 ml) and cooled to -78 °C. Boron tribromide (6.2 ml) was added and the reaction stirred at 0 °C for five minutes. Ammonium hydroxide (15 ml) was added and extracted with dichloromethane. The organic phase was washed with brine and dried over anhydrous magnesium sulfate. The solid was removed by filtration and the solvent removed in vacuo. The residue was purified by flash column chromatography on silica pressure eluting with hexane/ethyl acetate (3/1 then 2/1) to afford 0.19g of the title compound as a colorless solid, m.p. 134-136 °C.

EXAMPLE 110

2-Chloro-4-iodo-benzoic acid, methyl ester

4-Amino-2-methoxy-benzoic acid methyl ester (22.97 g) was cooled to an internal temperature of -10 °C in concentrated hydrochloric acid (110 ml) and stirred as a suspension. A precooled solution of sodium nitrite (98.71 g) in water (45 ml) was added to this mixture, at such a rate so as to maintain a reaction temperature of less than 0 °C. After stirring for 25 minutes at 0 °C the reaction was treated with a solution of potassium iodide (24.44 g) and iodine (18.37 g) in water (50 ml) at such a rate so as to maintain a reaction temperature of less than -4°C. Ethyl acetate (100 ml) was added during the addition and the dark mixture was stirred at 0 °C for one hour. The organic layer was diluted with ethyl acetate and washed well with saturated sodium thiosulfate solution. The resulting orange solution was washed with brine and dried over anhydrous magnesium sulfate. The solvent was evaporated in vacuo to yield an oil which was purified by suction filtration through silica gel eluting with hexane/ethyl acetate (50/1). The resulting purified oil solidified on cooling to give 33.71 g of the title compound. MS, *m/z*: 296 $(M)^+$.

EXAMPLE 111

4-Bromo-1-methyl-1H-pyrazole

To a suspension of prewashed (tetrahydrofuran) 60% sodium hydride in oil (11.67 g) in tetrahydrofuran (200 ml) was added dropwise a solution of 4-bromopyrazole (39.77 g) in tetrahydrofuran (50 ml). The solution was stirred at room temperature for two hours. Excess iodomethane (33 ml) in tetrahydrofuran (50 ml) was added at such a rate as to maintain a slight increase in temperature. The reaction was stirred further for two hours. The solvent was removed in vacuo and the residue stirred in diethyl ether. A precipitate was removed by suction filtration and washed with diethyl ether. The combined organic phase was evaporated in vacuo to give 42.22g of the title compound as an oil. MS, *m/z*: 160 $(M)^+$.

EXAMPLE 112

1-Methyl-4-tributylstannyl-1H-pyrazole

To a precooled (<-10°C internal temperature) solution of 1.6M n-butyl lithium in hexanes (100 ml) in anhydrous diethyl ether (100 ml) under argon was added a solution of 4-bromo-1-methyl-1H-pyrazole (23.42 g) from Example 111 in diethyl ether (50 ml) at a rate to maintain the temperature. The reaction was allowed to stir for a further 20 minutes before tributyltin chloride (43.4 ml) was added in diethyl ether (50 ml). The reaction temperature was allowed to rise to 20 °C. The reaction was diluted with diethyl ether and the insoluble material removed by suction filtration. Evaporation of the solvent in vacuo afforded 56 g of the title compound as an oil. MS, *m/z*: 373 $[M+H]^{+\cdot}$ Residual amounts of tin residues were removed from the oil by distillation using a kugelrohr apparatus under high vacuum at 170 °C.

EXAMPLE 113

2-Chloro-4-(1-methyl-1H-pyrazol-4-yl)-benzoic acid, methyl ester

An argon degassed dimethylformamide solution (70 ml) of 2-chloro-4-iodo-benzoic acid methyl ester (25.4 g) pyrazole from Example 110, 1-methyl-4-tributylstannyl-1H- (31.77 g), tetrakis(triphenylphosphine)palladium (0) (1.8 g) and catalytic copper (I) iodide was heated at 80 °C for 7 hours. The solvent was removed in vacuo and the residue adsorbed onto silica gel. Purification by suction filtration through a pad of silica gel eluting sequentially with hexane and followed by hexane/ethyl acetate (2/1) afforded after evaporation of the solvent a solid residue which was recrystallised from diisopropyl ether to give 7.82 g. of the title compound MS, m/z 250 $(M)^{+}$.

EXAMPLE 114

2-Chloro-4-(1-methyl-1H-pyrazol-4-yl)-benzoic acid

To a solution of 2-chloro-4-(1-methyl-1H-pyrazol-4-yl)-benzoic acid, methyl ester (6.25) from Example 113 in methanol (80 ml) was added 1N sodium hydroxide (30 ml). The reaction was heated under reflux for one hour. The volume of solvent was reduced in vacuo by three quarters and the residue treated with 2N hydrochloric acid at 0 °C. A precipitate was filtered and dried in vacuo to yield 5.84 g the title compound, MS *m/z*: 237 $[M+H]^+$.

EXAMPLE 115

[2-Chloro-4-(1-methyl-1H-pyrazol-4-yl)phenyl] (5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl)-methanone

Oxalyl chloride (0.49 ml) was added to a solution of 2-chloro-4-(1-methyl-1H-pyrazol-4-yl)-benzoic acid (0.41 g) from Example 114 and dimethylformamide (0.012 ml) in anhydrous tetrahydrofuran (20 ml). The reaction was heated at 35 °C for ten minutes. The resulting solution was evaporated in vacuo to dryness to yield the crude 2-chloro-4-(1-methyl-1H-pyrazol-4-yl)-benzoic acid carbonyl chloride. Following co-evaporation with anhydrous methylene chloride, the acid chloride was dissolved in dichloromethane (20 ml) followed by the addition of 10,11-dihydro-5H-pyrrolo[2,1-c][1,4]-benzodiazepine (0.888 g) and diisopropylethylamine (1.06 ml). The resulting solution was stirred at room temperature for 2 hours. The reaction was diluted with dichloromethane and washed with water followed by 1N hydrochloric acid. The organic phase was washed with brine and dried over anhydrous magnesium sulfate. The dichloromethane was filtered and concentrated in vacuo to dryness. . The residue was purified by flash column chromatography on silica pressure eluting with hexane/ethyl acetate (2/1) to afford 1.4 g of the title compound as a colorless solid m.p. 105-109 °C.

EXAMPLE 116

[2-Chloro-4-(3-methyl-pyrazol-1-yl)-phenyl]-(4H,10H-pyrazolo[5,1-c][1,4]-benzodiazepin-5-yl)-methanone

To solution of 2-chloro-4-(3-methyl-pyrazol-1-yl)-benzoyl chloride (0.214 g) Example 18 Step e in dichloromethane (10 ml) was added 5H-10,11-dihydropyrazolo[5,1-c][1,4] benzodiazepine (0.153 g) and diisopropylethylamine (0.173 ml). The reaction was stirred at room temperature for 2 hours. The reaction was diluted with dichloromethane and washed with water followed by 1N hydrochloric acid. The organic phase was washed with brine and dried over anhydrous magnesium sulfate. The dichloromethane solution was filtered and concentrated in vacuo to dryness. The residue was purified by flash column chromatography on silica pressure eluting with hexane/ethyl acetate (1/1) to afford 0.3 g of the title compound as a colorless solid, m.p. 187-188 °C.

EXAMPLE 117

2-Chloro-4-(3-methyl-pyrazol-1-yl)-phenyl]-(5,10-dihydro-4H-tetrazolo[5,1-c][1,4]benzodiazepin-5-yl)-methanone

To a solution of 2-chloro-4-(3-methyl-pyrazol-1-yl)-benzoyl chloride (0.18 g) Example 18 Step e in dichloromethane (10 ml) was added 10,11-dihydro-5H-tetrazole[5,1-c][1,4]benzodiazepine (0.13 g) and diisopropylethylamine (0.145 ml). The reaction was stirred at room temperature for 2 hours. The reaction was diluted with dichloromethane and washed with water followed by 1N hydrochloric acid. The organic phase was washed with brine and dried over anhydrous magnesium sulfate. The dichloromethane solution was filtered and concentrated in vacuo to dryness. The residue was purified by flash column chromatography on silica eluting with hexane/ethyl acetate (1/1) to give 0.14 g of the title compound as a colorless solid. m.p. 110-114°C.

EXAMPLE 118

1-[4-(4H,10H-pyrazolo[5,1-c][1,4]benzodiazepine-5-carbonyl) phenyl]-ethanone

A mixture of 5,10-dihydro-4H-pyrazolo[5,1-c][1,4]benzodiazepine (0.555 g), 4-acetylbenzoyl chloride (0.657 g) and N,N-diisopropylethylamine (0.464 g) in dichloromethane (15 ml) was stirred at room temperature for 4 hours. The mixture is poured into water and extracted with dichloromethane. The dichloromethane extract was washed with saturated sodium hydrogen carbonate, water and brine and dried over anhydrous sodium sulfate. The extract is filtered through a thin pad of hydrous magnesium silicate and the filter pad washed with dichloromethane. The filtrate is concentrated in vacuo to give 1.53 g of yellow solid. Trituration of the solid with ethyl acetate gave 0.747 g of the title compound as a glass, m.p. 201-210°C. The mother liquors from the trituration were evaporated and the residue (0.30 g) was chromatographed on thick layer silica gel plates (200 micron) using hexane-ethyl acetate (1:1) as solvent. The solid is triturated with ethyl acetate and combined with the 0.747 g of initially isolated product. The combined solids were precipitated from a mixture of dichloromethane -hexane to give 0.73 g of product as a glass .

EXAMPLE 119

1-[4-(4H,10H-pyrazolo[5,1-c][1,4]benzodiazepine-5-carbonyl)phenyl]-3-(dimethylamino)-prop-2-en-1-one

A mixture of 1-[4-(4H,10H-pyrazolo[5,1-c][1,4]benzodiazepine-5-carbonyl) phenyl]ethanone (0.73 g), tert-butoxybis-[dimethylamino]methane (0.964 g) in dichloromethane (10 ml) was stirred at room temperature for 2 days. The mixture is concentrated in vacuo and the residue crystallized from dichloromethane-hexane to give 0.65 g of the title compound as yellow crystals, m.p. 225-230°C.

EXAMPLE 120

[4-(1-Methyl-1H-pyrazol-3-yl)phenyl](4H,10H-pyrazolo[5,1c][1,4]-benzodiazepin-5-yl) methanone (Isomer A)

and

[4-(2-Methyl-1H-pyrazol-3-yl)phenyl](4H,10H-pyrazolo[5,1c][1,4]-benzodiazepin-5-yl) methanone (Isomer B)

A mixture of 1-[4-(4H,10H-pyrazolo[5,1-c][1,4]benzodiazepine-5-carbonyl)phenyl]-3-(dimethylamino)-prop-2-en-1-one (0.83 g), hydrazine (0.198 g)and acetic acid (0.336 g) in 10 ml of ethanol is refluxed for 4 hours. The volatiles were removed in vacuo and the residue dissolved in dichloromethane. The solution is washed with water, 1N sodium hydrogen carbonate, water and brine and dried over anhydrous sodium sulfate. The solution is filtered through a thin pad of hydrous magnesium silicate and the filter pad washed with ethyl acetate. The filtrate is concentrated in vacuo to give 0.56 g of light yellow solid. The solid was chromatographed on thick layer silica gel plates (200 microns) with ethyl acetate as solvent to give 0.35 g of white solid as a mixture of A and B (1:4). Multiple fractional crystallizations from ethyl acetate gives 89 mg of crystals, m.p. 155-156°C as a mixture of A and B (9:1) and 65 mg of a glass as a mixture of A and B (1:6)

EXAMPLE 121

1-[4-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepine-10-carbonyl)-3-chlorophenyl]-ethanone

Step a) Triethylamine (8.80 ml) was added to a solution of (4-bromo-2-chlorophenyl)-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (2.37 g) in pyridine (1.80 ml), in a 20 ml Carrius tube. The resultant solution was purged with nitrogen for 25 minutes then (trimethylsilyl)acetylene (1.67 ml), bis(triphenylphosphine)palladium(II) chloride (0.08 g) and copper(I) iodide (0.01 g) were added. The tube was filled with nitrogen-purged triethylamine, sealed and heated on an oil bath at 90 °C for 80 hours. The solution was cooled to room temperature, the solvent evaporated in vacuo, and the residue partitioned between dichloromethane and water. The dichloromethane extract was dried over anhydrous sodium sulfate, filtered,

and evaporated in vacuo to a brown foam. Purification by flash chromatography on silica gel eluting with hexane-ethyl acetate (1:1) resulted in the intermediate acetylene as an off-white foam (2.11 g), MS *m/z*: 418 $(M)^+$. This material was used without further purification in the next step.

Step b) A solution of 1% sulfuric acid in tetrahydrofuran was saturated with mercury (II) sulfate. The intermediate acetylene (1.00 g) in tetrahydrofuran (5 ml) was stirred for 50 hours with 30 ml of the aforementioned mercury (II) sulfate-tetrahydrofuran solution. An additional amount of mercury (II) sulfate (0.01 g) and water 0.3 ml was added. After stirring for 120 hours, the reaction mixture was poured into water and extracted with dichloromethane. The dichloromethane solution was washed sequentially with saturated aqueous sodium bicarbonate and water. The dichloromethane solution was dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness to yield a brown solid. Purification by flash chromatography on silica gel eluting with hexane-ethyl acetate (1:1) gave a white solid (0.30 g), mp 98-100°C, MS *m/z*: 364 $(M)^+$.

EXAMPLE 122

1-[4-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepine-10-carbonyl)-3-chlorophenyl]-ethanone

Tributyl(ethoxyvinyl)tin (1.17 g) was added to a solution of (4-bromo-2-chlorophenyl)-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone (1.24 g) in toluene (10 ml). The resultant solution was purged with nitrogen for 10 minutes, then bis(triphenylphosphine)palladium (II) chloride (0.11 g) was added. The reaction mixture was heated to reflux for 24 hours. The solution was cooled to room temperature and 5% aqueous hydrochloric acid (10 ml) was added. After stirring for one hour, the mixture was filtered through a pad of diatomaceous. Diethyl ether (5 ml) was added to the filtrate, and the resulting mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, filtered, and evaporated in vacuo to yield a brown glass. Purification by flash chromatography on silica gel eluting with hexane-ethyl acetate (1:1) resulted in a white solid (0.30 g), MS, *m/z*: 364 $(M)^+$.

EXAMPLE 123

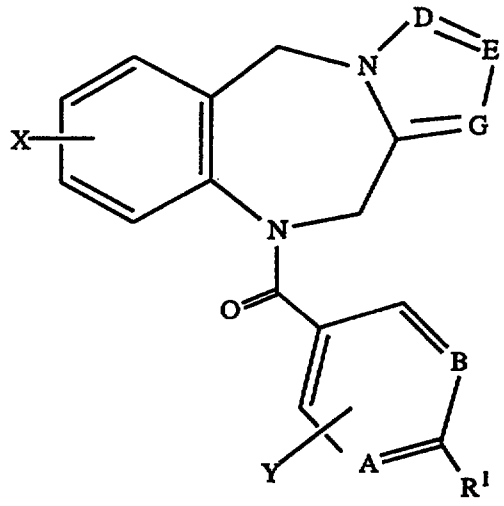
[2-Chloro-4-(3-methyl-4-ethynyl-phenyl) (5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl)-methanone

Treatment of the intermediate acetylene of Example 121 step A with a 1M solution of tetrabutylammonium fluoride in tetrahydrofuran at room temperature provided upon solvent removal an 84% yield the title compound as an orange -yellow solid, m.p. 84-86°C, MS, m/z: 346 $(M)^+$.

* C L M S *

CLAIMS:

1. A compound of formula (I):



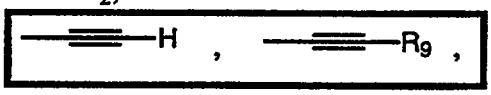
(I)

wherein:

A, B, E, G are, independently, CH or nitrogen;

D is, independently, C-W or nitrogen;

R^1 is alkanoyl of 2 to 7 carbon atoms, a group selected from CN, COOH, $CONH_2$,

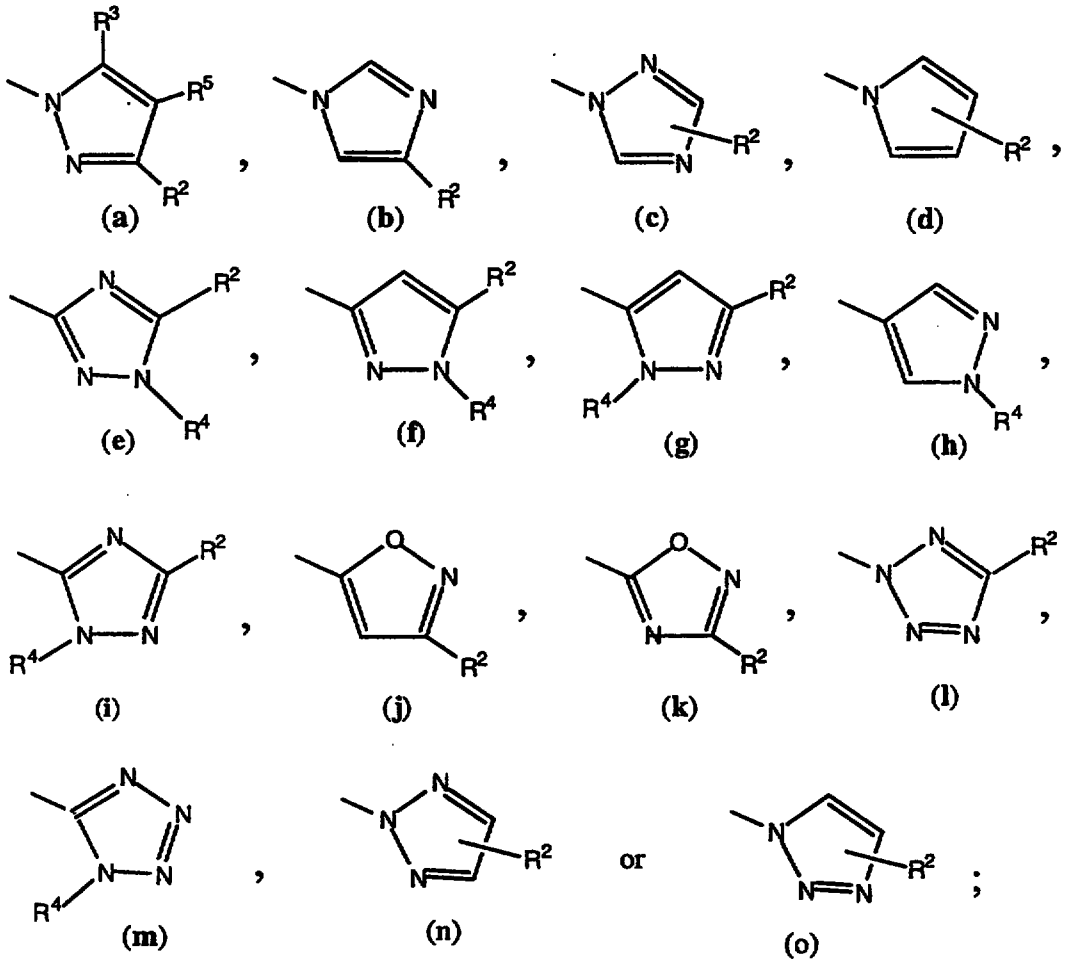


or a moiety selected from the group of:

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R^2, R^3 and R^5 are, independently, hydrogen, straight chain alkyl of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7 carbon atoms, cycloalkyl of 3 to 7 carbon atoms, or perfluoroalkyl of 1 to 6 carbons;

R^4 is hydrogen, straight chain alkyl of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7 carbon atoms, cycloalkyl of 3 to 7 carbon atoms, alkoxyalkyl of 2 to 7 carbon atoms, or an acyl substituent selected from the group consisting of alkanoyl of 2 to 7 carbon atoms, alkenoyl of 3 to 7 carbon atoms, cycloalkanoyl of 3 to 7 carbon atoms, aroyl, or arylalkanoyl;

X and Y are, independently, hydrogen, straight chain alkyl of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7 carbon atoms, cycloalkyl of 3 to 7 carbon atoms, perfluoroalkyl of 1 to 6 carbons, alkoxyalkyl of 2 to 7 carbon atoms, halogen

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(including chlorine, bromine, fluorine, and iodine), alkoxy of 1 to 6 carbons, hydroxy, CF_3, or perfluoroalkyl of 2 to 6 carbons;

W is hydrogen, halogen (preferably chloro, bromo or iodo), alkyl, alkoxyalkyl of 2 to 7 carbons, hydroxyalkyl of 1 to 6 carbons, or $CH_2NR^6R^7$;

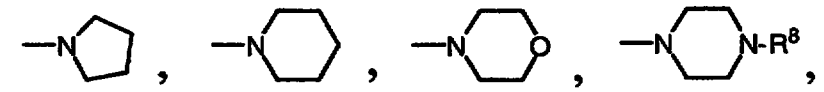
R^6 and R^7 are, independently, hydrogen, straight chain alkyl of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7 carbon atoms; or, taken together with the nitrogen atom of $CH_2NR^6R^7$, R^6 and R^7 form a five or six membered ring optionally containing one or more additional heteroatoms;

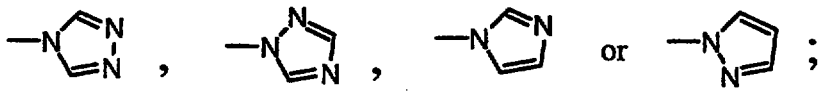
R^8 is a straight chain alkyl of 1 to 6 carbon atoms;

R^9 is independently hydrogen, trimethylsilyl or a straight chain alkyl of 1 to 6 carbon atoms;

or a pharmaceutically acceptable salt thereof.

2. A compound as claimed in Claim 1 wherein R^6 and R^7, taken together with the nitrogen atom of $CH_2NR^6R^7$, form a five or six membered ring selected from the group:



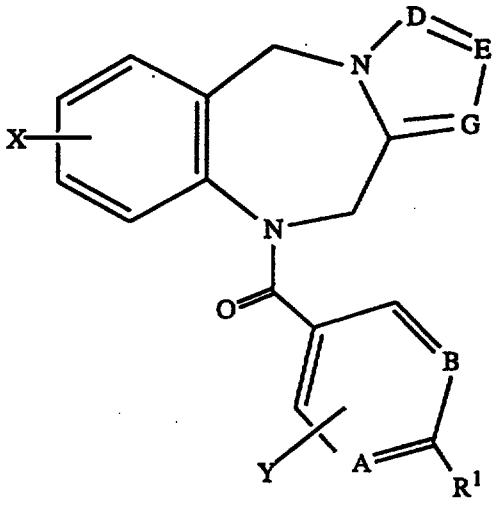


or a pharmaceutically acceptable salt thereof.

3. A compound as claimed in Claim 1 having the formula (I):

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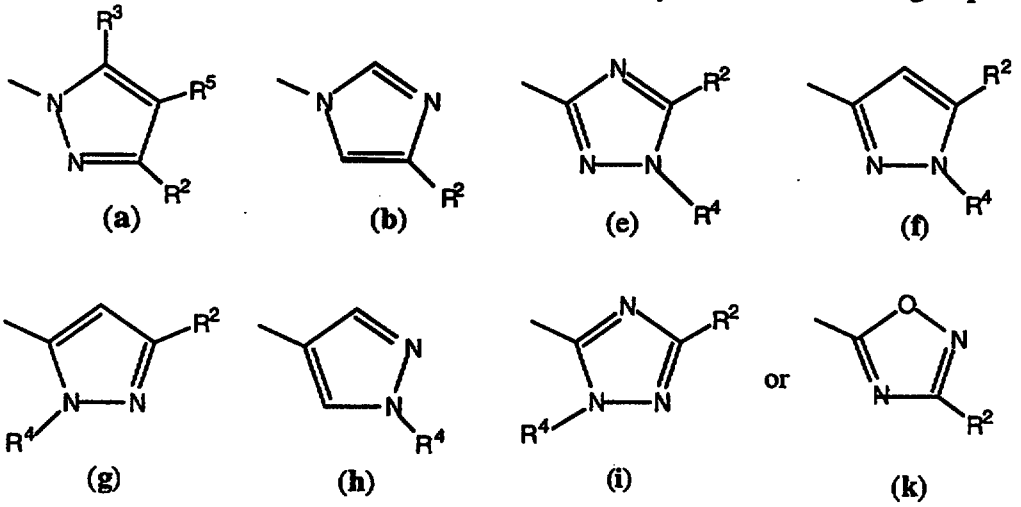
(I)

wherein:

A, B, E, G are, independently, CH or nitrogen;

D is, independently, C-W or nitrogen;

R^1 is alkanoyl of 2 to 7 carbon atoms or a moiety selected from the group of:



(a) (b) (e) (f)

(g) (h) (i) or (k)

R^2, R^3 and R^5 are, independently, hydrogen, straight chain alkyl of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7 carbon atoms, cycloalkyl of 3 to 7 carbon atoms, or perfluoroalkyl of 1 to 6 carbons; and

R^4, X, Y, W, R^6, R^7, and R^8 are as defined in Claim 1;

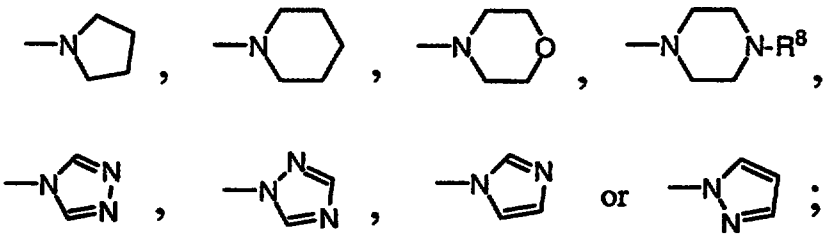
or a pharmaceutically acceptable salt thereof.

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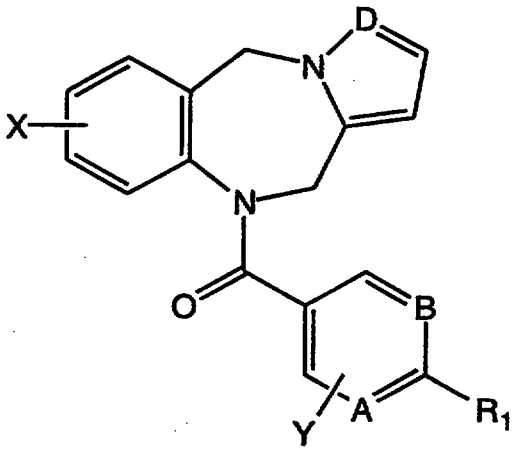
* C L M S *

4. A compound as claimed in Claim 3 wherein R^6 and R^7, taken together with the nitrogen atom of $CH_2NR^6R^7$, form a five or six membered ring selected from the group:



or a pharmaceutically acceptable salt thereof.

5. A compound of the formula:



wherein:

A and B are, independently, CH or N;

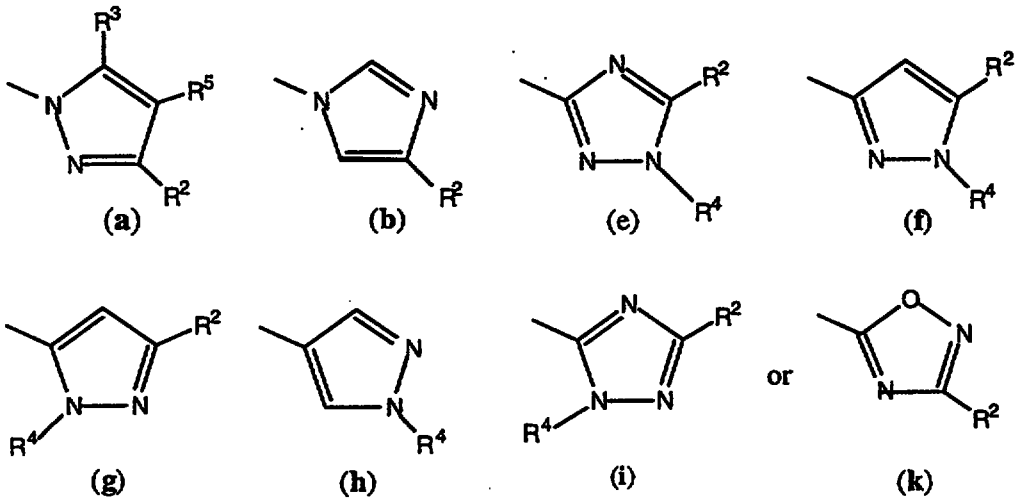
D is C-W or N;

R^1 is alkanoyl of 2 to 7 carbon atoms or a group selected from

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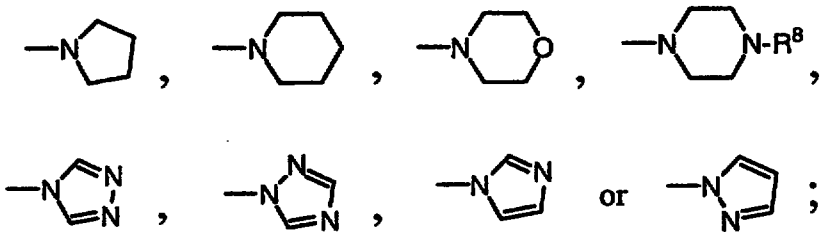


R^2, R^3 and R^5 are, independently, hydrogen, straight chain alkyl of 1 to 6 carbon atoms, branched chain alkyl of 3 to 7 carbon atoms, cycloalkyl of 3 to 7 carbon atoms, or perfluoroalkyl of 1 to 6 carbons;

R^4, X, Y, W, R^6, R^7, and R^8 are as defined in Claim 1;

or a pharmaceutically acceptable salt thereof.

6. A compound as claimed in Claim 5 wherein R^6 and R^7, taken together with the nitrogen atom of $CH_2NR^6R^7$, form a five or six membered ring selected from the group:

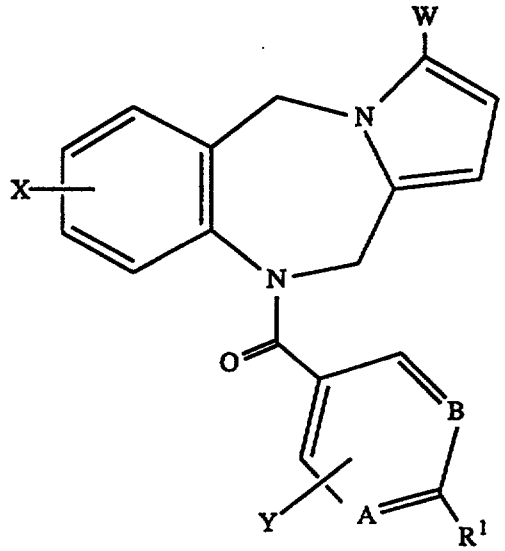


or a pharmaceutically acceptable salt thereof.

7. A compound of the formula:

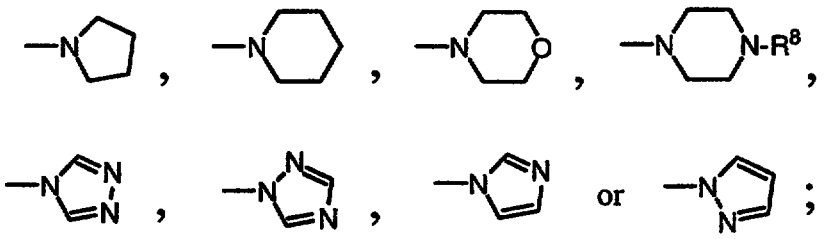
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wherein A, B, W, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, X, and Y are as defined in Claim 1;
or a pharmaceutically acceptable salt thereof.

8. A compound as claimed in Claim 7 wherein R^6 and R^7, taken together with the nitrogen atom of $CH_2NR^6R^7$, form a five or six membered ring selected from the group:



or a pharmaceutically acceptable salt thereof.

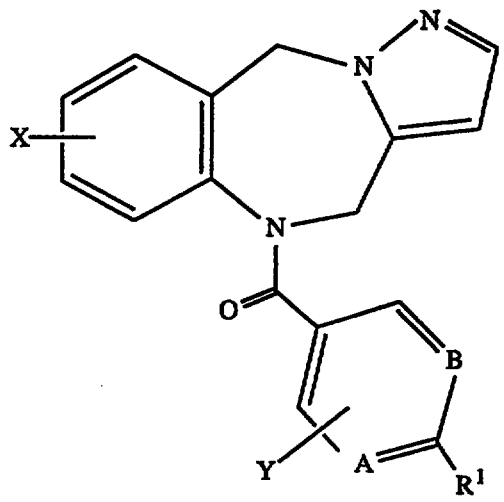
9. A compound as claimed in Claim 8 wherein:
W is H;
A and B are each CH; and
R^1, R^2, R^3, R^4, R^5, R^8, R^9, X, and Y are as defined in Claim 1;
or a pharmaceutically acceptable salt thereof.

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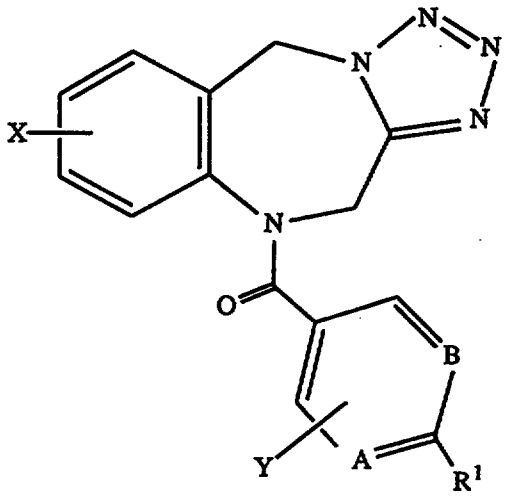
* C L M S *

10. A compound of the formula:



wherein A, B, R^1, R^2, R^3, R^4, R^5, R^9, X, and Y, are as defined in Claim 1; or a pharmaceutically acceptable salt thereof.

11. A compound of the formula:



wherein A, B, R^1, R^2, R^3, R^4, R^5, X, and Y, are as defined in Claim 1; or a pharmaceutically acceptable salt thereof.

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12. A compound as claimed in Claim 1 which is [4-(3-methyl-pyrazol-1-yl)-2-trifluoromethyl-phenyl](5H,11H-pyrrolo[2,1-c]-[1,4]benzodiazepin-10-yl)-methanone,

[4-(4-methyl-pyrazol-1-yl)-2-trifluoromethyl-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone,

(4-pyrazol-1-yl-2-trifluoromethyl-phenyl)-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone,

[4-(3-cyclopropyl-pyrazol-1-yl)-2-trifluoromethy-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone,

[4-(4-methyl-imidazol-1-yl)-2-trifluoromethyl-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone,

(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-(4-[1,2,4]triazol-1-yl-2-trifluoromethylphenyl)-methanone,

[2-chloro-4-(3-methyl-pyrazol-1-yl)-phenyl]-(5H,11H)-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone,

[2-chloro-4-(5-methyl-pyrazol-1-yl)-phenyl]-(5H,11H)-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone,

[2-chloro-4-(4-methyl-pyrazol-1-yl)-phenyl-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone,

[2-chloro-4-(4-methyl-imidazol-1-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone,

[2-chloro-4-(3-trifluoromethyl-pyrazol-1-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone,

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[2-chloro-4-(1,2,4-triazol-1-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone,

(2-chloro-4-pyrrol-1-yl-phenyl)-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone,

(2-chloro-4-pyrazol-1-yl-phenyl)(5H,11H-Pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone,

[2-chloro-4-(1H-imidazol-1-yl)-phenyl)-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone,

[2-chloro-4-(3-methylpyrazol-1-yl)-phenyl]-(3-methyl-5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone,

[2-(3-methyl-pyrazol-1-yl)-4-trifluoromethyl-pyrimidin-5-yl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone,

[2-(4-methyl-pyrazol-1-yl)-4-trifluoromethyl-pyrimidin-5-yl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone,

1-[4-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepine-10-carbonyl)-phenyl]-ethanone,

[4-(1H-pyrazol-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone,

[4-(1-methyl-1H-pyrazolyl-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl)-methanone,

[4-(1-ethyl-1H-pyrazol-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl)-methanone,

[4-(1-propyl-1H-pyrazol-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl)-methanone,

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[4-(1-butyl-1H-pyrazol-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl)-methanone,

[4-(1-methoxymethyl-1H-pyrazol-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl)-methanone,

1-{3-[4-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepine-10-carbonyl)-phenyl]-pyrazol-1-yl}-ethanone,

1-{3-[4-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepine-10-carbonyl)-phenyl]-pyrazol-1-yl}-propan-1-one,

[4-(1-cyclopropanecarbonyl-1H-pyrazol-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone,

1-{3-[4-(5H,11H-pyrrolo[2,1-c][1,4] benzodiazepine-10-carbonyl)-phenyl]-pyrazol-1-yl}-butan-1-one,

(5H,11H-pyrrolo[2,1-c][1,4] benzodiazepin-10-yl)-{4-[1-(thiophene-2-carbonyl)-1H-pyrazoly-3-yl]phenyl}-methanone,

{4-[1-(5-fluoro-2-methyl-benzoyl)-1H-pyrazol-3-yl]-phenyl}-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone,

{4-[1-(2-methyl-benzoyl)-1H-pyrazol-3-yl]-phenyl}-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone,

{4-[1-(2-chloro-4-fluoro-benzoyl)-1H-pyrazol-3-yl]-phenyl}-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl}methanone,

{4-[1-(2,4-dichloro-benzoyl)-1H-pyrazol-3-yl]-phenyl}-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone,

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2-(2,4-dichloro-phenyl)-1-{3-[4-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepine-10-carbonyl)-phenyl]-pyrazol-1-yl}-ethanone,

{4-[1-(biphenyl-2-carbonyl)-1H-pyrazol-3-yl]-phenyl}-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone,

{4-[1-(4'-trifluoromethyl-biphenyl-2-carbonyl)-1H-pyrazol-3-yl]-phenyl}-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone,

[4-(5-methyl-1H-pyrazol-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl)-methanone,

(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-[4-(2H-[1,2,4]triazol-3-yl)-phenyl]-methanone,

[4-(2-methyl-2H-[1,2,4]triazol-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl)-methanone,

[4-(5-methyl-2H-[1,2,4]triazol-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl)-methanone,

[4-(2,5-dimethyl-2H-[1,2,4]triazol-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c]-[1,4]benzodiazepin-10-yl)-methanone,

[4-(3-methyl[1,2,4]oxadiazol-5-yl)-phenyl]-(5H,11H-pyrrolo-[2,1-c][1,4]-benzodiazepin-10-yl)-methanone,

[4-(1-methyl-1H-pyrazol-4-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl)-methanone,

[6-(1-methyl-1H-pyrazol-4-yl)-pyridin-3-yl]-(5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl)-methanone,

[4-(pyrazol-1-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone,

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[4-(3-methyl-pyrazol-1-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl)-methanone,

[4-(4-methyl-pyrazol-1-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl)-methanone,

[4-(3,5-dimethyl-pyrazol-1-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl)-methanone,

(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-[4-(3-trifluoromethyl-pyrazol-1-yl)-phenyl]-methanone,

[4-(imidazol-1-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone,

[4-(4-methyl-imidazol-1-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl)-methanone,

[2-chloro-4-(1-methyl-1H-pyrazol-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c]-[1,4]benzodiazepine-10-yl)-methanone,

[2-chloro-4-(2-methyl-1H-pyrazol-3-yl)-pheny]-(5H,11H-pyrrolo[2,1-c] [1,4]benzodiazepine-10-yl)-methanone,

3-chloro-4-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepine-10-carbonyl)-benzonitrile,

3-chloro-4-(5H,11H-Pyrrolo[2,1-c][1,4]benzodiazepine-10-carbonyl)-benzoic acid,

3-chloro-4-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepine-10-carbonyl)-benzamide,

[2-chloro-4-(5-methyl-2H-[1,2,4]triazol-3-yl)phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepine-10-carbonyl)-methanone,

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[2-chloro-4-(2H-1,2,4-triazol-3-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl)-methanone,

[2-chloro-4-(2-methyl-2H-[1,2,4]triazol-3-yl)-phenyl]-(5H,11H-pyrrolo [2,1-c][1,4]benzodiazepin-10-carbonyl)-methanone,

4-[(2,5-dimethyl-2H-[1,2,4]triazol-3-yl)-2-chloro-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-carbonyl)-methanone,

[2-chloro-4-(1H-tetrazol-5-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4] benzodiazepin-10-yl)- methanone,

[2-chloro-4-(3-methyl-pyrazol-1-yl)-phenyl]-(3-dimethylaminomethyl-5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone,

(3-bromo-5H,11H pyrrolo[2,1c][1,4]benzodiazepin-10-yl)[2-chloro-4-(3-methyl-pyrazol-1-yl)-phenyl]-methanone,

[2-bromo-4-(3-methyl-pyrazol-1-yl)-phenyl]-(5H,11H)-pyrrolo[2,1-c] [1,4]benzodiazepin-10-yl)-methanone,

(2,4-difluoro-phenyl)-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone,

[2-fluoro-4-(3-methyl-pyrazol-1-yl)-phenyl]-(5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl)-methanone,

[4-(3-methylpyrazol-1-yl)-2-trifluoromethylphenyl]-(5H,11H-pyrazolo[5,1-c]-[1,4]benzodiazepin-10-yl)-methanone,

(2-chloro-6-pyrazol-1-yl-pyridin-3-yl)-(5H,11H-pyrrolo[2,1-c][1,4] benzodiazepin-10-yl)-methanone,

[2-chloro-6-(3-methylpyrazol-1-yl)-pyridin-3-yl]-(5H,11H-pyrrolo[2,1-c] [1,4]benzodiazepin-10-yl)-methanone,

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[2-chloro-6-(4-methylpyrazol-1-yl)-pyridin-3-yl](5H,11H- pyrrolo[2,1-c] [1,4]benzodiazepin-10-yl)-methanone,

[2-chloro-4-(3-methyl-1,2,4-triazol-1-yl)-phenyl](5H,11H- pyrrolo[2,1-c]-[1,4]benzodiazepin-10-yl)-methanone,

[4-(3-methyl-1,2,4-triazol-1yl)-2-trifluoromethyl-phenyl](5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)-methanone,

[2-methoxy-4-(3-methyl-pyrazol-1-yl)-phenyl](5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl) methanone,

(3-dimethylaminomethyl-5H,11H-pyrrolo[2,1-c][1,4]benzodiazepin-10-yl)[2-methoxy-4-(3-methyl-pyrazol-1-yl)-phenyl]-methanone,

[2-hydroxy-4-(3-methyl-pyrazol-1-yl](5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl)-methanone,

[2-chloro-4-(1-methyl-1H-pyrazol-4-yl)phenyl) (5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl)-methanone,

[2-chloro-4-(3-methyl-pyrazol-1-yl)-phenyl]-(4H,10H-pyrazolo[5,1-c][1,4]-benzodiazepin-5-yl)-methanone,

2-chloro-4-(3-methyl-pyrazol-1-yl)-phenyl]-(5,10-dihydro-4H-tetrazolo[5,1-c][1,4]benzodiazepin-5-yl)-methanone,

1-[4-(4H,10H-pyrazolo[5,1-c][1,4]benzodiazepine-5-carbonyl) phenyl]-ethanone,

[4-(1-methyl-1H-pyrazol-3-yl)phenyl](4H,10H-pyrazolo[5,1c][1,4]-benzodiazepin-5-yl) methanone,

[4-(2-methyl-1H-pyrazol-3-yl)phenyl](4H,10H-pyrazolo[5,1c][1,4]-benzodiazepin-5-yl) methanone,

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1-[4-(5H,11H-pyrrolo[2,1-c][1,4]benzodiazepine-10-carbonyl)-3-chlorophenyl]-ethanone,

or [2-chloro-4-(3-methyl-4-ethynyl-phenyl) (5H,11H-pyrrolo[2,1-c][1,4]-benzodiazepin-10-yl)-methanone.

13. A pharmaceutical composition useful for treating a disease or condition in a mammal in which vasopressin agonist activity is desired, the pharmaceutical composition comprising an effective amount of a compound as claimed in any one of Claims 1 to 12, or a pharmaceutically acceptable salt, ester or prodrug form thereof, and a suitable pharmaceutical carrier.

14. A pharmaceutical composition as claimed in Claim 13 wherein the disease or condition in a mammal in which vasopressin agonist activity is desired is diabetes insipidus, nocturnal enuresis, nocturia, urinary incontinence, bleeding and coagulation disorders, or the inability to temporarily delay urination.

15. A method for treating disease or condition in a mammal in which vasopressin agonist activity is desired, the method comprising administering to a mammal in need thereof an effective amount of a compound as claimed in any one of Claims 1 to 12, or a pharmaceutically acceptable salt, ester or prodrug form thereof, and a suitable pharmaceutical carrier.

16. A method as claimed in Claim 15 wherein the disease or condition in a mammal in which vasopressin agonist activity is desired is diabetes insipidus, nocturnal enuresis, nocturia, urinary incontinence, bleeding and coagulation disorders, or the inability to temporarily delay urination.

17. Use of a compound as claimed in any one of claims 1 to 12 as a medicament.

18. Use of a compound as claimed in any one of claims 1 to 12 in the preparation of a medicament for the treatment of diabetes insipidus, nocturnal enuresis, nocturia, urinary incontinence, bleeding and coagulation disorders, or the inability to temporarily delay urination.

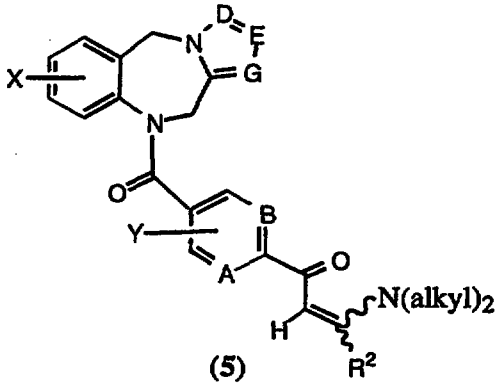
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19. A process for the preparation of a compound of formula I which comprises:

a) reacting a compound of formula 5



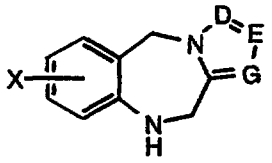
(5)

wherein A, B, D, E, G, X, Y and R^2 are each as defined Claim 1,

with hydroxylamine or an appropriate substituted hydrazine of formula R^4-$NHNH_2$ wherein R^4 is as defined Claim 1,

to provide the desired compound of formula I wherein R^1 is a heterocyclic moiety selected from groups f, g and j defined Claim 1;

b) reacting a compound of formula 1



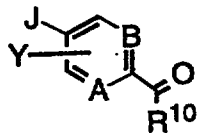
(1)

wherein D, E, G and X are each as defined in Claim 1,

with a compound of formula

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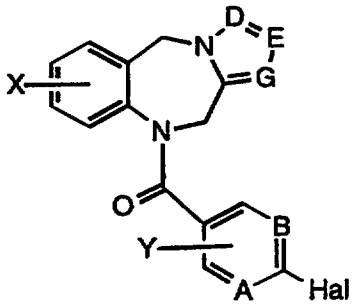
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wherein A, B and Y are each as defined in Claim 1, J is an acylating group and R^{10} is an alkyl group,

to provide a compound of formula I wherein R^1 is a an alkanoyl group;

c) reacting a compound of formula

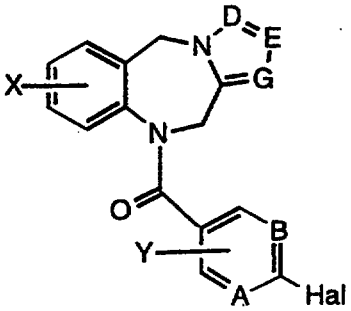


wherein A, B, D, E, G, X and Y are each as defined Claim 1

with a compound of formula $HC{\equiv}C{-}R^9$, wherein R^9 is as defined Claim 1,

to provide a compound of formula I wherein R^1 is $-C{\equiv}C{-}R^9$ and R^9 is as defined Claim 1;

d) converting a compound of formula

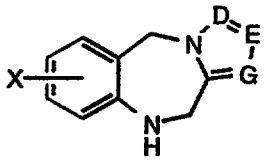


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wherein A, B, D, E, G, X and Y are each as defined Claim 1 to the corresponding compound of formula I wherein R^1 is an alkanoyl group;

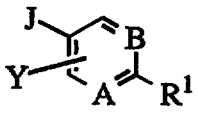
e) reacting a compound of formula 1



(1)

wherein D, E, G and X are as defined in Claim 1,

with an acylating agent of formula 9

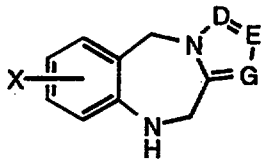


(9)

wherein A and B are carbon, J is an acylating moiety, R^1 is a heterocyclic moiety selected from group g defined in Claim 1 and R^2 is hydrogen;

to provide the desired compound of formula I wherein A and B are carbon, R^1 is a heterocyclic moiety selected from group g defined in Claim 1 and R^2 is hydrogen;

f) reacting a compound of formula 1



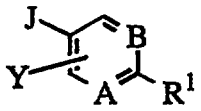
(1)

wherein D, E, G and X are as defined in Claim 1,

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with an acylating agent of formula 9

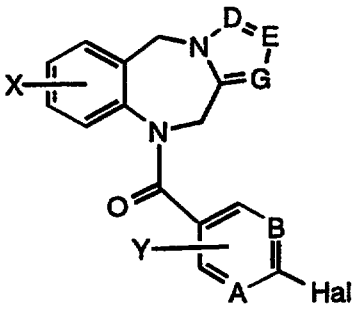


(9)

wherein A and B are as defined in Claim 1, J is an acylating moiety, R^1 is a heterocyclic moiety selected from group f defined in Claim 1 and R^2 is hydrogen;

to provide the desired compound of formula I wherein R^1 is a heterocyclic moiety selected from group f defined in Claim 1 and R^2 is hydrogen;

g) reacting a compound of formula



wherein A, B, D, E, G, X and Y are each as defined Claim 1,

with the appropriate compound of formula R^1H, wherein R^1 is a heterocyclic moiety selected from groups a, b, c, d, l, n and o defined Claim 1,

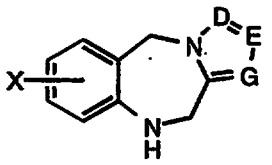
to provide the desired compound of formula I wherein R^1 is the a heterocyclic moiety selected from groups a, b, c, d, l, n and o defined Claim 1,

h) reacting a compound of formula 1

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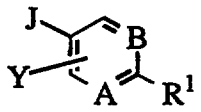
* C L M S *



(1)

wherein D, E, G and X are as defined in Claim 1,

with an acylating agent of formula 9

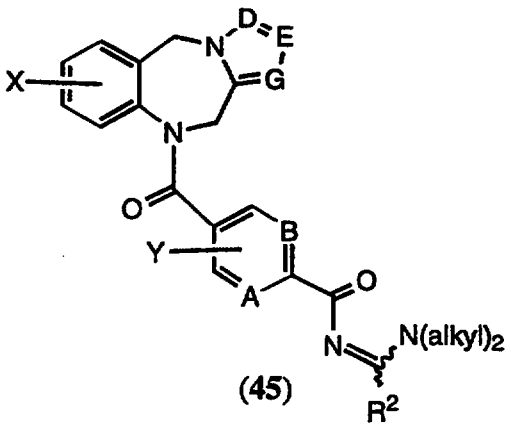


(9)

wherein A and B are as defined Claim 1, J is an acylating moiety and R^1 is a heterocyclic moiety selected from groups a, b, c, d, l, n and o defined Claim 1;

to provide the desired compound of formula I wherein R^1 is a heterocyclic moiety selected from groups a, b, c, d, l, n and o defined Claim 1;

i) converting a compound of formula 45



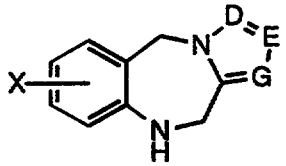
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wherein A, B, D, E, G, X, Y and R^2 are each as defined Claim 1, to the corresponding compound of formula I wherein R^1 is a heterocyclic moiety selected from groups e, i and k defined Claim 1;

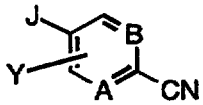
j) reacting a compound of formula 1



(1)

wherein D, E, G and X are as defined in Claim 1,

with a compound of formula 43



(43)

wherein A, B and Y are as defined in Claim 1 and J is an acylating agent,

to provide the desired compound of formula I wherein R^1 is CN or $CONH_2$;

k) converting a compound of formula I which is a free acid to the corresponding pharmaceutically acceptable salt;

or l) converting one compound of formula I to another.

20. A process as claimed in Claim 19 wherein step l comprises:

i) converting a compound of formula I, wherein R^1 is the group $-C{\equiv}CR^9$ and R^9 is as defined in claim 1, to the corresponding compound wherein R^1 is an alkanoyl group;

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ii) alkylating or acylating a compound of formula I wherein the group R^1 is a heterocyclic moiety as defined in Claim 1 which includes the group R^2 or R^4 which is hydrogen, to provide the corresponding compound of formula I wherein the group R^2 or R^4 is other than hydrogen;

iii) converting a compound of formula I wherein Y is an alkoxy group to the corresponding compound of formula I wherein Y is a hydroxyl group;

iv) converting a compound of formula I wherein R^1 is CN to the corresponding compound of formula I wherein R^1 is heterocyclic moiety m defined Claim 1;

v) converting a compound of formula I R^1 is a heterocyclic moiety selected from groups a, c, e, f, g, h, i, j, k, l, m, n and o defined Claim 1, D is CW and W is hydrogen, to the corresponding compound of formula I wherein D is CW and W is halogen or the group $CH_2NR^6R^7$;

or vi) converting a compound of formula 1 wherein R^1 is CN a compound of formula I wherein R^1 is $CONH_2$.

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