

PATENT SPECIFICATION

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(54) NOVEL, 1-(BENZAZOLYLALKYL)PIPERIDINE DERIVATIVES

(71) We, JANSSEN PHARMACEUTICA N.V., a Belgian Body Corporate, of, Turnhoutsebaan 30, Beerse, Belgium, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to certain novel 1-(benzazolyalkyl)piperidine derivatives which are useful as antiemetic agents.

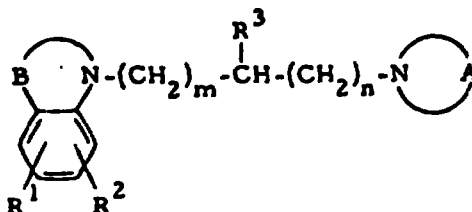
Certain benzazolyalkyl and indolyalkyl substituted piperidine derivatives and a number of aminoalkyl substituted benzazoles are known some of which have pharmacological, e.g. antidepressant, anticonvulsant, antihistaminic or anti spasmogenic activities.

The compounds of the present invention differ from these known compounds by the nature of respectively the benzazole and/or substituted piperidine moiety within their structure.

A number of the aforementioned prior art compounds are described in the following references:

- Int. Pharmacopsychiat 1968 (1), p. 214;
 C.A., 64, 2093 b (1966);
 C.A., 72, 111466 (1970);
 C.A., 81, 120632 b (1974);
 French Patent No. 2,042,321; and
 Belgian Patent No. 753,472.

The 1-(benzazolyalkyl)piperidine derivatives of this invention may structurally be represented by the following formula:



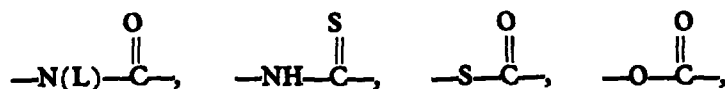
(1)

and the pharmaceutically acceptable acid addition salts thereof wherein:

R^1 and R^2 are each independently a hydrogen atom, a lower alkyl or a trifluoromethyl group;

B is a bivalent radical of the formula

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$-\text{N}=\text{N}-$ or $-\text{N}=\text{CH}-$, wherein L is a hydrogen atom, a lower alkyl, lower alkylcarbonyl or lower alkenyl group and the bivalent radical is attached to the benzene nucleus by the heteroatom;

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R^3 is a hydrogen atom or a methyl group;

m and n are each an integer of 1 or 2; and the radical

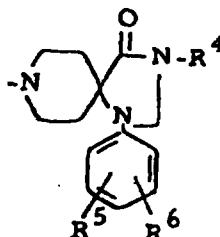
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is

a) a radical having the formula:

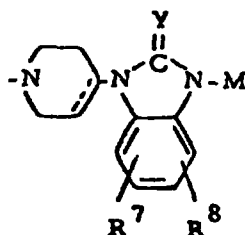
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wherein R^4 is a hydrogen atom or a lower alkyl group; and R^5 and R^6 are each independently a hydrogen or halogen atom, a lower alkyl or trifluoromethyl group;

b) a radical having the formula:



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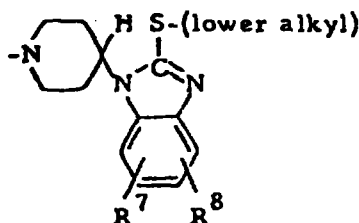
wherein R^7 and R^8 are each independently a hydrogen or halogen atom, a lower alkyl or trifluoromethyl group; Y is an O or S atom; M is a hydrogen atom, a lower alkyl or lower alkylcarbonyl group; and the dotted line indicates that the double bond between the 3 and 4 carbon atoms of the piperidine nucleus is optional, provided that when Y is an S atom, then there is a single bond between the 3 and 4 carbon atoms of the piperidine nucleus, and then M is a hydrogen atom;

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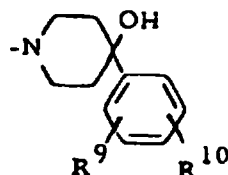
c) a radical having the formula:

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wherein R^7 and R^8 are each independently a hydrogen or halogen atom, a lower alkyl or trifluoromethyl group; and

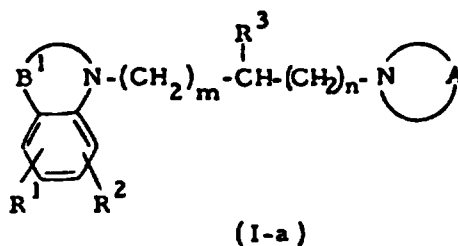
d) a radical having the formula:



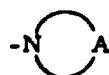
wherein R^9 is a hydrogen or halogen atom, a lower alkyl or trifluoromethyl group, and R^{10} is a hydrogen or halogen atom.

By the term "lower alkyl" as used herein is meant a straight or branched chain group having from 1 to 5 carbon atoms, such as, methyl, ethyl, propyl, 1-methylethyl, butyl or pentyl; by the term "lower alkenyl" as used herein is meant a straight or branched chain alkenyl radical having from 2 to 5 carbon atoms, such as, 1-methylethenyl, 2-propenyl, 2-butenyl, 3-butenyl or 2-pentenyl; and by the term "halo" is meant halogens of atomic weight less than 127, i.e. fluoro, chloro, bromo, and iodo.

Compounds of formula (1-a) which may be represented by the formula:



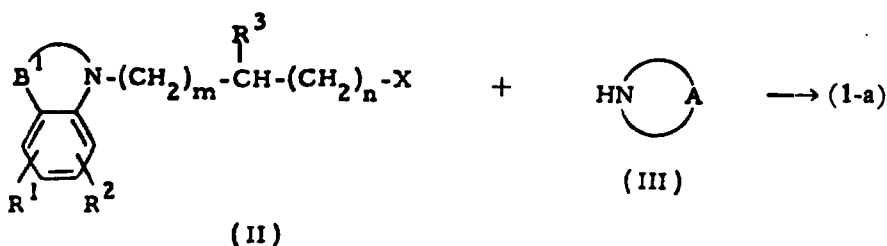
wherein R^1 , R^2 , R^3 , m , n and



are as previously defined and B^1 is as defined for B, but other than an $-NH-C(S)-$ radical, may be conveniently prepared by reacting an appropriate reactive ester of formula (II) wherein X is an appropriate reactive ester function derived from the corresponding alcohol, such as, halo, methanesulfonyl or 4-methylbenzenesulfonyl with an appropriate piperidine derivative of formula (III) wherein the



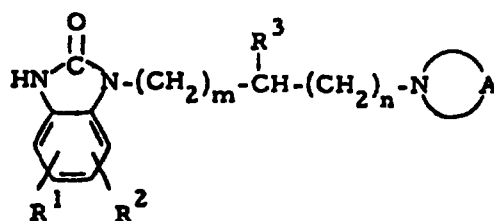
group is as above defined.



The foregoing condensation reaction is preferably carried out in an appropriate organic solvent, such as, a lower alkanol, e.g. methanol, ethanol, propanol, or butanol;

an aromatic hydrocarbon, e.g. benzene, methylbenzene or dimethylbenzene; a ketone, e.g. 4-methyl-2-pentanone; an ether, e.g. 1,4-dioxane, or 1,1'-oxybisethane; N,N-dimethylformamide, or nitrobenzene. The addition of an appropriate base, such as, an alkali metal or earth alkali metal carbonate or hydrogen carbonate, may be utilized to pick up the acid liberated during the course of the reaction. A small amount of an appropriate metal iodide, e.g. sodium or potassium iodide, may be added as a reaction promotor, especially when the reactive ester of formula (II) is a chloride. Elevated temperatures may be used to enhance the rate of the reaction and, preferably, the reaction is carried out at the reflux temperature of the reaction mixture. In this and following procedures, the reaction products are separated from the medium and, if necessary, further purified by the application of known techniques.

Compounds of formula (I) which may be represented by the formula:

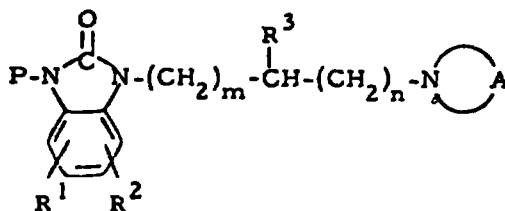


(I-b)

wherein R^1 , R^2 , m , n , R^3 are

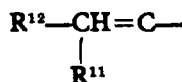


are as previously defined may also be prepared starting from the corresponding compounds of formula (IV)



(IV)

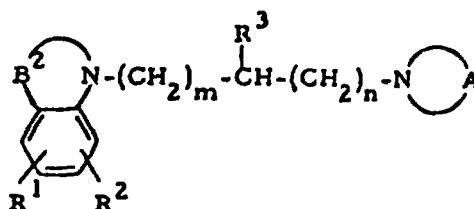
wherein P is an appropriate protecting group, by the removal of the protecting group according to known conventional procedures. Examples of such protecting groups are, among others, lower alkyloxycarbonyl, 4-methylbenzenesulfonyl, or methanesulfonyl and, preferably a substituted ethenyl group of the formula:



wherein R^{11} and R^{12} are different groups. R^{11} is preferably a lower alkyl group and R^{12} is preferably a hydrogen atom, a lower alkyl or phenyl group.

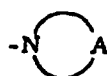
When the protecting group is a lower alkyloxycarbonyl, 4-methylbenzenesulfonyl or methanesulfonyl group, it may easily be removed by alkaline hydrolysis, and when the protecting group is a substituted ethenyl group it is conveniently eliminated by subjecting the appropriate intermediate (IV) to acid hydrolysis. In carrying out the acid hydrolysis to remove the substituted ethenyl group from (IV) a wide variety of protonic acids may be employed including mineral acids, such as, hydrochloric, hydrobromic, sulfuric, nitric and phosphoric acid, and organic acids such as, acetic or propanoic acids. Furthermore the reaction may be carried out in a reaction inert organic solvents as commonly employed in such a type of hydrolytic reactions, e.g., methanol, ethanol or 2-propanone.

Compounds within the scope of formula (I) which may be represented by the formula:

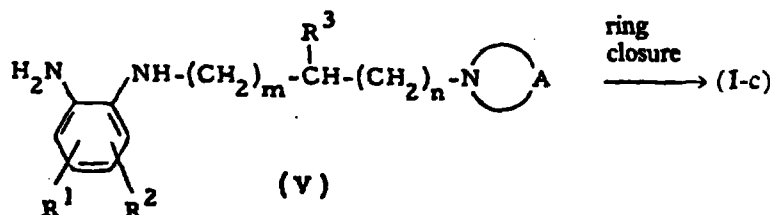


(1-c)

wherein R^1 , R^2 , m , n , R^3 and



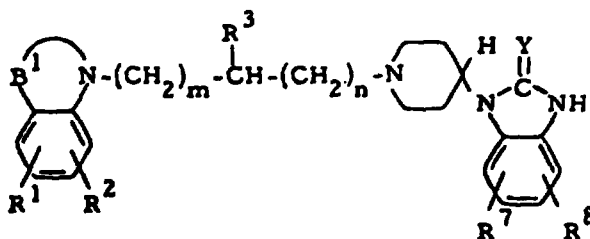
are as previously defined and B^2 is $-\text{NH}-\text{C}(\text{O})-$, $-\text{NH}-\text{C}(\text{S})-$ and $-\text{N}=\text{CH}-$, may be prepared by subjecting an appropriate benzenediamine of formula (V) to ring closure with an appropriate cyclizing agent, the nature of which depends on the nature of B^2 in the desired product.



The foregoing cyclization reaction may be performed by known procedures of preparing 1H - benzimidazoles, 1,3 - dihydro - 2H - benzimidazol - 2 - ones, and 1,3 - dihydro - 2H - benzimidazol - 2 - thiones starting from 1,2 - benzenediamines. Suitable cyclizing agents which may advantageously be employed to prepare compounds (I-c) wherein B^2 is $-\text{NH}-\text{C}(\text{O})-$, include urea, carbonyl dichloride and alkali metal isocyanates, and the cyclisation reaction may be carried out by generally known techniques. For example, when urea is used as the cyclizing agent the desired compounds may easily be obtained by stirring and heating the reactants together in the absence of any solvent.

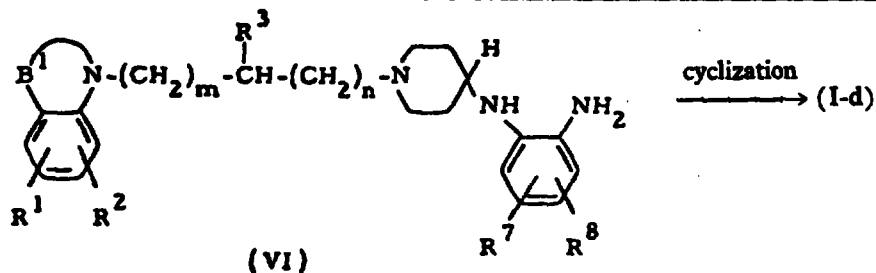
When B^2 in the desired compounds (I-c) is $-\text{NH}-\text{C}(\text{S})-$, cyclizing agents such as, carbon disulfide, thiourea, carbonothioic dichloride and ammonium thiocyanate may be used and when B^2 is $-\text{N}=\text{CH}-$, formic acid or an appropriate tri-(alkyloxy)methane may be used as a cyclizing agent.

In a manner similar to that described hereabove compounds of the formula I-a may be prepared:



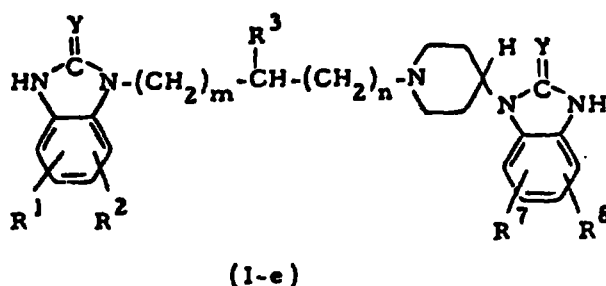
(1-d)

wherein R^1 , R^2 , R^3 , R^7 , R^8 , m , n , B^1 and Y are as previously defined, by cyclizing an appropriate benzenediamine of formula (VI) with an appropriate cyclizing agent.

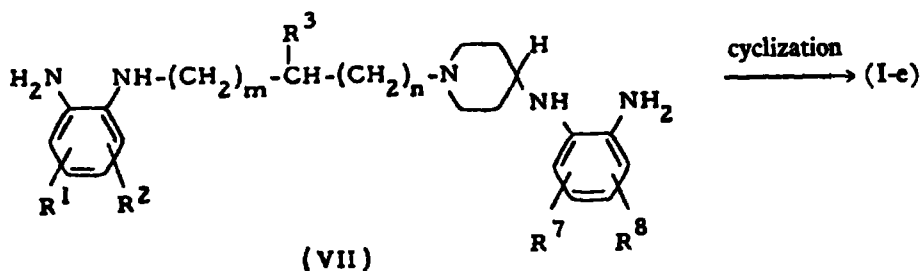


In carrying out this cyclization reaction the same cyclizing agents described herebefore for the preparation of compounds (I-C) starting form (V) may be used, more specifically for the preparation of compounds (I-c) wherein B^1 is $-NH-C(O)-$ or $-NH-C(S)-$.

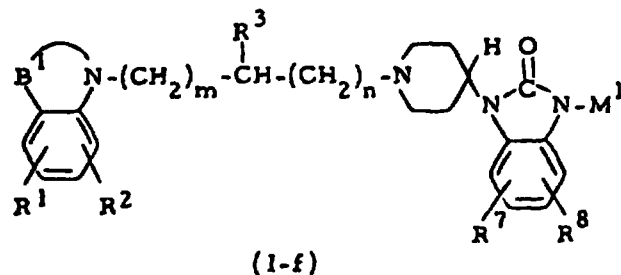
In a similar manner compounds of the formula:



wherein R^1 , R^2 , R^3 , R^7 , R^8 , m and n are as previously defined and the two Y groups are both O or both S may be prepared starting from the corresponding intermediates of formula (VII) by cyclizing both benzenediamine groups in (VII) in one reaction step with an appropriate cyclizing agent as described hereinabove for the preparation of respectively 1,3 - dihydro - 1H - benzimidazol - 2 - ones and 1,3 - dihydro - 1H - benzimidazol - 2 - thiones.



Compounds having the formula:



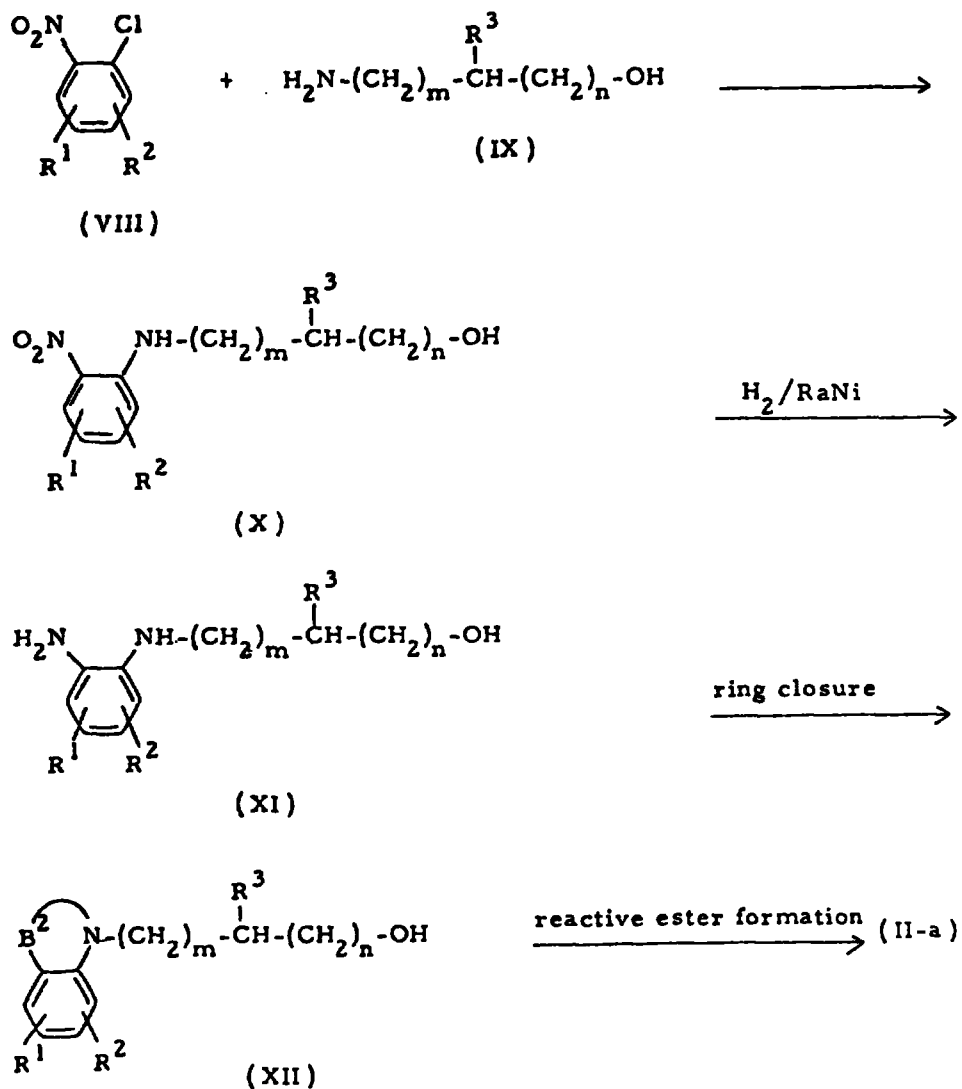
wherein R^1 , R^2 , R^3 , R^7 , R^8 , m , n and B^1 are as previously defined. M^1 is a lower alkyl or lower alkylcarbonyl group may be prepared by respectively N-alkylating or

wherein R^1 , R^2 , R^3 , m , n , B^2 and X are as previously defined may be prepared as follows:

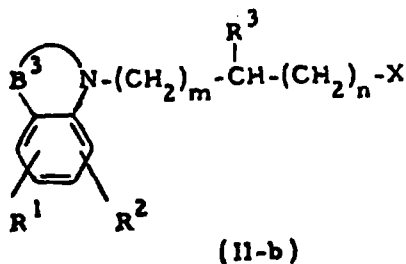
An appropriately substituted 2-chloronitrobenzene of formula (VIII) is reacted with an appropriate aminoalkanol (IX) by refluxing the reactants together in an appropriate reaction-inert solvent such as, a lower alkanol, e.g. ethanol, 2-propanol or butanol, whereupon a [(2-nitrophenyl)amino]alkanol of formula (X) is obtained, which in turn is subjected to a nitro-to-amine reduction, e.g. by catalytic hydrogenation using a Raney-nickel catalyst. The [(2-aminophenyl)amino]alkanol of formula (XI) so-obtained is then reacted with an appropriate cyclizing agent as described hereinbefore for the preparation of the compounds (I-c) starting from (V), and the alcohol (XII) so-obtained is subsequently converted into the desired reactive ester (II-a) by the application of known techniques.

Halides are conveniently prepared by the reaction of (XII) with an appropriate halogenating agent such as, sulfinyl chloride, sulfonyl chloride, phosphorus pentachloride, phosphorus pentabromide, or phosphoryl chloride. When the reactive ester is an iodide, it is preferably derived from the corresponding chloride or bromide by the replacement of that halogen with iodine. Other reactive esters such as methanesulfonates and 4-methylbenzenesulfonates are obtained by the reaction of the alcohol with an appropriate sulfonyl halide such as, methanesulfonyl chloride and 4-methylbenzenesulfonyl chloride respectively.

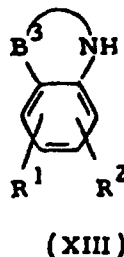
The foregoing reactions are more clearly illustrated in the following schematic representation.



Intermediates of formula (II) which may be represented by the formula



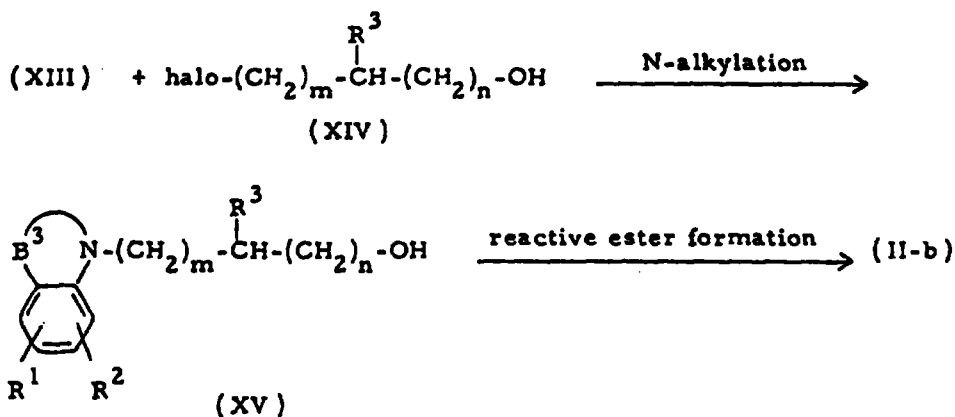
wherein R^1 , R^2 , R^3 , m , n and X are as previously defined and B^3 is $-S-C(O)-$, $-O-C(O)-$, $-N\equiv M-$, $-N=CH-$, or $-N(L^1)-C(O)-$ wherein L^1 is a lower alkyl, lower alkenyl or lower alkylcarbonyl group may also conveniently be prepared by the introduction of the reactive ester side chain into a starting material of the formula

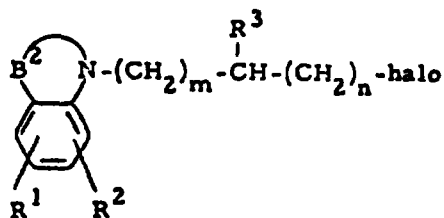
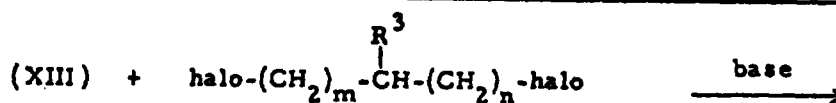


following procedures known in the art. For example, one may first introduce a hydroxyalkyl chain by N-alkylating (XIII) with an appropriate haloalkanol of formula (XIV) following common N-alkylating procedure to obtain an alcohol of formula (XV), the hydroxyl group of which is subsequently converted into a reactive ester group according to conventional procedures as previously described. In place of the haloalkanol (XIV) a tetrahydro-2H-pyran-2-yl ether derivative thereof may also be used in which case the corresponding ether derivative of (XV) is obtained, the ether function of which is split open by acid hydrolysis, e.g., by stirring and heating the ether compound in diluted hydrochloric acid.

When the reactive ester (II-b) is a halide, (II-b-1), it may alternatively be prepared by the reaction of (XIII) with an equivalent of an appropriate dihaloalkane (XVI), in the presence of an appropriate strong base such as, sodium methanolate, or following a Mackosza procedure using aqueous alkali and a quaternary ammonium catalyst, e.g., N,N,N-triethylbenzenemethanaminium chloride.

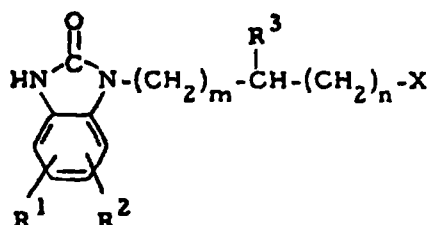
The foregoing procedure may be illustrated as follows.





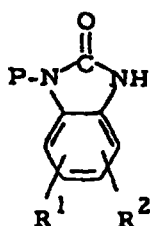
(II-b-1)

Intermediates of the formula:



(II-c)

wherein R^1 , R^2 , R^3 , m , n and X are as previously defined be prepared by introducing the reactive ester side chain into a starting material of formula (XVII)

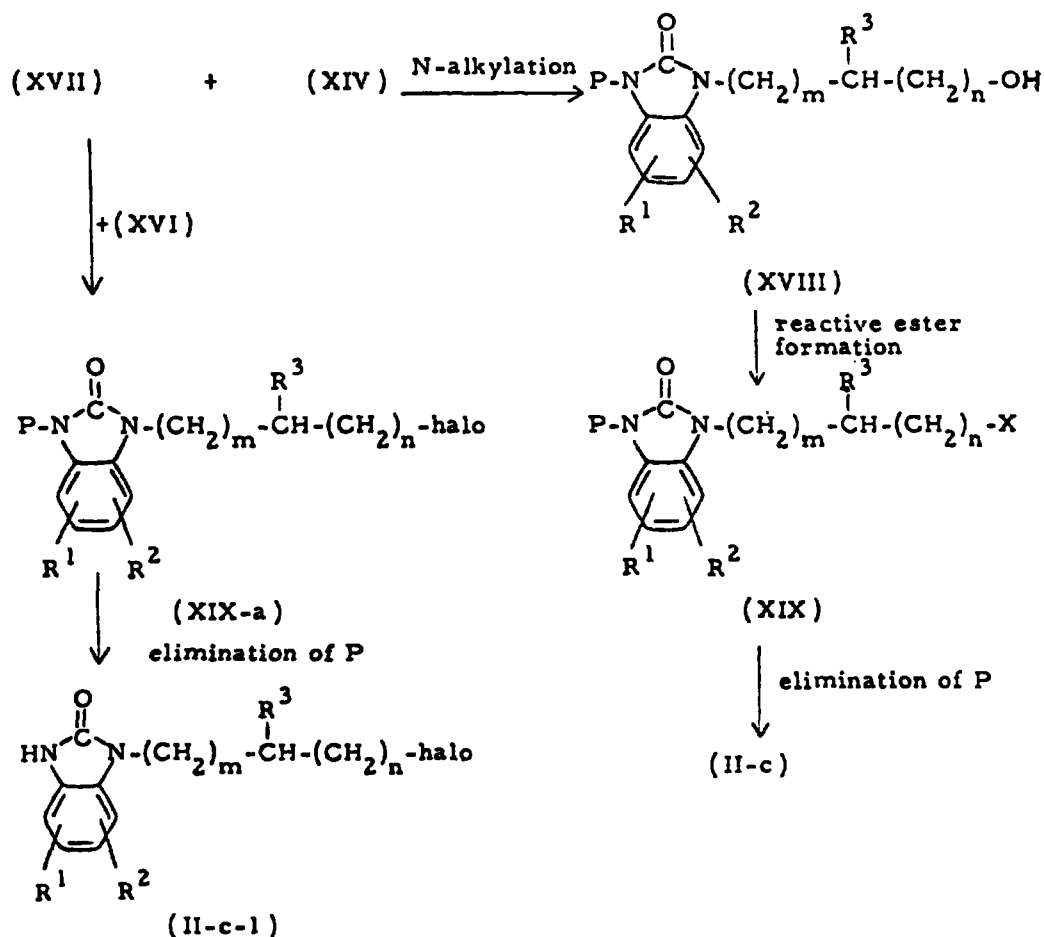


(XVII)

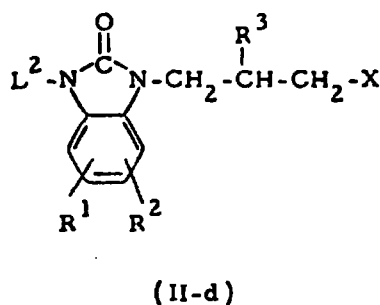
wherein P is an appropriate protecting group as previously defined, and thereafter eliminating the protecting group of the so-obtained (XIX) according known procedures as described hereinabove. The introduction of the reactive ester side chain may be performed following similar procedures to those described hereabove for the introduction of said chain into starting materials of formula (XIII). More particularly a hydroxyalkyl chain may be first introduced whereafter the hydroxyl group of the thus obtained intermediate (XVIII) is converted into a reactive ester group to obtain (XIX), or, when the reactive ester is a halide, (XIX-a) the halide may be obtained directly by the reaction of (XVII) with an appropriate dihaloalkane.

When the protecting group P is one subject to alkaline hydrolysis e.g. a lower alkyloxycarbonyl, methanesulfonyl or 4-methylbenzenesulfonyl group, the N -alkylation reaction to introduce respectively the hydroxyalkyl or haloalkyl chain should be carried out under nonhydrolytic conditions, using for example an appropriate metal base such as, sodium hydride or sodium methanolate in an appropriate aprotic organic solvent such as, N,N -dimethylformamide N,N -dimethylacetamide or hexamethylphosphoric triamide.

The foregoing reactions are more clearly illustrated in the following schematic representation.

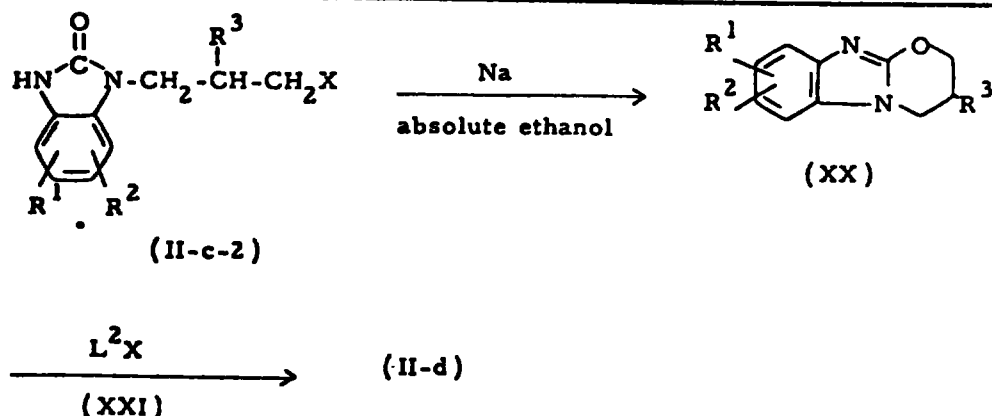


Intermediates having the formula

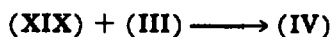


wherein R^1 , R^2 , R^3 and X are as previously defined and L^2 is a lower alkyl or lower alkenyl group, said lower alkenyl having its unsaturation at the β , γ or δ -position, may be prepared as follows.

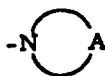
An appropriate intermediate of formula (II-c), wherein m and n are each 1, (II-c-2), is treated with sodium metal in absolute ethanol whereby a cyclic ether of formula (XX) is formed. The latter is subsequently reacted with an appropriate reactive ester L^2X (XXI), wherein L^2 and X are as previously defined, e.g., by refluxing the reactants together in an appropriate organic solvent such as, 2-propanone, whereby the desired intermediate (II-d) is obtained.



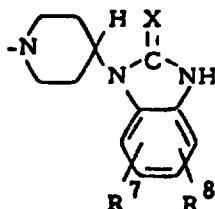
The compounds of formula (IV), used as intermediates in the preparation of the compounds (I-b), are generally be obtained by a condensation reaction of an intermediate of formula (XIX) with an appropriate intermediate of formula (III) under similar conditions to those described hereinabove for the preparation of the compounds (I-a) starting from (II) and (III).



The intermediates of formula (IV) wherein

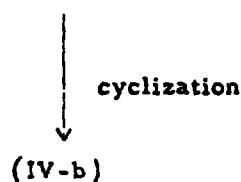
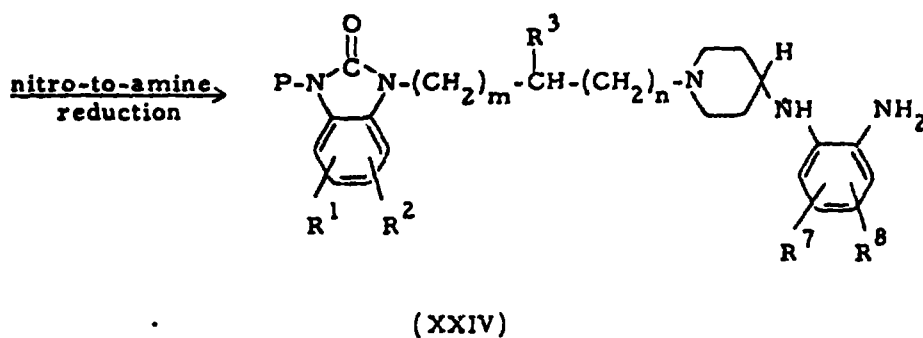
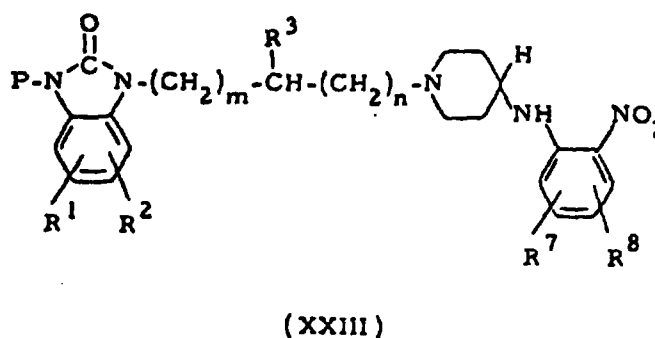
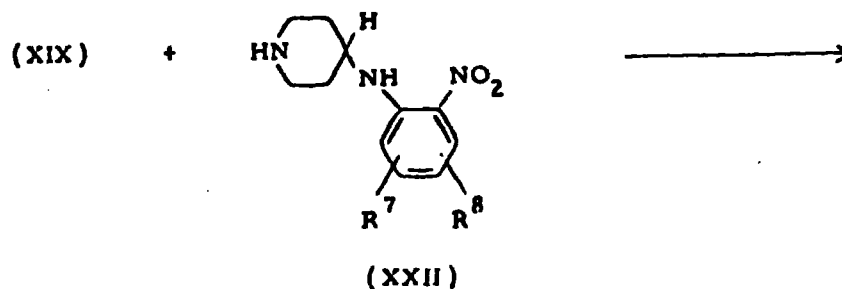


has the formula



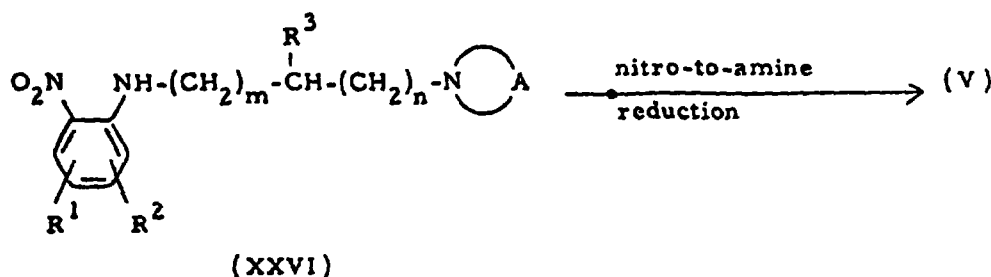
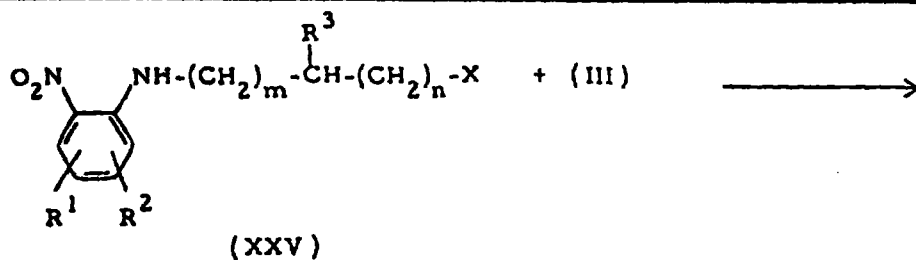
and which are indicated as (IV-b) may be prepared by the condensation of an appropriate reactive ester of formula (XIX) with an appropriate N-(2-nitrophenyl)-4-piperidinamine of formula (XXII), followed by the reduction of the nitro group of the so-obtained (XXIII) according to standard nitro-to-amine reduction procedures, e.g., by the reaction of the nitro compound with nascent hydrogen or by catalytic hydrogenation in the presence of an appropriate catalyst such as, Raney-nickel and cyclization of the resulting benzenediamine (XXIV) with an appropriate cyclizing agent as described hereinabove.

The foregoing reactions are illustrated in the following schematic representation.



The starting materials of formula (XXII) herein may be prepared following the procedures outlined in United States Patent No. 3,910,930.

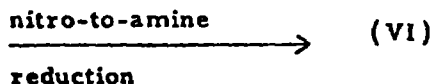
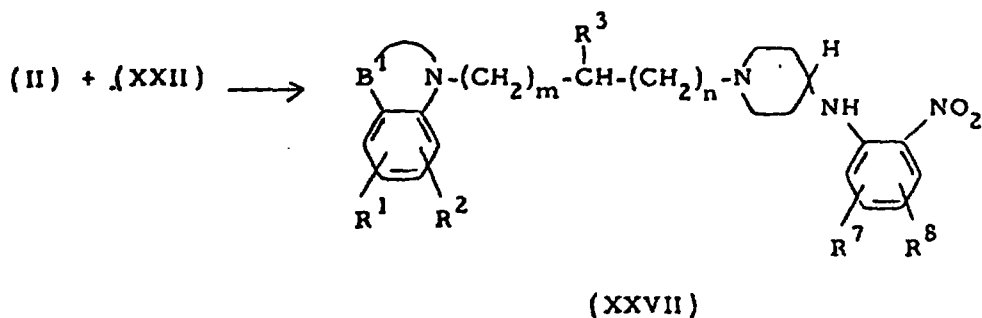
The intermediates of formula (V) are obtained by the condensation of an appropriate reactive ester of formula (XXV) with an appropriate piperidine derivative of formula (III), followed by the reduction of the nitro group of the thus obtained intermediate (XXVI) to an amino group according to standard nitro-to-amine reduction procedures.



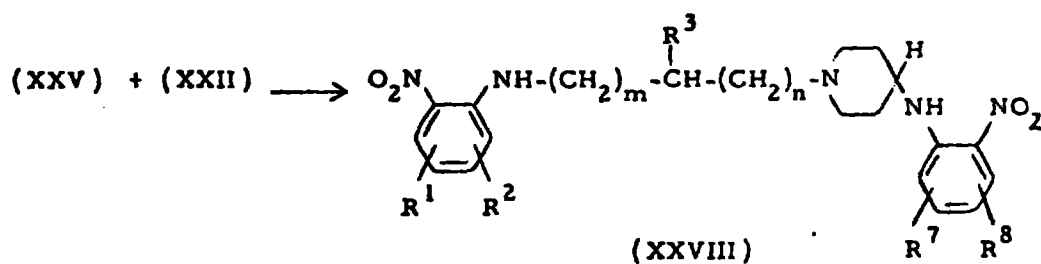
The reactive esters of formula (XXV), used as starting materials herein are easily prepared starting from an alcohol of formula (X) by the conversion of the hydroxyl function thereof into a reactive ester group following standard procedures as previously described herein.

The intermediates of formula (VI) are generally prepared by the condensation of an appropriate reactive ester of formula (II) with an appropriate N-(2-nitrophenyl)-4-piperidinamine of formula (XXII) and subsequent reduction of the nitro group of the thus obtained (XXVII) to an amine group following standard nitro-to-amine reduction procedures as previously described.

It is to be noted that when the nitro-to-amine reduction is accomplished by catalytic hydrogenation using palladium-on-charcoal catalyst dehalogenation in compounds wherein aromatic halogen substituents are present may occur.



The intermediates of formula (VII) may similarly be prepared by the condensation of a reactive ester of formula (XXV) with a piperidine derivative of formula (XXII) followed by the reduction of both nitro groups in the thus obtained (XXVIII) according to standard procedures as previously indicated.

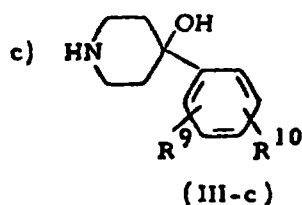
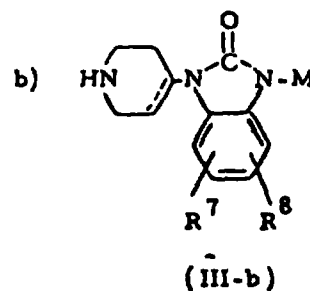
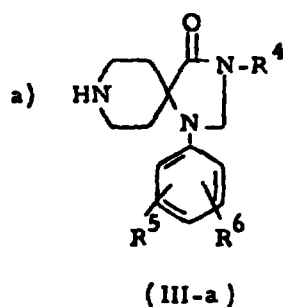


nitro-to-amine

reduction

(VII)

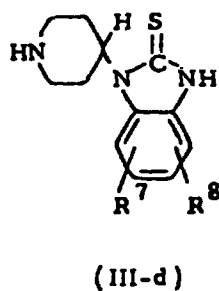
Starting materials of formula (III), represented by the formulas:



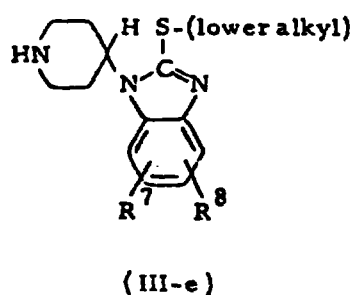
and methods of preparing the same may respectively be found in the following references:

- a) United States Patent No. 3,238,216
- b) United States Patent No. 3,161,645; Belgian Patent No. 830,403
- c) United States Patent No. 3,518,276; and United States Patent No. 3,575,990

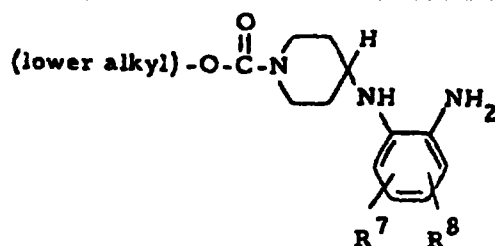
Starting materials of formula (III) which are represented by the formulas:



and



may generally be prepared starting from an appropriate N-(2-aminophenyl)-4-piperidinamine of formula:



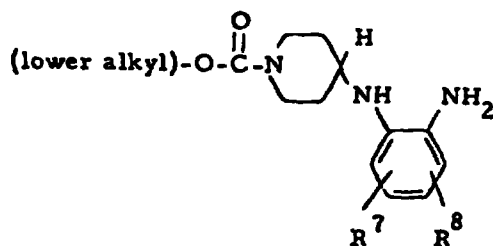
(XXIX)

The starting materials (III-d) are conveniently prepared by the cyclization of (XXIX) with an appropriate cyclizing agent e.g., carbon disulfide and subsequent removal of the lower alkoxy carbonyl group of the so-obtained (XXX) by alkaline hydrolysis.

The starting materials (III-e) can be prepared by S-alkylating (XXX) as described hereinabove followed by elimination of the lower alkoxy carbonyl group of the resulting (XXXI).

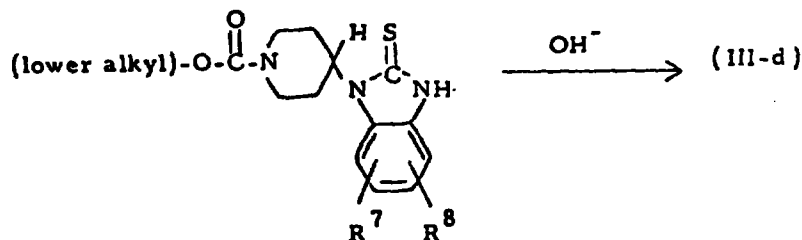
The N-(2-aminophenyl)-4-piperidinamines of formula (XXIX), a number of which are known compounds, may be prepared following the procedures described in United States Patent No. 3,910,930 and Belgian Patent No. 830,403.

The foregoing procedures are illustrated in the following schematic representation.



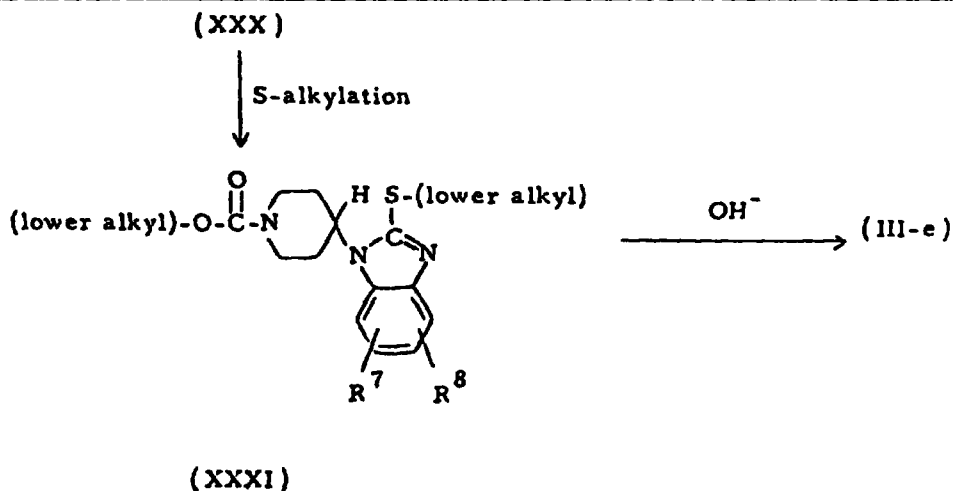
(XXIX)

cyclization



(XXX)

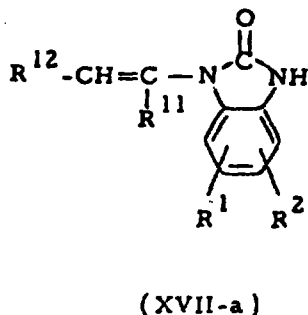
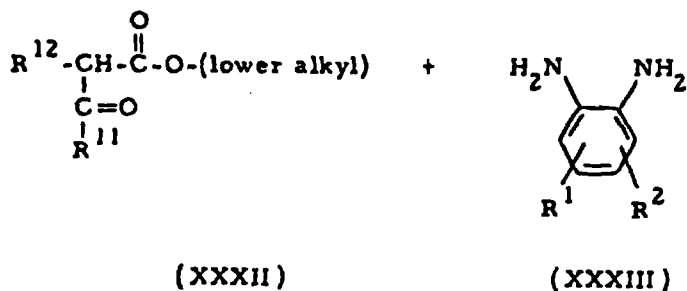
$\text{OH}^- \rightarrow$ (III-d)



The ultimate starting materials in all of the foregoing preparations are generally known or their preparation may be performed following known procedures of preparing similar compounds.

For example, the preferred starting materials of formula (XVII) wherein P is an appropriately substituted ethenyl group, (XVII-a), an important number of which are known compounds, may be prepared following the procedures outlined in J. Chem. Soc., 1960, p. 308 and p. 314.

More particularly such compounds are conveniently prepared by the reaction of an appropriate ester of the formula (XXXII) wherein R¹¹ and R¹² have the previously indicated meaning, with an appropriate benzenediamine of formula (XXXIII). Said reaction is preferably carried out by stirring and refluxing the reactants together in an appropriate reaction-inert organic solvent with azeotropic water removal. Suitable reaction-inert organic solvents for this purpose include, for example, aromatic hydrocarbons such as benzene, methylbenzene, and dimethylbenzene.



The intermediates of formulas (V), (VI) and (VII) are deemed to be novel and, as useful intermediates in the preparation of the desired compounds of formula (I), they constitute an additional feature of this invention.

The compounds of this invention may be converted to their therapeutically useful acid addition salts by treatment with an appropriate acid, such as, an inorganic acid, such as hydrohalic acid, e.g., hydrochloric, or hydrobromic, sulfuric acid, nitric acid, phosphoric acid; or an organic acid such as acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, propanedioic, butanedioic, (Z) - 2-butenedioic, (E) - 2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, benzoic, 3-phenyl-2-propenoic, α -hydroxybenzeneacetic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, and 4-amino-2-hydroxybenzoic acid. Conversely the salt form can be converted by treatment with alkali into the free base form.

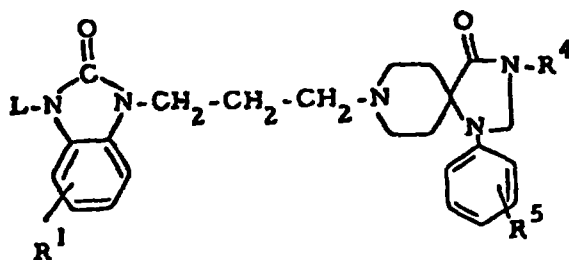
The compounds of formula (I) and the therapeutically active acid addition salts thereof have been found to possess strong antiemetic activity as is shown by their ability to block apomorphine-induced vomiting in dogs. The method used has previously been described by P. A. J. Janssen and C. J. E. Niemegeers in: *Arzneim.-Forsch. (Drug Res.)* 9, 765-767 (1959).

The compounds listed below were administered subcutaneously to beagle dogs at different doses and the animals were challenged 1 hour thereafter with a standard dose of 0.31 mg/kg (subcutaneous) of apomorphine.

The tables below give the ED₅₀ values of a number of the compounds under consideration. As used herein the ED₅₀ value represents the dose which protects 50% of the animals from emesis.

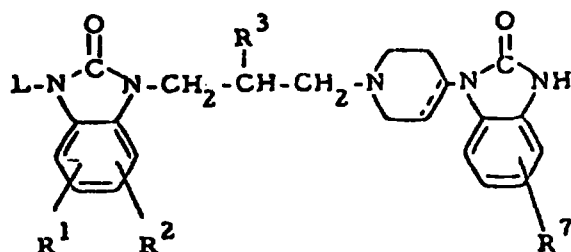
It is understood that the compounds shown in the tables are not listed for the purpose of limiting the invention thereto, but only to exemplify the outstanding antiemetic properties of all the compounds within the scope of formula (I).

TABLE I



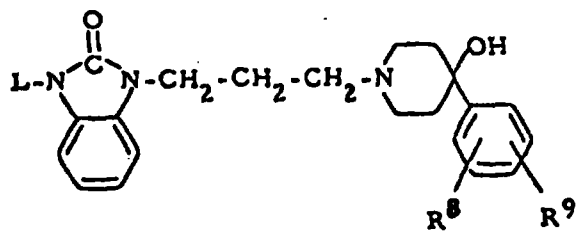
L	R ¹	R ⁴	R ⁵	ED ₅₀ mg/kg s. c.
H	H	H	H	0.03
H	5-Cl	H	H	0.05
H	5-CH ₃	H	H	0.06
CH ₃	H	H	H	0.08
CH ₂ =CH-CH ₂	H	H	H	0.25
H	H	H	4-F	0.04
H	5-Cl	H	4-F	0.015
H	H	H	3-CF ₃	0.025
H	H	CH ₃	H	0.015

TABLE II



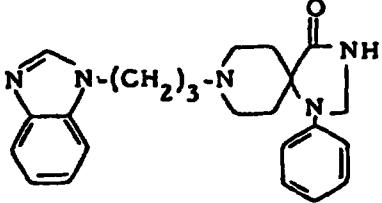
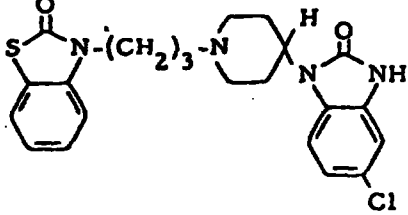
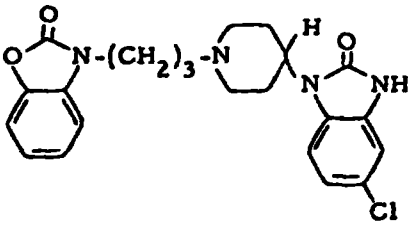
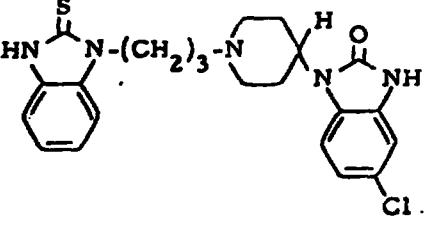
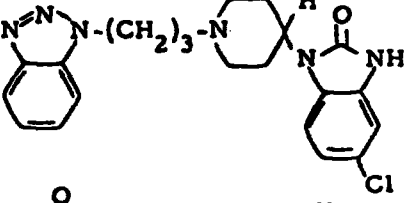
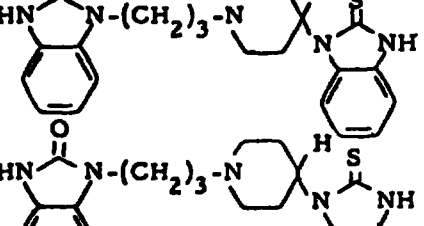
L	R ¹	R ²	R ³		R ⁷	Salt and Solvate form	ED ₅₀ mg/kg s. c.
H	H	H	H		H	-	0.02
H	5-Cl	H	H	"	H	-	0.10
H	5-CH ₃	6-CH ₃	H	"	H	CH ₃ -CHOH-CH ₃	0.45
H	H	H	CH ₃	"	5-Cl	-	0.06
H	H	H	H	"	5-Cl	-	0.01
H	5-Cl	H	H	"	5-Cl	-	0.12
CH ₃	H	H	H	"	5-Cl	-	0.16
=CH-CH ₂	H	H	H	"	5-Cl	-	0.12
H	H	H	H		H	-	0.04
H	5-F	H	H		5-Cl	HCl H ₂ O	0.004
H	5-CH ₃	H	H	"	5-Cl	HCl H ₂ O	0.12
H ₃)=CH ₂	H	H	H	"	5-Cl	-	0.20
H	5-CH ₃	H	H	"	H	HCl H ₂ O	0.20

TABLE III



L	R ⁸	R ⁹	ED ₅₀ mg/kg s. c.
H	4-Cl	H	0.06
CH ₂ =CH-CH ₂	4-Cl	H	0.50
H	4-Cl	3-CF ₃	0.015

TABLE IV

Compound	ED ₅₀ mg/kg s. c.
	0.25
	0.001
	0.03
	0.004
	0.06
	0.025
	0.004

5 In view of their useful antiemetic activity, the compounds of Formula (I) may
10 be formulated into various pharmaceutical compositions for administration purposes.
15 To prepare the pharmaceutical compositions of this invention, an effective antiemetic
20 amount of the particular compound, in base or acid-addition salt form, as the active
ingredient is combined in intimate admixture with a pharmaceutically acceptable
carrier, which carrier may take a wide variety of forms depending on the form of
preparation desired for administration. These pharmaceutical compositions are
desirable in unitary dosage form suitable, preferably, for administration orally, rectally
or by parenteral injection. For example, in preparing the compositions in oral dosage
form, any of the usual pharmaceutical media may be employed, such as, water,
glycols, oils and alcohols for oral liquid preparations such as suspensions syrups,
elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants,
binders, and disintegrating agents for powders, pills, capsules and tablets. Because
of their ease in administration, tablets and capsules are the most advantageous oral
dosage unit form, for which solid pharmaceutical carriers are obviously employed.
For parenteral compositions, the carrier will usually comprise sterile water, at least
in large part, though other ingredients, for example, may be prepared in which the
carrier comprises saline solution, glucose solution or a mixture of saline and glucose
solution. Injectable suspensions may also be prepared for which appropriate liquid
carriers and suspending agents may be employed. Acid addition salts of (I), due to
their increased water solubility compared to the corresponding base form, are obviously
more suitable in the preparation of aqueous compositions.

25 It is especially advantageous to formulate the aforementioned pharmaceutical
30 compositions in dosage unit form for ease of administration and uniformity of dosage.
By the term "dosage unit form" as used herein is meant physically discrete units
suitable as unitary dosages, each unit containing a predetermined quantity of active
ingredient calculated to produce the desired therapeutic effect in association with the
required pharmaceutical carrier. Examples of such dosage unit forms are tablets
(including scored or coated tablets), capsules, pills, powder packets, wafers, injectable
solutions or suspensions, teaspoonsfull and tablespoonsful, and segregated multiples
thereof.

The amount of active ingredient per dosage unit will generally be from 0.25 mg
to 100 mg and, preferably from 1 to 50 mg.

35 The following formulations exemplify typical antiemetic pharmaceutical com-
positions in dosage unit form suitable for systemic administration to animal and
human subjects in accordance with the present invention.

40 *Oral drops:* The following formulation provides 50 liters of an oral-drop solution
comprising 10 milligrams of 5 - chloro - 1 - {1 - [3 - (2,3 - dihydro - 2 - oxo - 1H-
benzimidazol - 1 - yl)propyl] - 4 - piperidinyl} - 1,3 - dihydro - 2H - benzimidazol -
2 - one as the active ingredient (A.I.) per milliliter.

	A.I.	500 grams	
	2-hydroxypropanoic acid	0.5 liter	
	Sodium saccharin	1750 grams	
	Cocoa flavor	2.5 liters	
45	Purified water	2.5 liters	45
	Polyethylene glycol q.s. ad	50 liters.	

50 The A.I. is dissolved in the 2-hydroxypropanoic acid and 1.5 liters of poly-
ethylene glycol at 60° to 80°C. After cooling to 30 to 40°C 35 liters of polyethylene
glycol are added and the mixture is stirred well. A solution of the sodium saccharin
in 2.5 liters of purified water is added and while stirring the cocoa flavor and poly-
ethylene glycol q.s. ad volume are added. The resulting solution is filled into suitable
containers.

55 *Injectable solution:* The following formulation provides 20 liters of a parenteral
solution comprising 2 milligrams of 5 - chloro - 1 - {1 - [3 - (2,3 - dihydro - 2 -
oxo - 1H - benzimidazol - 1 - yl)propyl] - 4 - piperidinyl} - 1,3 - dihydro - 2H -
benzimidazol - 2 - one as the active ingredient per milliliter.

	A.I.	40 grams	
	2,3-dihydroxybutanedioic acid	20 grams	
	methyl 4-hydroxybenzoate	36 grams	
60	propyl 4-hydroxybenzoate	4 grams	60
	water for injection q.s. ad 20 liters		

The methyl and propyl 4-hydroxybenzoates are dissolved in about 10 litres of boiling water for injection. After cooling to about 50°C the 2,3-dihydroxybutanedioic acid and thereafter the A.I. are added while stirring. The solution is cooled to room temperature and supplemented with water for injection q.s. ad volume. The solution is sterilized by filtration (U.S.P. XVII p. 811) and filled in sterile containers.

Oral solution: The following formulation provides 20 liters of an oral solution comprising 5 milligrams of 5 - chloro - 1 - {1 - [3 - (2,3 - dihydro - 2 - oxo - 1H-benzimidazol - 1 - yl)propyl] - 4 - piperidinyl} - 1,3 - dihydro - 2H - benzimidazol-2 - one as the active ingredient per teaspoonful (5 milliliters).

10	A.I.		10
	2,3-dihydroxybutanedioic acid	20 grams	
	Sodium saccharin	10 grams	
	1,2,3-propanetriol	40 grams	
	Sorbitol 70% solution	12 liters	
15	Methyl 4-hydroxybenzoate	3 liters	15
	Propyl 4-hydroxybenzoate	9 grams	
	Raspberry essence	1 gram	
	Gooseberry essence	2 milliliters	
	Purified water q.s. ad 20 liters.	2 milliliters	

The methyl and propyl 4-hydroxybenzoates are dissolved in 4 liters of boiling purified water. First the 2,3-dihydroxybutanedioic acid and thereafter the A.I. are dissolved in 3 liters of this solution. This solution is combined with the remaining part of the former solution and the 1,2,3-propanetriol and the sorbitol solution are added thereto. The sodium saccharin is dissolved in 0.5 liters of water and the raspberry and gooseberry essences are added. The latter solution is combined with the former, water is added q.s. ad volume and the resulting solution is filled in suitable containers.

Film-coated tablets: 10,000 Compressed tablets, each containing as the active ingredient 10 milligrams of 5 - chloro - 1 - {1 - [3 - (2,3 - dihydro - 2 - oxo - 1H-benzimidazol - 1 - yl)propyl] - 4 - piperidinyl} - 1,3 - dihydro - 2H - benzimidazol-2 - one, are prepared from the following formulation:

	Tablet core:		
	A.I.	100 grams	
	Lactose	570 grams	
35	Starch	200 grams	35
	Polyvinylpyrrolidone (Kollidon K 90)	10 grams	
	Microcrystalline cellulose (Avicel)	100 grams	
	Sodium dodecyl sulfate	5 grams	
	Hydrogenated vegetable oil (Sterotex)	15 grams	
40	Coating:		40
	Methyl cellulose (Methocel 60 HG)	10 grams	
	Ethyl cellulose (Ethocel 22 cps)	5 grams	
	1,2,3-Propanetriol	2.5 milliliters	
	Polyethylene glycol 6000	10 grams	
45	Concentrated colour suspension (Opaspray K—1—2109)	30 milliliters	45
	Polyvinylpyrrolidone (Povidone)	5 grams	
	Magnesium octadecanoate	2.5 grams	

(AVICEL, METHOCEL, ETHOCEL and OPASPRAY are Registered Trade Marks).

Preparation of tablet core:

A mixture of the A.I., the lactose and the starch is mixed well and thereafter humidified with a solution of the sodium dodecyl sulfate and the polyvinylpyrrolidone in about 200 milliliters of water. The wet powder mixture is sieved, dried and sieved again. The microcrystalline cellulose and the hydrogenated vegetable oil are added. The whole is mixed well and compressed into tablets.

Coating:

A solution of the ethyl cellulose in 150 milliliters of dichloromethane is added to a solution of the methyl cellulose in 75 milliliters of denaturated ethanol. To this mixture are added 75 milliliters of dichloromethane and the 1,2,3-propanetriol. The polyethylene glycol is melted and dissolved in 75 milliliters of dichloromethane. The latter solution is added to the former and the magnesium octadecanoate, the polyvinylpurrolidone and the concentrated colour suspension are added thereto and the whole is homogenised.

The tablet cores are coated with the thus obtained mixture in a coating apparatus.

Suppositories: One hundred suppositories each containing 30 milligrams of 5-chlor - 1 - {1 - [3 - (2,3 - dihydro - 2 - oxo - 1H - benzimidazol - propyl) - 4-piperidinyl] - 1,3 - dihydro - 2H - benzimidazol - 2 - one as the active ingredient are prepared from the following formulations:

A.I.

2,3-Dihydroxybutanedioic acid	3 grams
Polyethylene glycol 400	3 grams
Surfactant (Span)	25 milliliters
Triglycerides (Witepsol 555) q.s. ad 300 grams.	12 grams

(SPAN and WITEPSOL are Registered Trade Marks).

The A.I. is dissolved in a solution of the 2,3-dihydroxybutanedioic acid in the polyethylene glycol 400. The surfactant and the triglycerides are melted together. The latter mixture is mixed well with the former solution. The thus obtained mixture is poured into moulds at a temperature of 37—38°C to form the suppositories.

In view of the antiemetic activity of the subject compounds, it is evident that the present invention provides a method of inhibiting emesis in warm-blooded animals by the systemic administration of an effective antiemetic amount of a compound of formula (I) and the pharmaceutically acceptable acid addition salts thereof in admixture with a pharmaceutical carrier.

The following examples are intended to illustrate but not to limit the scope of the present invention. Unless otherwise stated all parts therein are by weight.

Example I.

A mixture of 100 parts of 1 - chloro - 2 - nitro - 4 - (trifluoromethyl)benzene, 90 parts of 3 - amino - 1 - propanol and 200 parts of butanol is stirred and heated till reflux. Stirring at reflux is continued overnight. The reaction mixture is cooled and evaporated. Water is added to the residue and the whole is acidified with a hydrochloric acid solution. The product is extracted with methylbenzene. The extract is dried, filtered and evaporated. The solid residue is crystallized from petroleum ether. The product is filtered off and dried, yielding 141 parts (100%) of 3 - {[2-nitro - 4 - (trifluoromethyl)phenyl]amino} - 1 - propanol.

Example II.

Following the procedure of Example I and using equivalent amounts of the appropriate starting materials there are prepared:

- 3 - [(4 - methyl - 2 - nitrophenyl)amino] - 1 - propanol as a residue;
 3 - [(4,5 - dichloro - 2 - nitrophenyl)amino] - 1 - propanol; mp. 97°C; and
 3 - [(2 - chloro - 6 - nitrophenyl)amino] - 1 - propanol as a residue.

Example III.

A mixture of 70 parts of 3 - [(4 - methyl - 2 - nitrophenyl)amino] - 1 - propanol and 400 parts of methanol is hydrogenated at normal pressure and at room temperature with 10 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen is taken up, the catalyst is filtered off and the filtrate is evaporated, yielding 54 parts (91%) of 3 - [(2 - amino - 4 - methylphenyl)amino] - 1 - propanol as a residue.

Example IV.

A mixture of 141 parts of 3 - {[2 - nitro - 4 - (trifluoromethyl)phenyl]amino} - 1 - propanol and 1200 parts of methanol is hydrogenated at normal pressure and at room temperature with 15 parts of Raney-nickel catalyst. After the calculated amount of hydrogen is taken up, the catalyst is filtered off and the filtrate is evaporated.

The residue is crystallized from 2,2'-oxybispropane, yielding 110 parts (100%) of 3 - {[2 - amino - 4 - (trifluoromethyl)phenyl]amino} - 1 - propanol.

Example V.

Following the procedure of Example IV and using equivalent amounts of the appropriate starting materials there are prepared:

3 - [(2 - amino - 4,5 - dichlorophenyl)amino] - 1 - propanol hydrochloride mp. $\pm 185^{\circ}\text{C}$;

3 - [(2 - amino - 6 - chlorophenyl)amino] - 1 - propanol as a residue; and

3 - [(2 - amino - 4 - chlorophenyl)amino] - 1 - propanol as an oily residue.

Example VI.

To a stirred and cooled solution of 54 parts of 3 - [(2 - amino - 4 - methylphenyl)amino] - 1 - propanol in 30 parts of hydrochloric acid solution 10% and 200 parts of water is added dropwise a solution of 28 parts of potassium cyanate in 50 parts of water at a temperature below 10°C . Upon completion, stirring is continued first for 1 hour at room temperature and further for 24 hours at reflux temperature. After cooling to room temperature, the product is extracted with trichloromethane. The extract is washed with a hydrochloric acid solution 5%, dried, filtered and evaporated. The residue is crystallized from 4 - methyl - 2 - pentanone, yielding 19.5 parts (31%) of 1,3 - dihydro - 1 - (3 - hydroxypropyl) - 5 - methyl - 2H - benzimidazol - 2 - one; mp. 114.1°C .

Example VII.

Following the procedure of Example VI and using equivalent amounts of the appropriate starting materials there are prepared:

1,3 - dihydro - 1 - (3 - hydroxypropyl) - 5 - (trifluoromethyl) - 2H - benzimidazol - 2 - one;

5,6 - dichloro - 1,3 - dihydro - 1 - (3 - hydroxypropyl) - 2H - benzimidazol - 2 - one; mp. 174.7°C ;

4 - chloro - 1,3 - dihydro - 3 - (3 - hydroxypropyl) - 2H - benzimidazol - 2 - one; and

5 - chloro - 1,3 - dihydro - 1 - (3 - hydroxypropyl) - 2H - benzimidazol - 2 - one; mp. 148.8°C .

Example VIII.

To a stirred solution of 18.5 parts of 1,3 - dihydro - 1 - (3 - hydroxypropyl) - 5 - methyl - 2H - benzimidazol - 2 - one in 325 parts of dichloromethane are added 11.9 parts of N,N - diethylethanamine. Then there are added dropwise (slowly) 11.5 parts of methanesulfonyl chloride. Upon completion, stirring is continued for 1 hour at reflux temperature. After cooling, the reaction mixture is washed with water, dried, filtered and evaporated. The solid residue is crystallized from 4 - methyl - 2 - pentanone, yielding 15 parts (58%) of 1,3 - dihydro - 1 - (3 - hydroxypropyl) - 5 - methyl - 2H - benzimidazol - 2 - one methanesulfonate; mp. 125°C .

Example IX.

Following the procedure of Example VIII and using equivalent amounts of the appropriate starting materials there are prepared:

3 - (5,6 - dichloro - 2,3 - dihydro - 2 - oxo - 1H - benzimidazol - 1 - yl)propyl methanesulfonate as an oily residue;

3 - (7 - chloro - 2,3 - dihydro - 2 - oxo - 1H - benzimidazol - 1 - yl)propyl methanesulfonate; and

3 - (5 - chloro - 2,3 - dihydro - 2 - oxo - 1H - benzimidazol - 1 - yl)propyl methanesulfonate; mp. $\pm 140^{\circ}\text{C}$.

Example X.

A mixture of 30 parts of 1H-benzimidazole, 49 parts of 2 - (4 - chlorobutoxy) - tetrahydro - 2H - pyran, 21 parts of potassium hydroxide and 200 parts of ethanol is stirred and refluxed overnight. The reaction mixture is cooled to room temperature, filtered and the filtrate is evaporated. The residue is stirred in water and acidified with a diluted hydrochloric acid solution. The whole is stirred and heated for 30 minutes in a water-bath. After cooling to room temperature, the product is extracted with methylbenzene. The aqueous phase is separated and alkalized with ammonium hydroxide. The product is extracted with dichloromethane. The extract is dried,

filtered and evaporated, yielding 50 parts of 1H - benzimidazole - 1 - butanol as an oily residue.

Example XI.

To a stirred mixture of 23 parts of 1,3 - dihydro - 1 - (3 - hydroxypropyl) - 5-(trifluoromethyl) - 2H - benzimidazol - 2 - one in 150 parts of trichloromethane are added dropwise 32 parts of sulfinyl chloride. Upon completion, the whole is heated to reflux and stirring is continued for 1 hour at reflux temperature. After cooling, the reaction mixture is evaporated and the residue is crystallized from 2,2' - oxybispropane, yielding 14 parts (56%) of 1 - (3 - chloropropyl) - 1,3 - dihydro - 5-(trifluoromethyl) - 2H - benzimidazol - 2 - one.

Example XII.

Following the procedure of Example XI and using therein an equivalent amount of an appropriate hydroxy compound as a starting material the following chlorides are prepared:

5 - chloro - 1 - (3 - chloropropyl) - 1,3 - dihydro - 2H - benzimidazol - 2 - one; mp. 122°C; and

6 - chloro - 1 - (3 - chloropropyl) - 1,3 - dihydro - 2H - benzimidazol - 2 - one; mp. 122°C; and

1 - (4 - chlorobutyl) - 1H - benzimidazole as an oily residue.

Example XIII.

To a stirred and refluxing mixture of 35 parts of 4 - fluoro - 1,2 - benzene-diamine in 270 parts of dimethylbenzene is added dropwise, during a 2 hours-period, a solution of 57 parts of ethyl α -acetylbenzeneacetate in 90 parts of dimethylbenzene while meantime the formed water and the ethanol are distilled off (water-separator). The reaction mixture is evaporated and the residue is crystallized from 2-propanol. The product is filtered off and purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (98:2 by volume) as eluent. The pure fractions are collected and the eluent is evaporated, yielding 11 parts of 6-fluoro - 1,3 - dihydro - 1 - (1 - methyl - 2 - phenylethenyl) - 2H - benzimidazol - 2 - one; mp. 190°C.

Example XIV.

To a stirred solution of 8.5 parts of 1,3 - dihydro - 1 - (1 - methylethenyl) - 2H - benzimidazol - 2 - one in 45 parts of N,N - dimethylformamide are added portionwise 1.7 parts of a sodium hydride dispersion 78%. After stirring for 1 hour at room temperature, the whole is cooled to 0—5°C and 8.65 parts of 1 - bromo - 3-chloropropane are added dropwise (slowly). Upon completion, stirring is continued for 3 hours at room temperature. The reaction mixture is poured onto crushed ice and the product is extracted with methylbenzene. The extract is washed with water, dried, filtered and evaporated. The residue is crystallized from 2-propanol, yielding 5.5 parts (44%) of 1 - (3 - chloropropyl) - 1,3 - dihydro - 3 - (1 - methylethenyl) - 2H - benzimidazol - 2 - one; mp. 115°C.

Example XV.

To a stirred and hot (55°C) mixture of 22.2 parts of 1,3 - dihydro - 5,6-dimethyl - 3 - (1 - methyl - 2 - phenylethenyl) - 2H - benzimidazol - 2 - one, 3 parts of N,N,N - triethylbenzenemethanaminium chloride and 112.5 parts of a sodium hydroxide solution 60% are added dropwise 15.8 parts of 1 - bromo - 3 - chloropropane (slightly exothermic reaction). Upon completion, stirring is continued for 5 hours at 55°C. After cooling, water is added and the oily product is extracted with methylbenzene. The extract is dried, filtered and evaporated. The residue is crystallized from 2,2'-oxybispropane, yielding, after drying, 25 parts (88.5%) of 1 - (3-chloropropyl) - 1,3 - dihydro - 5,6 - dimethyl - 3 - (1 - methyl - 2 - phenylethenyl) - 2H - benzimidazol - 2 - one; mp. 98°C.

Example XVI.

Following the procedure of Example XV and using equivalent amounts of the appropriate starting materials there are prepared:

1 - (3 - chloropropyl) - 1,3 - dihydro - 3 - (2 - propenyl) - 2H - benzimidazol - 2 - one as a residue;

1 - (3 - chloro - 2 - methylpropyl) - 1,3 - dihydro - 3 - (1 - methylethenyl) - 2H - benzimidazol - 2 - one as a residue; and

1 - (3 - chloropropyl) - 5 - fluoro - 1,3 - dihydro - 3 - (1 - methyl - 2 - phenylethenyl) - 2H - benzimidazol - 2 - one as an oily residue.

Example XVII.

A solution of 13 parts of 1 - (3 - chloropropyl) - 1,3 - dihydro - 3 - (1 - methylethenyl) - 2H - benzimidazol - 2 - one in 6 parts of a hydrochloric acid solution and 40 parts of ethanol is stirred for 2 hours at room temperature. The reaction mixture is evaporated and the solid residue is crystallized from 2-propanol, yielding 9.5 parts (90%) of 1 - (3 - chloropropyl) - 1,3 - dihydro - 2H - benzimidazol - 2 - one; mp. 115°C.

Example XVIII.

A mixture of 25 parts of 1 - (3 - chloropropyl) - 1,3 - dihydro - 5,6 - dimethyl - 3 - (1 - methyl - 2 - phenylethenyl) - 2H - benzimidazol - 2 - one, 165 parts of a hydrochloric acid solution 6N and 160 parts of ethanol is stirred and refluxed for 6 hours. The reaction mixture is evaporated and the residue is dissolved in trichloromethane. This solution is dried, filtered and evaporated. The residue is crystallized from a mixture of 2,2'-oxybispropane and 2-propanol, yielding, after drying, 16 parts (94.7%) of 1 - (3 - chloropropyl) - 1,3 - dihydro - 5,6 - dimethyl - 2H - benzimidazol - 2 - one; mp. 140°C.

Example XIX.

A solution of 180 parts of 3 - [(2 - nitrophenyl)amino] - 1 - propanol in 200 parts of methanol and 100 parts of a hydrochloric acid solution 10N is hydrogenated at normal pressure and at a temperature at 50°C, in the presence of 5 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen (3 moles) is taken up, hydrogenation is stopped. The catalyst is filtered off and the filtrate is evaporated. The residue (mainly 3 - [(2 - aminophenyl)amino] - 1-propanol hydrochloride) is dissolved in 500 parts of water. To this solution is added a solution of 88.8 parts of potassium isocyanate in 150 parts of water and the whole is stirred and refluxed for 15 hours. The reaction mixture is cooled and the product is extracted with trichloromethane. The extract is dried and evaporated. The residue is dissolved in 250 parts of boiling water, treated with activated charcoal and crystallized at room temperature. The precipitate is filtered off and recrystallized from 400 parts of water, followed by recrystallization from ethylacetate, yielding 58 parts of 1,3 - dihydro - 1 - (3 - hydroxypropyl) - 2H - benzimidazol - 2 - one hydrate; mp. 48—65°C.

To a solution of 52.5 parts of 1,3 - dihydro - 1 - (3 - hydroxy - propyl) - 2H - benzimidazol - 2 - one hydrate in 200 parts of pyridine is added dropwise 63 parts of methanesulfonyl chloride. The mixture is stirred and cooled on the air for 2 hours. The pyridine is evaporated. To the residue is added 500 parts of water and the formed precipitate is filtered off. It is dissolved in 350 parts of trichloromethane. This solution is dried over magnesium sulfate and evaporated. The residue is crystallized from 40 parts of methylbenzene, yielding 25.5 parts of 1,3 - dihydro - 1 - (3 - hydroxypropyl) - 2H - benzimidazol - 2 - one methanesulfonate; mp. 118—120°C.

To a solution of 0.5 parts of sodium in 40 parts of absolute ethanol are added in the cold 5.4 parts of 1,3 - dihydro - 1 - (3 - hydroxypropyl) - 2H - benzimidazol - 2 - one methanesulfonate. The whole is stirred until all solid enters solution. The solution is further stirred and refluxed for 2 hours. After cooling, the reaction mixture is filtered from some inorganic matter and the filtrate is evaporated. The residue is dissolved in 80 parts of methylbenzene, boiled with activated charcoal, filtered and the filtrate is evaporated again. The solid residue is washed with cold methylbenzene and crystallized from 16 parts of methylbenzene, yielding 2.6 parts of 3,4 - dihydro - 2H - [1,3]oxazino[3,2-a]benzimidazole; mp. 116.5—118.5°C.

To a solution of 5.7 parts of 3,4 - dihydro - 2H - [1,3]oxazino - [3,2-a]benzimidazole in 80 parts of 2-propanone is added 5.7 parts of iodomethane and the whole is stirred and refluxed for 2h. 50. Then there is added a second portion of 5.7 parts of iodomethane and the whole is further stirred and refluxed for 2h. 50. The solvent is evaporated, yielding 1,3 - dihydro - 1 - (3 - iodopropyl) - 3 - methyl - 2H - benzimidazol - 2 - one as an oily residue.

Example XX.

A mixture of 84 parts of ethyl 4 - [(4 - chloro - 2 - nitrophenyl)amino] - 1-piperidinecarboxylate and 750 parts of a hydrobromic acid solution 48% in water

is stirred and refluxed for 4 hours. The precipitated product is filtered off, washed with water and petroleum-ether, and dried, yielding 71 parts (81%) of N - (4-chloro - 2 - nitrophenyl) - 4 - piperidinamine hydrobromide; mp. 275°C.

5 A mixture of 105 parts of 1 - (3 - chloropropyl) - 1,3 - dihydro - 3 - (1 - methyl-
ethenyl) - 2H - benzimidazol - 2 - one, 71 parts of N - (4 - chloro - 2 - nitrophenyl) -
4 - piperidinamine hydrobromide, 53 parts of sodium carbonate, 0.2 parts of potassium
10 iodide and 320 parts of 4-methyl-2-pentanone is stirred and refluxed for 24 hours
with water-separator. The reaction mixture is cooled, water is added and the layers
are separated. The organic phase is dried, filtered and evaporated, yielding 98.5 parts
(100%) of 1 - [3 - {4 - [(4 - chloro - 2 - nitrophenyl)amino] - 1 - piperidinyl}-
propyl] - 1,3 - dihydro - 3 - (1 - methylethenyl) - 2H - benzimidazol - 2 - one as a
residue. 10

15 A solution of 98.5 parts of 1 - [3 - {4 - [(4 - chloro - 2 - nitrophenyl)amino] -
1 - piperidinyl}propyl] - 1,3 - dihydro - 3 - (1 - methylethenyl) - 2H - benzimidazol -
2 - one in 360 parts of methylbenzene is acidified with 2-propanol, previously saturated
with gaseous hydrogen chloride. After boiling for a while, an oil precipitates. The
supernatant phase is decanted and the residual oil is suspended in water. The sus-
pension is alkalized with a concentrated ammonium hydroxide solution. The product
20 is extracted with methylbenzene. The extract is dried, filtered and evaporated. The
residue is crystallized from 4 - methyl - 2 - pentanone. The product is filtered off
and dried, yielding 68 parts (75.5%) of 1 - [3 - {4 - [(4 - chloro - 2 - nitro-
phenyl)amino] - 1 - piperidinyl}propyl] - 1,3 - dihydro - 2H - benzimidazol - 2 -
one. 20

25 A mixture of 21.5 parts of 1 - [3 - {4 - [(4 - chloro - 2 - nitrophenyl)amino] -
1 - piperidinyl}propyl] - 1,3 - dihydro - 2H - benzimidazol - 2 - one and 240 parts
of methanol is hydrogenated at normal pressure and at room temperature with 5 parts
of Raney-nickel catalyst. After the calculated amount of hydrogen is taken up, the
catalyst is filtered off and the filtrate is evaporated, yielding 20 parts (100%) of
30 1 - [3 - {4 - [(2 - amino - 4 - chlorophenyl)amino] - 1 - piperidinyl}propyl] - 1,3-
dihydro - 2H - benzimidazol - 2 - one as a residue. 30

Example XXI.

35 A mixture of 21.5 parts of 1 - [3 - {4 - [(4 - chloro - 2 - nitrophenyl)amino] -
1 - piperidinyl}propyl] - 1,3 - dihydro - 2H - benzimidazol - 2 - one and 240 parts
of methanol is hydrogenated at normal pressure and at room temperature with 10
parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen
is taken up, the catalyst is filtered off and the filtrate is evaporated, yielding 18.5
parts (100%) of 1 - [3 - {4 - [(2 - aminophenyl)amino] - 1 - piperidinyl}propyl] -
1,3 - dihydro - 2H - benzimidazol - 2 - one as a residue. 35

Example XXII.

40 To a stirred mixture of 39.2 parts of 3 - (2 - nitrophenyl)amino - 1 - propanol
and 225 parts of trichloromethane are added dropwise 35.7 parts of sulfinyl chloride
(exothermic reaction: the temperature rises to 45°C). Upon completion, stirring is
continued for 6 hours at reflux temperature. The reaction mixture is evaporated,
45 yielding 43 parts (100%) of N - (3 - chloropropyl) - 2 - nitrobenzenamine as a
residue. 45

A mixture of 43 parts of N - (3 - chloropropyl) - 2 - nitrobenzenamine 47.8
parts of 5 - chloro - 1,3 - dihydro - 1 - (4 - piperidinyl) - 2H - benzimidazol - 2 -
one, 30.3 parts of N,N - diethylethanamine and 180 parts of N,N - dimethylacetamide
is stirred and heated for 6 hours at 100°C. The reaction mixture is cooled and poured
50 onto 1500 parts of water. The precipitated product is filtered off, washed with water
and with 2,2'-oxybispropane and dried, yielding 64 parts (78.3%) of 5 - chloro -
1,3 - dihydro - 1 - {1 - [3 - (2 - nitrophenylamino)propyl] - 4 - piperidinyl} - 2H-
benzimidazol - 2 - one; mp. 220°C. 50

55 A mixture of 64 parts of 5 - chloro - 1,3 - dihydro - 1 - {1 - [3 - (2 - nitro-
phenylamino)propyl] - 4 - piperidinyl} - 2H - benzimidazol - 2 - one in 200 parts
of methanol and 225 parts of tetrahydrofuran is hydrogenated at normal pressure and
at room temperature with 10 parts of Raney-nickel catalyst. After the calculated
amount of hydrogen is taken up, the catalyst is filtered off over hyflo and the filtrate
is evaporated. The residue is crystallized from a mixture of 2-propanol and ethanol.
60 The product is filtered off and dried, yielding 42 parts (70.5%) of 1 - [1 - {3 -
[N - (2 - aminophenyl)amino]propyl} - 4 - piperidinyl] - 5 - chloro - 1,3 - dihydro -
2H - benzimidazol - 2 - one; mp. 196°C. 60

Example XXIII.

A mixture of 4.6 parts of 1 - (3 - chloropropyl) - 1,3 - dihydro - 2H - benzimidazol - 2 - one, 5 parts of 1 - (p - fluorophenyl) - 1,3,8 - triazaspiro[4,5]decan - 4 - one, 10 parts of sodium carbonate, 0.2 parts of potassium iodide and 80 parts of 4 - methyl - 2 - pentanone is stirred and refluxed overnight. After cooling, the precipitated product is filtered off and triturated twice: first in a boiling mixture of 4 - methyl - 2 - pentanone and 2 - propanol and then in boiling methanol. It is filtered off again and crystallized from a mixture of N,N - dimethyl formamide and water, yielding 4.5 parts of 8 - [3 - (1,3 - dihydro - 2 - oxo - 2H - benzimidazol - 1 - yl)propyl] - 1 - (4 - fluorophenyl) - 1,3,8 - triazaspiro[4,5]decan - 4 - one; mp. 215.4°C.

Example XXIV.

Following the procedure of Example XXIII and using equivalent amounts of the appropriate starting materials the following compounds are prepared:

8 - [3 - (6 - chloro - 2,3 - dihydro - 2 - oxo - 1H - benzimidazol - 1 - yl)propyl] - 1 - (4 - fluorophenyl) - 1,3,8 - triazaspiro[4,5]decan - 4 - one hemihydrate; mp. 233°C;

1 - (4 - fluorophenyl) - 8 - [3 - (2,3 - dihydro - 5,6 - dimethyl - 2 - oxo - 1H - benzimidazol - 1 - yl)propyl] - 1,3,8 - triazaspiro[4,5]decan - 4 - one; mp. 245.2°C;

8 - [3 - [2,3 - dihydro - 2 - oxo - 3 - (2 - propenyl) - 1H - benzimidazol - 1 - yl]propyl] - 1 - phenyl - 1,3,8 - triazaspiro[4,5]decan - 4 - one; mp. 114°C;

8 - [3 - (2,3 - dihydro - 2 - oxo - 1H - benzimidazol - 1 - yl)propyl] - 1 - [3 - (trifluoromethyl)phenyl] - 1,3,8 - triazaspiro[4,5]decan - 4 - one; mp. 198.2°C;

8 - [3 - (2,3 - dihydro - 2 - oxo - 1H - benzimidazol - 1 - yl)propyl] - 1 - phenyl - 1,3,8 - triazaspiro[4,5]decan - 4 - one; mp. 228°C;

8 - [3 - (5 - chloro - 2,3 - dihydro - 2 - oxo - 1H - benzimidazol - 1 - yl)propyl] - 1 - (4 - fluorophenyl) - 1,3,8 - triazaspiro[4,5]decan - 4 - one; mp. 171.7°C;

8 - [3 - (6 - chloro - 2,3 - dihydro - 2 - oxo - 1H - benzimidazol - 1 - yl)propyl] - 1 - phenyl - 1,3,8 - triazaspiro[4,5]decan - 4 - one; mp. 255—256°C;

1 - (4 - fluorophenyl) - 8 - [3 - [2,3 - dihydro - 2 - oxo - 5 - (trifluoromethyl) - 1H - benzimidazol - 1 - yl]propyl] - 1,3,8 - triazaspiro[4,5]decan - 4 - one; mp. 259.7°C;

8 - [3 - (2,3 - dihydro - 2 - oxo - 1H - benzimidazol - 1 - yl)propyl] - 3 - methyl - 1 - phenyl - 1,3,8 - triazaspiro[4,5]decan - 4 - one; mp. 186°C;

1 - (4 - chloro - 3 - methylphenyl) - 8 - [3 - (2,3 - dihydro - 2 - oxo - 1H - benzimidazol - 1 - yl)propyl] 1,3,8 - triazaspiro[4,5]decan - 4 - one; mp. 208.6°C; and

8 - [3 - (1H - benzimidazol - 1 - yl)propyl] - 1 - phenyl - 1,3,8 - triazaspiro[4,5]decan - 4 - one; mp. 191°C.

Example XXV.

A mixture of 4.2 parts of 4 - chloro - 1,3 - dihydro - 3 - (3 - hydroxypropyl) - 2H - benzimidazol - 2 - one methanesulfonate, 2.5 parts of 1 - phenyl - 1,3,8 - triazaspiro[4,5]decan - 4 - one, 10 parts of sodium carbonate and 80 parts of 4 - methyl - 2 - pentanone is stirred and refluxed overnight. The reaction mixture is cooled and water is added. The precipitated product is filtered off and crystallized twice from a mixture of N,N - dimethylformamide and water, yielding 0.8 parts (17%) of 8 - [3 - (7 - chloro - 1,3 - dihydro - 2 - oxo - 2H - benzimidazol - 1 - yl)propyl] - 1 - phenyl - 1,3,8 - triazaspiro[4,5]decan - 4 - one; mp. 258.4°C.

Example XXVI.

Following the procedure of Example XXV and by carrying out the reaction in N,N - dimethylformamide as a solvent, the following compounds are prepared from the appropriate starting materials:

8 - [3 - (5 - chloro - 2,3 - dihydro - 2 - oxo - 1H - benzimidazol - 1 - yl)propyl] - 1 - phenyl - 1,3,8 - triazaspiro[4,5]decan - 4 - one; mp. 233.7°C; and

8 - [3 - (2,3 - dihydro - 5 - methyl - 2 - oxo - 1H - benzimidazol - 1 - yl)propyl] - 1 - phenyl - 1,3,8 - triazaspiro[4,5]decan - 4 - one; mp. 255.5°C.

Example XXVII.

A mixture of 5 parts of 1,3 - dihydro - 1 - (3 - iodopropyl) - 3 - methyl - 2H - benzimidazol - 2 - one, 3.4 parts of 1 - phenyl - 1,3,8 - triazaspiro[4,5]decan - 4 -

one, 2.65 parts of sodium carbonate and 22.5 parts of N,N - dimethylformamide is stirred and heated for 2 hours at 70°C. The reaction mixture is cooled and poured onto water, whereupon an oily precipitate is formed. The supernatant aqueous phase is decanted and the residual oil is dissolved in trichloromethane. The solution is dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and 5% of methanol as eluent. The pure fractions are collected and the eluent is evaporated, yielding 1 part of 8 - [3 - (1,3 - dihydro - 3 - methyl - 2 - oxo - 2H - benzimidazol - 1 - yl)propyl] - 1-phenyl - 1,3,8 - triazaspiro[4,5]decan - 4 - one; mp. 164°C.

Example XXVIII.

A mixture of 8 parts of 5,6 - dichloro - 1,3 - dihydro - 1 - (3 - hydroxypropyl)-2H - benzimidazol - 2 - one methanesulfonate, 9.2 parts of 1 - phenyl - 1,3,8-triazaspiro[4,5]decan - 4 - one and 90 parts of N,N - dimethylformamide is stirred and heated at 60°C for one hour. The reaction mixture is evaporated and water is added to the residue. The whole is made alkaline with ammonium hydroxide and the product is extracted with trichloromethane. The extract is dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and 10% of methanol as eluent. The pure fractions are collected and the eluent is evaporated. The solid residue is triturated in 4 - methyl-2 - pentanone. The product is filtered off and dried, yielding 2 parts of 8 - [3 - (5,6 - dichloro - 1,3 - dihydro - 2 - oxo - 2H - benzimidazol - 1 - yl)propyl] - 1-phenyl - 1,3,8 - triazaspiro[4,5]decan - 4 - one; mp. 275.2°C.

Example XXIX.

A mixture of 2.3 parts of 1 - (3 - chloropropyl) - 1,3 - dihydro - 2H - benzimidazol - 2 - one, 2.5 parts of 5 - chloro - 1,3 - dihydro - 1 - (4 - piperidinyl)-2H - benzimidazol - 2 - one, 3.2 parts of sodium carbonate, 0.1 parts of potassium iodide and 80 parts of 4 - methyl - 2 - pentanone is stirred and refluxed for 24 hours. The reaction mixture is cooled to room temperature and water is added. The undissolved product is filtered off and purified by column chromatography over silica gel using a mixture of trichloromethane and 10% of methanol as eluent. The pure fractions are collected and the eluent is evaporated. The residue is crystallized from 4 - methyl - 2 - pentanone. The product is filtered off and recrystallized from a mixture of N,N - dimethylformamide and water, yielding 1.3 parts (30%) of 5 - chloro 1 - {1 - [3 - (1,3 - dihydro - 2 - oxo - 2H - benzimidazol - 1 - yl)propyl] - 4 - piperidinyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one; mp. 242.5°C.

Example XXX.

Following the procedure of Example XXIX and using equivalent amounts of the appropriate starting materials, the following compounds are prepared:

5 - chloro - 1 - [1 - {3 - [2,3 - dihydro - 3 - (1 - methylethenyl) - 2 - oxo - 1H - benzimidazol - 1 - yl] - 2 - methylpropyl} - 4 - piperidine] - 1,3 - dihydro - 2H - benzimidazol - 2 - one as an oily residue;

6 - chloro - 1 - {3 - [4 - (5 - chloro - 2,3 - dihydro - 2 - oxo - 1H - benzimidazol - 1 - yl) - piperidinyl]propyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one hydrate; mp. 179.6°C;

1 - {3 - [4 - (2,3 - dihydro - 2 - oxo - 1H - benzimidazol - 1 - yl) - 1 - piperidinyl]propyl} - 1,3 - dihydro - 5,6 - dimethyl - 2H - benzimidazol - 2 - one 2-propanolate; mp. 159°C;

6 - chloro - 1,3 - dihydro - 1 - {3 - [4 - (2,3 - dihydro - 2 - oxo - 1H - benzimidazol - 1 - yl) - 1 - piperidinyl]propyl} - 2H - benzimidazol - 2 - one; mp. 273°C;

1 - {3 - [4 - (2,3 - dihydro - 2 - oxo - 1H - benzimidazol - 1 - yl) - 1 - piperidinyl]propyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one; mp. 225°C;

1,3 - dihydro - 1 - {3 - [4 - (2,3 - dihydro - 2 - oxo - 1H - benzimidazol - 1 - yl) - 1 - piperidinyl]propyl} - 5 - (trifluoromethyl) - 2H - benzimidazol - 2 - one; mp. 263.4°C;

5 - chloro 1 - {3 - [4 - (2,3 - dihydro - 2 - oxo - 1H - benzimidazol - 1 - yl) - 1 - piperidinyl]propyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one; mp. 253—255°C;

5 - chloro - 1 - [1 - {3 - [2,3 - dihydro - 2 - oxo - 3 - (2 - propenyl) - 1H - benzimidazol - 1 - yl]propyl} - 4 - piperidinyl] - 1,3 - dihydro - 2H - benzimidazol - 2 - one; mp. 153.4°C;

- 1 - {3 - [3,6 - dihydro - 4 - (2,3 - dihydro - 2 - oxo - 1H - benzimidazol - 1 - yl) - 1 - (2H) - pyridinyl]propyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one; mp. 206.6°C;
- 5 - chloro - 1 - [1 - {3 - [2,3 - dihydro - 3 - (1 - methylethenyl) - 2 - oxo - 1H - benzimidazol - 1 - yl]propyl} - 4 - piperidinyl] - 1,3 - dihydro - 2H - benzimidazol - 2 - one; mp. 165.2°C; and
- 1 - {1 - [4 - (1H - benzimidazol - 1 - yl)butyl] - 4 - piperidinyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one; mp. 157.1°C.

Example XXXI.

A mixture of 5.3 parts of 1 - (3 - chloropropyl) - 1,3 - dihydro - 5 - methyl - 3 - (1 - methylethenyl) - 2H - benzimidazol - 2 - one, 4.3 parts of 1,3 - dihydro - 1 - (4 - piperidinyl) - 2H - benzimidazol - 2 - one, 6.4 parts of sodium carbonate and 200 parts of 4 - methyl - 2 - pentanone is stirred and refluxed overnight with water-separator. After cooling, water is added and the layers are separated. The 4-methyl - 2 - pentanone-phase is dried, filtered and evaporated. The oily residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (90:10 by volume) as eluent. The pure fractions are collected and the eluent is evaporated, yielding 6 parts (67%) of 1 - {3 - [4 - (2,3 - dihydro - 2 - oxo - 1H - benzimidazol - 1 - yl) - 1 - piperidinyl]propyl} - 1,3 - dihydro - 5 - methyl - 3 - (1 - methylethenyl) - 2H - benzimidazol - 2 - one as an oily residue.

Example XXXII.

Following the procedure of Example XXXI and using equivalent amounts of the appropriate starting materials, the following compounds are prepared:

- 1 - {3 - [4 - (5 - chloro - 2,3 - dihydro - 2 - oxo - 1H - benzimidazol - 1 - yl) - 1 - piperidinyl]propyl} - 1,3 - dihydro - 5 - methyl - 3 - (1 - methylethenyl) - 2H - benzimidazol - 2 - one as an oily residue;
- 3 - {3 - [4 - (5 - chloro - 2,3 - dihydro - 2 - oxo - 1H - benzimidazol - 1 - yl) - 1 - piperidinyl]propyl} - 1,3 - dihydro - 5 - methyl - 1 - (1 - methylethenyl) - 2H - benzimidazol - 2 - one as an oily residue;
- 1 - {1 - [3 - (1H - benzimidazol - 1 - yl)propyl] - 4 - piperidinyl} - 5 - chloro - 1,3 - dihydro - 2H - benzimidazol - 2 - one; mp. 224°C; and
- 5 - chloro - 1 - {1 - [3 - (2 - oxo - 3(2H) - benzoxazolyl)propyl] - 4 - piperidinyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one; mp. 212.3°C.

Example XXXIII.

A mixture of 5.4 parts of 3 - (3 - bromopropyl) - 2(3H) - benzothiazolone, 4.5 parts of 5 - chloro - 1,3 - dihydro - 1 - (4 - piperidinyl) - 2H - benzimidazol - 2 - one, 5.3 parts of sodium carbonate, 0.1 parts of potassium iodide and 200 parts of 4 - methyl - 2 - pentanone is stirred and refluxed for 3 hours with water-separator. After cooling, water is added and the layers are separated. The organic phase is dried, filtered and evaporated. The residue is crystallized from a mixture of 4-methyl - 2 - pentanone and 2 - propanone. The product is filtered off and dried, yielding 2.5 parts (31%) of 5 - chloro - 1,3 - dihydro - 1 - {1 - [3 - (2 - oxo - 3(2H) - benzothiazolyl)propyl] - 4 - piperidinyl} - 2H - benzimidazol - 2 - one; mp. 184.1°C.

Example XXXIV.

Following the procedure of Example XXXIII there is prepared 1 - {1 - [3 - (1H - benzotriazol - 1 - yl)propyl] - 4 - piperidinyl} - 5 - chloro - 1,3 - dihydro - 2H - benzimidazol - 2 - one; mp. 203.4°C by reaction of 1 - (3 - bromopropyl) - 1H - benzotriazole with 5 - chloro - 1,3 - dihydro - 1 - (4 - piperidinyl) - 2H - benzimidazol - 2 - one.

Example XXXV.

A mixture of 5 parts of 1,3 - dihydro - 1 - (3 - iodopropyl) - 3 - methyl - 2H - benzimidazol - 2 - one, 3.75 parts of 5 - chloro - 1,3 - dihydro - 1 - (4 - piperidinyl) - 2H - benzimidazol - 2 - one, 2.65 parts of sodium carbonate and 22.5 parts of N,N-dimethylformamide is stirred at 70—80°C for 2 hours. The reaction mixture is cooled, poured onto water and the precipitated product is filtered off. It is dissolved in trichloromethane. The solution is dried, filtered and evaporated. The residue is crystallized from 4 - methyl - 2 - pentanone, yielding 3 parts (43%) of 5 - chloro - 1 - {1 - [3 - (1,3 - dihydro - 3 - methyl - 2 - oxo - 2H - benzimidazol - 1 - yl) - propyl] - 4 - piperidinyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one; mp. 166.5°C.

Example XXXVI.

A mixture of 7.6 parts of 5 - chloro - 1,3 - dihydro - 1 - (3 - hydroxypropyl) - 2H - benzimidazol - 2 - one methanesulfonate, 5.5 parts of 5 - chloro - 1,3 - dihydro - 1 - (4 - piperidiny) - 2H - benzimidazol - 2 - one, 5 parts of sodium carbonate and 63 parts of N,N - dimethylformamide is stirred and heated in an oil-bath at 50—60°C for 2 hours. The reaction mixture is poured onto water. The precipitated product is filtered off, dried and purified by column-chromatography over silica gel using a mixture of trichloromethane and 10% of methanol as eluent. The pure fractions are collected and the eluent is evaporated. The solid residue is crystallized from 4 - methyl - 2 - pentanone. The product is filtered off and recrystallized from a mixture of N,N - dimethylformamide and water. It is filtered off again and dissolved in a mixture of 4 - methyl - 2 - pentanone and a small amount of N,N - dimethylformamide. The solution is filtered till clear and the filtrate is concentrated to a volume of about 10 parts. The concentrate is triturated in methanol. The precipitated product is filtered off and dried, yielding 1.27 parts of 5 - chloro - 1 - {3 - [4 - (5 - chloro - 1,3 - dihydro - 2 - oxo - 2H - benzimidazol - 1 - yl) - 1 - piperidiny]propyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one; mp. 229—236°C.

Example XXXVII.

A mixture of 7 parts of 1 - (3 - chloropropyl) - 5 - fluoro - 1,3 - dihydro - 3 - (1 - methyl) - 2 - phenylethenyl) - 2H - benzimidazol - 2 - one, 5 parts of 5 - chloro - 1,3 - dihydro - 1 - (4 - piperidiny) - 2H - benzimidazol - 2 - one, 4.25 parts of sodium carbonate, 0.1 parts of potassium iodide and 200 parts of 4 - methyl - 2 - pentanone is stirred and refluxed overnight. The mixture is cooled to room temperature, water is added and the layers are separated. The organic phase is dried, filtered and evaporated. The residue is stirred and refluxed overnight with a solution of 55 parts of a hydrochloric acid solution 6N in 40 parts of ethanol. The solvent is evaporated and the residue is taken up in water. The whole is alkalinized with ammonium hydroxide and the product is extracted with trichloromethane. The extract is dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (95:5 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is converted into the hydrochloride salt in 2-propanol. The salt is filtered off and dried, yielding 1.2 parts of 1 - {3 - [4 - (5 - chloro - 2,3 - dihydro - 2 - oxo - 1H - benzimidazol - 1 - yl) - 1 - piperidinyl]propyl} - 5 - fluoro - 1,3 - dihydro - 2H - benzimidazol - 2 - one hydrochloride hydrate; mp. 250°C.

Example XXXVIII.

Following the procedure of Example XXXVII, there are prepared: 5 - chloro 1 - {1 - [4 - (2,3 - dihydro - 2 - oxo - 1H - benzimidazol - 1 - yl)butyl] - 4 - piperidiny} - 1,3 - dihydro - 2H - benzimidazol - 2 - one hemihydrate; mp. 258°C by the reaction of 1 - (4 - chlorobutyl) - 1,3 - dihydro - 3 - (1 - methylethenyl) - 2H - benzimidazol - 2 - one with 5 - chloro - 1,3 - dihydro - 1 - (4 - piperidiny) - 2H - benzimidazol - 2 - one; and 1 - {1 - [3 - (2,3 - dihydro - 2 - oxo - 1H - benzimidazol - 1 - yl)propyl] - 4 - piperidiny} - 1,3 - dihydro - 3 - (1 - methylethyl) - 2H - benzimidazol - 2 - one; mp. 174.3°C, by the reaction of 1 - (3 - chloropropyl) - 1,3 - dihydro - 3 - (1 - methylethenyl) - 2H - benzimidazol - 2 - one with 1 - (1 - methylethyl) - 3 - (4 - piperidiny) - 2H - benzimidazol - 2 - one.

Example XXXIX.

A mixture of 6 parts of 1 - {3 - [4 - (2,3 - dihydro - 2 - oxo - 1H - benzimidazol - 1 - yl) - 1 - piperidiny]propyl} - 1,3 - dihydro - 5 - methyl - 3 - (1 - methylethenyl) - 2H - benzimidazol - 2 - one, 12 parts of a hydrochloric acid solution, 30 parts of water and 40 parts of ethanol is stirred first for a while at 50°C and further for 1 hour at room temperature. The reaction mixture is evaporated and the residue is crystallized from a mixture of 4 - methyl - 2 - pentanone and 2 - propanol. The product is filtered off and dried, yielding 3.7 parts (40%) of 1 - {3 - [4 - (2,3 - dihydro - 2 - oxo - 1H - benzimidazol - 1 - yl) - 1 - piperidiny]propyl} - 1,3 - dihydro - 5 - methyl - 2H - benzimidazol - 2 - one hydrochloride hydrate; mp. 251.4°C.

Example XL.

Following the procedure of Example XXXIX the following compounds are derived from the corresponding (1-methylethenyl)-substituted analogs:

- 5 5 - chloro - 1 - {1 - [3 - (2,3 - dihydro - 5 - methyl - 2 - oxo - 1H - benzimidazol - 1 - yl)propyl] - 4 - piperidinyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one hydrochloride . hydrate; mp. 213.3°C; 5
- 5 - chloro - 1 - {1 - [3 - (2,3 - dihydro - 6 - methyl - 2 - oxo - 1H - benzimidazol - 1 - yl)propyl] - 4 - piperidinyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one hemihydrate; mp. 195.4°C; and
- 10 5 - chloro - 1 - {1 - [3 - (2,3 - dihydro - 2 - oxo - 1H - benzimidazol - 1 - yl) - 2 - methylpropyl] - 4 - piperidinyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one; mp. 244°C. 10

Example XLI.

- 15 A mixture of 38 parts of carbon disulfide, 6 parts of 1 - [1 - {3 - [N - (2-aminophenyl)amino]propyl] - 4 - piperidinyl] - 5 - chloro - 1,3 - dihydro - 2H - benzimidazol - 2 - one and 32 parts of ethanol is stirred and refluxed for 24 hours. The reaction mixture is evaporated and the residue is crystallized from ethanol. The product is filtered off and recrystallized from a mixture of N,N - dimethylformamide and water, yielding 3 parts (45.5%) of 5 - chloro - 1 - {1 - [3 - (2,3 - dihydro - 2-thioxo - 1H - benzimidazol - 1 - yl)propyl] - 4 - piperidinyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one; mp. 266.6°C. 15
- 20 20

Example XLII.

- 25 A mixture of 4 parts of 1 - [1 - {3 - [N - (2 - amino - 5 - chlorophenyl)-amino]propyl] - 4 - piperidinyl] - 1,3 - dihydro - 2H - benzimidazol - 2 - one, 6 parts of a concentrated hydrochloric acid solution and 30 parts of formic acid is stirred and refluxed overnight. The reaction mixture is evaporated and water is added to the residue. The whole is alkalinized with a diluted ammonium hydroxide solution and the product is extracted with trichloromethane. The extract is dried, filtered and evaporated. The residue is crystallized from 4 - methyl - 2 - pentanone. The product is filtered off and recrystallized from 2-propanol, yielding 1.1 parts (27%) of 1 - {1 - [3 - (6 - chloro - 1H - benzimidazol - 1 - yl)propyl] - 4 - piperidinyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one; mp. 214.9°C. 25
- 30 30

Example XLIII.

- 35 A mixture of 20 parts of 1 - [3 - {4 - [(2 - amino - 4 - chlorophenyl)amino] - 1 - piperidinyl]propyl] - 1,3 - dihydro - 2H - benzimidazol - 2 - one, 52 parts of carbon disulfide and 120 parts of ethanol is stirred and refluxed for 24 hours. The reaction mixture is filtered after cooling, and the filtrate is evaporated. The residue is crystallized from 2-propanol. The product is filtered off and recrystallized from ethanol, yielding, after drying, 7.5 parts (34%) of 1 - {3 - [4 - (5 - chloro - 2,3 - dihydro - 2 - thioxo - 1H - benzimidazol - 1 - yl) - 1 - piperidinyl]propyl] - 1,3 - dihydro - 2H - benzimidazol - 2 - one; mp. 254.3°C. 35
- 40 40

Example XLIV.

- 45 Following the procedure of Example XLIII there is prepared 1 - {3 - [4 - (2,3 - dihydro - 2 - thioxo - 1H - benzimidazol - 1 - yl) - 1 - piperidinyl]propyl] - 1,3 - dihydro - 2H - benzimidazol - 2 - one; mp. 248.5°C by the reaction of 1 - [3 - {4 - [(2 - aminophenyl)amino] - 1 - piperidinyl]propyl] - 1,3 - dihydro - 2H - benzimidazol - 2 - one with carbon disulfide. 45

Example XLV.

- 50 A mixture of 2.21 parts of 1 - {3 - [4 - (5 - chloro - 2,3 - dihydro - 2 - thioxo - 1H - benzimidazol - 1 - yl) - 1 - piperidinyl]propyl] - 1,3 - dihydro - 2H - benzimidazol - 2 - one, 0.71 parts of iodomethane, 0.28 parts of sodium methanolate and 40 parts of methanol is stirred overnight at room temperature. The reaction mixture is evaporated. The residue is stirred with water and the product is extracted with trichloromethane. The extract is dried, filtered and evaporated. The residue is crystallized from 4 - methyl - 2 - pentanone. The product is filtered off and dried, yielding 1.1 parts of 1 - [3 - {4 - [5 - chloro - 2 - (methylthio) - 1H - benzimidazol - 1 - yl] - 1 - piperidinyl]propyl] - 1,3 - dihydro - 2H - benzimidazol - 2 - one; mp. 196.1°C. 50
- 55 55

Example XLVI.

A mixture of 5 parts of 5 - chloro - 1 - {1 - [3 - (2,3 - dihydro - 2 - oxo - 1H - benzimidazol - 1 - yl)propyl] - 4 - piperidinyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one, 10 parts of acetic acid anhydride and 90 parts of methylbenzene is stirred and refluxed overnight. The reaction mixture is cooled, water is added and the whole is alkalized with a diluted sodium carbonate solution. The layers are separated and the organic phase is dried, filtered and evaporated. The residue is crystallized from methylbenzene. The product is filtered off and recrystallized from methylbenzene, yielding 4.5 parts of 3 - acetyl - 5 - chloro - 1 - {1 - [3 - (3 - acetyl - 2,3 - dihydro - 2 - oxo - 1H - benzimidazol - 1 - yl)propyl] - 4 - piperidinyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one; mp. 185.3°C.

Example XLVII.

To a stirred solution of 1 part of 5 - chloro - 1 - {1 - [3 - (1,3 - dihydro - 2 - oxo - 2H - benzimidazol - 1 - yl)propyl] - 4 - piperidinyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one in 32 parts of ethanol is added a solution of 0.35 parts of ($\pm$) - 2,3 - dihydroxy - 1,4 - butanedioic acid in 8 parts of ethanol. Upon stirring, the product is allowed to crystallize. It is filtered off and dried, yielding 1 part of ($\pm$) - 5 - chloro - 1 - {1 - [3 - (1,3 - dihydro - 2 - oxo - 2H - benzimidazol - 1 - yl)propyl] - 4 - piperidinyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one 2,3 - dihydroxybutanedioate ethanolate; mp. 153.5°C.

Example XLVIII.

A stirred solution of 1 part of 5 - chloro - 1 - {1 - [3 - (1,3 - dihydro - 2 - oxo - 2H - benzimidazol - 1 - yl)propyl] - 4 - piperidinyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one in 20 parts of ethanol is saturated with gaseous hydrogen chloride. The formed hydrochloride salt is allowed to crystallize while stirring. It is filtered off and dried, yielding 0.6 parts (53%) of 5 - chloro - 1 - {1 - [3 - (1,3 - dihydro - 2 - oxo - 2H - benzimidazol - 1 - yl)propyl] - 4 - piperidinyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one hydrochloride hydrate; mp. 195.7°C.

Example IL.

A solution of 1 part of 5 - chloro - 1 - {1 - [3 - (1,3 - dihydro - 2 - oxo - 2H - benzimidazol - 1 - yl)propyl] - 4 - piperidinyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one in 40 parts of ethanol is acidified with 2-propanol, previously saturated with gaseous hydrogen chloride. While cooling, the formed hydrochloride salt is allowed to crystallize, yielding 1 part (83%) of 5 - chloro - 1 - {1 - [3 - (1,3 - dihydro - 2 - oxo - 2H - benzimidazol - 1 - yl)propyl] - 4 - piperidinyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one hydrochloride ethanolate; mp. 213.7°C.

Example L.

10.2 Parts of 5 - chloro - 1 - {1 - [3 - (2,3 - dihydro - 2 - oxo - 1H - benzimidazol - 1 - yl)propyl] - 4 - piperidinyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one are converted into the (+) - 2,3 - dihydroxybutanedioate salt in 100 parts of water at reflux temperature. The solution is treated for 10 minutes with a mixture of 0.5 parts of activated charcoal and 0.2 parts of hyflo. The latter is filtered off over hyflo and the filtrate is cooled till an oily precipitate is formed. The oily product solidifies upon heating for a while. The whole is allowed to cool to room temperature and stirred for 3 hours at this temperature. The product is filtered off, washed with water and dried in vacuo for 18 hours at 60°C, yielding 10.24 parts (85.3%) of 5 - chloro - 1 - {1 - [3 - (2,3 - dihydro - 2 - oxo - 1H - benzimidazol - 1 - yl)propyl] - 4 - piperidinyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one hemi - [R-(R*,R*)](+) - 2,3 - dihydroxybutanedioate hydrate; mp. 184.1°C; $[\alpha] = +5.13^\circ$ (c=1% CH₃OH).

Example LI.

A mixture of 6.7 parts of 5 - chloro - 1,3 - dihydro - 1 - (3 - hydroxypropyl) - 2H - benzimidazol - 2 - one methanesulfonate, 4.2 parts of 4 - (4 - chlorophenyl) - 4 - piperidinol, 3.2 parts of sodium carbonate and 32 parts of 4 - methyl - 2 - pentanone is stirred and heated at 50—60°C for 1.50 hours. The reaction mixture is poured onto ice-water. The precipitated product is filtered off and dissolved in trichloromethane. The solution is washed with water, dried, filtered and evaporated. The solid residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and 10% of methanol as eluent. The pure fractions are collected.

and the eluent is evaporated. The solid residue is stirred in a small amount of trichloromethane. The product is filtered off and recrystallized from 4 - methyl - 2 - pentanone, yielding 2 parts (24%) of 5 - chloro - 1 - {3 - [4 - (4 - chlorophenyl) - 4 - hydroxy - 1 - piperidinyl]propyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one; mp. 190.8°C.

Example LII.

A mixture of 3.58 parts of 1 - (3 - chloropropyl) - 1,3 - dihydro - 5,6 - dimethyl - 2H - benzimidazol - 2 - one, 3.17 parts of 4 - (4 - chlorophenyl) - 4 - piperidinol, 5.3 parts of sodium carbonate, 0.2 parts of potassium iodide and 160 parts of 4 - methyl - 2 - pentanone is stirred and refluxed for 24 hours with water-separator. After cooling, water is added and the layers are separated. The organic phase is dried, filtered and evaporated. The residue is converted into the hydrochloride salt in methanol and 2-propanol. The salt is filtered off and dried, yielding 1.7 parts of 1 - {3 - [4 - (4 - chlorophenyl) - 4 - hydroxy - 1 - piperidinyl]propyl} - 1,3 - dihydro - 5,6 - dimethyl - 2H - benzimidazol - 2 - one hydrochloride; mp. 260.8°C.

Example LIII.

A mixture of 2.3 parts of 1 - (3 - chloropropyl) - 1,3 - dihydro - 2H - benzimidazol - 2 - one, 2.12 parts of 4 - (4 - chlorophenyl) - 4 - piperidinol, 3.2 parts of sodium carbonate, 0.1 parts of potassium iodide and 80 parts of 4 - methyl - 2 - pentanone is stirred and refluxed for 36 hours. After cooling to room temperature, water is added and the layers are separated. The organic phase is dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and 10% of methanol as eluent. The pure fractions are collected and the eluent is evaporated. The residue is crystallized from methylbenzene, yielding 1 part (26%) of 1 - {3 - [4 - (4 - chlorophenyl) - 4 - hydroxy - 1 - piperidinyl]propyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one; mp. 134.2°C.

Example LIV.

Following the procedure of Example LIII and using equivalent amounts of the appropriate starting materials, the following compounds are prepared:
6 - chloro - 1 - {3 - [4 - (4 - chlorophenyl) - 4 - hydroxy - 1 - piperidinyl]propyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one; mp. 180.6°C;
1 - {3 - [4 - [4 - chloro - 3 - (trifluoromethyl)phenyl] - 4 - hydroxy - 1 - piperidinyl]propyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one; mp. 189.2°C;
1 - {3 - [4 - (4 - chlorophenyl) - 4 - hydroxy - 1 - piperidinyl]propyl} - 1,3 - dihydro - 3 - (2 - propenyl) - 2H - benzimidazol - 2 - one; mp. 141.3°C;
1 - {4 - [4 - (4 - chlorophenyl) - 4 - hydroxy - 1 - piperidinyl]butyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one; mp. 160.6°C; and
1 - [3 - (1H - benzimidazol - 1 - yl)propyl] - 4 - (4 - chlorophenyl) - 4 - piperidinol; mp. 160°C.

Example LV.

A mixture of 5 parts of 1 - (3 - chloropropyl) - 1,3 - dihydro - 3 - (1 - methyl-ethenyl) - 2H - benzimidazol - 2 - one, 3.9 parts of 4 - (4 - fluorophenyl) - 4 - piperidinol, 5.3 parts of sodium carbonate and 80 parts of 4 - methyl - 2 - pentanone is stirred and refluxed for 48 hours with water-separator. The reaction mixture is cooled to room temperature, water is added and the whole is alkalized with 15 parts of a sodium hydroxide solution 60%. The layers are separated and the organic phase is dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and 10% of methanol as eluent. The pure fractions are collected and the eluent is evaporated. The oily residue is dissolved in 2-propanone. The solution is acidified with 2-propanol, previously saturated with gaseous hydrogen chloride, and the whole is stirred and refluxed for 15 minutes. The solvent is evaporated and the formed hydrochloride salt is dissolved in water. The free base is liberated in the conventional manner with a diluted sodium hydroxide solution. The product is extracted with 4 - methyl - 2 - pentanone. The extract is dried, filtered and evaporated. The residue is crystallized from methylbenzene. The product is filtered off and dried, yielding 2.5 parts of 1 - {3 - [4 - (4 - fluorophenyl) - 4 - hydroxy - 1 - piperidinyl]propyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one; mp. 135.4°C.

Example LVI.

Following the procedure of Example XXIII and using equivalent amounts of the appropriate starting materials, the following compounds are still obtained:

- 1 - (4 - chlorophenyl) - 8 - [3 - dihydro - 2 - oxo - 2H - benzimidazol - 1 - yl) - propyl] - 1,3,8 - triazaspiro[4,5]decan - 4 - one; 5
- 1 - (4 - chlorophenyl) - 8 - [3 - (5 - chloro - 1,3 - dihydro - 2 - oxo - 2H - benzimidazol - 1 - yl)propyl] - 1,3,8 - triazaspiro[4,5]decan - 4 - one; 5
- 8 - [3 - (1,3 - dihydro - 2 - oxo - 2H - benzimidazol - 1 - yl) - 2 - methylpropyl] - 1 - (4 - fluorophenyl) - 1,3,8 - triazaspiro[4,5]decan - 4 - one; 10
- 8 - [3 - (1,3 - dihydro - 2 - oxo - 2H - benzimidazol - 1 - yl) - propyl] - 1 - (4 - fluorophenyl) - 3 - methyl - 1,3,8 - triazaspiro [4,5]decan - 4 - one; and 10
- 8 - [3 - (1,3 - dihydro - 2 - oxo - 2H - benzimidazol - 1 - yl)propyl] - 3 - ethyl - 1 - (4 - fluorophenyl) - 1,3,8 - triazaspiro [4,5]decan - 4 - one.

Example LVII.

Following the procedure of Example XXIX and using equivalent amounts of the appropriate starting materials, the following compounds are still obtained:

- 5 - chloro - 1 - {3 - [4 - (1,3 - dihydro - 5 - methyl - 2 - oxo - 2H - benzimidazol - 1 - yl) - 1 - piperidinyl]propyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one; 15
- 5 - chloro - 1 - {3 - [4 - [1,3 - dihydro - 2 - oxo - 5 - (trifluoromethyl) - 2H - benzimidazol - 1 - yl] - 1 - piperidinyl]propyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one; 20
- 1 - {3 - [4 - (5,6 - dichloro - 1,3 - dihydro - 2 - oxo - 2H - benzimidazol - 1 - yl) - 1 - piperidinyl]propyl} - 1,3 - dihydro - 2H - benzimidazole - 2 - one; 25
- 5 - chloro - 1 - {3 - [4 - (5 - chloro - 1,3 - dihydro - 2 - oxo - 2H - benzimidazol - 1 - yl) - 1 - piperidinyl] - 2 - methylpropyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one; 25
- 5 - bromo - 1 - {3 - [4 - (5 - chloro - 1,3 - dihydro - 2 - oxo - 2H - benzimidazol - 1 - yl) - 1 - piperidinyl]propyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one; and 30
- 1 - {3 - [4 - 5 - bromo - 1,3 - dihydro - 2 - oxo - 2H - benzimidazol - 1 - yl) - 1 - piperidinyl]propyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one. 30

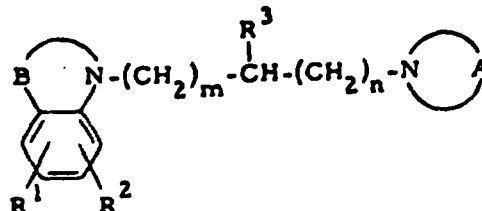
Example LVIII.

Following the procedure of Example LIII and using equivalent amounts of the appropriate starting materials, the following compounds are still obtained:

- 5 - chloro 1- {3 - {4 - [4 - chloro - 3 - (trifluoromethyl)phenyl] - 4 - hydroxy - 1 - piperidinyl]propyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one; 35
- 5 - chloro - 1{3 - [4 - (4 - chlorophenyl) - 4 - hydroxy - 1 - piperidinyl] - 2 - methylpropyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one; 40
- 5 - bromo - 1 - {3 - [4 - (4 - chlorophenyl) - 4 - hydroxy - 1 - piperidinyl]propyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one; 40
- 1 - {3 - [4 - (4 - bromophenyl) - 4 - hydroxy - 1 - piperidinyl]propyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one; 45
- 1 - {3 - [4 - (4 - chlorophenyl) - 4 - hydroxy - 1 - piperidinyl]propyl} - 1,3 - dihydro - 5 - (trifluoromethyl) - 2H - benzimidazol - 2 - one; 45
- 1 - {3 - [4 - (4 - chlorophenyl) - 4 - hydroxy - 1 - piperidinyl]propyl} - 5,6 - dichloro - 1,3 - dihydro - 2H - benzimidazol - 2 - one; and 45
- 5 - chloro - 1 - {3 - [4 - (4 - chlorophenyl) - 4 - hydroxy - 1 - piperidinyl] - propyl} - 1,3 - dihydro - 3 - (2 - propenyl) - 2H - benzimidazol - 2 - one.

WHAT WE CLAIM IS:—

1. 1-(benzazolylalkyl)piperidine derivative having the formula: 50



(I)

Example LVI.

Following the procedure of Example XXIII and using equivalent amounts of the appropriate starting materials, the following compounds are still obtained:

- 5 1 - (4 - chlorophenyl) - 8 - [3 - dihydro - 2 - oxo - 2H - benzimidazol - 1 - yl) - propyl] - 1,3,8 - triazaspiro[4,5]decan - 4 - one; 5
- 1 - (4 - chlorophenyl) - 8 - [3 - (5 - chloro - 1,3 - dihydro - 2 - oxo - 2H - benzimidazol - 1 - yl)propyl] - 1,3,8 - triazaspiro[4,5]decan - 4 - one;
- 8 - [3 - (1,3 - dihydro - 2 - oxo - 2H - benzimidazol - 1 - yl) - 2 - methylpropyl] - 1 - (4 - fluorophenyl) - 1,3,8 - triazaspiro[4,5]decan - 4 - one;
- 10 8 - [3 - (1,3 - dihydro - 2 - oxo - 2H - benzimidazol - 1 - yl) - propyl] - 1 - (4 - fluorophenyl) - 3 - methyl - 1,3,8 - triazaspiro [4,5]decan - 4 - one; and 10
- 8 - [3 - (1,3 - dihydro - 2 - oxo - 2H - benzimidazol - 1 - yl)propyl] - 3 - ethyl - 1 - (4 - fluorophenyl) - 1,3,8 - triazaspiro [4,5]decan - 4 - one.

Example LVII.

Following the procedure of Example XXIX and using equivalent amounts of the appropriate starting materials, the following compounds are still obtained:

- 15 5 - chloro - 1 - {3 - [4 - (1,3 - dihydro - 5 - methyl - 2 - oxo - 2H - benzimidazol - 1 - yl) - 1 - piperidinyl]propyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one; 15
- 20 5 - chloro - 1 - {3 - [4 - [1,3 - dihydro - 2 - oxo - 5 - (trifluoromethyl) - 2H - benzimidazol - 1 - yl] - 1 - piperidinyl]propyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one; 20
- 1 - {3 - [4 - (5,6 - dichloro - 1,3 - dihydro - 2 - oxo - 2H - benzimidazol - 1 - yl) - 1 - piperidinyl]propyl} - 1,3 - dihydro - 2H - benzimidazole - 2 - one;
- 25 5 - chloro - 1 - {3 - [4 - (5 - chloro - 1,3 - dihydro - 2 - oxo - 2H - benzimidazol - 1 - yl) - 1 - piperidinyl] - 2 - methylpropyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one; 25
- 5 - bromo - 1 - {3 - [4 - (5 - chloro - 1,3 - dihydro - 2 - oxo - 2H - benzimidazol - 1 - yl) - 1 - piperidinyl]propyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one; and
- 30 1 - {3 - [4 - 5 - bromo - 1,3 - dihydro - 2 - oxo - 2H - benzimidazol - 1 - yl) - 1 - piperidinyl]propyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one. 30

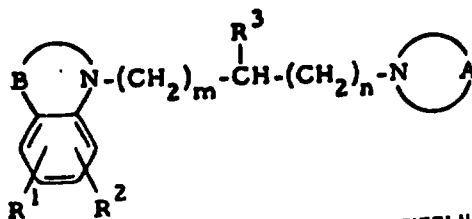
Example LVIII.

Following the procedure of Example LIII and using equivalent amounts of the appropriate starting materials, the following compounds are still obtained:

- 35 5 - chloro 1- [3 - {4 - [4 - chloro - 3 - (trifluoromethyl)phenyl] - 4 - hydroxy - 1 - piperidinyl]propyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one; 35
- 5 - chloro - 1 {3 - [4 - (4 - chlorophenyl) - 4 - hydroxy - 1 - piperidinyl] - 2 - methylpropyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one;
- 40 5 - bromo - 1 - {3 - [4 - (4 - chlorophenyl) - 4 - hydroxy - 1 - piperidinyl]propyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one; 40
- 1 - {3 - [4 - (4 - bromophenyl) - 4 - hydroxy - 1 - piperidinyl]propyl} - 1,3 - dihydro - 2H - benzimidazol - 2 - one;
- 1 - {3 - [4 - (4 - chlorophenyl) - 4 - hydroxy - 1 - piperidinyl]propyl} - 1,3 - dihydro - 5 - (trifluoromethyl) - 2H - benzimidazol - 2 - one;
- 45 1 - {3 - [4 - (4 - chlorophenyl) - 4 - hydroxy - 1 - piperidinyl]propyl} - 5,6 - dichloro - 1,3 - dihydro - 2H - benzimidazol - 2 - one; and 45
- 5 - chloro - 1 - {3 - [4 - (4 - chlorophenyl) - 4 - hydroxy - 1 - piperidinyl] - propyl} - 1,3 - dihydro - 3 - (2 - propenyl) - 2H - benzimidazol - 2 - one.

WHAT WE CLAIM IS:—

- 50 1. 1-(benzazolylalkyl)piperidine derivative having the formula: 50

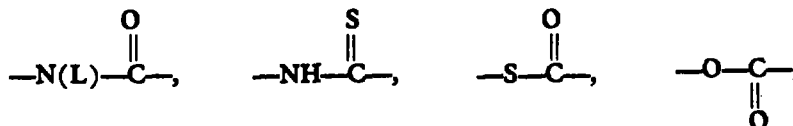


(I)



R^1 and R^2 are each independently a hydrogen atom, a lower alkyl or a trifluoromethyl group;

B is a bivalent radical of the formula



5 $-\text{N}=\text{N}-$ or $-\text{N}=\text{CH}-$, wherein L is a hydrogen atom, a lower alkyl, lower alkyl-carbonyl or lower alkenyl group and the bivalent radical is attached to the benzene nucleus by the heteroatom;

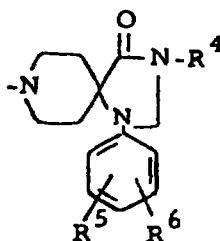
R^3 is a hydrogen atom or a methyl group;

10 m and n are each an integer of 1 or 2; and the radical



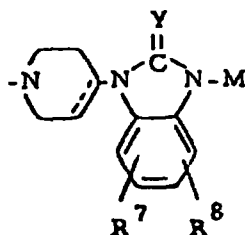
is

a) a radical having the formula:



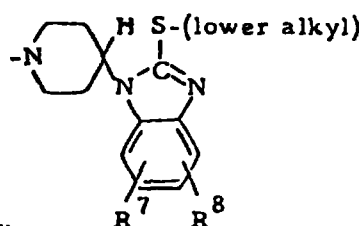
15 wherein R^4 is a hydrogen atom or a lower alkyl group; and R^5 , and R^6 are each independently a hydrogen or halogen atom, a lower alkyl or trifluoromethyl group;

b) a radical having the formula:



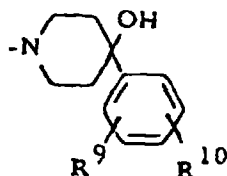
20 wherein R^7 and R^8 are each independently a hydrogen or halogen atom, a lower alkyl or trifluoromethyl group; Y is an O or S atom; M is a hydrogen atom, a lower alkyl or lower alkylcarbonyl group; and the dotted line indicates that the double bond between the 3 and 4 carbon atoms of the piperidine nucleus is optional, provided that when Y is an S atom, then there is a single bond between the 3 and 4 carbon atoms of the piperidine nucleus, and then M is a hydrogen atom;

25 c) a radical having the formula:



wherein R⁷ and R⁸ are each independently a hydrogen or halogen atom, a lower alkyl or trifluoromethyl group; and

d) a radical having the formula:



5 wherein R⁹ is a hydrogen or halogen atom, a lower alkyl or trifluoromethyl group, and R¹⁰ is a hydrogen or halogen atom. 5

2. 5 - Chloro - 1 - {1 - [3 - (1,3 - dihydro - 2 - oxo - 2H - benzimidazol - 1 - yl) - propyl] - 4 - piperidiny] - 1,3 - dihydro - 2H - benzimidazol - 2 - one.

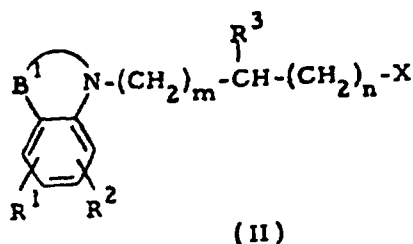
10 3. 8 - [3 - (1,3 - Dihydro - 2 - oxo - 2H - benzimidazol - 1 - yl) - propyl] - 1 - (4 - fluorophenyl) - 1,3,8 - triazaspiro[4,5]decan - 4 - one. 10

4. A compound of Formula (I) as claimed in claim 1 as hereinbefore specifically defined.

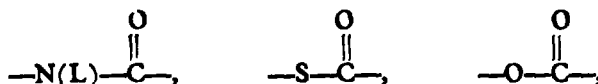
5. A pharmaceutically acceptable acid addition salt of a compound as claimed in any one of claims 1 to 4.

15 6. A process for preparing a 1 - (benzazolylalkyl) - piperidine derivative as defined as claimed 1 or a pharmaceutically acceptable acid addition salt thereof, which comprises 15

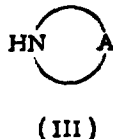
a) reacting a compound of the formula



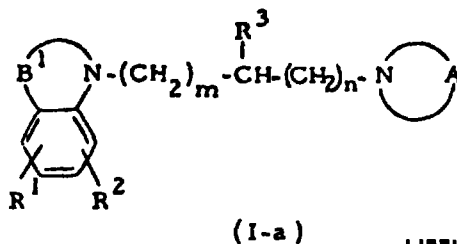
20 wherein B¹ is 20



—N=N— or —N=CH—, and X is a reactive ester function derived from a corresponding alcohol, with a compound of the formula



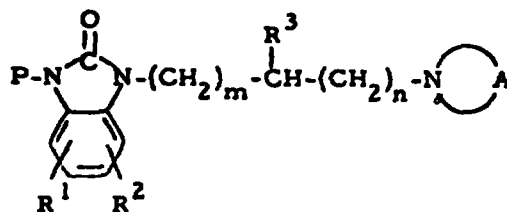
25 in an inorganic solvent, in order to prepare a compound of the formula 25



wherein R^1 , R^2 , R^3 , m , n and

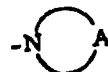


are as defined in claim 1 and B^1 is as above defined; or b) removing the protecting group P by known methods from a compound of the formula

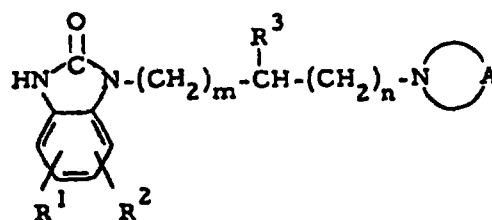


(IV)

wherein R^1 , R^2 , R^3 , m , n and

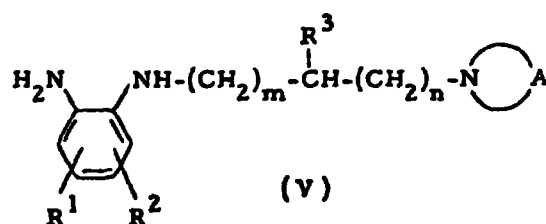


are as defined in claim 1 in order to prepare a compound of the formula



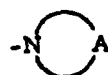
(I-b)

or c) subjecting a compound of the formula

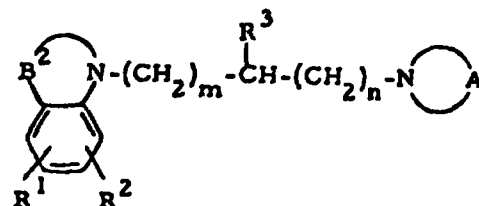


(V)

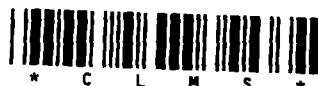
wherein R^1 , R^2 , R^3 , m , n and



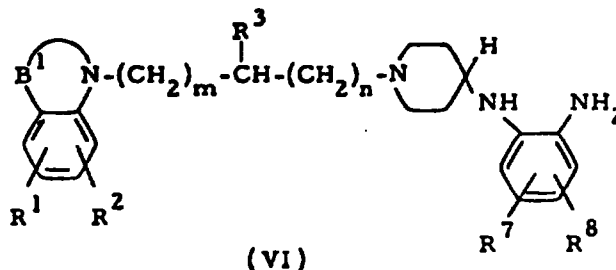
are as defined in claim 1 to ring closure by known methods, in order to prepare a compound of the formula



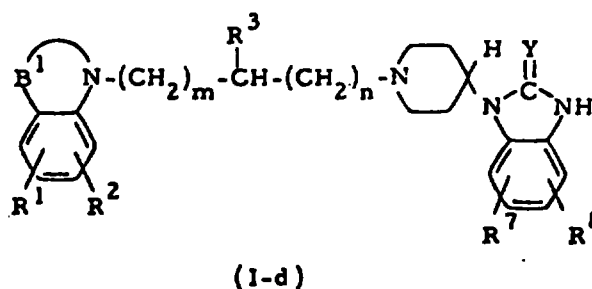
(I-c)



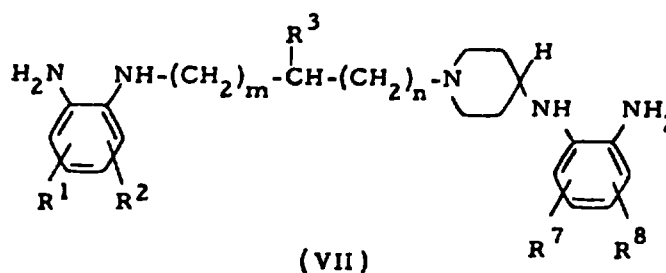
wherein B³ is —NH—C(O)—, —NH—C(S)— or —N=CH—, or d) cyclizing a compound of the formula



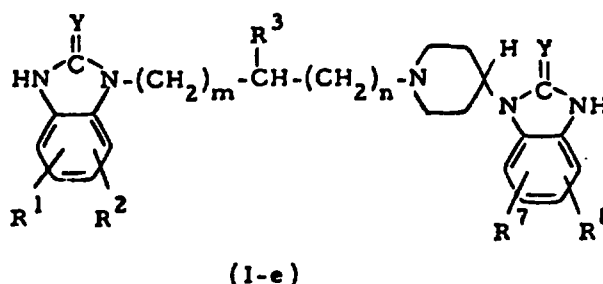
5 wherein R¹, R², R³, m, n, B¹, R⁷ and R⁸ are as defined in claim 1 in order to prepare a compound of the formula



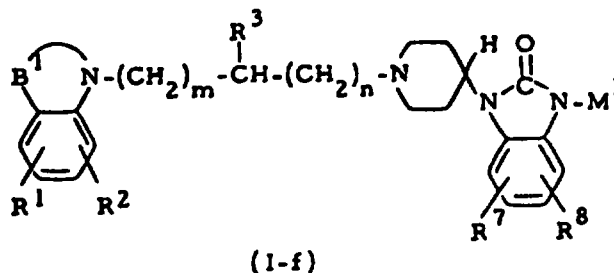
or e) cyclizing both benzenediamine groups in a compound of the formula



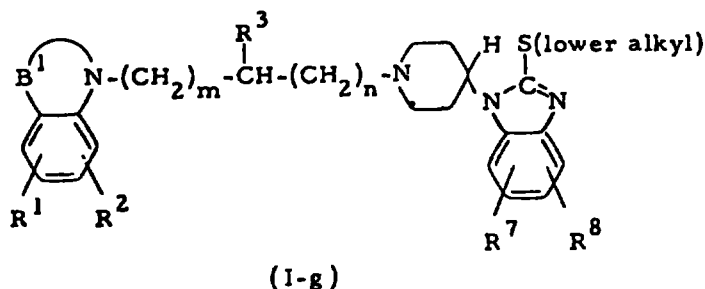
10 wherein R¹, R², R³, m, n, R⁷ and R⁸ are as defined in claim 1 in one reaction step, by known methods in order to prepare a compound of the formula



or f) preparing a compound of the formula



wherein R^1 , R^2 , R^3 , m , n , B^1 , R^7 and R^8 are as defined in claim 1 and M^1 is a lower alkyl or lower alkyl carbonyl group by respectively N-alkylating or N-acylating by known methods the corresponding unsubstituted compound; or g) S-alkylating a compound of the formula (I-d) as above defined wherein Y is S, by standard S-alkylating procedures in order to prepare a compound of the formula



wherein R^1 , R^2 , R^3 , m , n , B^1 , R^7 and R^8 are as defined in claim 1, and if desired, preparing pharmaceutically acceptable acid addition salts of the products of steps (i-a) to (I-g).

7. A process for preparing 5-chloro-1-{1-[3-(1,3-dihydro-2-oxo-2H-benzimidazol-1-yl)-propyl]-4-piperidinyl}-1,3-dihydro-2H-benzimidazol-2-one which comprises reacting 1-(3-chloropropyl)-1,3-dihydro-2H-benzimidazol-2-one with 5-chloro-1,3-dihydro-1-(4-piperidinyl)-2H-benzimidazol-2-one, and, if desired, preparing a pharmaceutically acceptable acid addition salt of the product thereof.

8. A process for preparing 8-[3-(1,3-dihydro-2-oxo-2H-benzimidazol-1-yl)propyl]-1-(4-fluorophenyl)-1,3,8-triazaspiro[4,5]decan-4-one which comprises reacting 1-(3-chloropropyl)-1,3-dihydro-2H-benzimidazol-2-one with 1-(p-fluorophenyl)-1,3,8-triazaspiro[4,5]decan-4-one and, if desired, preparing a pharmaceutically acceptable acid addition salt of the product thereof.

9. A process for preparing a compound of Formula (I) as claimed in claim 1 substantially as hereinbefore described with reference to any one of Examples XX to LVIII.

10. A compound of Formula (I) whenever prepared by a process as claimed in any one of claims 6 to 9.

11. A pharmaceutical composition which comprises an inert carrier material and as an active ingredient an effective antiemetic amount of a chemical compound as claimed in any one of claims 1 to 4 or claim 10 or a pharmaceutically acceptable acid addition salt thereof as claimed in claim 5.

12. A pharmaceutical composition as claimed in claim 11 in dosage unit form comprising per dosage unit an effective antiemetic amount of a compound having the Formula (I) herein, or the pharmaceutically acceptable acid addition salts thereof in admixture with a pharmaceutical carrier.

13. A pharmaceutical composition as claimed in claim 11 or claim 12 wherein the pharmaceutical carrier is a solid, ingestible carrier.

14. A pharmaceutical composition as claimed in claim 11 or claim 12 wherein the pharmaceutical carrier is a liquid, ingestible carrier.

15. A pharmaceutical composition as claimed in claim 11 or claim 12 wherein the pharmaceutical carrier is a sterile liquid suitable for parenteral use.

16. A method of inhibiting emesis in non-human animals which comprises the systemic administration in warm-blooded non-human animals of an effective antiemetic amount of a pharmaceutical composition as claimed in any one of claims 11 to 15.

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