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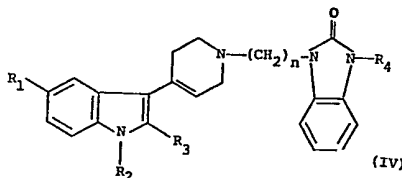
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(54) N-[4-(Indolyl)-piperidino-alkyl]-
benzimidazolones

(57) Compounds of formula I



wherein

R₁ represents a hydrogen or
halogen atom or a methoxy group;

R₂ represents a hydrogen atom or a
lower alkyl group;

R₃ represents a hydrogen atom or a
lower alkyl group;

R₄ is hydrogen, lower alkyl or
alkenyl of up to 3 carbon atoms; and
n is 2 to 6; and acid addition salts
thereof and method for their
preparation are provided. The
compounds and their
pharmacologically acceptable salts are
useful as antiallergics and
hypotensives and pharmaceutical
compositions containing such
components are also provided.

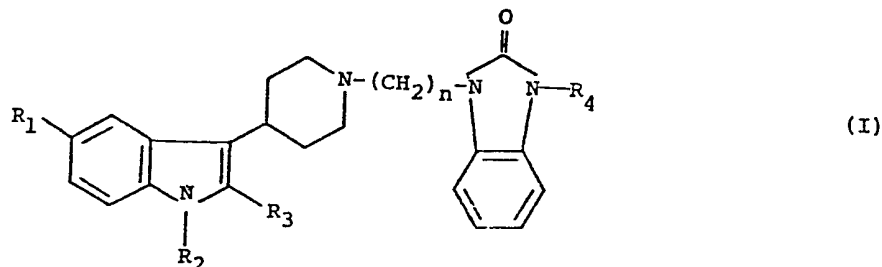
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SPECIFICATION

N-[4-(Indolyl)piperidino-alkyl]-benzimidazolones

This invention relates to novel substituted N-[4-(indolyl)-piperidino-alkyl]-benzimidazolones and acid addition salts thereof, to methods of preparing these compounds, to pharmaceutical composition
 5 containing them as active ingredients, and to methods of using them as antiallergics and hypotensives. 5
 Certain novel substituted N-[4-(indolyl)-piperidino-alkyl]-benzimidazolones have been found to possess interesting pharmacological, in particular anti-allergic and hypotensive, properties.

According to one aspect of the present invention we therefore provide compounds of formula I



10 (wherein R_1 represents a hydrogen or halogen atom or a methoxy group; R_2 represents a hydrogen atom or a lower alkyl group; R_3 represents a hydrogen atom or a lower alkyl group; R_4 represents a hydrogen atom, a lower alkyl group or an alkenyl group having up to 3 carbon atoms; and n is 2 to 6) and acid addition salts thereof. 10

The term "halogen" is intended to include fluorine, chlorine and bromine.

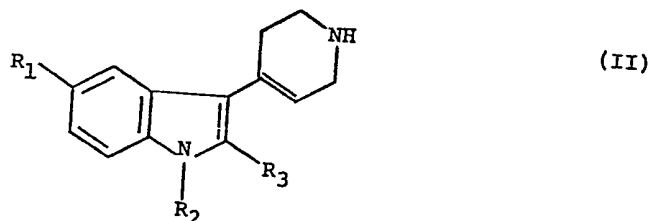
15 The term "lower alkyl" is intended to designate alkyl groups of 1 to 3 carbon atoms, preferably methyl. 15

The compounds of the invention contain at least one asymmetric carbon atom (at the 4-position in the piperidino ring) and may therefore exist in more than one stereoisomeric form. All such forms and mixtures thereof are deemed to fall within the scope of the present invention.

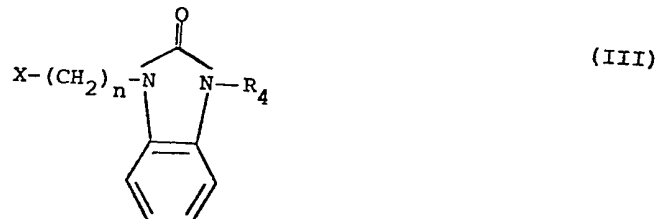
20 The compounds embraced by formula I may be prepared by various methods involving known chemical synthesis principles, among which the following are preferred. 20

Method A

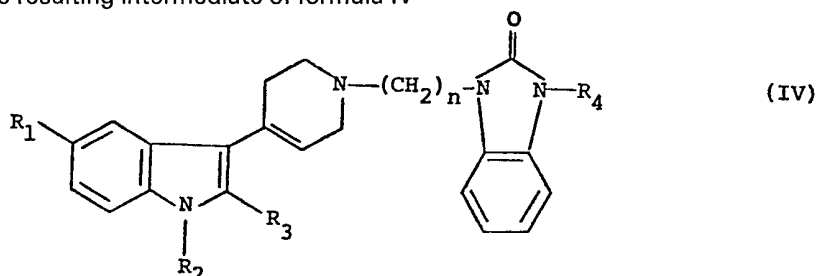
By alkylating a 3-(1,2,5,6-tetrahydro-4-pyridyl)-indole of formula II



25 (wherein R_1 , R_2 and R_3 are as hereinbefore defined) with an N-(ω -haloalkyl)-benzimidazolone of formula III 25



(wherein R_4 and n are as hereinbefore defined, and X represents a chlorine, bromine or iodine atom) and hydrogenating the resulting intermediate of formula IV



30

30

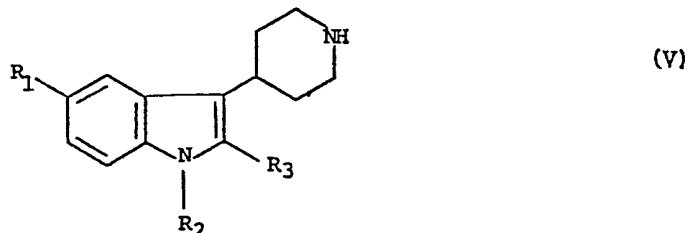
(wherein R_1 , R_2 , R_3 , R_4 and n are as hereinbefore defined) with hydrogen in the presence of a noble metal catalyst.

The alkylation reaction may be performed in the presence of an inert polar or non-polar organic solvent, such as ethanol, dimethyl formamide or tetrahydrofuran, and advantageously in the presence of an inorganic or organic acid-binding agent such as sodium hydroxide, sodium carbonate, sodium bicarbonate or triethylamine at temperatures between 20°C and the boiling point of the solvent.

The subsequent hydrogenation may be carried out at a temperature of 20°C at atmospheric or elevated pressure. Examples of suitable noble metal catalysts are palladium and platinum,

Method B

10 By alkylating a 3-(4-piperidyl)-indole of formula V 10



(wherein R_1 , R_2 and R_3 are as hereinbefore defined) with an N-(ω -halo-alkyl)-benzimidazolone of formula III (wherein R_4 and n are as hereinbefore defined and X represents a chlorine, bromine or iodine atom).

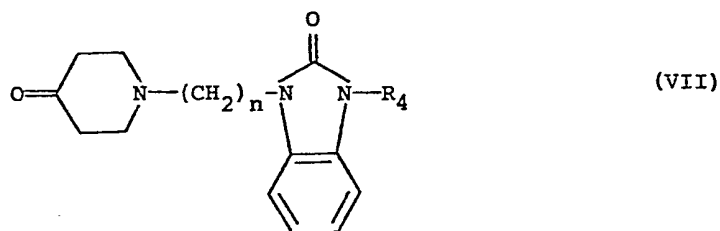
15 The alkylation reaction may be performed in the presence of an inert polar or non-polar organic solvent, such as ethanol, dimethyl formamide or tetrahydrofuran, and advantageously in the presence of an inorganic or organic acid-binding agent, such as sodium hydroxide, sodium carbonate, sodium bicarbonate or triethylamine at temperatures between 20°C and the boiling point of the solvent.

Method C

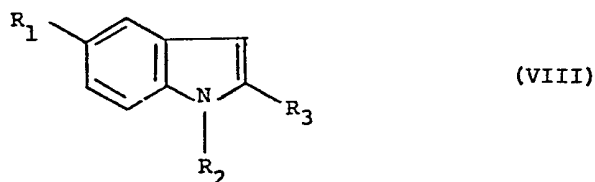
20 By alkylating 4-piperidone of the formula VI 20



with an N-(ω -halo-alkyl)-benzimidazolone of formula III (wherein R_4 and n are as hereinbefore defined and X represents a chlorine, bromine or iodine atom) to form a first intermediate of formula VII



25 (wherein R_4 and n are as hereinbefore defined), reacting the said first intermediate in acid solution with an indole of formula VIII 25



(wherein R_1 , R_2 and R_3 are as hereinbefore defined) to form a second intermediate of formula IV

30 (wherein R_1 , R_2 , R_3 , R_4 and n are as hereinbefore defined), and hydrogenating the said second intermediate with hydrogen in the presence of a noble metal catalyst. 30

The reaction of intermediate VII with the indole of the formula VIII may be carried out in aqueous acid solution at room temperature.

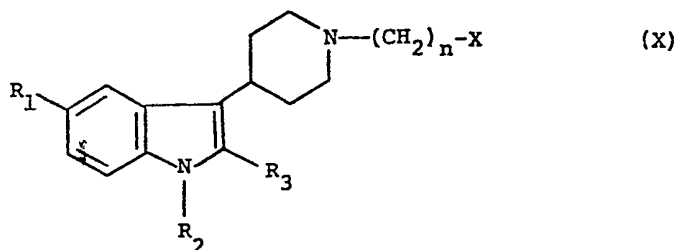
The subsequent hydrogenation may be carried out at a temperature of 20°C at atmospheric or elevated pressure. Examples of suitable noble metal catalysts are palladium and platinum.

Method D

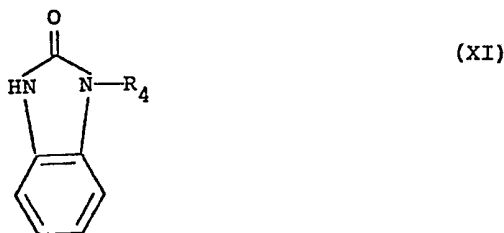
By alkylating a 3-(4-piperidyl)-indole of formula V (wherein R_1 , R_2 and R_3 are as hereinbefore defined) with an α,ω -dihalo-alkane of formula IX



- 5 (wherein n is as hereinbefore defined, and each X , which may be the same or different, represents a chlorine, bromine or iodine atom) to form an intermediate of formula X 5



(wherein R_1 , R_2 , R_3 , n and X are as hereinbefore defined), and alkylating the said intermediate with a benzimidazolone of formula XI



- 10 10

(wherein R_4 is as hereinbefore defined).

- The compounds embraced by formula I are basic and therefore form addition salts with inorganic or organic acids. While pharmacologically acceptable acid addition salts are preferred, other acid addition salts may be useful in the preparation of the free base or of pharmacologically acceptable acid addition salts and so are deemed to fall within the scope of the invention. Example of non-toxic, pharmacologically acceptable acid addition salts are those formed with hydrohalic acid, especially hydrochloric or hydrobromic acid, nitric acid, sulfuric acid, o-phosphoric acid, tartaric acid, citric acid, maleic acid, fumaric acid, propionic acid, butyric acid, acetic acid, succinic acid, methanesulfonic acid, benzenesulfonic acid and p-toluenesulfonic acid. 15

- 20 The starting compounds for methods A through D are known compounds or may be prepared by known methods. 20

Compounds of the formula II and methods for their preparation are described by K. Freter in J. Org. Chem. 40, 2525 (1975).

- 25 Compounds of the formulas III and XI are described by F. Awouters et al. in "Drugs Affecting the Respiratory System", ACS Symposium Series 118, page 179 (1980). 25

Compounds of the Formula V and methods for their preparation are described by D. Beck et al. in Helv. Chim. Acta 51, 260 (1968).

Compounds of the formulas VI and VIII and commercially available from Aldrich Chemical Co., Inc., Milwaukee, Wisconsin.

- 30 The compounds of the present invention, that is, those embraced by formula I above and their non-toxic, pharmacologically acceptable acid addition salts, have interesting pharmacodynamic properties. More particularly, compounds tested have been found to exhibit anti-allergic activity in warm-blooded animals such as rats, and may therefore be useful for the treatment of allergic diseases such as allergic asthma, rhinitis, conjunctivitis, hay fever, urticaria, food allergies and the like. 30

- 35 According to a further aspect of the present invention we provide compounds of formula I and pharmacologically acceptable acid addition salts thereof for use in a method of treatment of the human or animal body to suppress allergic reactions therein. 35

- 40 According to a still further aspect of the present invention we provide pharmaceutical compositions comprising as an active ingredient an effective amount of a compound of formula I or a pharmacologically acceptable acid addition salt thereof together with a pharmaceutical carrier or excipient. 40

- 45 According to a yet still further aspect of the present invention we provide a method of treatment of the human or animal body to suppress allergic reactions therein which method comprises administering to the said body an effective amount of a compound of formula I or a pharmacologically acceptable acid addition salt thereof. 45

For pharmaceutical purposes the compounds according to the present invention may be administered to warm-blooded animals topically, perorally, parenterally or by the respiratory route as active ingredients in customary dosage unit compositions, that is, compositions in dosage unit form consisting essentially of an inert pharmaceutical carrier and one effective dosage unit of the active ingredient, such as tablets, coated pills, capsules, wafers, powders, solutions, suspensions, inhalation aerosols, ointments, emulsions, syrups, suppositories and the like. One effective dosage unit of the compounds according to the present invention is from 0.013 to 0.26 mg/kg body weight.

Their pharmacological evaluation indicates that the compounds of the invention act through two biological mechanisms: First, they stabilize the mast cells, thus preventing the release of mediators, the normal consequence of antigen-antibody reaction of other stimuli. Secondly, they possess anti-histaminic properties, which is to say that they prevent the actions of histamine, the main mediator in human allergic disorders. The first property was demonstrated in the Mast Cell Stabilization Assay, the second one in Antihistamine Assays, and both together in the Passive Cutaneous Anaphylaxis Test as follows:

15 Rat Passive Cutaneous Anaphylaxis (PCA) Test

The test used was essentially that described by El-Azab, J. and Stewart, P. B., "Pharmacological Profile of a New Anti-Allergic Compound PRD—92—EA." *Int. Archs. Allergy Appl. Immunol.* 55: 350—361, 1977;

A dilution of anti-OA reaginic serum was used to give reproducible skin reactions with diameters between 10—15 mm in unsensitized rats. This anti-serum dilution was injected in a volume of 0.1 ml intradermally on each side of the shaved backs of male CD rats (150—160 gm) before antigen challenge. Test compounds which were evaluated by the intravenous (i.v.) route were dissolved in water, and mixed with 0.5 ml of a solution containing 5 mg ovalbumin and 2 percent Evans Blue and administered at a volume of 1 ml/kg. This mixture was injected 24 hours after the rats had been passively sensitized. For evaluation of oral activity, the test compound was suspended in a 1 percent acacia and administered in a volume of 1 ml/kg with an oral feeding needle. Twenty to thirty minutes after oral administration of the test substance, an antigenic challenge consisting of 0.015 mg of ovalbumin in 0.5 ml of 2% Evans Blue was administered. Fifteen minutes after antigenic challenge an intradermal injection of histamine, 3 μ g/0.1 ml in saline was given to assess potential antihistaminic activity.

Thirty minutes after antigenic challenge, i.e. for either intravenous or oral administration, the rats were killed by CO₂ asphyxiation. A midline incision was made along the spine and the skin was reflected and the diameter of the blueed areas were measured in millimeters. The mean area in square millimeters was determined for each spot and the mean circular area of that test group was calculated. The mean area in square millimeters of an untreated control group was considered as a 100 percent response, and the results of the test compound groups were expressed as a percent change from the control values. An ED₅₀ (i.e. defined as a 50 percent reduction in area) was determined using the method of Litchfield, J. T. Jr. and Wilcoxon, F. "A simplified Method of evaluating Dose-Effect Experiments", *J. Pharmacol. Exp. Therap.* 96: 99—113, 1949.

40 In Vivo Inhibition of Histamine-Induced Blueing in Rat Skin

Male CD rats (150—160 gm) were divided into two groups. The hair was removed from an area of the back with an electric clipper. An untreated control group received 10 ml/kg, p.o. of normal saline in 1 percent acacia. Experimental groups received test compound suspended in 1 percent acacia at a volume of 10 ml/kg, p.o. Two percent Evans Blue dye in normal saline in a volume of 0.5 ml was administered intravenously to all animals. Twenty minutes following administration of the test compound or vehicle, 3 μ g of histamine diphosphate in 0.1 ml of normal saline was injected intradermally in two sites of the shaved area on the backs of the rats. Fifteen minutes following histamine injection, all rats were killed by CO₂ asphyxiation.

An incision was made along the spine and the skin cleanly separated. The dorsal skin was reflected and the diameters of the blue-spotted wheals were measured. The area in square millimeters was determined for each resulting blue spot and the mean area for the control and test groups were calculated. The mean area for the control group was considered as a 100 percent response. Test group results were expressed as a percentage change from control. An ED₅₀ (i.e. defined as a 50 percent reduction in blue-spotted area) was determined by linear regression analysis.

55 Inhibition of Peritoneal Mast Cell Degranulation (MCD) in Rats Passively Sensitized with OA Antiserum or Induced by Compound 48/80

This test was adapted from that described by Mota, I. and Osler, A. G. "Mast Cell Degranulation", *Methods in Medical Research* (ed. H. H. Eisen), Yearbook Medical Publication, Chicago, 1964.

Male CD rats (150—160 gm) were divided into 5 groups as follows:

60	Group I:	Nonspecific MCD control (3 rats)	60
	Group II:	Positive MCD control (5 rats)	
	Groups III, IV, V:	Positive MCD following test compound (5 rats each)	

Group I was injected intraperitoneally with 3 ml of normal rat serum. Groups II through V were intraperitoneally administered 3 ml of an antiserum predetermined to produce a 60—80 percent greater degranulation than normal rat serum. Eighteen to 24 hours later, test compound was administered (i.e., i.v. immediately, i.p. 5 minutes, or p.o. 20 minutes) before i.p. antigen challenge with 0.5 mg/kg of 2×crystalline ovalbumin in a concentration of 0.005 percent saline. Fifteen minutes after challenge, the rats were killed by asphyxiation with CO₂.

In the case of experiments utilizing Compound 48/80 (N-methyl-homoanisylamine-formaldehyde-copolymer) to induce degranulation of the mast cells, Group I was injected intraperitoneally with 3 ml of Hank's solution at a pH of 7.2—7.4. The positive control group and groups receiving test compound were injected i.p. with 20 μg/kg of Compound 48/80 in 3 ml of Hank's solution at a pH of 7.2—7.4. The rats were killed by asphyxiation with CO₂ five minutes after the i.p. injection of Compound 48/80.

Microscopic slides of the mesentery were prepared and analyzed by a modification of the method by Fügner, A. "An Improved Method for the Study of Reagin-mediated Mast Cell Degranulation in Rats", *Experientia*, 29: 708, 1973, to determine the degree of degranulation of mast cells in untreated and treated groups of rats.

The results were calculated and expressed as percent of inhibition of degranulation as follows:

$$\text{Percent Inhibition} = 100 - \left[\frac{\text{Experimental} - \text{Negative Control}}{\text{Positive Control} - \text{Negative Control}} \right] \times 100$$

The following tables shows the results obtained from these tests for a representative specie of the genus represented by formula I (namely the compound of Example 4 hereinafter) and for oxatomide, a known compound of similar activity.

Compound	PCA	ED ₅₀ 's mg/kg MCD	Antihist.
Oxatomide	8.3	neg.	8.1
Compound of Example 4	1.6	3.0—6.4	8.7

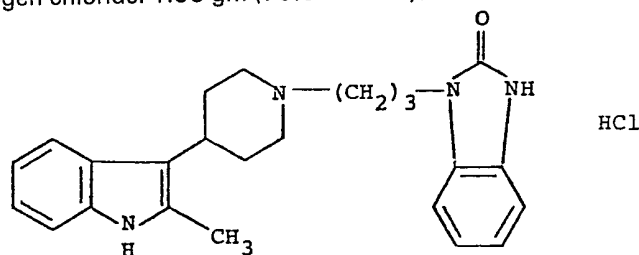
These results show that the compound of the present invention is superior in two respects, namely that it has demonstrable mast cell stabilizing in addition to antihistaminic properties and is some five times more potent.

The following Examples are provided to illustrate the present invention without restricting the scope of protection sought therefor.

Example 1
N-[3-[4-(2-Methyl-3-indolyl)-piperidino]-propyl]-benzimidazolone and its Hydrochloride (by Method A.)

A mixture consisting of 1.06 gm of 2-methyl-3-(1,2,5,6-tetrahydropyridyl-4)-indole, 1.05 gm of N-(3-chloro-propyl)-benzimidazolone, 0.42 gm of sodium bicarbonate, 20 ml of dimethylformamide and 20 ml of tetrahydrofuran was heated at 100°C for 18 hours while stirring. Thereafter, the reaction mixture was poured into a mixture of 200 gm of ice and 10 ml of concentrated ammonia, and the precipitate formed thereby was collected by filtration and recrystallized from ethanol, yielding 1.2 gm (62% of theory) of the intermediate of the formula IV (R₁=H, R₂=H, R₃=—CH₃, n=3, R₄=H) having a melting point of 215°C.

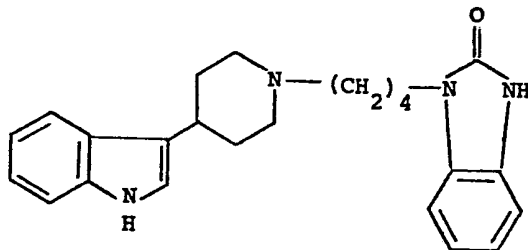
1.5 gm of the intermediate thus obtained were dissolved in 100 ml of acetic acid and shaken for 24 hours with 0.8 gm of palladium —5%—on—charcoal at 20°C in an atmosphere of hydrogen at 5 atmospheres pressure. Thereafter, the catalyst was removed by filtration, and the filtrate was poured into a mixture of ice and ammonia, whereupon the desired free base product precipitated. The precipitate was collected by filtration, dried, dissolved in ethanol and converted into its hydrochloride by addition of etheric hydrogen chloride. 1.05 gm (70% of theory) of the *title compound* of the formula



with a melting point of 264—269°C were obtained.

Example 2**N-[4-[4-(3-Indolyl)-piperidino]-butyl]-benzimidazolone (by Method B)**

A mixture consisting of 3.0 gm of 4-(3-indolyl)-piperidine, 4.0 gm of 1-(4-chloro-butyl)-3-isopropenylbenzimidazolone, 1.3 gm of sodium bicarbonate, 30 ml of dimethyl-formamide and 30 ml of tetrahydrofuran was refluxed for 16 hours. Thereafter, the reaction mixture was poured into a mixture of ice and ammonia, the aqueous mixture was extracted with ethyl acetate, and the extract solution was washed with water, dried and evaporated to dryness in vacuo. The residue was dissolved in ether, etheric hydrogen chloride was added to the solution, and the precipitate formed thereby was collected by filtration, dried and dissolved in 100 ml of ethanol. The resulting solution was cooled, 16 ml of concentrated sulfuric acid were carefully added while stirring, and the mixture was allowed to stand at 20°C for two hours, whereupon it was poured into a mixture of ice and ammonia. The precipitate formed thereby was collected by filtration and recrystallized from ethanol, yielding 3.2 gm (55% of theory) of the *title compound* of the formula

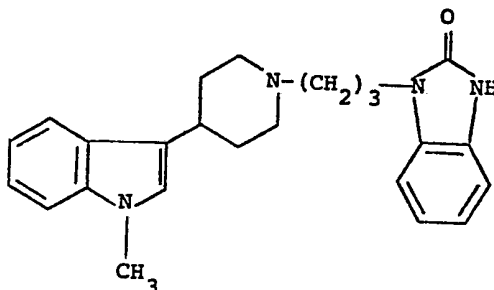


15 having a melting point of 196°C.

Example 3**N-[3-[4-(1-Methyl-3-indolyl)-piperidino]propyl]-benzimidazolone (by Method C)**

A mixture of 6.3 gm of N-(3-chloropropyl)-benzimidazolone, 4.6 gm of 4-piperidine hydrochloride monohydrate, 5.0 gm of sodium bicarbonate, 50 ml of tetrahydrofuran, and 50 ml of dimethylformamide, was heated to reflux for 36 hours. The product was worked up as before yielding 3.2 gm (39% of theory) of N-[3-(4-oxo-piperidino)-propyl]-benzimidazolone, m.p. 134—136°C.

A mixture consisting of 2.7 gm of N-[3-(4-oxo-piperidino)-propyl]-benzimidazolone, 1.3 gm of 1-methyl-indole, 40 ml of acetic acid and 10 ml of 2N phosphoric acid was allowed to stand at 20°C for 6 days. Thereafter, the reaction mixture was poured into a mixture of ice and ammonia, the aqueous mixture was extracted with ethyl acetate, and the extract solution was dried and evaporated in vacuo to dryness. The residue was purified by chromatography on silica, using methylene chloride/methanol/ammonia=90/9/1 as the eluant. The main fraction was hydrogenated without characterization as described in Example 1, and the end product was crystallized from ethanol, yielding 2.4 gm (62% of theory) of the *title compound* of the formula.



30 having a melting point of 180°C.

Example 4

Using a procedure analogous to that described in Example 1, N-[3-[4-(3-indolyl)-piperidino]-propyl]-benzimidazolone and its hydrochloride, m.p. 204°C, were prepared from 3-(1,2,3,4-tetrahydropyridyl-4)-indole and N-(3-chloro-propyl)-benzimidazolone.

Example 5

Using a procedure analogous to that described in Example 2, N-[3-[4-(5-methoxy-3-indolyl)-piperidino]-propyl]-benzimidazolone and its hydrochloride, m.p. 178°C, were prepared from 4-(5-methoxy-3-indolyl)-piperidine and N-(3-chloro-propyl)-benzimidazolone.

Example 6

Using a procedure analogous to that described in Example 2, N-[3-[4-(3-indolyl)-piperidino]-propyl]-N'-isopropenyl-benzimidazolone, m.p. 68°C, was prepared from 4-(3-indolyl)-piperidine and N-(3-chloro-propyl)-N'-isopropenyl-benzimidazolone.

Example 7

Using a procedure analogous to that described in Example 2, N-{3-[4-(1-isopropyl-3-indolyl)-piperidino]-propyl}-benzimidazolone and its hydrochloride, m.p. 145°C, were prepared from 4-(1-isopropyl-3-indolyl)-piperidine and N-(3-chloro-propyl)-benzimidazolone.

5 Example 8

Using a procedure analogous to that described in Example 2, N-{2-[4-(3-indolyl)-piperidino]-ethyl}-benzimidazolone, m.p. 116°C, was prepared from 4-(3-indolyl)-piperidine and N-(2-chloro-ethyl)-benzimidazolone.

Example 9

10 Using a procedure analogous to that described in Example 2, N-{3-[4-(3-indolyl)-piperidino]-propyl}-N'-methyl-benzimidazolone and its hydrochloride, m.p. 140°C, were prepared from 4-(3-indolyl)-piperidine and N-(3-chloro-propyl)-N'-methyl-benzimidazolone.

Example 10

15 Using a procedure analogous to that described in Example 3, N-{3-[4-(1-propyl-3-indolyl)-piperidino]-propyl}-benzimidazolone, m.p. 103°C, was prepared from N-[3-(4-oxopiperidino)-propyl]-benzimidazolone and 1-propyl-indole.

Example 11

20 Using a procedure analogous to that described in Example 2, N-{3-[4-(2-methyl-5-chloro-3-indolyl)-piperidino]-propyl}-benzimidazolone, m.p. 124°C, was prepared from 4-(2-methyl-5-chloro-3-indolyl)-piperidine and N-(3-chloro-propyl)-benzimidazolone.

Example 12

Using a procedure analogous to that described in Example 2, N-{5-[4-(3-indolyl)-piperidino]-pentyl}-benzimidazolone, m.p. 137—140°C, was prepared from 4-(3-indolyl)-piperidine and N-(5-bromopentyl)-benzimidazolone, m.p. 72—75°C.

25 Example 13

Using a procedure analogous to that described in Example 2, N-{6-[4-(3-indolyl)-piperidino]-hexyl}-benzimidazolone, m.p. 127—130°C, was prepared from 4-(3-indolyl)-piperidine and N-(6-bromo-hexyl)-benzimidazolone, m.p. 103—105°C.

Example 14

30 **N-[3-[4-(3-Indolyl)-piperidino]-propyl]-N'-isopropenyl-benzimidazolone (by Method D)**

A mixture of 2 gm of 4-(3-indolyl)-piperidine (formula V; R₁, R₂, R₃=H), and 20 ml of 1-bromo-3-chloro-propane was stirred at room temperature for 72 hours. The mixture was then extracted with 1N hydrochloric acid. The extracts were made slightly basic with sodium carbonate and the product was extracted with ethyl acetate. The residue, 1-chloro-propyl-4-(3-indolyl)-piperidine, after drying and evaporation was used without purification.

35 0.5 gm of the above intermediate were dissolved in 5 ml of tetrahydrofuran and added to a cooled suspension of N-isopropenyl-benzimidazolone sodium salt prepared from 0.34 gm of N-isopropenyl-benzimidazolone and 0.05 gm of sodium hydride in 5 ml of dimethylformamide. The mixture was stirred for 16 hours at room temperature and then poured on ice-water-ammonia. The crystalline product was filtered off and dried. Yield: 0.65 gm (81% of theory), m.p. 68°C, identical with the product obtained by method B in Example 6.

40 The following Examples illustrate pharmaceutical dosage unit compositions comprising a compound of the present invention as an active ingredient. The parts are parts by weight unless otherwise specified.

**45 Example A
Tablets**

The tablet composition is compounded from the following ingredients:

	N-{3-[4-(3-indolyl)-piperidino]-propyl}-benzimidazolone	0.010 parts	
	Stearic acid	0.010 parts	
50	Dextrose	1.890 parts	50
	Total	1.910 parts	

Preparation:

The ingredients are admixed in conventional manner, and the mixture is compressed into 1.91 gm-tablets, each of which is an oral dosage unit composition containing 10 mg of the active ingredient.

Example B Ointment

The ointment composition is compounded from the following ingredients:

	N-[3-[4-(3-indolyl)-piperidino]-propyl]-benzimidazolone	2.000 parts	
5	Fuming hydrochloric acid	0.011 parts	5
	Sodium pyrosulfite	0.050 parts	
	Mixture (1:1) of cetyl alcohol and stearyl alcohol	20.000 parts	
	White Vaseline®	5.000 parts	
	Synthetic bergamot oil	0.075 parts	
10	Distilled water q.s.ad	100.000 parts	10

Preparation:

The ingredients are uniformly blended in conventional manner into an ointment, 100 gm of which contain 2.0 gm of the active ingredient.

Example C

15 Inhalation Aerosol 15

The aerosol composition is compounded from the following ingredients:

	N-[3-[4-(3-indolyl)-piperidino]-propyl]-benzimidazolone	1.00 parts	
	Soybean lecithin	0.20 parts	
20	Propellant gas mixture (Frigen 11, 12 and 14) q.s.ad	100.00 parts	20

Preparation:

The ingredients are compounded in conventional manner, and the composition is filled into aerosol containers with a metering valve which releases 5 to 20 mg of active ingredient per actuation of the valve.

25 Example D 25 Injection Solution

The solution is compounded from the following ingredients:

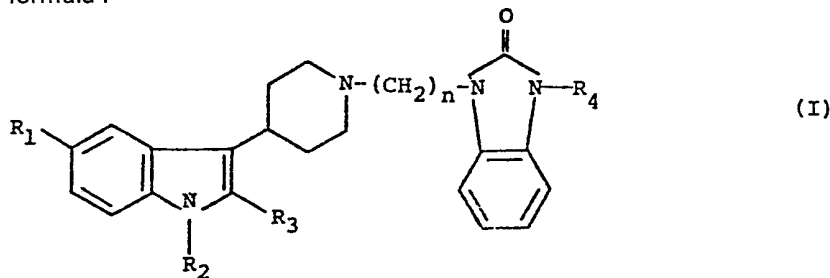
	N-[3-[4-(3-indolyl)-piperidino]-propyl]-benzimidazolone . HCl	5.0 parts	
	Sodium pyrosulfite	1.0 parts	
30	Sodium salt of EDTA	0.5 parts	30
	Sodium chloride	8.5 parts	
	Double-Distilled water q.s.ad	1000.0 parts	

Preparation:

35 The individual ingredients are dissolved in a sufficient amount of double-distilled water, the solution is diluted to the indicated concentration with additional double-distilled water, the resulting solution is filtered until free from suspended particles, and the filtrate is filled under aseptic conditions into 1 ml-ampoules which are subsequently sterilized and sealed. Each ampoule contains 5 mg of the active ingredient. 35

40 Claims 40

1. Compounds of formula I



(wherein R₁ represents a hydrogen or halogen atom or a methoxy group;

R₂ represents a hydrogen atom or a lower alkyl group;

R₃ represents a hydrogen atom or a lower alkyl group;

45 R₄ represents a hydrogen atom, a lower alkyl group or an alkenyl group having up to 3 carbon atoms; and n is 2 to 6) and acid addition salts thereof. 45

2. N-(3-[4-(3-Indolyl)-piperidino]-propyl)-benzimidazolone and acid addition salts thereof.

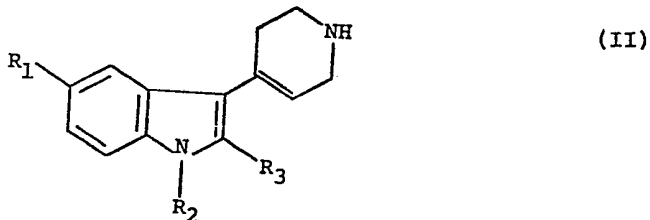
3. N-(4-[4-(3-Indolyl)-piperidino]-butyl)-benzimidazolone and acid addition salts thereof.

4. Compounds of formula I as claimed in claim 1 as herein specifically disclosed with the exception of compounds as claimed in either of claims 2 and 3.

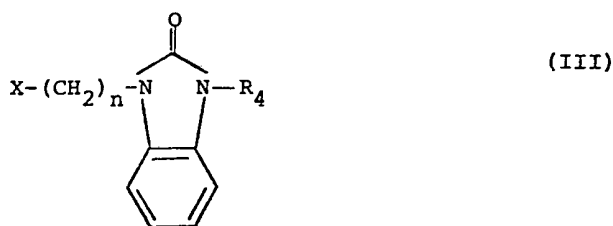
5. Compounds of formula I as claimed in any one of claims 1 to 4 in the form of pharmacologically acceptable acid addition salts.

6. A method of preparing a compound as claimed in claim 1 which method comprises one or more of the following steps:

a) alkylating a 3-(1,2,5,6-tetrahydro-4-pyridyl)-indole of formula II



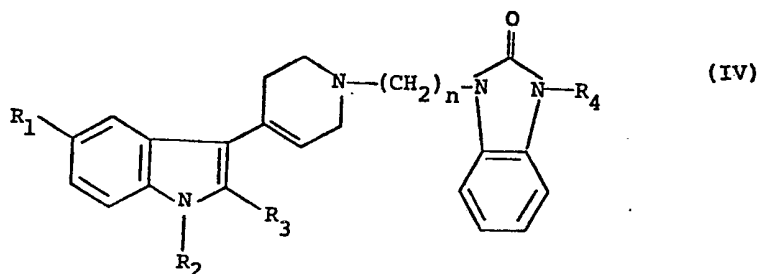
(wherein R_1 , R_2 and R_3 are as defined in claim 1) with an N-(ω -haloalkyl)-benzimidazolone of formula III



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(wherein R_4 and n are as defined in claim 1, and X represents a chlorine, bromine or iodine atom) and hydrogenating the resulting intermediate of formula IV

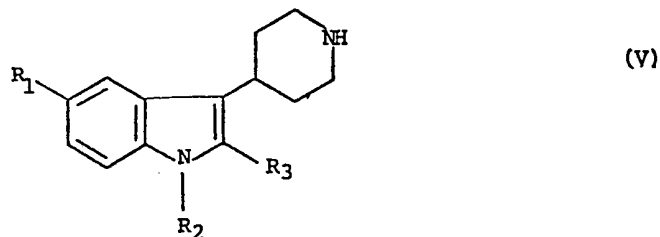


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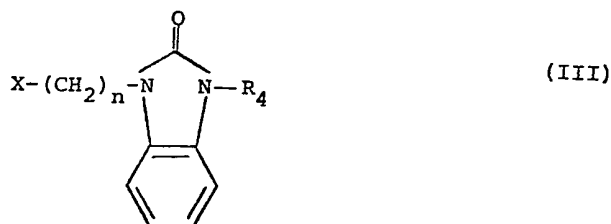
(wherein R_1 , R_2 , R_3 , R_4 and n are as hereinbefore defined) with hydrogen in the presence of a noble metal catalyst;

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(b) alkylating a 3-(4-piperidyl)-indole of formula V



(wherein R_1 , R_2 and R_3 are as defined in claim 1) with an N-(ω -halo-alkyl)-benzimidazolone of formula III



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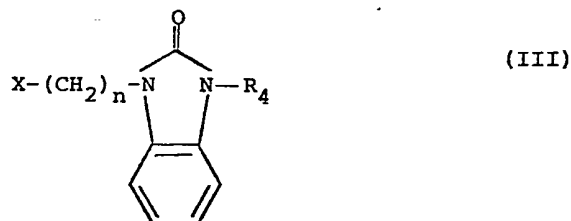
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(wherein R_4 and n are as defined in claim 1, and X represents a chlorine, bromine or iodine atom);

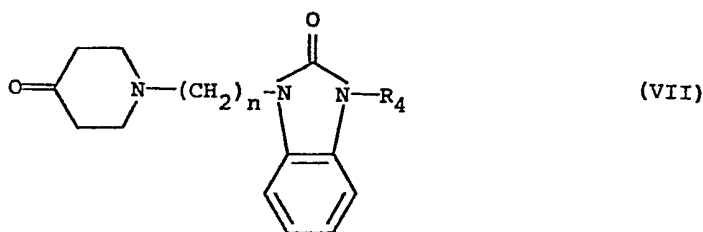
(c) alkylating 4-piperidone of formula VI



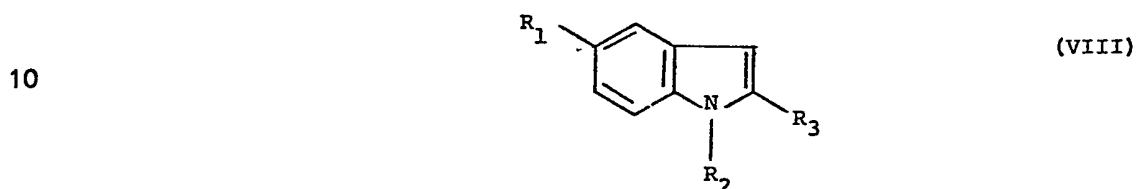
with an N-(ω -halo-alkyl)-benzimidazolone of formula III



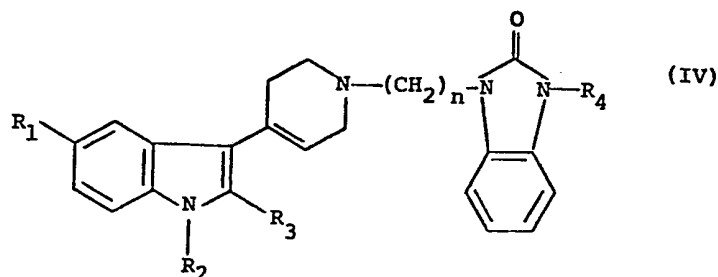
5 (wherein R_4 and n are as defined in claim 1, and X represents a chlorine, bromine or iodine atom) to form a first intermediate of formula VII



(wherein R_4 and n are as hereinbefore defined), reacting the said first intermediate in acid solution with an indole of formula VIII

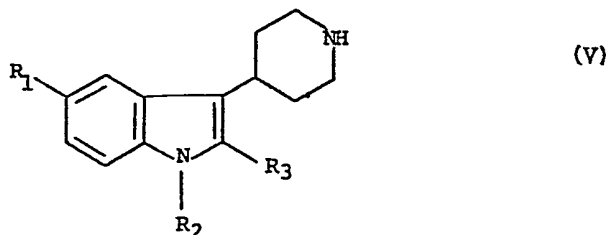


(wherein R_1 , R_2 and R_3 are as defined in claim 1) to form a second intermediate of formula IV

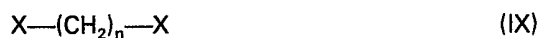


(wherein R_1 , R_2 , R_3 , R_4 and n are as hereinbefore defined), and hydrogenating the said second intermediate with hydrogen in the presence of a noble metal catalyst;

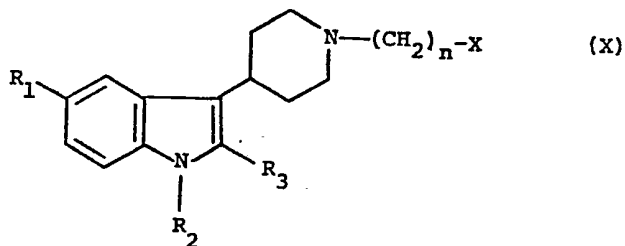
15 (d) alkylating a 3-(4-piperidyl)-indole of formula V



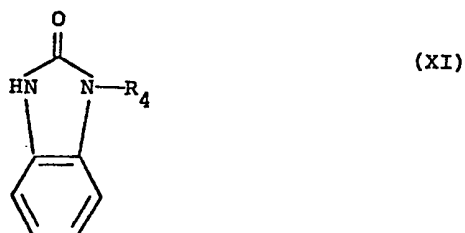
(wherein R_1 , R_2 and R_3 are as defined in claim 1) with an α,ω -dihalo-alkane of formula IX



(wherein n is as defined in claim 1, and each X, which may be the same or different, represents a chlorine, bromine or iodine atom) to form an intermediate of formula X



5 (wherein R_1 , R_2 , R_3 , n and X are as hereinbefore defined) and alkylating the said intermediate with a benzimidazolone of formula XI 5



(wherein R_4 is as defined in claim 1); and

10 (e) converting a compound of formula I (wherein R_1 , R_2 , R_3 , R_4 and n are as defined in claim 1) into an acid addition salt thereof. 10

7. A method as claimed in claim 6 substantially as herein described in any one of Examples 1 to 14.

8. A pharmaceutical composition comprising as an active ingredient an effective amount of a compound of formula I (as defined in claim 1) or a pharmacologically acceptable acid addition salt thereof together with a pharmaceutical carrier or excipient. 15

9. A composition as claimed in claim 8 substantially as herein described in any of Examples A to D.

10. Compounds of formula I (as defined in claim 1) and pharmacologically acceptable acid addition salts thereof for use in a method of treatment of the human or animal body to suppress allergic reactions therein. 20