

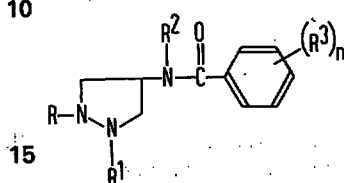
SPECIFICATION

N-(4-pyrazolidinyl) benzamides, and pharmaceutical compositions containing them

5 The present invention relates to N-(4-pyrazolidinyl) benzamides and provides certain such compounds which are believed to be novel and which have been found to possess anti-emetic properties and to facilitate gastric emptying of warm blooded animals, including human beings, with minimal side effects.

The invention embraces the compounds themselves and pharmaceutical compositions containing them.

The compounds of the invention are N-(1,2-hydrocarbyl-4-pyrazolidinyl) benzamides having the formula:



wherein;

R represents lower alkyl, lower cycloalkyl or phenyl lower alkyl;

20 R¹ represents lower alkyl, lower cycloalkyl or phenyl lower alkyl;

R² represents hydrogen, lower alkyl or phenyl;

R³ represents hydroxy, cyano, nitro, amino, fluoro, chloro, bromo, trifluoromethyl, lower alkyl, lower alkoxy, sulphamoyl or acetamido and where there is more than one R³ radical these can be the same radical or different; and

25 n is zero, 1, 2 or 3.

As used herein, the following terms have the meanings indicated.

"Lower alkyl" means a straight or branched chain alkyl radical containing 1 to 8 carbon atoms for example, methyl, ethyl, propyl, isopropyl, n-butyl, tertiary butyl, amyl, isoamyl, n-hexyl, n-heptyl and n-octyl.

A "lower alkoxy" radical has the formula -O-lower alkyl.

30 "Lower cycloalkyl" means a cyclic alkyl radical containing from 4 to 12 carbon atoms and includes such radicals as cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, methylcyclopentyl and ethylcyclohexyl.

"Phenyl" means the unsubstituted phenyl radical or phenyl radicals substituted by any radical or radicals which are not reactive or otherwise interfering under the conditions of reaction described herein such as

35 preferably no more than three substituents such as those mentioned above. These substituents can be in any available positions of the phenyl nucleus and, when more than one substituent is present, can be the same or different and can be in various position combinations relative to each other. The lower alkyl and lower alkoxy substituents each have preferably from 1 to 4 carbon atoms which can be arranged as straight or branched chains. Examples of the preferred substituents are methyl, ethyl, propyl, butyl, fluoro, bromo, 40 chloro, iodo, amino, hydroxy, cyano, acetamido, sulphamoxyl, methoxy, ethoxy, propoxy, butoxy and trifluoromethyl radicals.

Included in the term "phenyl lower-alkyl" are such groups as benzyl, phenethyl, phenpropyl and α -methylbenzyl.

45 The non-toxic pharmaceutically acceptable acid addition salts of the basic compounds of Formula I are also within the scope of this invention; such salts can likewise be used as anti-emetics or gastric emptying compounds. Organic and inorganic acids can be employed to form the pharmaceutically acceptable acid addition salts, illustrative acids being sulphuric, nitric, phosphoric, citric, acetic, lactic, tartaric, sulphamic, succinic, fumaric, maleic, hydrochloric, hydrobromic and benzoic acids. The salts are prepared by methods well known to the art.

50 The anti-emetic properties were determined using a modification of the methods of Chen and Enxer, J. Pharmac. Exp. Ther. 98, 245-250 (1950) and of Leonard *et al.*, J. Pharmac. Exp. Ther. 154, 339-345 (1966).

The gastric emptying activity was determined using the following procedure. Female Sprague-Dawley rats weighing 117-221 g were starved for 24 hours in individual screen-bottom cages with water *ad libitum*.

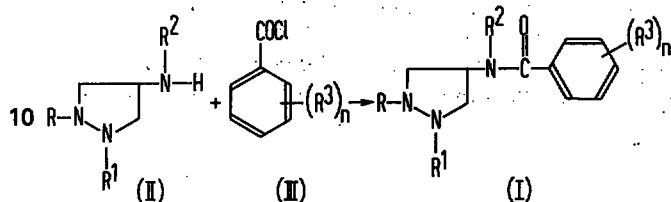
55 Animals were arranged in groups of eight. At time 0, 0 mg/kg of a test compound is administered intraperitoneally to the rats in 5% acacia (0.4 ml/100 g body weight). The control group is dosed with acacia alone, 4 ml/kg intraperitoneally. Thirty minutes following dosing, the rats are given orally, by stomach tube, 3 ml of a test meal consisting of methylcellulose base to which had been added beef bouillon, casein, powdered sugar and corn starch to yield a semi-solid homogenous paste. Sixty minutes following the test meal (ninety minutes total time), the rats are sacrificed by cervical dislocation, laparotomized and the 60 stomachs removed. The full stomachs are weighed on an analytical balance after which they are cut open, rinsed and the empty stomach weighed. The difference between full and empty stomach weights represents the amount of meal remaining in the stomach and is subtracted from the weight of 3.0 ml of test meal to yield the amount of meal emptied from the stomach during the test period.

The preferred compound of Example 6 hereof reduced emesis 87% when administered at a dose level of 5 65 mg/kg (s.c.) and increased the gastric emptying time significantly when administered at doses from 0.33 to

9.0 mg/kg.

Methods of Preparation

The preparation of the benzamido compounds of Formula I may be accomplished by contacting a 4-amino-1,2-hydrocarbylpyrazolidine (Formula II), with an appropriately substituted benzoyl chloride (Formula III) according to the following reaction sequence:



wherein R, R¹, R² and n are as defined above with the proviso that R³ cannot be primary amino.

Compounds of Formula I wherein R³ is primary amino may be prepared by catalytic hydrogenation of the precursor compound of Formula I wherein R³ is nitro. Alternately, a compound of Formula I wherein R³ is primary amino may be prepared from a compound of Formula I wherein R³ is acetamido by hydrolyzing the latter compound in dilute acid to generate the amino radical.

In another method of preparation 1,2-hydrocarbyl-4-phthalimidopyrazolidines are used as a reactant. The latter are prepared by the reaction between a 4-chloro-1,2-hydrocarbylpyrazolidine and potassium phthalimide. The 1,2-hydrocarbyl-4-phthalimidopyrazolidine is hydrolyzed in dilute mineral acid, the mixture filtered and the acid filtrate basified to liberate the free 4-amino-1,2-hydrocarbylpyrazolidine which is reacted with a selected benzoyl chloride to give the desired N-(1,2-hydrocarbyl-4-pyrazolidinyl) benzamide.

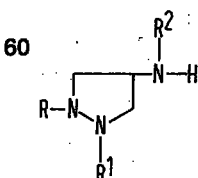
Another method which can be used in preparing the novel compounds of Formula I utilizes an appropriately substituted benzoic acid which is contacted with ethylchlorocarbonate in the presence of triethylamine in methylene chloride at from 0 to 5°C to form the mixed anhydride of the benzoic acid. After approximately one hour at the lower temperature, a solution of the 4-amino-1,2-hydrocarbylpyrazolidine is added. After an additional period of stirring, an aqueous sodium bicarbonate solution is added to the reaction mixture, the organic phase is separated and the benzamide compound is isolated therefrom by suitable means.

The substituted benzoyl chlorides (III) useful in preparing the compounds of the present invention are either known compounds or they can be prepared by procedures well known to the art, and include the following:

- 2-fluorobenzoyl chloride
- 3-bromobenzoyl chloride
- 4-bromobenzoyl chloride
- 3,5-dinitrobenzoyl chloride
- 3,4-dichlorobenzoyl chloride
- 3,4-diethoxybenzoyl chloride
- 3-trifluoromethylbenzoyl chloride
- 4-tertiarybutylbenzoyl chloride
- 4-butoxybenzoyl chloride
- 2,4-dimethoxybenzoyl chloride
- 4-methylbenzoyl chloride
- 4-cyanobenzoyl chloride
- 2-methoxy-5-sulphamoylbenzoyl chloride
- 2-methoxy-4-dimethylaminobenzoyl chloride
- 3-methoxy-4-nitrobenzoyl chloride
- 2-methoxy-3-fluoro-5-chlorobenzoyl chloride
- 2-ethoxy-4-bromobenzoyl chloride
- 2-methoxy-3-acetamido-5-trifluoromethylbenzoyl chloride.

In Formula I centres of asymmetry are present. The compounds can be resolved into their optically active forms by combining the compounds with optically active organic acids and separating the optically active forms by fractional crystallization. The invention embraces these optically active forms.

Certain 4-amino-1,2-hydrocarbylpyrazolidines of Formula II useful as intermediates in the preparation of compounds of Formula I are believed to be novel compounds, and these compounds form the subject matter of our copending British Patent Application No. 7901821 - Serial No. 2017678. These novel compounds of Formula II have the formula



wherein R, R¹ and R² are as defined above.

The compounds of Formula II wherein R² is hydrogen may be prepared by heating a mixture of a 4-halo-1,2-hydrocarbylpyrazolidine and concentrated ammonium hydroxide in a steel bomb at a temperature of from about 125°C to about 200°C for a period of several hours. Such a procedure is also applicable to prepare compounds wherein R² is lower alkyl such as methyl, ethyl or propyl. In the latter case a solution of the appropriate lower alkylamine in a lower alkanol is preferably used.

The compounds of Formula II wherein R² is phenyl may be prepared by reacting a 1,2-hydrocarbyl-4-arylsulphonyloxy-pyrazolidine and aniline or a substituted aniline together in a suitable solvent. A 1,2-hydrocarbyl-4-arylsulphonyloxy-pyrazolidine may be prepared by reacting the sodium salt of a 1,2-hydrocarbyl-4-pyrazolidinol with an arylsulphonyl chloride, for example benzenesulphonyl chloride or *p*-tolylsulphonyl chloride in a dry aprotic solvent such as toluene.

The 1,2-hydrocarbyl-4-pyrazolidinols from which the respective 4-aminopyrazolidinols are prepared are either disclosed in or they can be prepared by the procedures disclosed in U.S. Patent No. 3,660,426.

The novel basic compounds of Formulas I and II form fluosilicic acid addition salts which are useful as moth-proofing agents according to U.S. Patents 1,915,334 and 2,075,359.

The following Preparations describe the preparation of various intermediates, and the Examples describe the preparation of compounds of Formula I.

Preparation 1

20 4-Chloro-1,2-diethylpyrazolidine

A solution of triphenyl phosphine (52 g; 0.2 mole) in 150 ml of chloroform was treated with chlorine gas which was accompanied by a rise in the temperature of the mixture to 60°C until excess chlorine gas appeared over the surface of the mixture. Air was passed into the mixture until the greenish yellow gas disappeared. To the cooled (30°C) stirred mixture was added dropwise 28.8 g (0.2 mole) of 1,2-diethyl-4-pyrazolidinol at a rate which caused the reaction mixture to rise to 40°C. Subsequent to the addition, the stirred solution was refluxed for two hours, cooled to room temperature and extracted with water. The combined aqueous extracts were basified with concentrated sodium hydroxide solution and the basic mixture extracted with chloroform. The dried chloroform extract (sodium sulphate) was concentrated at reduced pressure and the residual material distilled at 92-94°C/30 mm to give 24.5 g (75%) of product.

Analysis:	Calculated for C ₇ H ₁₅ N ₂ Cl	:	C, 51.58;	H, 9.29;
				N, 17.22
	Found	:	C, 51.45;	H, 9.30;
				N, 17.29

Preparation 2

4-Amino-1,2-diethylpyrazolidine

A mixture of 100 g (0.615 mole) of 4-chloro-1,2-diethylpyrazolidine and 200 ml of concentrated ammonium hydroxide in a closed steel chamber was heated at 150°C for approximately 36 hours. The cooled reaction mixture was extracted with isopropyl ether, the aqueous layer saturated with potassium carbonate and continuously extracted with chloroform for six hours. The dried chloroform extract (sodium sulphate) was concentrated at reduced pressure and the residue distilled at 113-115°C/40 mm to give 40.5 g (45.5%) of product.

Preparation 3

4-Amino-1,2-dimethylpyrazolidine

A mixture of 300 g (2.22 mole) of 4-chloro-1,2-dimethylpyrazolidine and 600 ml of concentrated ammonium hydroxide was heated at 150°C for 18 hours in a steel bomb. The cooled mixture was saturated with potassium carbonate and continuously extracted for 18 hours with chloroform. The residual material after concentration of the chloroform extract was distilled at 90-100°C/40 mm to give 73 g of product.

Preparation 4

4-Anilino-1,2-dimethylpyrazolidine

A stirred suspension of 40 g (1.02 mole) of sodamide in dry toluene was treated dropwise with 116 g (1.0 mole) of 1,2-dimethyl-4-pyrazolidinol at 80°C. After 4.5 hours at reflux the mixture was cooled and maintained below 20°C while 161.0 g (1.0 mole) of benzenesulphonyl chloride was added dropwise. After stirring for 1 hour the reaction mixture was shaken with dilute sodium hydroxide, the separated toluene layer dried over sodium sulphate and concentrated at reduced pressure. The residue was dissolved in 300 ml of aniline, the mixture heated for 2.5 hours on a steam bath and refluxed for 3 hours. The cooled mixture was extracted with dilute sodium hydroxide solution and the separated aqueous layer extracted with isopropyl ether. The combined organic layers after drying over sodium sulphate were concentrated and the residue distilled to a pot temperature of 140°C/80 mm. The residue which would not crystallize was distilled at 110-125°C/0.1 mm to give 86 g of product.

Preparation 5**4-Anilino-1,2-diethylpyrazolidine**

To a stirred suspension of 7.9 g (0.2 mole) of sodamide in 100 ml of dry toluene was added 28.8 g (0.2 mole) of 1,2-diethyl-4-pyrazolidinol at a rate such that a pot temperature of 30-35°C was maintained. After stirring for 2 hours at room temperature, the solution was added dropwise to a solution of 38.0 g (0.2 mole) of *p*-toluenesulphonyl chloride in 200 ml of dry toluene with the pot temperature maintained below 30°C. After stirring for about one hour at room temperature, the reaction mixture was washed twice with water and dried over sodium sulphate. The dried filtered solution was concentrated to a volume of about 100 ml, aniline (100 ml) was added, the solution was refluxed for 3 hours and was then concentrated. The residue was partitioned between chloroform and dilute sodium hydroxide. The dried chloroform layer was concentrated and the residue distilled at 120°C/0.1 mm to give 4.0 g of product.

Preparation 6**1,2-Diethyl-4-phthalimido-pyrazolidine Maleate**

To 100 ml of dimethyl sulphoxide was added 32.4 g (0.2 mole) of 4-chloro-1,2-diethylpyrazolidine and 37 g (0.2 mole) of potassium phthalimide. The solution was stirred at 115°C for 48 hours, cooled and filtered. The filtrate was treated with an equal volume of water and extracted twice with 150 ml of ethyl acetate. The extracts were combined and concentrated. The residue was partitioned between dilute hydrochloric acid and ethyl acetate. The acid layer was made basic with potassium carbonate and extracted with chloroform. The chloroform was dried (sodium sulphate) and concentrated. The residue (22 g) was treated with 22 g of maleic acid and 75 ml of isopropyl alcohol and 75 ml of isopropyl ether. The maleate salt was recrystallized twice from the same solvent system to give 11.5 g (15%) of product which melted at 144-147°C.

25	Analysis:	Calculated for $C_{19}H_{23}N_3O_6$	:	C, 58.60;	H, 5.95;		25
					N, 10.79		
	Found		:	C, 58.64;	H, 6.03;	N, 10.73	

Preparation 7**30 4-Amino-1-benzyl-2-methylpyrazolidine**

4-Amino-1-benzyl-2-methylpyrazolidine, b.p. 115-125°C/1.0 mm, was prepared from 1-benzyl-2-methyl-4-pyrazolidinol according to Preparations 1 and 2.

Preparation 8**35 4-Amino-1-cyclohexyl-2-methylpyrazolidine Fumarate**

4-Amino-1-cyclohexyl-2-methylpyrazolidine, b.p. 90-100°C/0.5-1.0 mm, was prepared from 1-cyclohexyl-2-methylpyrazolidinol according to Preparations 1 and 2. The fumarate salt melted at 149-151°C.

40 Preparation 9**4-Amino-1-isopropyl-2-methylpyrazolidine**

4-Amino-1-isopropyl-2-methylpyrazolidine, b.p. 110-115°C/50 mm, was prepared from 1-isopropyl-2-methylpyrazolidinol according to Preparations 1 and 2.

45 Preparation 10

When in the procedure of Preparation 2, concentrated ammonium hydroxide is replaced by an equal molar amount of methylamine in methanol, there is obtained 4-methylamino-1,2-diethylpyrazolidine.

EXAMPLE 1**50 4-Chloro-N-phenyl-N-(1,2-dimethyl-4-pyrazolidinyl)-benzamide**

To a solution of 17 g (0.0525 mole) of 1,2-dimethyl-4-anilinopyrazolidine in 50 ml of chloroform was added with stirring 9.15 g (0.0525 mole) of *p*-chlorobenzoyl chloride with the temperature not exceeding 50°C. On completion of addition the solution was refluxed for one hour, cooled to room temperature and extracted with dilute sodium hydroxide. The chloroform layer was dried over sodium sulphate and concentrated at reduced pressure to give an oil which crystallized upon cooling. The solid was recrystallized twice from ligroin. Yield 13.1 g (76%); m.p. 104-108°C.

60	Analysis:	Calculated for $C_{18}H_{20}ClN_3O$	:	C, 65.54;	H, 6.11;	N, 12.74	60
					H, 6.08;	N, 12.86	
	Found		:	C, 65.77;	H, 6.08;	N, 12.86	

EXAMPLE 2**4-Fluoro-N-(1,2-diethyl-4-pyrazolidinyl) benzamide**

A solution of 10 g (0.026 mole) of 1,2-diethyl-4-phthalimidopyrazolidine maleate in 25 ml of 6N hydroch-

loric acid was refluxed two hours, and the resulting mixture was cooled and filtered. The filter cake was washed with water which was combined with the acidic solution. The acidic solution was made basic with dilute sodium hydroxide and cooled with ice. To the resulting solution was added 8.2 g (0.052 mole) of *p*-fluorobenzoyl chloride and the mixture shaken for 10 minutes. The resulting mixture was extracted with chloroform, the chloroform diluted with an equal volume of isopropyl ether and the resulting solution extracted with dilute hydrochloric acid. The acid layer was made basic with dilute sodium hydroxide and extracted with chloroform. The chloroform was dried (sodium sulphate) and concentrated. The residue was crystallized from isooctaneisopropyl ether and recrystallized from isooctaneisopropyl ether containing a few drops of ethyl acetate and clarified by charcoal treatment. The product (2.0 g; 29%) melted at 114-116°C.

Analysis:	Calculated for $C_{14}H_{20}N_3OF$	:	C,63.38;	H,7.60;
				N,15.84
	Found	:	C,63.36;	H,7.61;
				N,15.96

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EXAMPLE 3**3,4,5-Trimethoxy-N- (1,2-dimethyl-4- pyrazolidinyl)- benzamide**

To 10 g (0.09 mole) of 4-amino-1,2- dimethylpyrazolidine in chloroform was added with stirring 20.7 g (0.09 mole) of 3,4,5-trimethoxybenzoyl chloride. After 30 minutes of stirring the solution was extracted with dilute sodium hydroxide. The chloroform solution was dried (sodium sulphate), filtered, and the filtrate concentrated. The resulting crystalline material was recrystallized from equal portions of ethyl acetate and isopropyl ether. The product (12.1 g; 44%) melted at 163-166°C.

Analysis:	Calculated for $C_{15}H_{23}N_3O_4$	:	C,58.24;	H,7.49;
				N,13.58
	Found	:	C,58.20;	H,7.45;
				N,13.19

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EXAMPLE 4**30 4-Nitro-N- (1,2-diethyl-4-pyrazolidinyl) benzamide Hydrochloride**

To a solution of 40.5 g (0.28 mole) of 4-amino-1,2- diethylpyrazolidine in 200 ml of chloroform was added with stirring 52 g (0.28 mole) of *p*-nitrobenzoyl chloride in 200 ml chloroform. The solution was allowed to stand overnight and then extracted with dilute sodium hydroxide. The chloroform was dried (sodium sulphate) and concentrated. The residue was crystallized twice from isopropyl etherethyl acetate to give 73 g (80%) of the free base.

Analysis:	Calculated for $C_{14}H_{20}N_4O_3$	:	C,57.52;	H,6.90;
				N,19.17
	Found	:	C,57.56;	H,6.94;
				N,18.99

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The base was converted to the hydrochloride salt and crystallized from isopropyl alcohol which melted at 189-191°C (dec.).

Analysis:	Calculated for $C_{14}H_{21}N_4O_3Cl$	:	C,51.14;	H,6.44;
				N,17.04
	Found	:	C,50.96;	H,6.59;
				N,16.58

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EXAMPLE 5**4-Amino-N- (1,2-diethyl-4-pyrazolidinyl) benzamide**

A solution of 20 g (0.069 mole) of 4-nitro-N- (1,2-diethyl-4-pyrazolidinyl) benzamide in ethanol was treated with Raney nickel and shaken in three atmospheres of hydrogen in a Parr apparatus at room temperature for two hours. The mixture was filtered, the filtrate concentrated and the residue crystallized from isopropyl ether-ethyl acetate. The product (12.0 g; 66.5%) melted at 119-121°C.

Analysis:	Calculated for $C_{14}H_{22}N_4O$	:	C,64.09;	H,8.45;
				N,21.36
	Found	:	C,63.98;	H,8.55;
				N,21.37

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EXAMPLE 6**4-Amino-5-chloro-2- methoxy-N- (1,2-diethyl-4- pyrazolidinyl) benzamide.**

To 75 ml of thionyl chloride was added 12 g (0.05 mole) of 4-acetamido-5- chloro 2-methoxy-benzoic acid and the stirred suspension refluxed for one hour. The resulting solution was concentrated and 100 ml of chloroform added to the residue which was concentrated to remove traces of thionyl chloride. The residue was dissolved in 100 ml of chloroform and the solution added at a rapid drop rate to 7 g (0.05 mole) of

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4-amino-1,2-diethylpyrazolidine in 100 ml of chloroform while stirring and cooling to 20-25°C with an ice bath. After 30 minutes the chloroform solution was extracted twice with 100 ml of 3N hydrochloric acid and the chloroform solution retained. The acid extract was boiled for 10 minutes, cooled with ice, made basic with concentrated sodium hydroxide while cooling and extracted with chloroform. The chloroform was dried (sodium sulphate), concentrated and the residue crystallized from isopropyl etherisooctane to give 3 g of material which melted at 116-118°C. The retained chloroform solution was extracted with dilute sodium hydroxide and concentrated. The residue was dissolved in 3N hydrochloric acid and extracted with isopropyl ether. The acid solution was refluxed for 10 minutes, cooled with an ice bath, made basic with sodium hydroxide while cooling and extracted with chloroform. The chloroform was dried (sodium sulphate) and concentrated. The residue was crystallized three times from isopropyl ether to give 0.7 g of material which melted at 117-119°C. A mixture of both materials gave no depression of the melting point. The combined yield was 3.7 g. (23%).

Analysis: Calculated for $C_{15}H_{23}N_4O_2$: C,55.13; H,7.09;
Found : C,55.23; H,7.10;
N,17.17

EXAMPLE 7

When in the procedure of Example 3 there are substituted for 3,4,5-trimethoxybenzoyl chloride equal molar amounts of:

- 4-cyanobenzoyl chloride,
- 3-trifluoromethylbenzoyl chloride,
- 4-methylbenzoyl chloride,
- 4-methoxybenzoyl chloride,
- 4-acetamidobenzoyl chloride, and
- 2-methoxy-5-sulphamoylbenzoyl chloride,

there are obtained, respectively:

- 4-cyano-N-(1,2-dimethyl-4-pyrazolidinyl) benzamide,
- 3-trifluoromethyl-N-(1,2-dimethyl-4-pyrazolidinyl)- benzamide,
- 4-methyl-N-(1,2-dimethyl-4-pyrazolidinyl) benzamide, 4-methoxy-N-(1,2-dimethyl-4-pyrazolidinyl)- benzamide,
- 4-acetamido-N-(1,2-dimethyl-4-pyrazolidinyl)- benzamide, and
- 2-methoxy-5-sulphamoyl-N-(1,2-dimethyl-4-pyrazolidinyl) benzamide.

EXAMPLE 8

4-Amino-5-chloro-2-methoxy-N-1,2-dimethyl-4-pyrazolidinylbenzamide

A stirred solution of equal molar amounts of 4-amino-5-chloro-2-methoxybenzoic acid and triethylamine in methylene chloride (0.5°C) was treated dropwise with a slight excess of ethylchlorocarbonate. After 1.0 hour a solution of 4-amino-1,2-dimethylpyrazolidine in methylene chloride was added and the mixture was stirred for about two hours at room temperature. An aqueous solution of sodium bicarbonate was added to the reaction mixture, and the organic phase separated and concentrated to give the product which melted at 169-171°C.

EXAMPLE 9

4-Amino-5-chloro-2-methoxy-N-(1-benzyl-2-methyl-4-pyrazolidinyl) benzamide Fumarate

4-Amino-5-chloro-2-methoxy-N-(1-benzyl-2-methyl-4-pyrazolidinyl) benzamide was prepared from 4-amino-5-chloro-2-methoxybenzoic acid and 4-amino-1-benzyl-2-methylpyrazolidine according to the procedure of Example 8. The fumarate salt was prepared; it melted at 129-131°C.

EXAMPLE 10

4-Amino-5-chloro-2-methoxy-N-(1-cyclohexyl-2-methyl-4-pyrazolidinyl) benzamide was prepared from 4-amino-5-chloro-2-methoxybenzoic acid and 4-amino-1-cyclohexyl-2-methylpyrazolidine according to the procedure of Example 8. The melting point of the hydrochloride hydrate was 105-120°C.

EXAMPLE 11

4-Amino-5-chloro-2-methoxy-N-(1-isopropyl-2-methyl-4-pyrazolidinyl) benzamide Dihydrochloride

4-Amino-5-chloro-2-methoxy-N-(1-isopropyl-2-methyl-4-pyrazolidinyl) benzamide was prepared from 4-amino-5-chloro-2-methoxybenzoic acid and 4-amino-1-isopropyl-2-methylpyrazolidine according to the procedure of Example 8. The dihydrochloride salt was prepared; it melted at 182-186°C.

The pharmaceutical compositions of this invention comprise compounds of Formula I or pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier. Unit dosage forms of the compositions contain from 1.0 mg to 100 mg active medicament per unit dose. Preferably, the compositions contain from 5 mg to 100 mg of medicament, advantageously from 5 mg to 50 mg, per unit dose.

The pharmaceutical carrier may be either solid or liquid. Exemplary of solid carriers are lactose, mag-

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nesium stearate, terra alba, sucrose, talc, stearic acid, gelatin, agar, pectin and acacia. Exemplary of liquid carriers are vegetable oils and water. The carrier may include a sustained release material such as glyceryl monostearate or glyceryl distearate alone or with a wax.

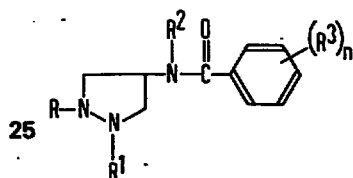
A wide variety of pharmaceutical forms of the composition can be employed. Thus, if a solid carrier is used the composition can be tableted or prepared as a powder, a troche or a lozenge. Gelatin capsules containing the medicament can also be prepared. If a liquid carrier is used, the composition can be in the form of a soft gelatin capsule, a liquid suspension or a syrup. Parenteral dosage forms are obtained by dissolving a water-soluble salt of a compound of Formula I in water or saline solution in a concentration such that 1 ml. of the solution contains from 1.0 mg to 25 mg of the said salt. The solution can be filled into single or multiple dose ampoules.

The invention also includes such a compound (base or salt) or a pharmaceutical composition containing the same for administration to warm blooded animals, including human beings, in an amount sufficient to control emesis and/or facilitate gastric emptying. The administration may be oral or parenteral and may be in repeated doses until satisfactory response is obtained. The daily dosage will generally be from about 10 mg to about 300 mg of active medicament, advantageously from 5 mg to 50 mg.

CLAIMS

1. Compounds having the formula:

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wherein;

- R represents lower alkyl, lower cycloalkyl or phenyl lower alkyl;
- R¹ represents lower alkyl, lower cycloalkyl or phenyl lower alkyl;
- R² represents hydrogen, lower alkyl or phenyl;
- R³ represents hydroxy, cyano, nitro, amino, fluoro, chloro, bromo, trifluoromethyl, lower alkyl, lower alkoxy, sulphonyl or acetamido (where there is more than one R³ radical these can be the same or different); and
- n is zero, 1, 2 or 3.
2. 4-Chloro-N-phenyl-N-(1,2-dimethyl-4-pyrazolidinyl) benzamide.
3. 4-Fluoro-N-(1,2-diethyl-4-pyrazolidinyl) benzamide.
4. 4-Amino-5-chloro-2-methoxy-N-(1,2-diethyl-4-pyrazolidinyl) benzamide.
5. Compounds as claimed in Claim 1 which have been prepared substantially as described in any of Examples 1 to 8.
6. Pharmaceutically acceptable acid addition salts of compounds as claimed in any of the preceding Claims.
7. Salts as claimed in Claim 6 which have been prepared substantially as described in any of Examples 4 and 9 to 11.
8. A compound as claimed in any of Claims 1 to 5 or a salt as claimed in Claim 6 or Claim 7 for use in controlling emesis or facilitating gastric emptying of warm blooded animals.
9. A pharmaceutical composition useful for its antiemetic and gastric emptying facilitation properties, comprising a compound as claimed in any of Claims 1 to 5 or a salt as claimed in Claim 6 or Claim 7, and a pharmaceutically acceptable carrier.
10. A pharmaceutical composition as claimed in Claim 9 in unit dosage form containing from 1 to 100 milligrams of the compound or salt.



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nesium stearate, terra alba, sucrose, talc, stearic acid, gelatin, agar, pectin and acacia. Exemplary of liquid carriers are vegetable oils and water. The carrier may include a sustained release material such as glyceryl monostearate or glyceryl distearate alone or with a wax.

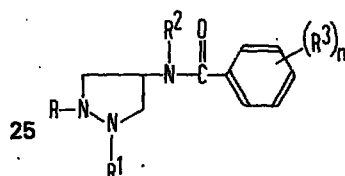
A wide variety of pharmaceutical forms of the composition can be employed. Thus, if a solid carrier is used the composition can be tableted or prepared as a powder, a troche or a lozenge. Gelatin capsules containing the medicament can also be prepared. If a liquid carrier is used, the composition can be in the form of a soft gelatin capsule, a liquid suspension or a syrup. Parenteral dosage forms are obtained by dissolving a water-soluble salt of a compound of Formula I in water or saline solution in a concentration such that 1 ml. of the solution contains from 1.0 mg to 25 mg of the said salt. The solution can be filled into single or multiple dose ampoules.

The invention also includes such a compound (base or salt) or a pharmaceutical composition containing the same for administration to warm blooded animals, including human beings; in an amount sufficient to control emesis and/or facilitate gastric emptying. The administration may be oral or parenteral and may be in repeated doses until satisfactory response is obtained. The daily dosage will generally be from about 10 mg to about 300 mg of active medicament, advantageously from 5 mg to 50 mg.

CLAIMS

1. Compounds having the formula:

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wherein;

R represents lower alkyl, lower cycloalkyl or phenyl lower alkyl;

- 30 R^1 represents lower alkyl, lower cycloalkyl or phenyl lower alkyl;

R^2 represents hydrogen, lower alkyl or phenyl;

R^3 represents hydroxy, cyano, nitro, amino, fluoro, chloro, bromo, trifluoromethyl, lower alkyl, lower alkoxy, sulphamoyl or acetamido (where there is more than one R^3 radical these can be the same or different); and

- 35 n is zero, 1, 2 or 3.

2. 4-Chloro-N-phenyl-N- (1,2-dimethyl-4- pyrazolidinyl) benzamide.

3. 4-Fluoro-N-(1,2-diethyl-4- pyrazolidinyl) benzamide.

4. 4-Amino-5- chloro-2- methoxy-N- (1,2-diethyl-4- pyrazolidinyl) benzamide.

5. Compounds as claimed in Claim 1 which have been prepared substantially as described in any of

- 40 Examples 1 to 8.

6. Pharmaceutically acceptable acid addition salts of compounds as claimed in any of the preceding Claims.

7. Salts as claimed in Claim 6 which have been prepared substantially as described in any of Examples 4 and 9 to 11.

- 45 8. A compound as claimed in any of Claims 1 to 5 or a salt as claimed in Claim 6 or Claim 7 for use in controlling emesis or facilitating gastric emptying of warm blooded animals.

9. A pharmaceutical composition useful for its antiemetic and gastric emptying facilitation properties, comprising a compound as claimed in any of Claims 1 to 5 or a salt as claimed in Claim 6 or Claim 7, and a pharmaceutically acceptable carrier.

- 50 10. A pharmaceutical composition as claimed in Claim 9 in unit dosage form containing from 1 to 100 milligrams of the compound or salt.