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ΚΥΠΡΙΑΚΟ ΓΡΑΦΕΙΟ ΔΙΠΛΩΜΑΤΩΝ ΕΥΡΕΣΙΤΕΧΝΙΑΣ
THE PATENT OFFICE OF CYPRUS

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ΑΡΙΘΜΟΣ ΔΗΜΟΣΙΕΥΣΗΣ
ΓΡΑΦΕΙΟΥ ΔΙΠΛΩΜΑΤΩΝ ΕΥΡΕΣΙΤΕΧΝΙΑΣ
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(54) **Sulphonamides**

(57) The invention provides N-(1-methyl-2-pyrrolidylmethyl)- 2,3-dimethoxy-5-methylsulphamoylbenzamide, its N-oxide and acid addition and quaternary ammonium salts thereof, which are useful in treating disorders of the urinary tract, and pharmaceutical compositions containing such compounds. The compounds may be made by amidating 2,3-dimethoxy-5-methylsulphamoylbenzoic acid or one of its reactive derivatives with 1-methyl-2-aminomethylpyrrolidine or one of its reactive derivatives.

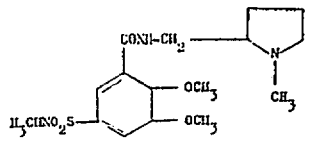
GB 2 033 900 A

SPECIFICATION

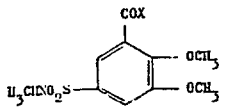
Novel veratramides, their preparation and pharmaceutical compositions containing them

The present invention relates to veratramides. The present invention provides the novel compound N-(1-methyl-2-pyrrolidinyl-methyl)-2,3-dimethyoxy-5-methylsulphamoyl benzamide, together with its pharmacologically acceptable acid-addition salts, it quaternary ammonium salts and its oxides, in both levorotatory and dextrorotatory form.

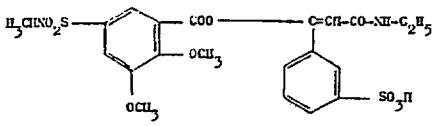
In accordance with the invention, the compound of the invention, which has the formula:



is prepared by reacting a compound of formula:



in which X stands for a halogen atom, a hydroxyl group or a group capable of forming a reactive acid derivative, with 1-methyl-2-aminomethyl-pyrrolidine or a reactive derivative of that compound. In the starting compound, examples of the groups capable of forming a reactive acid derivative are groups forming a lower alkyl ester such as a methyl, ethyl, propyl, butyl, isobutyl, pentyl or isopentyl, ester, a reactive acid ester such as a methoxymethyl ester, a cyanomethyl ester, a substituted or unsubstituted aromatic ester or an N-hydroxyimide ester, acid azides, acid hydrazides, symmetrical anhydrides, mixed anhydrides such as, for example, those formed from carboxylic acid esters and haloformic esters, azolides such as triazolides, tetrazolides and in particular imidazolides, substituted ω-trihaloacetophenone, substituted α-oxobenzeneacetonitriles, nuclear-substituted benzamides or other equivalents or the compound of general formula:



(which is formed from 2,3-dimethyoxy-5-methylsulphamoyl benzoic acid and an isoxazolium salt). However, the invention is not limited to the reactive derivatives referred to hereinbefore.

According to the process of the invention, the amine can react in the form of a reactive derivative. For example, reference can be made to reaction products of the amine with phosphorus chlorides, phosphorus oxychloride, dialkyl or diaryl orthophenylene chlorophosphites, alkyl or aryl dichlorophosphites or 1-methyl-2-aminomethylpyrrolidine isothiocyanate or symmetrical or non-symmetrical N-(1-methyl-2-pyrrolidinylmethyl)-sulphamides or N, N'-bis-(1-methyl-2-pyrrolidinylmethyl)-urea or N-(1-methyl-2-pyrrolidinylmethyl)-enamine or any other equivalent.

The reactive derivatives referred to hereinbefore can react with the acid *in situ* or after preliminary isolation. However, the invention is not limited to the reaction derivatives described hereinbefore.

It is also possible to carry out the reaction of the free acid and the free amine in the presence of a condensing agent such as, for example, silicon tetrachloride, phosphoric anhydride or a carbodiimide such as dicyclohexylcarbodiimide or alkoxyacetylenes such as methoxyacetylene or ethoxyacetylene.

The amidification reaction can be carried out in the presence or absence of a solvent, optionally on ion-exchange resins.

Suitable solvents, which are inert with respect to the amidification reaction, include alcohols, polyols, benzene, toluene, dioxan, chloroform, diethyleneglycol and dimethyl ether. The solvent can also be in the form of an excess of the amine used as the starting substance. It may be preferable to heat the reaction mixture during amidification, e.g. up to the boiling point of the solvents referred to hereinbefore. The compound obtained according to the process of the invention can, if necessary, react with pharmaceutically acceptable organic or mineral acids such as hydrochloric, hydrobromic, sulphuric, phosphoric, oxalic, acetic, tartaric, citric and methanesulphonic acids in order to give acid-addition salts.

If necessary, it may also react with alkyl halides or sulphates to give quaternary ammonium salts. It may also be oxidized by a *per se* known process, e.g. by means of hydrogen peroxide and manganese dioxide, to give the N-oxide.

The following Examples illustrate but do not limit the present invention.

EXAMPLE 1

N-(1-methyl-2-pyrrolidinyl-methyl)-2,3-dimethoxy-5-methylsulphamoyl-benzamide.

Stage I: *2,3-dimethyoxy-5-chlorosulphonyl-benzoic acid*

1620 cc of chlorosulphonic acid was placed in a round-bottomed flask equipped with a stirrer, a condenser and a thermometer, after which 164 g of 2,3-dimethoxybenzoic acid was added in portions, while the temperature was maintained at between 10 and 15°C. After the temperature has been allowed to rise again, the mixture was stirred for 4 minutes at between 22 and 28°C and was then maintained at ambient temperature. The solution was then poured dropwise into a round-bottomed flask containing 600g of crushed ice externally cooled so as to keep the temperature between 0 and 5°C. The precipitate formed was suction filtered, washed with water and dried with air. 207 g of 2,3-dimethoxy-5-chlorosulphonyl-benzoic acid was obtained (melting point 155 to 156°C, yield 92%).

Stage II: *2,3-dimethoxy-5-methylsulphamoyl-benzoic acid*

200 g of a 33% aqueous methylamine solution was placed in a round-bottom flask equipped with a stirrer and a thermometer, after which 98.5g of 2,3-dimethoxy-5-chlorosulphonyl-benzoic acid was added in portions, while the temperature was maintained at between 0 and 5°C. After the temperature had been allowed to rise again, the mixture was poured onto 1.7 litres of crushed ice. The solution was then filtered and treated with 130 cc of concentrated hydrochloric acid. The crystals formed were suction filtered, washed with water and dried at 50°C. 83g of 2,3-dimethoxy-5-methylsulphamoyl benzoic acid was obtained (melting point 164 to 165°C, yield 84%.

Stage III: *methyl-2,3-dimethoxy-5-methylsulphamoyl-benzoate*

310 cc of ethyl alcohol was placed in a round-bottomed flask equipped with a condenser, Then, accompanied by cooling, 15.5g of 93% sulphuric acid was poured in portionwise and finally 76g of 2,3-dimethoxy-5-methylsulphamoyl-benzoic acid was added. After refluxing for 6 hours, the solution was cooled and poured into 3 litres of water containing 20g of sodium carbonate. The crystals formed were suction filtered, washed with water and dried in air. 76g of methyl-2,3-dimethoxy-5-methylsulphamoyl benzoate was obtained (melting point 76°C, yield 95%).

Stage IV: *N-(1-methyl-2-pyrrolidinylmethyl)-2,3-dimethoxy-5-methylsulphamoyo-benzamide*

95g of methyl-2,3-dimethoxy-5-methylsulphamoyl benzoate and 443 cc of ethylene glycol were introduced into a round-bottomed flask equipped with a stirrer and a thermometer, accompanied by heating to 90°C. The mixture was then cooled to 50°C, whereupon 45g of 1-methyl-2-aminomethyl-pyrrolidine was added. The solution was stirred at 50°C and kept at this temperature for a few hours. The solution was then taken up in 1.8 litres of water and acidified with 50 cc of concentrated hydrochloric acid. The acid solution was filtered and then treated with 75 cc of 20% ammonia. The crystals formed were suction filtered, washed with water and dried at 50°C. After purification by conversion to hydrochloride and recrystallisation of the base in isopropyl alcohol, 66 g of N-(1-methyl-2-pyrrolidinyl-methyl)-2,3-dimethyoxy-5-methylsulphamoyl-benzamide was obtained (melting point 120 to 121°C, yield 54%).

EXAMPLE 2

Levorotatory N-(1-methyl-2-pyrrolidinylmethyl)-2,3-dimethoxy-5-methylsulphamoyl-benzamide

170g of methyl-2,3-dimethoxy-5-methyl-sulphamoyl benzoate and 850 cc of ethylene glycol were placed in a 2-litre round-bottomed flask. The mixture was heated to 60°C until completely dissolved and then cooled to 50°C. 80g of levorotatory 1-methyl-2-aminomethyl pyrrolidine was added and the solution was kept at 50°C until a sample was completely soluble in dilute acids. The reaction mixture was then taken up in 3.5 litre of water. The crystals formed were suction filtered, washed with water and dried at 40°C. The 150g of base obtained was dissolved in 500 cc of absolute alcohol and then 155 cc of a ethanolic hydrochloric acid was added. The solution was heated and then filtered after adding vegetable black. After cooling, the hydrochloride precipitate was suction filtered, washed with absolute alcohol and dried at 50°C.

141g of hydrochloride was obtained (melting point 156 to 158°C). The 141g of hydrochloride was then dissolved in 423 cc of water. The solution obtained was filtered in the presence of vegetable black and then the base was precipitated by adding 35 cc of 20% ammonia. The precipitate formed was suction filtered, washed with water and then dried at 50°C. 108.5g of levorotatory N-(1-methyl-2-pyrrolidinylmethyl)-2,3-dimethoxy-5-methylsulphamoyl benzamide was obtained (melting point 111 to 112°C, yield 49.5%, $[\alpha]_D^{20}$ = 38° in a 5% dimethylformamide solution).

EXAMPLE 3

Dextrorotatory N-(1-methyl-2-pyrrolidinylmethyl)-2,3-dimethoxy-5-methylsulphamoyl-benzamide

170 g of methyl 2,3-dimethoxy-5-methylsulphamoyl benzoate and 850 cc of ethylene glycol were placed in a 2-litre round-bottomed flask. The mixture was heated to 50°C until dissolved and then 82g of dextrorotatory 1-methyl-2-aminomethylpyrrolidine was added. The solution was kept at 50°C until a sample was completely soluble in dilute acids.

After cooling, the reaction mixture was taken up in 3.4 litres of water and 80 cc of concentrated hydrochloric acid. The solution was filtered after adding vegetable black and then treated with 70 cc of 20% ammonia. The precipitate formed after adding 300g of potassium carbonate was suction filtered, washed with water and dried. The 180g of base obtained was purified in accordance with the process of Example 2. 133g of dextrorotatory N-(1-methyl-2-pyrrolidinylmethyl)-2,3-dimethoxy-5-methylsulphamoyl benzamide

was obtained (melting point 109 to 110°C, yield 61%, $[\alpha]_D^{20} = 38°,15'$ in a 5% dimethyl formamide solution.

EXAMPLE 4

N-(1-methyl-2-pyrrolidinylmethyl)-2,3-dimethoxy-5-methyl-sulphamoyl-benzamide N-oxide

261 g of N-(1-methyl-2-pyrrolidinylmethyl)-2,3-dimethoxy-5-methylsulphamoyl-benzamide and 875 cc of absolute ethanol were placed in a 2-litre round-bottom flask, followed by 142 cc of 110-volume hydrogen peroxide. The solution was heated at 45°C for a few hours and then cooled to 40°C. 2g of manganese dioxide was then added portionwise and the mixture was stirred for half an hour. After adding 20g of vegetable black and filtration, the filtrate was evaporated. The product obtained was recrystallized in water. 97g of N-(1-methyl-2-pyrrolidinylmethyl)-2,3-dimethoxy-5-methylsulphamoyl-benzamide N-oxide was obtained (melting point 142 to 142°C, yield 35.5%).

The products according to the invention may be used in the form of gelatin capsules, tablets, pastes, pills, granules and injectable solution, which are prepared in known manner. It is possible to use substances that are inert relative to the compounds of the invention such as lactose, magnesium stearate, starch, talc, cellulose, levilite, alkali metal lauryl sulphates, saccharose and vehicles conventionally used in medicinal preparations.

In order to prepare tablets, the chosen compound is mixed with starch and lactose by the process of successive dilutions. The mixture is granulated with methyl cellulose. Levilite, magnesium stearate and talc are added to the granular material before tableting is carried out.

It is possible to replace the methyl cellulose with any other appropriate granulating agent, as for example ethyl cellulose, polyvinyl pyrrolidone, starch paste or gum arabic. The starch can also be replaced by a different disintegrating agent such as maize stach, carboxymethyl amylases, alginates or microcrystalline cellulose.

To prepare injectable solutions, it is possible to dissolve the compound according to the invention in hydrochloric, levulinic, gluconic or glucoheptonic acid. The resulting solution, which is prepared in sterile manner, is made isotonic by an alkali metal chloride such as sodium chloride, after which preservatives are added.

It is possible to prepare the same solution without adding preservatives, the ampoule being filled under nitrogen and sterilised for 30 minutes at 100°C.

The compounds according to the invention can be administered at doses of 100 to 300mg daily, the prepared daily dose being 150mg. The following examples illustrate pharmaceutical preparations obtained in conventional manner from the compounds of the invention.

EXAMPLE 5

Gelatin capsules

N-(1-methyl-2-pyrrolidinylmethyl)-2,3-dimethoxy-5-methylsulphamoyl-benzamide	.....	50 mg
dry potato starch	.....	30 mg
lactose	.....	113 mg
methyl cellulose 1500	.....	1.6 mg
talc	.....	2.7 mg
magnesium stearate	.....	2.7 mg
	for 1 capsule of	200 mg

EXAMPLE 6

Injectable solution

N-(1-methyl-2-pyrrolidinylmethyl)-2,3-dimethoxy-5-methylsulphamoyl-benzamide	.....	100 mg
N hydrochloric acid	.....	0.27 mg
sodium chloride	.....	8 mg
water for injectable preparation	.....	2 ml

for 2 ml of solution

The compounds according to the invention have interesting pharmacological properties and are particularly active in the treatment of disorders of the lower urinary apparatus. Their low toxicity is compatible with use in human therapy without risk of side effects.

The acute toxicity of the compounds of the invention was determined on Swiss mice parenterally, (intravenously, intraperitoneally and subcutaneously) and orally.

Measurement of the lethal doses of N-(1-methyl-2-pyrrolidinylmethyl)-2,3-dimethoxy-5-methylsulphamoyl benzamide (compound 1) and its laevorotatory isomer (compound 2) gave the following results;

TOXICITIES

Compound	LD_{50} in mg/kg			
	I.V.	S.C.	I.P.	P.O.
1	130-135	936-960	315-323	992-1050
2	90-94.6	741-780	310-336	1080-1152

A pharmacological study of the compound of the invention which consisted of studying its action on the results of cystomanometry in the rabbit and rat was performed under the following conditions:

The animals were anaesthesized with pentobarbitol and were given artificial respiration. The left outer jugular vein was catheterized to permit the I.V. injection of the studied product. The bladder was then exteriorized and the two ureters were connected and provided with two catheters, one of which was used to measure the intravesical pressure and the other for the vesical filling.

The vesical was filled by perfusion of 0.9% (weight/volume) salt water at a constant flow rate of 40 ml/min. for the rabbit and 5 ml/min. for the rat.

The intravesical pressure before perfusion and the perfused water volume were measured.

The following parameters were studied:

the intravesical pressure before perfusion (p_1)

the intravesical pressure at the time of starting urination (p_2)

$\Delta P = P_2 - P_1$

the volume of salt water perfused

the quantity discharged during urination

the residual quantity only in the bladder.

The cystomanometry study was performed as follows: A first perfusion was carried out after stabilising the preparation for 5 minutes. A second perfusion was carried out 15 minutes after the first. A third perfusion was carried out 5 minutes after the second.

The study was performed by chronic and acute administration to the rabbit and acute administration to the rat.

The study of the rabbit was performed in the following manner: 10 male rabbits having an average weight of 2500 ± 100 g were used as the control batch. For the chronic administration study, 10 male rabbits with an average weight of 2500 ± 100 g treated every morning for 8 days with N-(1-methyl-2-pyrrolidinyl-methyl)-2,3-dimethoxy-5-methylsulphamoyl-benzamide intramuscularly injected at a dosage of 10 mg/kg/day. The final injection was carried out 30 minutes before the experiment.

For the acute administration study, 2 batches of 10 male rabbits with an average weight of 2500 ± 100 g were treated with N-(1-methyl-2-pyrrolidinylmethyl)-2,3-dimethoxy-5-methyl-sulphamoyl benzamide intravenously administered at doses of 5 and 50 mg/kg.

The acute administration study in the rat was carried out in the following manner: 10 male rats weighing on average 4 490 ± 20 g were used as the control batch. 20 male rats of average weight 480 ± 20 g were treated with N-(1-methyl-2-pyrrolidinylmethyl)-2,3-dimethoxy-5-methylsulphamoyl benzamide administered intravenously at doses of 50 and 100 mg/kg.

For the controls and for all the treated batches the first perfusion is used as a standard for the following perfusions (each animal serving as its own control).

In the case of the acute administration of N-(1-methyl-2-pyrrolidinylmethyl)-2,3-dimethoxy-5-methylsulphamoyl-benzamide to both the rabbit and the rat, the product was injected at the end of the first perfusion.

There was a delay of 15 minutes before the two other perfusions (this was also respected for the controls in order to adhere to the same experimental conditions).

The following results were observed in the rabbit.

The intramuscular administration for 8 days of N-(1-methyl-2-pyrrolidinylmethyl)-2,3-dimethoxy-5-methylsulphamoyl-benzamide at a rate of 10 mg/kg/day modifies the parameters, compared with the control batch, by reduction by about a third of the ΔP as from the first perfusion, the difference compared with the controls being reduced at the third perfusion, and by considerable decrease of about half compared with the

controls of the perfusion volume. Variations in the same direction of the same parameters and in the same proportions are noted during the second and third perfusions after the acute I.V. administration of N-(1-methyl-2-pyrrolidinylmethyl)-2,3-dimethoxy-5-methylsulphamoyl-benzamide at doses of 5 and 50 mg/kg. The differences compared with the controls are highly significant and on the basis thereof it is concluded that N-(1-methyl-2-pyrrolidinylmethyl)-2,3-dimethoxy-5-methylsulphamoyl-benzamide lowers the urinary threshold in the anaesthetized rabbit.

In the rat, the same phenomena as in the rabbit are not observed. However, there is a significant increase in the urinary volume during the second and third perfusion, particularly at an I.V. dosage of 50 mg/kg. These results in the animal show a modified vesical behaviour which varies with species and have led to an investigation of the action on urination in man.

The gaseous cystomanometric study in man revealed an increase in the vesical tolerance in two cases of serious neurological bladder.

A 34-year-old man suffering from multiple schlerosis suffered from incontinence, pollakisuria and a very frequent need to urinate. The intramuscular injection of two 100 mg ampules of the compound of the invention delayed the need to urinate for a volume of 150 cc, compared with 80 cc before treatment.

A 58-year-old woman having psychogenic urinary disorders with incontinence and pollakisuria received two 100-mg ampules of the compound according to the invention by the intramuscular route. She only needed to urinate for a volume of 400 cc, compared with 200 cc before treatment. She was able to voluntarily prevent urination for 2 minutes compared with 15 seconds before treatment.

Open studies on more than 200 patients were then carried out. They led to the retention of two indications, viz. (i) functional disorders of the lower urinary apparatus of man and particularly in the case of prostatism and (ii) cystalgias with clear urine in women. To check these impressions, two studies were carried out according to the double-blind procedure:

(a) *In females*

Due to the absence of a reference product the activity of the present product was compared with a placebo. The superiority of N-(1-methyl-2-pyrrolidinylmethyl)-2,3-dimethoxy-5-methyl-sulphamoyl-benzamides is very significant:
$p < 0.001$.

(b) *In males*

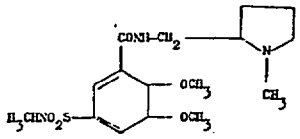
The study was carried out in comparison with the only possible reference product: lipidosterolic complex extracted from pygeum africanum. Here again, the superiority of the product is statistically significant: $p < 0.05$.

For both the above indications, the ease of oral treatment was appreciated and the tolerance was excellent.

The product was also found to be remarkably active by the intramuscular or intravenous routes in the treatment of pelvic spasms on probe after urological or gynaecological surgery.

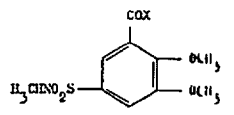
CLAIMS

1. N-(1-methyl-2-pyrrolidinylmethyl)-2,3-dimethoxy-5-methylsulphamoyl-benzamide, which has the formula:



its oxide and pharmacologically acceptable acid-addition salts and quaternary ammonium salts thereof, all such compounds being in laevorotatory or dextrorotatory isomeric form.

2. A process for the preparation of the compound having the formula set forth in Claim 1, comprising treating a compound of formula:



in which X represents a halogen atom, a hydroxyl group or a group capable of forming a reactive acid derivative, with 1-methyl-2-aminomethylpyrrolidone or a reactive derivative of that compound

3. A process for preparing a compound as claimed in Claim 1, substantially as hereinbefore described in any one of Examples 1 to 4.

4. A compound as claimed in Claim 1 when prepared by a process as claimed in Claim 2 or 3.

5. Pharmaceutical composition containing a compound according to Claim 1 as the active ingredient in association with a pharmaceutically acceptable excipient.

6. A composition as claimed in Claim 5 substantially as hereinbefore described in Example 5 or 6.
7. A composition as claimed in Claim 5 in any of the forms hereinbefore individually specified.
8. The use of a compound as claimed in Claim 1 in the production of a medicament particularly suitable for treating disorders of the lower urinary apparatus.

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