

PATENT SPECIFICATION

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(54) NEW PYRAZINE DERIVATIVES

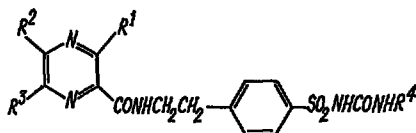
(71) We, CARLO ERBA S.p.A., an Italian Body Corporate of Via Carlo Imbonati 24, Milan, Italy, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new pyrazine derivatives having therapeutic utility, to processes for their production, and to pharmaceutical compositions containing them.

Sulphonylurea and biguanide derivatives have been used in recent years in diabetes therapy. These drugs can be given by mouth either separately or in combination. The daily doses required for humans is approximately 200 mg to 3 g. These doses are rather high, so that these drugs cannot be said to act at doses at the same level as do the hormones produced in the human body.

We have now found that if a pyrazine ring is introduced into benzenesulphonyl-ureas, substances having hypoglycemic properties at dosages of only a few milligrams are obtained.

The invention provides benzenesulphonyl-ureas containing a pyrazine ring and having the general formula (I)

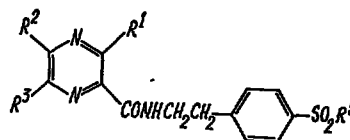


wherein each of the groups R^1 , R^2 and R^3 , which may be the same or different, is a hydrogen or halogen atom or an unsubstituted or substituted alkyl, alkoxy, hydroxy, amino, acetylamino or phenyl group, R^4 is an alkyl (e.g. ethyl, propyl, isopropyl, butyl or isobutyl) group, or the corresponding alkenyl (e.g. allyl) group, or is, preferably, a cycloaliphatic hydrocarbon group, which can if desired be substituted with an alkyl or alkoxy group e.g. cyclopentyl, cyclohexyl and methyl-

cyclohexyl. Preferably, at least one of R^1 , R^2 and R^3 is a chlorine atom or a methyl or methoxy group, and the remainder are hydrogen atoms.

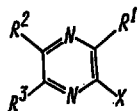
Specific examples of compounds having the above general formula and which exhibit hypoglycemic activity are N - {4 - [β - (pyrazine - 2 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexyl - urea; N - {4 - [β - (6 - methoxypyrazine - 2 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexyl - urea; N - {4 - [β - (6 - chloropyrazine - 2 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexyl - urea; N - {4 - [β - (5 - methylpyrazine - 2 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexyl - urea; N - {4 - [β - (2,3 - dimethylpyrazine - 5 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexyl - urea; and N - {4 - [β - (3 - chloropyrazine - 2 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexyl - urea.

The invention also provides a process for preparing the above compounds by reacting a compound of the general formula (II):

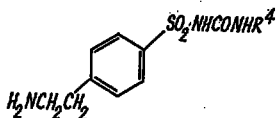


wherein R^1 to R^3 are as defined above and R^5 is an isocyanate, amino or acylamino group, or a urethane or urea residue, with an amine or isocyanate containing the above mentioned R^4 group. The introduction of the pyrazine group into the starting material takes place by acylation.

The above compounds can also be prepared by reacting a compound of general formula (III):—



wherein R^1 to R^3 are as defined above, and X is a carboxy group or a functional derivative thereof, for example an acid halide or a mixed anhydride, with a compound of general formula (IV)



wherein R^4 is as defined above.

The hypoglycemic activity of the compounds of general formula (I) may be illustrated by the following test carried out on male New Zealand white rabbits which had been starved for 16 hours with various compound of general formula (I). In the Table, the second and third columns show the percentage blood sugar reduction as compared with the figure obtained before the treatment.

The invention also provides pharmaceutical compositions comprising at least one pyrazine derivative of general formula (I) in association with pharmaceutically acceptable carriers or diluents and/or other conventional adjuvants. The compositions are preferably in a form suitable for oral administration, for example tablets, capsules, powder packets, liquid solutions, suspensions or elixirs.

TABLE

Compound	Dose (mg/kg)	Hours after treatment	
		3.00	6.00
N-{4-[β -(pyrazine-2-carboxamido)ethyl]benzenesulphonyl}-N'-cyclohexylurea	3.0 0.3	—	26% 6%
N-{4-[β -(6-methoxypyrazine-2-carboxamidoethyl)benzenesulphonyl]-N'-cyclohexylurea	7.5 1.5	—	33% 20%
N-{4-[β -(6-chloropyrazine-2-carboxamidoethyl)benzenesulphonyl]-N'-cyclohexylurea	7.5	—	26%
N-{4-[β -(5-methylpyrazine-2-carboxamido)benzenesulphonyl]-N'-cyclohexylurea	1.5 0.3	46% 31%	55% 50%
N-{4-[β -(2,3-dimethylpyrazine-5-carboxamido)ethyl]benzenesulphonyl}-N'-cyclohexylurea	1.5 0.3	42% 28%	46% 35%
N-{4-[β -(3-chloropyrazine-2-carboxamido)ethyl]benzenesulphonyl}-N'-cyclohexylurea	7.5 1.5	26% 10%	29% 10%
N-{4-[β -(2-chloro-5,6-dimethylpyrazine-3-carboxamido)ethyl]benzenesulphonyl}-N'-cyclohexylurea	7.5 1.5	26% 13%	33% 23%
N-{4-[β -(3-methoxypyrazine-2-carboxamido)ethyl]benzenesulphonyl}-N'-cyclohexylurea	7.5	16%	19%
N-{4-[β -(6-methylpyrazine-2-carboxamido)ethyl]benzenesulphonyl}-N'-cyclohexylurea	7.5	28%	35%

The following Examples illustrate the invention.

EXAMPLE 1

Pyrazine - 2 - carboxylic acid (4.96 g.) was refluxed with thionyl chloride (2.9 ml.) in anhydrous benzene (50 ml.) for about 12 hours, and then the benzene and unreacted thionyl chloride were removed by distillation. Anhydrous dioxan was then added, and the resulting acid chloride solution added dropwise to 8 g. of a suspension of *p* - (β - aminoethyl)benzenesulphonamide in dioxan and anhydrous pyridine (6.5 ml.). The mixture was then refluxed for 3 hours.

The dioxan was then removed by distillation, and the residue treated with water and acetic acid; the crude sulphonamide was filtered off and crystallised from 95% ethanol to give a product (4.2 g.), m.p. 220—222°C, of which a portion (4 g.), suspended in 2N sodium hydroxide (6.4 ml.) and acetone (50 ml.) was treated dropwise with cyclohexylisocyanate (1.5 g.), the temperature being kept at 0° to 5°C. The mixture was stirred for 3 hours at room temperature, diluted with water, and the undissolved products removed by filtration; the filtrate was acidified with dilute hydrochloric acid to give after recrystallisation from ethanol N - {4 - [β - (pyrazine - 2 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexyl - urea (2.9 g.), m.p. 174—6°C.

The following compounds have been obtained by analogous methods:

- 35 N - {4 - [β - (6 - methoxypyrazine - 2 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexyl - urea, m.p. 167—168°C. (crystallisation solvent: ethanol), starting from 6 - methoxypyrazine - 2 - carboxylic acid;
- 40 N - {4 - [β - (6 - chloropyrazine - 2 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexyl - urea, m.p. 170°C, (crystallisation solvent: ethanol), starting from 6 - chloropyrazine - 2 - carboxylic acid;
- 45 N - {4 - [β - (5 - methylpyrazine - 2 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexyl - urea, m.p. 200—203°C (crystallisation solvent: ethanol), starting from 5 - methylpyrazine - 2 - carboxylic acid;
- 50 N - {4 - [β - (2,3 - dimethylpyrazine - 5 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexyl - urea, m.p. 165—7°C, (crystallisation solvent: ethanol), starting from 2,3 - dimethylpyrazine - 5 - carboxylic acid.
- 55 N - {4 - [β - (2 - chloro - 5,6 - dimethylpyrazine - 3 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexyl - urea, m.p. 192—193°C (crystallisation solvent: ethanol), starting from 2 - chloro - 5,6 - dimethylpyrazine - 3 - carboxylic acid;
- 60 N - {4 - [β - (5 - methoxypyrazine - 2 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexylurea (crystallisation solvent: ethanol), starting from 5 - methoxy - pyrazine - 2 - carboxylic acid;
- 65 N - {4 - [β - (3 - methoxypyrazine - 2 -

carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexylurea, m.p. 204—206°C, (crystallisation solvent: ethanol), starting from 3 - methoxy - pyrazine - 2 - carboxylic acid;

N - {4 - [β - (6 - methylpyrazine - 2 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexylurea, m.p. 185—187°C, (crystallisation solvent: ethanol), starting from 6 - methylpyrazine - 2 - carboxylic acid;

N - {4 - [β - (3 - chloropyrazine - 2 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexylurea, m.p. 192°C (crystallisation solvent: ethanol), starting from 3 - chloro - pyrazine - 2 - carboxylic acid.

EXAMPLE 2

5 - Methylpyrazine - 2 - carboxylic acid (6.9 g.) in anhydrous acetone (50 ml.) and triethylamine (7.02 ml.) was stirred for 15 minutes at 0°C, and then added dropwise to ethylchloroformate (4.78 ml.); the mixture was further stirred for 30 minutes, cooled to -5°C., and then treated quickly with *p* - (β - aminoethyl)benzenesulphonamide (10 g.) in water (50 ml.) and triethylamine (7.02 ml.). The mixture was stirred for 3 hours at room temperature. The acetone was then removed by distillation, and the mixture acidified with dilute hydrochloric acid to give a solid which was filtered off and recrystallised from alcohol/water to yield a product (4.4 g.), m.p. 198—200°C, which was treated as in Example 1 with acetone (50 ml.), 2N-sodium hydroxide (10.65 ml.) and cyclohexyl isocyanate (2.52 g.) to give, after crystallisation from ethanol, N - {4 - [β - (5 - methylpyrazine - 2 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexyl - urea (2.7 g.), m.p. 200—203°C.

The following products have been obtained by analogous methods:

- 105 N - {4 - [β - (6 - chloropyrazine - 2 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexyl - urea, m.p. 170°C, (crystallisation solvent: ethanol), starting from 6 - chloropyrazine - 2 - carboxylic acid;
- 110 N - {4 - [β - (6 - methoxypyrazine - 2 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexyl - urea, m.p. 167—8°C (crystallisation solvent: ethanol), starting from 6 - methoxypyrazine - 2 - carboxylic acid;
- 115 N - {4 - [β - (pyrazine - 2 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexyl - urea, m.p. 174—6°C (crystallisation solvent: ethanol), starting from pyrazine - 2 - carboxylic acid;
- 120 N - {4 - [β - (2,3 - dimethylpyrazine - 5 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexyl - urea, m.p. 165—7°C (crystallisation solvent: ethanol), starting from 2,3 - dimethylpyrazine - 5 - carboxylic acid.
- 125 N - {4 - [β - (2 - chloro - 5,6 - dimethylpyrazine - 3 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexyl - urea, m.p. 192—193°C (crystallisation solvent: ethanol), starting from 2 - chloro - 5,6 - dimethylpyrazine - 3 - carboxylic acid;
- 130

N - {4 - [β - (5 - methoxypyrazine - 2 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexylurea (crystallisation solvent: ethanol), starting from 5 - methoxy - pyrazine - 2 - carboxylic acid;

5 N - {4 - [β - (3 - methoxypyrazine - 2 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexylurea, m.p. 204—206°C, (crystallisation solvent: ethanol), starting from 3 - methoxy - pyrazine - 2 - carboxylic acid;

10 N - {4 - [β - (6 - methylpyrazine - 2 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexylurea, m.p. 185—187°C, (crystallisation solvent: ethanol), starting from 6 - methyl - pyrazine - 2 - carboxylic acid;

15 N - {4 - [β - (3 - chloropyrazine - 2 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexylurea, m.p. 192°C (crystallisation solvent: ethanol), starting from 3 - chloro - pyrazine - 2 - carboxylic acid.

EXAMPLE 3

N - {4 - [β - (3 - chloro - 2 - pyrazine-amido)ethyl]benzenesulphonyl} - N' - methylurethane (9 g.), suspended in xylene (150 ml.) was treated with cyclohexylamine (2 g.) and then heated at 140°C with vigorous stirring. The xylene was removed by decantation to give after recrystallisation from ethanol N - {4 - [β - (3 - chloropyrazine - 2 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexyl - urea, m.p. 192°C.

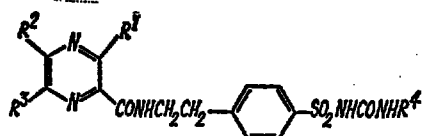
The compounds listed in Example 1 could also be prepared by the above technique.

EXAMPLE 4

35 2,3 - Dimethylpyrazine - 5 - carboxylic acid (3.04 g.) was reacted with thionyl chloride (2.5 ml.) in anhydrous benzene (25 ml.) for approximately 12 hours, and then the benzene and unreacted thionyl chloride were removed by distillation. A little anhydrous chloroform was added to the resulting acid chloride solution which was then added dropwise to a suspension in chloroform of N - {4 - [β - aminoethyl]benzenesulphonyl} - N' - cyclohexyl - urea (6.5 g.) containing anhydrous pyridine (3.65 ml.). The mixture was refluxed for 6 hours and the chloroform then removed by distillation. The residue was treated repeatedly with 1% ammonium hydroxide, filtered and acidified with 5% hydrochloric acid to give after filtration, the crude product which was crystallised from ethanol to give N - {4 - [β - (2,3 - dimethylpyrazine - 5 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexyl - urea (3.2 g.), m.p. 165—7°C.

WHAT WE CLAIM IS:—

1. A pyrazine derivative of general formula (I)



wherein each of the groups R¹, R² and R³, which may be the same or different, is a hydrogen or halogen atom or an unsubstituted or substituted alkyl, alkoxy, hydroxy, amino, acetylamino or phenyl group, R⁴ is an alkyl or alkenyl group or an unsubstituted or alkyl- or alkoxy-substituted cycloaliphatic hydrocarbon group.

2. A pyrazine derivative according to claim 1 wherein at least one of R¹, R² and R³ is a chlorine atom or a methyl or methoxy group, and the remainder are hydrogen atoms.

3. A pyrazine derivative according to claim 1 or 2 wherein R⁴ is an ethyl, n-propyl, isopropyl, n-butyl, isobutyl or allyl group.

4. A pyrazine derivative according to claim 1 or 2 wherein R⁴ is a cyclopentyl, cyclohexyl or methylcyclohexyl group.

5. A pyrazine derivative according to claim 3 or 4 wherein none of R¹, R² and R³ is an acetylamino group.

6. N - {4 - [β - (pyrazine - 2 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexyl - urea.

7. N - {4 - [β - (6 - methoxypyrazine - 2 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexyl - urea.

8. N - {4 - [β - (6 - chloropyrazine - 2 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexyl - urea.

9. N - {4 - [β - (5 - methylpyrazine - 2 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexyl - urea.

10. N - {4 - [β - (2,3 - dimethylpyrazine - 5 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexyl - urea.

11. N - {4 - [β - (3 - chloropyrazine - 2 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexyl - urea.

12. N - {4 - [β - (2 - chloro - 5,6 - dimethylpyrazine - 3 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexylurea.

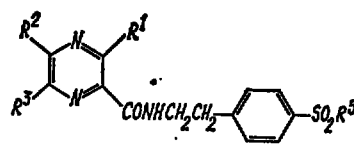
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14. N - {4 - [β - (3 - methoxypyrazine - 2 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexylurea.

15. N - {4 - [β - (6 - methylpyrazine - 2 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexylurea.

16. A pyrazine derivative according to claim 1 substantially as described herein.

17. A process for the preparation of a pyrazine derivative according to any one of the preceding claims, the process comprising reacting a compound of the general formula (II)



- N - {4 - [β - (5 - methoxypyrazine - 2 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexylurea (crystallisation solvent: ethanol), starting from 5 - methoxy - pyrazine - 2 - carboxylic acid;
- 5 N - {4 - [β - (3 - methoxypyrazine - 2 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexylurea, m.p. 204—206°C, (crystallisation solvent: ethanol), starting from 3 - methoxy - pyrazine - 2 - carboxylic acid;
- 10 N - {4 - [β - (6 - methylpyrazine - 2 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexylurea, m.p. 185—187°C, (crystallisation solvent: ethanol), starting from 6 - methyl - pyrazine - 2 - carboxylic acid;
- 15 N - {4 - [β - (3 - chloropyrazine - 2 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexylurea, m.p. 192°C (crystallisation solvent: ethanol), starting from 3 - chloro - pyrazine - 2 - carboxylic acid.

EXAMPLE 3

- N - {4 - [β - (3 - chloro - 2 - pyrazine-amido)ethyl]benzenesulphonyl} - N' - methylurethane (9 g.), suspended in xylene (150 ml.)
- 25 was treated with cyclohexylamine (2 g.) and then heated at 140°C with vigorous stirring. The xylene was removed by decantation to give after recrystallisation from ethanol N - {4 - [β - (3 - chloropyrazine - 2 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexyl - urea, m.p. 192°C.
- 30

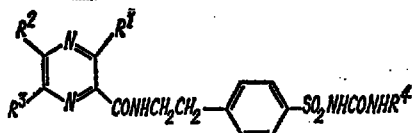
The compounds listed in Example 1 could also be prepared by the above technique.

EXAMPLE 4

- 35 2,3 - Dimethylpyrazine - 5 - carboxylic acid (3.04 g.) was reacted with thionyl chloride (2.5 ml.) in anhydrous benzene (25 ml.) for approximately 12 hours, and then the benzene and unreacted thionyl chloride were removed by distillation. A little anhydrous chloroform
- 40 was added to the resulting acid chloride solution which was then added dropwise to a suspension in chloroform of N - {4 - [β - aminoethyl]benzenesulphonyl} - N' - cyclohexyl - urea (6.5 g.) containing anhydrous pyridine (3.65 ml.). The mixture was refluxed for 6 hours and the chloroform then removed by distillation. The residue was treated repeatedly with 1% ammonium hydroxide,
- 45 filtered and acidified with 5% hydrochloric acid to give after filtration, the crude product which was crystallised from ethanol to give N - {4 - [β - (2,3 - dimethylpyrazine - 5 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexyl - urea (3.2 g.), m.p. 165—7°C.
- 50
- 55

WHAT WE CLAIM IS:—

1. A pyrazine derivative of general formula (I)



wherein each of the groups R¹, R² and R³, which may be the same or different, is a hydrogen or halogen atom or an unsubstituted or substituted alkyl, alkoxy, hydroxy, amino, acetyl amino or phenyl group, R⁴ is an alkyl or alkenyl group or an unsubstituted or alkyl- or alkoxy-substituted cycloaliphatic hydrocarbon group.

2. A pyrazine derivative according to claim 1 wherein at least one of R¹, R² and R³ is a chlorine atom or a methyl or methoxy group, and the remainder are hydrogen atoms.

3. A pyrazine derivative according to claim 1 or 2 wherein R⁴ is an ethyl, n-propyl, isopropyl, n-butyl, isobutyl or allyl group.

4. A pyrazine derivative according to claim 1 or 2 wherein R⁴ is a cyclopentyl, cyclohexyl or methylcyclohexyl group.

5. A pyrazine derivative according to claim 3 or 4 wherein none of R¹, R² and R³ is an acetyl amino group.

6. N - {4 - [β - (pyrazine - 2 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexyl - urea.

7. N - {4 - [β - (6 - methoxypyrazine - 2 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexyl - urea.

8. N - {4 - [β - (6 - chloropyrazine - 2 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexyl - urea.

9. N - {4 - [β - (5 - methylpyrazine - 2 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexyl - urea.

10. N - {4 - [β - (2,3 - dimethylpyrazine - 5 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexyl - urea.

11. N - {4 - [β - (3 - chloropyrazine - 2 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexyl - urea.

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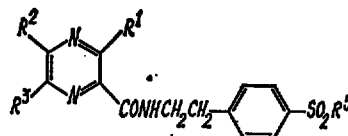
13. N - {4 - [β - (5 - methoxypyrazine - 2 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexylurea.

14. N - {4 - [β - (3 - methoxypyrazine - 2 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexylurea.

15. N - {4 - [β - (6 - methylpyrazine - 2 - carboxamido)ethyl]benzenesulphonyl} - N' - cyclohexylurea.

16. A pyrazine derivative according to claim 1 substantially as described herein.

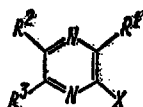
17. A process for the preparation of a pyrazine derivative according to any one of the preceding claims, the process comprising reacting a compound of the general formula (II)



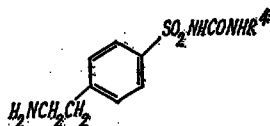
wherein R^1 , R^2 and R^3 are as defined in claim 1 and R^4 is an isocyanate, amino or acylamino group, or a urethane or urea residue, with an amine or isocyanate containing the group R^4 as defined in claim 1.

18. A process according to claim 17 substantially as described in any one of Examples 1 to 3.

19. A process for preparing a pyrazine derivative according to any one of claims 1 to 16, the process comprising reacting a compound of general formula (III)



15 wherein R^1 , R^2 and R^3 are as defined in claim 1, and X is a carboxy group or a functional derivative thereof, with a compound of general formula (IV)



wherein R^4 is as defined in claim 1.

20. A process according to claim 19 wherein

the functional derivative is an acid halide or a mixed anhydride.

21. A process according to claim 19 substantially as described in Example 4.

22. A pyrazine derivative prepared by a process according to claim 17 or 18.

23. A pyrazine derivative prepared by a process according to any one of claims 19 to 21.

24. A pharmaceutical composition comprising at least one pyrazine derivative according to any one of claims 1 to 16, 22 and 23 and a pharmaceutically acceptable carrier or diluent.

25. A composition according to claim 24 in a form suitable for oral administration.

26. A composition according to claim 25 in the form of a tablet, capsule, powder packet, liquid solution, suspension or elixir.

27. A pharmaceutical composition comprising at least one pyrazine derivative according to any one of claims 5, 6, 9 and 11 and a pharmaceutically acceptable carrier or diluent.

28. A pharmaceutical composition comprising at least one pyrazine derivative according to any one of claims 7, 8 and 10 and a pharmaceutically acceptable carrier or diluent.

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