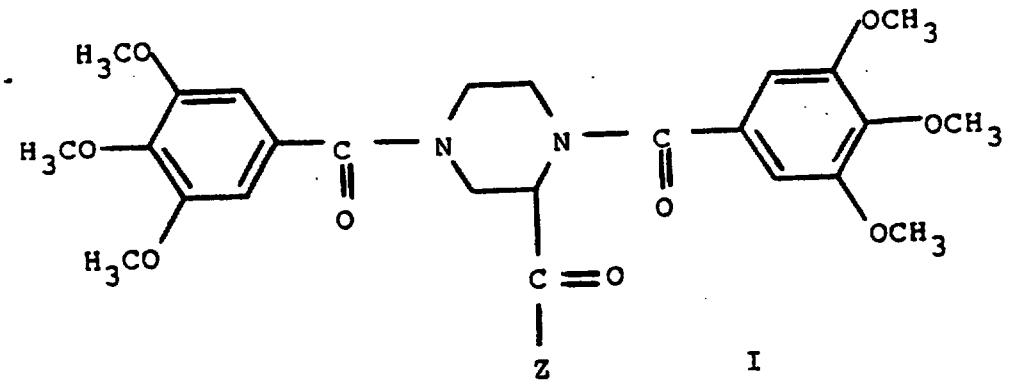
TITLE

Piperazine Derivatives

DESCRIPTION

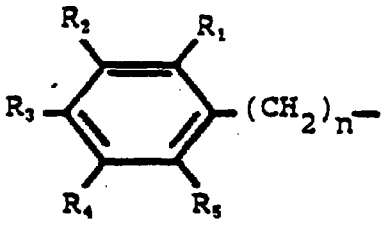
The invention relates to piperazine derivatives, to a method for their preparation and to pharmaceutical compositions containing them.

The invention provides piperazine derivatives having the general formula I:



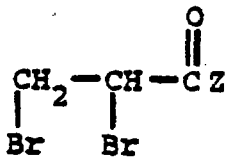
I

wherein Z represents a substituent OA or NA_1A_2 wherein A represents a straight orbranched chain alkyl group having from 1 to 12 carbon atoms, a cycloalkyl or alkyl-cyclo--alkyl group having from 5 to 10 carbon atoms or a group of the general formula:



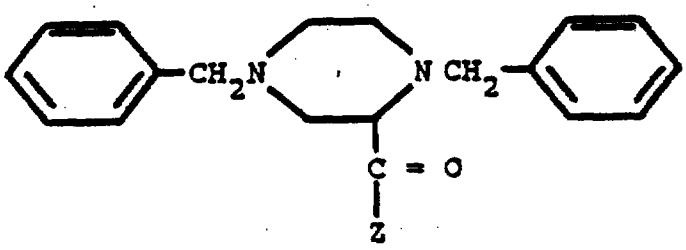
wherein n is zero or an integer of from 1 to 5 and each of R_1, R_2, R_3, R_4 and R_5 independently represents a hydrogen, chlorine or bromine atom, or a trifluoromethyl, trifluoromethoxy, trifluoromethylthio, methyl or methoxy group, and either each of A_1 and A_2 independently represents a hydrogen atom or a group A as above defined or A_1 and A_2 together represent an alkylene group having from 5 to 10 carbon atoms.

The invention further provides a process for the preparation of the piperazine derivatives I. This process comprises reacting a compound of the general formula II



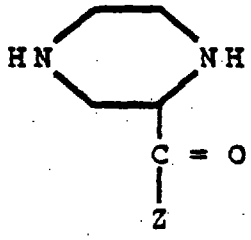
II

wherein Z is as above defined, with an equimolar quantity of N,N'-dibenzylethylenediamine. The reaction is suitably carried out in an aprotic solvent (such as benzene or toluene) at 80°C in the presence of an organic base such as triethylamine. The resultant trisubstituted piperazine of the general formula III:



III

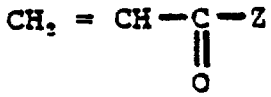
is then hydrogenolysed, suitably in the presence of Pd/charcoal in an alcoholic solvent such as ethanol at 40°C under pressure, and the resultant monosubstituted piperazine of the general formula IV:



IV

is then di-substituted by treatment with 3,4,5-trimethoxy-benzoyl chloride, suitably in an aprotic solvent such as benzene and in the presence of an organic base such as triethylamine, at room temperature.

The starting material of the general formula II may be prepared by treating the corresponding ethylenic compound of the general formula V:



V

with bromine.

The piperazine derivatives I of the invention have anti--ischemic and anti-inflammatory properties, and accordingly the invention further provides pharmaceutical compositions comprising a piperazine derivative I in admixture with a pharmaceutically acceptable diluent or carrier.

The following Examples illustrate the invention.

EXAMPLE 1

Step A

N,N'-dibenzyl-2-n.hexyloxycarbonyl-piperazine (III, Z = $O(CH_2)_5CH_3$).

A solution of 48.5 g (154 mmoles) of n-nexyl 2,3--dibromopropionate (II, Z = $O(CH_2)_5CH_3$) in 100 ml of dry benzene stirred at 40°C was added dropwise to a warm solution (80°C) of 37 g (154 mmoles) of N,N'-dibenzyl-ethylenediamine and 55 ml of triethylamine in 100 ml benzene. The mixture was stirred for 3 hours at 80°C. After cooling and filtering off the triethylammonium chloride, the solvent was evaporated off. The crude residue was treated with diethyl ether and washed with water. The organic layer was dried on anhydrous magnesium sulphate evaporated and chromatographed on a silica gel column using diethyl ether : petroleum ether (10:90 by vol) as eluent, yielding 52.5 g (86.5%) of the title compound as an oil.

IR (film): 3080, 3060, 3030 (Aromatic C-H), 2940, 2800 (C-H), 1740 (C = 0), 1600 (Aromatic C =)), 1145 (C-0) cm^{-1}.
^{1}HNMR (90 MHz, $CDCl_3$, HMDS) δ ppm : 7.25 (large s, 10H, ArH), 4.17 (t, 2H, CH_2OC = 0), 4.01 - 3.41 (m, 4H, $CH_2\phi$), 3.37 - 2.12 (m, 7H, piperazinyl), 1.5 (m, 2H, CH_2-C-OC = 0), 1.2 (large s, 6H, $(CH_2)_3$), 0.80 (t, 3H, CH_3).

Step B

2-n.hexyloxycarbonyl-piperazine IV, Z = $O(CH_2)_5CH_3$)

A solution of 25 g (63.5 mmoles) of the compound prepared in step A and 200 mg PD(10%)/charcoal in 200 ml of ethanol was treated with hydrogen under a pressure of 2.8 bars under stirring at 40°C overnight. After filtration, ethanol was evaporated off under reduced pressure and the crude residue, purified on a silica gel column using methanol : chloroform (5:95 by vol) as eluent, yielded 12.5 g (92%) of the title compound as a highly hygroscopic compound.

IR (film) : 3195 (N-H), 2930, 2850 (C-H), 1735 (C = 0) cm^{-1}.

^{1}HNMR (80 MHz, $CDCl_3$, HMDS) δ ppm : 4.2 (t, 2H, CH_2OC = O), 3.53 - 3.23 (m, 1H, CH-C = O), 3.17 - 2.65 (m, 6H, CH_2 piperazine), 1.90 (s, 2H, NH), 1.5 (m, 2H, CH_2-C-OC = O), 1.22 (large s, 6H, $(CH_2)_3$), 0.85 (t, 3H, CH_3).

Step c

N,N'-di-(3,4,5-trimethoxybenzoyl)-2-n-hexyloxycarbonyl--piperazine (I, Z = $O(CH_2)_5CH_3$)

A solution of 10 g (47 mmoles) of the compound prepared in step B in 150 ml of dry benzene and 25 ml of triethylamine was added dropwise to a solution of 22.7 g (99 mmoles) of 3,4,5-trimethoxybenzoyl chloride in 50 ml of dry benzene. The mixture was kept stirring at room temperature overnight. The excess of acylchloride was then decomposed by the addition of 5 ml ethanol. After evaporating off the solvents under reduced pressure, the residue was treated with chloroform and washed with water, dilute aqueous sodium bicarbonate, and water again. After drying over anhydrous magnesium sulphate and evaporating off the chloroform, a purification on a silca gel column using methanol : chloroform (0.5:99.5 by vol) yielded 25 g (88%) of a syrup which crystallized in diethyl ether; mp = 142.2°C.

IR (film) : 3010 (ArC-H), 2940, 2860 (C-H), 1740 (C = O ester), 1645 (C = O amide), 1590 (ArC = C) cm^{-1}.
^{1}HNMR (80 MHz, $CDCl_3$, HMDS) δ ppm : 6.65 (s, 4H, ArH), 4.85 (m, 1H, CHC = O), 4.12 (m, 4H, CH_2OC = O and O = C-NCH_2-C-C = O), 3.82 (s, 18H, CH_3O), 3.62 - 3.05 (m, 4H, O = C-N-CH_2), 1.58 (m, 2H, CH_2-C-C = O), 1.21 (large s, 6H, $(CH_2)_3$), 0.81 (t, 3H, CH_3).

EXAMPLE 2

N,N'-di-(3,4,5-trimethoxybenzoyl)-2-ethoxycarbonyl--piperazine (I: Z = OCH_2CH_3

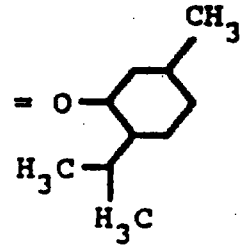
The title compound was obtained as described in Example

1, steps A, B and C but starting with ethyl- 2,3-dibromo-propionate instead of n-hexyl 2,3-dibromopropionate; white crystals, m.p. 129.5°C.

IR (film) : 3010 (ArC-H), 2940, 2830 (C-H), 1735 (C = 0 ester), 1635 (c = 0 amide), 1580 (ArC = C) cm^{-1}.
^{1}HNMR (60 MHz, $CDCl_3$, HMDS) δ ppm : 6.66 (s, 4H, Aromatic H), 4.86 (m, 1H, CHC = 0), 4.13 (m, 4H, CH_2OC = O + O = $CN-CH_2-C-C$ = 0), 3.9 (s, 18H, CH_3O), 3.6 - 2.88 (m, 4H, CH_2-NCO), 0.9 (t, 3H, CH_3).

EXAMPLE 3

N,N'-di- 3,4,5-trimethoxybenzoyl)-2-(2-isopropyl-5--methyl-cyclohexyloxycarbonyl)-piperazine

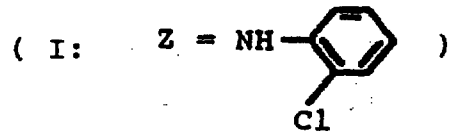
(I: )

The title compound was obtained as described in Example 1, steps A, B and C, but starting with 2-isopropyl-5--methyl-cyclohexyl 2,3-dibromopropionate instead of n-hexyl 2,3-dibromopropionate; white crystals, mp = 151.9°C.

IR (nujol): 1740 (C = 0 ester), 1645 (C = 0 amide), 1585 (ArC = 0) cm^{-1}.
^{1}HNMR (80 MHz, $CDCl_3$, HMDS) δ ppm : 6.67 (m, 4H, ArH), 5.3 (M, 1H, CHOC = 0), 4.87 (m, 1H, CHC = 0), 4.15 (m, 2H, O = $CN-CH_2-C-C$ = 0), 3.67 - 2.75 (m, 4H, CH_2N = 0), 2.17 - 1.11 (m, 9H, CH_2 of the cyclohexyl + $(CH_3)_2\underline{CH}$), 0.87 (m, 9H, CH_3).

EXAMPLE 4

N,N'-di-(3,4,5-trimethoxybenzoyl-2-(o-chlorophenyl-carbamoyl)-piperazine

(I: )

The title compound was obtained as described in Example 1 steps A, B and C, but starting from 2-chlorophenyl 2,3-dibromopropionamide instead of n-hexyl 2,3-dibromo-propionate; white crystals, mp: 144.2°C.

IR (film): 3280 (N-H), 3070 (ArC-H), 2950, 2840 (C-H), 1710 (O = CNAr), 1635 (Ar-C-N), 1590 (ArC = C) cm^{1}.

^{1}HNMR (80 MHz, $CDCl_3$, HMDS) δ ppm: 8.27 (m, 1H, NH), 7.5 - 6.9 (m, 4H, orthochlorophenyl), 6.77 (d, 4H, trimethoxy-benzoyl ArH), 5.22 (m, 1H, CHCON), 4.47 - 4.05 (m, 2H, O = CN-CH_2-C-C = 0). 3.87 (s, 18H, CH_3O), 3.65 = 2.95 (m, 4H, CH_2NCO).

EXAMPLE 5

N,N'-di-(3,4,5-trimethoxybenzoyl)-2-(n-hexyl-carbamoyl)--piperazine (I: Z = NH-$(CH_2)_5CH_3$

The title compound was obtained as described in Example 1, steps A, B and C but starting from n-hexyl 2,3--dibromopropionamide instead of n-hexyl 2,3-dibromo-propionate; white crystals, mp = 189.2°C.

IR (film): 3330 (N-H), 3010 (ArC-H), 2940, 2820 (C-H), 1665 (AlNC = 0), 1635 (ArNC = 0), 1590 (ArC = C) cm^{-1}.
^{1}HNMR (80 MHz, $CDCl_3$, HMDS) δ ppm : 6.71 (large s, 5H, ArH + NH), 4.8 (m, 1H, CHCON), 4.72 - 3.97 (m, 2H, O = CN-CH_2-C-C = 0), 3.47 - 2.97 (m, 6H, CH_2CON + CH_2NCO), 1.70 - 1.08 (m, 8H, $(CH_2)_4$), 0.82 (t, 3H, CH_3).

EXAMPLE 6

According to the process described in Example 1, steps A, B and C, the following compound was prepared (only modification of the ^{1}HNMR spectrum is given):

N,N-di-(3,4,5-trimethoxybenzoyl)-2-benzylcarbamoyl--piperazine

(I: Z = -NH-CH_2-⬡)

Waxy compound ^{1}HNMR δ ppm : 7.22 (s, 5H, C_6H_5), 4.40 (d, 2H, $NCH_2Ø$).

TOXICOLOGY

The compounds of the invention have been administered per os to mice for determination of acute LD_{50}. For all the compounds of the invention, LD_{50} was over 800 mg/kg.

PHARMACOLOGY

A proof of the pharmaceutical interest of the compounds of the invention has been established by the following pharmaceutical experimentation :

Inhibition of the platelets aggregation on New Zealand rabbits.

The experimentation was conducted on platelets with plasma of New Zealand rabbits.
Blood samples were taken from auricular artery and placed in a citrate buffer (3.8%; pH 7.4); blood was further centrifuged for 15 mn at 1200 RPM.

The tested sample was prepared in DMSO, then poured on platelets rich plasma for 1 mn, then a dose of 2.5 nM of PAF was added. The determination is made on a Cronolog Coutronics apparatus which determines the transmission percentage corresponding to the maximum height of the peak before the desaggregation.

The percentage of variation of the inhibition with respect to the transmission percentage is calculated (control : pure DMSO). This method was described in detail in LABORATORY INVESTIGATIONS, Vol. 41, No. 3, p. 275, 1979, JEAN-PIERRE CAZENAVE, Dr. MED., JACQUES BENVENISTE, DR. MED., AND J. FRASER MUSTARD, M.D. "Aggregation of rabbits platelets by platelet-activating factor is independent of the release reaction and the arachidonate pathway and inhibited by membrane-active drugs".

The results demonstrate the the compounds inhibit the aggregation induced by 2.5 nM of PAF. Five tests made on 5 different rabbits allowed us to calculate the IC_{50} of the various compounds using the linear regression test.

The values for IC_{50} on platelets have been found as follows:

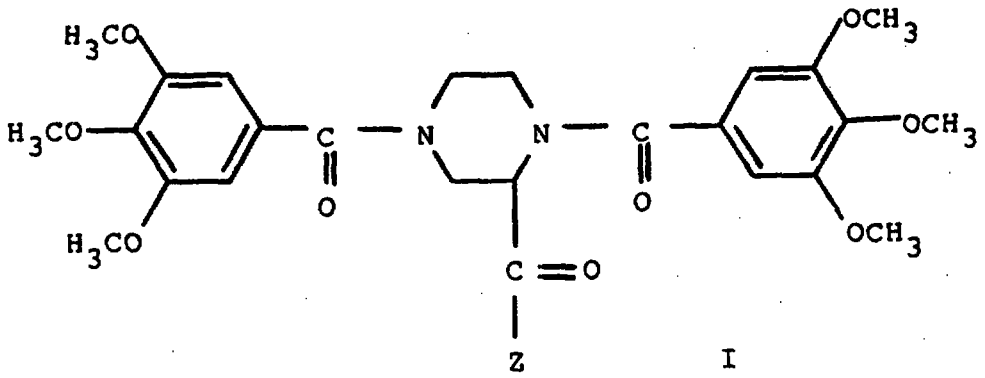
Example 1:	2.15	$.10^{-6}$
Example 2:	1.29	$.10^{-6}$
Example 3:	1.6	$.10^{-5}$
Example 4:	3.36	$.10^{-6}$
Example 5:	8.84	$.10^{-6}$
Example 6:	1.97	$.10^{-5}$

PRESENTATION-POSOLOGY

In human therapy, active doses are 1.50mg/kg per day in oral administration (tablets and gelatine capsules containing 50 mg or 100 mg per unit dose, for instance) or 0.1 to 5 mg/kg in IV administration (unit does of 5 mg to 100 mg in individual phials.

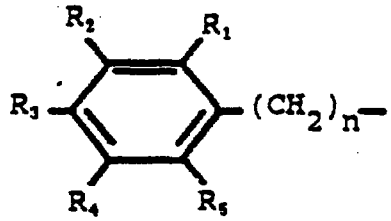
CLAIMS:

1. A piperazine derivative having the general formula I:



I

wherein Z represents a substituent OA or NA_1A_2 wherein A represents a straight or branched chain alkyl group having from 1 to 12 carbon atoms; a cycloalkyl or alkyl-cycloalkyl group having from 5 to 10 carbon atoms or a group of the general formula:



wherein n is zero or an integer of from 1 to 5 and each of R_1, R_2, R_3, R_4 and R_5 independently represents a hydrogen, chlorine or bromine atom, or a trifluoromethyl, trifluoromethoxy, trifluoromethylthio, methyl or methoxy group; and either each of A_1 and A_2 independently represents a hydrogen atom or a group A as above defined or A_1 and A_2 together represent an alkylene group having from 5 to 10 carbon atoms.

2. N,N'-di-(3,4,5-trimethoxybenzoyl)-2-n.hexyloxy-carbonyl-piperazine.

3. N,N'-di-(3,4,5-trimethoxybenzoyl)-2-ethoxycarbonyl--piperazine.

* C L M S *

4. N,N'-di-(3,4,5-trimethoxybenzoyl)-2-(2-isopropyl--5-methyl-cyclohexyloxycarbonyl)-piperazine.

5. N,N'-di-(3,4,5-trimethoxybenzoyl)-2-(o-chlorophenyl-carbamoyl)-piperazine.

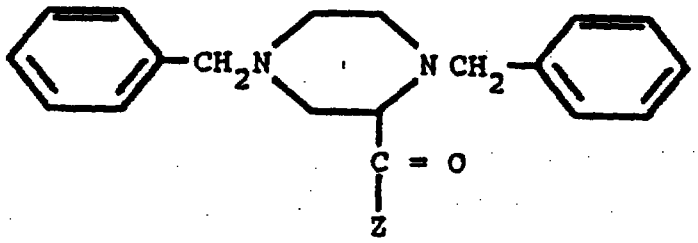
6. N,N'-di-(3,4,5-trimethoxybenzoyl)-2-(n-hexyl--carbamoyl)-piperazine.

7. N,N'-di-(3,4,5-trimethoxybenzoyl)-2-benzyl-carbamoyl-piperazine.

8. A process for the preparation of a piperazine derivative according to claim 1, the process comprising the steps of:

(a) reacting N,N'-dibenzylethylenediamine with an equimolar quantity of a compound of the general formula $BrCH_2$-CHBr-CO-Z wherein Z is as defined in claim 1;

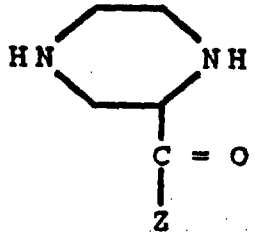
(b) hydrogenolysing the resultant compound of the general formula III



III

wherein Z is as defined in claim 1; and

(c) treating the resultant compound of the general formula IV



IV

with 3,4,5-trimethoxybenzoyl chloride in an aprotic solvent in the presence of an organic base.

9. A process acording to claim 8 in which step (a) is carried out in an aprotic solvent in the presence of an organic base.

10. A process according to claim 9 in which the aprotic solvent used in step (a) is benzene or toluene, and step (a) is performed at approximately 80°C.

11. A process according to claim 9 or claim 10 in which the organic base used in step (a) is triethylamine.

12. A process according to any of claims 8 to 11 in which the aprotic solvent used in step (c) is benzene, and step (c) isperformed at ambient temperature.

13. A process according to any of claims 8 to 12 in which the organic base used in step (c) is triethylamine.

14. A process according to any of claims 8 to 13 in which the hydrogenolysis is effected using palladium-on -charcoal in an alcoholic solvent.

15. A pharmaceutical composition comprising a piperazine derivative according to any of claims 1 to 7 in admixture with a pharmaceutically acceptable diluent or carrier.

16. A pharmaceutical composition according to claim 15 in unit dose form.

17. A pharmaceutical composition according to claim 16 in a form for oral administration and containing from 50 to 100 mg of the piperazine derivative.

* C L M S *

18. A pharmaceutical composition according to claim 16 in a form for intravenous administration and containing 5 to 100 mg of the piperazine derivative.

* C L M S *