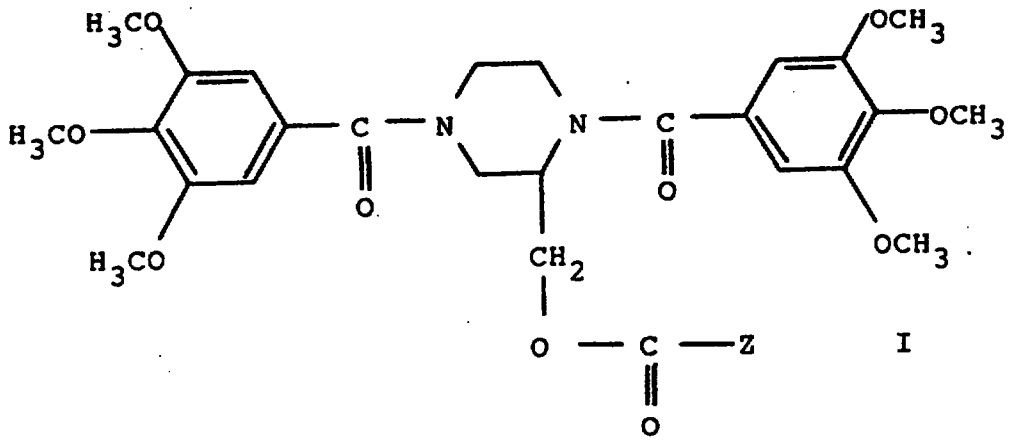
Piperazine Derivatives

DESCRIPTION

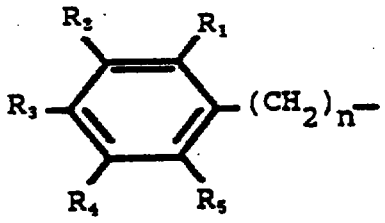
The invention relates to piperazine derivatives, to a method for their preparation and to pharmaceutical compositions containing them.

The invention provides piperazine derivatives having the general formula I:



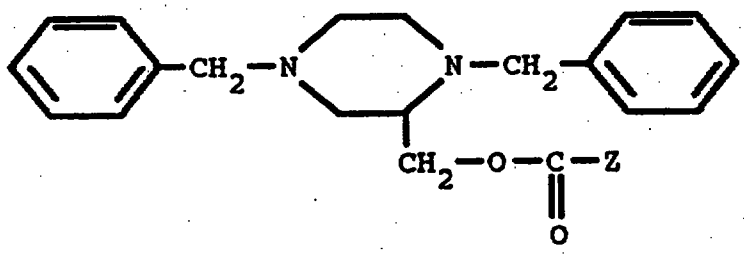
I

wherein Z represents a substituent A or NH-A wherein A represents a straight or branched chain alkyl group having from 1 to 17 carbon atoms, a cycloalkyl group having from 5 to 10 carbon atoms or a group of the general formula:



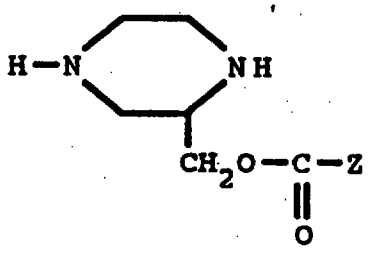
wherein n is zero or an integer of from 1 to 5 and each of R_1, R_2, R_3, R_4 and R_5 independently represents a hydrogen, chlorine or bromine atom or a trifluoromethyl, trifluoromethylthio, trifluoromethoxy, methyl or methoxy group.

The invention further provides a process for the preparation of a piperazine derivative I as above defined, the process comprising (a) reacting N,N'-dibenzyl-2--hydroxymethyl-piperazine with a compound A.CO.Cl (to obtain compounds I in which Z = A) or A-N=C=O (to obtain compounds I in which Z = NH-A) in an aprotic solvent in the presence of an organic base, (b) hydrogenolysing the resultant compound of the general formula II



II

and (c) treating the resultant compound of the general formula III



III

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

Suitably the compound A.CO.Cl is reacted in diethyl ether, tetrahydrofuran, benzene or toluene at ambient temperature, whereas the compound A-N=C=O is reacted in benzene or toluene at approximately 80°C. The organic base for steps (a) and (c) may be triethylamine. The hydrogenolysis is preferably effected using 10% Pd/C in ethanol. Step (c) may be performed at ambient temperature in benzene.

The piperazine derivatives I as above defined are active as anti-ischemic and anti-inflammatory agents, useful in various fields, such as renal disease. Accordingly the invention further provides a pharmaceutical composition comprising a piperazine derivative I as above defined in admixture with a pharmaceutically acceptable diluent or carrier.

The following Examples illustrate the invention:

EXAMPLE 1

Step A

N,N'-dibenzyl-2-cyclohexylcarbonyloxymethyl--piperazine (II, Z = cyclohexyl)

A solution of 2 g (6.8 mmoles) of N,N'-dibenzyl--2-hydroxymethyl-piperazine in 30 ml dry benzene and 1 ml of triethylamine was added dropwise to 1.1 g (6.8 mmoles) of cyclohexanecarbonyl chloride in 10 ml benzene. After stirring overnight at room temperature, the solvents were eliminated under reduced pressure and the crude residue treated with chloroform. It was then washed with water, dilute aqueous sodium bicarbonate solution, and water again. The organic layer was then dried on anhydrous magnesium sulphate, evaporated and chromatographed on a silica gel column using diethyl ether:petroleum (10:90 by vol) as eluent.

This purification gave 1.87 g (68 %) of the title compound as an oil.

IR (film) : 3090, 3070, 3030 (ArC-H), 2940, 2860, 2810 (C-H), 1735 (C = O), 1600 (ArC = C) cm^{-1}.
^{1}H NMR (80 MHz, $CDCl_3$, HMDS) δ ppm : 7.27 (large s, 10H, ArH), 4.55 (m, 2H, CH_2OC = O), 4.12 - 3.25 (m, 5H, $CH_2\Phi$ + CH-N), 2.95 - 2.02 (m, 7H, CH_2 piperazine + CH-C = O), 1.72 (m, 4H, CH_2-C-C = O), 1.25 (m, 6H, CH_2 cyclohexyl).

Step B

2-cyclohexylcarbonyloxymethyl-piperazine (III, Z = cyclohexyl)

A solution of 1.5 g (3.7 mmoles) of the compound prepared in step A and 50 mg Pd(10 %)/charcoal in 50 ml ethanol was treated with hydrogen under a pressure of 2.8 bars under stirring at 40°C overnight. After filtration, the 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. This operation yielded 0.75 g (90 %) of the title compound as a very hygroscopic product.

IR (film) : 3340 (N-H), 2960, 2860 (C-H), 1730 (C = O) cm^{-1}.
^{1}H NMR (80 MHz, $CDCl_3$, HMDS) δ ppm : 3.95 (d, 2H, CH_2OC = O), 3.72 - 3.27 (m, 1H, CH-N), 3.45 (s, 2H, disappear with D_2O, NH), 3.25-2.27 (m, 7H, CHC = O + CH_2 piperazine), 1.62 (m, 4H, CH_2-C-C = O), 1.2 (m, 6H, CH_2, cyclohexyl).

Step C

N,N'-di-(3,4,5-trimethoxybenzoyl)-2-cyclohexylcarbonyloxy-methyl-piperazine (I,Z = cyclohexyl)

A solution of 0.5 g (2.2 mmoles) of the compound prepared in step B in 30 ml of dry benzene and 1.5 ml triethylamine was added dropwise to 1 g (4.6 mmoles) of 3,4,5-trimethoxybenzoyl chloride in 10 ml of dry benzene. The mixture was kept overnight under stirring at room temperature. The excess of acyl chloride was then decomposed by the addition of 1 ml of ethanol. After evaporating off the solvents under reduced pressure, the residue was treated with chloroform, and washed with water, dilute aqueous sodium bicarbonate solution and then water again. After drying on anhydrous magnesium sulphate and evaporating off the chloroform, a purification on a silica gel column using methanol:chloroform (0.5:99.5 by vol) yielded 1.1 g (74 %) of the title compound as a wax.

IR (film) : 3050, 3000 (ArC-H), 2940, 2860 (C-H), 1720 (C = O ester), 1650 (C = O amide), 1585 (ArC = C) cm^{-1}.
^1H NMR (60 MHz, $CDCl_3$, HMDS) δ ppm : 6.57 (s, 4H, ArH), 4.83 (d, 2H, $CH_2OC=O$), 4.45 - 3.97 (m, 3H, O = C $NCH_2-CH-NC=O$), 3.86 (large s, 18H, CH_3O), 3.5 - 2.66 (m, 4H, $CH_2NC=O$), 2.6 - 2.23 (m, 1H, CHC = O), 1.93 - 0.9 (m, 10H, CH_2 cyclohexyl).

EXAMPLE 2

N,N'-di-(3,4,5-trimethoxybenzoyl)-2-t.butylcarbonyloxy-methyl-piperazine (I:Z = t.butyl)

The title compound was obtained as a waxy substance by the method described in Example 1, steps A, B and C, but starting with 2,2-dimethyl-propanoyl chloride instead of cyclohexanecarbonyl chloride.

IR (film) : 3060 (ArC-H), 2960, 2840 (C-H), 1730 (C = O ester), 1640 (C = O amide), 1585 (ArC = C) cm^{-1}.
^{1}HNMR (60 MHz, $CDCl_3$, HMDS) δ ppm : 6.63 (s, 4H, ArH), 4.93 - 4.5 (m, 2H, $CH_2OC = O$), 4.43 - 3.96 (m, 3H, $O = CNCH_2CHNC = O$), 3.86 (s, 18 H, CH_3O), 3.5 - 2.8 (m, 4H, $CH_2NC = O$), 1.06 (s, 9H, CH_3).

EXAMPLE 3

N,N'-di(3,4,5-trimethoxybenzoyl)-2-n.butanoyloxy-methyl-piperazine (I:Z = n.propyl)

The title compound was obtained as an oil by the method described in Example 1, steps A, B and C, but starting with n-butanoyl chloride instead of cyclohexane-carbonyl chloride.

IR (film) : 3080 (ArC-H), 2930 - 2860 (C-H), 1720 (C = O ester), 1640 (C = O amide), 1585 (ArC = C) cm^{-1}.
^{1}HNMR (80 MHz, $CDCl_3$, HMDS) δ ppm : 6.62 (s, 4H, ArH), 4.66 (m, 2H, $CH_2OC = O$), 4.55 - 4.05 (m, 3H, $O = CNCH_2CHNC = O$), 3.85 (large s, 18H, CH_3O), 3.52 - 2.8 (m, 4H, CH_2NCO), 2.3 (m, 2H, CH_2CO), 1.77 - 1.35 (m, 2H, $CH_2-C-C = O$), 0.87 (t, 3H, CH_3).

EXAMPLE 4

N,N'-di-(3,4,5-trimethoxybenzoyl)-2-n.octanoyl-oxymethyl-piperazine (I:Z = n.heptyl)

The title compound was obtained as a viscous substance by the method described in Example 1, steps A, B and C, but starting with n-octanoyl chloride instead of cyclohexanecarbonyl chloride.

IR (film) : 3060, 3000 (ArC-H), 2940, 2860 (C-H), 1735 (C = O ester), 1640 (C = O amide), 1585 (ArC = C) cm^{-1}.
^1H NMR (80 MHz, $CDCl_3$, HMDS) δ ppm : 6.62 (s, 4H, ArH), 4.85 - 4.05 (m, 5H, $CH_2OC=O + O=CNCH_2-CHNCO$), 3.77 (s, 18H, CH_3O), 3.57 - 2.7 (m, 4H, $CH_2NC=O$), 2.2 (t, 2H, $CH_2C=O$), 1.52 (m, 2H, $CH_2-C-C=O$), 1.33 (large s, 8H, $(CH_2)_4$), 0.82 (t, 3H, CH_3).

EXAMPLE 5

N,N'-di-(3,4,5-trimethoxybenzoyl)-2-n.decanoyl-oxymethyl-piperazine (I:Z = n.nonyl)

The title compound was obtained as a viscous compound by the method described in Example 1, steps A, B and C, but starting with n-decanoyl chloride instead of cyclohexane-carbonyl chloride.

IR (film) : 3060 (ArC-H), 2920, 2850 (C-H), 1740 (C = O ester), 1635 (C = O amide), 1580 (ArC = C) cm^{-1}.
^1H NMR (80 MHz, $CDCl_3$, HMDS) δ ppm : 6.6 (s, 4H, ArH), 4.6 (m, 2H, $CH_2OC=O$), 4.45 - 3.97 (m, 3H, $O=CNCH_2-CH-NC=O$), 3.87 (s, 18H, CH_3O), 3.65 - 2.85 (m, 4H, $CH_2NC=O$), 2.12 (t, 2H, $CH_2C=O$), 1.42 (m, 2H, $CH_2-C-C=O$), 0.75 (t, 3H, CH_3).

EXAMPLE 6

N,N'-di(3,4,5-trimethoxybenzoyl)-2-octadecanoyl-oxymethyl-piperazine (I:Z = n.heptadecyl)

The title compound was obtained as a viscous oil by the method described in Example 1, steps A, B and C, but starting with octadecanoyl chloride instead of cyclohexane-carbonyl chloride.

IR (film) : 3020 (ArC-H), 2940, 2870 (C-H), 1725 (C = O ester), 1650 (C = O amide), 1595 (ArC = C) cm^{-1}.
^1H NMR (80 MHz, $CDCl_3$, HMDS) δ ppm : 6.57 (s, 4H, ArH), 4.75 - 4.0 (m, 5H, $CH_2OC=O + O=CNCH_2CHNC=O$), 3.87 (s, 9H, CH_3O), 3.48 - 2.75 (m, 4H, $CH_2NC=O$), 2.22 (t, 2H, $CH_2C=O$), 1.47 (m, 2H, $CH_2-C-C=O$), 1.21 (large s, 28H, $(CH_2)_{14}$), 0.77 (t, 3H, CH_3).

EXAMPLE 7

N,N'-di-(3,4,5-trimethoxybenzoyl)-2-o.chlorobenzoyl-oxymethyl-piperazine (I:Z = o.chlorobenzyl)

The title compound was obtained an oily product by the method described in Example 1, steps A, B and C, but starting with 2-chlorobenzoyl chloride instead of cyclohexanecarbonyl chloride.

IR (film) : 3070, 3020 (ArC-H), 2930, 2860 (C-H), 1720 (C = O ester), 1630 (C = O amide), 1590 (ArC = C) cm^{-1}.
^1H NMR (60 MHz, $CDCl_3$, HMDS) δ ppm : 7.63 - 7.13 (m, 4H, chlorophenyl H), 6.56 (d, 4H, trimethoxyphenyl Ar-H), 4.83 (m, 2H, $CH_2OC=O$), 4.63 - 3.96 (m, 3H, $O=CNCH_2-CHNC=O$), 3.8 (s, 18H, CH_3O), 3.5 - 2.73 (m, 4H, $CH_2NC=O$).

EXAMPLE 8

Step A

N,N'-dibenzyl-2-(N''-n.butyl-carbamoyloxy-methyl)-piperazine (II, Z = $NH(CH_2)_3CH_3$)

A mixture of 10 g (34 mmoles) of N,N'-dibenzyl--2-hydroxymethyl-piperazine, 10 g (102 mmoles) of n-butyl isocyanate and 15 ml of triethylamine in 100 ml of dry benzene was refluxed under stirring for 48 hours. After evaporation of the solvents, the crude residue was treated with chloroform and then washed with water, dilute aqueous sodium bicarbonate solution, and water again. The chloroformic layer was dried over anhydrous magnesium

sulphate, concentrated under reduced pressure and purified on a silica gel column using diethyl ether:petroleum ether (10:90 by vol) as eluent to give 11.7 g (87 %) of the title compound as an oil.

IR (film) : 3330 (N-H), 3080, 3060, 3020 (ArC-H), 2940, 2860 (C-H), 1720 (C = O urethane).
^{1}H NMR (80 MHz, $CDCl_3$, HMDS) δ ppm : 7.27 (large s, 10H, ArH), 4.63 (m, 1H, NH), 4.37 (m, 2H, $CH_2OC=O$), 4.02 and 3.63 (2 s, 4H, CH_2O), 3.28 - 2.45 (m, 9H, piperazine + $CH_2NC=O$),

Steps B and C

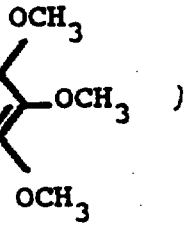
N,N'-di-(3,4,5-trimethoxybenzoyl)-2-[N''-(n.butyl)--carbamoyloxymethyl]-piperazine (I: Z = NH-$(CH_2)_3$-CH_3)

The title compound was obtained as described in Example 1, steps B and C. It appeared as white crystals, mp 90°C.

IR (Nujol (R.T.M)) : 3340 (N-H), 1720 (C = O methane), 1635 (C = O amide), 1590 (ArC = C) cm^{-1}.
^{1}H NMR (80 MHz, $CDCl_3$, HMDS) δ ppm : 6.6 (s, 4H, ArH), 4.72 (m, 2H, $CH_2OC=O$), 4.65 - 3.92 (m, 4H, $O=CNCH_2CHNC=O$ + NH), 3.87 (large s, 18H, CH_3O), 3.42 - 2.7 (m, 6H, $CH_2NC=O$), 1.3 (m, 4H, $(CH_2)_2$), 0.8 (t, 3H, CH_3).

EXAMPLE 9

N,N'-di-(3,4,5-trimethoxybenzoyl)-2-[N'-(3,4,5--trimethoxyphenyl)-carbamoyloxymethyl]-piperazine

(I: Z = )

The title compound was obtained as described in Example 8, step A, but starting with equimolar quantities of N,N'-dibenzyl-2-hydroxymethyl-piperazine and 3,4,5--trimethoxyphenyl isocyanate instead of n-butyl isocyanate. Steps B and C were as in Example 1. The title compound was a pale yellow solid, mp = 122°C.

IR (Nujol) : 3300 (N-H), 1735 (C = O urethane), 1630 (C = O amide), 1590 (ArC = C) cm^{-1}.
^{1}H NMR (80 MHz, $CDCl_3$, HMDS) δ ppm : 6.80 (m, 1H, NH), 6.62 (m, 6H, ArH), 4.9 - 4.52 (m, 2H, $CH_2OC=O$), 4.47 - 3.97 (m, 3H, $O=CNCH_2-CHNC=O$), 3.58 - 2.75 (m, 4H, $CH_2NC=O$).

According to the process described in Example 1, steps A, B and C, the following compounds were prepared (only modifications of the ^{1}H NMR spectra are given):

EXAMPLE 10

N,N'-di-(3,4,5-trimethoxybenzoyl)-2-(2-ethyl-butanoyloxymethyl)-piperazine (I:Z = 1-ethylpropyl)

mp = 170.2°C. ^{1}H NMR δ ppm : 2.12 (quintet, 1H, $CHEt_2$), 1.47 (quintet, 4H, CH_2CH_3), 0.77 (t, 6H, CH_3).

EXAMPLE 11

N,N'-di-(3,4,5-trimethoxybenzoyl)-2-n.hexanoyl-oxymethyl-piperazine (I:Z = n.pentyl)

waxy solid. ^{1}H NMR δ ppm : 2.27 (m, 2H, $CH_2C=O$), 1.51 (m, 2H, $CH_2-C-C=O$), 1.25 (m, 4H, CH_2), 0.77 (t, 3H, CH_3).

EXAMPLE 12

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

mp = 59°C. ^{1}H NMR δ ppm : 1.93 (s, 3H, $CH_3C=O$).

EXAMPLE 13

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

mp : 86.6°C. ^{1}H NMR δ ppm : 2.05 (s, 2H, $CH_2C=O$), 0.92 (s, 9H, CH_3).

According to the process described in Example 8, steps A, B and C, the following compounds were prepared (only modifications of the ^{1}H NMR spectra are given):

EXAMPLE 14

N,N'-di-(3,4,5-trimethoxybenzoyl)-2-[N'-(1-ethylpropyl)carbamoyloxymethyl]-piperazine (I:Z = $-NH-CH(CH_2CH_3)_2$)

mp = 90.2°C. ^{1}H NMR δ ppm : 3.55 - 2.92 (m, 5H, $CH_2NC=O$ + CHNCOO), 1.37 (m, 4H, CH_2CH_3), 0.82 (t, 6H, CH_3).

EXAMPLE 15

N,N'-di-(3,4,5-trimethoxybenzoyl)-2-[N'-(t.butyl)-carbamoyloxymethyl]-piperazine (I:Z = $-NH-C(CH_3)_3$)

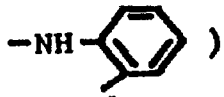
viscous compound. ^{1}H NMR δ ppm : 1.20 (s, 9H, CH_3).

EXAMPLE 16

N,N'-di-(3,4,5-trimethoxybenzoyl)-2-[N'--(neopentyl)-carbamoyloxymethyl]-piperazine (I:Z = $-NH-CH_2-C(CH_3)_3$)

mp = 80°C. ^{1}HNMR δ ppm : 0.80 (s, 9H, CH_3).

EXAMPLE 17

N,N'-di-(3,4,5-trimethoxybenzoyl)-2-[N'--(o-chlorophenyl)-carbamoyloxymethyl]-piperazine (I:Z = )

mp = 115°C. ^{1}HNMR δ ppm : 7.3 and 6.7 (2 s, 4H, C_6H_4), 6.67 - 6.42 (m, 4H, C_6H_2).

EXAMPLE 18

N,N'-di-(3,4,5-trimethoxybenzoyl)-2-[N'--(1-methylbutyl)-carbamoyloxymethyl]-piperazine

(I: Z = $-NH-\underset{CH_3}{\underset{|}{CH}}-(CH_2)_2-CH_3$)

mp = 78°C. ^{1}HNMR δ ppm : 1.27 (m, 4H, CH_2), 1.02 (d, 3H, $C\underline{H}_3CH$), 0.85 (t, 3H, CH_3).

EXAMPLE 19

N,N'-di-(3,4,5-trimethoxybenzoyl)-2-[N'--(1,2,2-trimethylpropyl)-carbamoyloxymethyl]-piperazine

(I: Z = $-NH-\underset{CH_3}{\underset{|}{CH}}-C(CH_3)_3$)

mp = 86°C. ^{1}HNMR δ ppm : 0.92 (m, 3H, $C\underline{H}_3CH$), 0.79 (s, 9H, CH_3C).

EXAMPLE 20

N,N'-di-(3,4,5-trimethoxybenzoyl)-2-[N'--(isopentyl)-carbamoyloxymethyl]-piperazine

(I: Z = $-NH-(CH_2)_2-CH\langle^{CH_3}_{CH_3}$)

mp = 71°C. ^{1}H NMR δ ppm : 2.17 - 1.80 (m, 1H, $CH(CH_3)_2$), 1.27 (m, 2H, CH_2), 0.80 (d, 6H, CH_3).

EXAMPLE 21

N,N'-di-(3,4,5-trimethoxybenzoyl)-2-N'--(1,3-dimethyl-butyl)-carbamoyloxymethyl]-piperazine

(I: Z = $-NH-\underset{CH_3}{CH}-CH_2-CH\langle^{CH_3}_{CH_3}$)

mp = 76°C. ^{1}H NMR δ ppm : 2.35 - 1.91 (m, 1H, $CH(CH_3)_2$), 1.18 (m, 2H, CH_2), 098 (d, 3H, CH_3-C-N), 0.78 (d, 6H, CH_3).

EXAMPLE 22

N,N'-di-(3,4,5-trimethoxybenzoyl)-2-[N'--(2-methylbutyl)-carbamoyloxymethyl]-piperazine

(I: Z = $-NH-CH_2-\underset{CH_3}{CH}-CH_2-CH_3$)

mp = 70°C. ^{1}H NMR δ ppm : 1.70 (m, 1H, CH), 1.22 (m, 2H, CH_2), 0.85 (m, 6H, CH_3).

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 700 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 1 200 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 Coultronics 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 that the compounds inhibit the aggregation induced by 2.5 nM of PAF. Nine tests made on 9 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:

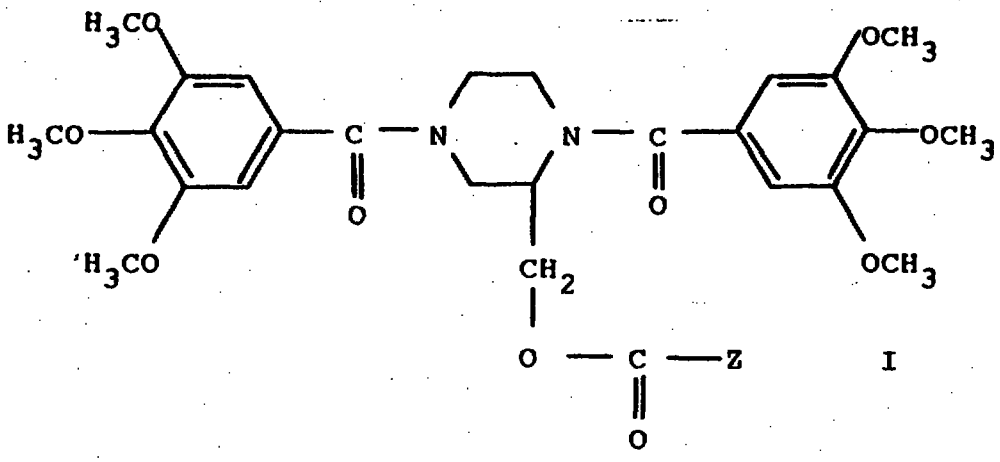
Example 1 :	2.80	$.10^{-7}$
Example 2 :	1.00	$.10^{-7}$
Example 3 :	3.60	$.10^{-6}$
Example 4 :	3.14	$.10^{-7}$
Example 5 :	2.82	$.10^{-6}$
Example 6 :	4.5	$.10^{-5}$
Example 7 :	1.69	$.10^{-7}$
Example 8 :	2.41	$.10^{-7}$
Example 9 :	1.38	$.10^{-5}$
Example 10 :	7.12	$.10^{-8}$
Example 11 :	4.97	$.10^{-6}$
Example 12 :	4.3	$.10^{-7}$
Example 13 :	1.21	$.10^{-7}$
Example 14 :	1.34	$.10^{-7}$
Example 15 :	1.34	$.10^{-7}$
Example 16 :	1.05	$.10^{-6}$
Example 17 :	2.12	$.10^{-5}$
Example 18 :	1.04	$.10^{-7}$
Example 19 :	1.69	$.10^{-7}$
Example 20 :	1.37	$.10^{-7}$
Example 21 :	2.82	$.10^{-7}$
Example 22 :	4.73	$.10^{-7}$

PRESENTATION - POSOLOGY

In human therapy, active doses are 1-50 mg/kg per day in oral administration (tablets or gelatine capsules containing 50 mg or 100 mg per unit dose, for instance) or 0.1 to 5 mg/kg in IV administration (unit doses of 5 to 100 mg in individual phials).

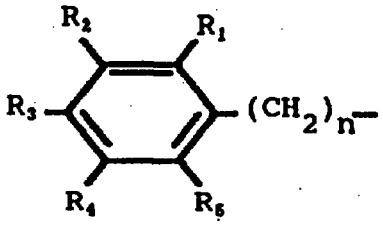
CLAIMS

1. A piperazine derivative having the general formula I:



I

wherein Z represents a substituent A or NH-A wherein A represents a straight or branched chain alkyl group having from 1 to 17 carbon atoms, a 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, trifluoromethylthio, trifluoromethoxy, methyl or methoxy group.

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

3. N,N'-di-(3,4,5-trimethoxybenzoyl)-2--t.butylcarbonyloxymethyl-piperazine.

* C L M S *

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

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

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

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

8. N,N'-di-(3,4,5-trimethoxybenzoyl)-2-
-o.chlorobenzoyloxymethyl-piperazine.

9. N,N'-di-(3,4,5-trimethoxybenzoyl)-2-
-[N'-(n.butyl)-carbamoyloxymethyl]-piperazine.

10. N,N'-di-(3,4,5-trimethoxybenzoyl)-2-
-[N'-(3,4,5-trimethoxyphenyl)-carbamoyloxymethyl]-
-piperazine.

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

12. N,N'-di-(3,4,5-trimethoxybenzoyl)-2-
-n.hexanoyloxymethyl-piperazine.

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

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

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15. N,N'-di-(3,4,5-trimethoxybenzoyl)-2-
-[N'-(1-ethylpropyl)-carbamoyloxymethyl]-piperazine.

16. N,N'-di-(3,4,5-trimethoxybenzoyl)-2-
-[N'-(t.butyl)-carbamoyloxymethyl]-piperazine.

17. N,N'-di-(3,4,5-trimethoxybenzoyl)-2-
-[N'-(neopentyl)-carbamoyloxymethyl]-piperazine.

18. N,N'-di-(3,4,5-trimethoxybenzoyl)-2-
-[N'-(o-chlorophenyl)-carbamoyloxymethyl]-piperazine.

19. N,N'-di-(3,4,5-trimethoxybenzoyl)-2-
-[N'-(1-methylbutyl)-carbamoyloxymethyl]-piperazine.

20. N,N'-di-(3,4,5-trimethoxybenzoyl)-2-
-[N'-(1,2,2-trimethylpropyl)-carbamoyloxymethyl]-piperazine.

21. N,N'-di-(3,4,5-trimethoxybenzoyl)-2-
-[N'-(isopentyl)-carbamoyloxymethyl]-piperazine.

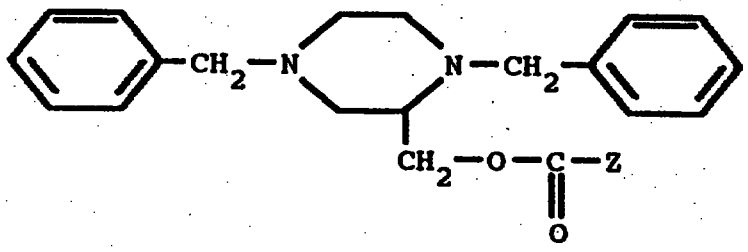
22. N,N'-di-(3,4,5-trimethoxybenzoyl)-2-
-[N'-(1,3-dimethylbutyl)-carbamoyloxymethyl]-piperazine.

23. N,N'-di-(3,4,5-trimethoxybenzoyl)-2-
-[N'-(2-methylbutyl)-carbamoyloxymethyl]-piperazine.

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

a) reacting N,N'-dibenzyl-2-hydroxymethyl-piperazine with a compound of the general formula A.CO.Cl or A-N=C=O wherein A is as defined in claim 1 in an aprotic solvent in the presence of an organic base;

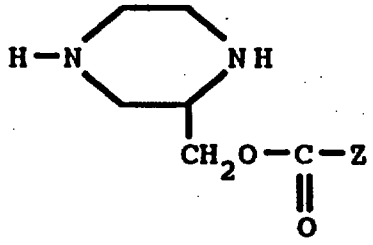
b) hydrogenolysing the resultant compound of the general formula II



II

wherein Z is as defined in claim 1, and

c) treating the resultant compound of the general formula III



III

wherein Z is as defined in claim 1 with 3,4,5--trimethoxybenzoyl chloride in an aprotic solvent in the presence of an organic base.

25. A process according to claim 24 in which the organic base used in step (a) is triethylamine.

26. A process according to claim 24 or claim 25 in which the organic base used in step (c) is triethylamine.

27. A process according to any of claims 24 to 26 in which the hydrogenolysis is effected using palladium-on-charcoal in ethamol.

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28. A process according to any of claims 24 to 27 in which the compound used in step (a) is A.CO.Cl, the aprotic solvent used in step (a) is diethyl ether, tetrahydrofuran, benzene or toluene, and the reaction of step (a) is conducted at ambient temperature.

29. A process according to any of claims 24 to 27 in which the compound used in step (a) is A-N=C=O, the aprotic solvent used in step (a) is benzene or toluene, and the reaction of step (a) is conducted at a temperature of approximately 80°C.

30. A process according to any of claims 24 to 29 in which the aprotic solvent used in step (c) is benzene and the reaction of step (c) is conducted at ambient temperature.

31. A pharmaceutical composition comprising a piperazine derivative according to any of claims 1 to 23 in admixture with a pharmaceutically acceptable diluent or carrier.

32. A pharmaceutical composition according to claim 31 in unit dose form.

33. A pharmaceutical composition according to claim 32 for oral administration and containing from 50 to 100 mg of the piperazine derivative.

34. A pharmaceutical composition according to claim 32 for intravenous administration and containing from 5 to 100 mg of the piperazine derivative.

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