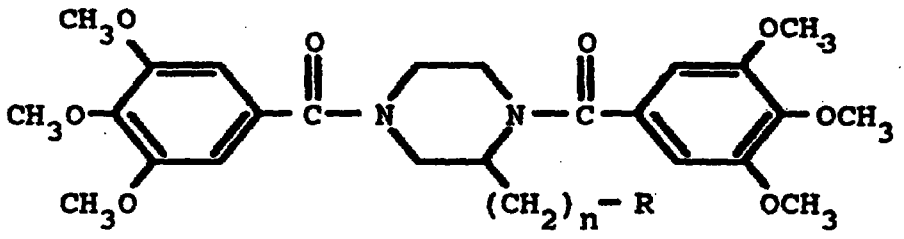
TITLE:

2-Substituted N,N-ditrimethoxybenzoyl Piperazines and Pharmaceutical Uses thereof.

DESCRIPTION

The present invention relates to piperazine derivatives of the general formula I



I

wherein

$-(CH_2)_n-$ represents a straight or branched chain alkyl group having from n = 1 to n = 20 carbon atoms,

and

R represents a hydrogen atom, a branched alkyl residue, a cycloalkyl group having from 5 to 10 carbon atoms, a phenyl group, optionally substituted by one or several chlorine atoms, methyl or methoxy groups, or straight or branched chain alkenyl groups having from 3 to 11 carbon atoms,

and to pharmaceutically acceptable salts thereof.

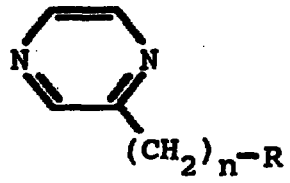
In the European patent EP 284 359 are disclosed 1,4-substituted piperazines with a 3,4,5-(trimethoxy) benzoyl group but only one of the substituents is a 3,4,5-(trimethoxy)benzoyl group, the other one being a condensed polycyclic carbonyl group.

The present invention relates to 1,2,4-substituted piperazine compounds which present a 1,4-bis-substitution by a 3,4,5-(trimethoxy)benzoyl group. This series of new piperazine derivatives is prepared in few steps and

provides greater pharmaceutical activities than the 1,4-substituted piperazines of the prior art.

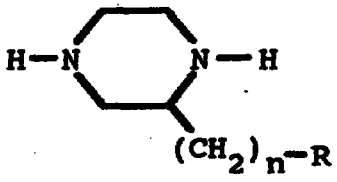
This invention also relates to a preparation process of the compounds of the general formula I, which process comprises reacting a compound of the general formula $R-(CH_2)_{n-1}-X$ wherein R and n are as above defined and X is a bromine or a chlorine atom with pyrazylmethyl sodium. Pyrazylmethyl sodium may be prepared from methylpyrazine and sodium amide in liquid ammonia. The reaction is suitably carried out in a mixture of liquid ammonia/diethyl ether at - 50°C (dry ice cooling).

The resulting substituted methylpyrazine of the general formula II



II

is then reduced either with hydrogen over a palladium (10 %) on charcoal catalyst (in ethanol) or by sodium in ethanol (the latter being preferred when R is unsaturated) leading to the substituted piperazine of the general formula III



III

which on acylation by treatment with 3,4,5-trimethoxybenzoyl chloride, preferably in benzene in the presence of triethylamine at room temperature, gives the final product of the general formula I.

The invention relates, finally, to therapeutic compositions containing at least one of the compounds I, in admixture with a carrier suitable for the selected administration route.

EXAMPLE 1

N,N'-bis-(3',4',5'-trimethoxybenzoyl)-2-n-octyl piperazine

R = H, n = 8

Step a

Preparation of n-octyl pyrazine
(Compound II in which R = H and n = 8)

To 15.6 g (0.4 mole) of sodium amide in 400 ml of anhydrous liquid ammonia cooled at - 50°C, there were added 37.6 g (0.4 mole) of methyl pyrazine. The mixture was stirred for half an hour at the same temperature.

Then, n-heptyl bromide (35.8 g, 0.2 mole), diluted with an equal volume of anhydrous diethyl ether, was added over a 20 minutes period and the mixture was stirred for an additional hour. The reaction was quenched by the addition of 25 g of solid ammonium chloride and the ammonia was replaced by diethyl ether. The mixture was heated until the diethyl ether just started to reflux, and was then poured into ice, rendered strongly acidic by the addition of concentrated HCl and extracted with diethyl ether. The aqueous layer was then rendered basic by the addition of NaOH and extracted with $CHCl_3$.

After drying over $MgSO_4$ and filtration, the evaporation of the organic phase led to a residue which was chromatographed on a silica gel column using diethyl ether/petroleum ether (15:85, v:v) as eluent.

The title compound II (33.4 g, yield 87 %) was recovered as a pale yellow liquid.

IR (film) : 3050 (aromatic C-H), 2940, 2860 (C-H), 1580, 1525 (aromatic ring) cm^{-1}.

^{1}H NMR (60 MHz, $CDCl_3$, HMDS) δ ppm : 8.5 (large s, 3H, aromatic H), 2.75 (t, 2H, CH_2-C = N), 1.7 (m, 2H, CH_2-C-C = N), 1.25 (large s, 10H, $(CH_2)_5$), 0.8 (t, 3H, CH_3).

Step b

Preparation of 2-n-octyl piperazine
(Compound III in which R = H and n = 8).

A solution of 3.4 g (20 mmoles) of the compound II, prepared in step (a) above and 50 mg Pd (10 %)/ charcoal in 100 ml ethanol was treated with H_2 under a pressure of 2.8 bars under stirring for 3 hours at room temperature. After filtration and evaporation of the ethanol, the title compound was recovered with a 100 % yield as a very hygroscopic solid.

IR (in paraffin oil) : 3240 (N-H), 2920, 2850 (C-H) cm^{-1}.

Step c

Preparation of N,N'-bis-(3',4',5'-trimethoxybenzoyl)-2-n-octyl piperazine
(Compound I in which R = H and n = 8)

A solution of 3 g (15 mmoles) of the compound III prepared in step (b) above in 30 ml of dry benzene and 1.5 ml of $(C_2H_5)_3N$ was added dropwise to a solution of 7.6 g (33 mmoles) of 3,4,5-trimethoxybenzoyl chloride in 30 ml of dry benzene. The mixture was stirred overnight at room temperature. Then, the excess of acyl chloride was decomposed by the addition of 2 ml of ethanol whilst stirring for a 1 hour at room temperature. H_2O was added and the organic layer was washed with a 5 % solution of $NaHCO_3$, then with H_2O.

After drying over $MgSO_4$ and evaporation of the solvent, a purification on a silica gel column using $CHCl_3$ then MeOH/$CHCl_3$ (0.5:99.5, v:v) gave 6.5 g (yield 74 %) of the title compound as white crystals ; m.p. : 174°C.

IR (in paraffin oil) : 2930, 2850 (C-H), 1625 (C=O), 1585 (Ar C=C) cm^{-1}.

^1H NMR (80 MHz, $CDCl_3$, HMDS) δ ppm : 6.56 (s, 4H, Ar H), 4.62-3.87 (m, 4H, CH_2NCO), 3.81 (large s, 18H, CH_3O), 3.4-2.7 (m, 3H, CH_2NCO + CHNCO), 1.73-1.4 (m, 2H, RCH_2-C-NCO), 1.16 (large s, 12H, $(CH_2)_6$) 0.8 (t, 3H, CH_3).

EXAMPLE 2

N,N'-bis-(3',4',5'-trimethoxybenzoyl) 2-(3'',3''-dimethyl) -butyl piperazine

Compound I in which R = $-C(CH_3)_3$, n = 2

Step a

Preparation of (3,3-dimethyl)-butyl pyrazine (Compound II in which R = H, n = 6 and $-(CH_2)_6H = -(CH_2)_2\ C(CH_3)_3$)

Proceeding as described in example 1 step (a) but starting with neopentyl bromide instead of the n-heptyl bromide, the title compound was recovered as a liquid.

IR (film) : 3050 (aromatic C-H), 2940, 2860 (C-H), 1580, 1525 (aromatic ring) cm^{-1}.

^1H NMR (80 MHz, $CDCl_3$, HMDS) δ ppm : 8.43 (large s, 3H, aromatic H), 2.73 (m, 2H, CH_2-C = N), 1.55 (m, 2H, CH_2-C-C = N), 0.92 (s, 3H, CH_3).

Step b

Preparation of 2-(3',3'-dimethyl)-butyl piperazine (Compound III in which R = H, n = 6 and $-(CH_2)_6H = -(CH_2)_2\ C(CH_3)_3$).

To a solution of 6.5 g (40 mmoles) of the compound II prepared in step (a) above in 200 ml of absolute ethanol, there were added in small portions and over a period of 1 hour 9.2 g (44 mmoles) of sodium and the mixture was stirred for an additional hour. The mixture was then poured into ice, extracted with $CHCl_3$, washed with water and dried over Na_2SO_4. The evaporation of the solvent led to a crude residue which was used as such in the next step.

Step c

Preparation of N,N'-bis-(3',4',5'-trimethoxybenzoyl) 2-(3'',3''-dimethyl)-butyl piperazine (Compound I in which R = H, n = 6 and $-(CH_2)_6H = -(CH_2)_2\ C(CH_3)_3$).

This step was conducted as in example 1, step (c). The title compound was recovered as a wax.

IR (film) : 2930, 2850 (C-H), 1625 (C=O), 1585 (Ar C=C) cm^{-1}.

^1H NMR (80 MHz, $CDCl_3$, HMDS) δ ppm : 6.58 (d, 4H, Ar H), 4.5-3.95 (m, 2H, CH_2NCO), 3.81 (s, 18H, CH_3O), 3.37-2.65 (m, 5H, CH_2NCO and CHNCO), 1.57 (m, 2H, CH_2-C-NCO), 1.31-1.00 (m, 2H, CH_2CMe_3), 0.82 (s, 9H, CH_3).

EXAMPLE 3

N,N'-bis-(3',4',5'-trimethoxybenzoyl) 2-methyl piperazine

R = H, n = 1

Step a and b

Commercial 2-methyl piperazine

Step c

Proceeding as described in example 1, step (c), the title compound cas recovered as a white powder ; m.p. :176-177°C.

IR (in paraffin oil) : the same as for example 1.

^{1}H NMR (80 MHz, $CDCl_3$, HMDS) δ ppm : 6.65 (d, 4H, ArH), 4.60-4.12 (m, 3H, CH_2NCO + CHNCO), 3.77 (large s, 18H, CH_3O), 3.57-2.75 (m, 4H, CH_2NCO), 1.27 (d, 3H, CH_3).

EXAMPLE 4

N,N'-bis-(3',4',5'-trimethoxybenzoyl) 2-n-pentyl piperazine

Proceeding as described in example 1 steps (a), (b), (c), but starting with n-butyl bromide instead of the n-heptyl bromide, the title compound was recovered as white crystals ; m.p. : 139-140°C.

IR (in paraffin oil) : 2925, 2850 (C-H), 1620 (C=O), 1580 (Ar C=C) cm^{-1}.

^{1}H NMR (80 MHz, $CDCl_3$, HMDS) δ ppm : 6.53 (d, 4H, Ar H), 4.48-3.92 (m, 3H, CH_2NCO + CHNCO), 3.81 (large s, 18H, CH_3O), 3.6-2.68 (m, 4H, CH_2NCO), 1.75-1.37 (m, 2H, CH_2-C-NCO), 1.12 (large s, 6H, $(CH_2)_3$), 0.77 (t, 3H, CH_3).

EXAMPLE 5

N,N'-bis-(3',4',5'-trimethoxybenzoyl) 2-n-pentadecyl piperazine

R = H, n = 15

Proceeding as described in example 1 steps (a), (b), (c), but starting with n-tetradecanyl bromide instead of the n-heptyl bromide, the title compound was recovered as a white powder ; m.p. : 68°C.

IR (in paraffin oil) : the same as the compound described in example 1.

^{1}H NMR (80 MHz, $CDCl_3$, HMDS) δ ppm : 6.56 (d, 4H, Ar H), 4.47-3.90 (m, 3H, CH_2NCO + CHNCO), 3.80 (large s, 18H, CH_3O), 3.40-2.87 (m, 4H, CH_2NCO), 1.85-1.40 (m, 2H, CH_2-C-NCO), 1.17 (large s, 26H, $(CH_2)_{13}$), 0.82 (t, 3H, CH_3).

EXAMPLE 6

N,N'-bis-(3',4',5'-trimethoxybenzoyl) 2-n-nonadecyl piperazine

R = H, n = 19

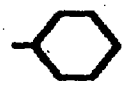
Proceeding as described in example 1, steps (a), (b), (c), but starting with n-octadecyl bromide instead of the n-heptyl bromide, the title compound was recovered as a white powder ; m.p. : 76°C.

IR (in paraffin oil) : the same as the compound described in example 1.

^{1}H NMR (80 MHz, $CDCl_3$, HMDS) δ ppm : 6.51 (d, 4H, Ar H), 4.61-4.10 (m, 3H, CH_2NCO + CHNCO), 3.85 (large s, 18H, CH_3O), 3.45-2.90 (m, 4H, CH_2NCO), 1.85-1.47 (m, 2H, CH_2-C-NCO), 1.22 (large s, 34H, $(CH_2)_{17}$), 0.83 (t, 3H, CH_3).

EXAMPLE 7

N,N'-bis-(3',4',5'-trimethoxybenzoyl)-2-n-(cyclohexylethyl) piperazine

R =  n = 2

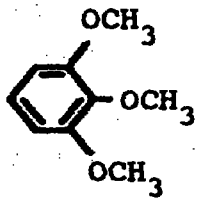
Proceeding as described in example 1, steps (a), (b) and (c), but starting with cyclohexylmethyl bromide instead of the n-heptyl bromide ; the title compound was recovered as a white powder ; m.p. : 123-125°C.

IR : the same as for example 1.

^{1}H NMR (80 MHz, $CDCl_3$, HMDS) δ ppm : 6.52 (d, 4H, ArH), 4.60-4.10 (m, 3H, CH_2NCO + CHNCO), 3.80 (large s, 18H, CH_3O), 3.50-2.77 (m, 4H, CH_2NCO), 1.84-1.40 (m, 3H, CH_2-C-NCO + CH ); 1.22 (large s, 12H, CH_2-cyclohexyl + CH_2 of the cyclohexyl).

EXAMPLE 8

N,N'-bis-(3',4',5'-trimethoxybenzoyl)-2-n-(3,4,5-(trimethoxy)phenethyl) piperazine

R =  n = 2

Proceeding as described in example 2, steps (a), (b) and (c), but starting with 3,4,5-(trimethoxy)benzyl chloride instead of the n-heptyl bromide ; the title compound was recovered as white crystals ; m.p.: 117-121°C.

IR (in paraffin oil) : 3060, 3015, 3000 (aromatic C-H), 2940, 2860 (C-H), 1630 (C=O), 1585 (Ar C=C) cm^{-1}.

^{1}H NMR (80 MHz, $CDCl_3$, HMDS) δ ppm : 6.60 (large s, 6H, ARH), 4.60-4.12 (m, 3H, CH_2NCO + CHNCO), 3.80 (large s,

27H, CH_3O), 3.50-2.40 (m, 6H, CH_2NCO + $CH_2\phi(OMe)_3$), 1.70 (m, 2H, CH_2-C-NCO).

EXAMPLE 9

N,N'-bis-(3',4',5'-trimethoxybenzoyl)-2-n-(benzyl) piperazine

R =  n = 1

Proceeding as described in example 1, steps (a), (b) and (c), but starting with phenyl bromide instead of the n-heptyl bromide ; the title compound was recovered as a white powder ; m.p. : 168-170°C.

IR : the same as for example 8.

^1H NMR : (80 MHz, $CDCl_3$, HMDS) δ ppm : 7.24 (large s, 5H, C_6H_5), 6.55 (d, 4H, trimethoxyphenyl ArH), 4.58-4.10 (m, 3H, CH_2NCO + CHNCO), 3.80 (large s, 18H, CH_3O), 3.50-2.72 (m, 6H, CH_2NCO + $CH_2\phi$).

EXAMPLE 10

N,N'-bis-(3',4',5'-trimethoxybenzoyl)-2-n-(phenethyl) piperazine

R =  n = 2

Proceeding as described in example 2, steps (a), (b) and (c), but starting with benzyl bromide instead of the n-heptyl bromide ; the title compound was recovered as a white powder ; m.p. : 153-156°C.

IR : the same as for example 8.

^{1}H NMR (80 MHz, $CDCl_3$, HMDS) δ ppm : 7.25 (large s, 5H, C_6H_5), 6.58 (d, 4H, trimethoxyphenyl ArH), 4.60-4.10 (m, 3H, CH_2NCO + CHNCO), 3.80 (large s, 18H, CH_3O), 3.50-2.70 (m, 6H, CH_2NCO + $CH_2\phi$), 2.03 (m, 2H, CH_2-C-NCO).

EXAMPLE 11

N,N'-bis-(3',4',5'-trimethoxybenzoyl)-2-n-(phenyl-n-propyl) piperazine

R =  n = 3

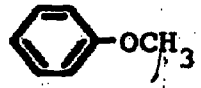
Proceeding as described in example 2, steps (a), (b) and (c), but starting with (phenethyl)bromide instead of the n-heptyl bromide ; the title compound was recovered as crystals ; m.p. : 133-135°C.

IR : the same as for example 8.

^{1}H NMR (80 MHz, $CDCl_3$, HMDS) δ ppm : 7.22 (large s, 5H, C_6H_5), 6.55 (d, 4H, trimethoxyphenyl ArH), 4.56-4.10 (m, 3H, CH_2NCO + CHNCO), 3.78 (large s, 18H, CH_3O), 3.47-2.70 (m, 6H, CH_2NCO + $CH_2\phi$), 1.80-1.45 (m, 4H, CH_2-C-NCO + CH_2-C-ϕ).

EXAMPLE 12

N,N'-bis-(3',4',5'-trimethoxybenzoyl)-2-n-(p-(methoxy) phenethyl) piperazine

R =  n = 2

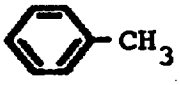
Proceeding as described in example 2, steps (a), (b) and (c), but starting with p-(methoxy)benzyl chloride instead of the n-heptyl bromide ; the title compound was recovered as crystals ; m.p. : 99-103°C.

IR : the same as for example 8.

^{1}H NMR (80 MHz, $CDCl_3$, HMDS) δ ppm : 7.09 (d, 2H, ortho mono methoxyphenyl ArH), 6.80 (d, 2H, meta monomethoxyphenyl ArH), 6.60 (d, 4H, trimethoxybenzoyl ArH), 4.60-4.08 (m, 3H, CH_2NCO + CHNCO), 3.78 (large s, 21H, CH_3O), 3.45-2.60 (m, 6H, CH_2NCO + $CH_2\phi OMe$), 1.92 (m, 2H, CH_2-C-NCO).

EXAMPLE 13

N,N'-bis-(3',4',5'-trimethoxybenzoyl)-2-n-(p-(methyl) phenylpropyl) piperazine

R =  n = 3

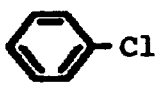
Proceeding as described in example 2, steps (a), (b) and (c), but starting with p-(methyl)phenethyl bromide instead of the n-heptyl bromide ; the title compound was recovered as white crystals ; m.p. : 83-85°C.

IR : the same as for example 8.

^{1}H NMR (80 MHz, $CDCl_3$, HMDS) δ ppm : 7.10 (s, 4H, methylphenyl ArH), 6.58 (d, 4H, trimethoxybenzoyl ArH) 4.55-4.12 (m, 3H, CH_2NCO + CHNCO), 3.80 (large s, 18H, CH_3O), 3.45-2.68 (m, 6H, CH_2NCO + $CH_2\phi Me$), 2.33 (s, 3H, $CH_3\phi$), 1.82-1.44 (m, 4H, CH_2-C-NCO + CH_2-C-ϕMe).

EXAMPLE 14

N,N'-bis-(3',4',5'-trimethoxybenzoyl)-2-n-(p-(chloro) phenethyl) piperazine

R =  n = 2

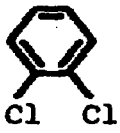
Proceeding as described in example 2, steps (a), (b) and (c), but starting with 4-chlorobenzyl chloride the title compound was recovered as crystals ; m.p. : 92-93°C.

IR : the same as for example 8.

^{1}H NMR (80 MHz, $CDCl_3$, HMDS) δ ppm : 7.38 (s, 4H, p-chlorophenyl ArH), 6.60 (d, 4H, trimethoxyphenyl ArH), 4.60-4.10 (m, 3H, CH_2NCO + CHNCO), 3.78 (large s, 18H, CH_3O), 3.52-2.65 (m, 6H, CH_2NCO + $CH_2\phi Cl$), 2.0 (m, 2H, CH_2-C-NCO).

EXAMPLE 15

N,N'-bis-(3',4',5'-trimethoxybenzoyl)-2-n-(2,3-(dichloro) phenethyl) piperazine

R = 

n = 2

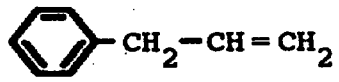
Proceeding as described in example 2, steps (a), (b) and (c), but starting with 2,3-(dichloro)benzyl bromide instead of the n-heptyl bromide ; the title compound was recovered as crystals ; m.p. : 108- 110°C.

IR (in paraffin oil) : the same as for example 8.

^{1}H NMR (80 MHz, $CDCl_3$, HMDS) δ ppm : 7.38 (m, 3H, C_6H_3), 6.60 (d, 4H, trimethoxyphenyl ArH), 4.55-4.12 (m, 3H, CH_2NCO + CHNCO), 3.82 (large s, 18H, CH_3O), 3.55-2.65 (m, 6H, CH_2NCO + $CH_2\phi Cl_2$), 2.03 (m, 2H, CH_2-C-NCO).

EXAMPLE 16

N,N'-bis-(3',4',5'-trimethoxybenzoyl)-2-n-(p-(allyl) phenethyl) piperazine

R =  n = 2

Proceeding as described in example 1, steps (a), (b) and (c), but starting with p-(allyl)benzyl bromide instead of the n-heptyl bromide ; the title compound was recovered as a white powder ; m.p. : 111-114°C.

IR (in paraffin oil) : 3080 (=C-H), 3060, 3030, 3000 (Ar C-H), 1640 (C=O and C=C), 1585 (Ar C=C) cm^{-1}.

^1H NMR (80 MHz, $CDCl_3$, HMDS) δ ppm : 7.12 (s, 4H, C_6H_4), 6.58 (d, 4H, trimethoxyphenyl Ar H), 5.94 (m, 1H, CH=), 5.05 (m, 2H, $=CH_2$), 4.50-4.10 (m, 3H, CH_2NCO + CHNCO), 3.81 (large s, 18H, CH_3O), 3.50-2.63 (m, 8H, CH_2NCO + $CH_2\phi CH_2$), 2.0 (m, 2H, CH_2-C-NCO).

TOXICOLOGY

The compounds of the invention have been administered to mice for determination of acute LD_{50}. For all the compounds tested, LD_{50} was over 600 mg/kg.

PHARMACOLOGY

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

1.- Inhibition of the platelets aggregation on New Zealand Rabbits

The derivatives of the present invention revealed an interesting PAF-antagonist activity with respect to platelet aggregation induced by 2.5 nm of PAF on platelet rich plasma (PRP) according to Born method.

This activity was evidenced by binding studies on a rabbit platelet homogenate. In this preparation indeed, those derivatives inhibit the specific bond of $^{3}[H]$-PAF, whereas they are without significant effect on the binding of the appropriate ligands on tissue homogenates rich in benzodiazepinic (central and peripheral), histaminergic (H_1 and H_2) and adrenergic (α_1, α_2, β_2, β_3) receptors, to angiotensine II or to ANF. Their affinity is therefore characteristic of PAF receptors.

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 centrifugated 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 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".

Results are reported in the following table.

EXAMPLE	AGGREGATION IC50 (Mol)	BINDING IC50 (Mol)
1	$1.2\ 10^{-7}$	$6.2\ 10^{-8}$
2	$7.1\ 10^{-7}$	$2.5\ 10^{-7}$
3	$5.6\ 10^{-7}$	$6.7\ 10^{-7}$
4	$1.9\ 10^{-7}$	$3.2\ 10^{-8}$
5	$5.8\ 10^{-6}$	$6.3\ 10^{-6}$
6	$2.4\ 10^{-6}$	$4.7\ 10^{-6}$
7	$4.3\ 10^{-7}$	$7.4\ 10^{-7}$
8	$7.1\ 10^{-8}$	$3.8\ 10^{-8}$
9	$4.1\ 10^{-7}$	$7.3\ 10^{-7}$
10	$5.4\ 10^{-6}$	$4.1\ 10^{-6}$
11	$1.1\ 10^{-8}$	$3.1\ 10^{-8}$
12	$6.2\ 10^{-8}$	$6.0\ 10^{-8}$
13	$3.5\ 10^{-7}$	$1.4\ 10^{-7}$
14	$1.7\ 10^{-7}$	$4.5\ 10^{-7}$
15	$3.7\ 10^{-7}$	$6.8\ 10^{-7}$
16	$2.9\ 10^{-7}$	$5.3\ 10^{-7}$

2.- Passive cutaneous anaphilaxy (rats)

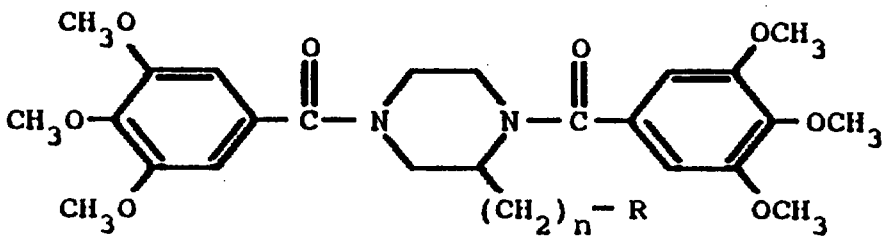
The derivatives according to the invention, when administered at 6.5 and 12.5 mg/kg, by IP route, in rats significantly dose-effect antagonized the passive cutaneous anaphylaxy reaction (local sensibilization induced by injection of homologous immunserum rich in IgE, then immediate hypersensitivity reaction by systemic injection of the antigen). This protective activity was recovered after oral administration of 25 mg/kg of any of the compounds of the invention (protection varying between 39 and 83 % according to the compound).

3.- Immun bronchospasm on guinea-pigs

The compounds of the invention were also studied on the immun bronchospasm induced by antigen injection on a guinea-pig passively conditioned by injection of an heterologous immunserum containg IgE. The 25 mg/kg dose per os of any of the compounds reduces this bronchospasm to 15 to 49 % and the 5 mg/kg dose IV to 25 % to 53 % according to the compound.

CLAIMS:

1. Piperazine derivatives of the general formula I



I

wherein

$-(CH_2)_n-$ represents a straight or branched chain alkyl group having from n=1 to n=20 carbon atoms,

and

R represents a hydrogen atom, a branched alkyl residue, a cycloalkyl group having from 5 to 10 carbon atoms, a phenyl group, optionally substituted by one or several chlorine atoms, methyl or methoxy groups, or straight or branched chain alkenyl groups having from 3 to 11 carbon atoms,

and therapeutically acceptable salts thereof.

2. N,N'-bis-(3',4',5'-trimethoxybenzoyl)-2-n-octyl piperazine.

3. N,N'-bis-(3',4',5'-trimethoxybenzoyl) 2-(3'',3''--dimethyl)-butyl piperazine.

4. N,N'-bis-(3',4',5'-trimethoxybenzoyl) 2-methyl piperazine.

5. N,N'-bis-(3',4',5'-trimethoxybenzoyl) 2-n-pentyl piperazine.

6. N,N'-bis-(3',4',5'-trimethoxybenzoyl) 2-n--pentadecyl piperazine.

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7. N,N'-bis-(3',4',5'-trimethoxybenzoyl) 2-n-nonadecyl piperazine.

8. N,N'-bis-(3',4',5'-trimethoxybenzoyl)-2-n--(cyclohexylethyl) piperazine.

9. N,N'-bis-(3',4',5'-trimethoxybenzoyl)-2-n-(3,4,5--(trimethoxy)phenethyl) piperazine.

10. N,N'-bis-(3',4',5'-trimethoxybenzoyl)-2-n-(benzyl) piperazine.

11. N,N'-bis-(3',4',5'-trimethoxybenzoyl)-2-n--(phenethyl) piperazine.

12. N,N'-bis-(3',4',5'-trimethoxybenzoyl)-2-n-(phenyl--n-propyl) piperazine.

13. N,N'-bis-(3',4',5'-trimethoxybenzoyl)-2-n-(p--(methoxy) phenethyl) piperazine.

14. N,N'-bis-(3',4',5'-trimethoxybenzoyl)-2-n--(p-(methyl) phenylpropyl) piperazine.

15. N,N'-bis-(3',4',5'-trimethoxybenzoyl)-2-n--(p-(chloro) phenethyl) piperazine.

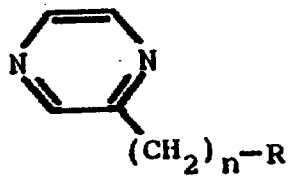
16. N,N'-bis-(3',4',5'-trimethoxybenzoyl)-2-n-(2,3--(dichloro) phenethyl) piperazine.

17. N,N'-bis-(3',4',5'-trimethoxybenzoyl)-2-n--(p-allyl) phenethyl) piperazine.

18. A process of preparing a compound according to any preceding claim comprising reacting a compound of the general formula $R-(CH_2)_{n-1}-X$ wherein R and n are as above defined and X is a bromine or chlorine atom with

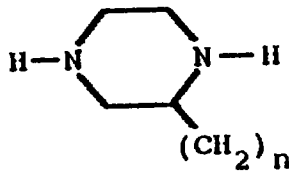
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with pyrazylmethyl sodium, reducing the resulting substituted methylpyrazine of the general formula II



II

to a substituted piperazine of the general formula III



III

and acylating the resulting substituted piperazine by treatment with 3,4,5-trimethoxybenzoyl chloride.

19. A process according to claim 18 in which the reducing is effected with hydrogen over a palladium (10%) on charcoal catalyst (in ethanol).

20. A process according to claim 18 in which the reducing is effected by sodium in ethanol.

21. A process according to any of claims 18 to 20 in which the acylating is effected in benzene in the presence of triethylamine at room temperature.

22. A process of preparing a compound according to any of claims 1 to 17 as herein described in any of the Examples.

23. A compound prepared by a process according to any of claims 18 to 22.

24. A therapeutic composition containing at least one compound according to any of claims 1 to 17 or 23 in

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admixture with a carrier suitable for the selected administration route.

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