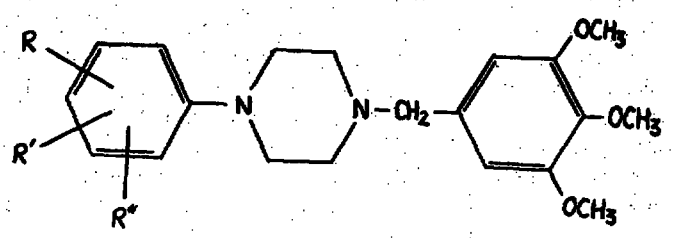
SPECIFICATION

Arylpiperazines

Cinnarizine is a known circulation stimulant. Disubstituted benzylpiperazines are reported to have adrenolytic or antihistaminic action in J. Med. Chem. *6* (5), 1963, pages 541—544. The N-substituted trialkylbenzylpiperazines disclosed in DE—SO 27 14 996, and the more complex substituted piperazines of DE—OS 25 11 022, are reported to have cardiovascular properties.

The compounds of this invention are of formula I



I

wherein R is trifluoromethyl, hydroxy, nitro, halogen, lower alkyl or lower alkoxy; R′ is hydrogen, trifluoromethyl, halogen, lower alkyl or lower alkoxy; and R″ is hydrogen or lower alkoxy; or two of R, R′ and R″ are lower alkylenedioxy. Acid addition salts of the compounds of formula I are included within the scope of this invention.

"Lower" means that the alkyl or alkoxy group has 1 to 8 carbon atoms; the group may be straight or branched. Examples of C_{1-8} alkyl are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, amyl, hexyl, heptyl and octyl.

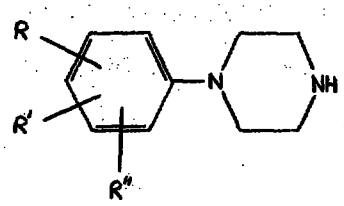
N-(trimethoxybenzyl)piperazines within the scope of the invention have been prepared and found to possess stimulating activity on mammalian circulation, in particular cerebrovascular blood supply, while being apparently free of untoward side-effects. The compounds may therefore be employed in human or veterinary medicine, as described below.

With respect to formula I, lower alkyl, lower alkoxy and lower alkylenedioxy preferably contain from 1 to 4 carbon atoms. Halogen means fluorine, chlorine, bromine or iodine, and is preferably fluorine or chlorine.

R is preferably trifluoromethyl, hydroxy, nitro, halogen, C_{1-4} alkyl or C_{1-4} alkoxy, more preferably trifluoromethyl, hydroxy, nitro, halogen (preferably fluorine or chlorine) or C_{1-4} alkoxy. R may be, for example, trifluoromethyl, hydroxy, nitro, chlorine methyl, ethyl, methoxy or ethoxy. Individual preferences for R are fluorine or chlorine, trifluoromethyl, and C_{1-8}, more preferably C_{1-4}, alkoxy.

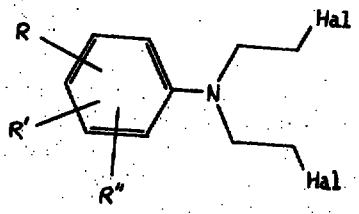
R′ is preferably hydrogen, trifluoromethyl, halogen, C_{1-4} alkyl or C_{1-4} alkoxy, and more preferably hydrogen, trifluoromethyl, chlorine, methyl or methoxy. R″ is preferably hydrogen or C_{1-4} alkoxy, and more preferably hydrogen or methoxy. When two of R, R′ and R″ are alkylenedioxy, that group is preferably methylenedioxy.

A first method for preparing a compound of formula I comprises heating a 3,4,5-trimethoxybenzyl halide with a compound of the formula



wherein R, R′ and R″ are as defined above, in a solvent. The reaction may be conducted in the presence of an acid-binding agent at from 50—180°C for from 2 to 24 hours. The halide may be the bromide or, preferably, the chloride. Equimolar amounts of the reactants, or an excess of the basic reaction component, may be used, dissolved or suspended in a solvent such as dimethylformamide. The acid-binding agent may be, for example, sodium carbonate, sodium bicarbonate or triethylamine. The reaction takes place on heating, preferably under reflux, within a few hours. Insoluble matter is removed by filtration, centrifugation or decantation, and the solvent is evaporated. The residue is recrystallized from a suitable solvent or, if an acid addition salt is desired, the crude reaction product is mixed with the respective acid, the resulting salt being recrystallised from a suitable solvent. The yields by this method range between 40 and 90% of the theoretical value.

A second method for preparing compounds of formula I comprises heating 3,4,5-trimethoxybenzylamine with a dihalide of the formula



wherein Hal is halogen and R, R' and R'' are as defined above, in a solvent. The reaction is preferably conducted at from 50—200°C for from 2 to 24 hours. The reaction is preferably conducted in the presence of an inert diluent and/or an inert gas. Hal may be, for example, bromine or, preferably, chlorine. The preferred solvent is dimethylformamide. The 3,4,5-trimethoxybenzylamine is preferably used in excess, e.g. in an amount of from 1.5 to 2.5 moles per mole of the diahalide. The use of an inert diluent, e.g. diphenyl, or a high-boiling hydrocarbon mixture and/or in inert protective gas such as nitrogen, is preferred with reaction mixtures which can be stirred only with difficultly and/or which tend to darken.

After the reaction time of, for example, 2 to 24 hours, the reaction mixture is allowed to cool and, after addition of base, e.g. NaOH, the unreacted 3,4,5-trimethoxybenzylamine and, if necessary, the diluent is distilled over. After appropriate purification, the amine may be used again. Further processing of the starting material may be carried out in the manner described for the first method. The yields are 40—95% of the theoretical value, based upon the N,N-bis (2-haloethyl)aniline employed.

The following Examples are given by way of illustration.

EXAMPLE 1

3.53 g of N-(4-fluorophenyl)-N,N-bis-(2-chloroethyl)-amine and 7 g of 3,4,5-trimethoxybenzyl amine is heated to 120°C for 8 hours under N_2 atmosphere. After cooling of the reaction mixture 50 ml of 1 N NaOH is added, and the excess 3,4,5-trimethoxybenzyl amine removed by distillation with steam.

After drying of the residue by steam, it is mixed with methanol and hydrochloric acid gas introduced in the solution. After sucking off and drying of the resulting precipitate, 3.6 g of N-(3,4,5-trimethoxy-benzyl)-N'-(4-fluorophenyl)-piperazine hydrochloride is obtained. Mp: 270°C.

Elementary analysis:	C	calculated:	60.52%	found:	60.42%
	H		6.60%		6.48%
	N		7.06%		6.96%
	Cl		8.93%		8.88%

EXAMPLE 2

8.66 g of 3,4,5-trimethoxybenzyl chloride, 7.05 g of N-(2-methylphenyl)-piperazine and 7.00 g of finely-powdered KOH is boiled for 8 hours in 50 ml of dimethyl formamide under reflux.

After sucking off insoluble matter the filtrate is evaporated to dryness, the residue is dissolved in methanol, hydrochloric acid gas is introduced into the solution and the precipitate sucked off. 8.00 g of N-(3,4,5-trimethoxybenzyl)-N'-(2-methylphenyl)-piperazine is obtained. Mp.: 89°C.

Elementary analysis:	C	calculated:	70.76%	found:	70.96%
	H		7.92%		7.88%
	N		7.86%		7.87%

The hydrochloride is obtained by redissolving the free base and further treatment with hydrogen chloride.

EXAMPLE 3

8.66 g of 3,4,5-trimethoxybenzyl chloride and 7.73 g of N-(3-methoxyphenyl)-piperazine and 7.00 g of K_2CO_3 is reacted and processed according to example 2. 8.00 g of N-(3,4,5-trimethoxy-benzyl)-N'-(3-methoxyphenyl)-piperazine hydrochloride is obtained. Mp.: 242°C.

Elementary analysis:	C	calculated:	61.68%	found: 61.30%
	H		7.15%	7.01%
	N		6.85%	6.73%
	Cl		8.67%	8.63%

EXAMPLE 4

8.3 g of 3,4,5-trimethoxybenzyl chloride and 3.8 g of N-(2-ethylphenyl)-piperazine and 3.5 g of K_2CO_3 are reacted and processed according to example 2. 6.5 g of N-(3,4,5-trimethoxy-benzyl)-N'-(2-ethylphenyl)-piperazine dihydrochloride is obtained. Mp.: 179°C.

Elementary analysis:	C	calculated:	59.65%	found: 59.45%
	H		7.28%	7.26%
	N		6.32%	6.24%
	Cl		16.00%	15.90%

EXAMPLE 5

8.3 g of 3,4,5-trimethoxybenzyl chloride and 4.1 g of N-(2-ethoxyphenyl)-piperazine and 3.5 g of K_2CO_3 are reacted and processed according to example 2. 7.2 g of N-(3,4,5-trimethoxy-benzyl)-N'-(2-ethoxyphenyl)-piperazine dihydrochloride is obtained. Mp.: 212°C.

Elementary analysis:	C	calculated:	57.52%	found: 57.34%
	H		7.02%	6.82%
	N		6.10%	6.01%
	Cl		15.43%	15.63%

EXAMPLE 6

8.3 g of 3,4,5-trimethoxybenzyl chloride and 4.15 g of N-(2-nitrophenyl)-piperazine and 3.5 g of K_2CO_3 are reacted and processed according to example 2. 5.5 g of N-(3,4,5-trimethoxy-benzyl)-N'-(2-nitrophenyl)-piperazine hydrochloride is obtained. Mp.: 248°C.

Elementary analysis:	C	calculated:	56.67%	found: 56.68%
	H		6.18%	6.20%
	N		9.91%	9.92%
	Cl		8.36%	8.53%

EXAMPLE 7

8.3 g of 3,4,5-trimethoxybenzyl chloride and 3.5 g of N-(4-hydroxyphenyl)-piperazine and 3.5 g of K_2CO_3 are reacted and processed according to example 2. 4.2 g of N-(3,4,5-trimethoxy-benzyl)-N'-(4-hydroxyphenyl)-piperazine hydrochloride is obtained. Mp.: 268°C (decomposition).

Elementary analysis:	C	calculated:	60.83%	found: 61.02%
	H		6.88%	6.75%
	N		7.09%	7.16%
	Cl		8.98%	9.14%

EXAMPLE 8

4.33 g of 3,4,5-trimethoxybenzyl chloride and 3.93 g of N-(2-chlorophenyl)-piperazine and 3.5 g of K_2CO_3 are reacted and processed according to example 2. 5.0 g of N-(3,4,5-trimethoxy-benzyl)-N'-(2-chlorophenyl)-piperazine dihydrochloride is obtained. Mp.: 225°C.

Elementary analysis:		calculated:		found:	
	C		58.12%		57.99%
	H		6.34%		6.25%
	N		6.78%		6.69%
	Cl		17.75%		17.02%

EXAMPLE 9

3.85 g of N-(2-methoxyphenyl)-piperazine, 4.33 g of 3,4,5-trimethoxybenzyl chloride and 3.5 g of K_2CO_3 are reacted and processed according to example 2. 5.0 g of N-(3,4,5-trimethoxy-benzyl)-N'-(2-methoxyphenyl)-piperazine dihydrochloride is obtained. Mp.: 219°C.

Elementary analysis:		calculated:		found:	
	C		56.63%		56.72%
	H		6.79%		6.76%
	N		6.29%		6.28%
	Cl		15.92%		15.91%

EXAMPLE 10

3.85 of N-(4-methoxyphenyl)-piperazine, 4.33 g of 3,4,5-trimethoxybenzyl chloride and 3.5 g of K_2CO_3 are reacted and processed according to example 2. 4.5 g of N-(3,4,5-trimethoxy-benzyl)-N'-(4-methoxyphenyl)-piperazine dihydrochloride is obtained. Mp.: 242°C.

Elementary analysis:		calculated:		found:	
	C		56.63%		55.60%
	H		6.79%		6.57%
	N		6.29%		6.94%
	Cl		15.92%		15.42%

EXAMPLE 11

3.53 g of N-(2-fluorophenyl)-N,N-bis-(2-chloroethyl)-amine and 7 g of 3,4,5-trimethoxybenzyl amine are reacted and processed according to example 1. 3.5 g of N-(3,4,5-trimethoxy-benzyl)-N'-(2-fluorophenyl)-piperazine hydrochloride is obtained. Mp.: 240°C.

Elementary analysis:		calculated:		found:	
	C		60.54%		60.42%
	H		6.60%		6.48%
	N		7.06%		6.96%
	Cl		8.93%		8.88%

EXAMPLE 12

8.66 g of 3,4,5-trimethoxybenzyl chloride, 7.05 g of N-(3-methylphenyl)-piperazine and 7.00 g of finely powdered KOH are reacted and processed according to example 2. 8.00 g of N-(3,4,5-trimethoxy-benzyl)-N'-(3-methylphenyl)-piperazine hydrochloride is obtained. Mp.: 215°C.

Elementary analysis:		calculated:		found:	
	C		64.19%		64.30%
	H		7.44%		7.46%
	N		7.13%		7.09%
	Cl		9.02%		8.86%

EXAMPLE 13

8.66 g of 3,4,5-trimethoxybenzyl chloride, 7.05 g of N-(4-methylphenyl)-piperazine and 7.00 g of finely powdered KOH are reacted and processed according to example 2. 8.00 g of N-(3,4,5-trimethoxy-benzyl)-N'-(4-methylphenyl)-piperazine hydrochloride is obtained. Mp.: 255°C.

Elementary analysis:	C	calculated:	64.19%	found: 64.44%
	H		7.44%	7.41%
	N		7.13%	7.14%
	Cl		9.02%	8.88%

EXAMPLE 14

50 ml of dimethyl formamide, 8.64 g of 3,4,5-trimethoxybenzyl chloride, 7.60 g of N-(3,4,5-dimethylphenyl)-piperazine and 7.00 g of K_2CO_3 are boiled for 8 hours under reflux. After sucking off insoluble matter the filtrate is evaporated to dryness and the residue is dissolved in methanol. Subsequently hydrochloric acid gas is introduced in the solution and the precipitate sucked off. After drying 10.4 g of N-(3,4,5-trimethoxy-benzyl)-N'-(3,4-dimethylphenyl)-piperazine hydrochloride. Mp.: 242°C.

Elementary analysis:	C	calculated:	64.92%	found: 64.61%
	H		7.68%	7.94%
	N		6.88%	6.70%
	Cl		8.71%	8.86%

EXAMPLE 15

3.23 g of N-(3-trifluoromethyl-4-chlorophenyl)-N,N-bis-(2-chloroethyl)-amine and 7 g of 3,4,5-trimethoxybenzyl amine are heated to 120°C under N_2 atmosphere for 8 hours. After cooling of the reaction mixture 50 ml of 1 N NaOH is added, excess 3,4,5-trimethoxybenzyl amine being removed by distillation by steam. After evaporation of the residue to dryness it is mixed with methanol, and hydrochloric acid gas is introduced in the solution. After sucking off and drying the resulting precipitate, 3.6 g of N-(3,4,5-trimethoxy-benzyl)-N'-(3-trifluoromethyl-4-chlorophenyl)-piperazine hydrochloride is obtained. Mp.: 228°C.

Elementary analysis:	C	calculated:	52.39%	found: 52.22%
	H		5.23%	5.20%
	N		5.82%	5.70%
	F		11.84%	11.84%
	Cl		7.36%	7.41%
	Cl^-		7.36%	7.26%

EXAMPLE 16

9.00 g of 3,4,5-trimethoxybenzyl chloride and 8.20 g of N-(3,4-methylenedioxyphenyl)-piperazine and 10.00 g of K_2CO_3 are reacted and processed according to example 14. 13.00 g of N-(3,4,5-trimethoxy-benzyl)-N'-(3,4-methylene dioxyphenyl)-piperazine dihydrochloride is obtained. Mp.: 235°C.

Elementary analysis:	C	calculated:	54.90%	found: 52.86%
	H		6.14%	6.22%
	N		6.09%	5.87%
	Cl		15.43%	14.70%

EXAMPLE 17

13.50 g of 3,4,5-trimethoxybenzyl chloride, 17.31 g of N-(3,4,5-trimethoxyphenyl)-piperazine and 15.00 g of K_2CO_3 are reacted and processed according to example 14. 10.00 g of N-(3,4,5-trimethoxy-benzyl)-N'-(3,4,5-trimethoxyphenyl)-piperazine hydrochloride is obtained. Mp.: 216°C.

Elementary analysis:	C	calculated:	58.90%	found:	58.73%
	H		7.09%		7.09%
	N		5.97%		5.95%
	Cl		7.56		7.46%

EXAMPLE 18

9.00 g of 3,4,5-trimethoxybenzyl chloride, 11.92 g of N-(3,5-di-trifluoromethylphenyl)-piperazine and 10.00 g of K_2CO_3 are reacted and processed according to example 14. 14.2 g of N-(3,4,5-trimethoxybenzyl)-N'-(3,5-di-trifluoromethylphenyl)-piperazine hydrochloride is obtained. Mp.: 247°C.

Elementary analysis	C	calculated:	51.31%	found:	51.15%
	H		4.89%		4.78%
	N		5.44%		5.36%
	F		22.14%		22.31%
	Cl^-		6.89%		6.88%

EXAMPLE 19

11.0 g of 3,4,5-trimethoxybenzyl chloride, 9.51 g of N-(2,6-dimethylphenyl)-piperazine and 7.00 g of K_2CO_3 are reacted and processed according to example 14. 8.6 g of N-(3,4,5-trimethoxy-benzyl)-N'-(2,6-dimethylphenyl)-piperazine hydrochloride is obtained. Mp.: 218°C.

Elementary analysis:	C	calculated	64.93%	found:	65.24%
	H		7.68%		7.84%
	N		6.88%		6.77%
	Cl		8.73%		8.12%

When isolating these and other compounds of Formula I in the form of an acid addition salt, the acid is preferably selected so as to contain an anion which is non-toxic and pharmacologically acceptable, at least in usual therapeutic doses. Representative salts which are included in this preferred group are the hydrochlorides, hydrobromides, sulphates, acetates, phosphates, nitrates, methanesulphonates, ethanesulphonates, lactates, citrates, tartrates or bitartrates, and maleates of the amine of Formula I. Other acids are likewise suitable and may be employed if desired. For example, fumaric, benzoic, ascorbic, succinic, salicyclic, bismethylenesalicyclic, propionic, gluconic, malic, malonic, mandelic, cinnamic, citraconic, stearic, palmitic, itaconic, glycolic, benzenesulphonic, and sulphamic acids may also be employed as acid addition salt-forming acids.

The circulation-enhancing activity of the substances according to the invention can be demonstrated by known methods. One of these methods is the measurement of cerebrovascular resistance on the rabbit according to H. Hutten and P. Vaupel (cf. die Medizinische Welt *28*, 1567, 1977). The therapeutic effect is expressed in terms of decrease in vascular resistance.

For this purpose 0.1 ml of a 1% solution of the test substance, i.e., according to the invention, was administered to the rabbit by arterial application. The decrease in vascular resistance (R) and the relative decrease in vascular resistance (ΔR%) were recorded and expressed in mm Hg min/l or in the valid S.I. unit k Pa min/ml, i.e., absolute decrease of resistance x time.

From Arch. Int. Pharmacodyn. Ther. *204*, 37 (1973), the use of Cinnarizine as a circulation-stimulating agent is already known. The activity of this compound was tested by means of the aforementioned method. Comparative tests have however demonstrated that the N-(trimethoxybenzyl)-piperazines according to the invention show an incomparably higher decrease in vascular resistance (ΔR-), as can be observed from the following Tables, wherein the test results in comparison with Cinnarizine are given.

In the Tables, the compounds of the above Examples are given by their Example numbers, so that, for example, N-(4-fluorophenyl)-N'-(3,4,5-trimethoxybenzyl)piperazine is 1.

TABLE 1

Compound	Absolute decrease of vascular-resistance R (mm Hg min/ml)	ΔR (%)
Cinnarizine	2.9	19.3
1	4.6	26.4
2	3.3	24.5
3	3.0	28.5
4	3.0	21.7
5	2.85	20.4
6	3.1	20.6
7	2.8	19.5
8	3.0	27.9
9	2.94	22.2
10	3.9	27.8
11	3.0	23.0
12	3.2	22.0
13	3.3	23.0
14	3.0	24.3
15	3.5	26.3
16	3.1	22.0
17	3.0	21.5
18	3.3	20.6
19	3.2	23.0

TABLE 2

Compound	ED_{50} i.v. (mg/kg)	LD_{50} i.v. (mg/kg)	LD_{50}/ED_{50}
Cinnarizine	0.6	670	1110
1	0.37	580	1570
2	0.48	700	1450
3	0.42	850	2010
4	0.40	900	2240
5	0.45	900	1990
6	0.50	650	1300
7	0.45	1260	2800
8	0.38	810	2130
9	0.42	1150	2750
10	0.30	910	3050
11	0.40	920	2280
12	0.46	700	1520
13	0.44	720	1630
14	0.02	260	13000
15	0.09	283	3150
16	0.11	297	2700
17	0.05	350	7000
18	0.05	280	5600
19	0.07	265	3800

TABLE 3

Compound	Acute Oral Toxicity (mg/kg) 24 hours	14 days
1	349.6	274.9
2	456.7	310.8
3	410.7	285.2
4	456.2	311.0
5	410.7	266.2
6	273.7	200.8
7	306.2	244.8
8	294.8	255.2
12	452.5	310.3
13	458.6	312.1
14	347.9	263.3
15	328.3	283.2
16	312.1	296.0
17	347.7	347.7
18	300.1	280.2
19	347.7	264.7

Compounds of the invention may be administered to mammals, including humans, for the enhancement or stimulation of circulation. For this purpose, the compounds may be given alone (encapsulated) or as a composition. A pharmaceutical composition according to the invention comprises a compound of the invention in association with a pharmaceutical carrier.

For administration, the novel compounds are preferably employed in the form of a pharmaceutically acceptable acid addition salt, e.g. a hydrochloride or hydrobromide. If necessary, an acid addition salt which is not pharmaceutically acceptable can be readily converted to another which is. The solution of any salt, after alkalisation, can be extracted with a suitable solvent, e.g. ether, and dried, e.g. with sodium sulphate, to give a solution of the selected free base which then can be precipitated as a pharmaceutically acceptable salt with an acid such as hydrochloric, hydrobromic, oxalic, maleic, citric, tartaric, sulphuric or methanesulphonic acid.

A novel composition may contain 0.01 to 67, preferably 0.04 to 12.15, % by weight of the novel compound. Suitable formulations are illustrated in U.S. Patent Specification No. 3,402,244. The compounds and their non-toxic salts, especially the hydrochlorides, may be advantageously employed for circulation stimulation in amounts approximating those employed for the known product Cinnarizine, a clinically-useful compound used for comparative testing as reported herein, but dosages will generally be somewhat reduced in view of the superiority of the compounds of the invention with respect to Cinnarizine. Oral or parenteral administration is preferred. Parenteral dosages are usually less than oral dosages, but the compounds and the administration are subject to wide variations in optimum daily and unit dosages, due to variations in patient body weight, condition, and ancillary factors, so that the exact dosage, both unit and daily, will of course have to be determined according to established medical principles by the physician or veterinarian in charge. In addition, the active ingredients of the present invention or compositions containing the same may either be administered together with or include other physiologically active materials and/or medicaments, such as buffering agents, antacids, sedatives, stimulants, anti-cholinergics or analgesics.

Examples of

The present invention also relates to new preparations containing the compounds according to the invention as active components. When manufacturing the preparations according to the invention the active ingredient is incorporated in a suitable carrier, e.g., a pharmaceutical carrier. Examples for suitable pharmaceutical carriers which may be used in the formulation of the preparations according to the invention are starch, gelatin, magnesium carbonate, lactose, and malt.

The present invention also relates to liquid preparations, and examples of suitable liquid carriers are ethyl alcohol, propylene glycol, glycerin, and glucose syrup.

The preparations according to the invention will be further illustrated by the following examples:

Drug capsules:

Capsules containing 25 mg, 50 mg and 100 mg of the active ingredient were produced.

Typical mixtures for encapsulation:

	25 mg per capsule
Active ingredient (from Examples)	25.0
Lactose	251.7
Starch	129.0
Magnesium stearate	4.3
total	410.0 mg

Additional capsule formulations have preferably a higher active content and are given in the following:

	100 mg per capsule
Active ingredient (from Examples)	100.0
Lactose	306.5
Starch	99.2
Magnesium stearate	4.3
total	510.0 mg

The active ingredient chosen is preferably mixed with lactose, starch and magnesium stearate, the mixture being encapsulated.

Tablets:

A typical formulation for a tablet containing 50 mg of the active ingredient per tablet is the following:

This formulation may also be used for other active contents by adjusting the weight of dicalcium phosphate:

	50 mg per tablet
Active ingredient (from Examples)	50.0
Cornstarch	13.6
Cornstarch (Paste)	3.4
Lactose	79.2
Dicalcium phosphate	68.0
Calcium stearate	0.8
total	215.0 mg

The adjuvants are intimately mixed with the active ingredient, the resulting mixture being subsequently granulated by using water as granulating agent. The still moist granules are passed through a sieve (inside width of mesh 2.36 cm) and dried. The dried granules are mixed with calcium stearate and pressed.

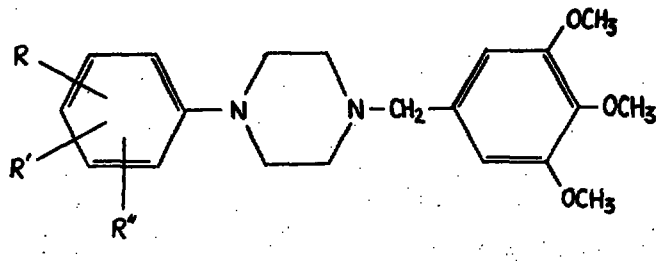
Injectable 2% Sterile Solutions:

	per cm^3
Active ingredient (from Examples)	20 mg
Preservative, e.g. chlorobutanol	0.5% weight/vol.
Water	if necessary

The solution is prepared, cleared by filtration, filled into tubes or ampoules, closed and heated in an autoclave.

CLAIMS

1. A compound of the formula



I

where R is trifluoromethyl, hydroxy, nitro, halogen, C_{1-8} alkyl or C_{1-8} alkoxy; R′ is hydrogen, trifluoromethyl, halogen, C_{1-8} alkyl or C_{1-8} alkoxy; and R″ is hydrogen or C_{1-8} alkoxy; or two of R, R′ and R″ are C_{1-8} alkylenedioxy; or an acid addition salt thereof.

2. A compound as claimed in claim 1 wherein R is trifluoromethyl, hydroxy, nitro, halogen, C_{1-4} alkyl or C_{1-4} alkoxy.

3. A compound as claimed in claim 1 wherein R is trifluoromethyl, hydroxy, nitro, halogen or C_{1-4} alkoxy.

4. A compound as claimed in claim 1 wherein R is trifluoromethyl, hydroxy, nitro, fluorine, chlorine or C_{1-4} alkoxy.

5. A compound as claimed in claim 1 wherein R is trifluoromethyl, hydroxy, nitro, chlorine, methyl, ethyl, methoxy or ethoxy.

6. A compound as claimed in claim 1 wherein R is fluorine or chlorine.

7. A compound as claimed in claim 1 wherein R is trifluoromethyl.

8. A compound as claimed in claim 1 wherein R is C_{1-8} alkoxy.

9. A compound as claimed in claim 1 wherein R is C_{1-4} alkoxy.

10. A compound as claimed in any preceding claim wherein R′ is hydrogen, trifluoromethyl, halogen, C_{1-4} alkyl or C_{1-4} alkoxy.

11. A compound as claimed in claim 10 wherein R′ is hydrogen, trifluoromethyl, chlorine, methyl or methoxy.

12. A compound as claimed in any preceding claim wherein R″ is hydrogen or C_{1-4} alkoxy.

13. A compound as claimed in claim 12 wherein R″ is hydrogen or methoxy.

14. N-(3,4,5-Trimethoxybenzyl)-N′-(4-fluorophenyl)piperazine or an acid addition salt thereof.

15. N-(3,4,5-Trimethoxybenzyl)-N′-(2-methylphenyl)piperazine or an acid addition salt thereof.

16. N-(3,4,5-Trimethoxybenzyl)-N′-(3-methoxyphenyl)piperazine or an acid addition salt thereof.

17. N-(3,4,5-Trimethoxybenzyl)-N′-(2-ethylphenyl)piperazine or an acid addition salt thereof.

18. N-(3,4,5-Trimethoxybenzyl)-N′-(2-ethoxyphenyl)piperazine or an acid addition salt thereof.

19. N-(3,4,5-Trimethoxybenzyl)-N′-(2-nitrophenyl)piperazine or an acid addition salt thereof.

20. N-(3,4,5-Trimethoxybenzyl)-N′-(4-hydroxyphenyl)piperazine or an acid addition salt thereof.

21. N-(3,4,5-Trimethoxybenzyl)-N′-(2-chlorophenyl)piperazine or an acid addition salt thereof.

22. N-(3,4,5-Trimethoxybenzyl)-N′-(2-methoxyphenyl)piperazine or an acid addition salt thereof.

23. N-(3,4,5-Trimethoxybenzyl)-N′-(4-methoxyphenyl)piperazine or an acid addition salt thereof.

24. N-(3,4,5-Trimethoxybenzyl)-N′-(2-fluorophenyl)piperazine or an acid addition salt thereof.

25. N-(3,4,5-Trimethoxybenzyl)-N′-(3-methylphenyl)piperazine or an acid addition salt thereof.

26. N-(3,4,5-Trimethoxybenzyl)-N′-(4-methylphenyl)piperazine or an acid addition salt thereof.

27. N-(3,4,5-Trimethoxybenzyl)-N′-(3,4-dimethylphenyl)piperazine or an acid addition salt thereof.

28. N-(3,4,5-Trimethoxybenzyl)-N′-(3-trifluoromethyl-4-chlorophenyl)piperazine or an acid addition salt thereof.

29. N-(3,4,5-Trimethoxybenzyl)-N′-(3,4-methylenedioxyphenyl)piperazine or an acid addition salt thereof.

30. N-(3,4,5-Trimethoxybenzyl)-N′-(3,4,5-trimethoxyphenyl)piperazine or an acid addition salt thereof.

31. N-(3,4,5-Trimethoxybenzyl)-N′-[3,5-di(trifluoromethyl)-phenyl]piperazine or an acid addition salt thereof.

32. N-(3,4,5-Trimethoxybenzyl)-N′-(2,6-dimethylphenyl)piperazine or an acid addition salt thereof.

33. A compound as claimed in any preceding claim in pharmaceutically acceptable salt form.

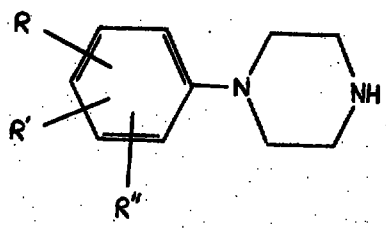
34. A compound as claimed in claim 33 as a hydrochloric acid addition salt.

35. A compound as claimed in claim 1 substantially as described in any of Examples 1 to 19.

36. A pharmaceutical composition comprising a compound as claimed in any preceding claim in association with a pharmaceutical carrier.

37. A composition according to claim 36 with reference to any of the Capsules, Tablets or Solutions described herein.

38. A method for preparing a compound as claimed in claim 1, which comprises heating a 3,4,5-trimethoxybenzyl halide with a compound of the formula

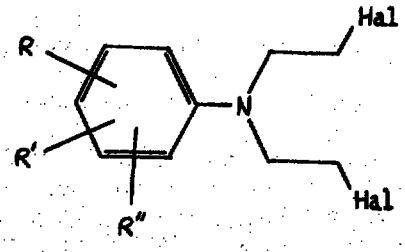


wherein R, R' and R'' are as defined in claim 1, in a solvent.

39. A method according to claim 38 which is conducted in the presence of an acid-binding agent at from 50 to 180°C for from 2 to 24 hours.

40. A method according to claim 38 or claim 39 wherein the halide is the chloride.

41. A method for preparing a compound as claimed in claim 1, which comprises heating 3,4,5-trimethoxybenzylamine with a compound of the formula



wherein Hal is halogen and R, R' and R'' are as defined in claim 1, in a solvent.

42. A method according to claim 41 is conducted at from 50 to 200°C for from 2 to 24 hours.

43. A method according to claim 41 or claim 42 which is conducted in the presence of an inert diluent and/or an inert gas.

44. A method according to any of claims 41 to 43 wherein Hal is chlorine.

45. A method according to any of claims 38 to 44 wherein the solvent is dimethylformamide.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1983. Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.