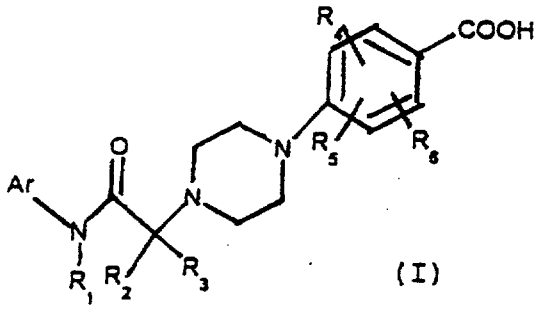
NEW 4-(1-PIPERAZINYL)BENZOIC ACID DERIVATIVES, PROCESS FOR PREPARING THEM AND THEIR THERAPEUTIC APPLICATIONS

The present invention relates to new 4-(1-piperazinyl)benzoic acid derivatives which are useful in the treatment of diabetes.

The subject of the preesent invention is thus compounds of general formula (I):



(I)

in which:

Ar is selected from

- a mono-, bi- or tricyclic aryl group having from 6 to 14 carbon atoms,

- a heteroaromatic group selected from the pyridyl, pyrimidyl, pyrrolyl, furyl, thienyl, quinolyl, indolyl, benzothienyl, benzofuryl, benzopyrranyl, benzothiopyrannyl, dibenzofuryl, carbazolyl and benzothiazinyl groups,

it being possible for the Ar group to carry 1 to 3 substituents selected from a C_1-C_8 alkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, C_1-C_8 alkoxy, (C_3-C_8)cycloalkyloxy(C_1-C_6)alkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_3-C_8)cycloalkyloxy, (C_3-C_8)cycloalkyl(C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, C_6-C_{14} aryl, C_6-C_{14} heteroaryl, (C_6-C_{14})heteroaryl(C_1-C_6)alkyl, (C_6-C_{14})aryl(C_1-C_6)alkyl, (C_6-C_{14})aryl(C_1-C_6)alkyl(C_6-C_{14})aryl, (C_6-C_{14})aryloxy, (C_6-C_{14})aryloxy(C_1-C_6)alkyl, (C_6-C_{14})aryl(C_1-C_6)alkyloxy or (C_6-C_{14})aryl(C_1-C_6)alkyloxy(C_1-C_6)alkyl group, a halogen, a trifluoromethyl, trifluoromethoxy, cyano, hydroxyl, nitro, amino, carboxyl, (C_1-C_6)alkoxycarbonyl, carbamoyl, (C_1-C_8)alkylthio, (C_1-C_8)alkylsulphinyl, (C_1-C_8)alkylsulphonyl, sulphoamino, (C_1-C_8)alkylsulphonylamino, sulphamoyl or (C_1-C_8)alkylcarbonylamino group, or two of these substituents forming a methylenedioxy group.

R_1, R_2 and R_3 are selected, independently of each

other, from:

- a hydrogen atom,
- a C_1-C_8 alkyl or (C_1-C_6)alkoxy(C_1-C_6)alkyl group,
- a cycloalkyl group containing from 3 to 8 carbon atoms, a (C_3-C_8)cycloalkyl(C_1-C_6)alkyl group, a (C_3-C_8)cycloalkyloxy(C_1-C_6)alkyl or (C_3-C_8)cycloalkyl(C_1-C_6)-alkoxy(C_1-C_6)alkyl group,
- a C_6-C_{14} aryl, C_6-C_{14} heteroaryl, (C_6-C_{14})heteroaryl(C_1-C_6)alkyl, (C_6-C_{14})aryl(C_1-C_6)alkyl, (C_6-C_{14})aryl(C_1-C_6)alkyl(C_6-C_{14})aryl, (C_6-C_{14})aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl or (C_6-C_{14})aryloxy(C_1-C_6)alkyl group,

or alternatively R_1 forms with the nitrogen atom to which R_1 is attached and the Ar group a ring selected from indolinyl, quinolyl, indolyl and tetrahydroquinolyl,

R_4, R_5, R_6 are selected, independently of each other, from:

- a hydrogen atom,
- a C_1-C_8 alkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, C_1-C_8 alkoxy, (C_3-C_8)cycloalkyloxy(C_1-C_6)alkyl, (C_3-C_8)cycloalkyloxy, (C_3-C_8)cycloalkyl(C_1-C_6)alkoxy, (C_3-C_8)cycloalkyl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C_1-C_6)alkyl, C_6-C_{14} aryl, (C_6-C_{14})aryl(C_1-C_6)alkyl, (C_6-C_{14})aryl(C_1-C_6)alkyl(C_6-C_{14})aryl, (C_6-C_{14})aryloxy, (C_6-C_{14})aryloxy(C_1-C_6)alkyl, (C_1-C_{14})aryl(C_1-C_6)alkoxy or (C_6-C_{14})aryl(C_1-C_6)alkyloxy(C_1-C_6)alkyl group, a halogen, a trifluoromethyl, trifluoromethoxy, cyano, carboxyl, hydroxyl, nitro, amino, (C_1-C_6)alkoxycarbonyl, carbamoyl, (C_1-C_8)alkylthio, (C_1-C_8)alkylsulphinyl, (C_1-C_8)alkylsulphonyl, sulphoamino, (C_1-C_8)alkylsulphonylamino, sulphamoyl or (C_1-C_8)alkylcarbonylamino group, it being possible for two of these groups to form a methylenedioxy group,

it being possible for the various aryl groups themselves to be substituted with 1 to 3 substituents selected from a C_1-C_8 alkyl or C_1-C_8 alkoxy group, a halogen, a trifluoromethyl, trifluoromethoxy, hydroxyl, nitro and amino group,

their solvates and their pharmaceutically acceptable salts.

As an example of an aryl group, there may be

mentioned the phenyl, α-naphthyl, β-naphthyl and fluorenyl groups.

The C_1-C_8 alkyl groups may be linear or branched. As examples, there may be mentioned the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl and pentyl groups.

The C_1-C_8 alkoxy groups may likewise be linear or branched. As examples, there may be mentioned the methoxy, ethoxy, propoxy, isopropoxy, butoxy and isobutoxy groups.

The halogens may be selected from fluorine, chlorine, bromine and iodine.

The invention also relates to the tautomeric, enantiomeric, diastereoisomeric and epimeric forms of the compounds of general formula (I).

The compounds of general formula (I) have a carboxylic acid functional group and may be salified, they then being in the form of salts with bases.

Examples of salts with bases of the compounds of general formula (I) include the pharmaceutically acceptable salts such as the sodium salts, potassium salts, calcium salts and other salts of the same type.

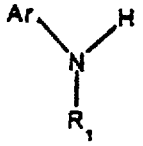
The compounds of general formula (I) can also be salified with amines in order to form pharmaceutically acceptable salts. By way of example, it will be possible for the compounds of general formula (I) to be salified with glucamine, N-methylglucamine, N,N-dimethylglucamine, ethanolamine, morpholine, N-methylmorpholine or lysine.

The compounds of general formula (I) possess basic nitrogen atoms and can be monosalified or disalified with inorganic or organic acids. Examples of salts with acids of the compounds of general formula (I) include the pharmaceutically acceptable salts such as, and non-exhaustively, hydrochloride, hydrobromide, sulphate, succinate, maleate, fumarate, malate, tartrate and sulphonates such as methanesulphonate, benzenesulphonate and toluenesulphonate.

Among the compounds of general formula (I) according to the invention, there may be mentioned more

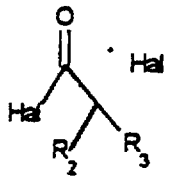
particularly, as preferred compound, 4-{4-[2(N-isopropyl-N-phenylamino)-2-oxoethyl]-1-piperazinyl}benzoic acid, 4-{4-[2-(N-[2,6-dimethylphenyl]amino)-2-oxoethyl]-1-piperazinyl}benzoic acid and 4-{4-[2-(N-[2,6-diisopropyl-phenyl]amino)-2-oxoethyl]-1-piperazinyl}benzoic acid.

The invention also relates to a process for the preparation of the compounds of general formula (I). A process of preparation according to the invention comprises reacting an aromatic amine of general formula (II):



(II)

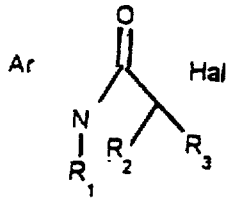
in which Ar and R_1 are as defined above,
with a haloacyl halide of general formula (III):



(III)

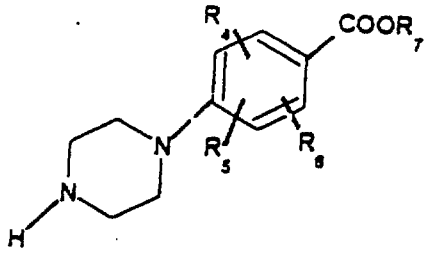
in which Hal represents a chlorine or bromine atom,

R_2 and R_3 are as defined above,
in order to form a compound of general formula (IV):



(IV)

in which Ar, R_1, R_2, R_3 and Hal are as defined above, and reacting the compound of general formula (IV) with a compound of general formula (V):

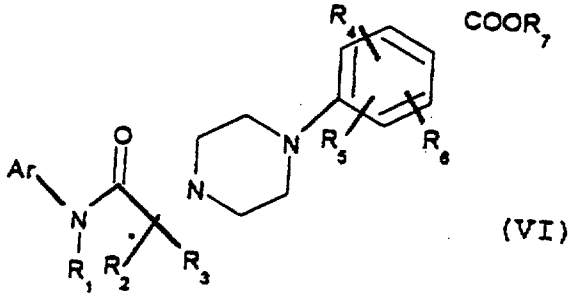


(V)

i n

which R_4, R_5 and R_6 are as defined above and R_7 is a hydrogen atom or a C_1-C_6 alkyl group,

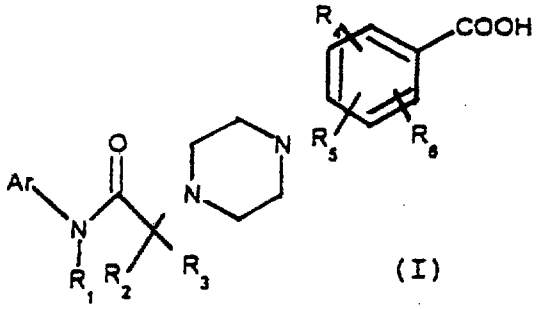
in the presence of a basic agent such as triethylamine in order to form the compound of general formula (VI):



(VI)

in which Ar, R_1, R_2, R_3, R_4, R_5, R_6 and R_7 are as defined above.

In the case where R_7 is an alkyl group, the compound of general formula (VI) can be hydrolyzed by conventional acidic or basic means in order to give the compound of general formula (I):



(I)

in which Ar, R_1, R_2, R_3, R_4, R_5 and R_6 are as defined above.

The compounds of formula (V) are known compounds. They can be synthesized according to the procedure described by V. Prelog and Z. Blazek in Collection Czechloslov. Chem. Communications 6, 211-24 (1934) for

ethyl 4-(1-piperazinyl)benzote.

By way of example, the compound (VI), in which R_7 is an alkyl group, can be hydrolyzed in the presence of a basic agent such as dilute sodium hydroxide.

The enantiomers of the compounds of formula (I) can be separated by successive recrystallization of the salt of the acid (I) with an optically active base from solvents such as acetone, ethyl acetate or isopropanol, followed by displacement from the salt into an optically active acid by an inorganic or organic acid, according to a conventional method.

The compounds according to the present invention can be used in the treatment of diabetes, in particular of non-insulin-dependent diabetes because of their hypoglycaemic effect and of their lack of toxicity at the active doses.

The subject of the present invention is therefore also pharmaceutical compositions comprising, as active ingredient, a compound according to the invention.

The pharmaceutical compositions according to the invention can be provided in forms intended for administration by the parenteral, oral, rectal, permucosal or percutaneous route.

They can therefore be provided in the form of injectable solutions or suspensions or in multidose vials, in the form of plain or coated tablets, sugar-coated tablets, capsules, gelatin capsules, pills, cachets, powders, suppositories or rectal capsules, of solutions or suspensions, for percutaneous use in a polar solvent, for permucosal use.

The excipients which are suitable for such administrations are cellulose derivatives or microcrystalline cellulose, alkaline-earth metal carbonates, magnesium phosphate, starches, modified starches, and lactose for the solid forms.

For rectal use, cocoa butter or polyethylene glycol stearates are the preferred excipients.

For parenteral use, water, aqueous solutions, physiological saline or isotonic solutions are the

vehicles most conveniently used.

The dosage may vary within wide limits depending on the therapeutic indication and the route of administration, as well as the age and weight of the subject.

The following examples illustrate the preparation of the compounds of formula I.

EXAMPLE 1

Preparation of 4-{4-[2-(4-chlorophenylamino)-2-oxoethyl]-1-piperazinyl}benzoic acid (Compound No. 5).

A - Preparation of 2-chloro-N-(4-chlorophenyl)-acetamide

34.5 ml of chloroacetyl chloride are added dropwise to 50 g of 4-chloroaniline and 108 g of potassium carbonate in 400 ml of chloroform.

The reaction medium is then filtered and the solid obtained is taken up in 1500 ml of water. After stirring for 1 h, the solid in suspension is filtered and thoroughly washed with water.

70.5 g of 2-chloro-N-(4-chlorophenyl)acetamide are thus obtained in the form of a white solid whose melting point is 169-170°C.

IR (KBr): 1669 cm^{-1} (C = O amide)

^1H NMR: (DMSO-d_6, 200 MHz) δ ppm 4.25 (2H, s, CH_2), 7.30 (2H, d, phenyl protons), 7.60 (2H, d, phenyl protons), 10.40 (1H, s, NH).

B - Preparation of the ethyl ester of 4-{4-[2-(4-chlorophenylamino)-2-oxoethyl]-1-piperazinyl}benzoic acid

25 g of 2-chloro-N-(4-chlorophenyl)acetamide, 35.2 g of ethyl 4-(1-piperazinyl)benzoate and 80 g of potassium carbonate in 300 ml of DMF are reacted overnight at room temperature, with stirring.

The reaction medium is filtered in order to separate the insoluble matter and the filtrate thus obtained is poured over 1000 ml of water. A solid crystallizes. This solid is filtered and washed with water in order to give 39 g of the ethyl ester of 4-{4-[2chlorophenylamino)-2-oxoethyl]-1-piperazinyl}benzoic acid in the form of a solid whose melting point is 172-174°C.

IR (KBr): 1686 cm^{-1} (C = O ester)

^1H NMR: (DMSO-d_6, 200 MHz) δ ppm 1.20 (3H, t, CH_3), 2.50 (4H, s, $2CH_2$), 3.05 (2H, s, CH_2), 3.20 δ 54H, s, $2CH_2$), 4.05 (2H, q, CH_2), 6.80 (2H, d, phenyl protons), 7.20 (2H, d, phenyl protons), 7.60 (4H, m, phenyl protons), 9.80 (1H, s, NH).

C - <u>Preparation of 4-{4-[2-(4-chlorophenylamino)-2-oxoethyl]-1-piperazinyl}benzoic acid</u>

20 g of the ethyl ester of 4-{4-[2-(4-chlorophenylamino)-2-oxoethyl]-1-piperazinyl}benzoic acid, 165 ml of a 1 N aqueous sodium hydroxide solution and 150 ml of ethanol are heated under reflux, with stirring, for 1 h.

The mixture is acidified with concentrated hydrochloric acid to pH 5. A solid crystallizes. This solid is filtered and washed with ethanol in order to give 16.4 g of the desired crude product. Recrystallization, in a DMF/acetonitrile (1/1) mixture, gives 13.6 g of 4-{4-[2-(4-chlorophenylamino)-2-oxoethyl]-1-piperazinyl}benzoic acid in the form of a white solid which melts at 263-265°C.

IR (KBr): 1676 cm^{-1} (C = O acid)

^1H NMR: (DMSO-d_6, 200 MHz) δ ppm 2.7 (4H, s, $2CH_2$), 3.20 (2H, s, CH_2) 3.40 (4H, s, $2CH_2$) 7.0 (2H, d, phenyl protons), 7.40 (2H, d, phenyl protons) 7.75 (4H, m, phenyl protons), 9.90 (1H, s, NH), 12.40 (1H, broad s, acidic OH).

The formulae and characteristics of the compounds according to the invention are assembled in Table 1 below.

TABLE 1

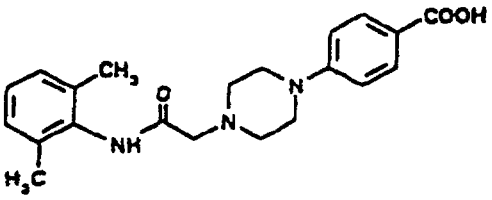
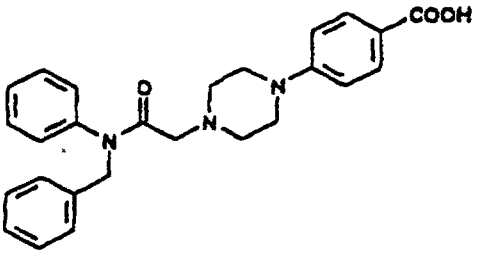
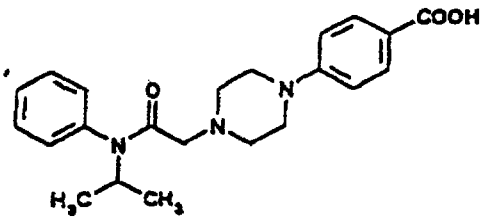
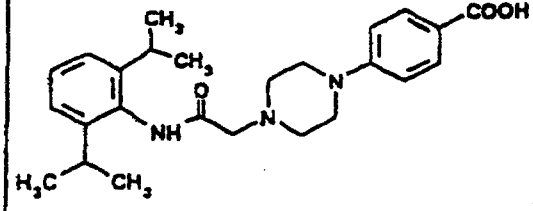
Compound No.	Structure	m.p. in °C (Köfler)	^{1}H NMR (200 MHz) δ ppm
1		199-201	DMSO-d6 2.16(s,6H) 2.75(s,4H) 3.22(s,2H) 3.46(s,4H) 7.0+7.1(d+s,5H) 7.83(d,2H) 9.32(s,1H) 12.38(s,1H)
2		188-190	DMSO-d6 2.50(s,4H) 3.05(s,2H) 3.25(s,4H) 4.87(s,2H) 6.90(d,2H) 7.26(m,10H) 7.77(d,2H) 12.32(s,1H)
3		229-231	DMSO-d6 1.0(d,6H) 2.40(s,4H) 2.75(s,2H) 3.25(s,4H) 4.82(m,1H) 6.90(d,2H) 7.25(d,2H) 7.50(s,3H) 7.80(d,2H) 12.35(s,1H)
4		239-241	DMSO-d6 1.1(d,12H) 2.7(s,4H) 3.05(m,2H) 3.25(s,2H) 3.40(s,4H) 6.95(d,2H) 7.2(m,3H) 7.5(d,2H) 9.3(s,1H) 12.4(s,1H)

TABLE 1 (continuation)

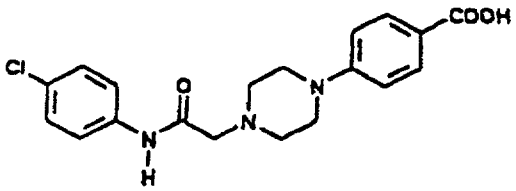
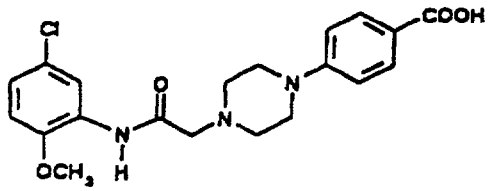
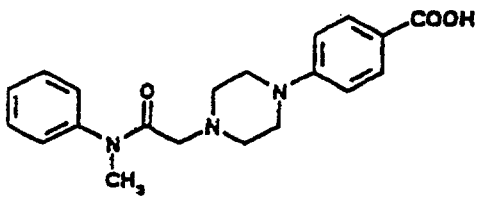
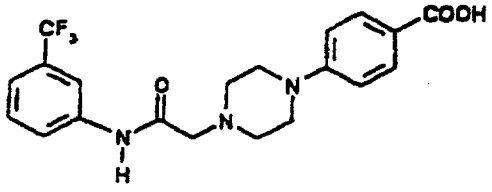
Compound No.	Structure	m.p. in °C (Köfler)	^{1}H NMR (200 MHz) δ ppm
5		263-265	DMSO-d6 2.70(s,4H) 3.20(s,2H) 3.40(s,4H) 7.00(d,2H) 7.40(d,2H) 7.75(m,4H) 9.90(s,1H) 12.4(s,1H)
6		>265	CF3COOD 3.65(s,3H) 4.20(s,8H) 4.55(s,2H) 6.80(d,1H) 7(d,1H) 7.60(d,3H) 8.25(d,2H)
7		206-207	CF3COOD 3.20(s,3H) 3.95(m,10H) 6.90(s,2H) 7.20(s,3H) 7.50(d,2H) 8.10(d,2H)
8		259-261	CF3COOD 4.15(s,8H) 4.45(s,2H) 7.32(s,3H) 7.50(m,3H) 8.10(d,2H)

TABLE 1 (continuation)

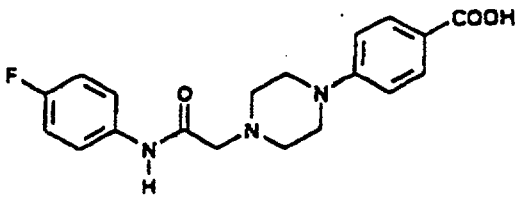
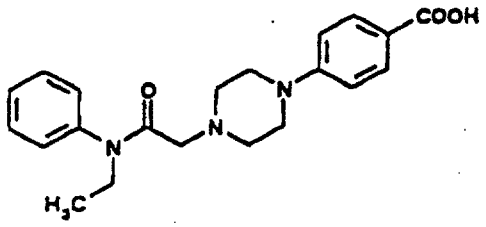
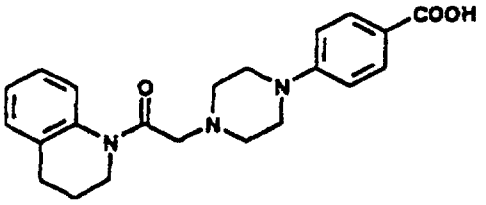
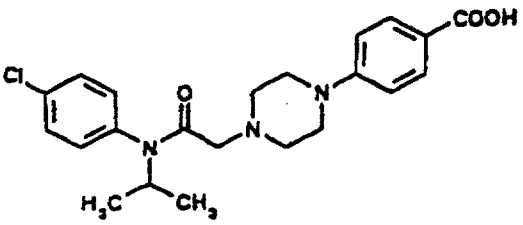
Compound No.	Structure	m.p. in °C (Köfler)	^{1}H NMR (200 MHz) δ ppm
9		263-265	CF3COOD 4.25(s,8H) 4.55(s,2H) 7.00(s,2H) 7.25(s,2H) 7.70(d,2H) 8.30(d,2H)
10		201-203	CF3COOD 1.12(t,3H) 3.75(q,2H) 4.38(m,10H) 7.13(d,2H) 7.46(s,3H) 7.87(d,2H) 8.28(d,2H)
11		226-228	CF3COOD 1.94(s,2H) 2.64(s,2H) 4.19(m,12H) 7.12(m,4H) 7.70(d,2H) 8.28(s,2H)
12		252-254	CF3COOD 1.11(s,6H) 4.03+4.20(s+s,8H) 4.49(s,2H) 4.86(s,1H) 7.13(s,2H) 7.48(s,2H) 7.74(s,2H) 8.34(s,2H)

TABLE 1 (continuation)

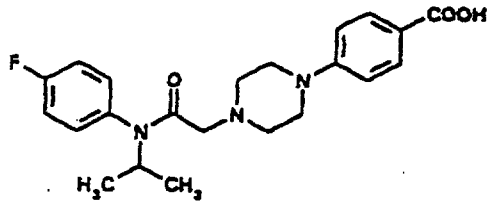
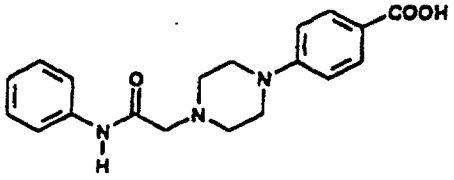
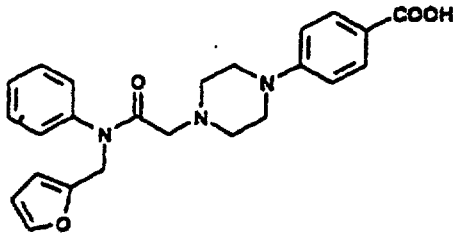
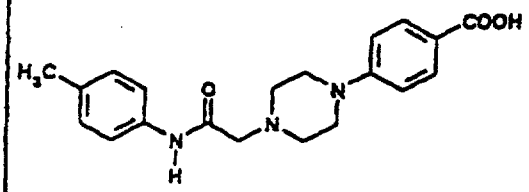
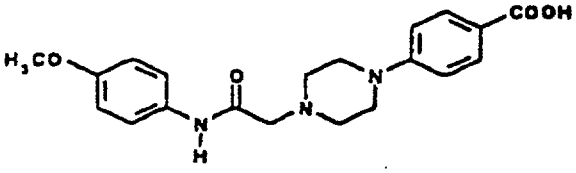
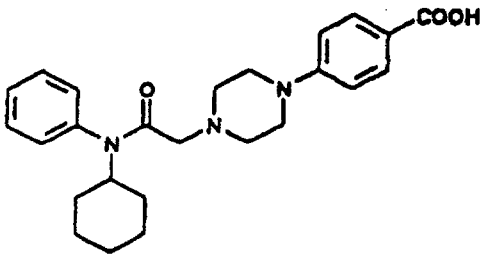
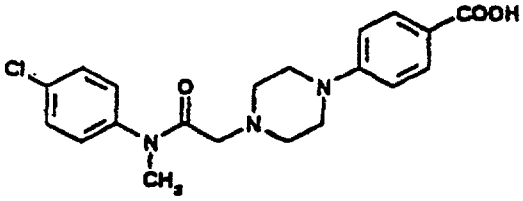
Compound No.	Structure	m.p. in °C (Köfler)	^{1}H NMR (200 MHz) δ ppm
13		233-235	CF3COOD 1.05(s,6H) 3.80+4.30(s+s,10H) 4.75(s,1H) 7.05(s,4H) 7.60(s,2H) 8.26(s,2H)
14		257-259	CF3COOD 4.25(s,8H) 4.6(s,2H) 7.25(s+m,5H) 7.69(d,2H) 8.29(d,2H)
15		163-165	CF3COOD 2.28(s,4H) 2.72(s,2H) 2.97(s,4H) 4.62(s,2H) 5.94(s,1H) 6.10(s,1H) 6.70(d,2H) 6.95(d,2H) 7.13(d,3H) 7.33(s,1H) 7.55(d,2H) 12.10(s,1H)
16		259-261	CF3COOD 2.29(s,3H) 4.34(s,8H) 4.60(s,2H) 7.18(s+m,4H) 7.77(d,2H) 8.38(d,2H)

TABLE 1 (continuation)

Compound No.	Structure	m.p. in °C (Köfler)	^{1}H NMR (200 MHz) δ ppm
17		245-247	CF3COOD 3.88(s,3H) 4.29(s,8H) 4.57(s,2H) 6.98(d,2H) 7.28(d,2H) 7.73(d,2H) 8.33(d,2H)
18		208-210	CF3COOD 1.18(m,6H) 1.78(t,4H) 3.97(s,4H) 4.17(d,4H) 4.45(d,3H) 7.08(m,2H) 7.47(d,3H) 7.70(d,2H) 8.30(d,2H)
19		217-219	CF3COOD 3.46(s,3H) 4.27(m+s,10H) 7.26(d,2H) 7.56(d,2H) 7.82(d,2H) 8.43(d,2H)

Results of pharmacological studies will be given below.

Study of the antidiabetic activity in NOSTZ rats

The antidiabetic activity of the compounds of formula I is determined by the oral route on an experimental model of non-insulin-dependent diabetes, induced in rats by streptozotocin.

The non-insulin-dependent diabetes model is obtained in rats by neonatal injection (on the day of birth) of streptozotozin.

The diabetic rats used are 8 weeks old. The animals are housed, from the day they are born to the day of the experiment, in an animal house at a regulated temperature of 21 to 22°C, and it is subjected to a fixed light (from 7 a.m. to 7 p.m.) and dark (from 7 p.m. to 7 a.m.) cycle. Their food consisted of a maintenance diet, water and food were provided "ad libitum", with the exception of the 2 hours fasting preceding the tests during which food is withdrawn (postabsorptive state).

The rats are treated by the oral route during the day with the test product. Two hours after the last administration of the product and 30 minutes after anaesthetizing the animals with sodium pentobarbital (Nembutal®), a 300 μl blood sample is collected at the end of the tail.

Table II assembles the principal results obtained. These results show the efficacy of the compounds of formula I in causing a decrease in glycaemia in the diabetic animals.

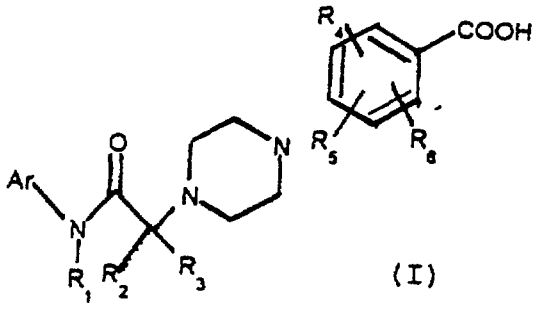
These results are expressed as a percentage variation in the glycaemia at D4 (4 days of treatment) compared with D0 (before treatment).

TABLE 2

Compound	20 mg/kg/d	20 mg/kg/d
	% Glycaemia at D4	% Glycaemia at D4
1	-6	-16
2	-2	-10
3	-13	-22
4	-8	-16
5	-9	-12

CLAIMS

1. Compounds of general formula (I):



(I)

in which:

Ar is selected from

- a mono-, bi- or tricyclic aryl group having from 6 to 14 carbon atoms,

- a heteroaromatic group selected from the pyridyl, pyrimidyl, pyrrolyl, furyl, thienyl, quinolyl, indolyl, benzothienyl, benzofuryl, benzopyrranyl, benzothiopyrannyl, dibenzofuryl, carbazolyl and benzothiazinyl groups,

it being possible for the Ar group to carry 1 to 3 substituents selected from a C_1-C_8 alkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, C_1-C_8 alkoxy, (C_3-C_8)cycloalkyloxy(C_1-C_6)alkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_3-C_8)cycloalkyloxy, (C_3-C_8)cycloalkyl(C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, C_6-C_{14} aryl, C_6-C_{14} heteroaryl, (C_6-C_{14})heteroaryl(C_1-C_6)alkyl, (C_6-C_{14})aryl(C_1-C_6)alkyl, (C_6-C_{14})aryl(C_1-C_6)alkyl(C_6-C_{14})aryl, (C_6-C_{14})aryloxy, (C_6-C_{14})aryloxy(C_1-C_6)alkyl, (C_6-C_{14})aryl(C_1-C_6)alkyloxy or (C_6-C_{14})aryl(C_1-C_6)alkyloxy(C_1-C_6)alkyl group, a halogen, a trifluoromethyl, trifluoromethoxy, cyano, hydroxyl, nitro, amino, carboxyl, (C_1-C_6)alkoxycarbonyl, carbamoyl, (C_1-C_8)alkylthio, (C_1-C_8)alkylsulphinyl, (C_1-C_8)alkylsulphonyl, sulphoamino, (C_1-C_8)alkylsulphonylamino, sulphamoyl or (C_1-C_8)alkylcarbonylamino group, or two of these substituents forming a methylenedioxy group.

R_1, R_2 and R_3 are selected, independently of each other, from:

- a hydrogen atom,

- a C_1-C_8 alkyl or (C_1-C_6)alkoxy(C_1-C_6)alkyl group,

* C L M S *

- a cycloalkyl group containing from 3 to 8 carbon atoms, a (C_3-C_8)cycloalkyl(C_1-C_6)alkyl group, a (C_3-C_8)cycloalkyloxy(C_1-C_6)alkyl or (C_3-C_8)cycloalkyl(C_1-C_6)-alkoxy(C_1-C_6)alkyl group,

- a C_6-C_{14} aryl, C_6-C_{14} heteroaryl, (C_6-C_{14})heteroaryl(C_1-C_6)alkyl, (C_6-C_{14})aryl(C_1-C_6)alkyl, (C_6-C_{14})aryl(C_1-C_6)alkyl(C_6-C_{14})aryl, (C_6-C_{14})aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl or (C_6-C_{14})aryloxy(C_1-C_6)alkyl group,

or alternatively R_1 forms with the nitrogen atom to which R_1 is attached and the Ar group a ring selected from indolinyl, quinolyl, indolyl and tetrahydroquinolyl,

R_4, R_5, R_6 are selected, independently of each other, from:

- a hydrogen atom,

- a C_1-C_8 alkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, C_1-C_8 alkoxy, (C_3-C_8)cycloalkyloxy(C_1-C_6)alkyl, (C_3-C_8)cycloalkyloxy, (C_3-C_8)cycloalkyl(C_1-C_6)alkoxy, (C_3-C_8)cycloalkyl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C_1-C_6)alkyl, C_6-C_{14} aryl, (C_6-C_{14})aryl(C_1-C_6)alkyl, (C_6-C_{14})aryl(C_1-C_6)alkyl(C_6-C_{14})aryl, (C_6-C_{14})aryloxy, (C_6-C_{14})aryloxy(C_1-C_6)alkyl, (C_1-C_{14})aryl(C_1-C_6)alkoxy or (C_6-C_{14})aryl(C_1-C_6)alkyloxy(C_1-C_6)alkyl group, a halogen, a trifluoromethyl, trifluoromethoxy, cyano, carboxyl, hydroxyl, nitro, amino, (C_1-C_6)alkoxycarbonyl, carbamoyl, (C_1-C_8)alkylthio, (C_1-C_8)alkylsulphinyl, (C_1-C_8)alkylsulphonyl, sulphoamino, (C_1-C_8)alkylsulphonylamino, sulphamoyl or (C_1-C_8)alkylcarbonylamino group, it being possible for two of these groups to form a methylenedioxy group,

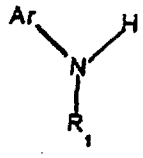
it being possible for the various aryl groups themselves to be substituted with 1 to 3 substituents selected from a C_1-C_8 alkyl or C_1-C_8 alkoxy group, a halogen, a trifluoromethyl, trifluoromethoxy, hydroxyl, nitro and amino group,

their solvates and their pharmaceutically acceptable salts.

2. Compound according to Claim 1, which is 4-{4-[2(N-isopropyl-N-phenylamino)-2-oxoethyl]-1-piperazinyl}-benzoic acid, 4-{4-[2-(N-[2,6-dimethylphenyl]amino)-2-oxoethyl]-1-piperazinyl}benzoic acid and 4-{4-[2-(N-[2,6-

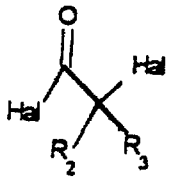
diisopropylphenyl]amino)-2-oxoethyl]-1-piperazinyl}benzoic acid.

3. Process for the preparation of compounds according to Claim 1, comprising reacting an aromatic amine of general formula (II):



(II)

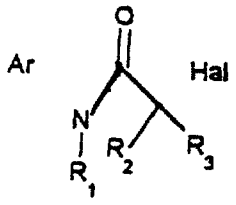
in which Ar and R_1 are as defined above,
with a haloacyl halide of general formula (III):



(III)

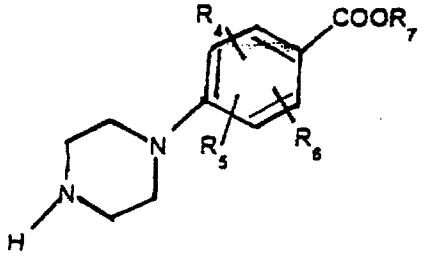
in which Hal represents a chlorine or bromine atom,

R_2 and R_3 are as defined above,
in order to form a compound of general formula (IV):



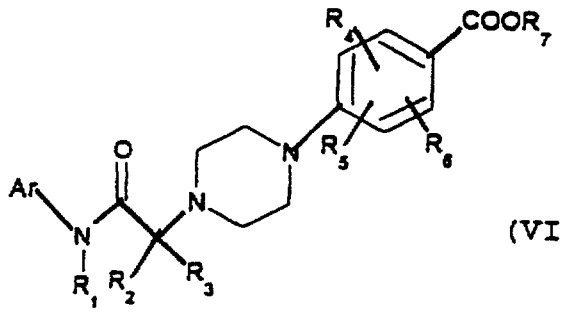
(IV)

in which Ar, R_1, R_2, R_3 and Hal are as defined above, and reacting the compound of general formula (IV) with a compound of general formula (V):



(V)

in which R_4, R_5 and R_6 are as defined above and R_7 is a hydrogen atom or a C_1-C_6 alkyl group,
in the presence of a basic agent such as triethylamine in order to form the compound of general formula (VI):



(VI)

in which Ar, R_1, R_2, R_3, R_4, R_5, R_6 and R_7 are as defined above,
and in the case where R_7 is an alkyl group, hydrolyzing this compound in order to form a compound of general formula (I).

4. Pharmaceutical composition comprising, as active ingredient, a compound according to Claim 1 or Claim 2.

* C L M S *