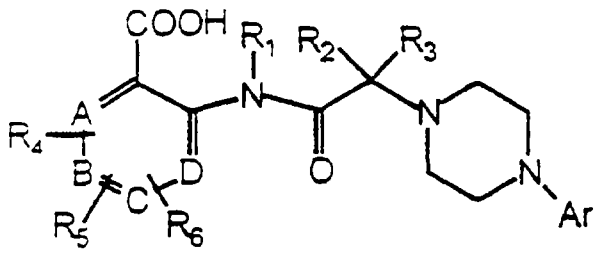
α-(1-PIPERAZINYL)ACETAMIDO ARENECARBOXYLIC ACID DERIVATIVES AS ANTIDIABETIC AGENTS

The present invention relates to new α-(1-piperazinyl)acetamido arenecarboxylic acid derivatives which are useful in the treatment of diabetes

The subject of the present 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, pyrimidinyl, pyrrolyl, furyl, thienyl, quinolyl, indolyl, benzothienyl, benzofuryl, benzopyranyl, benzothiopyranyl, 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_1C_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,

the 4-carboxyphenyl and substituted 4-carboxyphenyl groups being excluded from the definition of Ar,

R_1, R_2 and R_3 are selected, independently of one another, 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_6)cycloalkyl(C_1-C_6)alkyl group or 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,

A, B, C and D are =CH- groups, it being possible for one or two of them also to be a nitrogen atom,

R_4, R_5 and R_6 are selected, independently of one another, 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_6-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 or a trifluoromethyl, trifluoromethoxy, cyano, carboxyl, hydroxyl, nitro, amino, (C_1-C_6)alkoxycarbonyl, carbamoyl, (C_1-C_6)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 or a phenyl ring condensed with the ring to which they are attached,

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

their solvates and their pharmaceutically acceptable salts

Mention may be made, as an example of the aryl group, of the phenyl, α-naphthyl, β-naphthyl and fluorenyl groups.

The C_1-C_8 alkyl groups can be linear or branched Mention may be made, as examples, of the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl and pentyl groups

The C_1-C_8 alkoxy groups can likewise be linear or branched Mention may be made, as examples, of the methoxy ethoxy, propoxy, isopropoxy, butoxy and isobutoxy groups.

The halogens can be selected from fluorine chlorine, bromine and iodine

The heteroaryl groups in the definition of R_1 R_2 and R_3 may be defined in particular as defined for the heteroaromatic groups in the definition of Ar

The invention also relates to the tautomeric forms and to the enantiomers, diastereoisomers and epimers of the compounds of general formula (I)

The compounds of general formula (I) possess a carboxylic acid functional group and can be salified, then existing in the form of salts with bases.

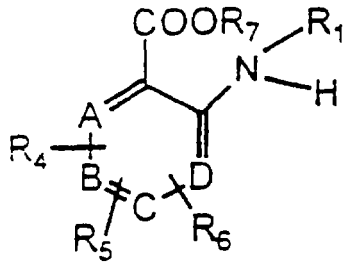
Examples of salts with bases of the compounds of general formula (I) include the pharmacologically acceptable salts, such as the sodium salts, potassium salts, calcium salts and other salts of the same type.

The compounds of general formula (I) can also be salified with amines in order to form pharmaceutically acceptable salts. By way of example, the compounds of general formula (I) could 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, the hydrochloride, the hydrobromide, the sulphate, the succinate, maleate, fumarate,

malate or tartrate and the sulphonates, such as the methanesulphonate the benzenesulphonate or the toluenesulphonate.

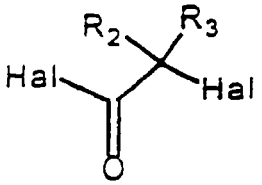
The invention also relates to a process for the preparation of the compounds of general formula (I). A preparation process according to the invention comprises the reaction of an aromatic amine of general formula (II)



(II)

in which A, B, C, D, R_1, R_4, R_5 and R_6 are as defined above and R_7 is a hydrogen atom, a C_1-C_6 alkyl group or a benzyl group,

with a haloacyl halide of general formula (III)

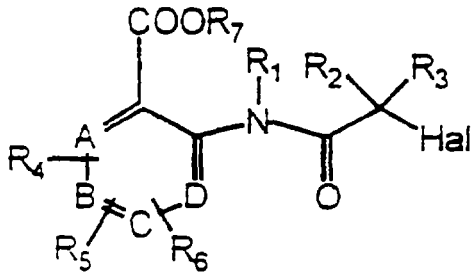


(III)

in which R_2 and R_3 are as defined above,

Hal represents a chlorine or bromine atom,

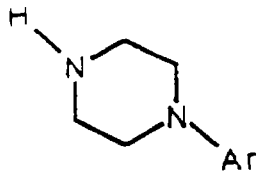
in order to form a compound of general formula (IV)



(IV)

in which A, B, C, D, R_1, R_2, R_3, R_4, R_5, R_6, R_7 and Hal are as defined above,

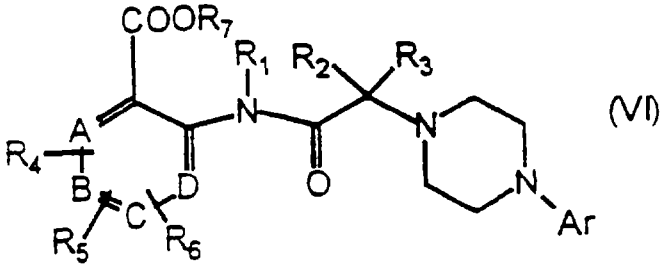
and the reaction of the compound of general formula (IV) with a compound of general formula (V)



(V)

in which Ar is as defined above,

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



(VI)

in which Ar, A, B, C, D, 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 hydrolysed by conventional acidic or basic means in order to give the compound of general formula (I).

In the case where R_7 is a benzyl group, the compound of general formula (VI) can be hydrogenolysed in the presence of a catalyst, such as palladium-on-charcoal, in order to give the compound of general formula (I)

The compounds of formulae (II) and (V) are known compounds or can be prepared according to known processes

Thus, compounds of formula (II) are described in Organic Preparation and Procedures International, 13, 189, 1981

The compounds of formula (V) can be prepared as described by R Ratouis et al. (J. Med. Chem., 8, 104, 1965) or by Prelog et al (Collection Czechoslov Chem. Communications, 6, 211, 1934).

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

The enantiomers of the compounds of formula (I) can be separatec by successive recrystallization of the salt of the acid (I) with an optically active base in solvents such as acetone, ethyl acetate or isopropanol and then 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 absence of toxicity at the active doses.

Another subject of the present invention is thus pharmaceutical compositions comprising an effective amount of a compound according to the invention

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

They will thus be presented in the form of injectable solutions or suspensions, or multi-dose containers, in the form of uncoated or coated tablets, of sugar-coated tablets, of capsules, including hard gelatin capsules, of pills, of cachets, of powders, of suppositories or of rectal capsules, of solutions or of suspensions, for percutaneous use in a polar solvent or for permucosal use

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

Cocoa butter or polyethylene glycol stearates are the preferred excipients for rectal use

Water, aqueous solutions, physiological solution or isotonic solutions are the most conveniently used vehicles for parenteral use.

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

The following examples illustrate the preparation of the compounds of formula (I) and of the intermediates of formulae (II) and (IV)

A - Example of the preparation of a compound of formula (II).

Preparation of methyl 2-cyclohexylmethylamino-5-methoxybenzoate

17.6 g of methyl 5-methoxyanthranilate, 11.8 ml of cyclonexanecarboxaldehyde and 2 g of 10% palladium-on-charcoal (50% water) are charged to 200 ml of methanol in a 1 litre hydrogenation apparatus

The apparatus is placed under a hydrogen atmosphere and agitated at room temperature for 3 hours

300 ml of dichloromethane are added, the palladium-on-charcoal is separated off by filtration and the filtrate obtained is concentrated under vacuum

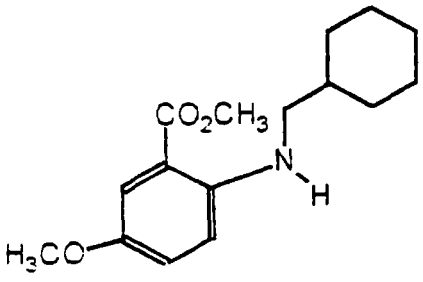
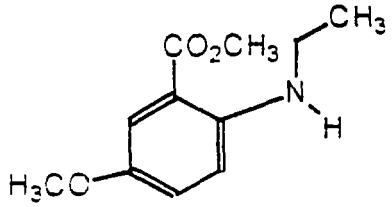
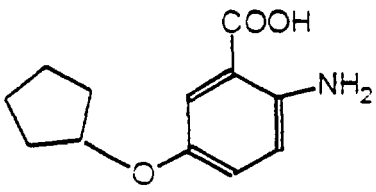
The oil obtained crystallizes from an ethanol (200 ml) and water (50 ml) mixture to give 25.4 g of a yellow solid which melts at 58-60°C.

IR (KBr) 1683 cm^{-1} (C=O), 1528 cm^{-1} (C=O)

^1H NMR: ($CDCl_3$, 200 MHz) δ ppm: 1.06-1.64 (11H, m, cyclohexyl), 2.93 (2H t CH_2), 3.68 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 6.56 (1H, d, phenyl proton), 6.96 (1H, dd, phenyl proton), 7.34 (2H, d + s, phenyl proton + NH)

The formulae and characteristics of the compounds of formula (II) have been combined in Table I

TABLE I

Compound	Structure	
1		M.p in °C (Köfler) 58-60
2		^{1}H NMR (200 MHz) $CDCl_3$ δ PPM 1.28 (t. 3H) 3.20 (q. 2H) 3.77 (s 3H) Oil 3.88 (s.3H) 6 71 (d, 1H) 7.09 (dd. 1H) 7.28 (s, 1H) 7 50 (d, 1H)
3		M.p in °C (Köfler) 147-149

B - Example of the preparation of a compound of formula (IV).

Preparation of 4-chloro-2-(chloroacetamido)benzoic acid

25.5 ml of chloroacetyl chloride are added dropwise with stirring to 50 g of 2-amino-4-chlorobenzoic acid in 600 ml of dioxane, the reaction mixture being maintained at 20°C

Stirring is then maintained for 2 hours at room temperature and then 1200 ml of water are added The desired product precipitates, the mixture is stirred for one hour and then filtered and the solid obtained is washed with water.

After drying, 60.7 g of 4-chloro-2-(chloroacetamido)benzoic acid are obtained, the melting point of which is 194-196°C

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

^1H NMR (d_6-DMSO, 200 MHz) δ ppm: 4.30 (2H, s, CH_2), 7.1 (1H d phenyl proton), 7.7 (1H d phenyl proton), 8.5 (1H, s, phenyl proton), 11.75 (1H s, NH), 13.90 (1H, broad s, COOH)

The formulae and characteristics of the compounds of formula (IV) have been combined in Table II

TABLE II

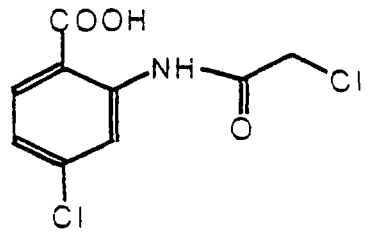
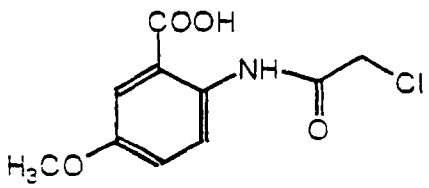
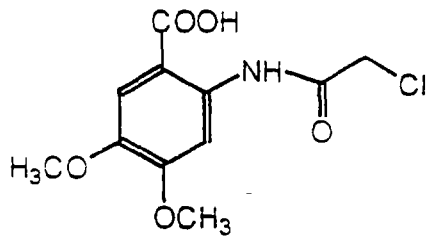
Compound	Structure	M.p. in ° C (Kofler)
1		194-196
2		182-184
3		236-238

TABLE II (continuation)

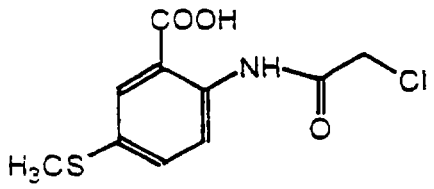
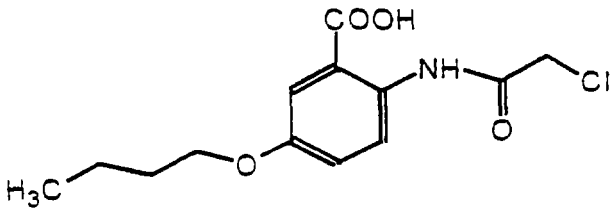
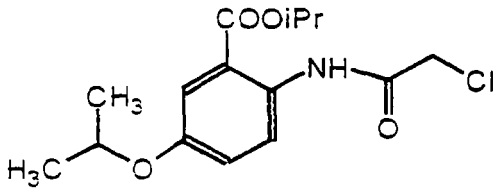
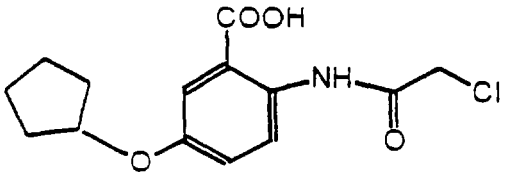
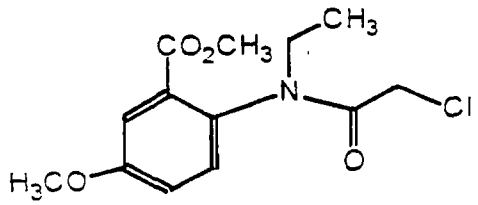
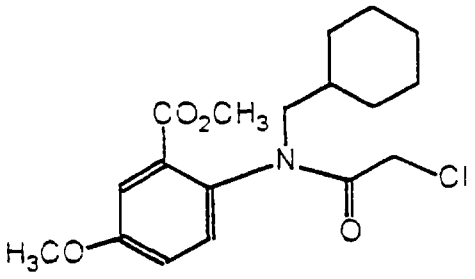
Compound	Structure	M.p. in ° C (Kofler)
4		180-182
5		155-157
6		83-85
7		217-219

TABLE II (continuation)

Compound	Structure	^{1}H NMR (200 MHz) $CDCl_3$ δ ppm
8		Oil: 0.99 (t, 3H); 3.35 (m, 1H); 3.63 (d, 2H); 3.89 (s+m, 7H); 7.12 (m, 2H); 7.40 (d, 1H)
9		Oil: 1.05 (t, 3H); 1.57 (m, 6H); 2.81 (dd, 1H); 3.66 (s, 2H); 3.81 (s, 6H); 3.88 (dd, 1H); 7.13 (m, 2H); 7.38 (d, 1H)

C - Example of the preparation of a compound of formula (II)

Preparation of 4-chloro-2-{[4-(2-methoxyphenyl)-1-piperazinyl]acetamido} benzoic acid

15 g of 4-chloro-2-(chloroacetamido)benzoic acid are added, with stirring and at room temperature, to 11.6 g of 1-(2-methoxyphenyl)piperazine and 17 ml of triethylamine in 120 ml of DMF

The reaction mixture is kept stirring for 48 hours at room temperature and then 500 ml of water are added. Extraction is carried out with 3 × 300 ml of dichloromethane. The solvent is evaporated under vacuum and the solid thus obtained is taken up again in 300 ml of a 2N aqueous sodium hydroxide solution. The solution is washed with 3 × 200 ml of diethyl ether and the aqueous phase is then acidified with acetic acid.

A solid crystallizes to give, after filtration, 22.5 g of crude product. After recrystallization from dioxane, 21.1 g of 4-chloro-2-{[4-(2-methoxyphenyl)-

1-piperazinyl]acetamido}benzoic acid are obtained in the form of a white solid which melts at 218-220°C.

IR: 1699 cm^{-1} (C=O), 1673 cm^{-1} (C=O)

^1H NMR: (CF_3COOD), δ ppm: 4.25 (3H, s, OCH_3), 4.65 (8H, broad s, 4 CH_2), 4.95 (2H, s, CH_2), 7.5 (2H, m, phenyl protons), 7.6 (1H, d, phenyl proton), 7.90 (2H, m, phenyl protons), 8.50 (1H, d, phenyl proton), 8.75 (1H, s, phenyl proton)

D - Alternative form of the preparation of a compound of formula (I)

Preparation of 2-{[4-(4-fluorophenyl)-1-piperazinyl]-acetamido}-4,5-(methylenedioxy)benzoic acid

15 g of 2-(chloroacetamido)-4,5-(methylenedioxy)benzoic acid are added with stirring and at room temperature, to 10.5 g of 1-(4-fluorophenyl)piperazine and 16.2 ml of triethylamine in 150 ml of DMF.

The reaction mixture is kept stirring for 48 hours at room temperature.

3.5 ml of acetic acid are added and 150 ml of water are slowly added. The acid crystallizes and is diluted with 300 ml of water. The mixture is stirred for 30 minutes and filtered and the solid obtained is washed with water.

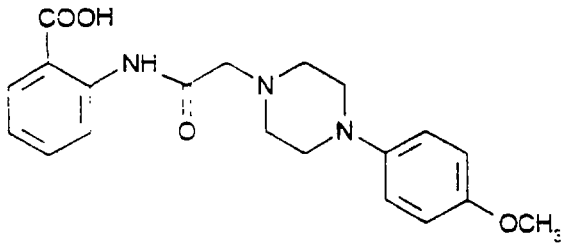
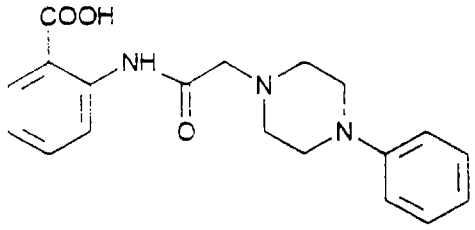
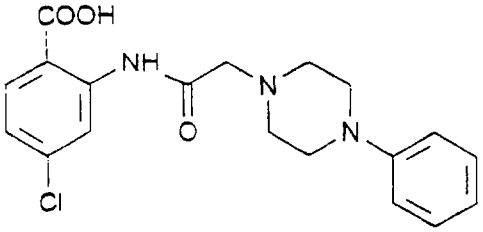
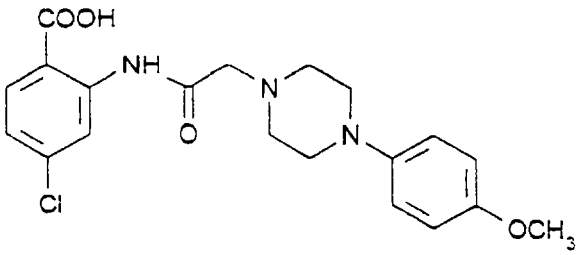
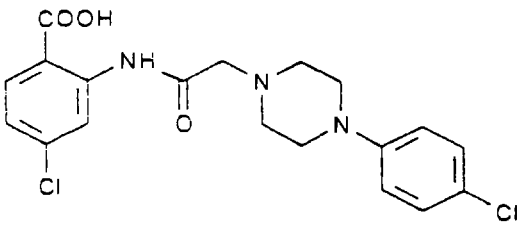
After recrystallization from a dioxane/DMF mixture, 14.9 g of 2-{[4-(4-fluorophenyl)-1-piperazinyl]acetamido}-4,5-(methylenedioxy)benzoic acid are obtained, which product melts at 254-256°C.

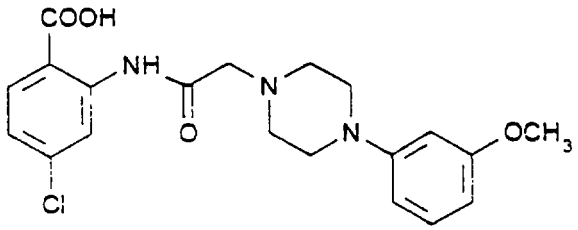
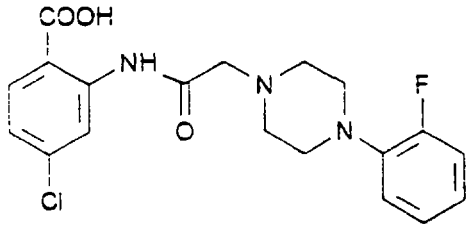
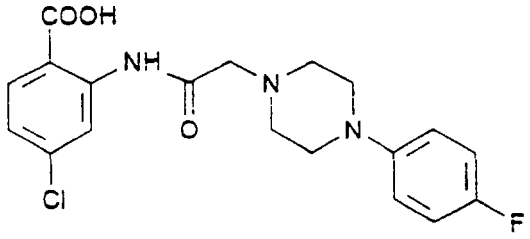
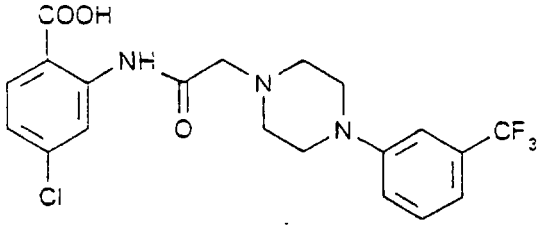
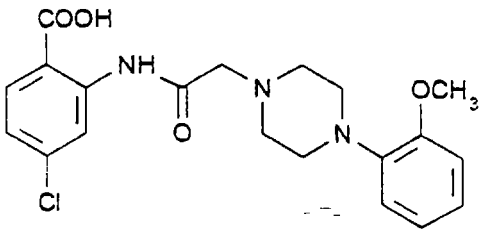
IR (KBr): 1654 cm^{-1} (C=O)

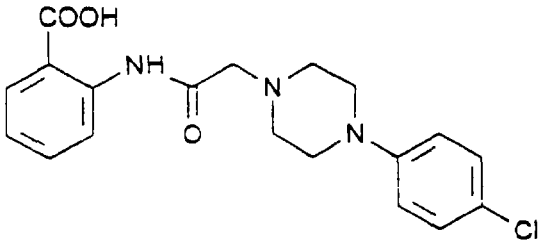
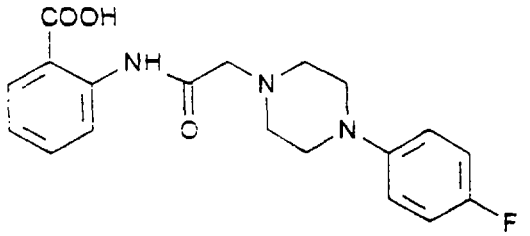
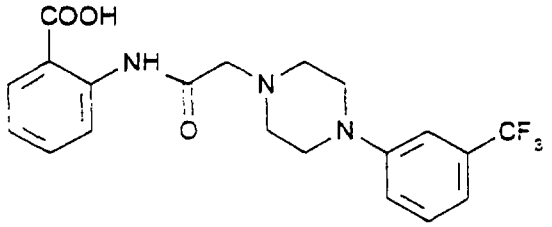
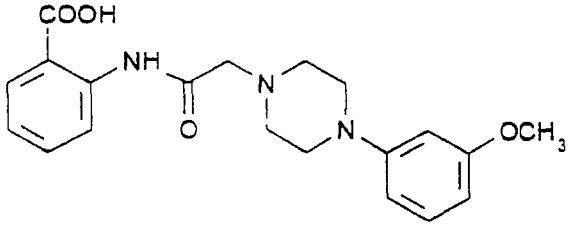
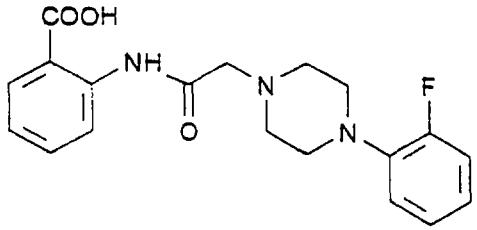
^1H NMR: (CF_3COOD, 200 MHz) δ ppm: 4.40 (8H, s, piperazinyl), 4.67 (2H, s, CH_2), 6.05 (2H, s, O-CH_2-O), 7.30 (2H, t, phenyl proton), 7.65 (3H, m, phenyl proton), 7.90 (1H, s, phenyl proton).

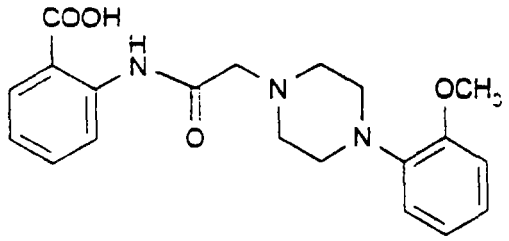
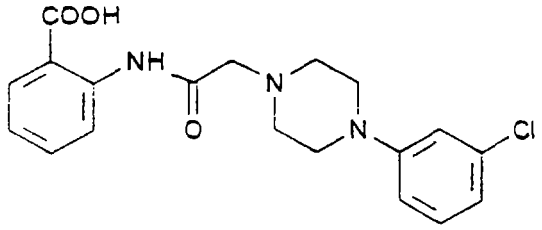
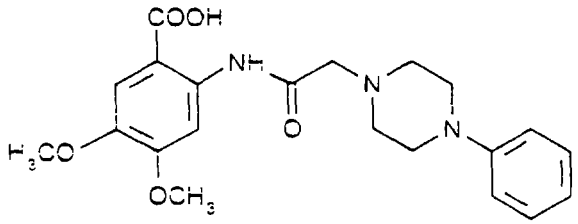
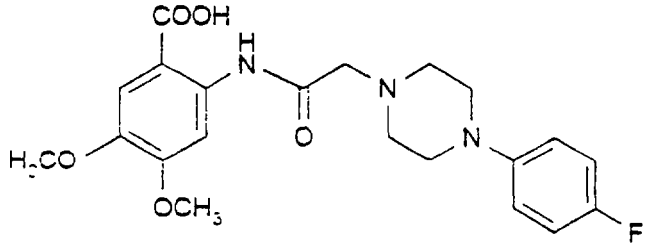
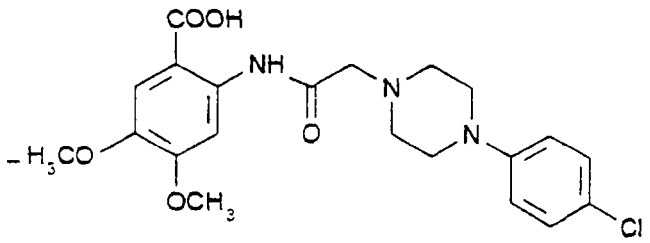
The formulae and characteristics of compounds of formula (I) have been combined in Table III.

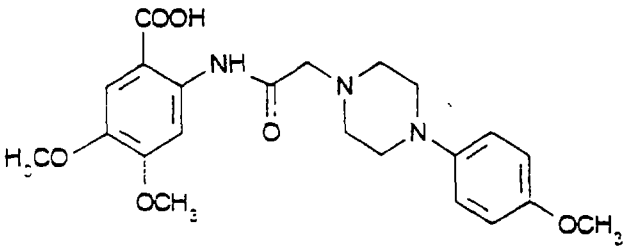
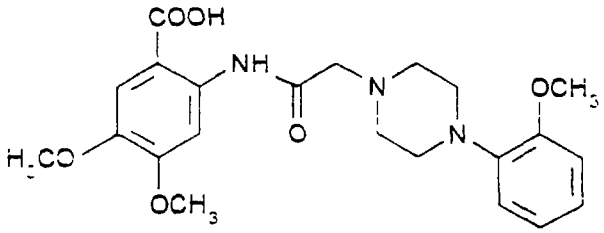
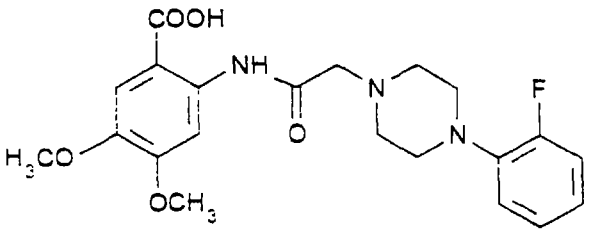
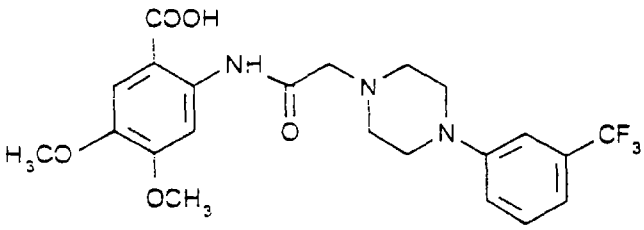
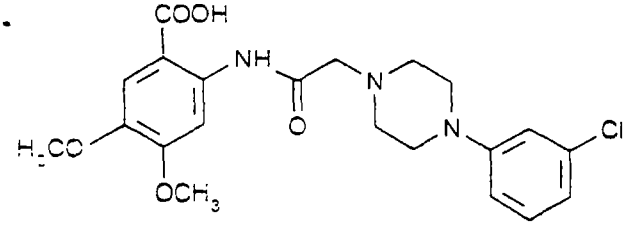
TABLE III

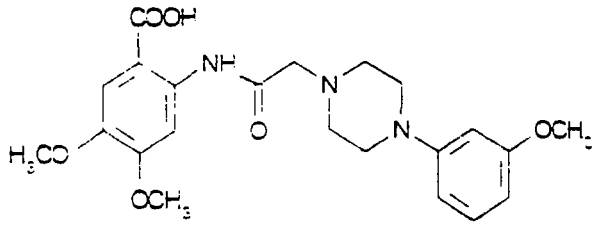
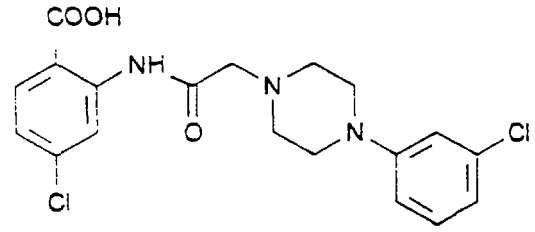
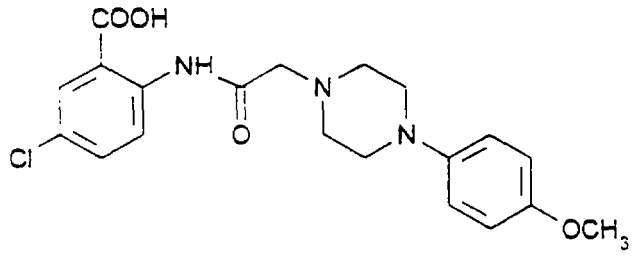
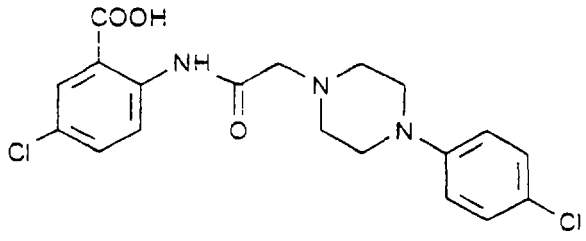
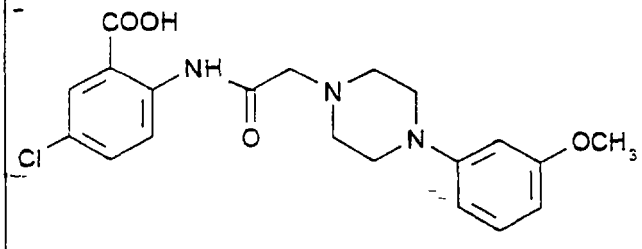
Com-pound	Structure	M.p. in °C (Kofler)	^{1}H NMR (200 MHz) δ ppm
1		185-187	d6-DMSO 2.60 (s,4H) 3.10 (s,4H) 3.20(s,2H) 3.70(s,3H) 6.80(q,4H) 7.10(t,1H) 7.55(t,1H) 8(d,1H) 8.7(d,1H)
2		233-235	CF_3COOD 4.25(s,8H) 4.65(s,2H) 7.30(t,1H) 7.55(s,5H) 7.70(t,1H) 8.25(m,2H)
3		248-250	CF_3COOD 4.25(s,8H) 4.55(s,2H) 7.10(d,1H) 7.50(s,5H) 8.05(d,1H) 8.30(s,1H)
4		241-243	CF_3COOD 4(s,3H) 4.5(s,8H) 4.8(s,2H) 7.2(d,2H) 7.4(d,1H) 7.65(d,2H) 8.25(d,1H) 8.60(s,1H)
5		> 265	CF_3COOD 4.20(s,8H) 4.62(s,2H) 7.20(d,1H) 7.55(s,4H) 8.10(d,1H) 8.35(s,1H)

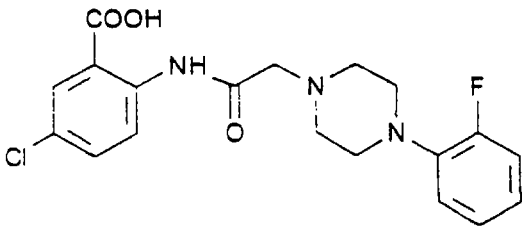
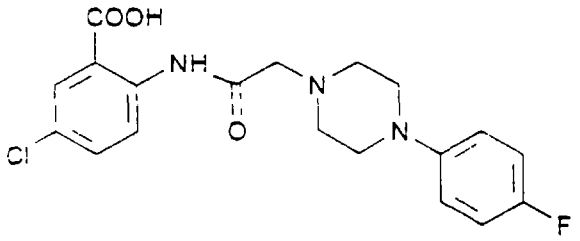
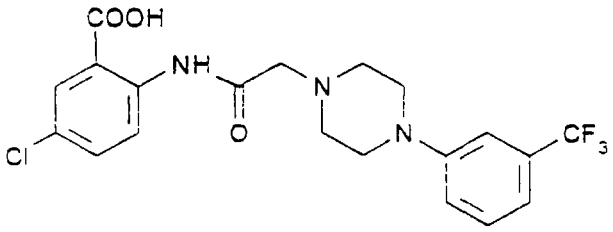
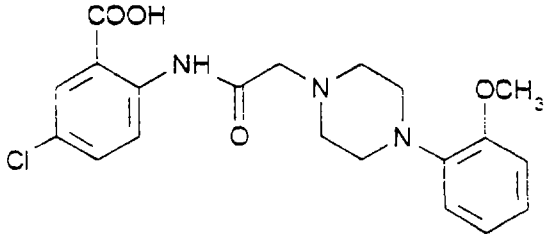
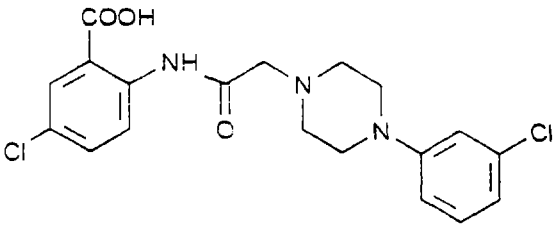
Com-pound	Structure	M.p in °C (Köfler)	^{1}H NMR (200 MHZ) δ ppm
6		199-201	CF_3COOD 3.8(s,3H) 4.25(s,8H) 4.60(s,2H) 7.20(m,4H) 7.5(m,1H) 8.15(d 1H) 8 40(s,1H)
7		238-240	CF_3COOD 4.60(d,8H) 4.90(s,2H) 7.50(m,3H) 7.85(m,2H) 8.35(d,1H) 8.65(s,1H)
8		244-246	CF_3COOD 4.10(s,8H) 4 45(s,2H) 7.05(d,3H) 7 45(m,2H) 7.95(d,1H) 8.20(s,1H)
9		191-193	CF_3COOD 4.25(d,8H) 4.60(s,2H) 7 15(d,1H) 7.75(m,4H) 8.10(d,1H) 8.30(s,1H)
10		218-220	CF_3COOD 4.25(s,3H) 4.65(s,8H) 4.95(s,2H) 7.5(m,2H) 7.6(d,1H) 7.9(m,2H) 8.5(d,1H) 8.75(s,1H)

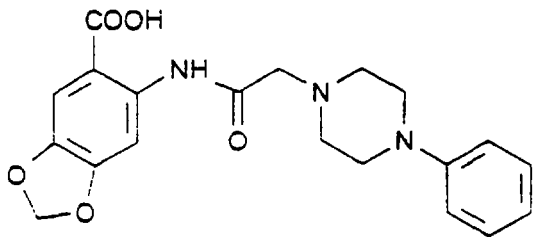
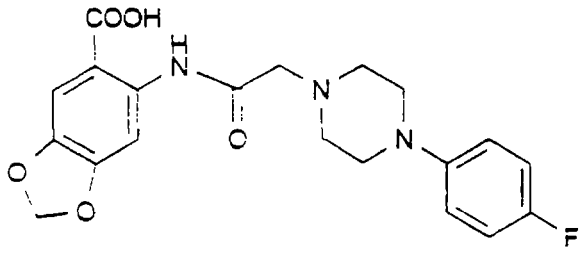
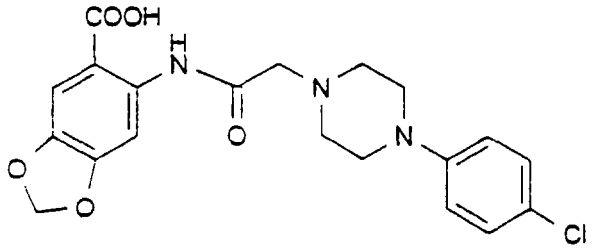
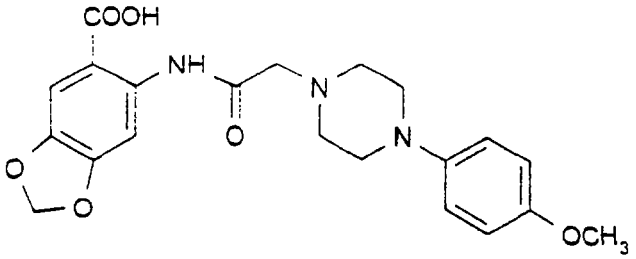
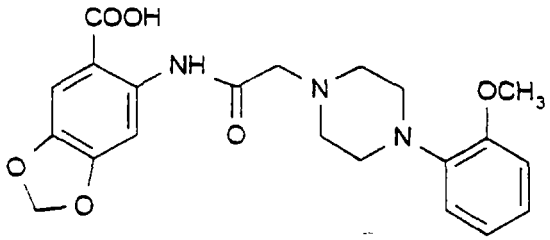
Com-pound	Structure	M.p in °C (Kofler)	H NMR (200 MHZ) δ ppm
11		260-262	CF_3COOD 4.3(s,8H) 4.7(s,2H) 7.25(t,1H) 7.55(s,4H) 7.70(t,1H) 8.25(m,2H)
12		249-251	CF_3COOD 4.2(s,8H) 4.6(s,2H) 7.2(m,3H) 7.6(m,3H) 8.15(m,2H)
13		174-176	$CDCl_3$ 2.65(s,4H) 3.10(s,2H) 3.20(s,4H) 7,00(m,7H) 8.65(d,1H) 10.00(s,1H) 11.8(s,1H)
14		190-192	CF_3COOD 3.85(s,3H) 4.30(s,8H) 4.75(s,2H) 7.5(m,6H) 8.15(t,2H)
15		169-171	$CDCl_3$ 2.74(s,3H) 3.15(s,8H) 3.20(s,2H) 6.80(m,5H) 7.5(t,1H) 7.75(d,1H) 8.80(d,1H) 11.45(s,1H) 12.00(s,1H)

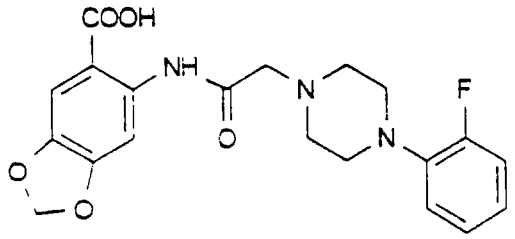
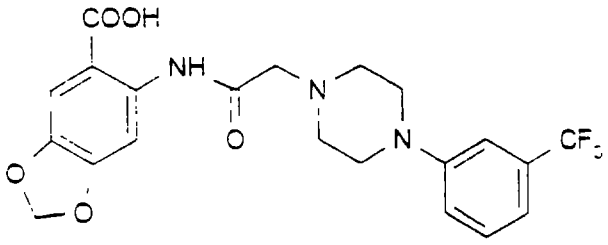
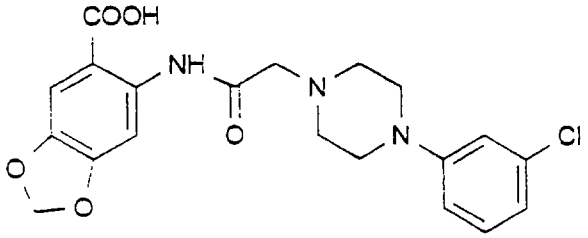
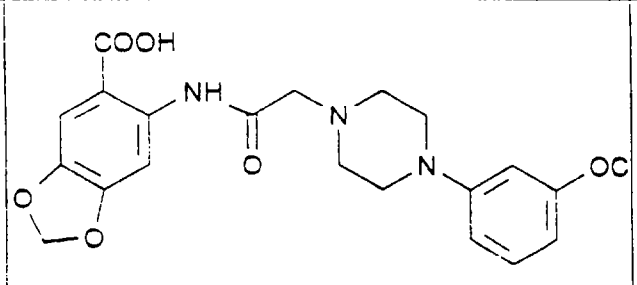
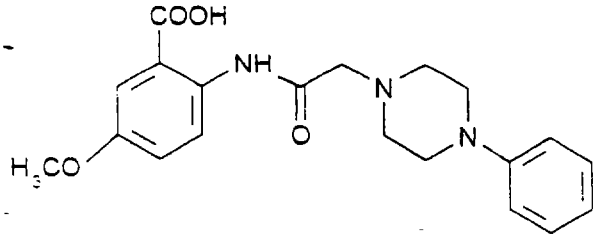
Com-pound	Structure	M.p. in °C (Köfler)	^{1}H NMR (200 MHZ) δ ppm
16		217-219	$CDCl_3$ 3.5(s,3H) 3.75(s,8H) 4.29(s,2H) 6.65(d,2H) 6.85(t,1H) 7 10(m,3H) 7.75(t,2H)
17		190-192	CF_3COOD 3.75(s,8H) 4.15(s,2H) 6.75(m,1H) 7.00(m,5H) 7.60(m,2H)
18		>265	CF_3COOD 3.65(s,6H) 4 15(s,8H) 4.5(s,2H) 7.55(s,5H) 7.65(s,1H) 7.85(s,1H)
19		>265	CF_3COOD 3.75(s,6H) 4.15(s,8H) 4.50(s,2H) 7.05(t,2H) 7 42(m,2H) 7.55(s,1H) 7.85(s,1H)
20		>265	CF_3COOD 3.80(s,6H) 4.15(s,8H) 4.50(s,2H) 7 40(s,4H) 7.60(s,1H) 7.90(s,1H)

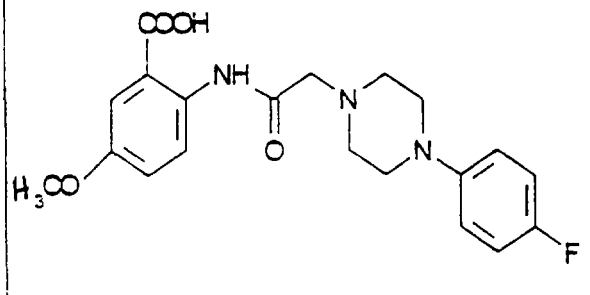
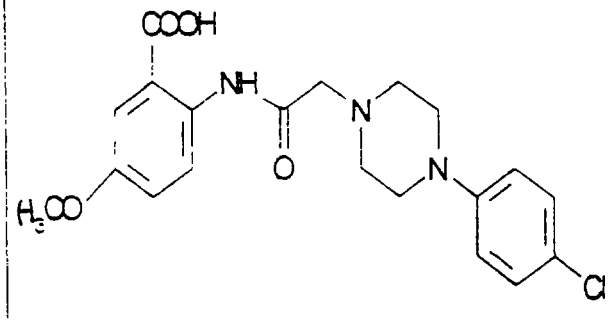
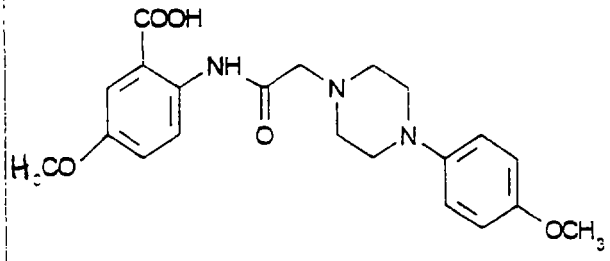
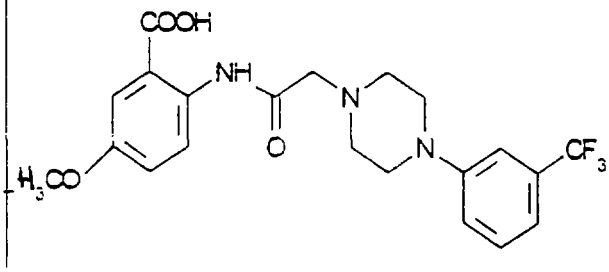
Com-pound	Structure	M.p in °C (Köfler)	^{1}H NMR (200 MHZ) δ ppm
21		246-248	CF_3COOD 3.75(s,3H) 3.85(s,6H) 4.15(s,8H) 4.50(s,2H) 6.90(d,2H) 7 40(d,2H) 7.60(s,1H) 7.95(s,1H)
22		244-246	CF_3COOD 3.80(s,9H) 4.25(s,8H) 4.50(s,2H) 7.00(d,2H) 7 40(d,2H) 7.60(s,1H) 7.95(s,1H)
23		245-247	CF_3COOD 3.80(s,6H) 4.20 +4.35(2s,8H) 4.50(s,2H) 7.20(q,2H) 7.50(m,3H) 7.95(s,1H)
24		255-257	CF_3COOD 3.75(s,6H) 4.10+4.20(2s,8H) 4.50(s,2H) 7.60(m,5H) 7.85(s,1H)
25		>265	CF_3COOD 3.80(s,6H) 4.15(s,8H) 4.50(s,2H) 7.35(m,4H) 7.55(s,1H) 8.85(s,1H)

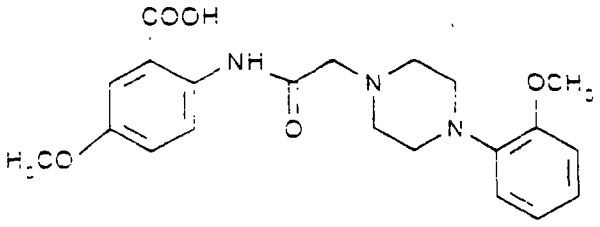
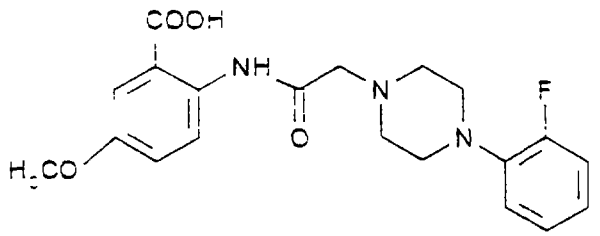
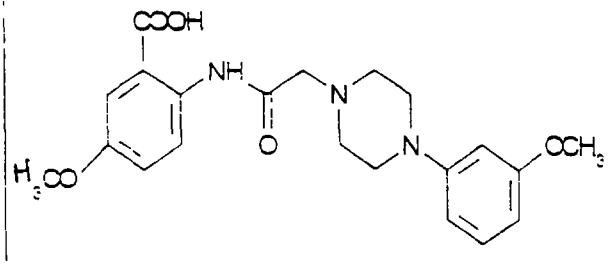
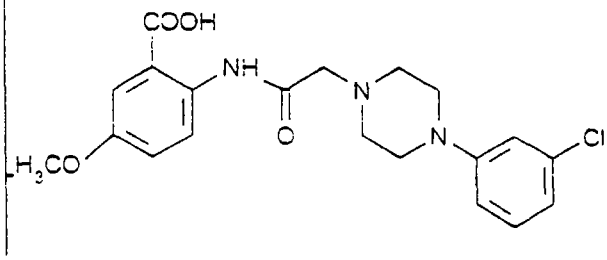
Com-pound	Structure	M.p. in °C (Kofler)	^{1}H NMR (200 MHZ) δ ppm
26		255-257	CF_3COOD 3.70(s,3H) 3.85(s,6H) 4.22(s,8H) 4.50(s,2H) 6.95(s,3H) 7.35(t,1H) 7.55(s,1H) 7.88(s,1H)
27		257-259	CF_3COOD 4.15+4.17(2s,8H) 4.50(s,2H) 7.10(d,1H) 7.40(m,4H) 8.00(d,1H) 8.25(s,1H)
28		239-241	CF_3COOD 3.70(s,3H) 4.10(s,8H) 4.50(s,2H) 6.90(d,2H) 7.30(d,2H) 7.40(d,1H) 8.00(s,1H) 8.10(d,1H)
29		>265	CF_3COOD 4.15(s,8H) 4.55(s,2H) 7.40(s+d,5H) 8.00(s,1H) 8.15(d,1H)
30		199-201	CF_3COOD 3.85(s,3H) 4.30(s,8H) 4.65(s,2H) 7.15(m,3H) 7.55(m,2H) 8.15(s,1H) 8.30(d,1H)

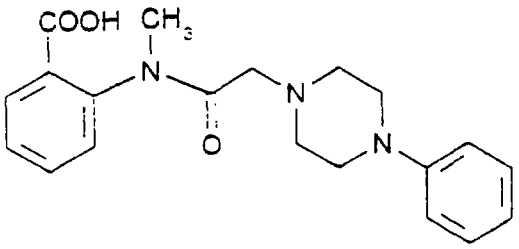
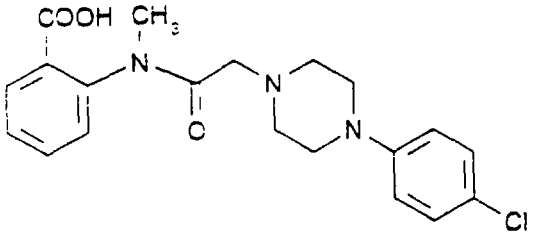
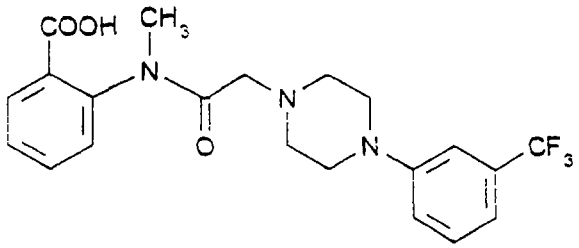
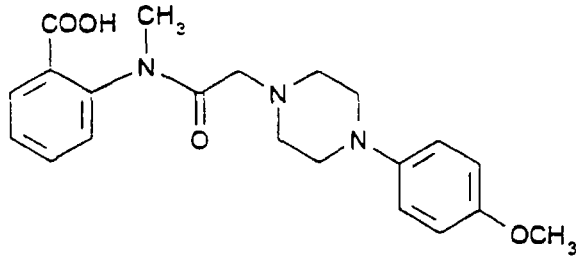
Com-pound	Structure	M.p. in °C (Köfler)	^{1}H NMR (200 MHZ) δ ppm
31		262-264	CF_3COOD 4.30+4.50(2s,8H) 4 67(s,2H) 7 30(m,2H) 7.65(m,3H) 8 15(s,1H) 8.25(d,1H)
32		245-247	CF_3COOD 4.05(s,8H) 4 40(s,2H) 7 05(t,2H) 7 40(d,3H) 7.90(s 1H) 8.05(d,1H)
33		213-215	CF_3COOD 4.25+4.40(2s,8H) 4.70(s,2H) 7.55(d,1H) 7.80(m,4H) 8.15(s,1H) 8.25(d,1H)
34		203-205	CF_3COOD 3.80(s,3H) 4.20(s,8H) 4.45(s,2H) 6.95(d,2H) 7 42(q,3H) 8.05(s+d,2H)
35		224-226	CF_3COOD 4 10(s,8H) 4 45(s,2H) 7.40(m,5H) 7.95(s,1H) 8.10(d,1H)

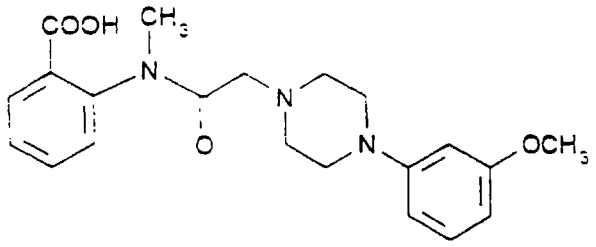
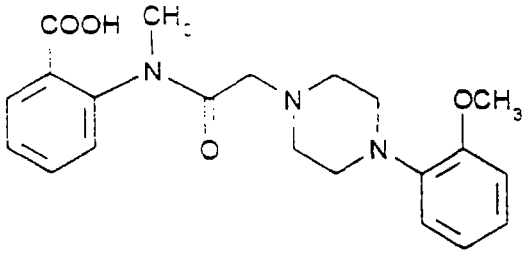
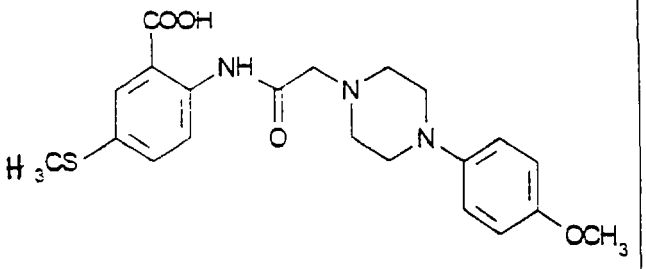
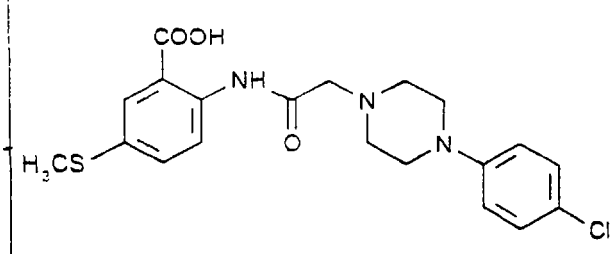
Com-pound	Structure	M.p. in °C (Köfler)	^{1}H NMR (200 MHZ) δ ppm
36		238-240	CF_3COOD 4.20(s,8H) 4.50(s,2H) 5.85(s,2H) 7.45(s,6H) 7.80(s,1H)
37		254-256	CF_3COOD 4 40(s,8H) 4.67(s,2H) 6.05(s,2H) 7.30(t,2H) 7.65(m,3H) 7 90(s,1H)
38		>265	CF_3COOD 4.22(s,8H) 4.57(s,2H) 5.92(s,2H) 7.52(s,5H) 7.80(s,1H)
39		236-238	CF_3COOD 3.83(s,3H) 4.25(s,8H) 4.59(s,2H) 6.0(s,2H) 7.13(d,2H) 7.49(t,3H) 7.82(s,1H)
40		257-259	CF_3COOD 3.97(s,3H) 4.29(s,8H) 4.59(s,2H) 6.06(s,2H) 7.15(d,2H) 7.55(s,3H) 7.82(s,1H)

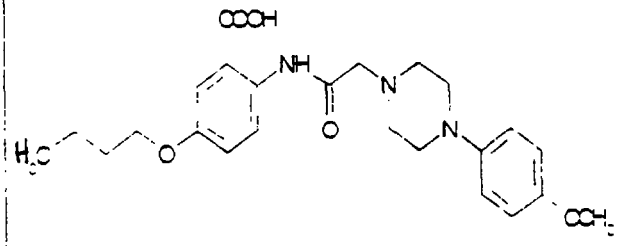
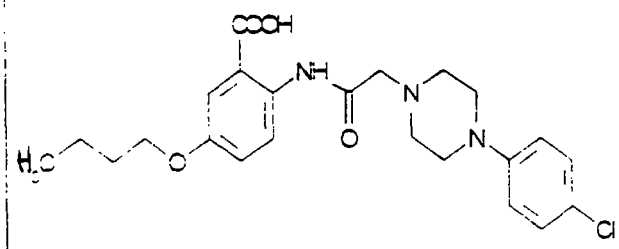
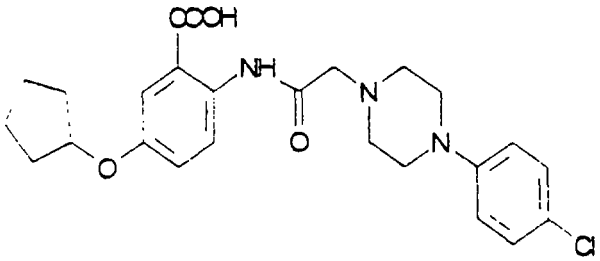
Com-pound	Structure	M.p. in °C (Köfler)	^{1}H NMR (200 MHZ) δ ppm
41		236-238	CF_3COOD 4.23+4.38(2s,8H) 4.56(s,2H) 5.97(s,2H) 7.31(m,2H) 7.55(m,3H) 7 76(s,1H)
42		228-230	CF_3COOD 4.05+4.15(2s,8H) 4.35(s,2H) 5.75(s,2H) 7.30(s 1H) 7.60(m,5H)
43		240-242	CF_3COOD 4.00(s,8H) 4.37(s,2H) 5 75(s,2H) 7.35(d,5H) 7 70(s,1H)
44		198-200	CF_3COOD 3.55(s,3H) 4.00(s,8H) 4.30(s,2H) 5.71(s,2H) 6.85(s,3H) 7.25(s,2H) 7.60(s,1H)
45		188-190	CF_3COOD 4.05(s,3H) 4.42(s,8H) 4.78(s,2H) 7.45(d,1H) 7.72(s,5H) 7.93(s,1H) 8.30(d,1H)

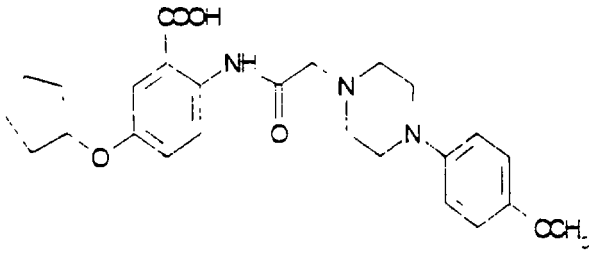
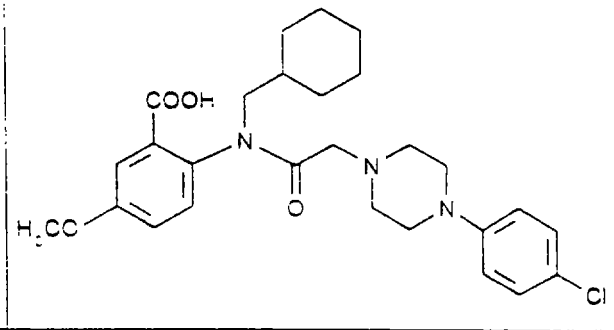
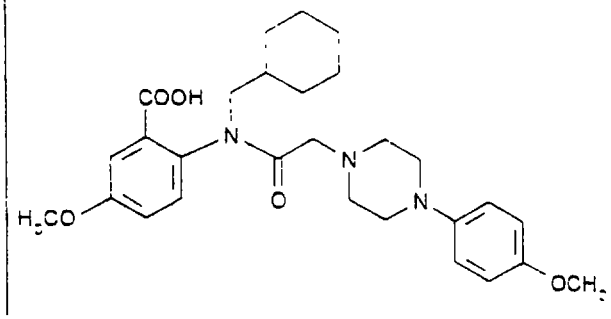
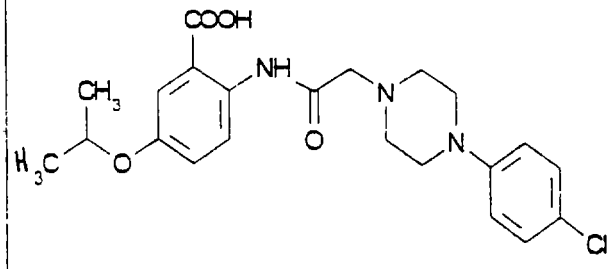
Com-pound	Structure	M.p. in °C (Kofler)	^{1}H NMR (200 MHz)
46		197-199	CF_3COOD 3.75(s,3H) 4.20(s,8H) 4.50(s,2H) 7.10(m,3H) 7.50(t,2H) 7.70(s,1H) 8.05(d,1H)
47		221-223	CF_3COOD 3.80(s,3H) 4.20(s,8H) 4.55(s,2H) 7.15(d,1H) 7.40(s,4H) 7.70(s,1H) 8.00(d,1H)
48		198-200	CF_3COOD 3.85(d,6H) 4.25(s,8H) 4.75(s,2H) 7.22(s,2H) 7.40(s,1H) 7.58(s,2H) 7.82(s,1H) 8.20(s,1H)
49		171-173	CF_3COOD 3.75(s,3H) 4.15(s,8H) 4.50(s,2H) 7.15(s,1H) 7.70(d,5H) 8.05(s,1H)

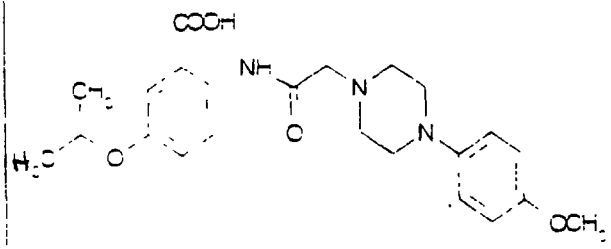
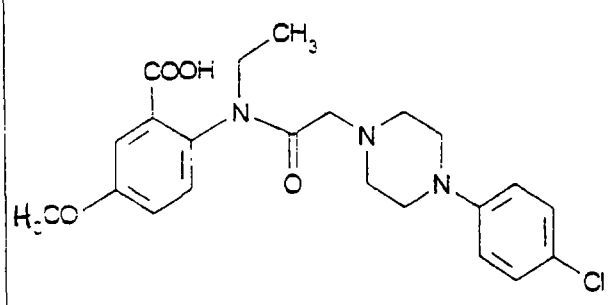
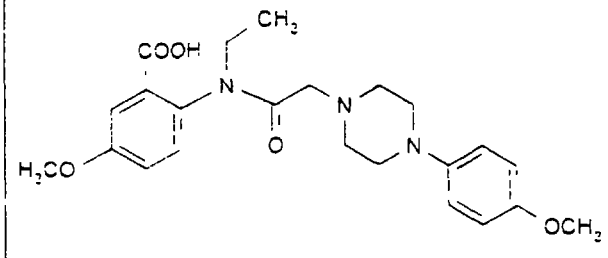
Com-pound	Structure	M.p in °C (Kofler)	^{1}H NMR (200 MHz)
50		200-202	CF_3COOD 3.65(s,3H) 3.70(s,3H) 4.12(s,8H) 4.42(s,2H) 7.00(d,2H) 7.10(d,1H) 7.40(m,2H) 7.65(s,1H) 8.00(d,1H)
51		179-181	CF_3COOD 3.72(s,3H) 4.25(d,8H) 4.50(s,2H) 7.15(m,3H) 7.50(q,2H) 7.65(d,1H) 8.00(d,1H)
52		177-179	CF_3COOD 3.88(s,3H) 3.96(s,3H) 4.34(s,8H) 4.72(s,2H) 7.20(m,1H) 7.39(dd,1H) 7.62(m,1H) 7.88(s,1H) 8.22(d,3H)
53		182-184	CF_3COOD 3.95(s,3H) 4.40(s,8H) 4.70(s,2H) 7.30(d,1H) 7.60(m,3H) 7.85(s,1H) 8.25(d,1H)

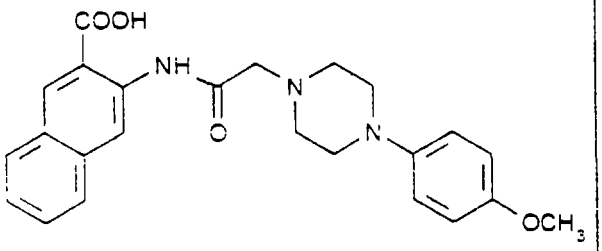
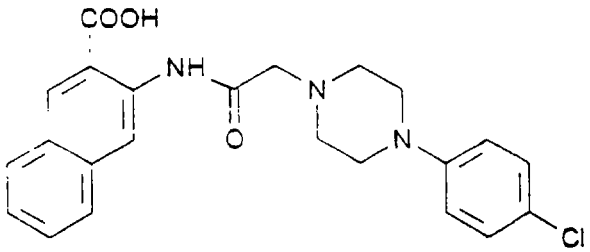
Com-pound	Structure	M.p. in °C (Kofler)	^{1}H NMF (200 MHz)
54		210-212	d_6-DMSO 2.42(d,4H) 2 90(s,2H) 3 10(s.4H) 3 18(s,3H) 6.80(t,1H) 6 93(d,2H) 7.25(t,2H) 7.50(m,2H) 7 70(t,1H) 8.00(d,1H)
55		226-227	d_6-DMSO 2.34(d,4H) 2.81(s,2H) 3.00+3.10(2s,7H) 6.93(d,2H) 7.22(d,2H) 7 47(m,2H) 7.70(d,1H) 7 95(d,1H)
56		193-195	d_6-DMSO 2.55(d,4H) 3.03(s,2H) 3.25(d,7H) 7.25(m,3H) 7.60(m,3H) 7.82(t,1H) 8 12(d,1H)
57		208-210	d_6-DMSO 2.55(s,4H) 3.00(d,6H) 3.25(s,3H) 3.80(s,3H) 7.00(s,4H) 7.65(m,2H) 7.82(d,1H) 8.10(d,1H)

Com-pound	Structure	M.p in °C (Kofler)	^{1}H NMR (200 MHz)
58		196-198	d_6-DMSO 2.15(s,4H) 2.65(s,2H) 2.80(s,4H) 2.90(s,3H) 3.55(s,3H) 6.20(t,3H) 6.85(t,1H) 7.25(m,2H) 7.50(d,1H) 7.75(d,1H)
59		144-145	d_6-DMSO 2.55(s,4H) 2.95(s,6H) 3.20(s,3H) 3.90(s,3H) 7.00(d,4H) 7.60(m,2H) 7.80(d,1H) 8.10(d,1H)
60		189-191	CF_3COOD 2.38(s,3H) 3.77(s,3H) 4.22(s,8H) 4.60(s,2H) 7.05(d,2H) 7.50(d,3H) 8.07(s,1H) 8.15(d,1H)
61		214-216	d_6-DMSO 2.50(s,3H) 2.83(s,4H) 3.39(2s,6H) 7.05(d,2H) 7.43(d,2H) 7.66(dd,1H) 7.96(s,1H) 8.79(d,2H) 12.20(s,1H) 13.80(s,1H)

Com-pound	Structure	M.p. in °C (Köfler)	^{1}H NMR (200 MHz)
62		167-169	d_6-DMSO 0.75(t,3H) 1.24(m,2H) 1.58(q,2H) 2.52(s,4H) 2.94(s,6H) 3.50(s,3H) 3.81(t,2H) 6.71(q,4H) 7.05(dd,1H) 7.28(s,1H) 8 45(d,1H) 11.77(s,1H) 13 43(s,1H)
63		159-161	d_6-DMSO 0.83(t,3H) 1.32(m,2H) 1.58(q,2H) 2.60(s,4H) 3.16+3.32(2s,6H) 3.88(t,2H) 6.87(d,2H) 7.10(d,3H) 7.35(d,1H) 8.60(d,1H) 11.81(s,1H) 13.50(s,1H)
64		187-189	d_6-DMSO 1.62(m,8H) 2.64(s,4H) 3.20+3.28(2s,6H) 4.75(s,1H) 6.86(d,2H) 7.13(m,3H) 7.39(s,1H) 8.56(d,1H) 10.15(s,1H)

Com-pound	Structure	M.p. in °C (Köfler)	^{1}H NMR (200 MHz)
65		171-173	d_6-DMSO 1.51(m,8H) 2.52(s,4H) 2 98(s,6H) 3.50(s,3H) 4.60(s,1H) 6.60(q,4H) 6 98(dd,1H) 7.28(s,1H) 8 45(d,1H) 11.77(s,1H) 13 43(s,1H)
66		236-238	d_6-DMSO 1.35(m,11H) 2.56(s,4H) 2.84(m,3H) 3.12(s,4H) 4.90(s+m,4H) 6.92(d,2H) 7.28(m,4H) 7 46(d,1H)
67		209-211	d_6-DMSO 1.00(m,5H) 1.66(m,6H) 2.49(s,4H) 2.90(m,7H) 3.73(s,3H) 3.85(s+m,4H) 6.83(q,4H) 7.24(q,2H) 7.40(s,1H)
68		218-220	d_6-DMSO 1.54(d,6H) 3.00(s,4H) 3.50(s,6H) 4.67(m,1H) 7.05(d,2H) 7.35(d,3H) 7.74(d,1H) 8.98(s,1H) 12.00(s,1H)

Com-pound	Structure	M.p in °C (Köfler)	^{1}H NMR (200 MHz)
69		132-134	d_6-DMSO 1.20(d.6H) 2.79(s,4H) 3.13(s 4H) 3.20(s.2H) 3 62(s 3H) 4.37(m 1H) 4.94(s.1H) 6.60(d.2H) 6 79(d.2H) 7.00(dd.1H) 7 43(s.1H) 8.56(d.1H) 11.88(s 1H)
70		161-163	d_6-DMSO 1.05(t.3H) 2.50(s,4H) 3 00(s.2H) 3.20(s.5H) 3.92(m+s,4H) 6.94(d.2H) 7.28(m.4H) 7 47(s.1H) 13.62(s large 1H)
71		150-152	CF_3COOD 3.58 s, 3.79 s, 3.92 m, 18H 6.83(d.2H) 7.10(s.2H) 7.28(d.2H) 7.58(s.1H)

Com-pound	Structure	M.p. in °C (Kofler)	^{1}H NMR (200 MHz)
72		261-263	CF_3COOD 3.90(s,3H) 4 41(s,8H) 4 75(s,2H) 7 13(d,2H) 7 45(m 4H) 7 88(m,2H) 8 64(s,1H) 8.90(s 1H)
73		> 265	CF_3COOD 4 40(s,8H) 4 77(s,2H) 7 67(s+m,6H) 7.92(m,2H) 8.68(s,1H) 8 92(s,1H)

Results of the pharmacological studies will be given hereinbelow

<u>Study of the anti-diabetic activity in the NOSTZ rat</u>

The anti-diabetic activity of the compounds of formula (I) by the oral route was determined with respect to an experimental model of non-insulin-dependent diabetes induced in the rat by streptozotocin.

The non-insulin-dependent diabetes model is obtained in the rat by a neonatal (the day of birth) injection of streptozotocin.

The diabetic rats used are 8 weeks old. The animals are kept, from the day of their birth to the day of the experiment, in an animal house at a temperature regulated from 21 to 22°C and subject to a fixed cycle of light (from 7 h to 19 h) and of darkness (from 19 h to 7 h). Their feeding consisted of a maintenance diet, water and food was supplied "ad libitum", except for fasting for 2 hours before the test when the food is withdrawn (post-absorptive state).

The rats are treated orally during the day with the test product. Two hours after the final administration of the product and 30 minutes after anaesthetizing the animals with sodium pentobarbital (Nembutal®), a 300 µl blood sample is taken from the end of the tail.

The main results obtained are combined in Table IV. These results show the effectiveness of the compounds of formula (I) in decreasing glycaemia in the diabetic animals.

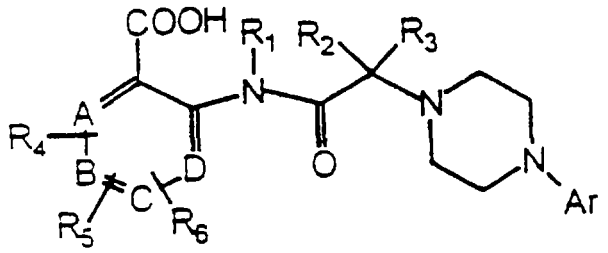
These results are expressed as percentage of change in glycaemia at D4 (4 days of treatment) in comparison with D0 (before treatment).

TABLE IV

Compound	20 mg/kg/d	200 mg/kg/d
	% Glycaemia at D4	% Glycaemia at D4
35	-12	-16
38	-6	-27
39	-15	-14
45	-9	-18
47	-16	-32
48	-20	-31
50	-17	-7
52	-14	-21

CLAIMS

1. A compound selected from the compounds of the formula (I)



(I)

in which,

Ar is selected from

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

- a heteroaromatic group selected from the pyridyl, pyrimidinyl pyrrolyl furyl, thienyl, quinolyl, indolyl, benzothienyl, benzofuryl, benzopyranyl, benzothiopyranyl, dibenzofuryl, carbazolyl and benzothiazinyl groups,

it being possible for the Ar group to carry 1 to 3 substituents selected from 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_5-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, (C_6-C_{14})aryl(C_1-C_6)alkyloxy(C_1-C_6)alkyl, halogen, trifluoromethyl, trifluoromethoxy, cyano, hydroxy, nitro, amino, carboxy, (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 and (C_1-C_8)alkylcarbonylamino, or two of these substituents forming methylenedioxy,

- 4-carboxyphenyl and substituted 4-carboxyphenyl being excluded from the definition of Ar,

R_1 R_2 and R_3 are selected, independently of one another, from

- hydrogen,

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

- cycloalkyl containing from 3 to 8 carbon atoms,(C_3-C_8)cycloalkyl(C_1-C_6)alkyl,(C_3-C_8)cycloalkyloxy- (C_1-C_6)alkyl and (C_3-C_8)cycloalkyl(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})aryl(C_1-C_6)-alkoxy(C_1-C_6)alkyl and (C_6-C_{14})aryloxy(C_1-C_6)alkyl,

A, B, C and D are =CH- groups, it being possible for one or two of them also to be a nitrogen atom.

R_4, R_5 and R_6 are selected, independently of one anotner, from:

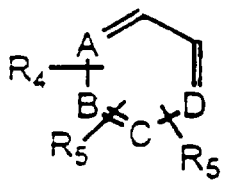
- hydrogen

- 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_6-C_{14})aryl(C_1-C_6)alkoxy, (C_6-C_{14})aryl(C_1-C_6)alkyloxy(C_1-C_6)alkyl, halogen, trifluoro- methyl, trifluoromethoxy, cyano, carboxyl, hydroxyl, nitro, amino, (C_1-C_6)alkoxycarbonyl, carbamoyl, (C_1-C_6)alkylthio, (C_1-C_8)alkylsulphinyl, (C_1-C_8)alkylsulphonyl, sulphoamino, (C_1-C_8)alkylsulphonylamino, sulphamoyl and (C_1-C_8)alkylcarbonylamino, it being possible for two of these groups to form methylenedioxy or phenyl ring condensed with the ring to which they are attached,

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

their solvates and their pharmaceutically acceptable salts

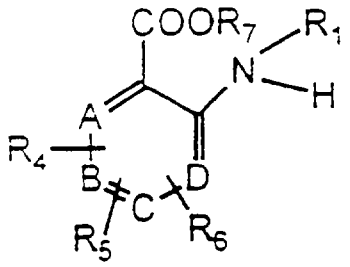
2 A compound as claimed in Claim 1, in which the base component of the ring system



is a phenyl ring.

3 A compound as claimed in Claim 2, in which at least one of the R_4, R_5 and R_6 groups is C_1-C_8 alkoxy or two of these groups form methylenedioxy

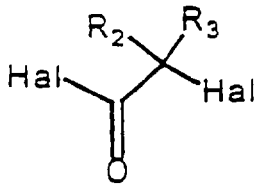
4 A process for the preparation of a compound according to Claim 1, comprising the reaction of an aromatic amine of the formula (II):



(II)

in which A, B, C, D, R_1, R_4, R_5 and R_6 are as defined above and R_7 is selected from hydrogen, C_1-C_6 alkyl and benzyl,

with a haloacyl halide of the formula (III)

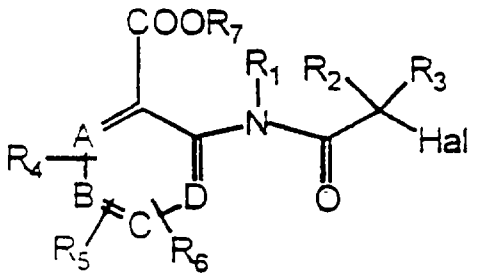


(III)

in which R_2 and R_3 are as defined above,

Hal is selected from chlorine and bromine,

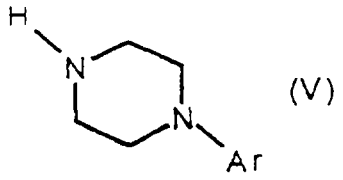
in order to form a compound of the formula (IV)



(IV)

in which A, B, C, D, R_1, R_2, R_3, R_4, R_5, R_6, R_7 and Hal are as defined above,

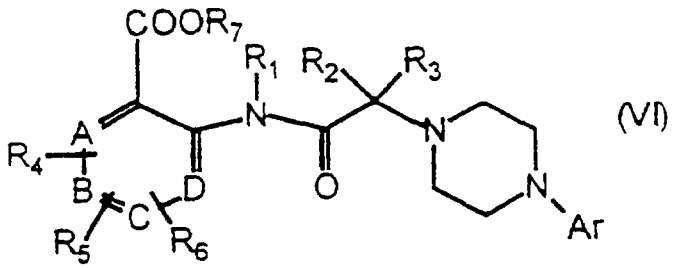
and the reaction of the compound of the formula (IV) with a compound of the formula (V)



(V)

in which Ar is as defined above,

in the presence of a basic agent, in order to form the compound of the formula (VI)



(VI)

in which Ar, A, B, C, D, 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 alkyl, the hydrolysis of this compound in order to form a compound of formula (I),

and, in the case where R_7 is benzyl, the hydrogenolysis of this compound in order to form a compound of formula (I).

5 A pharmaceutical composition comprising an effective amount of a compound as claimed in Claim 1

6 A pharmaceutical composition comprising an effective amount of a compound as claimed in Claim 2.

7 A pharmaceutical composition comprising an effective amount of a compound as claimed in Claim 3.

8 **Use of a compound as claimed in Claim 1 for the manufacture of a medicament for the treatment of diabetes.**

9 Use of a compound as claimed in Claim 2 for the manufacture of a medicament for the treatment of diabetes.

10 Use of a compound as claimed in Claim 3 for the manufacture of a medicament for the treatment of diabetes.