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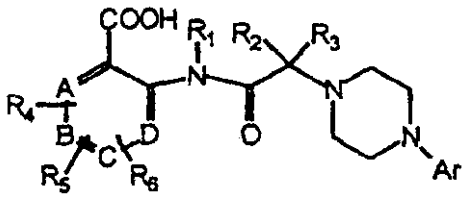
(54) Title: α–(1–PIPERAZINYL)ACETAMIDO ARENECARBOXYLIC ACID DERIVATIVES AS ANTIDIABETIC AGENTS



(I)

(57) Abstract

The invention relates to compounds of general formula (I). These compounds are useful in the treatment of diabetes.

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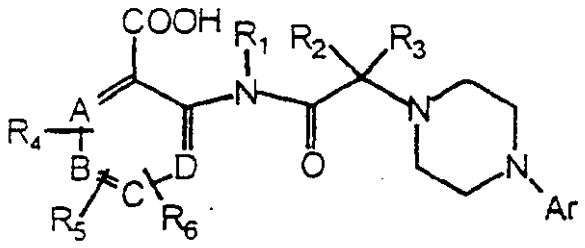
α-(1-PIPERAZINYL)ACETAMIDO ARENECARBOXYLIC ACID DERIVATIVES AS ANTIDIABETIC AGENTS

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-

$pH_2SO_2^-$

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_8)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.

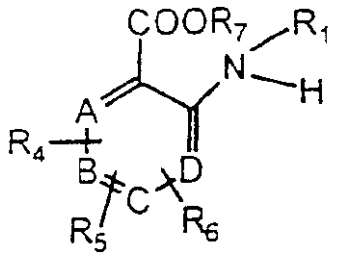
Examples of salts with bases of the compounds of general formula (I) include the pharmacologically acceptable salts, such as the sodium salts, potassium salts, calcium salts and other salts of the same type.

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.

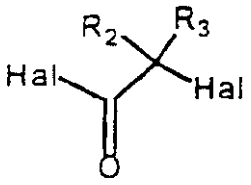
The invention also relates to a process for the preparation of the compounds of general formula (I). A preparation process according to the invention comprises the reaction of an aromatic amine of general formula (II):



(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):

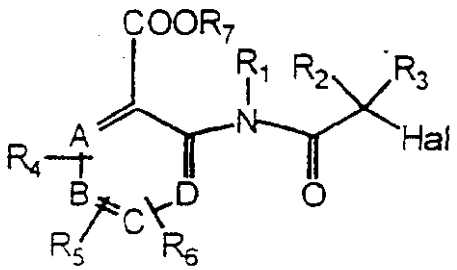


(III)

in which R_2 and R_3 are as defined above,

Hal represents a chlorine or bromine atom,

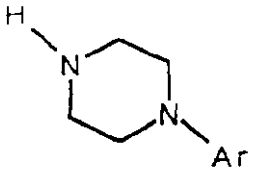
in order to form a compound of general formula (IV):



(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,

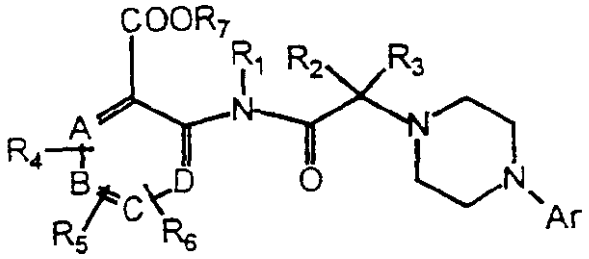
and the reaction of the compound of general formula (IV) with a compound of general formula (V):



(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 separated 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 cyclohexanecarboxaldehyde 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.

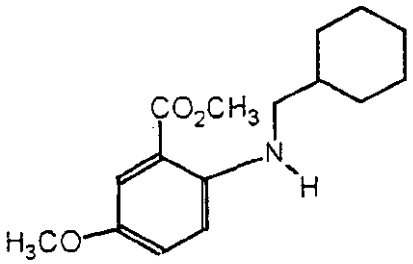
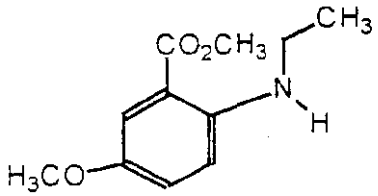
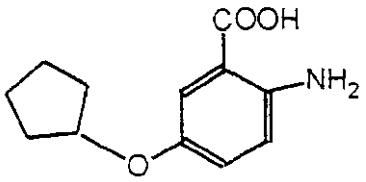
The oil obtained crystallizes from an ethanol (200 ml) and water (50 ml) mixture to give 25.4 g of a yellow solid which melts at 58-60°C.

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 Oil 1.28 (t, 3H) 3.20 (q, 2H) 3.77 (s, 3H) 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

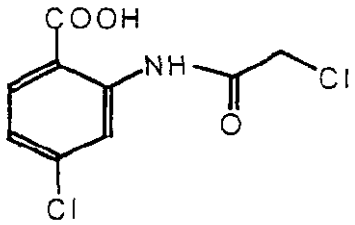
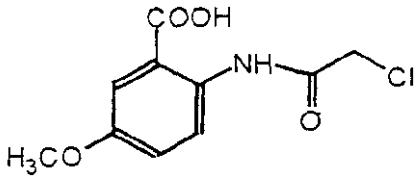
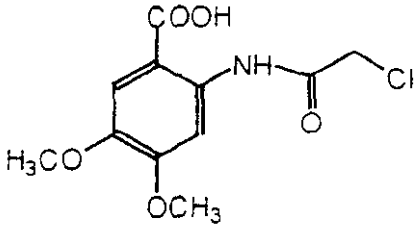
Compound	Structure	M.p. in ° C (Köfler)
1		194-196
2		182-184
3		236-238

TABLE II (continuation)

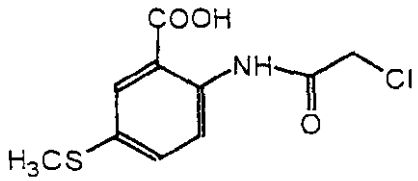
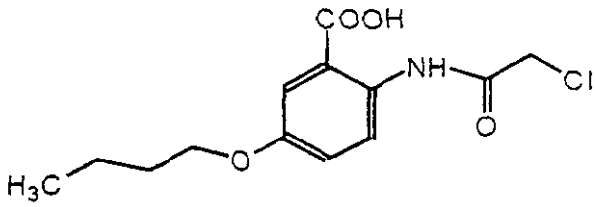
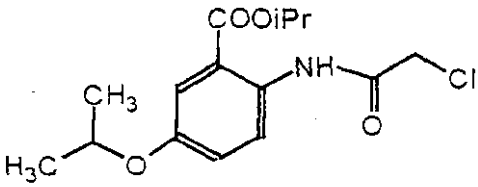
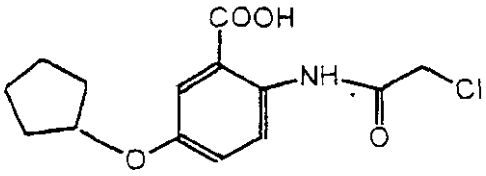
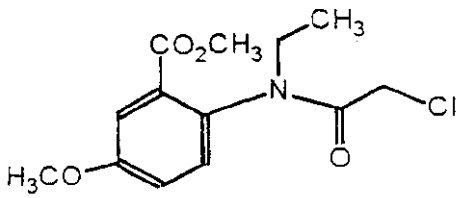
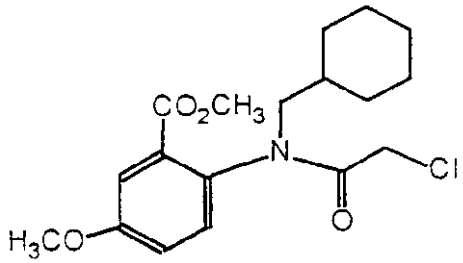
Compound	Structure	M.p. in ° C (Köfler)
4		180-182
5		155-157
6		83-85
7		217-219

TABLE II (continuation)

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

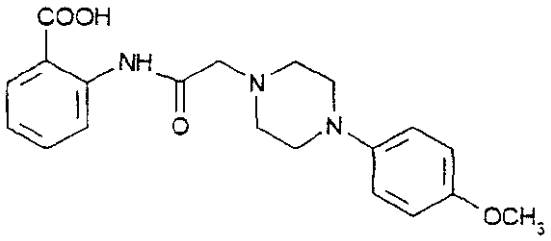
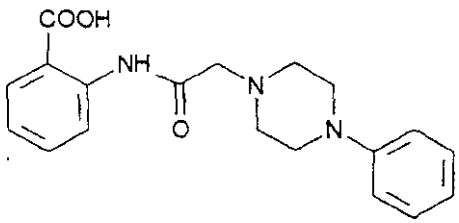
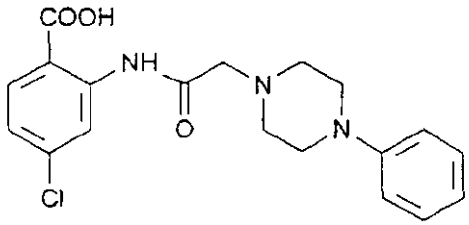
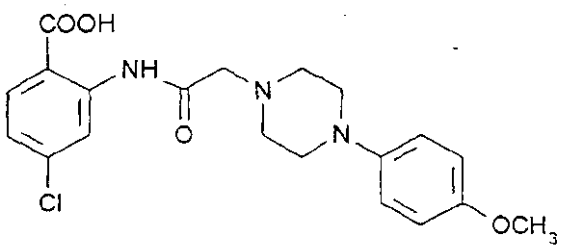
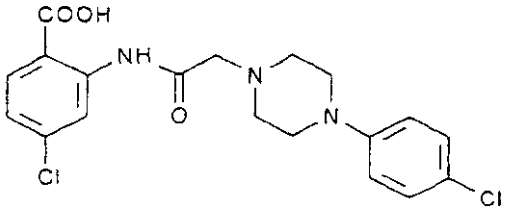
After recrystallization from a dioxane/DMF mixture, 14.9 g of 2-{[4-(4-fluorophenyl)-1-piperazinyl]acetamido}-4,5-(methylenedioxy)benzoic acid are obtained, which product melts at 254-256°C.

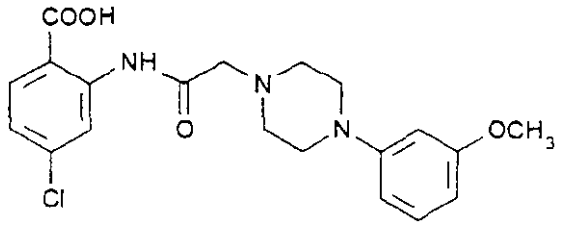
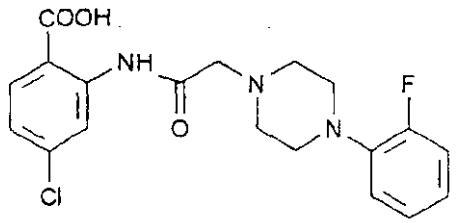
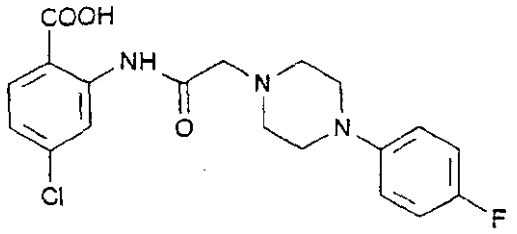
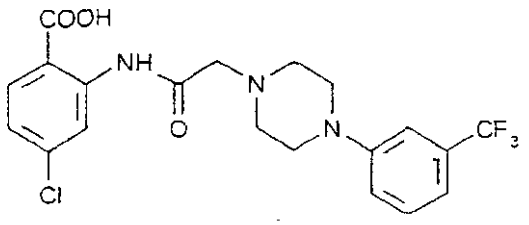
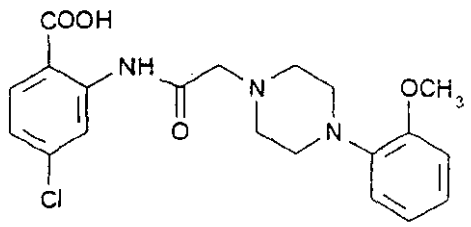
IR (KBr): 1654 cm^{-1} (C=O)

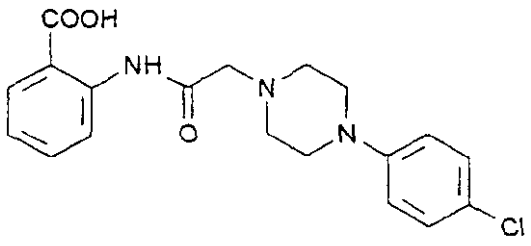
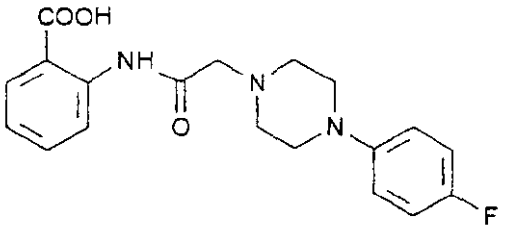
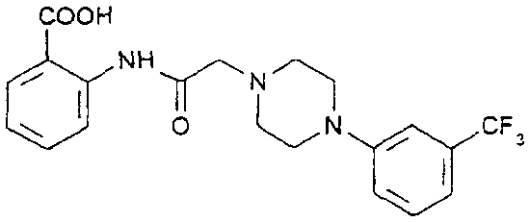
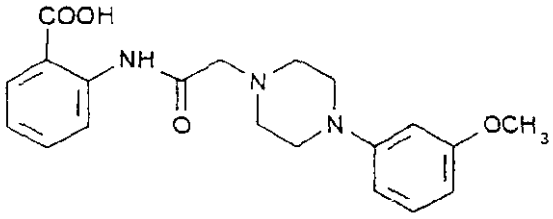
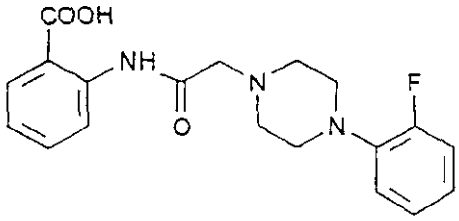
^1H NMR: (CF_3COOD, 200 MHz) δ ppm: 4.40 (8H, s, piperazinyl), 4.67 (2H, s, CH_2), 6.05 (2H, s, $O-CH_2-O$), 7.30 (2H, t, phenyl proton), 7.65 (3H, m, phenyl proton), 7.90 (1H, s, phenyl proton).

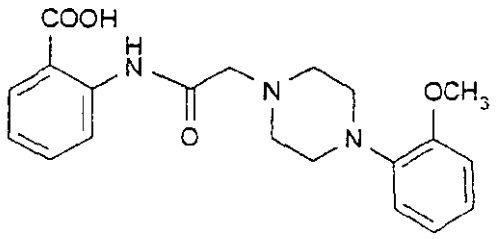
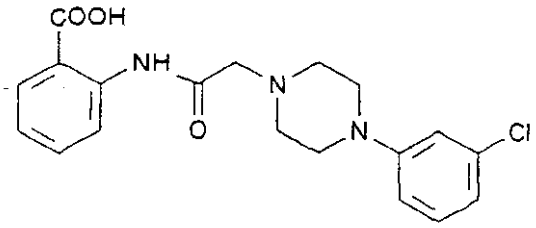
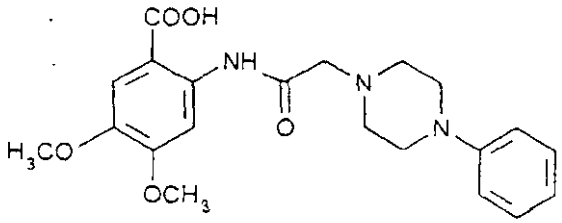
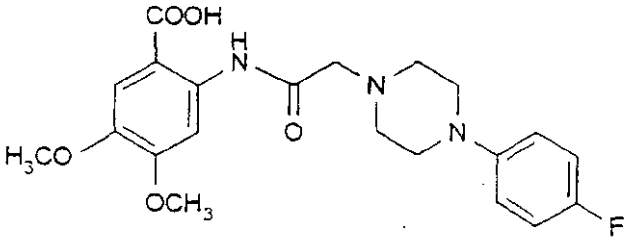
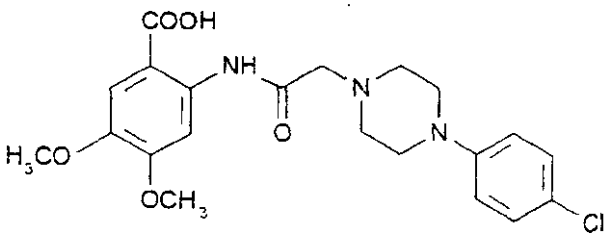
The formulae and characteristics of compounds of formula (I) have been combined in Table III.

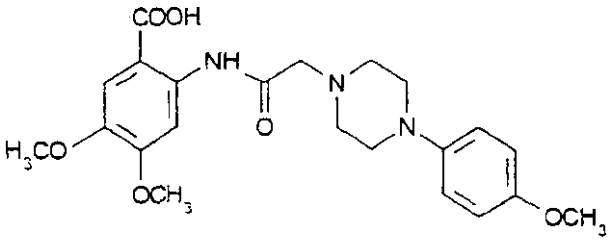
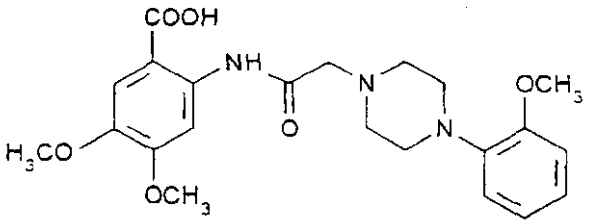
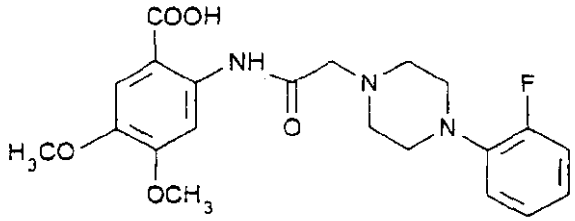
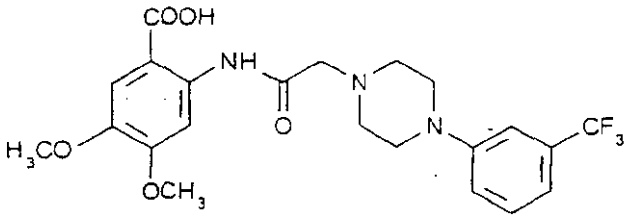
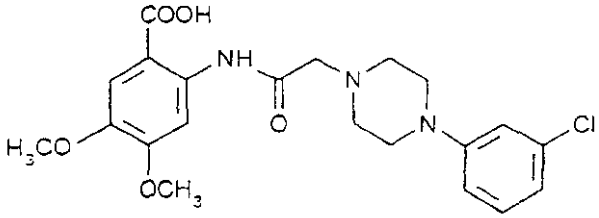
TABLE III

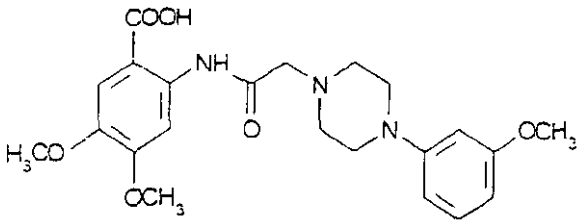
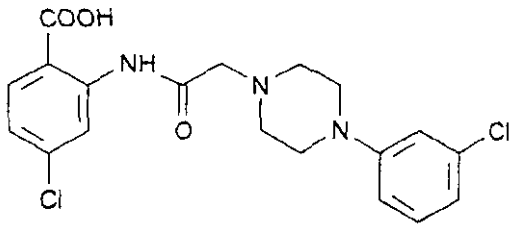
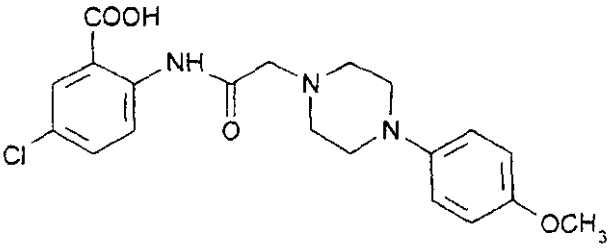
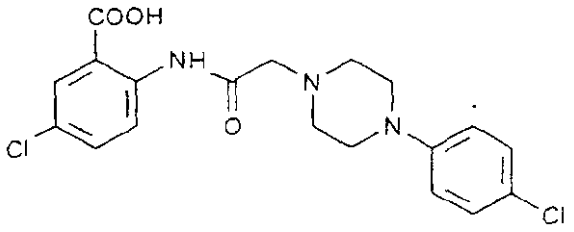
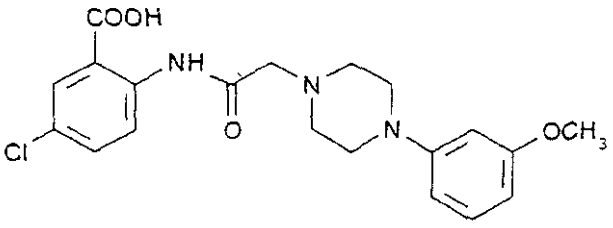
Compound	Structure	M.p. in °C (Köfler)	^{1}H NMR (200 MHz) δ ppm
1		185-187	d6-DMSO 2.60 (s,4H) 3.10 (s,4H) 3.20(s,2H) 3.70(s,3H) 6.80(q,4H) 7.10(t,1H) 7.55(t,1H) 8(d,1H) 8.7(d,1H)
2		233-235	CF_3COOD 4.25(s,8H) 4.65(s,2H) 7.30(t,1H) 7.55(s,5H) 7.70(t,1H) 8.25(m,2H)
3		248-250	CF_3COOD 4.25(s,8H) 4.55(s,2H) 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)

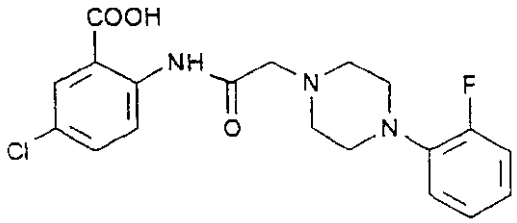
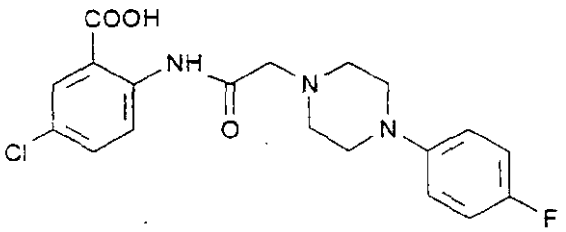
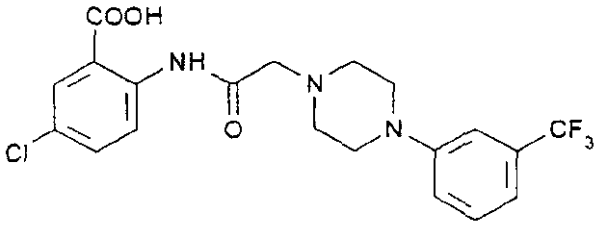
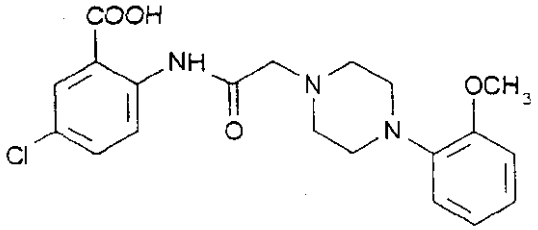
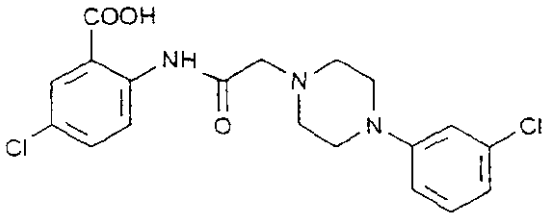
Com-pound	Structure	M.p. in °C (Köfler)	^{1}H NMR (200 MHZ) δ ppm
6		199-201	CF_3COOD 3.8(s,3H) 4.25(s,8H) 4.60(s,2H) 7.20(m,4H) 7.5(m,1H) 8.15(d,1H) 8.40(s,1H)
7		238-240	CF_3COOD 4.60(d,8H) 4.90(s,2H) 7.50(m,3H) 7.85(m,2H) 8.35(d,1H) 8.65(s,1H)
8		244-246	CF_3COOD 4.10(s,8H) 4.45(s,2H) 7.05(d,3H) 7.45(m,2H) 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)

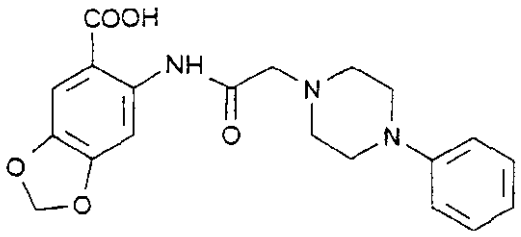
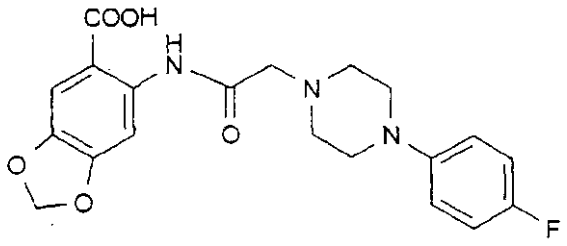
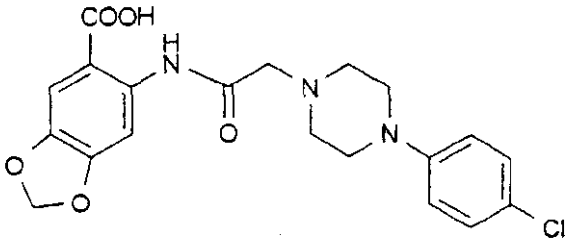
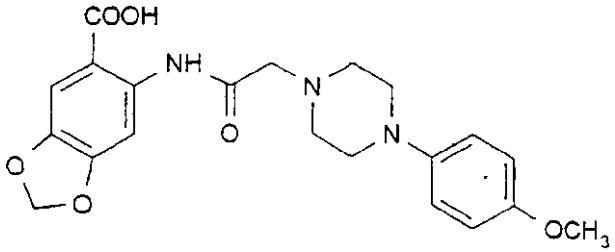
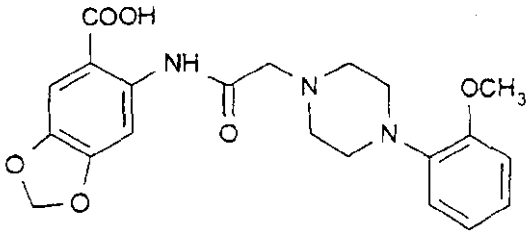
Com-pound	Structure	M.p. in °C (Köfler)	^{1}H NMR (200 MHZ) δ ppm
11		260-262	CF_3COOD 4.3(s,8H) 4.7(s,2H) 7.25(t,1H) 7.55(s,4H) 7.70(t,1H) 8.25(m,2H)
12		249-251	CF_3COOD 4.2(s,8H) 4.6(s,2H) 7.2(m,3H) 7.6(m,3H) 8.15(m,2H)
13		174-176	$CDCl_3$ 2.65(s,4H) 3.10(s,2H) 3.20(s,4H) 7,00(m,7H) 8.65(d,1H) 10,00(s,1H) 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)

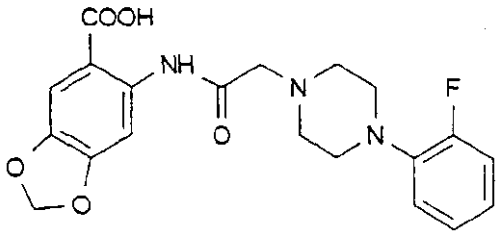
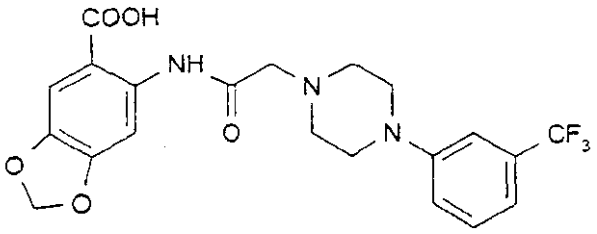
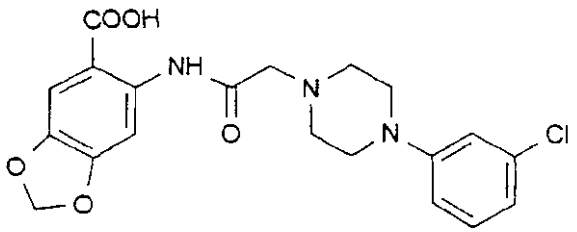
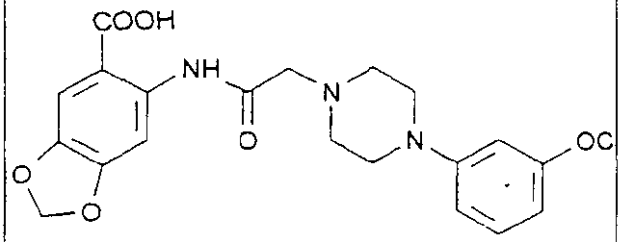
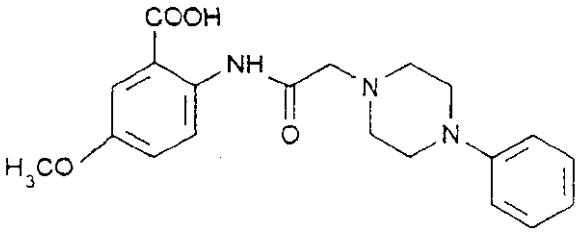
Com-pound	Structure	M.p. in °C (Köfler)	^{1}H NMR (200 MHZ) δ ppm
16		217-219	$CDCl_3$ 3.5(s,3H) 3.75(s,8H) 4.29(s,2H) 6.65(d,2H) 6.85(t,1H) 7.10(m,3H) 7.75(t,2H)
17		190-192	CF_3COOD 3.75(s,8H) 4.15(s,2H) 6.75(m,1H) 7.00(m,5H) 7.60(m,2H)
18		>265	CF_3COOD 3.65(s,6H) 4.15(s,8H) 4.5(s,2H) 7.55(s,5H) 7.65(s,1H) 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)

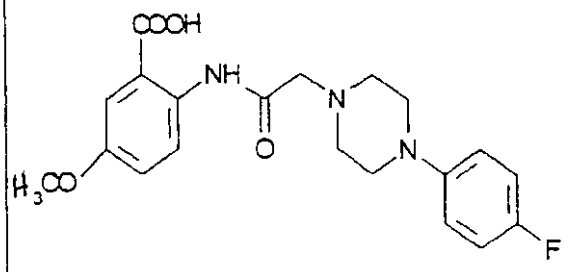
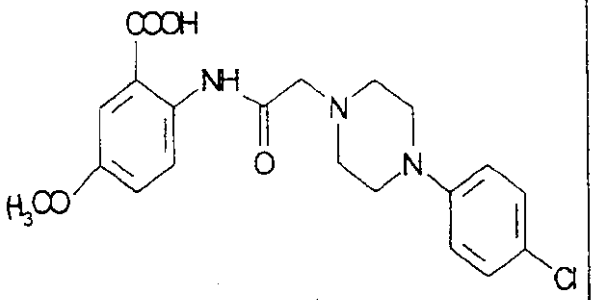
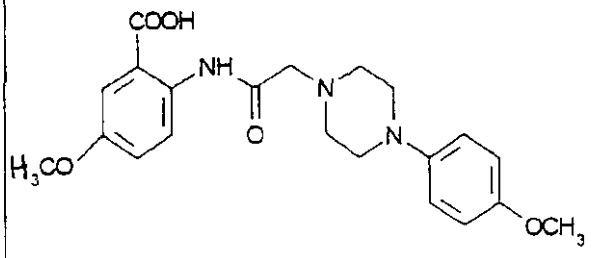
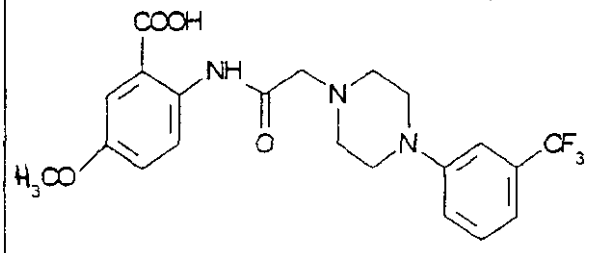
Com-pound	Structure	M.p. in °C (Köfler)	^{1}H NMR (200 MHZ) δ ppm
21		246-248	CF_3COOD 3.75(s,3H) 3.85(s,6H) 4.15(s,8H) 4.50(s,2H) 6.90(d,2H) 7.40(d,2H) 7.60(s,1H) 7.95(s,1H)
22		244-246	CF_3COOD 3.80(s,9H) 4.25(s,8H) 4.50(s,2H) 7,00(d,2H) 7.40(d,2H) 7.60(s,1H) 7.95(s,1H)
23		245-247	CF_3COOD 3.80(s,6H) 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)

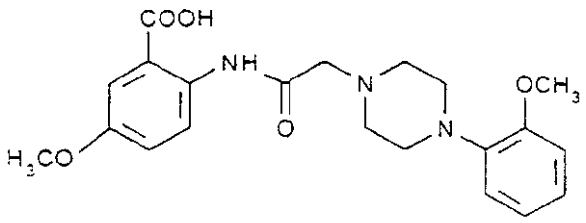
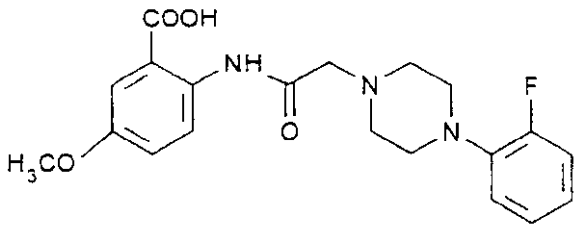
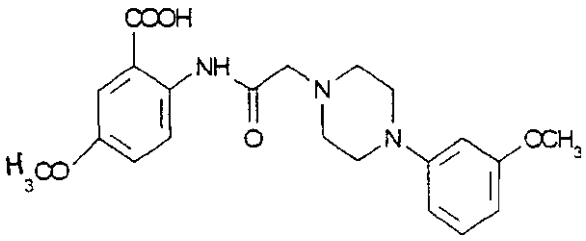
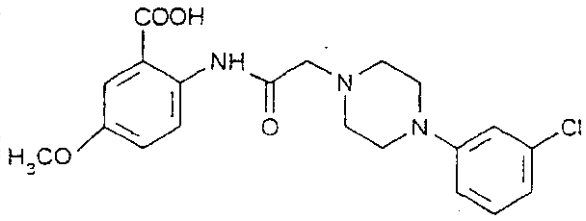
Com-pound	Structure	M.p. in °C (Köfler)	^{1}H NMR (200 MHZ) δ ppm
26		255-257	CF_3COOD 3.70(s,3H) 3.85(s,6H) 4.22(s,8H) 4.50(s,2H) 6.95(s,3H) 7.35(t,1H) 7.55(s,1H) 7.88(s,1H)
27		257-259	CF_3COOD 4.15+4.17(2s,8H) 4.50(s,2H) 7.10(d,1H) 7.40(m,4H) 8.00(d,1H) 8.25(s,1H)
28		239-241	CF_3COOD 3.70(s,3H) 4.10(s,8H) 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)

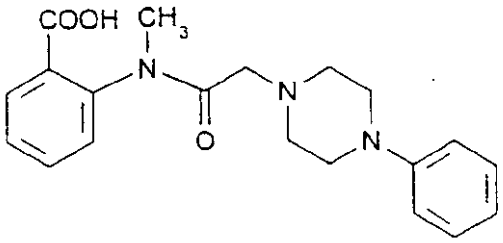
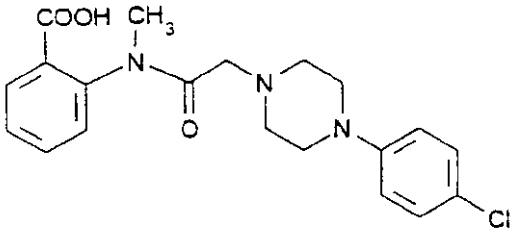
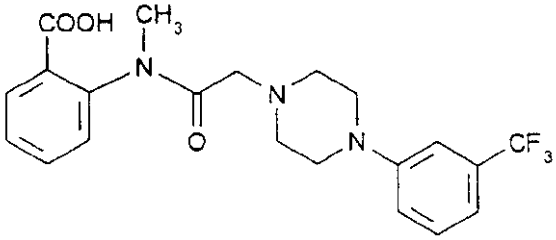
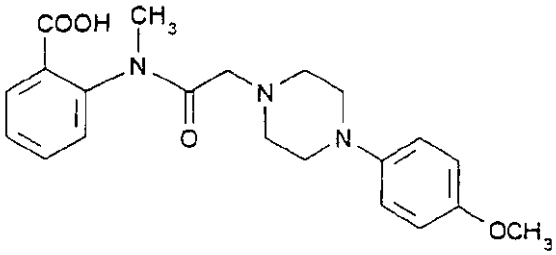
Com-pound	Structure	M.p. in °C (Köfler)	^{1}H NMR (200 MHZ) δ ppm
31		262-264	CF_3COOD 4.30+4.50(2s,8H) 4.67(s,2H) 7.30(m,2H) 7.65(m,3H) 8.15(s,1H) 8.25(d,1H)
32		245-247	CF_3COOD 4.05(s,8H) 4.40(s,2H) 7.05(t,2H) 7.40(d,3H) 7.90(s,1H) 8.05(d,1H)
33		213-215	CF_3COOD 4.25+4.40(2s,8H) 4.70(s,2H) 7.55(d,1H) 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)

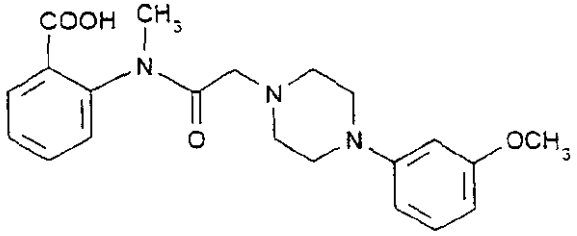
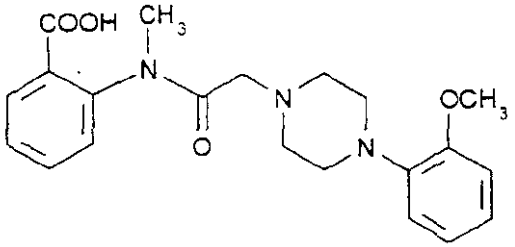
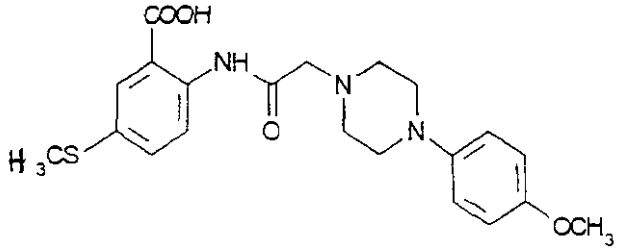
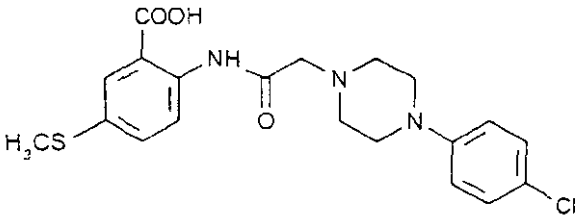
Com-pound	Structure	M.p. in °C (Köfler)	^{1}H NMR (200 MHZ) δ ppm
36		238-240	CF_3COOD 4.20(s,8H) 4.50(s,2H) 5.85(s,2H) 7.45(s,6H) 7.80(s,1H)
37		254-256	CF_3COOD 4.40(s,8H) 4.67(s,2H) 6.05(s,2H) 7.30(t,2H) 7.65(m,3H) 7.90(s,1H)
38		>265	CF_3COOD 4.22(s,8H) 4.57(s,2H) 5.92(s,2H) 7.52(s,5H) 7.80(s,1H)
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)

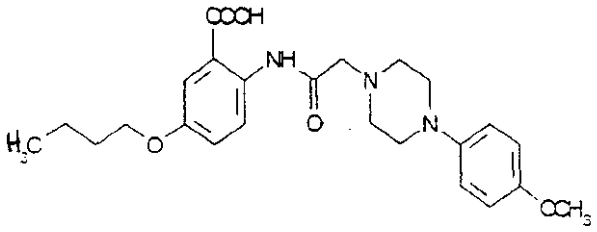
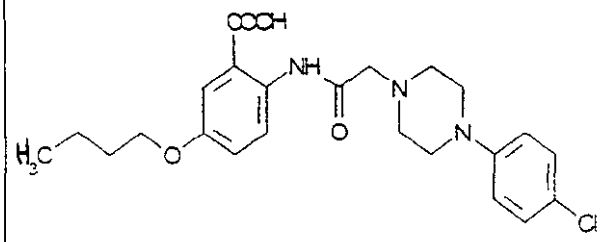
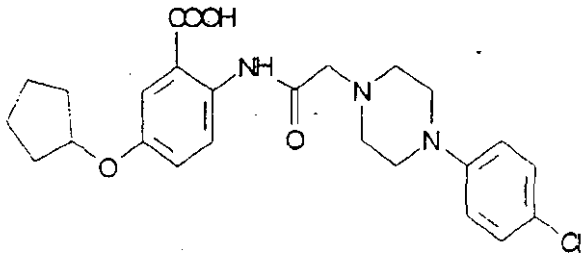
Com-pound	Structure	M.p. in °C (Köfler)	^{1}H NMR (200 MHZ) δ ppm
41		236-238	CF_3COOD 4.23+4.38(2s,8H) 4.56(s,2H) 5.97(s,2H) 7.31(m,2H) 7.55(m,3H) 7.76(s,1H)
42		228-230	CF_3COOD 4.05+4.15(2s,8H) 4.35(s,2H) 5.75(s,2H) 7.30(s,1H) 7.60(m,5H)
43		240-242	CF_3COOD 4.00(s,8H) 4.37(s,2H) 5.75(s,2H) 7.35(d,5H) 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)

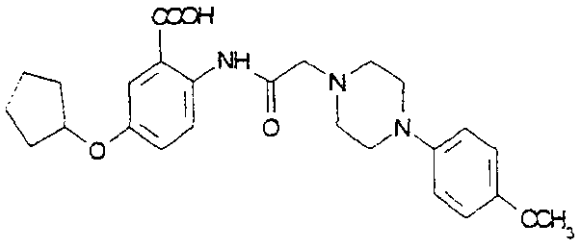
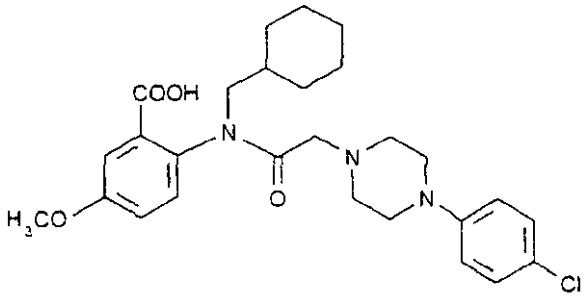
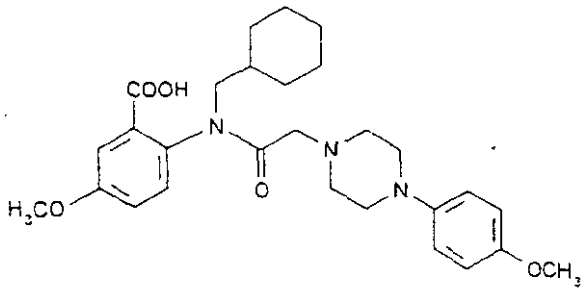
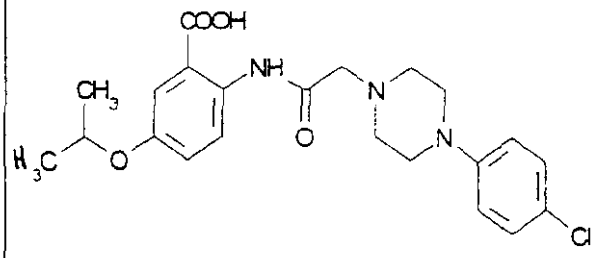
Com-pound	Structure	M.p. in °C (Köfler)	^{1}H NMR (200 MHz)
46		197-199	CF_3COOD 3.75(s,3H) 4.20(s,8H) 4.50(s,2H) 7.10(m,3H) 7.50(t,2H) 7.70(s,1H) 8.05(d,1H)
47		221-223	CF_3COOD 3.80(s,3H) 4.20(s,8H) 4.55(s,2H) 7.15(d,1H) 7.40(s,4H) 7.70(s,1H) 8.00(d,1H)
48		198-200	CF_3COOD 3.85(d,6H) 4.25(s,8H) 4.75(s,2H)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

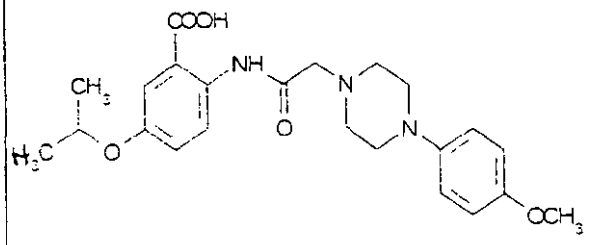
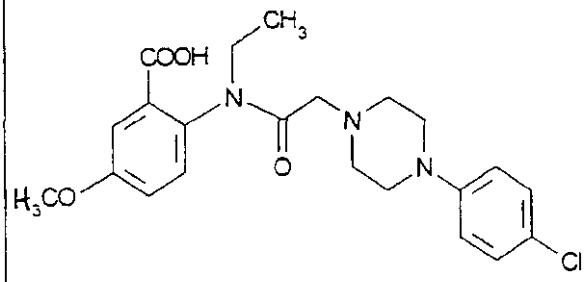
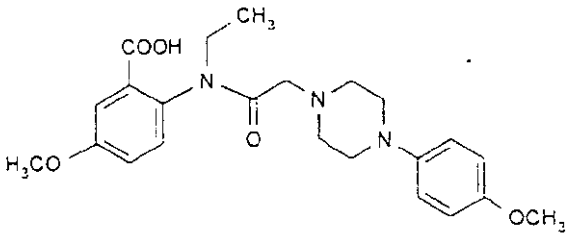
Com-pound	Structure	M.p. in °C (Köfler)	^{1}H NMR (200 MHz)
50		200-202	CF_3COOD 3.65(s,3H) 3.70(s,3H) 4.12(s,8H) 4.42(s,2H) 7.00(d,2H) 7.10(d,1H) 7.40(m,2H) 7.65(s,1H) 8.00(d,1H)
51		179-181	CF_3COOD 3.72(s,3H) 4.25(d,8H) 4.50(s,2H) 7.15(m,3H) 7.50(q,2H) 7.65(d,1H) 8.00(d,1H)
52		177-179	CF_3COOD 3.88(s,3H) 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)

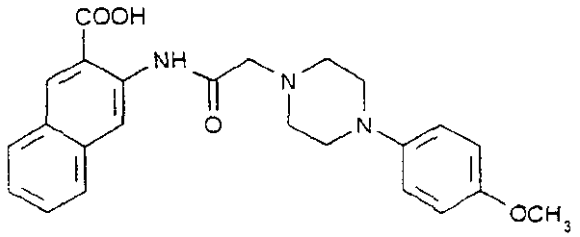
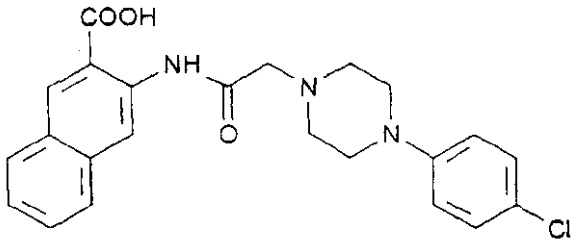
Com-pound	Structure	M.p. in °C (Köfler)	^{1}H NMR (200 MHz)
54		210-212	d_6-DMSO 2.42(d,4H) 2.90(s,2H) 3.10(s,4H) 3.18(s,3H) 6.80(t,1H) 6.93(d,2H) 7.25(t,2H) 7.50(m,2H) 7.70(t,1H) 8.00(d,1H)
55		226-227	d_6-DMSO 2.34(d,4H) 2.81(s,2H) 3.00+3.10(2s,7H) 6.93(d,2H) 7.22(d,2H) 7.47(m,2H) 7.70(d,1H) 7.95(d,1H)
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 (Köfler)	^{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 (Köfler)	^{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.

Study of the anti-diabetic activity in the NOSTZ rat

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).

30

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.

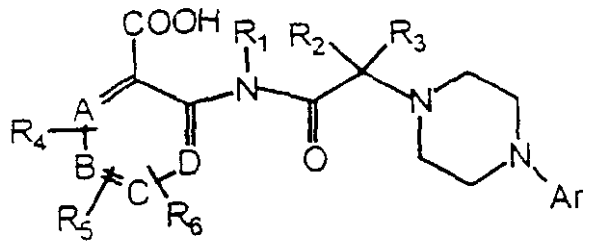
These results are expressed as percentage of change in glycaemia at D4 (4 days of treatment) in comparison with D0 (before treatment).

TABLE IV

Compound 化合物	20 mg/kg/d	200 mg/kg/d
	% 在D4的%血糖 Glycaemia at D4	% 在D4的%血糖 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_5)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, (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 another, from:

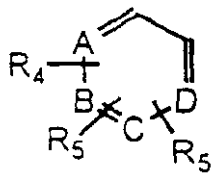
- hydrogen,

- 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.

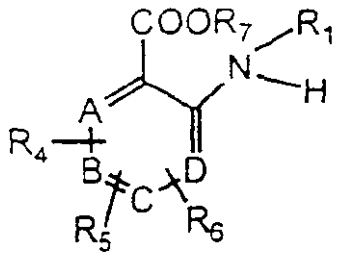
2. A compound as claimed in Claim 1, in which the base component of the ring system



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.

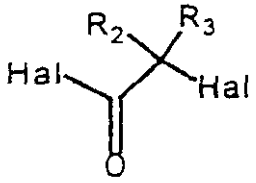
4. A process for the preparation of a compound according to Claim 1, comprising the reaction of an aromatic amine of the formula (II):



(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):

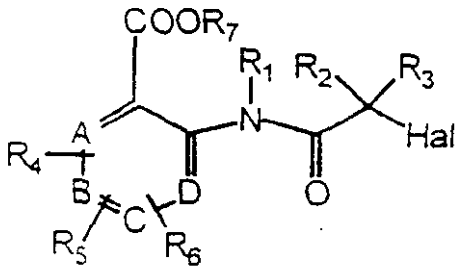


(III)

in which R_2 and R_3 are as defined above,

Hal is selected from chlorine and bromine,

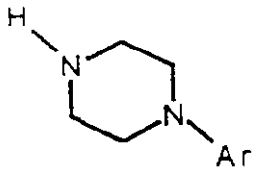
in order to form a compound of the formula (IV):



(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,

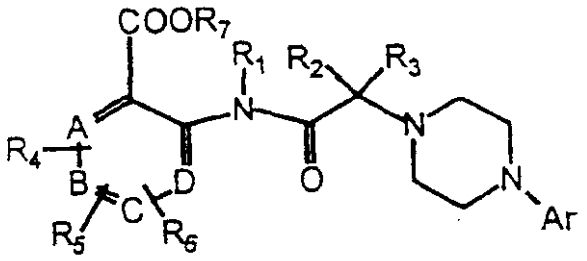
and the reaction of the compound of the formula (IV) with a compound of the formula (V):



(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. A method for the treatment of diabetes which comprises administering to a human in need thereof an effective amount of a compound as claimed in Claim 1.

9. A method for the treatment of diabetes which comprises administering to a human in need thereof an effective amount of a compound as claimed in Claim 2.

10. A method for the treatment of diabetes which comprises administering to a human in need thereof an effective amount of a compound as claimed in Claim 3.

INTERNATIONAL SEARCH REPORT

Inte I Application No
PCT/EP 98/03431

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D295/15 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 98 27078 A (MERCK PATENT GMBH) 25 June 1998 see claims 1-4	1-10
A	FR 2 693 722 A (LES LABORATOIRES MERAM S.A.) 21 January 1994 see claims 1-9	1-10
A	EP 0 638 568 A (ADIR ET COMPAGNIE) 15 February 1995 see claims 1-13	1-10
A	BE 850 709 A (LABORATOIRE L. LAFON) 16 May 1977 see claims 1-3	1-10

-/--

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 January 1999	05/02/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Herz, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte : Application No
PCT/EP 98/03431

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 26924 A (SUNTORY LTD.) 12 February 1997 see claims 1-13	1-10

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte ! Application No
PCT/EP 98/03431

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		HU 9602977 A	28-08-1997
		US 5723475 A	03-03-1998

[19]中华人民共和国国家知识产权局

[51]Int. Cl[7]
C07D295/15
A61K 31/495

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IHC 001955
C 003180

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[85]进入国家阶段日期 2000.12.5
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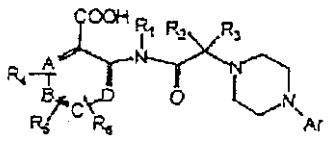
[74]专利代理机构 中国国际贸易促进委员会专利商标事务所
代理人 杜京英

权利要求书4页 说明书28页 附图页数0页

[54]发明名称 用作抗糖尿病剂的α-(1-哌嗪基)乙酰氨基芳烃羧酸衍生物

[57]摘要

本发明涉及通式(I)化合物。这些化合物可用于治疗糖尿病。

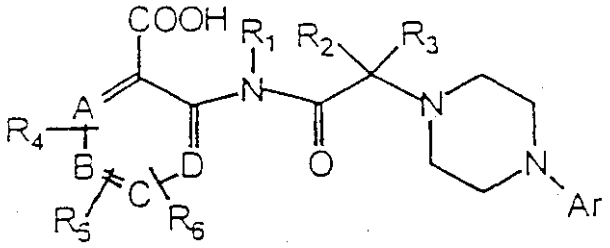


(I)

ISSN1008-4274

权 利 要 求 书

1. 选自式(I)化合物、其溶剂化物以及其可药用盐的化合物:



(I)

其中:

Ar选自

- 具有6-14个碳原子的单环、二环或三环芳基,

- 选自吡啶基、嘧啶基、吡咯基、呋喃基、噻吩基、喹啉基、吲哚基、苯并噻吩基、苯并呋喃基、苯并吡喃基、苯并噻喃基、二苯并呋喃基、咔唑基和苯并噻嗪基的杂芳基,

该Ar可带有1-3个选自下述的取代基: C_1-C_8烷基、(C_3-C_8)环烷基(C_1-C_6)烷基、C_1-C_8烷氧基、(C_3-C_8)环烷氧基(C_1-C_6)烷基、(C_3-C_8)环烷基(C_1-C_6)烷氧基(C_1-C_6)烷基、(C_3-C_8)环烷氧基、(C_3-C_8)环烷基(C_1-C_6)烷氧基、(C_1-C_6)烷氧基(C_1-C_6)烷基、C_6-C_{14}芳基、C_6-C_{14}杂芳基、(C_6-C_{14})杂芳基(C_1-C_6)烷基、(C_6-C_{14})芳基(C_1-C_6)烷基、(C_6-C_{14})芳基(C_1-C_6)烷基(C_6-C_{14})芳基、(C_6-C_{14})芳氧基、(C_6-C_{14})芳氧基(C_1-C_6)烷基、(C_6-C_{14})芳基(C_1-C_6)烷氧基、(C_6-C_{14})芳基(C_1-C_6)烷氧基(C_1-C_6)烷基、卤素、三氟甲基、三氟甲氧基、氰基、羟基、硝基、氨基、羧基、(C_1-C_6)烷氧基羰基、氨基甲酰基、(C_1-C_8)烷硫基、(C_1-C_8)烷基亚磺酰基、(C_1-C_8)烷基磺酰基、磺酰氨基、(C_1-C_8)烷基磺酰氨基、氨磺酰基、和(C_1-C_8)烷基羰基氨基,或者这些取代基中的两个形成亚甲二氧基,

在Ar的定义中,排除4-羧基苯基和取代的4-羧基苯基,

R_1、R_2和R_3彼此独立地选自:

- 氢原子,

- C_1-C_8烷基、(C_1-C_6)烷氧基(C_1-C_6)烷基,

- 含有 3 - 8 个碳原子的环烷基、(C_3-C_8)环烷基(C_1-C_6)烷基、(C_3-C_8)环烷氧基(C_1-C_6)烷基和(C_3-C_8)环烷基(C_1-C_6)烷氧基(C_1-C_6)烷基，

- C_6-C_{14} 芳基、C_6-C_{14} 杂芳基、(C_6-C_{14})杂芳基(C_1-C_6)烷基、(C_6-C_{14})芳基(C_1-C_6)烷基、(C_6-C_{14})芳基(C_1-C_6)烷基(C_6-C_{14})芳基、(C_6-C_{14})芳基(C_1-C_6)烷氧基(C_1-C_6)烷基和(C_6-C_{14})芳氧基(C_1-C_6)烷基，

A、B、C 和 D 是=CH-基团，它们中的一个或两个也可以是氮原子，

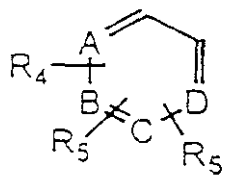
R_4、R_5和 R_6彼此独立地选自：

- 氢原子，

- C_1-C_8 烷基、(C_3-C_8)环烷基(C_1-C_6)烷基、C_1-C_8 烷氧基、(C_3-C_8)环烷氧基(C_1-C_6)烷基、(C_3-C_8)环烷氧基、(C_3-C_8)环烷基(C_1-C_6)烷氧基、(C_3-C_8)环烷基(C_1-C_6)烷氧基(C_1-C_6)烷基、(C_1-C_6)烷氧基(C_1-C_6)烷基、C_6-C_{14} 芳基、(C_6-C_{14})芳基(C_1-C_6)烷基、(C_6-C_{14})芳基(C_1-C_6)烷基(C_6-C_{14})芳基、(C_6-C_{14})芳氧基、(C_6-C_{14})芳氧基(C_1-C_6)烷基、(C_6-C_{14})芳基(C_1-C_6)烷氧基、(C_6-C_{14})芳基(C_1-C_6)烷氧基(C_1-C_6)烷基、卤素、三氟甲基、三氟甲氧基、氰基、羧基、羟基、硝基、氨基、(C_1-C_6)烷氧基羰基、氨基甲酰基、(C_1-C_6)烷硫基、(C_1-C_8)烷基亚磺酰基、(C_1-C_8)烷基磺酰基、磺酰氨基、(C_1-C_8)烷基磺酰氨基、氨磺酰基和(C_1-C_8)烷基羰基氨基，这些基团中的两个可形成亚甲二氧基或与它们所连接的环稠合的苯基环，

各芳基自身也可被 1 - 3 个选自下述的取代基取代：C_1-C_8 烷基、C_1-C_8 烷氧基、卤素、三氟甲基、三氟甲氧基、羟基、硝基和氨基。

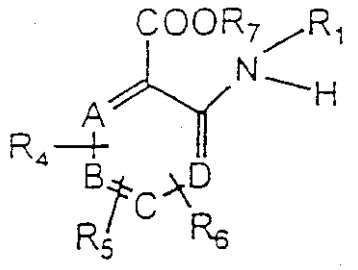
2. 权利要求 1 的化合物，其中所述环系的基本组成部分



是苯基环。

3. 权利要求 2 的化合物，其中 R_4、R_5和 R_6中至少一个是 C_1-C_8 烷氧基，或者这些基团中的两个形成亚甲二氧基。

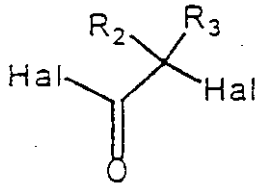
4. 制备权利要求 1 的化合物的方法，包括将式(II)芳胺



(II)

其中 A、B、C、D、R_1、R_4、R_5和 R_6定义同上，并且 R_7选自氢原子、C_1-C_6烷基和苄基，

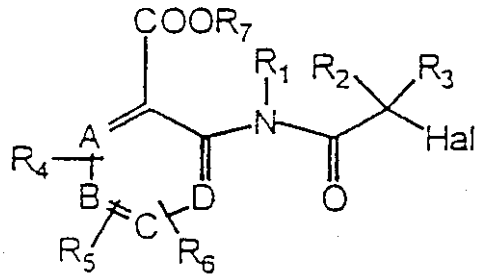
与式(III)卤代酰卤反应



(III)

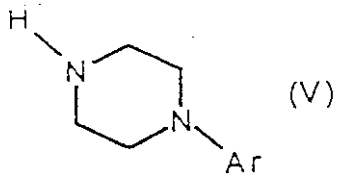
其中 R_2和 R_3定义同上，Hal 选自氯和溴，

以生成式(IV)化合物：



(IV)

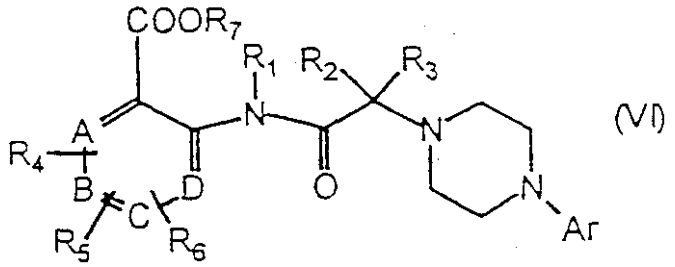
其中 A、B、C、D、R_1、R_2、R_3、R_4、R_5、R_6、R_7和 Hal 定义同上，并在碱性试剂存在下将式(IV)化合物与式(V)化合物反应：



(V)

其中 Ar 定义同上，

以生成式(VI)化合物：



(VI)

其中 Ar、A、B、C、D、R_1、R_2、R_3、R_4、R_5、R_6和 R_7 定义同上，

并且，当 R_7 是烷基时，将该化合物水解以生成式(I)化合物，

以及当 R_7 是苄基时，将该化合物氢解以生成式(I)化合物。

5. 包含有效量权利要求 1 的化合物的药物组合物。

6. 包含有效量权利要求 2 的化合物的药物组合物。

7. 包含有效量权利要求 3 的化合物的药物组合物。

8. 治疗糖尿病的方法，包括将有效量的如权利要求 1 所述的化合物对需要治疗的人给药。

9. 治疗糖尿病的方法，包括将有效量的如权利要求 2 所述的化合物对需要治疗的人给药。

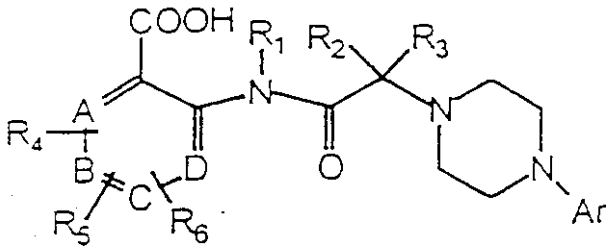
10. 治疗糖尿病的方法，包括将有效量的如权利要求 3 所述的化合物对需要治疗的人给药。

说　明　书

用作抗糖尿病剂的α-(1-哌嗪基)乙酰氨基芳烃羧酸衍生物

本发明涉及可用于治疗糖尿病的新的α-(1-哌嗪基)乙酰氨基芳烃羧酸衍生物。

因此，本发明的主题是通式(I)化合物、其溶剂化物以及其可药用盐：



(I)

其中：

Ar 选自

- 具有 6 - 14 个碳原子的单环、二环或三环芳基，
- 选自吡啶基、嘧啶基、吡咯基、呋喃基、噻吩基、喹啉基、吲哚基、苯并噻吩基、苯并呋喃基、苯并吡喃基、苯并噻喃基、二苯并呋喃基、咔唑基和苯并噻嗪基的杂芳基，

该 **Ar** 可带有 1 - 3 个选自下述的取代基：C_1-C_8烷基、(C_3-C_8)环烷基(C_1-C_6)烷基、C_1-C_8 烷氧基、(C_3-C_8)环烷氧基(C_1-C_6)烷基、(C_3-C_8)环烷基(C_1-C_6)烷氧基(C_1-C_6)烷基、(C_3-C_8)环烷氧基、(C_3-C_8)环烷基(C_1-C_6)烷氧基、(C_1-C_6)烷氧基(C_1-C_6)烷基、C_6-C_{14} 芳基、C_6-C_{14} 杂芳基、(C_6-C_{14})杂芳基(C_1-C_6)烷基、(C_6-C_{14})芳基(C_1-C_6)烷基、(C_6-C_{14})芳基(C_1-C_6)烷基(C_6-C_{14})芳基、(C_6-C_{14})芳氧基、(C_6-C_{14})芳氧基(C_1-C_6)烷基、(C_6-C_{14})芳基(C_1-C_6)烷氧基、(C_6-C_{14})芳基(C_1-C_6)烷氧基(C_1-C_6)烷基、卤素、三氟甲基、三氟甲氧基、氰基、羟基、硝基、氨基、羧基、(C_1-C_6)烷氧基羰基、氨基甲酰基、(C_1-C_8)烷硫基、(C_1-C_8)烷基亚磺酰

基、(C_1-C_8)烷基磺酰基、磺酰氨基、(C_1-C_8)烷基磺酰氨基、氨磺酰基、或(C_1-C_8)烷基羰基氨基，或者这些取代基中的两个形成亚甲二氧基，

在 Ar 的定义中，排除 4-羧基苯基和取代的 4-羧基苯基，

R_1、R_2 和 R_3 彼此独立地选自：

- 氢原子，

- C_1-C_8 烷基或(C_1-C_6)烷氧基(C_1-C_6)烷基，

- 含有 3 - 8 个碳原子的环烷基、(C_3-C_8)环烷基(C_1-C_6)烷基、(C_3-C_8)环烷氧基(C_1-C_6)烷基、或(C_3-C_8)环烷基(C_1-C_6)烷氧基(C_1-C_6)烷基，

- C_6-C_{14} 芳基、C_6-C_{14} 杂芳基、(C_6-C_{14})杂芳基(C_1-C_6)烷基、(C_6-C_{14})芳基(C_1-C_6)烷基、(C_6-C_{14})芳基(C_1-C_6)烷基(C_6-C_{14})芳基、(C_6-C_{14})芳基(C_1-C_6)烷氧基(C_1-C_6)烷基、或(C_6-C_{14})芳氧基(C_1-C_6)烷基，

A、B、C 和 D 是=CH-，它们中的一个或两个也可以是氮原子，

R_4、R_5 和 R_6 彼此独立地选自：

- 氢原子，

- C_1-C_8 烷基、(C_3-C_8)环烷基(C_1-C_6)烷基、C_1-C_8 烷氧基、(C_3-C_8)环烷氧基(C_1-C_6)烷基、(C_3-C_8)环烷氧基、(C_3-C_8)环烷基(C_1-C_6)烷氧基、(C_3-C_8)环烷基(C_1-C_6)烷氧基(C_1-C_6)烷基、(C_1-C_6)烷氧基(C_1-C_6)烷基、C_6-C_{14} 芳基、(C_6-C_{14})芳基(C_1-C_6)烷基、(C_6-C_{14})芳基(C_1-C_6)烷基(C_6-C_{14})芳基、(C_6-C_{14})芳氧基、(C_6-C_{14})芳氧基(C_1-C_6)烷基、(C_6-C_{14})芳基(C_1-C_6)烷氧基、或(C_6-C_{14})芳基(C_1-C_6)烷氧基(C_1-C_6)烷基、卤素或三氟甲基、三氟甲氧基、氰基、羧基、羟基、硝基、氨基、(C_1-C_6)烷氧基羰基、氨基甲酰基、(C_1-C_6)烷硫基、(C_1-C_8)烷基亚磺酰基、(C_1-C_8)烷基磺酰基、磺酰氨基、(C_1-C_8)烷基磺酰氨基、氨磺酰基、或(C_1-C_8)烷基羰基氨基，这些基团中的两个可形成亚甲二氧基或与它们所连接的环稠合的苯基，

各芳基自身也可被 1 - 3 个选自下述的取代基取代：C_1-C_8 烷基或 C_1-C_8 烷氧基、卤素或三氟甲基、三氟甲氧基、羟基、硝基和氨基。

可提及的芳基的实例有苯基、α-萘基、β-萘基和芴基。

C_1-C_8 烷基可以是直链或支链。可提及的实例有甲基、乙基、丙基、

异丙基、丁基、异丁基、叔丁基和戊基。

类似地，C_1-C_8 烷氧基可以是直链或支链。可提及的实例有甲氧基、乙氧基、丙氧基、异丙氧基、丁氧基和异丁氧基。

卤素可选自氟、氯、溴和碘。

在 R_1、R_2 和 R_3 的定义中，杂芳基可具体地定义为在 Ar 的定义中所定义的杂芳基。

本发明还涉及通式(I)化合物的互变异构体、对映异构体、非对映异构体以及差向异构体。

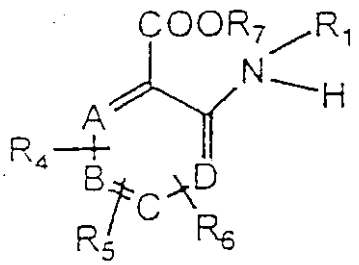
通式(I)化合物具有羧酸官能团，并且可成盐，从而以碱加成盐形式存在。

通式(I)化合物的碱加成盐的实例包括可药用盐，例如钠盐、钾盐、钙盐以及其它同类盐。

还可用胺使通式(I)化合物成盐以形成可药用盐。例如，可用葡糖胺、N-甲基葡糖胺、N,N-二甲基葡糖胺、乙醇胺、吗啉、N-甲基吗啉或赖氨酸使通式(I)化合物成盐。

通式(I)化合物具有氮原子，从而可用无机酸或有机酸使其形成单盐或双盐。通式(I)化合物的酸加成盐的实例包括可药用盐，例如但不限于盐酸盐、氢溴酸盐、硫酸盐、琥珀酸盐、马来酸盐、富马酸盐、苹果酸盐或酒石酸盐，以及磺酸盐例如甲磺酸盐、苯磺酸盐或甲苯磺酸盐。

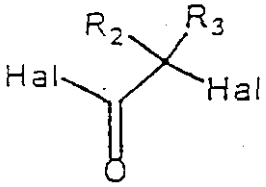
本发明还涉及制备通式(I)化合物的方法。本发明方法包括，将通式(II)芳胺



(II)

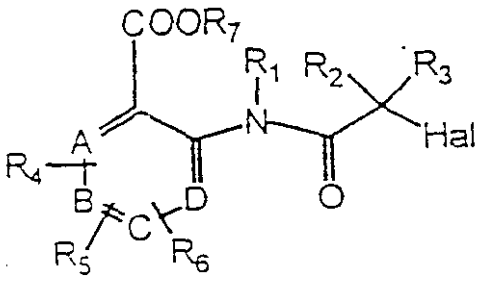
其中 A、B、C、D、R_1、R_4、R_5 和 R_6 定义同上，并且 R_7 是氢原子、C_1-C_6 烷基或苄基，

与通式(III)卤代酰卤反应



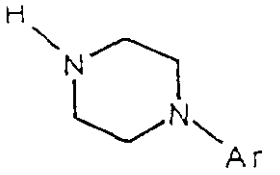
(III)

其中 R_2 和 R_3 定义同上，Hal 代表氯或溴原子，
以生成通式(IV)化合物：



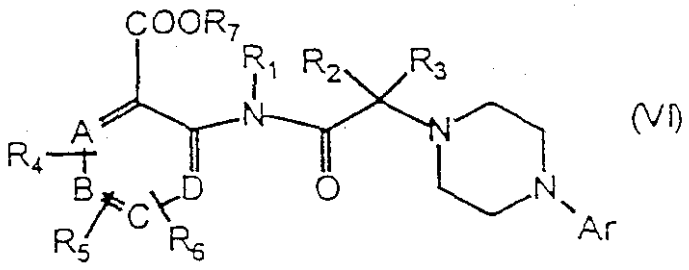
(IV)

其中 A、B、C、D、R_1、R_2、R_3、R_4、R_5、R_6、R_7 和 Hal 定义同上，并在碱性试剂，例如三乙胺存在下将通式(IV)化合物与通式(V)化合物反应：



(V)

其中 Ar 定义同上，
以生成通式(VI)化合物：



(VI)

其中 Ar、A、B、C、D、R_1、R_2、R_3、R_4、R_5、R_6 和 R_7 定义同上。

当 R_7 是烷基时，可通过常规酸性或碱性水解方法将通式(VI)化合物水解，以生成通式(I)化合物。

当 R_7 是苄基时，可在催化剂，例如钯/炭存在下将通式(VI)化合物氢解，以生成通式(I)化合物。

式(II)和(V)化合物是已知化合物，或者可依据已知方法制得。

例如，《有机制备和方法·国际》(Organic Preparation and Procedures International), 13, 189, 1981 中描述了式(II)化合物。

式(V)化合物可通过 R. Ratouis 等人(《药物化学杂志》J. Med. Chem., 8, 104, 1965)或 Prelog 等人(Collection Czechoslov. Chem. Communications, 6, 211, 1934)的方法制得。

例如，可在碱性试剂，例如稀氢氧化钠存在下将其中 R_7 是烷基的式(VI)化合物水解。

可通过下述方法分离式(I)化合物的对映异构体：将酸(I)与旋光性碱形成的盐在溶剂例如丙酮、乙酸乙酯或异丙醇中分级重结晶，然后依据常规方法用无机酸或有机酸将该盐置换成旋光性酸。

本发明化合物可用于治疗糖尿病，尤其是非胰岛素依赖型糖尿病，这是因为本发明化合物具有降低血糖作用、并且在活性剂量下没有毒性。

因此，本发明的另一主题是包含有效量本发明化合物的药物组合物。

本发明药物组合物可以呈用于非胃肠道给药、口服给药、直肠给药、经粘膜或经皮给药的剂型。

本发明药物组合物可以呈注射液或注射用悬浮液、或多剂量容器、或未包衣或包衣片剂、糖包衣片剂、包括硬明胶胶囊剂在内的胶囊剂、丸剂、扁囊剂、粉剂、栓剂、直肠给药用胶囊、在极性溶剂中的经皮给药用或经粘膜给药用的溶液或悬浮剂形式。

对于固体剂型，适用于所述给药的赋形剂是纤维素或微晶纤维素、碱土金属碳酸盐、磷酸镁、淀粉、改性淀粉或乳糖。

可可豆脂或聚乙二醇硬脂酸酯是优选的直肠给药用赋形剂。

水、水溶液、生理溶液或等渗溶液是最常用的非胃肠道给药用载体。

根据所治疗的适应征和给药途径以及患者年龄和体重，剂量可在宽的范围内变化。

下述实施例举例说明了式(I)化合物以及式(II)和(IV)中间体的制备。

A－制备式(II)化合物的实施例.

制备 2-环己基甲基氨基-5-甲氧基苯甲酸甲酯

在 1 升氢化装置中，将 17.6 g 5-甲氧基邻氨基苯甲酸甲酯、11.8 g 环己烷甲醛和 2 g 10％钯/炭（50％水）加入 200 ml 甲醇中。

将该装置置于氢气氛下并在室温搅拌 3 小时。

加入 300 ml 二氯甲烷，通过过滤除去钯/炭，将所得滤液真空浓缩。

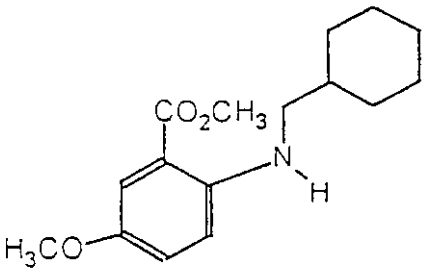
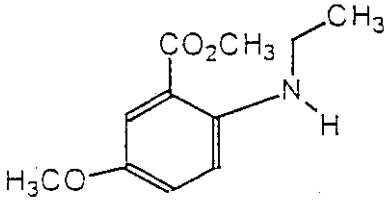
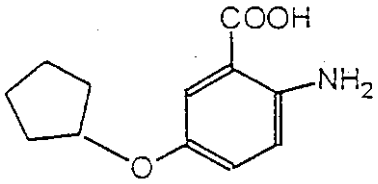
将所得油状物用乙醇（200 ml）和水（50 ml）混合物结晶，获得了 25.4 g 黄色固体，其熔点为 58－60℃。

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, 环己基), 2.93 (2H, t, CH_2), 3.68 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 6.56 (1H, d, 苯基质子), 6.96 (1H, dd, 苯基质子), 7.34 (2H, d + s, 苯基质子 + NH).

式(II)化合物的结构式和特征如表 I 所示。

表 I

化合物	结构式	
1		M.p. °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. °C (Köfler) 147-149

B - 制备式(IV)化合物的实施例

制备 4-氯-2-(氯乙酰氨基)苯甲酸

在搅拌下，将 25.5 ml 氯乙酰氯滴加到在 600 ml 二氧杂环己烷内的 50 g 2-氨基-4-氯苯甲酸中，将该反应混合物保持在 20℃。

然后在室温搅拌 2 小时，之后加入 1200 ml 水。沉淀出了所需产物，将该混合物搅拌 1 小时，然后过滤，用水洗涤所得固体。

干燥后，获得了 60.7 g 4-氯-2-(氯乙酰氨基)苯甲酸，其熔点为 194 - 196℃。

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

^{1}H NMR: (d_6-DMSO, 200 MHz) δ ppm: 4.30 (2H, s, CH_2), 7.1 (1H. d. 苯基质子), 7.7 (1H, d. 苯基质子), 8.5 (1H, s, 苯基质子), 11.75 (1H. s. NH), 13.90 (1H, 宽 s, COOH).

式(IV)化合物的结构式和特征如表 II 所示。

表 II

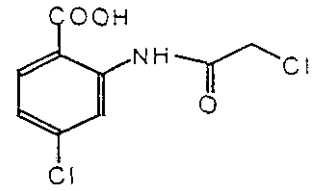
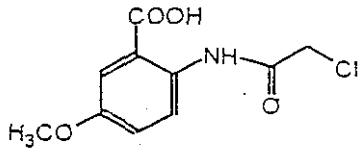
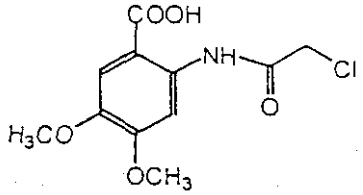
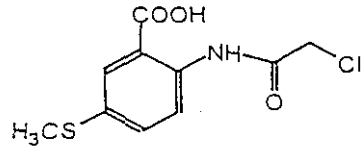
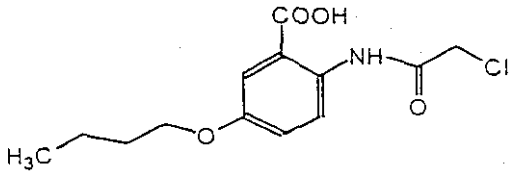
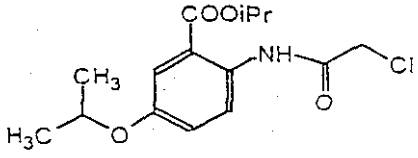
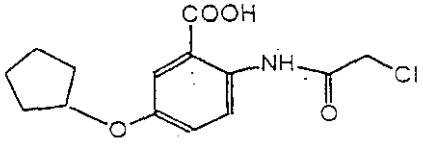
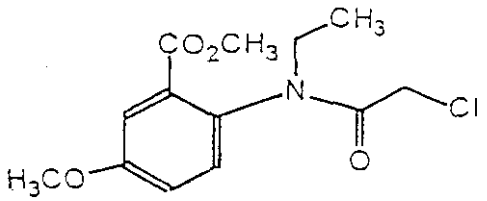
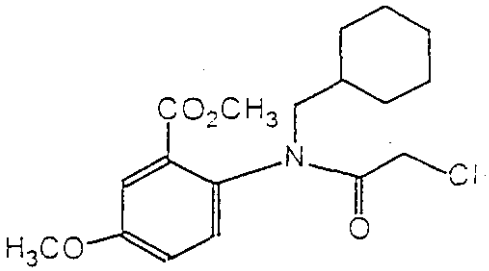
化合物	结构式	M.p. ° C (Köfler)
1		194-196
2		182-184
3		236-238
4		180-182
5		155-157
6		83-85
7		217-219

表 II（续）

化合物	结构式	^{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－制备式(II)化合物的实施例

制备 4-氯-2-{[4-(2-甲氧基苯基)-1-哌嗪基]乙酰氨基}苯甲酸

在室温及搅拌下，将 15 g 4-氯-2-(氯乙酰氨基)苯甲酸加到在 120 ml DMF 内的 11.6 g 1-(2-甲氧基苯基)哌嗪和 17 ml 三乙胺中。

将该反应混合物在室温搅拌 48 小时，然后加入 500 ml 水。用 3 × 300 ml 二氯甲烷进行萃取。将溶剂真空蒸发，把所得固体重新置于 300 ml 2N 氢氧化钠水溶液中。用 3 × 200 ml 乙醚洗涤该溶液，然后用乙酸将水相酸化。

过滤后，获得了 22.5 g 粗产物，为固体结晶。用二氧杂环己烷重结晶后，获得了 21.1 g 4-氯-2-{[4-(2-甲氧基苯基)-1-哌嗪基]乙酰氨基}苯甲酸，为白色固体，其熔点为 218－220℃。

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

^{1}H NMR: (CF_3COOD), δ ppm: 4.25 (3H, s, OCH_3), 4.65 (8H, 宽

s, 4 CH_2), 4.95 (2H, s, CH_2), 7.5 (2H, m, 苯基质子), 7.6 (1H, d, 苯基质子), 7.90 (2H, m, 苯基质子), 8.50 (1H, d, 苯基质子), 8.75 (1H, s, 苯基质子).

D－制备式(I)化合物的另一方式

制备 2-{[4-(4-氟苯基)-1-哌嗪基]乙酰氨基}-4,5-(亚甲二氧基)苯甲酸

在室温及搅拌下，将 15 g 2-(氯乙酰氨基)-4,5-(亚甲二氧基)苯甲酸加到在 150 ml DMF 内的 10.5 g 1-(4-氟苯基)哌嗪和 16.2 ml 三乙胺中。

将该反应混合物在室温搅拌 48 小时。

加入 3.5 ml 乙酸，并缓慢地加入 150 ml 水。酸结晶出来，并用 300 ml 水稀释。将该混合物搅拌 30 分钟，过滤，并将所得固体用水洗涤。

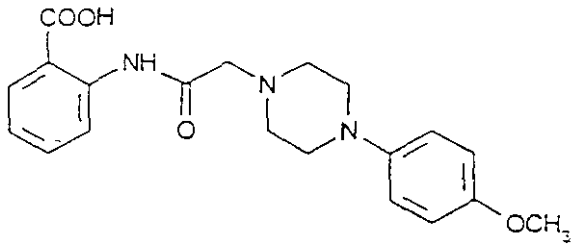
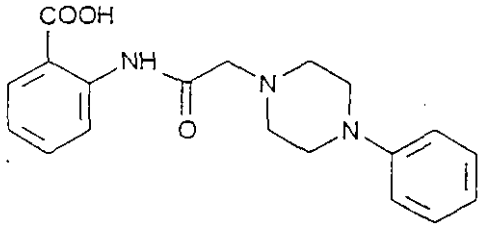
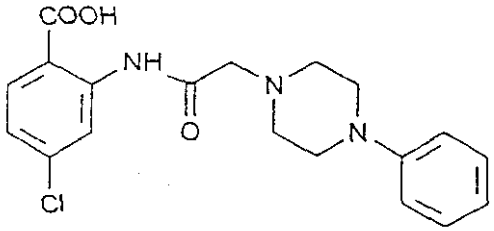
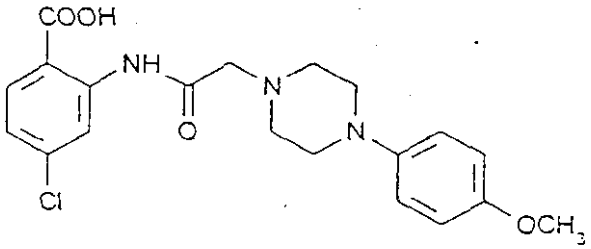
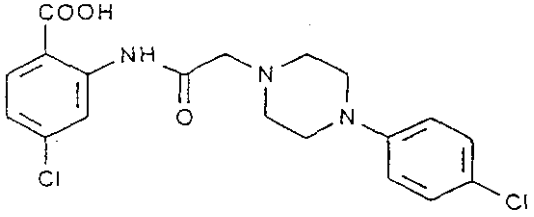
用二氧杂环己烷/DMF 混合物重结晶后，获得了 14.9 g 2-{[4-(4-氟苯基)-1-哌嗪基]乙酰氨基}-4,5-(亚甲二氧基)苯甲酸，该产物熔点为 254－256℃。

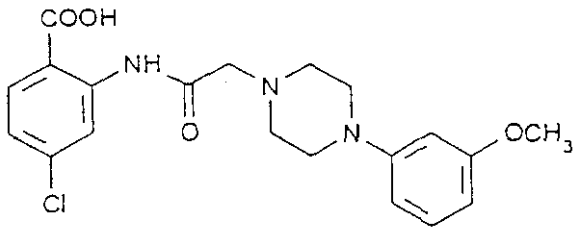
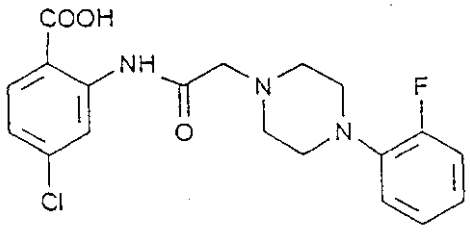
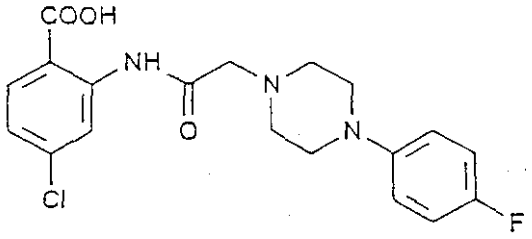
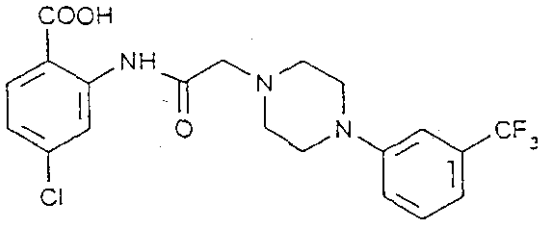
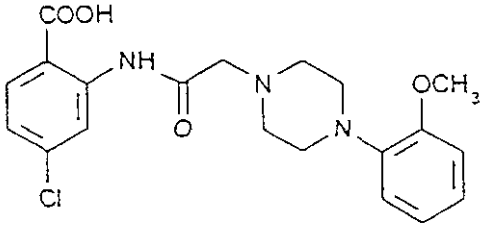
IR (KBr): 1654 cm^{-1} (C=O)

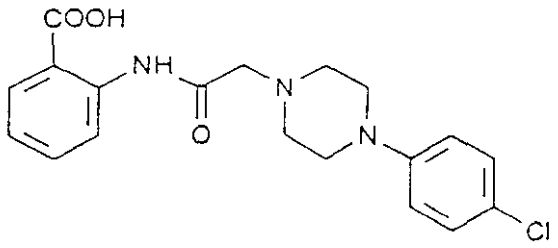
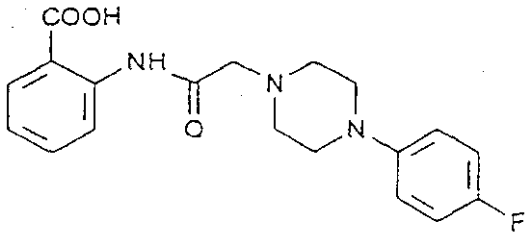
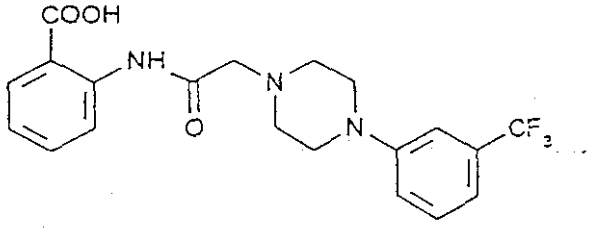
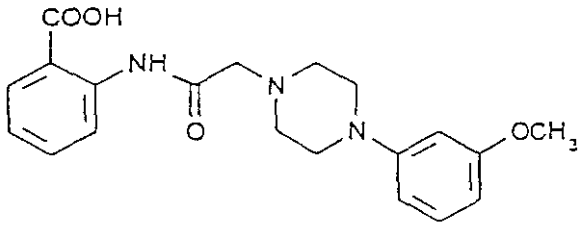
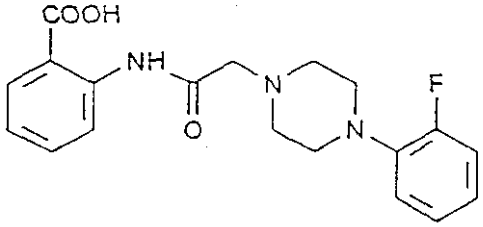
^1H NMR: (CF_3COOD, 200 MHz) δ ppm: 4.40 (8H, s, 派嗪基), 4.67 (2H, s, CH_2), 6.05 (2H, s, O-CH_2-O) 7.30 (2H, t, 苯基质子), 7.65 (3H, m, 苯基质子), 7.90 (1H, s, 苯基质子).

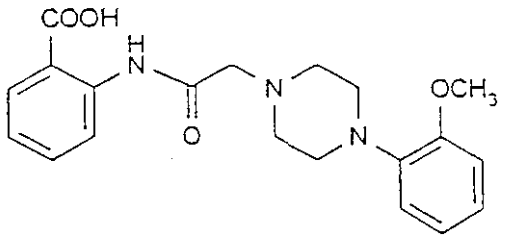
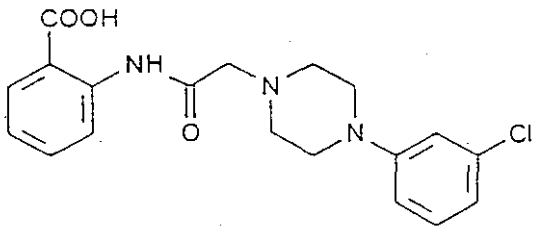
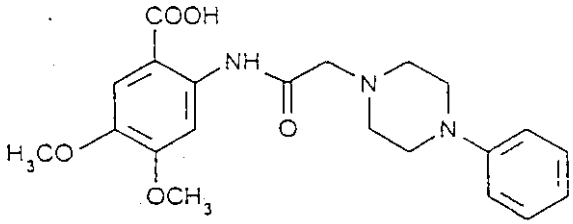
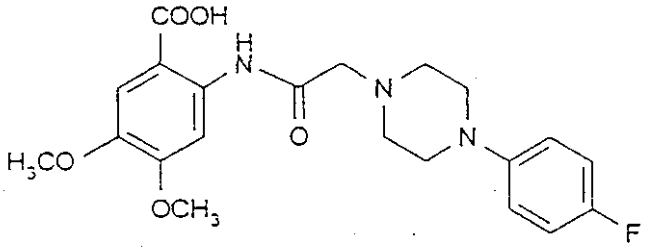
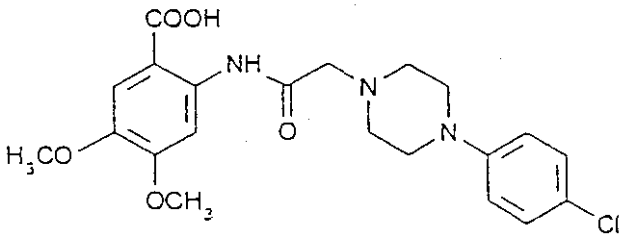
式(I)化合物的结构式和特征如表 III 所示。

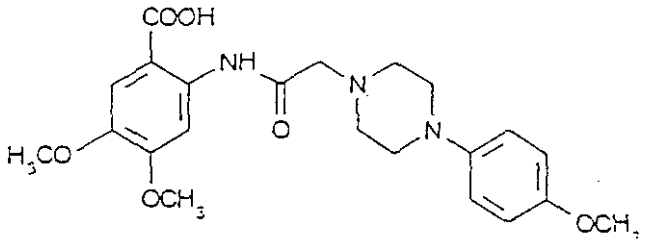
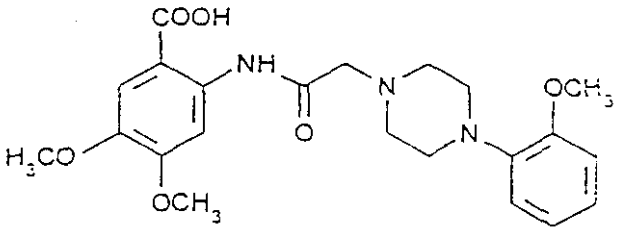
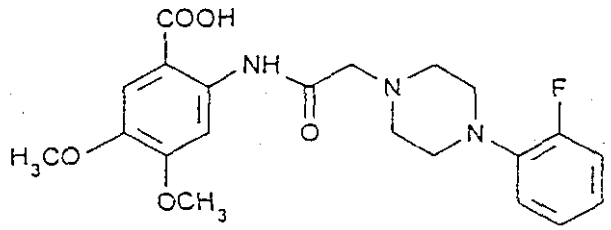
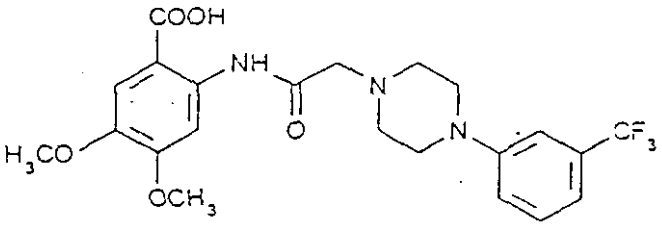
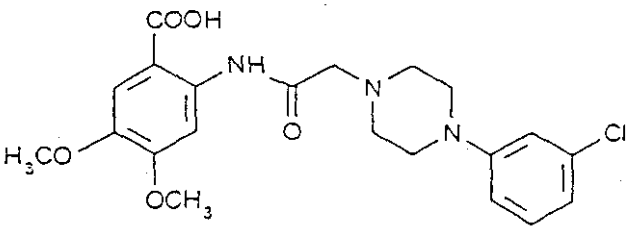
表 III

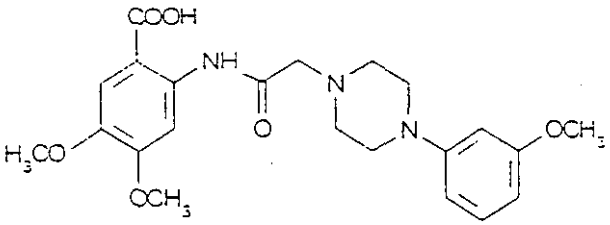
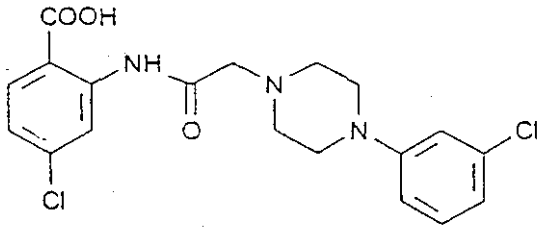
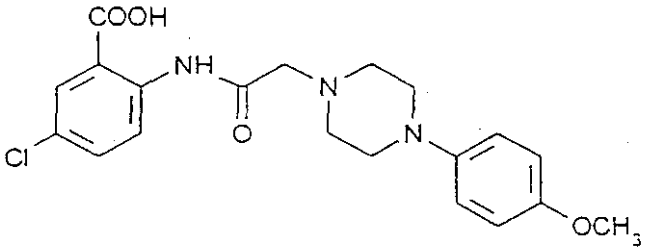
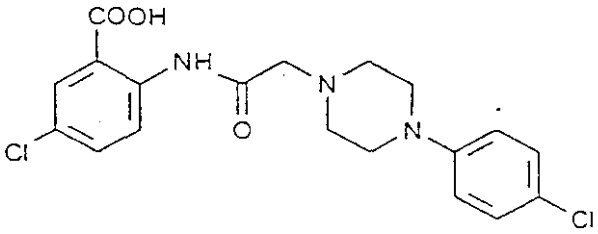
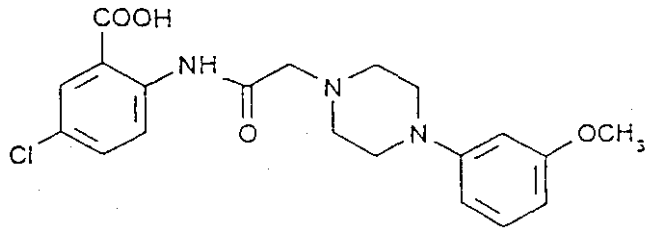
化合物	结构式	M.p. °C (Köfler)	^{1}H NMR (200 MHz) δ ppm
1		185-187	d6-DMSO 2.60 (s,4H) 3.10 (s,4H) 3.20(s,2H) 3.70(s,3H) 6.80(q,4H) 7.10(t,1H) 7.55(t,1H) 8(d,1H) 8.7(d,1H)
2		233-235	CF_3COOD 4.25(s,8H) 4.65(s,2H) 7.30(t,1H) 7.55(s,5H) 7.70(t,1H) 8.25(m,2H)
3		248-250	CF_3COOD 4.25(s,8H) 4.55(s,2H) 7.10(d,1H) 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)

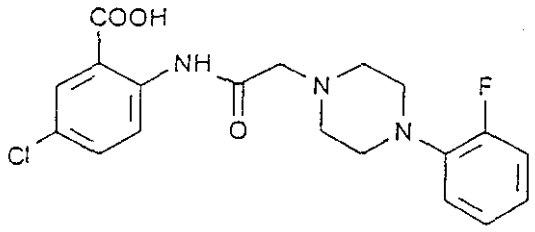
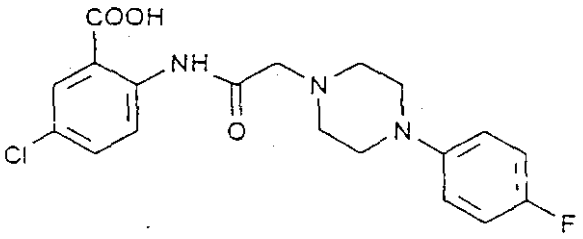
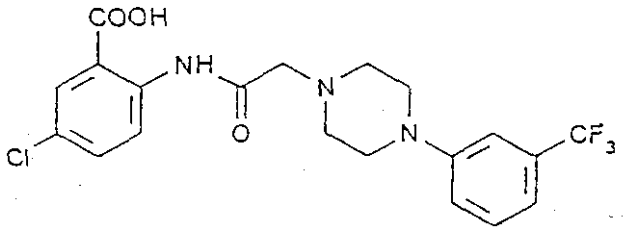
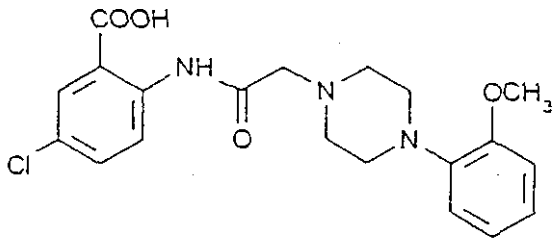
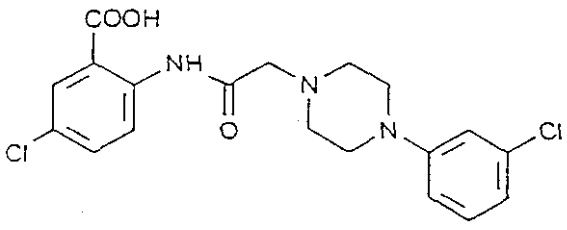
化合物	结构式	M.p. °C (Köfler)	^{1}H NMR (200 MHZ) δ ppm
6		199-201	CF_3COOD 3.8(s,3H) 4.25(s,8H) 4.60(s,2H) 7.20(m,4H) 7.5(m,1H) 8.15(d,1H) 8.40(s,1H)
7		238-240	CF_3COOD 4.60(d,8H) 4.90(s,2H) 7.50(m,3H) 7.85(m,2H) 8.35(d,1H) 8.65(s,1H)
8		244-246	CF_3COOD 4.10(s,8H) 4.45(s,2H) 7.05(d,3H) 7.45(m,2H) 7.95(d,1H) 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)

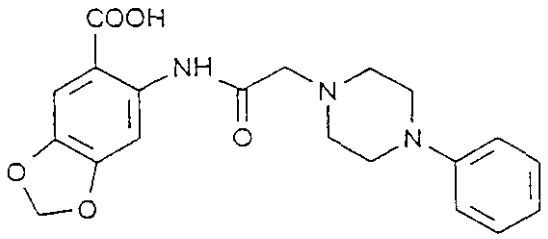
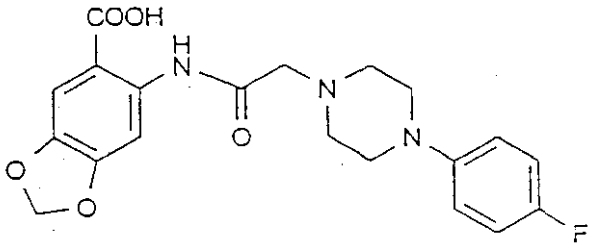
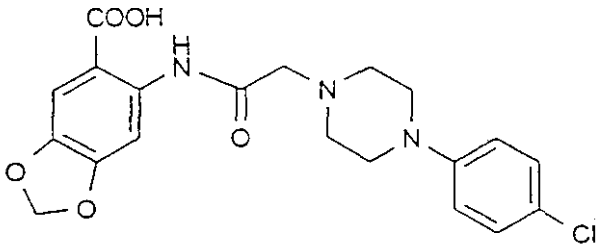
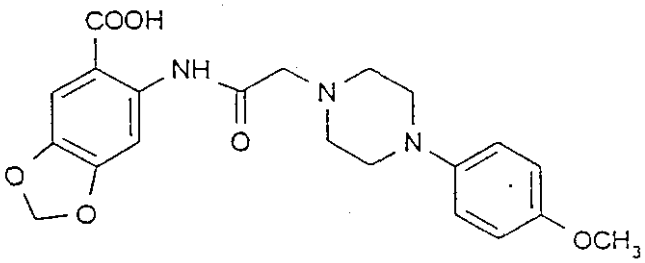
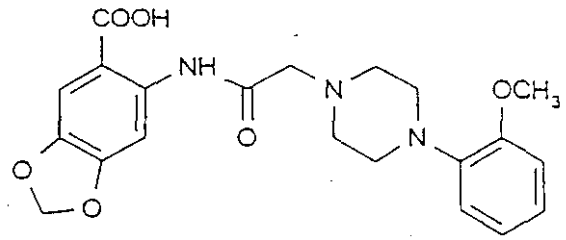
化合物	结构式	M.p. °C (Köfler)	^{1}H NMR (200 MHZ) δ ppm
11		260-262	CF_3COOD 4.3(s,8H) 4.7(s,2H) 7.25(t,1H) 7.55(s,4H) 7.70(t,1H) 8.25(m,2H)
12		249-251	CF_3COOD 4.2(s,8H) 4.6(s,2H) 7.2(m,3H) 7.6(m,3H) 8.15(m,2H)
13		174-176	$CDCl_3$ 2.65(s,4H) 3.10(s,2H) 3.20(s,4H) 7,00(m,7H) 8.65(d,1H) 10,00(s,1H) 11.8(s,1H)
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)

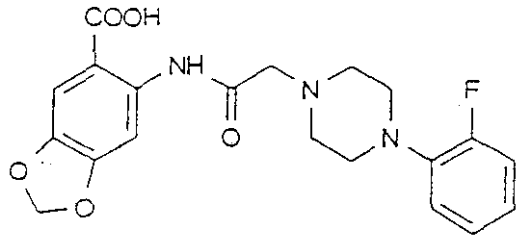
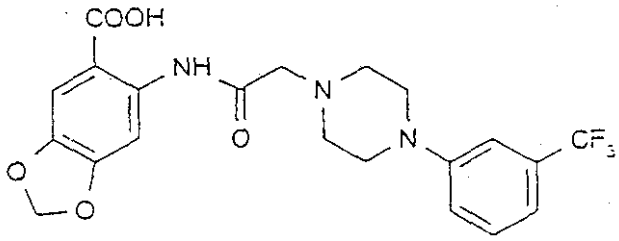
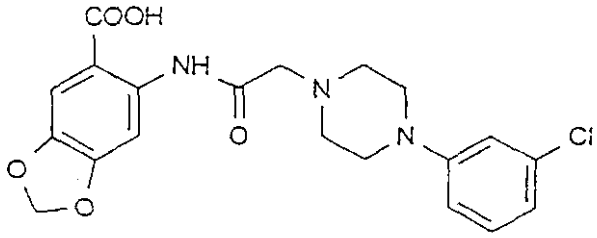
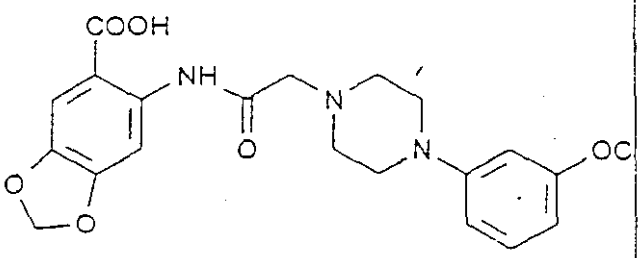
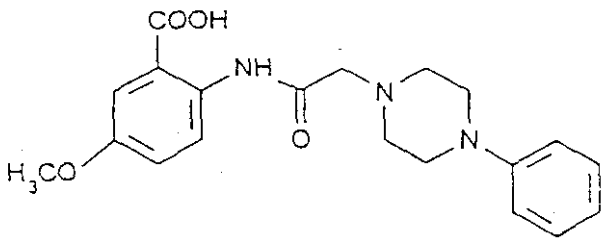
化合物	结构式	M.p. °C (Köfler)	^{1}H NMR (200 MHZ) δ ppm
16		217-219	$CDCl_3$ 3.5(s,3H) 3.75(s,8H) 4.29(s,2H) 6.65(d,2H) 6.85(t,1H) 7.10(m,3H) 7.75(t,2H)
17		190-192	CF_3COOD 3.75(s,8H) 4.15(s,2H) 6.75(m,1H) 7.00(m,5H) 7.60(m,2H)
18		>265	CF_3COOD 3.65(s,6H) 4.15(s,8H) 4.5(s,2H) 7.55(s,5H) 7.65(s,1H) 7.85(s,1H)
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)

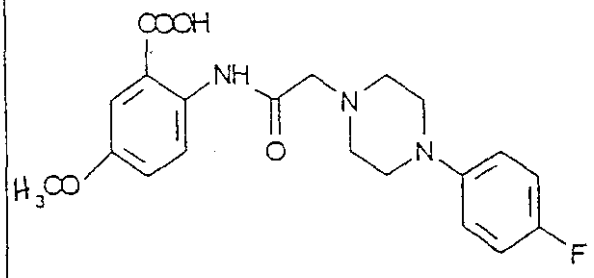
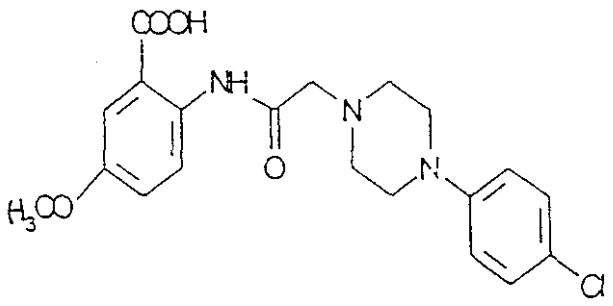
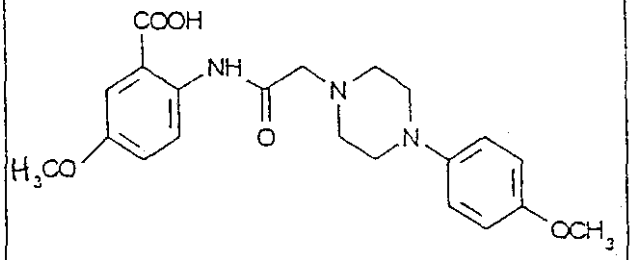
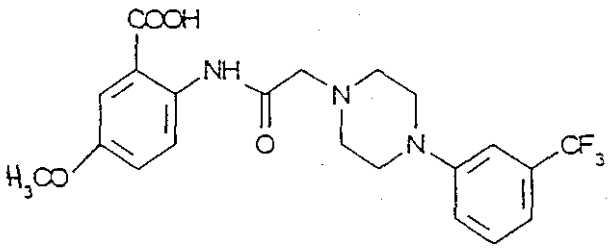
化合物	结构式	M.p. °C (Köfler)	^{1}H NMR (200 MHZ) δ ppm
21		246-248	CF_3COOD 3.75(s,3H) 3.85(s,6H) 4.15(s,8H) 4.50(s,2H) 6.90(d,2H) 7.40(d,2H) 7.60(s,1H) 7.95(s,1H)
22		244-246	CF_3COOD 3.80(s,9H) 4.25(s,8H) 4.50(s,2H) 7.00(d,2H) 7.40(d,2H) 7.60(s,1H) 7.95(s,1H)
23		245-247	CF_3COOD 3.80(s,6H) 4.20 +4.35(2s,8H) 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)

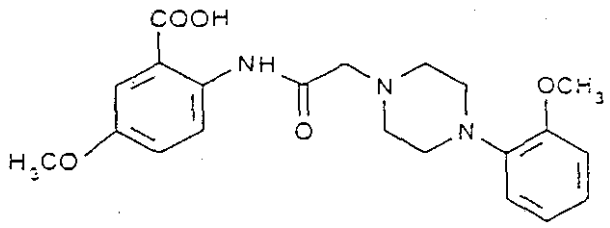
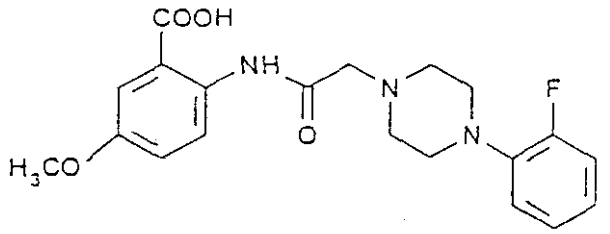
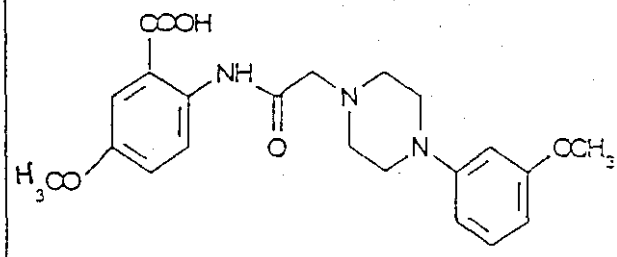
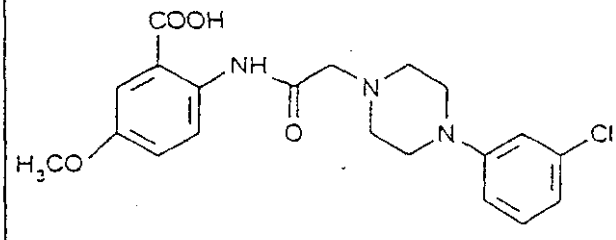
化合物	结构式	M.p. °C (Köfler)	^{1}H NMR (200 MHZ) δ ppm
26		255-257	CF_3COOD 3.70(s,3H) 3.85(s,6H) 4.22(s,8H) 4.50(s,2H) 6.95(s,3H) 7.35(t,1H) 7.55(s,1H) 7.88(s,1H)
27		257-259	CF_3COOD 4.15+4.17(2s,8H) 4.50(s,2H) 7.10(d,1H) 7.40(m,4H) 8.00(d,1H) 8.25(s,1H)
28		239-241	CF_3COOD 3.70(s,3H) 4.10(s,8H) 4.50(s,2H) 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)

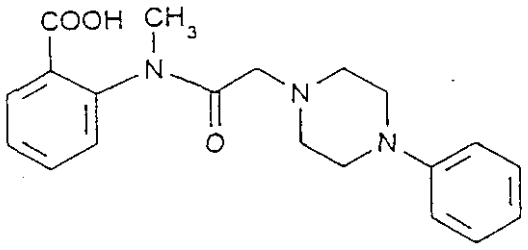
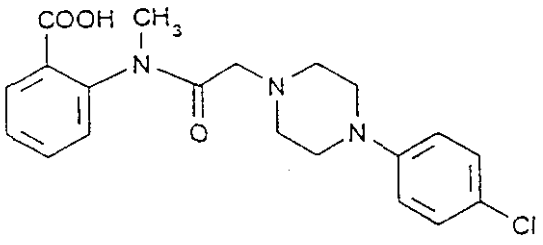
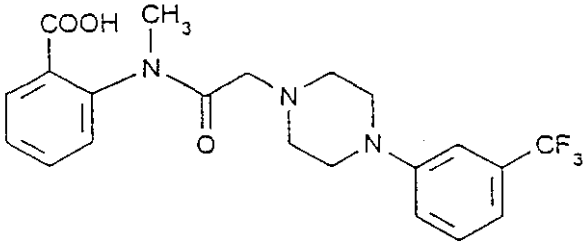
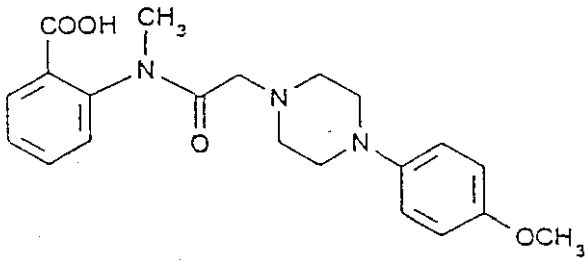
化合物	结构式	M.p. °C (Köfler)	^{1}H NMR (200 MHZ) δ ppm
31		262-264	CF_3COOD 4.30+4.50(2s,8H) 4.67(s,2H) 7.30(m,2H) 7.65(m,3H) 8.15(s,1H) 8.25(d,1H)
32		245-247	CF_3COOD 4.05(s,8H) 4.40(s,2H) 7.05(t,2H) 7.40(d,3H) 7.90(s,1H) 8.05(d,1H)
33		213-215	CF_3COOD 4.25+4.40(2s,8H) 4.70(s,2H) 7.55(d,1H) 7.80(m,4H) 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)

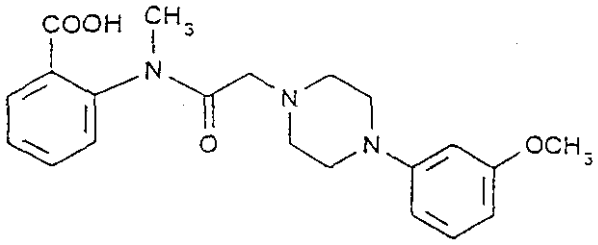
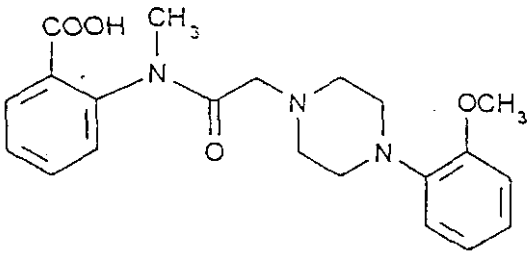
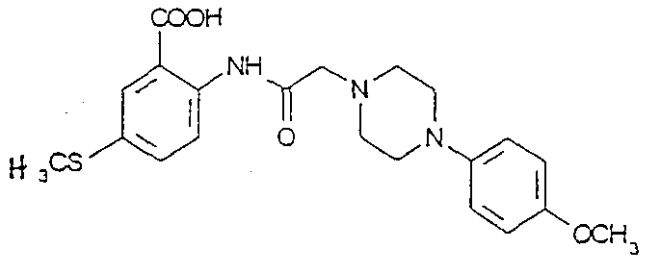
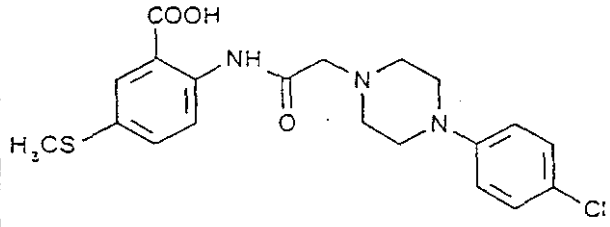
化合物	结构式	M.p. °C (Köfler)	^{1}H NMR (200 MHZ) δ ppm
36		238-240	CF_3COOD 4.20(s,8H) 4.50(s,2H) 5.85(s,2H) 7.45(s,6H) 7.80(s,1H)
37		254-256	CF_3COOD 4.40(s,8H) 4.67(s,2H) 6.05(s,2H) 7.30(t,2H) 7.65(m,3H) 7.90(s,1H)
38		>265	CF_3COOD 4.22(s,8H) 4.57(s,2H) 5.92(s,2H) 7.52(s,5H) 7.80(s,1H)
39		236-238	CF_3COOD 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)

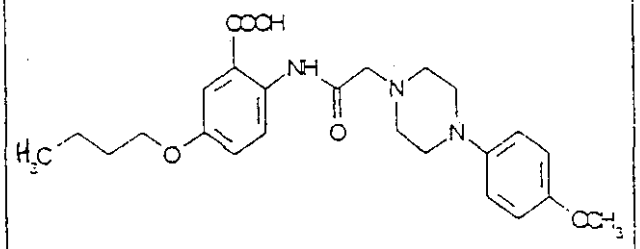
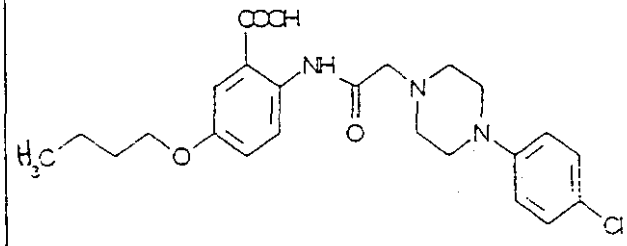
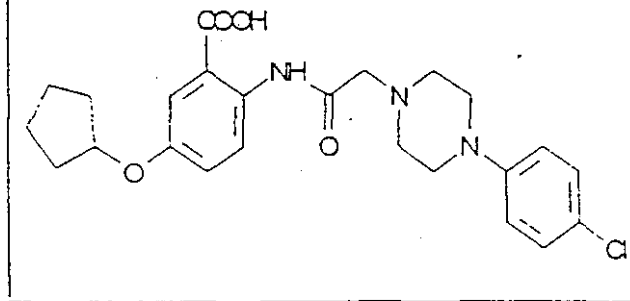
化合物	结构式	M.p. °C (Köfler)	^{1}H NMR (200 MHZ) δ ppm
41		236-238	CF_3COOD 4.23+4.38(2s,8H) 4.56(s,2H) 5.97(s,2H) 7.31(m,2H) 7.55(m,3H) 7.76(s,1H)
42		228-230	CF_3COOD 4.05+4.15(2s,8H) 4.35(s,2H) 5.75(s,2H) 7.30(s,1H) 7.60(m,5H)
43		240-242	CF_3COOD 4.00(s,8H) 4.37(s,2H) 5.75(s,2H) 7.35(d,5H) 7.70(s,1H)
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)

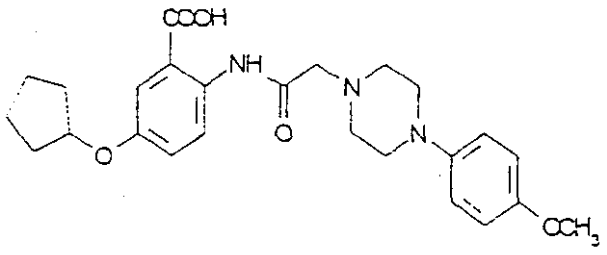
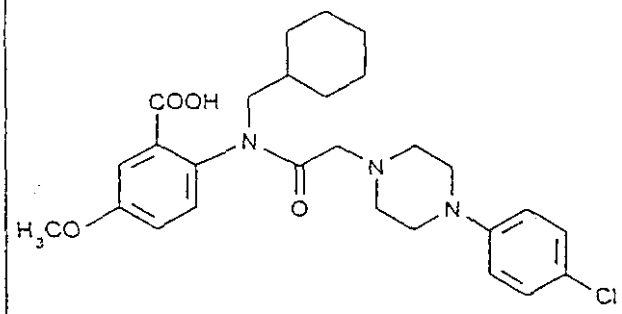
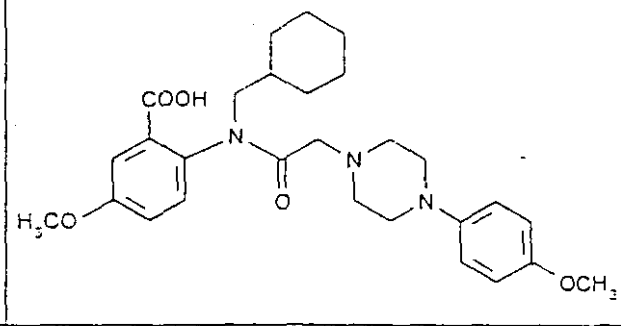
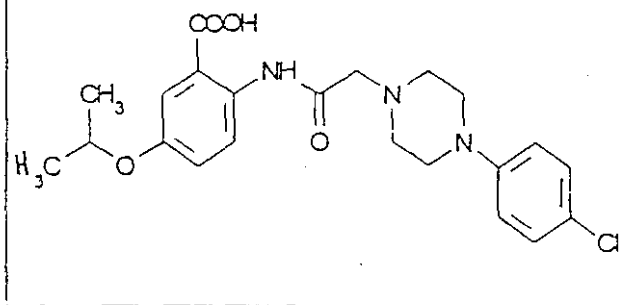
化合物	结构式	M.p. °C (Köfler)	^{1}H NMR (200 MHz)
46		197-199	CF_3COOD 3.75(s,3H) 4.20(s,8H) 4.50(s,2H) 7.10(m,3H) 7.50(t,2H) 7.70(s,1H) 8.05(d,1H)
47		221-223	CF_3COOD 3.80(s,3H) 4.20(s,8H) 4.55(s,2H) 7.15(d,1H) 7.40(s,4H) 7.70(s,1H) 8.00(d,1H)
48		198-200	CF_3COOD 3.85(d,6H) 4.25(s,8H) 4.75(s,2H) 7.22(s,2H) 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)

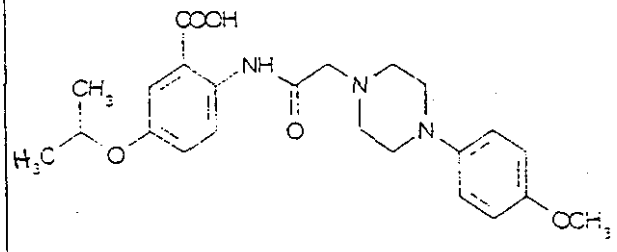
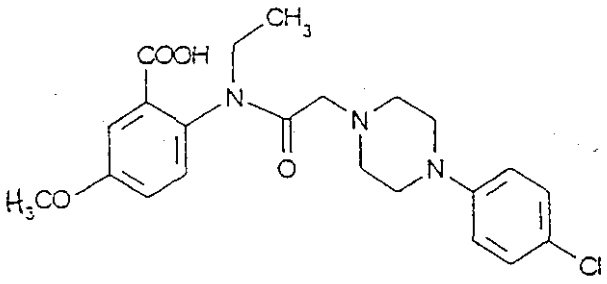
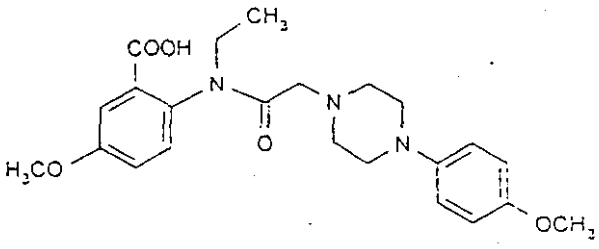
化合物	结构式	M.p. °C (Köfler)	^{1}H NMR (200 MHz)
50		200-202	CF_3COOD 3.65(s,3H) 3.70(s,3H) 4.12(s,8H) 4.42(s,2H) 7.00(d,2H) 7.10(d,1H) 7.40(m,2H) 7.65(s,1H) 8.00(d,1H)
51		179-181	CF_3COOD 3.72(s,3H) 4.25(d,8H) 4.50(s,2H) 7.15(m,3H) 7.50(q,2H) 7.65(d,1H) 8.00(d,1H)
52		177-179	CF_3COOD 3.88(s,3H) 3.96(s,3H) 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)

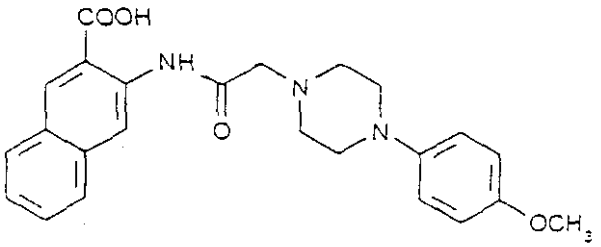
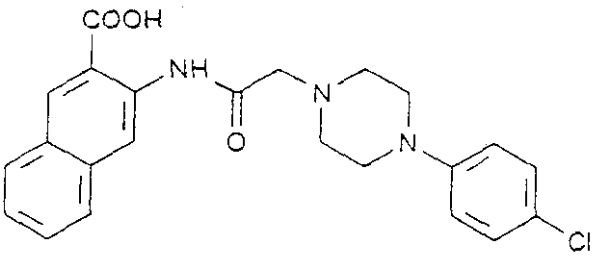
化合物	结构式	M.p. °C (Köfler)	^{1}H NMR (200 MHz)
54		210-212	d_6-DMSO 2.42(d,4H) 2.90(s,2H) 3.10(s,4H) 3.18(s,3H) 6.80(t,1H) 6.93(d,2H) 7.25(t,2H) 7.50(m,2H) 7.70(t,1H) 8.00(d,1H)
55		226-227	d_6-DMSO 2.34(d,4H) 2.81(s,2H) 3.00+3.10(2s,7H) 6.93(d,2H) 7.22(d,2H) 7.47(m,2H) 7.70(d,1H) 7.95(d,1H)
56		193-195	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)

化合物	结构式	M.p. °C (Köfler)	^{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)

化合物	结构式	M.p. °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)

化合物	结构式	M.p. °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)

化合物	结构式	M.p. °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)

化合物	结构式	M.p. °C (Köfler)	^{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)

下文中给出药理实验结果。

在 NOSTZ 大鼠中的抗糖尿病活性的研究

用通过链脲霉素在大鼠中诱导的非胰岛素依赖型糖尿病实验模型确定口服给药的式(I)化合物的抗糖尿病活性。

该非胰岛素依赖型糖尿病模型是通过给新生大鼠（出生当天）注射链脲霉素而获得的。

所用糖尿病大鼠是 8 周大小。在温度调节为 21－22℃、并具有固定光亮（第 7 时到第 19 时）和黑暗（第 19 时到第 7 时）循环的动物房中，将这些动物从其出生当天保持到实验那天。以动物能随意摄取的方式提供由维持饮食、水和食物构成的饲养，只是在当取消食物时的测试前 2 小时进行禁食（吸收后状态）。

在测试当天给大鼠口服测试产物。最后一次给药产物 2 小时后和用戊巴比妥钠（Nembutal）将动物麻醉 30 分钟后，从尾部末端采集 300 μl 血样。

所得主要结果如表 IV 所示。这些结果表明了式(I)化合物在糖尿病动物中降低血糖的有效性。

这些结果以与 D0（治疗前）相比在 D4（治疗第 4 天）时的血糖改变百分比表示。

表 IV

化合物	20 mg/kg/d	200 mg/kg/d
	在 D4 的 % 血糖	在 D4 的 % 血糖
35	-12	-16
38	-6	-27
39	-15	-14
45	-9	-18
47	-16	-32
48	-20	-31
50	-17	-7
52	-14	-21