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(54) Title: ACIDIC QUINOLONE DERIVATIVES

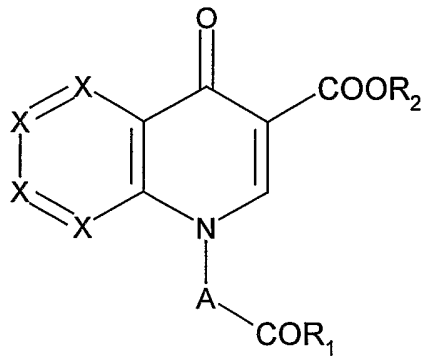
(57) Abstract: The invention relates to compounds of the general formula (I): in which R1, R2, X and A are as defined in Claim 1. These compounds may be used in the prevention or treatment of complications induced by diabetes.

Acidic Quinolone Derivatives

The present invention relates to acidic quinolone derivatives that are useful in the treatment or prevention of diabetic complications.

Diabetes is characterised by a high concentration of glucose in the blood. This glucose is normally metabolised by the enzyme hexokinase during the first step of glycolysis, resulting in degradation to pyruvate. When the glucose concentration is too high, the hexokinase is saturated and a second route of metabolisation of glucose comes into play; this is the polyol route, which successively involves two enzymes: aldose reductase, which converts the glucose to sorbitol, and sorbitol dehydrogenase, which converts the sorbitol to fructose. In the case of diabetes, the excess glucose accelerates the formation of sorbitol, which tends to accumulate. This results in serious metabolic disturbances such as, for example, an increase in osmotic pressure, which is liable to result in tissue degeneration. Aldose reductase inhibitors are thus useful for treating or preventing some of the complications induced by diabetes.

The compounds of the invention are of the general formula (I) below:



in which:

X represents, independently of each other, an optionally substituted methylene radical or a nitrogen, oxygen or sulfur atom,

R1 represents a group chosen from:

- radical of the formula OR2,

- Amine optionally substituted by one or more of the following groups: (C1-C5) alkyl, (C_3-C_8) cycloalkyl, (C_1-C_5) alkoxy, aryl, alkylaryl or aralkyl, these groups possibly being interrupted with one or more hetero atoms and/or possibly being substituted, especially with one or more halogen atoms, the nitrogen of the amine group also possibly forming part of a heterocycloalkyl,

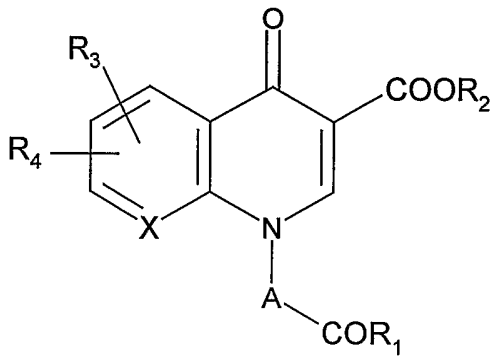
R2, which may be identical or different, represents a group chosen from:

- hydrogen,
- (C_1-C_{20}) alkyl optionally substituted by one or more of the following groups: halogen, (C1-C5) alkyl, (C_3-C_8) cycloalkyl, (C_1-C_5) alkoxy, substituted or unsubstituted amino, optionally substituted carbonyl, ester, amide, a sulfur or phosphorus atom,
- (C_2-C_{20}) alkylene optionally substituted by halogen, (C_1-C_5) alkyl, (C_1-C_5) alkoxy or (C_3-C_8) cycloalkyl
- (C_2-C_{20}) alkyne optionally substituted by halogen, (C_1-C_5) alkyl, (C_1-C_5) alkoxy or (C_3-C_8) cycloalkyl
- (C_3-C_8) cycloalkyl optionally substituted by (C_1-C_5) alkyl or (C_1-C_5) alkoxy
- (C_3-C_8) heterocycloalkyl bearing one or more hetero atoms chosen from N, O and S and optionally substituted by (C_1-C_5) alkyl or (C_1-C_5) alkoxy,
- (C_6-C_{14})aryl(C_1-C_{20})alkyl optionally substituted by amino, hydroxyl, thio, halogen, (C_1-C_5) alkyl, (C_1-C_5) alkoxy, (C_1-C_5) alkylthio, (C_1-C_5) alkylamino, (C_6-C_{14}) aryl, (C_6-C_{14}) aryloxy, (C_6-C_{14})aryl(C_1-C_5)alkoxy, cyano, trifluoromethyl, carboxyl, carboxymethyl or carboxyethyl,
- (C_6-C_{14}) aryl optionally substituted by amino, hydroxyl, thio, halogen, (C_1-C_5) alkyl, (C_1-C_5) alkoxy, (C_1-C_5) alkylthio, (C_1-C_5) alkylamino, (C_6-C_{14}) aryl, (C_6-C_{14}) aryloxy, (C_6-C_{14})aryl(C_1-C_5)alkoxy, cyano, trifluoromethyl, carboxyl, carboxymethyl or carboxyethyl,
- (C_1-C_{13}) heteroaryl bearing one or more hetero atoms chosen from N, O and S and optionally substituted by amino, hydroxyl, thio, halogen, (C_1-C_5) alkyl, (C_1-C_5) alkoxy, (C_1-C_5) alkylthio, (C_1-C_5) alkylamino, (C_6-C_{14}) aryl, (C_6-C_{14}) aryloxy, (C_6-C_{14})aryl(C_1-C_5)alkoxy, cyano, trifluoromethyl, carboxyl, carboxymethyl or carboxyethyl,

A represents a single bond or a (C_1-C_6) alkyl group optionally substituted by one or more of the following groups: halogen, (C_3-C_8) cycloalkyl, (C_1-C_5) alkoxy, substituted or unsubstituted amino, optionally substituted carbonyl, ester, amide, a sulfur or phosphorus atom,

and also the tautomeric forms, enantiomers, diastereoisomers and epimers, and the pharmaceutically acceptable salts.

One particular group of compounds of the formula (I) is the one in which the compounds are of the general formula (II) below:



(II)

in which R1, R2 and A are as defined above, and

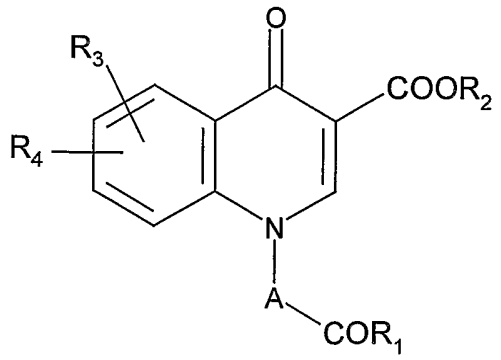
R3 and R4, which may be identical or different, represent groups chosen from:

- a hydrogen atom,
- (C_1-C_{20}) alkyl optionally substituted by one or more of the following groups: halogen, (C1-C5) alkyl, (C_3-C_8) cycloalkyl, (C_1-C_5) alkoxy, substituted or unsubstituted amino, optionally substituted carbonyl, ester, amide, a sulfur or phosphorus atom,
- (C_1-C_{20}) alkoxy optionally substituted by one or more of the following groups: halogen, (C1-C5) alkyl, (C_3-C_8) cycloalkyl, (C_1-C_5) alkoxy, substituted or unsubstituted amino,
- (C_2-C_{20}) alkylene optionally substituted by halogen, (C1-C5) alkyl, (C_1-C_5) alkoxy or (C_3-C_8) cycloalkyl,
- (C_2-C_{20}) alkyne optionally substituted by halogen, (C_1-C_5) alkyl, (C_1-C_5) alkoxy or (C_3-C_8) cycloalkyl

- (C_3-C_8) cycloalkyl optionally substituted by (C_1-C_5) alkyl or (C_1-C_5) alkoxy
- (C_3-C_8) heterocycloalkyl bearing one or more hetero atoms chosen from N, O and S and optionally substituted by (C_1-C_5) alkyl or (C_1-C_5) alkoxy,
- (C_6-C_{14})aryl(C_1-C_{20})alkyl optionally substituted by amino, hydroxyl, thio, halogen, (C_1-C_5) alkyl, (C_1-C_5) alkoxy, (C_1-C_5) alkylthio, (C_1-C_5) alkylamino, (C_6-C_{14}) aryl, (C_6-C_{14}) aryloxy, (C_6-C_{14})aryl(C_1-C_5)alkoxy, cyano, trifluoromethyl, carboxyl, carboxymethyl or carboxyethyl,
- (C_6-C_{14}) aryl optionally substituted by amino, hydroxyl, thio, halogen, (C_1-C_5) alkyl, (C_1-C_5) alkoxy, (C_1-C_5) alkylthio, (C_1-C_5) alkylamino, (C_6-C_{14}) aryl, (C_6-C_{14}) aryloxy, (C_6-C_{14})aryl(C_1-C_5)alkoxy, cyano, trifluoromethyl, carboxyl, carboxymethyl or carboxyethyl,
- (C_1-C_{13}) heteroaryl bearing one or more hetero atoms chosen from N, O and S and optionally substituted by amino, hydroxyl, thio, halogen, (C_1-C_5) alkyl, (C_1-C_5) alkoxy, (C_1-C_5) alkylthio, (C_1-C_5) alkylamino, (C_6-C_{14}) aryl, aryloxy (C_6-C_{14}), (C_6-C_{14})aryl(C_1-C_5)alkoxy, cyano, trifluoromethyl, carboxyl, carboxymethyl or carboxyethyl,

R3 and R4 may also together form a heterocycle adjacent to the phenyl ring.

A more particular group of compounds of the formula (I) is the one in which the compounds are of the general formula (III) below:



(III)

in which R1, R2, R3, R4 and A are as defined above.

According to the present invention, the alkyl radicals contain from 1 to 20 carbon atoms and preferably from 1 to 5 carbon atoms.

When they are linear, mention may be made especially of the methyl, ethyl, propyl, butyl, pentyl, hexyl, octyl, nonyl, decyl, dodecyl, hexadecyl and octadecyl radicals.

When they are branched or substituted by one or more alkyl radicals, mention may be made especially of the isopropyl, tert-butyl, 2-ethylhexyl, 2-methylbutyl, 2-methylpentyl, 1-methylpentyl and 3-methylheptyl radicals.

The alkoxy radicals according to the present invention are radicals of the formula -O-alkyl, the alkyl being as defined above.

Among the halogen atoms, mention is made more particularly of the fluorine, chlorine, bromine and iodine atoms.

The alkylene radicals contain one or more ethylenic unsaturations. Among the alkylene radicals that may be mentioned especially are the allyl and vinyl radicals.

The alkyne radicals contain one or more acetylenic unsaturations. Among the alkyne radicals that may especially be mentioned is acetylene.

The (C_3-C_8) cycloalkyl radical is a cyclic hydrocarbon-based radical such as, especially, cyclopropyl, cyclopentyl or cyclohexyl.

The aryl radical corresponds more particularly to an aromatic ring of 6 carbon atoms, such as the phenyl radical, optionally fused with one or two other aromatic rings containing 6 carbon atoms, such as the naphthyl radical.

Among the aryl radicals that may thus especially be mentioned is the phenyl radical, more particularly substituted by at least one halogen atom.

Among the (C_6-C_{14})aryl(C_1-C_{20})alkyl radicals that may be mentioned especially are the benzyl and phenethyl radicals.

The heteroaryl radical corresponds more particularly to a 5- or 6-atom aromatic heterocycle containing one or two hetero atoms chosen from N, S and O, optionally fused with one or two aromatic rings containing six carbon atoms or 5- or 6-atom heteroaromatic rings.

Among the heteroaryl radicals that may be mentioned are the furyl, pyridyl, quinolinyl, indolyl, isoindolyl, quinolyl, imidazolyl, pyrimidinyl and carbazolyl radicals.

Among the heterocycles that may especially be mentioned are the piperidine, morpholine, pyrrolidine, imidazolidine, pyrazolidine and piperazine rings.

When R3 and R4 together form a heterocycle adjacent to the phenyl ring, they can especially represent the ring -O-(CH2)n-O-, n being an integer ranging from 1 to 4.

When the nitrogen of the amine group represented by R1 forms part of a heterocycloalkyl, the said heterocycloalkyl is more particularly a piperidine ring.

One particular group of compounds of the formula (I), (II) or (III), as defined above, is that in which A is an optionally substituted methylene group. More particularly, A represents an unsubstituted methylene radical.

Another particular group of compounds of the formula (II) or (III) is the one in which R4 is a hydrogen atom and R3 represents an alkoxy radical.

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

The compounds of the invention of the formula (I) as defined above containing a sufficiently acidic function or a sufficiently basic function, or both, may include the pharmaceutically acceptable corresponding salts of an organic or mineral acid or of an organic or mineral base.

They may be, for example, salts such as the hydrochloride, acetate, benzoate, citrate, fumarate, embonate, chlorophenoxyacetate, glycolate, palmoate, aspartate, methanesulfonate, maleate, para-chlorophenoxyisobutyrate, formate, lactate, succinate, sulfate, tartrate, cyclohexanecarboxylate, hexanoate, octanoate, decanoate, hexadecanoate, octadecanoate, benzenesulfonate, trimethoxybenzoate, para-toluenesulfonate, adamantanecarboxylate, glycoxylate, glutamate, pyrrolidonecarboxylate, naphthalenesulfonate, glucose-1-phosphate, nitrate, sulfite, dithionate, phosphate, dobesilate, thioctate, hippurate, 3-benzamidopropanoate, glucuronate, L-pyrrolidone-5-carboxylate, cholate, α-glucose-1-phosphate, alginate, 4-aminobenzoate or chondroitin sulfate, and alkali metal salts, such as the sodium salt.

The compounds of the formula (I) may especially be chosen from:

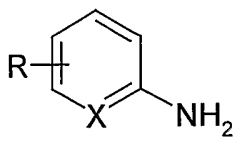
- 3-carboxy-6-methoxy-4-oxo-1,4-dihydroquinoline-1-acetic acid
- 3-carboxy-7-methoxy-4-oxo-1,4-dihydroquinoline-1-acetic acid,
- 3-carboxy-6,7-methylenedioxy-4-oxo-1,4-dihydroquinoline-1-acetic acid

- 3-carboxy-8-methoxy-4-oxo-1,4-dihydroquinoline-1-acetic acid
- 1-[2-(1,1-dimethylethylamino)-2-oxoethyl]-6-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 1-[2-(4-methylphenylamino)-2-oxoethyl]-6-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 1-[2-(4-chlorophenylamino)-2-oxoethyl]-6-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 1-[2-(3-chlorophenylamino)-2-oxoethyl]-7-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 1-[2-(4-chlorophenylamino)-2-oxoethyl]-7-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid,
- 1-[2-(3-chlorophenylamino)-2-oxoethyl]-6-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 1-[2-(N-piperidinoacetyl)-2-oxoethyl]-6-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 1-[2-(4-methylphenylamino)-2-oxoethyl]-7-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

The compounds of the general formula (I) may be prepared according to the method of Gould-Jacobs (J. Amer. Chem. Soc., 61, 2890, 1939) proposed in 1962 for the synthesis of nalidixic acid (Scheme 1).

The present invention thus also relates to a process for preparing compounds of the formula (I), comprising the following steps:

a) condensation of an arylamine or of a heteroarylamine, which is optionally substituted, with diethyl ethoxymethylenemalonate, the arylamine or heteroaryl-amine being of the formula (1) below:



in which formula (1) X represents a nitrogen or carbon atom and R represents R3 or R4 as defined above,

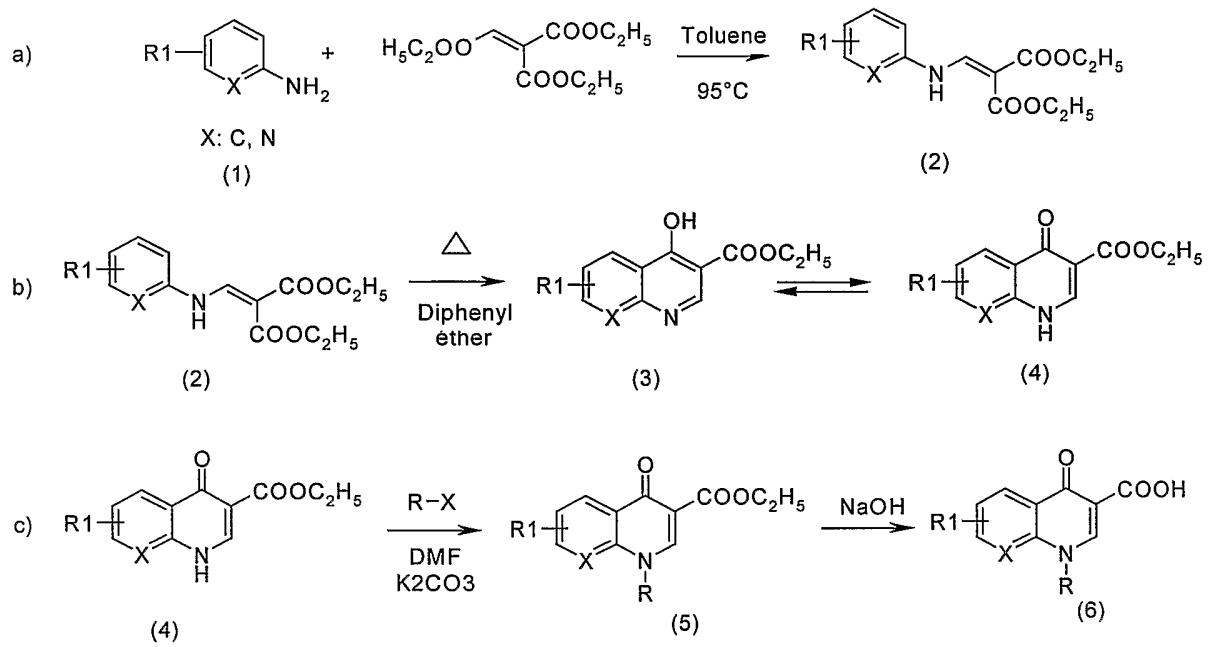
b) heat treatment of the malonic derivative obtained in step a) under conditions allowing cyclisation, more particularly by heating in a solvent of high boiling point,

preferably from 200 to 300°C, advantageously at 250°C, the solvent possibly being diphenyl ether or Dowtherm,

c) N-alkylation reaction of the tautomeric form of the cyclised product obtained in step b) by condensation in the presence of an alkaline agent,

d) optionally, saponification of the ester obtained in step c).

Scheme 1 is as follows:



Scheme 1

Step a) is the condensation of an optionally substituted arylamine or hetarylamine (1) with diethyl ethoxymethylenemalonate according to Claisen (Liebigs Annal. Chem, 297, 1, 1897).

Step b) is the thermal cyclisation of the malonic derivative (2) obtained. It is carried out by heating in a solvent with a high boiling point, preferably at 250°C in diphenyl ether or Dowtherm. The tautomeric form (4) of the cyclised product (3) is then conventionally N-alkylated: step (c). This condensation, which is well known in under the name Hoffman alkylation, may be carried out in the usual solvents, preferably anhydrous dimethylformamide or toluene, in the presence of an alkaline agent such as potassium carbonate. The ester (5) obtained is conventionally saponified to (6).

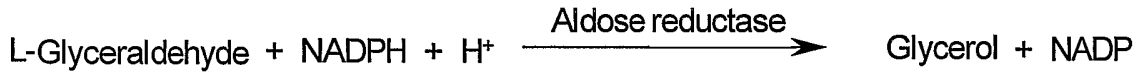
The compounds of the present invention have activity as aldose reductase inhibitors.

IN VITRO STUDY : INHIBITION OF ALDOSE REDUCTASE

Aldose reductase is partially purified from the lenses of male rats (Wistar, 200-240 g).

The extract is prepared by centrifugation and precipitation with ammonium sulfate according to W.H.J. WARD et al. (1990, Biochem. Pharmacol. 39, 2, 337-346).

The enzyme is preincubated at 37°C with or without the test products and NADPH (0.125 mM) in a phosphate buffer for 10 minutes. The reaction is started by addition of L-glyceraldehyde (5 mM) used as substrate.



The enzymatic activity is measured using a spectrophotometer at 340 nm.

The values measured are indicated in the table below:

TEST OF INHIBITION OF ALDOSE REDUCTASE	
Compound	**IC 50 (nM)**
1-Carboxymethyl-6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid	15
1-Carboxymethyl-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid	10
1-Carboxymethyl-6,7-methylenedioxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid	5
1-Carboxymethyl-7-methyl-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylic acid	50

The compounds of the formula (I) may thus be used as medicaments as aldose reductase inhibitors, and especially in the treatment of diabetes complications, these complications possibly being cataracts, retinopathies, neuropathies, nephropathies or certain vascular diseases.

The present invention thus also relates to pharmaceutical compositions comprising, as active principle, a compound according to the invention.

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

They will thus be presented in the form of injectable solutions or suspensions or multi-dose bottles, in the form of plain or coated tablets, sugar-coated tablets, wafer capsules, gel capsules, pills, cachets, powders, suppositories or rectal capsules, or solutions or suspensions, for percutaneous use in a polar solvent, or for permucous use.

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

The preferred excipients for rectal use are cocoa butter or polyethylene glycol stearates.

The vehicles that are most suitable for parenteral use are water, aqueous solutions, physiological saline and isotonic solutions.

The dosage may vary within a wide range (0.5 mg to 1000 mg) depending on the therapeutic indication and the route of administration, and also the age and weight of the individual.

The present invention thus also relates to the use of compounds of the general formula (I) for the preparation of pharmaceutical compositions intended for treating or preventing a complication induced by diabetes.

The examples that follow illustrate the invention without, however, limiting it. The starting materials used are known products or products prepared according to known procedures.

The percentages are expressed on a weight basis, except where otherwise mentioned.

Example 1 : 3-carboxy-6-methoxy-4-oxo-1,4-dihydroquinoline-1-acetic acid

- Diethyl 2-(4-methoxyphenylaminomethylene)malonate:

120 g (0.97 M) of para-anisidine and 199 ml (0.97 M) of diethyl ethoxymethylene-malonate are introduced into 400 ml of toluene. The mixture is brought to the

reflux point of the solvent. The ethanol formed is entrained by azeotropic distillation. When the reflux temperature reaches 110°C, refluxing is continued for 45 minutes. After cooling, the solution is purified by passing through silica, and then evaporated under reduced pressure.

280.8 g of red oil are obtained

Yield : 98%

^{1}H NMR ($CDCl_3$) :

10.87 (1H, d) ; 8.35 (1H, d) ; 7.00 (2H, d) ; 6.82 (2H, d) ; 4.16-4.22 (4H, 2q) ; 3.75 (3H, s) ; 1.24-1.29 (6H, 2t)

- Ethyl 6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate:

300 ml of Dowtherm-A are refluxed (about 250°C) under a nitrogen atmosphere. Next, 124.1 g (0.43 M) of diethyl 2-(4-methoxyphenylaminomethylene)malonate are introduced dropwise. Refluxing is continued for 10 minutes after the end of the introduction. The reaction mixture is then cooled to 15°C: a brown solid precipitates. It is filtered off by suction, washed with petroleum ether and then dried under vacuum.

58.8 g of brown solid are obtained.

Yield : 59%

m.p.>270°C (melting point)

^{1}H NMR (DMSO-d_6) :

8.38 (1H, s) ; 7.51 (1H, d) ; 7.50 (1H, d) ; 7.25 (1H, dd) ; 4.14 (2H, q) ; 3.78 (3H, s) ; 1.21 (3H, t)

- Ethyl 3-ethoxycarbonyl-6-methoxy-4-oxo-1,4-dihydroquinoline-1-acetate :

10.0 g (0.041 M) of ethyl 6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate and 11.0 g (0.080 M) of potassium carbonate are introduced into 100 ml of DMF. The reaction mixture is stirred for 15 minutes at room temperature. After addition of 5.0 ml (0.045 M) of ethyl bromoacetate and heating for two hours at about 60°C, the solvent is evaporated off under vacuum and the solid obtained is then taken up in demineralised water with stirring. The solid in suspension is filtered

off, washed thoroughly with water and then with ethyl ether and finally dried under vacuum.

13.4 g of beige-coloured powder are obtained.

Yield : 95%

m.p. = 207°C

^{1}H NMR (DMSO-d_6) :

8.62 (1H, s) ; 7.62 (1H, d,) ; 7.47 (1H, d,) ; 7.33 (1H, dd) ;

5.31 (2H, s) ; 4.18 (2H, q) ; 4.13 (2H, q) ; 3.82 (3H, s) ; 1.24 (3H, t) ;

1.17 (3H, t)

- 3-carboxy-6-methoxy-4-oxo-1,4-dihydroquinoline-1-acetic acid:

A suspension of 10.0 g (0.030 M) of ethyl 1-(2-ethoxy-2-oxoethyl)-6-methoxy-1,4-dihydroquinoline-3-carboxylate in 10 ml of 10% sodium hydroxide solution is refluxed for two hours. Once the solution has become clear, it is cooled and then acidified to pH 1 with 10% hydrochloric acid solution.

The white precipitate formed is filtered off, washed with demineralised water until the filtrate is neutral, and then dried under vacuum.

7.5 g of white solid are obtained.

Yield : 91%

m.p.=250°C

^{1}H NMR (DMSO-d_6) :

15.15 (1H, s) ; 13.50 (1H, s) ; 8.94 (1H, s) ; 7.68 (1H, d) ; 7.65 (1H, d) ; 7.48 (1H, dd) ; 5.37 (2H, s) ; 3.84 (3H, s)

By way of example, the following compounds are prepared according to the procedure of Example 1:

- 3-carboxy-6,7-methylenedioxy-4-oxo-1,4-dihydroquinoline-1-acetic acid
- 3-carboxy-8-methoxy-4-oxo-1,4-dihydroquinoline-1-acetic acid

Example 2 : 1-[2-(1,1-dimethylethylamino)-2-oxoethyl]-6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

- ethyl 1-[2-(1,1-dimethylethylamino)-2-oxoethyl]-6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate

10 g (0.04 M) of ethyl 6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate, 11.2 g (0.08 M) of potassium carbonate, 8.4 g (0.05 M) of potassium iodide and 7.6 g (0.05 M) of N-(1,1-dimethylethyl)chloroacetamide are added to 200 ml of anhydrous toluene. The reaction mixture is stirred for 24 hours at the reflux point of the solvent. After cooling, the precipitated solid is taken up in 50 ml of demineralised water.

The suspension is stirred for 45 minutes. The solid is filtered off, washed with demineralised water and dried under reduced pressure.

12.6 g of brown solid are obtained.

m.p. = >250°C

Yield : 87%

^{1}H NMR (DMSO-d_6) :

8.4 (1H, s) ; 8.1 (1H, s) ; 7.5 (1H, s) ; 7.3 (2H, m) ; 4.8 (2H, s) ; 4.1 (2H, q) ; 3.7 (3H, s) ; 1.1 (12H, s)

- 1-[2-(1,1-Dimethylethylamino)-2-oxoethyl]-6-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

15 ml of ethanol, 1.4 g (0.034 M) of sodium hydroxide pellets and then 12.4 g (0.034 M) of ethyl 1-[2-(1,1-dimethylethylamino)-2-oxoethyl]-6-methoxy-1,4-dihydroquinoline-3-carboxylate are added to 120 ml of demineralised water. The reaction medium is heated for two hours at the reflux point of the solvent. After cooling, the medium is filtered. The solution is acidified to pH 1 with concentrated hydrochloric acid solution. A solid precipitates out.

Stirring is continued for 30 minutes and the solid is then filtered off, washed with demineralised water and dried under reduced pressure.

11 g of cream-white solid are obtained.

m.p. : >250°C

Yield : 87%

^{1}H NMR (DMSO-d_6) :

7.8 (3H, m) ; 5.5 (2H, s) ; 3.9 (3H, s) ; 1.2 (9H, s)

Example 3 : 1-[2-(4-Methylphenylamino)-2-oxoethyl]-6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

- ethyl 1-[2-(4-methylphenylamino)-2-oxoethyl]-6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate

A suspension containing 6 g (0.024 M) of ethyl 6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate, 5 g (0.036 M) of potassium carbonate and 5.3 g (0.029 M) of N-(4-methylphenyl)chloroacetamide in 50 ml of N,N-dimethylformamide is heated at 50°C for 5 hours. The reaction mixture is cooled to -5°C.

The solid is filtered off by suction, washed with 10 ml of N,N-dimethylformamide, slurried in demineralised water until the filtrate is neutral, and dried under reduced pressure.

6.9 g of whitish solid are obtained.

Yield : 72%

m.p. = 266°C

^{1}H NMR (DMSO-d_6) :

10.42 (1H, s) ; 8.65 (1H, s) ; 7.66 (1H, d) ; 7.51 (1H, d) ; 7.43 (2H,d) ; 7.37 (1H, dd) ; 7.10 (2H, d) ; 5.23 (2H, s) ; 4.21 (2H, q) ; 3.83 (3H, s) ; 2.22 (3H, s) ; 1.27 (3H, t)

- 1-[2-(4-Methylphenylamino)-2-oxoethyl]-6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

A suspension of 6.9 g (0.017 M) of ethyl 1-[2-(4-methylphenylamino)-2-oxoethyl]-6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate in 70 ml of 10% sodium hydroxide solution and 70 ml of methanol is stirred at room temperature for 16 hours. The mixture is then acidified with 15 ml of 12N hydrochloric acid at 10°C and then stirred for three hours. The precipitated solid is filtered off by suction, washed thoroughly with demineralised water and then dried under reduced pressure.

6.4 g of cream-coloured solid are obtained.

Yield : 100%
m.p. > 270°C
^{1}H NMR (DMSO-d_6) :
10.76 (1H, s) ; 8.97 (1H, s) ; 7.80 (2H, m) ; 7.53 (1H, dd) ; 7.49 (2H, d) ; 7.11 (2H, d) ; 5.51 (2H, s) ; 3.90 (3H, s) ; 2.24 (3H, s)

By way of example, the following compounds are prepared according to the procedure of Example 3:

1-[2-(4-Chlorophenylamino)-2-oxoethyl]-6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid
1-[2-(3-Chlorophenylamino)-2-oxoethyl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid
1-[2-(4-Chlorophenylamino)-2-oxoethyl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

Example 4 : 1-[2-(3-Chlorophenylamino)-2-oxoethyl]-6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

- Ethyl 1-[2-(3-chlorophenylamino)-2-oxoethyl]-6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate

A suspension containing 5 g (0.02 M) of ethyl 6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate, 4.2 g (0.03 M) of potassium carbonate and 5.1 g (0.025 M) of N-(3-chlorophenyl)chloroacetamide in 50 ml of N,N-dimethylformamide is heated at 50°C for 5 hours. The reaction mixture is cooled to room temperature and then poured into 450 ml of cold demineralised water. The precipitate obtained is filtered off by suction and washed thoroughly with demineralised water. The solid that sublimes on drying is used wet in the following step.

15.4 g of wet solid are obtained.

m.p.=228°C

^{1}H NMR (DMSO-d_6) :
10.71 (1H, s) ; 8.67 (1H, s) ; 7.76 (1H, s) ; 7.68 (1H, d, J=2.6) ; 7.58-7.33 (4H, m) ; 7.14 (1H, dd, J=6.8) ; 5.29 (2H, s) ; 4.22 (2H, q, J=6.9) ; 3.85 (3H, s) ; 1.29 (3H, t, J=6.9)

- 1-[2-(3-Chlorophenylamino)-2-oxoethyl]-6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

The above ester is hydrolysed according to the method described in Example 3.
4.4 g of beige-coloured solid are obtained.

Overall yield: 57%
m.p.>270°C
^{1}H NMR (DMSO-d_6) :
15.25 (1H, s) ; 10.75 (1H, s) ; 9.05 (1H, s) ; 7.77 (3H, m) ; 7.56 (1H, dd, J=9.5, J=2.6) ; 7.45 (1H, d, J=7.7) ; 7.36 (1H, t, J=7.7) ; 7.15 (1H, d, J=8.6) ; 5.50 (2H, s) ; 3.91 (3H, s)

By way of example, the following compounds are prepared according to the procedure of Example 3:

1-[2-(N-Piperidinoacetyl)-2-oxoethyl]-6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

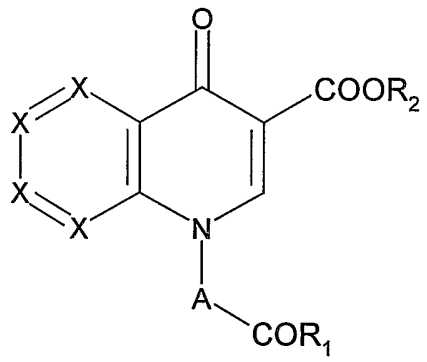
1-[2-(4-Methylphenylamino)-2-oxoethyl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

The compounds mentioned above were characterised by the following analytical techniques:

NMR :
The NMR spectra were acquired using a Brüker Advanced DPX 200 MHz spectrometer.
Melting points:
The melting points (m.p.) were measured on a block of Köfler Leica VMHB type.

CLAIMS

1- Compounds of the general formula (I)



in which:

X represents, independently of each other, an optionally substituted methylene radical or a nitrogen, oxygen or sulfur atom,

R1 represents a group chosen from:

- radical of the formula OR2,
- amine optionally substituted by one or more of the following groups: (C1-C5) alkyl, (C_3-C_8) cycloalkyl, (C_1-C_5) alkoxy, aryl, alkylaryl or aralkyl, these groups possibly being interrupted with one or more hetero atoms and/or possibly being substituted, especially with one or more halogen atoms, the nitrogen of the amine group also possibly forming part of a heterocycloalkyl,

R2, which may be identical or different, represents a group chosen from:

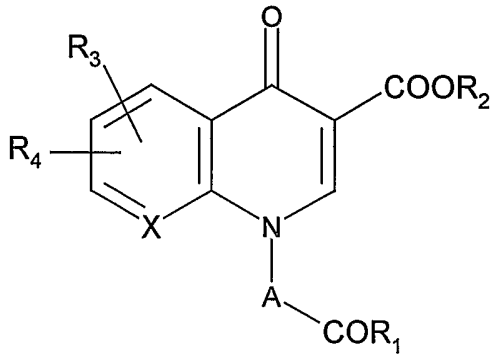
- hydrogen,
- (C_1-C_{20}) alkyl optionally substituted by one or more of the following groups: halogen, (C1-C5) alkyl, (C_3-C_8) cycloalkyl, (C_1-C_5) alkoxy, substituted or unsubstituted amino, optionally substituted carbonyl, ester, amide, a sulfur or phosphorus atom,
- (C_2-C_{20}) alkylene optionally substituted by halogen, (C_1-C_5) alkyl, (C_1-C_5) alkoxy or (C_3-C_8) cycloalkyl
- (C_2-C_{20}) alkyne optionally substituted by halogen, (C_1-C_5) alkyl, (C_1-C_5) alkoxy or (C_3-C_8) cycloalkyl

- (C_3-C_8) cycloalkyl optionally substituted by (C_1-C_5) alkyl or (C_1-C_5) alkoxy
- (C_3-C_8) heterocycloalkyl bearing one or more hetero atoms chosen from N, O and S and optionally substituted by (C_1-C_5) alkyl or (C_1-C_5) alkoxy,
- (C_6-C_{14})aryl(C_1-C_{20})alkyl optionally substituted by amino, hydroxyl, thio, halogen, (C_1-C_5) alkyl, (C_1-C_5) alkoxy, (C_1-C_5) alkylthio, (C_1-C_5) alkylamino, (C_6-C_{14}) aryl, (C_6-C_{14}) aryloxy, (C_6-C_{14})aryl(C_1-C_5)alkoxy, cyano, trifluoromethyl, carboxyl, carboxymethyl or carboxyethyl,
- (C_6-C_{14}) aryl optionally substituted by amino, hydroxyl, thio, halogen, (C_1-C_5) alkyl, (C_1-C_5) alkoxy, (C_1-C_5) alkylthio, (C_1-C_5) alkylamino, (C_6-C_{14}) aryl, (C_6-C_{14}) aryloxy, (C_6-C_{14})aryl(C_1-C_5)alkoxy, cyano, trifluoromethyl, carboxyl, carboxymethyl or carboxyethyl,
- (C_1-C_{13}) heteroaryl bearing one or more hetero atoms chosen from N, O and S and optionally substituted by amino, hydroxyl, thio, halogen, (C_1-C_5) alkyl, (C_1-C_5) alkoxy, (C_1-C_5) alkylthio, (C_1-C_5) alkylamino, (C_6-C_{14}) aryl, (C_6-C_{14}) aryloxy, (C_6-C_{14})aryl(C_1-C_5)alkoxy, cyano, trifluoromethyl, carboxyl, carboxymethyl or carboxyethyl,

A represents a single bond or a (C_1-C_6) alkyl group optionally substituted by one or more of the following groups: halogen, (C_3-C_8) cycloalkyl, (C_1-C_5) alkoxy, substituted or unsubstituted amino, optionally substituted carbonyl, ester, amide, a sulfur or phosphorus atom,

and also the tautomeric forms, enantiomers, diastereoisomers and epimers, and the pharmaceutically acceptable salts.

2- Compounds according to Claim 1, characterised in that they are of the general formula (II) below:



(II)

in which R1, R2, X and A are as defined in Claim 1, and

R3 and R4, which may be identical or different, represent groups chosen from:

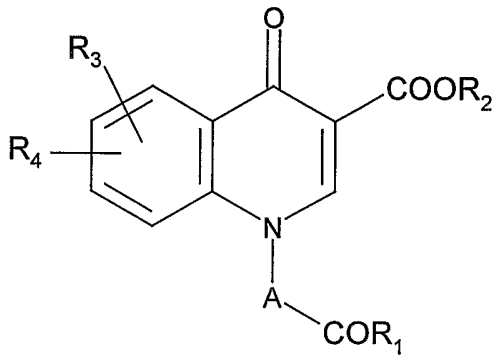
- a hydrogen atom,
- (C_1-C_{20}) alkyl optionally substituted by one or more of the following groups: halogen, (C1-C5) alkyl, (C_3-C_8) cycloalkyl, (C_1-C_5) alkoxy, substituted or unsubstituted amino, optionally substituted carbonyl, ester, amide, a sulfur or phosphorus atom,
- (C_1-C_{20}) alkoxy optionally substituted by one or more of the following groups: halogen, (C1-C5) alkyl, (C_3-C_8) cycloalkyl, (C_1-C_5) alkoxy, substituted or unsubstituted amino,
- (C_2-C_{20}) alkylene optionally substituted by halogen, (C1-C5) alkyl, (C_1-C_5) alkoxy, (C_3-C_8) cycloalkyl,
- (C_2-C_{20}) alkyne optionally substituted by halogen, (C_1-C_5) alkyl, (C_1-C_5) alkoxy or (C_3-C_8) cycloalkyl
- (C_3-C_8) cycloalkyl optionally substituted by (C_1-C_5) alkyl or (C_1-C_5) alkoxy
- (C_3-C_8) heterocycloalkyl bearing one or more hetero atoms chosen from N, O and S and optionally substituted by (C_1-C_5) alkyl or (C_1-C_5) alkoxy,
- (C_6-C_{14})aryl(C_1-C_{20})alkyl optionally substituted by amino, hydroxyl, thio, halogen, (C_1-C_5) alkyl, (C_1-C_5) alkoxy, (C_1-C_5) alkylthio, (C_1-C_5) alkylamino, (C_6-C_{14}) aryl, (C_6-C_{14}) aryloxy, (C_6-C_{14})aryl(C_1-C_5)alkoxy, cyano, trifluoromethyl, carboxyl, carboxymethyl or carboxyethyl,
- (C_6-C_{14}) aryl optionally substituted by amino, hydroxyl, thio, halogen,

(C_1-C_5) alkyl, (C_1-C_5) alkoxy, (C_1-C_5) alkylthio, (C_1-C_5) alkylamino, (C_6-C_{14}) aryl, (C_6-C_{14}) aryloxy, (C_6-C_{14})aryl(C_1-C_5)alkoxy, cyano, trifluoromethyl, carboxyl, carboxymethyl or carboxyethyl,

- (C_1-C_{13}) heteroaryl bearing one or more hetero atoms chosen from N, O and S and optionally substituted by amino, hydroxyl, thio, halogen, (C_1-C_5) alkyl, (C_1-C_5) alkoxy, (C_1-C_5) alkylthio, (C_1-C_5) alkylamino, (C_6-C_{14}) aryl, (C_6-C_{14}) aryloxy, (C_6-C_{14})aryl(C_1-C_5)alkoxy, cyano, trifluoromethyl, carboxyl, carboxymethyl or carboxyethyl,

R3 and R4 may also together form a heterocycle adjacent to the phenyl ring.

3- Compounds according to Claim 2, characterised in that they are of the general formula (III) below:



(III)

in which R1, R2, R3, R4 and A are as defined in Claim 1 or 2.

4- Compounds according to Claim 2 or 3, characterised in that, when R3 and R4 together form a heterocycle adjacent to the phenyl ring, they represent the ring -O-(CH2)n-O-, n being an integer ranging from 1 to 4.

5- Compounds according to Claim 2 or 3, characterised in that R4 is a hydrogen atom and R3 represents an alkoxy radical.

6- Compounds according to one of the preceding claims, characterised in that A is an optionally substituted methylene group.

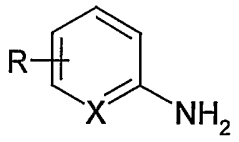
7- Compounds according to any one of the preceding claims, characterised in that, when the nitrogen of the amine group represented by R1 forms part of a heterocycloalkyl, this heterocycloalkyl is a piperidine ring.

8- Compounds according to any one of the preceding claims, characterised in that they are chosen from:

- 3-carboxy-6-methoxy-4-oxo-1,4-dihydroquinoline-1-acetic acid,
- 3-carboxy-7-methoxy-4-oxo-1,4-dihydroquinoline-1-acetic acid,
- 3-carboxy-6,7-methylenedioxy-4-oxo-1,4-dihydroquinoline-1-acetic acid,
- 3-carboxy-8-methoxy-4-oxo-1,4-dihydroquinoline-1-acetic acid,
- 1-[2-(1,1-dimethylethylamino)-2-oxoethyl]-6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid,
- 1-[2-(4-methylphenylamino)-2-oxoethyl]-6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid,
- 1-[2-(4-chlorophenylamino)-2-oxoethyl]-6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid,
- 1-[2-(3-chlorophenylamino)-2-oxoethyl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid,
- 1-[2-(4-chlorophenylamino)-2-oxoethyl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid,
- 1-[2-(3-chlorophenylamino)-2-oxoethyl]-6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid,
- 1-[2-(N-piperidinoacetyl)-2-oxoethyl]-6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid,
- 1-[2-(4-methylphenylamino)-2-oxoethyl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

9- Process for preparing compounds of the formula (I) as defined in Claim 1, comprising the following steps:

a) condensation of an arylamine or of a heteroarylamine, which is optionally substituted, with diethyl ethoxymethylenemalonate, the arylamine or heteroarylamine being of the formula (1) below:



in which formula (1) X represents a nitrogen or carbon atom and R represents R3 or R4 as defined in Claim 2,

b) heat treatment of the malonic derivative obtained in step a) under conditions allowing cyclisation, more particularly by heating in a solvent of high boiling point, preferably from 200 to 300°C, advantageously at 250°C,

c) N-alkylation reaction of the tautomeric form of the cyclised product obtained in step b) by condensation in the presence of an alkaline agent,

d) optionally, saponification of the ester obtained in step c).

10- Pharmaceutical composition comprising, as active principle, a compound according to any one of Claims 1 to 8.

11- Composition according to Claim 10, intended for presenting inhibitory activity on aldose reductase.

12- Composition according to Claim 10, intended for treating or preventing complications induced by diabetes.

13- Composition according to Claim 12, characterised in that the complications induced by diabetes are chosen from retinopathy, nephropathy, neuropathy and vascular diseases.

14- Use of at least one compound according to one of Claims 1 to 8, for the preparation of a pharmaceutical composition intended for treating or preventing a complication induced by diabetes.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/06881

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D215/56 C07D471/04 A61K31/47 A61P7/12 A61P3/10
//(C07D471/04,221:00,221:00)

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 7 C07D A61K A61P

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)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 287 458 A (DANIEL KAMINSKY ET AL) 22 November 1966 (1966-11-22) the whole document, especially example 15 and claim 14 ---	1-4,6,9, 10
X	TETSUO OKADA ET AL: "Synthesis and antibacterial activities of novel oxazine and thiazine ring-fused tricyclic quinolonecarboxylic acids" JOURNAL OF HETEROCYCLIC CHEMISTRY., vol. 28, no. 4, 1991, pages 1067-1074, XP002194320 HETEROCORPORATION. PROVO., US ISSN: 0022-152X page 1068, schemes 1 and 2, especially formulas 7,8,10; page 1071, right-hand column; page 1072, first paragraph --- -/--	1,9

[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

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"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
27 August 2002	05/09/2002

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	Chouly, J

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/06881

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 614 664 A (TAKEDA CHEMICAL INDUSTRIES LTD) 14 September 1994 (1994-09-14) claims	1,9,10
A	US 5 594 005 A (SLAVIN SHIMON ET AL) 14 January 1997 (1997-01-14) the whole document	1,9-14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 02/06881

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