4440
AUSTRALIA
Patents Act 1952

CONVENTION OR NON-CONVENTION APPLICATION
PATENT OR PATENT OF ADDITION

(a) Insert full name(s)
of applicant(s).

X/We (a) ISTITUTO LUSO-FARMACO d'ITALIA s.p.a.

(b) Insert full address(es) of applicant(s).

of (b) Via Carnia, 26.

MILAN, ITALY

(c) Delete whichever is inapplicable.

declare, apply for the grant of a (c) patent, patent of addition for an invention entitled
In support of the application No. (a) made by (b) ...... ISTITUTO LUSO FARMACO d'ITALIAG s.p.a.

for a patent/patent of addition for an invention entitled (c) "4-ARYL-5-AMINOALKYL-1,3-DIHYDRO-2-ONES, THEIR DERIVATIVES, ... PROCESSES FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM.

I, Giorgio Lorenzini,

of (d) Viale Pizzino 32, Milan, Italy

do solemnly and sincerely declare as follows:

1. (f) I am authorized by the abovementioned applicant for the patent/patent of addition to make this declaration on its behalf.

2. The basic application(s) as defined by Section 141 of the Act were made in the following country or countries on the following date(s) by the following applicant(s) namely:

   in (i) Italy on (j) 3rd March 1978
   by (k) Istituto Luso Farmaco d'Italia s.p.a.

3. (m) ELIO MARCHIGLI GIUSEPPE CASCIO, GIANCARLO FREGNAN and ROBERTO PORTA of (n) Via Baracca 17 Monza, Italy; Via Elvezia 14 Monza, Italy; Viale Sanpaolo 41 Milan, Italy; and Via Aquileia 1 Carmigiano Como, Italy respectively

   are the actual inventor(s) of the invention and the facts upon which the applicant(s) are entitled to make the application as follows:

   (o) The said applicant would be entitled to have assigned to it a patent granted to the said inventors in respect of the said inventions.

4. (p) The basic application(s) referred to in paragraph 2 of this Declaration were the first application(s) made in a Convention country in respect of the invention the subject of the application.

Declared at Milan this 14 day of February 1979

by (q) Istituto Luso Farmaco d'Italia s.p.a.
ABSTRACT

(1) AU -Al 44-404/79

(2) PATENT SPECIFICATION

(3) ABSTRACT

(4) AU

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(54) 4-ARYL-5-AMINOALKYL-1,3-DIOXOL-2-ONES

(71) ISTITUTO LUSO FARMACO D'ITALIA S.P.A.

(72) MANCHISI E., CASCIO G., FREGNAN G. AND PORTA R.

(74) HA

(57) CLAIMS

1. 4-Aryl-5-aminoalkyl-1,3-dioxol-2-ones and their derivatives having general formula (I)

\[
\text{Ar} - \text{C} = \text{C} - \text{Alk} - \text{N} - \text{C} - \text{O} - \text{Z} \quad \text{(I)}
\]

(and their pharmaceutically acceptable salts) where:

\( \text{Ar} \) represents a residue selected from the group including mono and polycyclic aryls, carrying or not one or more substituents, such as phenyl, lower alkyl phenyl, trifluoro methylphenyl, lower alkoxy phenyl, lower dialkyl amino phenyl, halogen phenyl, alkylmercaptophenyl, biphenyl, naphthyl;
Alk represents a saturated chain including one to three carbon atoms:

\[ \begin{aligned}
R_1 & \\
N & \left\langle \begin{array}{c}
R_2
\end{array} \right. \\
\end{aligned} \]

represents the residue of secondary amines such as N,N-dialkylamines, N-cycloalkyl-N-alkylamines, where cycloalkyl has 3 to 8 carbon atoms, N-alkyl-N-phenylalkylamines, N,N-alkylene-imines where alkylene has 4 to 6 carbon atoms, 4-phenyl substituted N,N-alkylene-imines, 4,4-disubstituted N,N-alkylene-imines such as 7,12-dioxo-3-azaspiro[5,5]dodec-3-yl or 3-azaspiro[5,5]undecan-3-yl; 4-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine; N,N-oxoalkylene-imines where alkylene preferably has 4 carbon atoms; N,N-thio-alkylene-imines where alkylene preferably has 4 carbon atoms; N,N-aza-alkylene-imines where alkylene has 4 to 6 carbon atoms and which may be linear or branched, whereas the "aza" nitrogen may be substituted with lower alkyl, lower alkoxyalkyl, lower acyloxyalkyl, lower arylalkyl, lower diarylalkyl groups (where aryl groups are preferably phenyl and may be substituted, on their turn, with halogen atoms or lower alkoxy), monocarbocyclic aryl, preferably phenyl groups, which may be on their turn substituted with one or more halogen atoms, lower alkyl, lower alkoxy or trifluoromethyl groups; or, finally, with...
etherocyclic monocyclic aryl groups;

Z represents an atom of oxygen or sulphur.

Pharmaceutical compositions with hypcholesterolemic, hypolipemic, antiulcer, antihistaminic and antiserotoninic activities, characterized by the fact that they contain, as active principles, one or more compounds according to claims 1-33 in form of free bases or pharmaceutically acceptable salts.
Name of Applicant(s): ISTITUTO LUSO FARMACO d'ITALIA s.p.a.

Address of Applicant(s): Via Carnia, 26, Milan, Italy.

Actual Inventor(s): Elso MANGHISI, Giuseppe CASCIO, Giancarlo FREGNAN, Roberto PORTA.

Address for Service: CLEMENT HACK & CO., 140 William Street, Melbourne, Victoria, 3000 Australia

Complete Specification for the invention entitled: "4-ARYL-5-AMINOALKYL-1,3-DIOXOL-2-ONES, THEIR DERIVATIVES, PROCESSES FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM"
This invention concerns a series of compounds having general formula (I)

\[
\text{Ar}-\text{C}=\text{C}-\text{Alk}-\text{N}^{R_1} \quad \text{(I)}
\]

In this formula, Ar represents a carbocyclic aryl group, in particular a monocarbocyclic aryl group such as phenyl, or phenyl substituted one or more times with equal or different substituents such as lower alkyl, trifluoromethyl, lower alkoxy, lower alkenyloxy, lower alkylenedioxy, halogen, alkylmercapto, nitro, amino, lower N,N-dialkylamino.

The carbocyclic aryl residue, moreover, may be a bicyclic group such as biphenyl, naphthyl or paphthyl substituted with one or more equal or different substituents; the substituted naphthyl groups may be, for instance, alkylnaphthyl, trifluoromethynaphthyl, alkoxyalnaphthyl, alkenyloxyalnaphthyl, halogenalnaphthyl, aminonaphthyl and so on.

Always in formula (I), Alk represents an alkylene group including 1 to 3 carbon atoms; whereas \( \text{N}^{R_1} \) represents an amino disubstituted group such as N,N-dialkylamino, N-cycloalkyl-alkyl-N-alkylamino (where cycloalkyl has 3 to 8 carbon atoms), N-lower alkyl-N-phenylalkylamino.

The \( \text{N}^{R_1} \) group may also be an N,N-alkylene-imino group where alkylene has 4 to 6 carbon atoms, a 4-phenyl
substituted N,N-alkylene-imino group, a 4,4-disubstituted N,N-alkylene-imino, such as 7,12-dioxo-3-azaspiro[5,6]dodec-3-yl or 3-azaspiro[5,5]undecan-3-yl; 4-(4-chlorophenyl)-1,2,3,6-tetrahydropyridino; N,N-oxo-alkylene-imino, where alkylene preferably has 4 carbon atoms; N,N-thio-alkylene-imino, where alkylene preferably has 4 carbon atoms; or N,N-azaalkylene-imino, where alkylene has 4 to 6 carbon atoms, which may be linear or branched, and where the "aza" nitrogen may carry substituents such as lower alkyl or lower alkoxyalkyl, lower acyloxyalkyl, lower arylalkyl, lower diarylalkyl (where aryls preferably are phenyls which may, on their turn, carry substituents such as halogen atoms or lower alkoxy groups), or monocarbocyclic aryl, preferably phenyl, substituted or not with one or more halogen atoms or with lower alkyl, trifluoromethyl, lower alkoxy; or, finally, an etherocyclic monocyclic aryl; Z represents oxygen or sulphur.

The invention also concerns the processes for the preparation of the substances with general formula (I).

Finally, the invention concerns pharmaceutical compositions having hypcholesterolemic, hypolipemic, antiulcer, antihistaminic and antiserotoninic activity, which contain, as active principles, one or more compounds with formula (I) or their pharmaceutically acceptable salts.

The compounds (I) may be obtained reacting compounds of general formula (II)
where $\text{Ar}$, $\text{Alk}$ and $\text{Nu}$ have the above meanings, with phosgene, thiophosgene, ethyl chlorocarbonate, trichloromethyl chlorocarbonate, ethyl carbonate, eventually in presence of proton acceptors (triethylamine, dimethylaniline and so on) in non polar solvents (chloroform, benzene, toluene and so on) and at temperatures ranging from $-10^\circ\text{C}$ to $+50^\circ\text{C}$, or with 1,1-carbonyldiimidazole in non polar solvents (benzene, toluene, 2-butane) at the solvent boiling temperature, for a few hours.

For the synthesis of the compounds having general formula II, see the methods reported in C.A. BO, 27292 k (1974), which mainly consist in reacting compounds of general formula (III).

$$\text{Ar-CO-CH-Alk-N} \begin{array}{c} \text{R}_1 \\ \text{OH} \end{array} \text{R}_2$$

(II)

where $\text{X}$ and $\text{Y}$ represent halogen atoms (while $\text{Ar}$ and $\text{Alk}$ have the above reported meanings), with alkoxydes or alkali and alkali-earth metals and subsequently with amines with formula

$$\begin{array}{c} \text{R}_1 \\ \text{HN} \\ \text{R}_2 \end{array}$$

where $\text{NR}_1\text{R}_2$ have the above reported meanings.

From the compounds of general formula (I) it is possible to prepare salts with pharmaceutically acceptable
inorganic acids, for instance hydrochloric, hydrobromic, nitric, sulphuric, phosphoric acid and so on; as well as with carboxylic organic acids, for instance acetic, propionic, glycolic, malonic, succinic, maleic, hydroxymaleic, fumaric, malic, tartaric, citric, glucuronic, benzoic, mandelic, salicylic, 4-aminosalicylic, 2-phenoxybenzoic, 2-acetoxybenzoic, pamoic, nicotinic, isonicotinic acid and so on; or with sulphonic organic acids, for instance methanesulphonic, ethanesulphonic, 2-hydroxy-ethanesulphonic, ethane-1, 2-disulphonic, p-toluenesulphonic, naphthalin-2-sulphonic acid and so on.

Mono or poly salts are obtained depending on the salifiable groups present in the molecules.

The products having general formula (I) and their pharmaceutically acceptable salts are endowed with strong hypcholesterolemic and hypolipemic activities, as well as with antiulcer, antihistaminic and antiserotoninic activities.

They may be administered by oral or rectal route, or injected, in suitable pharmaceutical formulations in solid or liquid form or in suspension (tablets, capsules, ampoules, syrups, suppositories, and so on).

The following tables report, as not limiting examples, the pharmacological characteristics of some compounds described in this application; these compounds are indicated by numbers which have the following meanings;
No. 1: 6-(4-fluorophenyl)-5-[2-(4-phenyl-1-piperazinyl)ethyl]-1,3-dioxol-2-one dihydrochloride

No. 2: 4-(4-fluorophenyl)-5-[2-(N-methyl-N-2-phenylethylamino)ethyl]-1,3-dioxol-2-one hydrochloride

No. 3: 4-(4-fluorophenyl)-5-[2-(4-(2-pyridyl)-1-piperazinyl)ethyl]-1,3-dioxol-2-one dihydrochloride

No. 4: 4-(4-fluorophenyl)-5-[2-(4-methyl-1-piperazinyl)ethyl]-1,3-dioxol-2-one dihydrochloride

No. 5: 4-(4-fluorophenyl)-5-[2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl]-1,3-dioxol-2-one dihydrochloride

No. 6: 4-phenyl-5-[2-(4-phenyl-1-piperazinyl)ethyl]-1,3-dioxol-2-one dihydrochloride

No. 7: 4-(4-chlorophenyl)-5-[2-(4-phenyl-1-piperazinyl)ethyl]-1,3-dioxol-2-one dihydrochloride

No. 8: 4-(4-fluorophenyl)-5-[2-(1-morpholinyi)ethyl]-1,3-dioxol-2-one hydrochloride

No. 9: 4-(4-tolyl)-5-[2-(4-phenyl-1-piperazinyl)ethyl]-1,3-dioxol-2-one hydrochloride

No. 10: 4-(4-fluorophenyl)-5-[2-(4(3,5-dichlorophenyl)-1-piperazinyl)ethyl]-1,3-dioxol-2-one hydrochloride

No. 11: 4-(4-fluorophenyl)-5-[2-(4-(4-chlorophenyl)-3-methyl-1-piperazinyl)ethyl]-1,3-dioxol-2-one dihydrochloride

No. 12: 4-(4-fluorophenyl)-5-[2-(4(2,5-dichlorophenyl)-1-piperazinyl)ethyl]-1,3-dioxol-2-one hydrochloride

No. 13: 4-(4-fluorophenyl)-5-[2-(4(3,4-dichlorophenyl)-1-piperazinyl)ethyl]-1,3-dioxol-2-one hydrochloride

- 6 -
No. 14: 4-(2-naphthyl)-5-[2-(4-phenyl-1-piperazinyl)ethyl]-1,3-dioxol-2-one hydrochloride

No. 15: 4-(4-methoxyphenyl)-5-[2-(4-phenyl-1-piperazinyl)ethyl]-1,3-dioxol-2-one dihydrochloride

No. 16: 4-(4-methylthiophenyl)-5-[2-(4-phenyl-1-piperazinyl)ethyl]-1,3-dioxol-2-one dihydrochloride

No. 17: 4-(4-fluorophenyl)-5-[2-(3-azaspiro[5,5]undecan-3-yl)ethyl]-1,3-dioxol-2-one hydrochloride

No. 18: 4-(4-chlorophenyl)-5-[2-(4-(4-chlorobenzylhydryl)-1-piperazinyl)ethyl]-1,3-dioxol-2-one dihydrochloride

No. 19: 4-(4-chlorophenyl)-5-[2-(4-(2-pyrimidinyl)-1-piperazinyl)ethyl]-1,3-dioxol-2-one maleate

No. 20: 4-(4-fluorophenyl)-5-[3-(4-phenyl-1-piperazinyl)propyl]-1,3-dioxol-2-one hydrochloride

No. 21: 3-(4-chlorophenyl)-5-[2-(4-(4-chlorophenyl)-1-piperazinyl)ethyl]-1,3-dioxol-2-one hydrochloride

No. 22: 4-(4-chlorophenyl)-5-[2-(4-phenyl)-1-piperidinyl)ethyl]-1,3-dioxol-2-one hydrochloride

No. 23: 4-(4-chlorophenyl)-5-[2-(4-benzhydryl-1-piperazinyl)ethyl]-1,3-dioxol-2-one hydrochloride

The toxicity of the compounds, according to the invention, is reported in tables 1, 2 and 3, which also contain the values of hypolipemic, hypcholesterolemic and antiulcer activities respectively, obtained according to the methods described hereunder.

a) Hypolipemic activity
It has been evaluated orally in rats treated five times in 4 days (once daily during the first three days, twice daily on the fourth day) with the drugs under study. The animals, kept on an empty stomach, were killed on the fifth day, 18 hours after the last treatment. The following tests were carried out:

- **determination of plasmatic cholesterol**

  The technique described by J.P. Blomhoff (Clin. Chim. Acta, 43, 247, 1973) for the gas-chromatographic determination of total cholesterol was followed. 0.5 ml of the animal serum are hydrolysed at 50°C for 1 hour with 5 ml of 2% alcoholic KOH. Cholesterol is extracted with 2% petroleum ether at 60-80°C and the gas-chromatographic analysis is carried out on the extract with cholesterol acetate as internal standard. The plasmatic cholesterol concentration of the treated animals is evaluated by comparing it with that of the controls. The calculated ED₃₀ represents the dose which reduces by 30% the content of plasmatic cholesterol.

- **determination of plasmatic triglycerides**

  The technique of M. Eggstein (Klin. Nachr., 44, 267, 1966) is used; it consists in determining, by enzymatic route, the total glycerol made free by hydrolysis of the seric neutral fats. In particular, the "Biochemia Test Combination" (Boehringer Mannheim GMBH) was used.

  In this case, too, the seric concentration of triglycerides in the treated animals was compared with that in the
control. The calculated ED₃₀ represents the dose which reduces by 30% the content of plasmatic triglycerides.

b) Antiulcer activity in the rat

The method described by Rossi et al. (Comp. Rend. Soc. Biol., 150, 2124, 1956) was followed: 30 minutes after the oral treatment with the drugs under study, the animals, kept on an empty stomach for 48 hours, were immobilized for a period of 4 hours. At the end of this time, the presence of ulcers is checked after killing the animals by ether. The calculated ED₃₀ represents the dose which protects 30% of the animals from ulcers.

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>Acute toxicity, DL₅₀ (mice) mg/kg ip</th>
<th>Hypcholesterolemic activity, DE₃₀ (rats) mg/kg os</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>420</td>
<td>10</td>
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<tr>
<td>3</td>
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<td>6</td>
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<td>7</td>
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<td>9</td>
<td>&gt;1000</td>
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<td>14</td>
<td>830</td>
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<td>19</td>
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<tr>
<td>20</td>
<td>&gt;500</td>
<td>30</td>
</tr>
<tr>
<td>Compound No.</td>
<td>Acute toxicity DL₅₀ (mice) mg/kg ip</td>
<td>Hypotriglyceremic activity DE₃₀ (rats) mg/kg os</td>
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<tr>
<td>-------------</td>
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</tr>
<tr>
<td>1</td>
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<tr>
<td>23</td>
<td>&gt;1000</td>
<td>100</td>
</tr>
<tr>
<td>Compound No.</td>
<td>Acute toxicity DL₅₀ (mice) mg/kg ip</td>
<td>Antiulcer activity DE₃₀ (rats) mg/kg os</td>
</tr>
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<td>-------------</td>
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<tr>
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<td>13</td>
<td>600</td>
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</table>

The following examples illustrate the invention without restricting it. The melting and boiling points are not correct. The identity and purity of the substances were checked by means of elemental analysis of C, H, N (and halogens if present), infra-red, N.M.R. and U.V. spectra.

**EXAMPLE 1**

4-(4-fluorophenyl)-5-[2-(4-(2-methoxyphenyl)1-piperazinyl]-ethyl]-1,3-dioxol-2-one dihydrochloride

A solution of 20 g of 1-p-fluorobenzoyl-1-hydroxy-3-
(4-(2-methoxyphenyl)-1-piperazinyl)propane in 200 cc of anhydrous chloroform is added in 60 minutes to 33 ml of a 20% phosgene solution in toluene, stirred and cooled to 0°C. The reaction mixture is stirred at room temperature for one hour, then refluxed for 6 hours. It is cooled to room temperature, the solid is filtered, then dissolved under heating in 300 ml of alcohol, and 15 ml of alcoholic HCl are added. The solution is then cooled and filtered. M.p. = 238-40°C (from alcohol)

The same compound is obtained by substituting phosgene by trichloromethyl chlorocarbonate.

Similarly the preparation of the following compound is carried out:

4-(4-fluorophenyl)-5-$\sqrt{2}$-diethylaminoethyl]-1,3-dioxol-2-one hydrochloride m.p. = 159-61°C (from ethanol)

4-(4-fluorophenyl)-5-$\sqrt{2}$-(4-phenyl-1-piperazinyl)ethyl]-1,3-dioxol-2-one dihydrochloride m.p. = 264-5°C (from ethanol)

4-(4-fluorophenyl)-5-$\sqrt{2}$-(N-methyl-N-2-phenylethylamino)ethyl]-1,3-dioxol-2-one hydrochloride m.p. = 166-8°C (from isopropanol)

4-(4-fluorophenyl)-5-$\sqrt{2}$-(4-(2-pyridyl)-1-piperazinyl)ethyl]-1,3-dioxol-2-one dihydrochloride m.p. = 265-7°C (from ethanol)

4-(4-fluorophenyl)-5-$\sqrt{2}$-(4-methyl-1-piperazinyl)ethyl]-1,3-dioxol-2-one dihydrochloride m.p. = 279°C (from ethanol)

4-(4-fluorophenyl)-5-$\sqrt{2}$-(7,12-dioxo-3-azaspiro[5,6]dodec-3-yl)ethyl]-1,3-dioxol-2-one hydrochloride m.p. = 211-3°C (from ethanol)
4-(4-chlorophenyl)-5-[2-(4-phenyl-1-piperazinyl)ethyl]-1,3-dioxol-2-one dihydrochloride m.p. = 262-5°C (from ethanol)
4-(4-fluorophenyl)-5-[2-(4-chlorophenyl)-1-(1,2,3,6-tetrahydropyridyl)]ethyl]-1,3-dioxol-2-one hydrochloride m.p. = 220°C (from methanol)

4-(4-fluorophenyl)-5-[2-(1-morpholinyl)ethyl]-1,3-dioxol-2-one hydrochloride m.p. = 188-90°C (from ethanol)
4-(4-tolyl)-5-[2-(4-phenyl-1-piperazinyl)ethyl]-1,3-dioxol-2-one hydrochloride m.p. = 252-4°C (from ethanol)

4-(4-fluorophenyl)-5-[2-(4-(3,5-dichlorophenyl)-1-piperazinyl)ethyl]-1,3-dioxol-2-one hydrochloride m.p. = 277-9°C (from ethanol)
4-(4-fluorophenyl)-5-[2-(4-(4-fluorophenyl)-5-(4-phenyl-1-piperazinyl)ethyl]-1,3-dioxol-2-one dihydrochloride m.p. = 228-30°C (from ethanol)
4-(4-fluorophenyl)-5-[2-(4-(2,5-dichlorophenyl)-1-piperazinyl)ethyl]-1,3-dioxol-2-one hydrochloride m.p. = 240-2°C (from ethanol)
4-(4-fluorophenyl)-5-[2-(4-(3,4-dichlorophenyl)-1-piperazinyl)ethyl]-1,3-dioxol-2-one hydrochloride m.p. = 228-30°C (from ethanol)

4-(2-naphtyl)-5-[2-(4-phenyl-1-piperazinyl)ethyl]-1,3-dioxol-2-one hydrochloride m.p. = 239-40°C (from ethanol)
4-(4-methoxyphenyl)-5-[2-(4-phenyl-1-piperazinyl)ethyl]-1,3-dioxol-2-one dihydrochloride m.p. = 256-8°C (from ethanol)
4-(4-methylthiophenyl)-5-[2-(4-phenyl-1-piperazinyl)ethyl]-1,3-dioxol-2-one dihydrochloride m.p. = 255°C (from ethanol)
4-(4-fluorophenyl)-5-[2-(3-azaspiro[5,5]undecan-3-yl)ethyl]-1,3-dioxol-2-one dihydrochloride m.p. = 255°C (from ethanol)
1,3-dioxol-2-one hydrochloride m.p. = 270-270°C (from ethanol)

4-(4-chlorophenyl)-5-ethyl]-1,3-dioxol-2-one dihydrochloride m.p. = 242-43°C (from ethanol)

4-(4-biphenyl)-5-ethyl]-1,3-dioxol-2-one dihydrochloride m.p. = 242-43°C (from ethanol)

4-(4-fluorophenyl)-5-ethyl]-1,3-dioxol-2-one dihydrochloride m.p. = 200-205°C (from ethanol)

4-(4-fluorophenyl)-5-propyl]-1,3-dioxol-2-one hydrochloride m.p. = 175-180°C (from ethanol)

4-(4-chlorophenyl)-5-ethyl]-1,3-dioxol-2-one hydrochloride m.p. = 251-2°C (from ethanol)

4-(4-chlorophenyl)-5-ethyl]-1,3-dioxol-2-one hydrochloride m.p. = 242-3°C (from ethanol)

4-(4-chlorophenyl)-5-ethyl]-1,3-dioxol-2-one hydrochloride m.p. = 159-60°C (from ethanol)

4-(4-fluorophenyl)-5-ethyl]-1,3-dioxol-2-one hydrochloride m.p. = 181-2°C (from ethanol)

4-(4-fluorophenyl)-5-ethyl]-1,3-dioxol-2-one hydrochloride m.p. = 242-3°C (from ethanol)
1,3-dioxol-2-one hydrochloride m.p. = 203-4°C (from ethanol)

4-(4-chlorophenyl)-5-[2-(4-phenylmethyl-1-piperazinyl)ethyl]-l,3-dioxol-2-one dihydrochloride m.p. = 275-6°C (from dimethylformamide).

The 1-ary1-l-hydroxy-3-aminopropanes are obtained as described in C.A. 80, 27292 k (1974).

**EXAMPLE 2**

4-Phenyl-5-[2-(4-phenyl-1-piperazinyl)ethyl]-1,3-dioxol-2-one dihydrochloride

A solution of 2.5 g of 1-benzoyl-l-hydroxy-3-(4-phenyl-1-piperazinyl)propane and 5 g of 1,1'-carbonyldiimidazole in 100 ml of anhydrous benzene is refluxed for 8 hours. The reaction mixture is repeatedly washed with water, dried on Na₂SO₄ and evaporated to dryness at reduced pressure.

The residue is transformed into the corresponding dihydrochloride.

M.p. = 246-8°C (from alcohol).
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. 4-Aryl-5-aminoalkyl-1,3-dioxol-2-ones and their derivatives having general formula (I)

\[
\text{Ar} \quad \text{C} \quad \text{Alk} \quad \text{N} \\
\text{O} \quad \text{O} \\
\text{Z}
\]

(and their pharmaceutically acceptable salts) where:

- Ar represents a residue selected from the group including mono and policarbocyclic aryls, carrying or not one or more substituents, such as phenyl, lower alkyl phenyl, trifluoro methylphenyl, lower alkoxy phenyl, lower dialkyl amino phenyl, halogen phenyl, alkylmercaptophenyl, biphenyl, naphthyl;

- Alk represents a saturated chain including one to three carbon atoms;

- \( R_1 \) represents the residue of secondary amines such as \( N,N \)-dialkylamines, \( N \)-cycloalkyl-\( N \)-alkylamines, \( N \)-cycloalkyl has 3 to 8 carbon atoms, \( N \)-alkyl-\( N \)-phenylalkylamines, \( N,N \)-alkylene-imines where alkylene has 4 to 6 carbon atoms, 4-phenyl substituted \( N,N \)-alkylene-imines, 4,4-disubstituted \( N,N \)-alkylene-imines such as 7,12-dioxo-3-azaspiro\( ^5,6 \)dodec-3-yl or 3-azaspiro\( ^5,5 \)undecan-3-yl;
4-(4-chlorophenyl)1,2,3,6-tetrahydropyridine; N,N-oxoalkylene-imines where alkylene preferably has 4 carbon atoms; N,N-thio-alkylene-imines where alkylene preferably has 4 carbon atoms; N,N-aza-alkylene-imines where alkylene has 4 to 6 carbon atoms and which may be linear or branched, whereas the "aza" nitrogen may be substituted with lower alkyl, lower alkoxyalkyl, lower acyloxyalkyl, lower arylalkyl, lower diarylalkyl groups (where aryl groups are preferably phenyl and may be substituted, on their turn, with halogen atoms or lower alkoxy), monocarbocyclic aryl, preferably phenyl groups, which may be on their turn substituted with one or more halogen atoms, lower alkyl, lower alkoxy or trifluoromethyl groups; or, finally, with etherocyclic monocyclic aryl groups; Z represents an atom of oxygen or sulphur.

2. A compound according to claim 1 which is 4-(4-fluorophenyl)-5-[2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl]-1,3-dioxol-2-one, and its pharmaceutically acceptable acid addition salts.

3. A compound according to claim 1 which is 4-(4-fluorophenyl)-5-[2-(4-phenyl)-1-piperazinyl)ethyl]-1,3-dioxol-2-one, and its pharmaceutically acceptable acid addition salts.

4. A compound according to claim 1 which is 4-(4-fluorophenyl)-5-[2-(N-methyl-N-2-phenylethylamino)ethyl]-1,3-dioxol-2-one, and its pharmaceutically acceptable acid addition salts.

5. A compound according to claim 1 which is 4-(4-fluorophenyl)-5-[2-(4-(2-pyridyl)-1-piperazinyl)ethyl]-1,3-dioxol-
2-one, and its pharmaceutically acceptable acid addition salts.

6. A compound according to claim 1 which is 4-(4-fluorophenyl)-5-\( \text{2} \)-\( \text{t} \)-4-methyl-1-piperazinyl)-ethyl-1,3-dioxol-2-one, and its pharmaceutically acceptable acid addition salts.

7. A compound according to claim 1 which is 4-(4-fluorophenyl)-5-\( \text{2} \)-\( \text{t} \)-7,12-dioxo-3-azaspiro[5,\( \text{6} \)]dodec-3-yl)ethyl-1,3-dioxol-2-one, and its pharmaceutically acceptable acid addition salts.

8. A compound according to claim 1 which is 4-(4-chlorophenyl)-5-\( \text{2} \)-\( \text{t} \)-4-phenyl-1-piperazinyl)ethyl-1,3-dioxol-2-one, and its pharmaceutically acceptable acid addition salts.

9. A compound according to claim 1 which is 4-(4-fluorophenyl)-5-\( \text{2} \)-\( \text{t} \)-4-(4-chlorophenyl)-1-(1,2,3,6-tetrahydropyridyl)ethyl-1,3-dioxol-2-one, and its pharmaceutically acceptable acid addition salts.

10. A compound according to claim 1 which is 4-(4-fluorophenyl)-5-\( \text{2} \)-\( \text{t} \)-(1-morpholinyl)ethyl-1,3-dioxol-2-one, and its pharmaceutically acceptable acid addition salts.

11. A compound according to claim 1 which is 4-(4-tolyl)-5-\( \text{2} \)-\( \text{t} \)-4-phenyl-1-piperazinyl)ethyl-1,3-dioxol-2-one, and its pharmaceutically acceptable acid addition salts.

12. A compound according to claim 1 which is 4-(4-fluorophenyl)-5-\( \text{2} \)-\( \text{t} \)-4-(3,5-dichlorophenyl)-1-piperazinyl)ethyl-1,3-dioxol-2-one, and its pharmaceutically acceptable acid addition salts.
13. A compound according to claim 1 which is 4-(4-fluoro-phenyl)-5-\( \sqrt{2} \)-(4-(4-chlorophenyl)-3-methyl-1-piperazinyl)ethyl-1,3-dioxol-2-one, and its pharmaceutically acceptable acid addition salts.

14. A compound according to claim 1 which is 4-(4-fluoro-phenyl)-5-\( \sqrt{2} \)-(4-(2,5-dichlorophenyl)-1-piperazinyl)ethyl-1,3-dioxol-2-one, and its pharmaceutically acceptable acid addition salts.

15. A compound according to claim 1 which is 4-(4-fluoro-phenyl)-5-\( \sqrt{2} \)-(4-(3,4-dichlorophenyl)-1-piperazinyl)ethyl-1,3-dioxol-2-one, and its pharmaceutically acceptable acid addition salts.

16. A compound according to claim 1 which is 4-(4-fluoro-phenyl)-5-\( \sqrt{2} \)-(2-diethylaminoethyl)-1,3-dioxol-2-one, and its pharmaceutically acceptable acid addition salts.

17. A compound according to claim 1 which is 4-(2-naphtyl)-5-\( \sqrt{2} \)-(4-phenyl-1-piperazinyl)ethyl-1,3-dioxol-2-one, and its pharmaceutically acceptable acid addition salts.

18. A compound according to claim 1 which is 4-(4-metoxy-phenyl)-5-\( \sqrt{2} \)-(4-phenyl-1-piperazinyl)ethyl-1,3-dioxol-2-one, and its pharmaceutically acceptable acid addition salts.

19. A compound according to claim 1 which is 4-(4-methyl-thiophenyl)-5-\( \sqrt{2} \)-(4-phenyl-1-piperazinyl)ethyl-1,3-dioxol-2-one, and its pharmaceutically acceptable acid addition salts.

20. A compound according to claim 1 which is 4-(4-fluoro-phenyl)-5-\( \sqrt{2} \)-(3-azaspiro[5,5]undecan-3-yl)ethyl-1,3-dioxol-
2-one, and its pharmaceutically acceptable acid addition salts.

21. A compound according to claim 1 which is 4-(4-chlorophenyl)-5-[2-(4-(4-chlorobenzhydryl)-1-piperazinyl)ethyl]-1,3-dioxol-2-one, and its pharmaceutically acceptable acid addition salts.

22. A compound according to claim 1 which is 4-(4-biphenyl)-5-[2-(4-phenyl-1-piperazinyl)ethyl]-1,3-dioxol-2-one, and its pharmaceutically acceptable acid addition salts.

23. A compound according to claim 1 which is 4-(4-fluorophenyl)-5-[2-(4-(α,α,α-trifluoro-3-tolyl)-1-piperazinyl)ethyl]-1,3-dioxol-2-one, and its pharmaceutically acceptable acid addition salts.

24. A compound according to claim 1 which is 4-(4-fluorophenyl)-5-[2-(4-(2-pyrimidinyl)-1-piperazinyl)ethyl]-1,3-dioxol-2-one, and its pharmaceutically acceptable acid addition salts.

25. A compound according to claim 1 which is 4-(4-fluorophenyl)-5-[2-(4-(3-chlorophenyl)-1-piperazinyl)ethyl]-1,3-dioxol-2-one, and its pharmaceutically acceptable acid addition salts.

26. A compound according to claim 1 which is 4-(4-fluorophenyl)-5-[3-(4-phenyl-1-piperazinyl)-propyl]-1,3-dioxol-2-one, and its pharmaceutically acceptable acid addition salts.

27. A compound according to claim 1 which is 4-phenyl-5-[2-(4-phenyl-1-piperazinyl)ethyl]-1,3-dioxol-2-one, and its pharmaceutically acceptable acid addition salts.
28. A compound according to claim 1 which is 4-(4-chlorophenyl)-5-[2-(4-(4-chlorophenyl)-1-piperazinyl)ethyl]-
1,3-dioxol-2-one, and its pharmaceutically acceptable acid
addition salts.

29. A compound according to claim 1 which is 4-(4-chlorophenyl)-5-[2-(4-phenyl-1-piperidinyl)ethyl]-1,3-dioxol-2-one,
and its pharmaceutically acceptable acid addition salts.

30. A compound according to claim 1 which is 4-(4-chlorophenyl)-5-[2-(4-benzhydryl-1-piperazinyl)ethyl]-1,3-dioxol-2-one,
and its pharmaceutically acceptable acid addition salts.

31. A compound according to claim 1 which is 4-(4-fluorophenyl)-5-[2-(1-piperidinyl)ethyl]-1,3-dioxol-2-one, and its
pharmaceutically acceptable acid addition salts.

32. A compound according to claim 1 which is 4-(4-fluorophenyl)-5-[2-(N-methyl-N-cyclohexylamino)ethyl]-1,3-dioxol-2-one,
and its pharmaceutically acceptable acid addition salts.

33. A compound according to claim 1 which is 4-(4-chlorophenyl)-5-[2-(4-phenylmethyl-1-piperazinyl)ethyl]-1,3-dioxol-2-one,
and its pharmaceutically acceptable acid addition salts.

34. Process for the preparation of 4-aryl-5-aminoalkyl-
1,3-dioxol-2-ones and their derivatives having general formula
(I), characterized by the fact that compounds of general
formula (II)

\[
\text{Ar} - \text{CO} - \text{CH} - \text{Alk} - \text{N} \quad \text{(II)}
\]
where Ar, Alk, N
\[ \text{have the above reported meanings, are} \]

reacted with phosgene, thiophosgene, ethyl chlorocarbonate, trichloromethyl chlorocarbonate, ethyl carbonate or with 1,1'-carbonyldiimidazole.

35. Pharmaceutical compositions with hypocholesterolemic, hypolipemic, antiulcer, antihistaminic and antiserotoninic activities, characterized by the fact that they contain, as active principles, one or more compounds according to claims 1-33 in form of free bases or pharmaceutically acceptable salts.

DATED this 19th day of February, 1979.

ISTITUTO LUSO FARMACO d'ITALIA s.p.a.
By its Patent Attorneys

CLEMENT HACK & CO.,