Title: DERIVATIVES OF PHENYLALKYL AND PHENOXYALKYL ACIDS FOR THE TREATMENT OF THE HYPERGLYCAEMIA AND HYPERTRIGLYCERIDAEMIA AND TYPE 2 DIABETES AND PROCESS FOR PREPARING THEM

Abstract: Formula (I) compounds are described, (I), where the groups are as defined in the text, their use as medications, in particular as serum glucose and serum lipid lowering agents. Said medicines are useful for the treatment of diabetes, particularly type 2 diabetes and its complications, syndrome X, the various forms of insulin resistance, and hyperlipidaemias, and present reduced side effects, particularly reduced or no hepatotoxicity.
before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.
The invention described herein relates to the preparation of new derivatives of mono- and dicarboxylic phenyl or phenoxyalkyl acids useful for the treatment of the hyperglycaemia and hypertriglyceridaemia typical of type 2 diabetes.

**Background to the invention**

Diabetes is a widespread disease throughout the world and is associated with major clinical complications including macrovascular (atherosclerosis) and microvascular (retinopathy, nephropathy and neuropathy) damage. Such complications are inevitable consequences of the disease and constitute a serious threat to the subject's life and well-being. Diabetes is associated with various abnormalities such as obesity, hypertension and hyperlipidaemia. Various clinical forms of diabetic disease are known, the most common being type 2 and type 1 diabetes. Type 2 diabetes is characterised by reduced sensitivity to the action of insulin (insulin resistance) and gives rise to an increase in actual insulin levels in the body in an attempt to compensate for this deficiency and to a consequent increase in glucose levels. Numerous reports have confirmed the involvement of insulin resistance in many disease conditions in addition to type 2 diabetes itself, such as dyslipidaemia, obesity, and arterial hypertension. The combination of insulin resistance and obesity, hypertension and dyslipidaemia is known as Syndrome X.
Drugs used for many years such as the biguanides and sulphonylurea drugs are available on the market for the treatment of type 2 diabetes. In the case of the biguanides (the best known of which is metformin) the mechanism of action is still unclear; it presents side effects such as acidosis and gastrointestinal disorders and is contraindicated in renal, cardiac and pulmonary insufficiency. Sulphonylurea drugs promote the secretion of insulin by the β-cells and may present episodes of hypoglycaemia as a possible side effect.


Peroxisome proliferator activated receptors (PPARs) are receptors belonging to the superfamily of nuclear receptors whose function is to control the expression of genes involved in carbohydrate and lipid metabolism (*J. Med. Chem.*, **2000**, 43, 527-550). Various subtypes of PPARs have been identified: PPARγ, PPARα and PPARβ (also known as PPAR δ). The gamma isoform (PPARγ) is involved in the regulation of the differentiation of adipocytes and in
energy homeostasis, whereas the alpha isoform (PPARα) controls fatty acid oxidation. In structure-activity relationship studies aimed at identifying new molecules endowed with potential antidiabetic action, a correspondence has been confirmed between PPARγ activation and serum glucose lowering activity \( (J. \ Med. \ Chem., 1996, 39, 665-668; J. \ Med. \ Chem., 1998, 41, 5020-5036; 5037-5054; 5055-5069) \). The insulin-sensitising action would appear to be related, as far as this first series of compounds is concerned, to the fatty acid recruitment action regulated by activated PPARγ which is thought to lead to an improvement in the insulin resistance of the tissues, enhancing serum glucose levels and lowering insulin levels. \( (Diabetes, 1998, 47, 507-514) \).

The side effects already observed with troglitazone and feared also in the case of the other compounds of this class are: severe liver toxicity (which caused the withdrawal of troglitazone from the US market), increased cholesterol, weight gain and oedema.

In recent years molecules with a mixed profile, i.e. ligands of PPARγ and PPARα have emerged (KRP 297, \textit{Diabetes}, \textbf{1998}, \textit{47}, 1841-1847; DRF 2725, \textit{Diabetes}, \textbf{2001}, \textit{50}, suppl. 2, A108; AZ 242, \textit{Diabetes}, \textbf{2001}, \textit{50}, suppl. 2, A121-A122). These compounds are potentially capable of exerting a good measure of control of diabetic disease, while presenting a serum glucose and serum lipid lowering action with fewer side effects typical of the first series of compounds in the thiazolidinedione class, consisting exclusively of PPARγ ligands. Not
all the scientific community, however, agrees with this line of thinking. Recent studies on new-generation compounds, whether thiazolidinedione derivatives or otherwise (MC555, *J. Biol. Chem.*, 1998, Vol. 273 (49), 32679-32684; NC2100 *Diabetes*, 2000, 49, 759-767, YM440, *Metabolism*, 2000, 49, 411-417), in gene transactivation tests, *in-vitro* glucose uptake experiments with muscle tissue and *in-vivo* experiments in transgenic animals with deficient PPARγ expression, have led to the hypothesis that there is no real direct relationship between PPARγ activation and the serum glucose and serum lipid lowering activity of these compounds (*Toxicology Letters*, 2001, 120, 9-19). In particular, for YM440, a serum glucose lowering activity has been reported which is not attributable to PPARγ activation, in that adipocyte differentiation and the consequent increase in body weight due to the increased fat mass are not observed. This strengthens the hypothesis that the serum glucose lowering activity of these molecules is not necessarily related to PPARγ activation and that these compounds may be capable of modulating carbohydrate and lipid metabolism through interaction with other biochemical targets. This is confirmed by the work of investigators who have opted for the use of *in-vivo* screening in diabetic animals (db/db mice, ob/ob mice) in order to identify possible insulin-sensitising agents which are not necessarily good PPAR ligands. These experiments have led to the selection of compounds still being investigated with promising antidiabetic

In conclusion, then, since the first compounds belonging to the thiazolidinedione class (troglitazone in particular) have proved to be associated with substantial hepatotoxic and other side effects, probably related to their PPARγ activity, the scientific community would now appear to be oriented towards the search for new compounds with a different mechanism of action which induce a similar or better effect on insulin sensitivity and glucose homeostasis without toxic side effects (J. Med. Chem., 2001, 44, 2601-2611).

We should also recall that, in addition to the above-mentioned YM440, the compounds of patents WO 93/03021 (Yamanouchi), WO 01/79150 A1 (Novo Nordisk), and US 5,063,240 (Beecham Group) have structures analogous to those of the compounds according to the present invention; in these patents, however, only in-vitro assays are reported, and only in one case (Beecham Group) is the ability to lower serum glucose demonstrated in db/db and ob/ob mice.

**Summary of the invention**

It has now been found that compounds with formula (I) have been reported as being active as serum glucose and serum lipid lowering agents and are endowed with low toxicity and are therefore useful as medicines, particularly for the treatment of hyperglycaemias and hyperlipidaemias.
The preferred applications are the prophylaxis and treatment of diabetes, particularly type 2 diabetes and its complications, Syndrome X, the various forms of insulin resistance and hyperlipidaemias.

The object of the invention described herein are formula (I) compounds:

\[ \text{in which:} \]

\[ m = 0, 1; \]

\[ n = 0 - 4; \]

when \( n = 0, m = 0 \) and the two aromatic rings are bound to form a biphenyl group;

when \( n \) is from 2 to 4 the alkyl chain can be saturated or unsaturated, \( R3 \) and \( R4 \) can be the same or different and can be selected from \( H \) and alkyl \( C_1-C_5 \);

\[ Z_1 \) and \( Z_2 = 0, 1 \) and can be the same or different;

\( Y \) can be \( O, -CH= \) or \(-CH_2 \) when \( Z_1 \) and \( Z_2 \) are equal to 1, or \( OH \) when the corresponding \( Z_1 \) or \( Z_2 \) is equal to zero;

\[ X \) can be \(-OH, -O\text{-alkyl} C_1-C_3 \);
R1 and R2 can be the same or different, and can be selected from the group consisting of: -H; alkyl C₁-C₅; alkoxy possibly substituted with halogens; phenoxy possibly substituted with halogens, nitro, hydroxy, alkyls; benzyloxy possibly substituted with halogens, nitro, hydroxy, alkyls; COX;

their pharmacologically acceptable salts, racemic mixtures, the single enantiomers, geometric isomers or stereoisomers and tautomers,

with the proviso that formula I compounds are excluded in which:

\[ R3 = R4 = CH₃; \]
\[ m = 0, n = 1; \]
\[ Y = O; \]
\[ R1 = R2 = CH₃; \]
\[ X = OH, -O-alkyl C₁-C₃; \]
\[ Z₁ = Z₂ = 1; \]

because these are described in patent DE 2017331 (1970).

A further object of the present invention is the use of formula I compounds as medicines.

A further object of the present invention is the use of formula I compounds for the preparation of a medicine for the treatment of hyperglycaemias and hyperlipidaemias, particularly for the treatment of type 2 diabetes and its complications.
Further objects of the present invention are pharmaceutical compositions containing as their active ingredient a formula I compound and at least one pharmaceutically acceptable excipient and/or diluent.

These and other objects will now be described in detail also by means of examples which illustrate but do not limit the invention.

**Detailed description of the invention**

In the formula (I) compounds, a first group of preferred compounds consists of compounds in which m = 1, n is from 1 to 4, preferably 2 or 4, and the alkyl can be saturated or unsaturated, R3 and R4 are the same and preferably equal to H, Y can be O, -CH= or –CH₂ and Z₁ may or may not be the same as Z₂; if Z₁ is not the same as Z₂ the latter is preferably equal to zero and the corresponding Y is OH. Within the context of this first group, R1 can be the same as R2 and equal to hydrogen or alkyl, preferably methyl; or R1 is preferably COₓ, with X equal to -O-alkyl, preferably methyl, and R2 is H.

A second group of preferred compounds consists of compounds in which m = 0 and n = 0, or m = 0 and n is preferably from 1 to 2, and in this case the alkyl can be saturated or unsaturated, preferably saturated, R3 and R4 are the same and can be equal to H or to alkyl, preferably methyl, Y is preferably O and Z₁ may or may not be the same as Z₂; if Z₁ is not the same as Z₂, the latter is preferably equal to zero and the corresponding Y is OH. In
the context of this second group, R1 may or may not be the same as R2; if R1 is the same as R2, it is preferably alkyl, preferably methyl; if R1 is different from R2, R1 is preferably COX, with X equal to -O-alkyl, preferably methyl, and R2 is preferably H.

A third group of preferred compounds consists of compounds where m and n are equal to zero, Y is preferably -CH≡, -CH2-, and Z1 is the same as Z2. In the context of this group, R1 is preferably COX, with X equal to -O-alkyl, preferably methyl, and R2 is H.

Even more preferred are the following compounds:

1. Dimethyl 2-4-{2-[4-[3-methoxy-2-(methoxycarbonyl)-3-oxopropyl]-phenoxy]ethoxy}benzyl]malonate (ST1720);

2. Dimethyl 2-{4'-[3-methoxy-2-(methoxycarbonyl)-3-oxo-1-propenyl]-[1,1'-biphenyl]-4-yl]-1,1-ethylenedicarboxylate (ST2013);

3. Dimethyl 2-{4'-[3-methoxy-2-(methoxycarbonyl)-3-oxopropyl][1,1'-biphenyl]-4-yl}methyl]malonate (ST2032);

4. Dimethyl 2-{4-[[2(Z)]-4-[4-[3-methoxy-2-(methoxycarbonyl)-3-oxo-1-propenyl]phenoxy]-2-butenyl]oxy]phenyl]-1,1-ethylenedicarboxylate (ST2012);


6. Dimethyl 2-{4-[4-[3-methoxy-2-(methoxycarbonyl)-3-oxopropyl]-phenoxy]butoxy]benzyl]malonate (ST2144);
7. Methyl 2-{3-[2-(3-hydroxyphenoxy)ethoxy]phenoxy}-2-methylpropanoate (ST1877);

8. Methyl 2-(3-{2-[3-(2-methoxy-1,1-dimethyl-2-oxoethoxy)phenoxy]ethoxy}phenoxy)-2-methylpropanoate (ST1878);

9. Dimethyl 2-{4-[1-(4-hydroxyphenyl)-1-methylethyl]-phenoxy}-malonate (ST2020)

10. Dimethyl 2-[4-{1-[4-[2-methoxy-1-(methoxycarbonyl)-2-oxoethoxy]phenyl]-1-methylethyl]phenoxy]malonate (ST2048);

11. Methyl 2-[[4'-{(2-methoxy-1,1-dimethyl-2-oxoethoxy)[1,1'-biphenyl]-4-yl]oxy}-2-methylpropanoate (ST2291).

The formula I compounds can be prepared using the reactions described in methods A-E.

Possible COX hydrolysis reactions, where X coincides with what is specified in the description of the general formula, for preparing the corresponding free acids, can be conducted according to the common laboratory procedures for this type of reaction.

The meaning of the various symbols, unless otherwise specified, is intended to coincide with the indications provided in the general formula.
METHOD A

The preparation of general formula I compounds was done by reacting a general formula II compound with a general formula III compound with a base, preferably inorganic, and preferably sodium hydride, to form the corresponding intermediate product IV, which was then reacted with a formula II compound in the classic Mitsunobu reaction conditions, as described in *Synthesis* 1981, 1-28, using anhydrous and aprotic solvents such as benzene, toluene, ether or preferably tetrahydrofuran, for time periods ranging from 30 minutes to 72
hours, preferably 18 hours, at temperatures ranging from 10 to 40°C, preferably 25°C.

Product V obtained could then be subjected to catalytic hydrogenation in the presence of H₂, at a pressure ranging from atmospheric pressure to 60 psi, preferably 50 psi, and with catalysts such as metals supported on C, such as Pd/C, in percentages ranging from 1 to 20%, preferably 10%. The amount of catalyst used was within the 1-100% p/p range, usually 10% p/p, in protic or non-protic solvents, such as MeOH, dioxane and THF, preferably MeOH, for reaction times ranging from 18 hours to 3 days, preferably 24 hours.

**METHOD B**

The general formula I compounds were synthesised starting from general formula VI compounds dissolved in aprotic solvents.
such as toluene, and reacted with a general formula VII compound, at reflux temperature with Dean-Stark, for time periods ranging from 5 to 24 hours, preferably 7 hours, in the presence of a catalysts such as a salt of an organic base with an organic acid, such as piperidine acetate, normally used in Knoevenagel reactions. Alternatively, the reaction was conducted in dipolar aprotic solvents such as DMF (Synthetic Communication, 2000, 30 (4), 713-726) possibly in the presence of an organic base such as piperidine, at temperatures ranging from 20 to 100°C, preferably 80°C for time periods ranging from 1 hour to 3 days, preferably 2 days. Compound VIII was then subjected to catalytic hydrogenation in the conditions and with the times described in method A (step 3) to yield the general formula I product.

METHOD C
Step 1
Base

Step 2
Reduction with metal hydride

Step 2'
Catalytic hydrogenation

IA (Y = -CH₂)
(n = 2 - 4 unsaturated)

IB (Y = -CH₃)
(n = 1 - 4 saturated)

X other than OH
n = 1-4
L = leaving group, preferably halogen, preferably Br
R_i = H
Z₁ = Z₂ = 1
The preparation of general formula **I A** and **I B** compounds was done by reacting two equivalents of a general formula **II** compound with one equivalent of a formula **IX** compound with a base, preferably inorganic, and preferably sodium hydride, to form the corresponding intermediate product **X**.

Intermediate product **X** was then reacted with a general formula **VII** compound, in the conditions described in general method B (step 1), to form the intermediate general formula **XI** product, which in turn was reacted with a general formula **VII** compound, in the conditions described in method B to form the intermediate product **XII**. Intermediate product **XII** was then subjected to reduction with metal hydrides, for example, sodium borohydride in a polar protic solvent, preferably MeOH, for a time period ranging from 2 to 24 hours, preferably 18 hours, to give compound **I A**. Product **I B**, on the other hand, was obtained by reduction with metal supported in a hydrogen atmosphere according to the specifications of general method A (step 3).

If the [CR₃R₄]ₙ group does not present unsaturations, **IA** and **IB** are the same; if the [CR₃R₄]ₙ group presents unsaturations **IA** and **IB** are not the same.
METHOD D

XII

1) Base
2) Chromatography

I

X other than OH
Y = O
L = leaving group
Z₁ = Z₂ = 1

XIV
The preparation of general formula I (and general formula XIV) compounds was done, for example, according to the description in *Tetrahedron*, 1990, 46 (3), 967-978 starting from product XII which was reacted with a general formula XIII compound containing a leaving group (for example, chlorine, bromine, iodine, mesyl, tosyl), for example, methyl-2-bromoisobutyrate in the presence, alternatively, of base alone, preferably sodium hydride, in polar aprotic solvents, preferably DMF at temperatures ranging from 25°C to the reflux temperature of the solvent selected or of a base, such as potassium carbonate, and a catalyst by phase transfer, such as, for example, tetrabutylammonium bromide (TBAB) in aprotic solvents such as toluene, at temperatures ranging from 25°C to the reflux temperature of the solvent selected, preferably the reflux temperature, for time periods ranging from 1 to 5 days, preferably 3 days. The two compounds obtained were separated using a chromatographic method, preferably chromatography on a silica gel column, using eluotropic mixtures of varying polarity from pure hexane to pure ethyl acetate, preferably mixtures of hexane/ethyl acetate, in varying ratios to one another, preferably 8/2.
METHOD E

The preparation of the general formula I compound was done by reacting a general formula XV compound with a general formula XVI compound in the presence of dimeric rhodium (II) acetate as the catalyst to form general formula compound XVII. Compound XVII was then reacted again, with a general formula XVI compound, in the same conditions as described above to yield general formula compound I, in a polar solvent such as acetonitrile, or preferably toluene, for a time period ranging from 18 to 48 hours, preferably 24 hours, at a temperature ranging from 10 to 130°C, preferably reflux temperature.
EXAMPLE 1

Preparation of dimethyl 2-[4-(2-[4-[3-methoxy-2-
(methoxycarbonyl)-3-oxopropyl]fenoxyl)ethoxy]benzyl]malonate
(ST1720)

Preparation of the intermediate product dimethyl 4-[(2-
hydroxyethyl)-oxy]benzylidenemalonate

Method A (step 1)

Sodium hydride (244 mg, 10.16 mmol) was added to dimethyl
4-hydroxybenzylidenemalonate (2 g, 8.47 mmol) in 40 mL of
anhydrous DMF. The suspension was left under magnetic stirring
for 30 minutes until solution was complete, and then 2-
bromoethanol (0.780 mL, 11.01 mmol) was added. The solution was
left overnight under magnetic stirring at room temperature. The
reaction was processed, diluting with AcOEt and washing with water. The organic phase was dried on anhydrous Na₂SO₄, and, after filtration, the solvent was evaporated in vacuo. The residue was purified by chromatography on silica gel using a hexane/AcOEt gradient in a ratio of 8:2 to 6:4 as the eluent. 1.760 g of product were obtained (yield: 74%); ¹HNMR (CDCl₃, 300 MHz) δ 7.80 (s, 1H), 7.40 (d, 2H), 6.90 (d, 2H), 4.20 (brd, 2H), 4.00 (brd, 2H), 3.80 (d, 6H).

Preparation of the intermediate product 1,2-bis[4-(methylenedicarboxylate dimethyl]phenoxy]ethane

Method A (step2)

To dimethyl 4-[(2-hydroxyethyl)-oxy]benzylidenemalonate (1.760 g, 6.28 mmol) (prepared as described above) dissolved in 50 mL of THF were added 4-hydroxybenzylidenedimethylmalonate (1.482 g, 6.28 mmol), PPh₃ (2.138 g, 8.16 mmol), and DEAD (1.28 mL, 8.16 mmol dissolved in 10 mL of THF). The solution thus obtained was left
under magnetic stirring for three days at room temperature. After
this time, the formation of an insoluble product was observed, which
by filtration yielded 1.3 g of product which was used as is for the
next reaction (yield: 41.5%); $^1$HNMR (CDCl$_3$, 300 MHz) $\delta$ 7.80 (s, 2H),
7.40 (d, 4H), 6.90 (d, 4H), 4.40 (s, 4H), 3.80 (d, 12H).

Preparation of dimethyl 2-[4-(2-{4-[(3-methoxy-2-
(methoxycarbonyl)-3-oxopropyl]phenoxy}ethoxy)benzyl]malonate
(ST1720)

10 Method A (step 3)

1.3 g of 1,2-bis[4-(methylene dicarboxylate dimethyl]phenoxy]-
ethane were solubilised in 70 mL of MeOH and 240 mg of 10% Pd/C
were added; the suspension was subjected to catalytic
hydrogenation at room temperature and at 60 psi hydrogen
pressure. The mixture was filtered in celite and the filtrate was
washed thoroughly with CHCl$_3$. 1,280 g of product were obtained
and purified by chromatography on silica gel using a hexane/AcOEt
gradient from 80:20 to 65:35 as the eluent. 460 mg of product were
obtained (yield: 35%); Mp (melting point): 90°C; TLC: silica gel;
eluent; hexane/AcOEt 1/1 Fr (frontal ratio): 0.55; $^1$HNMR (CDCl$_3$,
300 MHz) δ 7.10 (d, 4H), 6.80 (d, 4H), 4.30 (s, 4H), 3.70 (s, 12H), 3.60 (t, 2H), 3.25 (d, 4H); HPLC: Column: Inertisil ODS-3 (5µm), 4.6 x 250 mm, T: 30°C: mobile phase: CH₂OH/KH₂PO₄ 50 mM (65/35 v/v); flow rate: 1 mL/min; UV 205 nm detector, retention time: 22.69 min; E.A.: conforms for C₂₆H₃₀O₁₀.

**EXAMPLE 2**

Preparation of dimethyl 2-{4′-[3-methoxy-2-(methoxycarbonyl)-3-oxo-1-propenyl][1,1′-biphenyl]-4-yl}-1,1-ethylendicarboxylate (ST2013)

Method B (step 1)

To a solution of 4,4′-bis benzaldehyde (2 g, 9.51 mmol) in 30 mL of anhydrous DMF were added dimethyl malonate (3.76 g, 28.53 mmol) and piperidine (0.121 g, 1.425 mmol). The solution was heated to 80°C and left under magnetic stirring for 48 hours, and then poured into water and extracted three times with CHCl₃. The pooled organic phases were dried on anhydrous sodium sulphate
and the solvent evaporated in vacuo. The residue obtained was purified by chromatography on silica gel, eluting with hexane/AcOEt 8/2. 550 mg of product were obtained (yield: 13%); Mp: 163°C; TLC: silica gel; eluent: hexane/AcOEt 6/4, Fr: 0.43; $^1$HNMR (CDCl$_3$, 300 MHz) $\delta$ 7.80 (s, 2H), 7.60 (d, 4H), 7.50 (d, 4H), 3.90 (d, 12H); HPLC: Column: Symmetry-C$_{18}$ (3.5 μm); mobile phase: CH$_3$CN/H$_2$O 50/50 v/v, pH: as is; flow rate: 0.9 mL/min; temperature: RT; UV 205 nm detectors, retention time: 10.7 min; E.A.: conforms for C$_{24}$H$_{22}$O$_8$.

**EXAMPLE 3**

Preparation of dimethyl 2-[[4'-(3-methoxy-2-(methoxy-carbonyl)-3-oxopropyl][1,1'-biphenyl]-4-yl]methyl]malonate (ST 2032)

![Chemical Structure]

**Method B (step 2)**

To a solution of ST 2013 (550 mg, 1.24 mmol) (prepared as described in example 2) in 50 mL of THF were added 55 mg of 10% Pd/C. The suspension was subjected overnight to catalytic hydrogenation at room temperature and 60 psi hydrogen pressure.
After filtration of the mixture on celite, the solvent was evaporated in vacuo and the residue purified by chromatography on silica gel, eluting with hexane/AcOEt 8:2. 160 mg of product were obtained (yield: 30%); Mp: 128.5°C; TLC: silica gel; eluent: hexane/AcOEt 6:4, Fr: 0.58; $^1$HNMR (CDCl$_3$, 300 MHz) δ 7.50 (d, 4H), 7.25 (d, 4H), 3.75 (s, 12H), 3.25 (d, 4H); HPLC Column: Inertisil ODS 3 (5 μM); mobile phase: CH$_3$CN/H$_2$O 70/30 v/v; temperature: RT; pH: as is; flow rate: 0.75 mL/min; UV 205 nm detectors, retention time 10.82 min; E.A.: conforms for C$_{24}$H$_{26}$O$_8$.

**EXAMPLE 4**

Preparation of dimethyl 2-[4-][((2Z)-4-[4-[3-methoxy-2-(methoxy-carbonyl)-3-oxo-1-propenyl]phenoxy]-2-butenyl]oxy]-phenyl]-1,1-ethylenedicarboxylate(ST2012)

Preparation of intermediate product 1,4 dibromo-2-cis-butene
The preparation was done according to the procedure described in *Synth. Commun.* **1991**, 721-726.

**Preparation of the intermediate product 1,4-bis (4-formylphenoxy)-2-cis-butene**

![Chemical structure]

**Method C (step 1)**

To a solution of 4-hydroxybenzaldehyde (1 g, 8.18 mmol) in 15 mL of anhydrous DMF was added NaH (258 mg, 10.87 mmol). The suspension was left under magnetic stirring for 10 minutes at room temperature. After solubilisation, 1,4-dibromo-2-cis-butene (874 mg, 4.09 mmol) was added. The reaction was left overnight under magnetic stirring at room temperature, the solvent was then evaporated in vacuo and the semisolid obtained was treated several times with hexane until a dark solid was obtained. The residue was purified by chromatography on silica gel, eluting with hexane/AcOEt 8:2. 775 mg of product were obtained (yield: 32%); $^1$HNMR (CDCl$_3$, 300 MHz) $\delta$ 9.90 (s, 2H), 7.90 (d, 4H), 7.00 (d, 4H), 6.00 (m, 2H), 4.80 (s, 4H).

**Preparation of the intermediate product dimethyl 2-[(2Z)-4-(4-formylphenoxy)-2-butenyl]oxy]benzylidene]malonate**
The title product was prepared according to the procedure described in Method B step 1, adding dimethylmalonate (0.338 g, 2.56 mmol), piperidine (0.032 g, 0.38 mmol) and acetic acid (0.023 g, 0.38 mmol) to a solution of 1,4-bis (4-formylphenoxy)-2-cis-butene (380 mg, 1.28 mmol) in 30 mL of toluene. The solution was refluxed for 5 hours at 140°C, and then the solvent was evaporated in vacuo and the crude product obtained was purified by chromatography on silica gel, eluting with hexane/ethyl acetate 8:2. 320 mg of product were obtained (yield: 60%); ¹H NMR (CDCl₃, 300 MHz) δ 9.90 (s, 1H), 7.90 (d, 2H), 7.70 (s, 1H), 7.40 (d, 2H), 7.10 (d, 2H), 6.90 (d, 2H), 6.00 (m, 2H), 4.70 (m, 4H), 3.90 (d, 6H).

Preparation of dimethyl 2-4-{[[2Z]-4-{4-[3-methoxy-2-(methoxy-carbonyl)-3-oxo-1-propenyl]phenoxy}-2-butenyl]oxy}fenyl]-1,1-ethylenedicarboxylate (ST2012)

The title product was prepared according to the procedure described in Method B step 1, adding dimethylmalonate (0.080 g, 0.610 mmol), piperidine (0.013 g, 0.152 mmol) and acetic acid
(0.009 g, 0.152 mmol) to a solution of dimethyl 2-[(2Z)-4-[(4-formylphenoxy)-2-buteryl]oxy]benzylidene) malonate (320 mg, 0.610 mmol) in 35 mL of toluene. The mixture thus obtained was refluxed for 5 hours at 140°C, and then the solvent was evaporated in vacuo and the crude product obtained was purified by chromatography on silica gel, eluting with CHCl₃. 250 mg of product were obtained (yield: 78%); Mp: 80-82°C; TLC: silica gel; eluent: CHCl₃, Fr: 0,41; ¹H NMR (CDCl₃, 300 MHz) δ 7.70 (s, 2H), 7.40 (d, 4H), 6.90 (d, 4H), 5.95 (t, 2H), 4.70 (d, 4H), 3.85 (d, 12H); HPLC Column: Symmetry – C₁₈ (3.5 μm), mobile phase: CH₃CN/H₂O 50/50 v/v; pH: as is; temperature: RT, flow rate: 0.9 mL/min, retention time: 18.51 min; E.A.: conforms for C₂₈H₂₈O₁₀.

**EXAMPLE 5**


![Chemical Structure](image)

**Method C (step 2)**

To a solution of ST 2012 (2.4 g, 4.57 mmol) (prepared as described in example 4) in 50 mL of anhydrous methanol was added
NaBH₄ (0.451 g, 11.92 mmol). The suspension was left under magnetic stirring for 40 minutes at room temperature. The mixture was then poured into ethyl acetate and the organic phase washed with water and then dried on anhydrous sodium sulphate. The solvent was evaporated in vacuo and the residue purified by chromatography on silica gel (previously treated with triethylamine), eluting with hexane/AcOEt 8:2. 0.460 g of product were obtained (yield: 19%); TLC: silica gel; eluent: hexane/AcOEt 6:4, Fr: 0.49; ¹HNMR (CDCl₃ 300 MHz) δ 7.01 (d, 4H), 6.80 (d, 4H), 5.95 (t, 2H), 4.64 (d, 4H), 3.70 (s, 12H), 3.62 (t, 2H), 3.15 (d, 4H); HPLC: Column: Inertsil – ODS 3 (5 µM), 4.6 x 250 mm; mobile phase: CH₂CN/H₂O 70/30 v/v, temperature: RT; pH: as is; flow rate: 0.9 mL/min; UV 205 nm detectors, retention time 11.61 min; E.A.: conforms for C₂₈H₃₂O₁₀.

**EXAMPLE 6**

Method C (step 2')

To a solution of ST2012 (1.85 g, 3.52 mmol) (prepared as described in example 4) in 150 mL of THF were added 230 mg of 10% Pd/C. The suspension was subjected overnight to catalytic hydrogenation at room temperature and at 60 psi hydrogen pressure. After filtering the mixture on celite, the solvent was evaporated in vacuo and the residue purified by chromatography on silica gel, eluting with hexane/AcOEt 8:2. 940 mg of product were obtained (yield: 49); Mp: 83°C; TLC: silica gel; eluent: hexane/AcOEt 6:4, Fr: 0.53; 1HNMR (CDCl₃, 300 MHz) δ 7.05 (d, 4H), 6.80 (d, 4H), 4.00 (t, 4H), 3.70 (s, 12H), 3.60 (t, 2H), 3.15 (d, 4H); HPLC Column: Inertisil – ODS 3 (5 μM), 4.6 x 250 mm; mobile phase: CH₃CN/H₂O 70/30 v/v, temperature: RT; pH: as is; flow rate: 0.75 mL/min, UV 205 nm detectors, retention time 13.30 min; E.A. conforms for C₂₈H₃₄O₁₀.

EXAMPLE 7 AND EXAMPLE 8

Preparation of methyl 2-{3-{2-{3-hydroxyphenoxy}ethoxy}phenoxy}-2-methylpropanoate (ST1877) and methyl 2-{3-{2-{3-{2-...
methoxy-1,1-dimethyl-2-oxoethoxy)|phenoxy|ethoxy|phenoxy)-2-methylpropanoate (ST1878)

Method D

A mixture of 3,3'-ethylenedioxydiphenol (2.000 g, 8.1 mmol), K$_2$CO$_3$ (4.500 g, 32.4 mmol), TBAB (0.131 g, 0.4 mmol) and methyl-2-bromoisobutyrate (11.611 g, 64 mmol) in 100 mL of toluene was heated at 130°C for three days, and then cooled and filtered. The solid obtained was washed with toluene, the pooled organic phases were evaporated in vacuo and the oily residue was purified by chromatography on silica gel using hexane/AcOEt 8:2 as the eluent. Two products were obtained: the monoderivative ST1877 (0.700 g; yield: 25%) and the biderivative ST1878 (1.100 g; yield: 30.4%).

Analytical data for ST 1877 (monoderivative, Example 7)

Mp: 77-79°C; $^1$HNMR (CDCl$_3$, 300 MHz) δ 7.13 (t, 2H), 6.62 – 6.40 (m, 6H), 4.25 (s, 4H), 3.78 (s, 3H), 1.60 (s, 7H); HPLC: Column: Inertil ODS – 3 (5 µm), 4.6 x 250 mm, T: 30°C, mobile phase: CH$_3$CN/H$_2$O (60/40 v/v), pH: 3.2, flow rate: 1.0 mL/min, UV 205 nm detector, retention time: 8.76 min; E.A. conforms for C$_{19}$H$_{22}$O$_6$.

Analytical data for ST 1878 (biderivative, Example 8)
Mp: 60-62°C; 1H NMR (CDCl₃, 300 MHz) δ 7.13 (t, 2H), 6.60 (d, 2H), 6.41 (m, 4H), 4.26 (s, 4H), 3.78 (s, 6H), 1.60 (s, 12H); HPLC: Column: Inertisil ODS – 3 (5 µm), 4.6 x 250 mm, T: 30°C; mobile phase: CH₃CN/H₂O (60/40 v/v), pH: 3.2, flow rate: 1.0 mL/min; UV 205 nm detector, retention time: 23.92 min; E.A.: conforms for C₂₄H₃₉O₈.

**EXAMPLE 9**

Preparation of dimethyl 2-[4-[1-(4-hydroxyphenyl)-1-methylethyl]fenoxymalonate (ST2020)

![Chemical Structure](image)

**Method E (step 1)**

To a suspension of rhodium diacetate (0.220 g, 0.5 mmol) and bisphenol A (3.400 g, 15 mmol) in 100 mL of anhydrous toluene was added dropwise, under nitrogen flow, a solution of diazomalonate (3.000 g, 18 mmol, prepared as described in *Org. Synth.* 1973, V, 179) in 100 mL of anhydrous toluene, taking care to keep the temperature during the addition between 15 and 20°C. The reaction mixture was then refluxed at 120-130°C for 24 hours under nitrogen. After this time period, the mixture was filtered and the toluene evaporated in vacuo. The residue obtained was purified by means of chromatography on silica gel using hexane/AcOEt 8:2 as
the eluent. 1.700 g of oil product were obtained (yield: 32%); TLC: silica gel; eluent hexane/AcOEt 7:3, Fr: 0.23; 1H NMR (CDCl₃, 300 MHz) δ 7.16 (m, 4H), 6.90 (d, 2H), 6.87 (d, 2H), 5.12 (s, 1H), 3.90 (s, 6H), 1.62 (s, 6H); HPLC: Column: Inertisil ODS - 3 (5 μm) 4.6 x 250 mm T: 30°C; mobile phase: CH₃CN/H₂O 70/30 (v/v), pH: as is, flow rate: 0.75 mL/min; UV 205 nm detector, retention time 7.0 min; E.A. conforms for C₂₀H₂₂O₆.

**EXAMPLE 10**

Preparation of dimethyl 2-[4-(1-{4-[2-methoxy-1-(methoxycarbonyl)-2-oxoethoxy]phenyl}-1-methylethyl)-phenoxy]malonate (ST2048)

Method E (step 2)

The product was prepared starting from rhodium diacetate (0.885 g, 0.2 mmol) and ST 2020 (1.230 g, 3.4 mmol) (prepared as described in example 9) in 36 mL of anhydrous toluene, adding diazomalonate (1.882 g 11.9 mmol of preparation as described in *Org. Synth.* **1973**, V, 179) dropwise in 18 mL of anhydrous toluene, taking care to keep the temperature between 15 and 20°C. The reaction mixture was refluxed at 120-130°C for 24 hours under nitrogen. The mixture was filtered and the toluene evaporated in
vacuo. The residue obtained was purified by chromatography on a silica gel column using hexane/AcOEt 8:2 as the eluent. 0.430 g of oily product were obtained (yield: 26%); TLC: silica gel; eluent: hexane/AcOEt 6:4, Fr: 0.46; 1H NMR (CDCl₃, 300 MHz) δ 7.20 (d, 4H), 6.90 (d, 4H), 5.22 (s, 2H), 3.90 (s, 12H), 1.61 (s, 6H); HPLC: Column: Inertisil ODS - 3 (5 µm) 4.6 x 250 mm, T: 30°C; mobile phase: CH₃CN/H₂O 70/30 (v/v), pH: as is, flow rate: 0.75 mL/min, UV 205 nm detector, retention time 9.68 min; KF: 0.7% H₂O; E.A. conforms for C₂₅H₂₈O₁₀.

EXAMPLE 11

Preparation of methyl 2-[[4'-[(2-methoxy-1,1-dimethyl-2-oxoethoxy)[1,1'-biphenyl]-4-yl]oxy]-2-methylpropanoate (ST2291)

Method D

The title product was prepared starting from a solution of 4,4’ bisphenol (0.5 g, 2.68 mmol), in 25 mL of anhydrous DMF, to which were added sodium hydride (0.321 g, 10.72 mmol), and after 10 minutes at room temperature methyl-2-bromoisobutyrate (1.06 g, 5.89 mmol). The mixture was left under magnetic stirring for 3 days at room temperature, and then poured into ethyl acetate. The
organic phase was washed with a 5% NaOH solution and then with water, and then dried on anhydrous sodium sulphate, filtered and evaporated in vacuo. The residue was purified by chromatography on a silica gel column, eluting with hexane/AcOEt 8/2. 0.175 of the product were obtained (yield: 18%) Mp: 58-59°C; TLC: silica gel; eluent: hexane/AcOEt 7:3, Fr: 0.6; 'H NMR (CDCl₃, 300 MHz) δ 7.40 (d, 4H), 6.85 (d, 4H), 3.80 (s, 6H), 1.65 (s, 12H); HPLC: Column: Symmetry C₁₈ 4.6 x 150 mm (5 μm), T: RT; mobile phase: CH₃CN/H₂O 60/40 (v/v), pH: as is; flow rate: 0.8 mL/min; UV 205 nm detector, retention time 16.48 min; KF: 0.75% H₂O; E.A. conforms for C₂₂H₂₆O₆.

The compounds according to the present invention are useful as medicines, and particularly for the preparation of medicines with serum glucose and serum lipid lowering activity. Preferred applications are the prophylaxis and treatment of diabetes, particularly type 2 diabetes and its complications, X syndrome, the various forms of insulin resistance and hyperlipidaemias.

In a thoroughly advantageous manner, the compounds according to the present invention are endowed with good pharmacological activity and present reduced liver toxicity.

**EXAMPLE 12**

**Antidiabetic and serum lipid lowering activity in db/db mice**

Mutations in laboratory animals have made it possible to develop models that present non-insulin-dependent diabetes
associated with obesity, hyperlipidaemia and insulin resistance and that make it possible to test the efficacy of new antidiabetic compounds (Reed and Scribner, Diabetes, obesity and metabolism 1: 75 - 86, 1999).

A genetically diabetic mouse model much used in the laboratory is the C57BL/KsJ db/db mouse. The genetic basis of this model is a defect in the leptin receptor gene that determines leptin resistance and leads to hyperphagia, obesity, hyperinsulinaemia and insulin resistance, with subsequent symptoms of insufficient insular secretion and hyperglycaemia (Kodama et al., Diabetologia 37: 739 - 744, 1994; Chen et al., Cell 84: 491 - 495, 1996).

Since hyperglycaemia is accompanied by obesity and insulin resistance, the db/db mouse model presents characteristics that cause it to resemble type 2 diabetes in man and is useful for assaying insulin-sensitising compounds.


Of the three thiazolidinediones launched on the market, troglitazone was withdrawn owing to serious liver toxicity, while the other two compounds, rosiglitazone and pioglitazone, are effective in reducing diabetic hyperglycaemia despite presenting unwanted side

The C57BL/KsJ db/db mice used in the experiments were supplied by Jackson Lab (via Ch. River). After 10 days’ acclimatisation in standard conditions (22 ± 2°C; 55 ± 15% humidity; 15 - 20 air changes/hour; 12 hour light-dark cycle with light from 7.00 a.m. to 7 p.m.) on a standard 4 RF21 diet (Mucedola), blood samples were taken in post-absorption conditions (fasting from 8.30 a.m. to 4.30 p.m.) from the caudal vein with the aid of a Jelco 22G catheter (Johnson and Johnson). Levels of glucose, triglycerides and cholesterol were measured in plasma for a well matched distribution of the mice in the treatment groups.

The body weight of the animals was checked at the start of treatment and the monitoring of water and animal feed consumption was arranged.

The mice were treated twice daily (8.30 a.m. and 6.30 p.m.), orally, for 11 days.

The compounds were administered at the dose of 35 mg/kg [ST2145 (example 5)], in 10 ml/kg of vehicle (1% CMC containing Tween 80 0.5% in deionised H₂O). The reference compound, rosiglitazone, was administered at the dose of 5 mg/kg (Lohray et al. J. Med Chem 41, 1619 - 1630, 1998).
The animals were sacrificed (by decapitation) in post-absorption conditions (fasting from 9.30 a.m. to 4.30 p.m.), 7 hours after the last treatment. Serum levels of a number of important lipid and carbohydrate metabolism parameters were determined.

The compounds according to the invention are capable of lowering serum glucose levels, of reducing weight gain and of reducing the production of transaminase (GPT), which is an indicator of less liver damage. By way of an example, we give the serum glucose lowering activity and the changes in weight and transaminase levels for ST2145 compared to rosiglitazone.

The results obtained are presented in Table 1.

**TABLE 1**

<table>
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<th>Serum glucose and serum lipid lowering activity, and variations in serum GPT levels in db/db mice, and weight gain, after 11 days’ treatment</th>
</tr>
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<tr>
<td><strong>Compound</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Rosiglitazone</td>
</tr>
<tr>
<td>ST2145</td>
</tr>
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</table>

Student’s 't'-test: ▲ indicates $P < 0.001$; △ indicates $P < 0.01$; ■ indicates $P < 0.02$ vs. Controls.

Also objects of the present invention are pharmaceutical compositions containing as their active ingredient at least one
formula (I) compound, alone or in combination with one or more
formula (I) compounds, or, said formula (I) compound or compounds
in combination with active ingredients useful for the treatment of the
diseases indicated in the present invention, for example, other
products with serum glucose and serum lipid lowering activity; also
in separate dosage forms or in forms suitable for combined
therapies. The active ingredient according to the invention will be in
a mixture with suitable vehicles and/or excipients commonly used
in pharmacy, such as, for example, those described in “Remington’s
Pharmaceutical Sciences Handbook”, latest edition. The
compositions according to the present invention will contain a
therapeutically active amount of the active ingredient. The doses will
be determined by the expert in the sector, e.g. the clinician or
primary care physician, according to the type of disease to be treated
and the patient’s condition, or concomitantly with the
administration of other active ingredients. By way of an example,
doses ranging from 0.1 to 200 mg/day may be indicated.

Examples of pharmaceutical compositions are those that
permit oral or intravenous, intramuscular, subcutaneous, or
transdermal parenteral administration. Pharmaceutical
compositions suitable for the purpose are tablets, rigid or soft
capsules, powders, solutions, suspensions, syrups, and solid forms
for extempore liquid preparations. Compositions for parenteral
administration are, for example, all the intramuscular, intravenous,
subcutaneous injectable forms, in the form of solutions, suspensions, or emulsions. We should also mention the liposomal formulations. Also included are the forms with controlled release of the active ingredient, whether as oral administration forms, tablets coated with appropriate layers, microencapsulated powders, complexes with cyclodextrins, depot forms, for example, subcutaneous ones, such as depot injections or implants.
1. Formula (I) compound:

\[ \text{in which:} \]

\[ m = 0, 1; \]
\[ n = 0 - 4; \]

when \( n = 0 \), \( m = 0 \) and the two aromatic rings are bound to form a biphenyl group;

when \( n \) is from 2 to 4 the alkyl chain can be saturated or unsaturated, \( R_3 \) and \( R_4 \) can be the same or different and can be selected from \( H \) and alkyl \( C_1-C_5 \);

\( Z_1 \) and \( Z_2 = 0, 1 \) and can be the same or different;

\( Y \) can be \( O, -CH= \) or \( -CH_2 \) when \( Z_1 \) and \( Z_2 \) are equal to 1, or \( OH \) when the corresponding \( Z_1 \) or \( Z_2 \) is equal to zero;

\( X \) can be \( -OH, -O-alkyl C_1-C_3 \);

\( R_1 \) and \( R_2 \) can be the same or different, and can be selected from the group consisting of: \( -H; \) alkyl \( C_1-C_5 \); alkoxy possibly substituted with halogens; phenoxy possibly substituted with halogens, nitro, hydroxy, alkyls; benzyloxy possibly substituted with halogens, nitro, hydroxy, alkyls; COX;
their pharmaceutically acceptable salts, racemate mixtures, the
single enantioners, geometric isomers or stereoisomers and
tautomers,

with the proviso that formula I compounds are excluded in which:

\[
\begin{align*}
R3 &= R4 = \text{CH}_3; \\
& m = 0, \ n = 1; \\
Y &= \text{O}; \\
R1 &= R2 = \text{CH}_3; \\
X &= \text{OH}, \ -\text{O-alkyl C}_1\text{-C}_3; \\
Z_1 &= Z_2 = 1.
\end{align*}
\]

2. Compound according to claim 1 in which:

\[
m = 1, \ n \text{ is from 1 to 4, preferably 2 or 4, and the alkyl can be}
\text{saturated or unsaturated, R3 and R4 are the same and}
\text{preferably equal to H, Y can be O, -CH= or -CH}_2 \text{ and Z}_1 \text{ may or}
\text{may not be the same as Z}_2; \text{ if Z}_1 \text{ is not the same as Z}_2, \text{ the latter is}
\text{preferably equal to zero and the corresponding Y is OH;}
\text{R1 can be the same as R2 and equal to hydrogen or alkyl,}
\text{preferably methyl; or R1 is preferably COX, with X equal to -O-}
\text{alkyl, preferably methyl, and R2 is H.}
\]

3. Compound according to claim 1 in which:

\[
m = 0 \text{ and n = 0, or } m = 0 \text{ and n is preferably from 1 to 2, and in}
\text{this case the alkyl can be saturated or unsaturated, preferably}
\text{saturated, R3 and R4 are the same and can be equal to H or to}
\text{alkyl, preferably methyl, Y is preferably O and Z}_1 \text{ may or may not}
\]
be the same as \( Z_2 \); if \( Z_1 \) is not the same as \( Z_2 \), the latter is preferably equal to zero and the corresponding \( Y \) is \( \text{OH} \);

\( R_1 \) may or may not be the same as \( R_2 \); if \( R_1 \) is the same as \( R_2 \) it is preferably alkyl, preferably methyl; if \( R_1 \) is different from \( R_2 \), \( R_1 \) is preferably \( \text{COX} \), with \( X \) equal to -O-alkyl, preferably methyl, and \( R_2 \) is preferably \( \text{H} \).

4. Compound according to claim 1 in which:

\( m \) and \( n \) are equal to zero, \( Y \) is preferably \(-\text{CH}=, -\text{CH}_2-\) and \( Z_1 \) is the same as \( Z_2 \); \( R_1 \) is preferably \( \text{COX} \), with \( X \) equal to -O-alkyl, preferably methyl, and \( R_2 \) is \( \text{H} \).

5. Formula (I) compound selected from the group consisting of:

- **Dimethyl 2-{4-[(2Z)-4-{3-methoxy-2-(methoxycarbonyl)-3-oxopropyl}phenoxy]-ethoxy}benzyl]malonate (ST1720);**
- **Dimethyl 2-{4'-[3-methoxy-2-(methoxycarbonyl)-3-oxo-1-propenyl]-[1,1'-biphenyl]-4-yl]-1,1-ethylenedicarboxylate (ST2013);**
- **Dimethyl 2-{[4'-[3-methoxy-2-(methoxycarbonyl)-3-oxopropyl][1,1'-biphenyl]-4-yl]methyl}malonate (ST2032);**
- **Dimethyl 2-{[4-{[2(Z)-4-{3-methoxy-2-(methoxycarbonyl)-3-oxo-1-propenyl}phenoxy]-2-butenyl}oxy]phenyl]-1,1-ethylenedicarboxylate (ST2012);**
- **Dimethyl 2-{[4-{[2(Z)-4-{3-methoxy-2-(methoxycarbonyl)-3-oxopropyl}phenoxy]-2-butenyl}oxy]benzyl]malonate (ST2145);**
Dimethyl 2-[4-{(4-[3-methoxy-2-(methoxycarbonyl)-3-oxopropyl]-phenoxy)butoxy]benzyl}malonate (ST2144);

Methyl 2-{3-[2-(3-hydroxyphenoxy)ethoxy]phenoxy}-2-methylpropanoate (ST1877);

Methyl 2-(3-{2-[3-(2-methoxy-1,1-dimethyl-2-oxoethoxy)phenoxy]-ethoxy}phenoxy)-2-methylpropanoate (ST1878);

Dimethyl 2-{4-[1-(4-hydroxyphenyl)-1-methylethyl]-phenoxy}-malonate (ST2020)

Dimethyl 2-[4-{[4-[2-methoxy-1-(methoxycarbonyl)-2-oxoethoxy]-phenyl]-1-methylethyl}phenoxy]malonate (ST2048);

Methyl 2-[[4'-(2-methoxy-1,1-dimethyl-2-oxoethoxy)[1,1'-biphenyl]-4-yl]oxy]-2-methylpropanoate (ST2291).

6. Compounds according to claims 1-5 as medicines.

7. Pharmaceutical compositions containing at least one compound according to claims 1-5 in mixtures with one or more pharmaceutically acceptable vehicles and/or excipients.

8. Composition according to claim 7, in the form of tablets, rigid or soft capsules, powders, solutions, suspensions, syrups, solid forms for extemporaneous liquid preparations, emulsions, liposomal forms, forms with controlled release of the active ingredient, tablets coated with appropriate layers, microencapsulated powders, complexes with cyclodextrins, depot forms, for example, subcutaneous ones, such as depot injections or implants.
9. Composition according to claim 8, which can be administered orally or parenterally.

10. Use of compounds according to claims 1-5, for the preparation of a medicine with serum glucose and serum lipid lowering activity.

11. Use of compounds according to claims 1-5, for the preparation of a medicine for the prophylaxis and treatment of diabetes, particularly type 2 diabetes, and its complications, syndrome X, various forms of insulin resistance, hyperlipidaemias and obesity.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

| IPC | C07C69/616 | C07C69/618 | C07C69/734 | A61K31/216 | A61P3/10 |

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

B. FIELDS SEARCHED

| IPC | C07C |

Minimum documentation searched (classification system followed by classification symbols)

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, PAJ, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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<td>X</td>
<td>WO 01/79150 A (NOVO NORDISK AS) 25 October 2001 (2001-10-25) claims 1-14; examples 1,4,6</td>
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<td>WO 01/55085 A (NOVO NORDISK AS) 2 August 2001 (2001-08-02) claims 1,77; examples 79,80</td>
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<td>WO 03/011807 A (NOVO NORDISK AS) 13 February 2003 (2003-02-13) claims 1,41; examples 20,21</td>
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Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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<td>document defining the general state of the art which is not considered to be of particular relevance</td>
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<td>earlier document but published on or after the international filing date</td>
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<td>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)</td>
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<td>document referring to an oral disclosure, use, exhibition or other means</td>
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Date of the actual completion of the international search

2 August 2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 661 epo nl, Fax (+31-70) 340-3018

Date of mailing of the international search report

03/11/2004

Authorized officer

Cooper, S
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<td>BRIAN J. BALL ET AL: &quot;Calcium Ionophores as cardiac stimulants&quot; EUR. J. MED. CHEM. - CHIM. THER., vol. 20, no. 2, 1985, pages 137-143, XP001194647 Compounds 2a-c,e,f; first and third compounds in the right-hand column of p.138</td>
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<td>X</td>
<td>DE 26 51 500 A (ROLLAND SA A) 26 May 1977 (1977-05-26) claim 1; examples 3-8,16-19,26-30</td>
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<td>DE 20 17 331 A (ALBERT ROLLAND S.A.) 12 November 1970 (1970-11-12) cited in the application Starting material in examples 5,9,11,17,46,47; product in examples 9,11,13,18,26,27,31,40,46,47 claims 1,15</td>
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<td>DATABASE CROSSFIRE BEILSTEIN Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 2903481, 3482501 XP002290650 abstract &amp; GAZZ. CHIM. ITAL., vol. 87, 1957, pages 586-591,</td>
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<td>DATABASE CROSSFIRE BEILSTEIN, Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 3003235, 3005812 XP002290658 abstract &amp; J. ORG. CHEM., vol. 46, no. 6, 1981, pages 1210-1212,</td>
<td>1-5</td>
</tr>
<tr>
<td>X</td>
<td>DATABASE CROSSFIRE BEILSTEIN, Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 5112602, 5087069, 2135405 XP002290659 abstract &amp; J. ORG. CHEM. USSR, vol. 18, 1982, pages 1508-1512,</td>
<td>1-5</td>
</tr>
<tr>
<td>X</td>
<td>DATABASE CROSSFIRE BEILSTEIN, Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 3520472, 3505373, 3452720, 3466427 XP002290660 abstract &amp; J. CHEM. SOC., 1955, pages 2708-2713,</td>
<td>1-5</td>
</tr>
<tr>
<td>X</td>
<td>DATABASE CROSSFIRE BEILSTEIN, Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 7488735, 7490027 XP002290661 abstract &amp; J. ORG. CHEM., vol. 61, no. 9, 1996, pages 3127-3137,</td>
<td>1-5</td>
</tr>
<tr>
<td>X</td>
<td>DATABASE CROSSFIRE BEILSTEIN, Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 2587739, 2600269 XP002290662 abstract &amp; J. CHEM. SOC. C, 1971, pages 3950-3957,</td>
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<tr>
<td>Category</td>
<td>Citation of document, with indication, where appropriate, of the relevant passages.</td>
<td>Relevant to claim No.</td>
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XP002290663  
abstract  
| X        | DATABASE CROSSFIRE BEILSTEIN  
Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE;  
Database accession no. 2046444  
XP002290664  
abstract  
| X        | GB 970 969 A (SHELL INT RESEARCH)  
23 September 1964 (1964-09-23)  
claim 1; examples 1-3 | 1-5 |
| X        | DATABASE CROSSFIRE BEILSTEIN  
Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE;  
Database accession no. 6361484  
XP002290720  
abstract  
| X        | DATABASE CROSSFIRE BEILSTEIN  
Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE;  
Database accession no. 8784613  
XP002290721  
abstract  
& CHEM. PHARM. BULL., vol. 48, no. 8, 2000, pages 1228-1229, ___ | 1-5 |
| X        | DATABASE CROSSFIRE BEILSTEIN  
Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE;  
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XP002290722  
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<td>X</td>
<td>DATABASE CROSSFIRE BEILSTEIN Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 9208407 XP002290723 abstract &amp; PHARM. CHEM. J., vol. 35, no. 12, 2001, pages 653-656, ___</td>
<td>1-5</td>
</tr>
<tr>
<td>X</td>
<td>DATABASE CROSSFIRE BEILSTEIN Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 2485587 XP002290724 abstract &amp; J. CHEM. SOC. PERKIN TRANS. 1, 1979, pages 3113-3126, ___</td>
<td>1-5</td>
</tr>
<tr>
<td>X</td>
<td>DATABASE CROSSFIRE BEILSTEIN Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 2294304 XP002290725 abstract &amp; FARMACO ED. SCI., vol. 8, 1953, pages 503-508, ___</td>
<td>1-5</td>
</tr>
<tr>
<td>X</td>
<td>DATABASE CROSSFIRE BEILSTEIN Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 2170597 XP002290726 abstract &amp; RECL. TRAV. CHIM. PAYS.BAS, vol. 50, 1931, pages 415-419, ___</td>
<td>1-5</td>
</tr>
<tr>
<td>X</td>
<td>DATABASE CROSSFIRE BEILSTEIN Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 1915491 XP002290727 abstract &amp; J. ORG. CHEM., vol. 42, no. 20, 1977, pages 3271-3279, ___</td>
<td>1-5</td>
</tr>
</tbody>
</table>
# INTERNATIONAL SEARCH REPORT

<table>
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<tr>
<th>Category</th>
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<tr>
<td>X</td>
<td>DATABASE CROSSFIRE BEILSTEIN Beachstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 1915490 XP002290728 abstract &amp; J. CHEM. SOC. C, 1967, pages 328-329,</td>
<td>1-5</td>
</tr>
<tr>
<td>X</td>
<td>DATABASE CROSSFIRE BEILSTEIN Beachstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 8851909 XP002290729 abstract &amp; J. MED. CHEM., vol. 44, no. 9, 2001, pages 1396-1406,</td>
<td>1-5</td>
</tr>
<tr>
<td>X</td>
<td>DATABASE CROSSFIRE BEILSTEIN Beachstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 2629105 XP002290730 abstract &amp; J. AM. CHEM. SOC., vol. 84, 1962, pages 1449-1455,</td>
<td>1-5</td>
</tr>
<tr>
<td>X</td>
<td>DATABASE CROSSFIRE BEILSTEIN Beachstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 2621550 XP002290731 abstract &amp; SYNTHESIS, vol. 2, 1987, pages 177-179,</td>
<td>1-5</td>
</tr>
<tr>
<td>X</td>
<td>DATABASE CROSSFIRE BEILSTEIN Beachstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 2597334 XP002290732 abstract &amp; CAN. J. CHEM., vol. 79, no. 11, 2001, pages 1632-1654,</td>
<td>1-5</td>
</tr>
</tbody>
</table>

Form PCT/ISA210 (continuation of second sheet) (January 2004)
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
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| X        | DATABASE CROSSFIRE BEILSTEIN  
Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE;  
Database accession no. 2664557  
XP002290733  
abstract  
& FARMACO ED. SCI.,  
vol. 18, 1963, pages 582-594, | 1-5 |
| X        | DATABASE CROSSFIRE BEILSTEIN  
Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE;  
Database accession no. 2772994  
XP002290734  
abstract  
& NEFTEKHIMIYA,  
vol. 5, 1965, pages 256-259, | 1-5 |
| X        | DATABASE CROSSFIRE BEILSTEIN  
Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE;  
Database accession no. 2183199  
XP002290735  
abstract  
& TETRAHEDRON,  
vol. 46, no. 3, 1990, pages 967-978, | 1-5 |
| X        | DATABASE CROSSFIRE BEILSTEIN  
Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE;  
Database accession no. 9213370  
XP002290736  
abstract  
& PHARM. CHEM. J.,  
vol. 35, no. 12, 2001, pages 10-13, | 1-5 |
| X        | DATABASE CROSSFIRE BEILSTEIN  
Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE;  
Database accession no. 2194198  
XP002290737  
abstract  
& J. CHEM. SOC. CHEM. COMMUN.,  
1978, pages 1001-1001, | 1-5 |
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
</table>
| X        | DATABASE CROSSFIRE BEILSTEIN
Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE;
Database accession no. 2908617
XP002290738
abstract & KOGYO KAGAKU ZASSHI,
v. 66, 1963, pages 1724-1727, | 1-5 |
| X        | DATABASE CROSSFIRE BEILSTEIN
Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE;
Database accession no. 1908886, 1638363
XP002290739
abstract & XENOBIOTICA,
v. 30, no. 10, 2000, pages 1005-1018, | 1-9 |
| P,X      | DATABASE CROSSFIRE BEILSTEIN
Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE;
Database accession no. 1946628, 2046425
XP002290740
abstract & BIOORG. MED. CHEM.,
v. 11, no. 16, 2003, pages 3457-3474, | 1-9 |
| X        | US 2 158 064 A (HUME CAROTHERS WALLACE)
16 May 1939 (1939-05-16)
page 2, left-hand column, line 57-62 | 1-5 |
| X        | DE 12 14 238 B (GOODRICH CO B F)
14 April 1966 (1966-04-14)
column 10, line 18,19; example 16 | 1-5 |
<table>
<thead>
<tr>
<th>Patent document cited in search report</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
<th>Publication date</th>
</tr>
</thead>
<tbody>
<tr>
<td>WO 0179150 A</td>
<td>25-10-2001</td>
<td>AU 4827901 A</td>
<td>30-10-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EO 0179150 A1</td>
<td>25-10-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 1276710 A1</td>
<td>22-01-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2004501076 T</td>
<td>15-01-2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2002262656 A1</td>
<td>21-02-2002</td>
</tr>
<tr>
<td>WO 0155085 A</td>
<td>02-08-2001</td>
<td>AU 2831901 A</td>
<td>07-08-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BR 0107901 A</td>
<td>05-11-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 235298 A1</td>
<td>02-08-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 1396903 T</td>
<td>12-02-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 0155085 A1</td>
<td>02-08-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1254101 A1</td>
<td>06-11-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HU 020457 A2</td>
<td>28-05-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2003520838 T</td>
<td>08-07-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NO 10023566 A</td>
<td>25-09-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2003195200 A1</td>
<td>16-10-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 6555577 B1</td>
<td>29-04-2003</td>
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<tr>
<td></td>
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<td>ZA 200204799 A</td>
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<tr>
<td>WO 03011807 A</td>
<td>13-02-2003</td>
<td>CA 2452665 A1</td>
<td>13-02-2003</td>
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<tr>
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<td>CZ 20040133 A3</td>
<td>16-06-2004</td>
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<td>WO 03011807 A1</td>
<td>13-02-2003</td>
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<tr>
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<td></td>
<td>EP 1414778 A1</td>
<td>06-05-2004</td>
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<tr>
<td></td>
<td></td>
<td>US 2003139473 A1</td>
<td>24-07-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AR 212749 A1</td>
<td>29-09-1978</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 1951676 A</td>
<td>18-05-1978</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BE 848310 A1</td>
<td>12-05-1977</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CH 598179 A5</td>
<td>28-04-1978</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CS 191324 B2</td>
<td>29-06-1979</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DD 127468 A5</td>
<td>28-09-1977</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 2651500 A1</td>
<td>26-05-1977</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ES 453309 A1</td>
<td>16-11-1977</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FR 2381017 A2</td>
<td>15-09-1978</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GB 1561561 A</td>
<td>27-02-1980</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HU 172710 B</td>
<td>28-11-1978</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 52093726 A</td>
<td>06-08-1977</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LU 76183 A1</td>
<td>03-06-1977</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NL 7612515 A</td>
<td>17-05-1977</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PL 103867 B1</td>
<td>31-07-1979</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PT 685835 A,B</td>
<td>01-12-1976</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 4148915 A</td>
<td>10-04-1979</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 50010299 B</td>
<td>19-04-1975</td>
</tr>
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<td>JP 50010308 B</td>
<td>19-04-1975</td>
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<tr>
<td></td>
<td></td>
<td>JP 49039995 B</td>
<td>30-10-1974</td>
</tr>
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<td>US 3821404 A</td>
<td>28-06-1974</td>
</tr>
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<td>DE 2017331 A1</td>
<td>12-11-1970</td>
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<tr>
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<td></td>
<td>AT 300278 B</td>
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</tr>
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<td></td>
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<td>AT 300315 B</td>
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<td>BE 748970 A1</td>
<td>16-09-1970</td>
</tr>
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<td>CA 964273 A1</td>
<td>11-03-1975</td>
</tr>
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<td></td>
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<td>CH 539012 A</td>
<td>31-08-1973</td>
</tr>
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<td>CH 556807 A</td>
<td>13-12-1974</td>
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<td></td>
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<td>DE 2017331</td>
<td>A</td>
<td>DK 128731 B</td>
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</tr>
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<td></td>
<td></td>
<td>ES 378565 A1</td>
<td>16-06-1972</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FI 52570 B</td>
<td>30-06-1977</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FR 2042333 A5</td>
<td>12-02-1971</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NL 7005400 A , B</td>
<td>20-10-1970</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NO 127298 B</td>
<td>04-06-1973</td>
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<td></td>
<td></td>
<td>SE 387331 B</td>
<td>06-09-1976</td>
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<td></td>
<td>SE 416805 B</td>
<td>09-02-1981</td>
</tr>
<tr>
<td></td>
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<td>SU 521835 A3</td>
<td>15-07-1976</td>
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<td></td>
<td>SU 508175 A3</td>
<td>25-03-1976</td>
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<tr>
<td></td>
<td></td>
<td>US 4031134 A</td>
<td>21-06-1977</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 3716583 A</td>
<td>13-02-1973</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 3959484 A</td>
<td>25-05-1976</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ZA 7002272 A</td>
<td>27-01-1971</td>
</tr>
<tr>
<td>GB 970969</td>
<td>A</td>
<td>23-09-1964</td>
<td>02-07-1965</td>
</tr>
<tr>
<td>FR 1404919 A</td>
<td></td>
<td>1404919 A</td>
<td>02-07-1965</td>
</tr>
<tr>
<td>US 2158064</td>
<td>A</td>
<td>16-05-1939</td>
<td>16-05-1939</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 745028 C</td>
<td>23-02-1944</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2223916 A</td>
<td>03-12-1940</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2191556 A</td>
<td>27-02-1940</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FR 50150 E</td>
<td>13-12-1939</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FR 826070 A</td>
<td>22-03-1938</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GB 523506 A</td>
<td>16-07-1940</td>
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<tr>
<td></td>
<td></td>
<td>GB 487734 A</td>
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DE 1214238 B 14-04-1966 NONE