

(RS)-2-(2,3-DIHYDRO-5-HYDROXY-4,6,7-TRIMETHYLBENZOFURANYL) ACETIC ACID,
2-(2,3-DIHYDRO-5-ACYLOXY-4,6,7-TRIMETHYLBENZOFURANYL) ACETIC ACID
AND ESTERS THEREOF

The present invention relates to (RS)-2-(2,3-dihydro-5-hydroxy-4,6,7-trimethylbenzofuranyl) acetic acid and 2-(2,3-dihydro-5-acyloxy-4,6,7-trimethylbenzofuranyl) acetic acid and esters thereof, a process for producing them and their therapeutical use as mucoregulators and antiischaemic agents.

It is well-known that the damage caused by the formation of free radicals and oxidizing metabolites from oxygen under pathological conditions affects various organs including the respiratory system, brain and heart, and are involved in the pathogenesis of inflammatory processes, blood platelet aggregation, tumoral processes, and myocardial and cerebral necrosis.

In particular, with respect to the respiratory system, oxygen free radicals contribute, by inactivation of the inhibitor of alpha-1-protease, to pulmonary emphysema and to amplification of inflammatory processes.

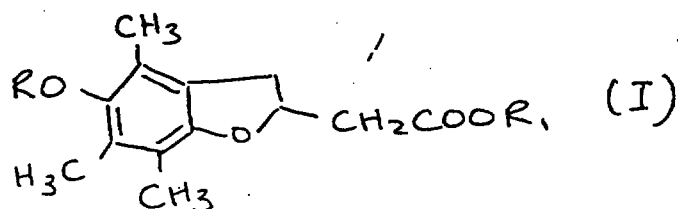
With regard to the central nervous system, oxygen free radicals are important mediators of tissue damage occurring during reperfusion after cerebral ischaemia.

As to myocardial ischaemia, oxygen free radicals contribute to cause myocardial damage both during ischaemia and during post-ischaemic reperfusion.

Substances having antioxidizing and radical scavenger activity, by neutralizing oxygen reactive metabolites, can be useful therapeutical agents for the treatment of pulmonary emphysema and of inflammatory processes of the mucous membranes of the respiratory apparatus and for the sequences of cerebral and cardiac infarct.

We have now synthesized substances to the end and have found that they, surprisingly, have mucolytic and mucoregulating activity.

According to one aspect of the present invention there is provided compounds of formula (I)



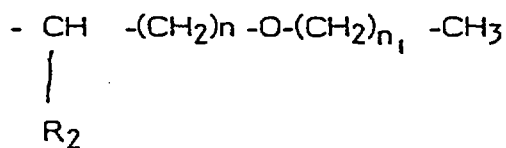
or pharmaceutically acceptable salts thereof, wherein:

R is:

- hydrogen
- an acyl group, either linear or branched, with 1 to 7 carbon atoms, for example an acetyl, propanoyl, butanoyl or isobutanoyl group;
- a hemiacyl radical of a dicarboxylic acid, for example a hemisuccinoyl group; or
- a lower alkyl group with 1 to 6 carbon atoms for example methyl or ethyl;

R₁ is:

- hydrogen,
- a linear or branched alkyl group with 1 to 20 carbon atoms, for example methyl, ethyl, isobutyl, octyl or octadecyl,
- an alkyl ether group of the formula:



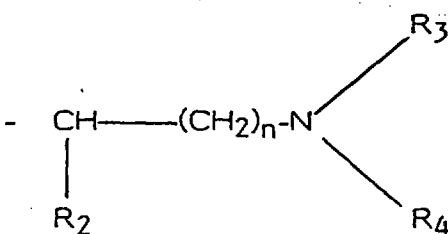
wherein n and n₁ are independently numbers from 0 to 6 and R₂ is a lower alkyl group e.g. containing from 1 to 6 carbon atoms,

- an alkyl diether group of the formula:



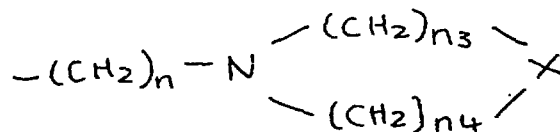
wherein n and n_1 are independently from 1 to 6, and n_2 is a number from 0 to 6,

- an alkylamine group of the type:



wherein n is a number from 0 to 6, R_2 is as defined above, and R_3 and R_4 are independently lower alkyl groups having 1 to 4 carbon atoms for example the alkylamine group can be dimethylaminoethyl, or;

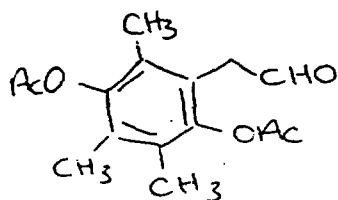
- a N-alkylheterocyclic group of the formula:



wherein X is CH_2 , S , O or NR_2 (wherein R_2 is as defined above), n is a number from 1 to 6, n_3 and n_4 are independently numbers from 1 to 3; for example the N-alkylheterocyclic group can be a N-ethylmorpholine or N-ethyl-N'-methylpiperazine group;

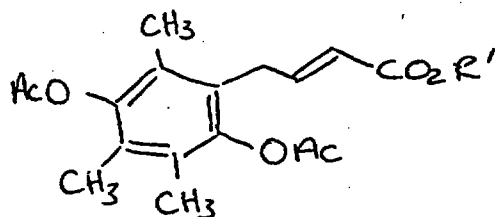
with the proviso that when R is H , R is not a C alkyl group.

According to another aspect of the present invention there is provided a process for preparing a compound according to the present invention, ~~the process for preparing a compound of formula (i) according to claim 1,~~ wherein $R=R_1=H$, comprising reacting a compound of formula:



-3a-

where Ac is an acetyl group or any other protecting group, with $\text{Ph}_3\text{P}=\text{CHC}(=\text{O})_2\text{R}'$, where R' is an alkyl group, to give a compound of formula:-



which is then saponified and the resulting solution acidified to give (RS)-2-(2,3-dihydro-5-hydroxy-4,6,7-trimethylbenzofuranyl) acetic acid; wherein $\text{R}=\text{R}_1=\text{H}$, comprising reacting as starting product 2,5-diacetoxy-3,4,6-trimethylphenylacetaldehyde with carboethoxymethyltriphenylphosphorane in an inert solvent to give ethyl trans - 4 - (2,5-diacetoxy-3,4,6-trimethylphenyl)-2-butenolate, which is treated with a solution of an alkaline hydroxide to give (RS)-2-(2,3-dihydro-5-hydroxy-4,6,7-trimethylbenzofuranyl) acetic acid; wherein R is an acyl group and R_1 hydrogen, comprising acylating (RS)-2-(2,3-dihydro-5-hydroxy-4,6,7-trimethylbenzofuranyl) acetic acid by means of an acid anhydride and an organic base; and wherein R is hydrogen and R_1 is methyl or ethyl, comprising esterifying (RS)-2-(2,3-dihydro-5-hydroxy-4,6,7-trimethylbenzofuranyl) acetic acid by means of diazomethane or diazoethane.

According to a further aspect of the present invention there is provided a pharmaceutical composition comprising a compound according to the present invention together with a pharmaceutically acceptable carrier or excipient.

According to the further aspects of the invention there is provided processes for preparing new compounds. They may be synthesized according to a general synthesis scheme (see diagram 1 below).

Various preferred features and embodiments of the invention will now be described by way of non-limiting example.

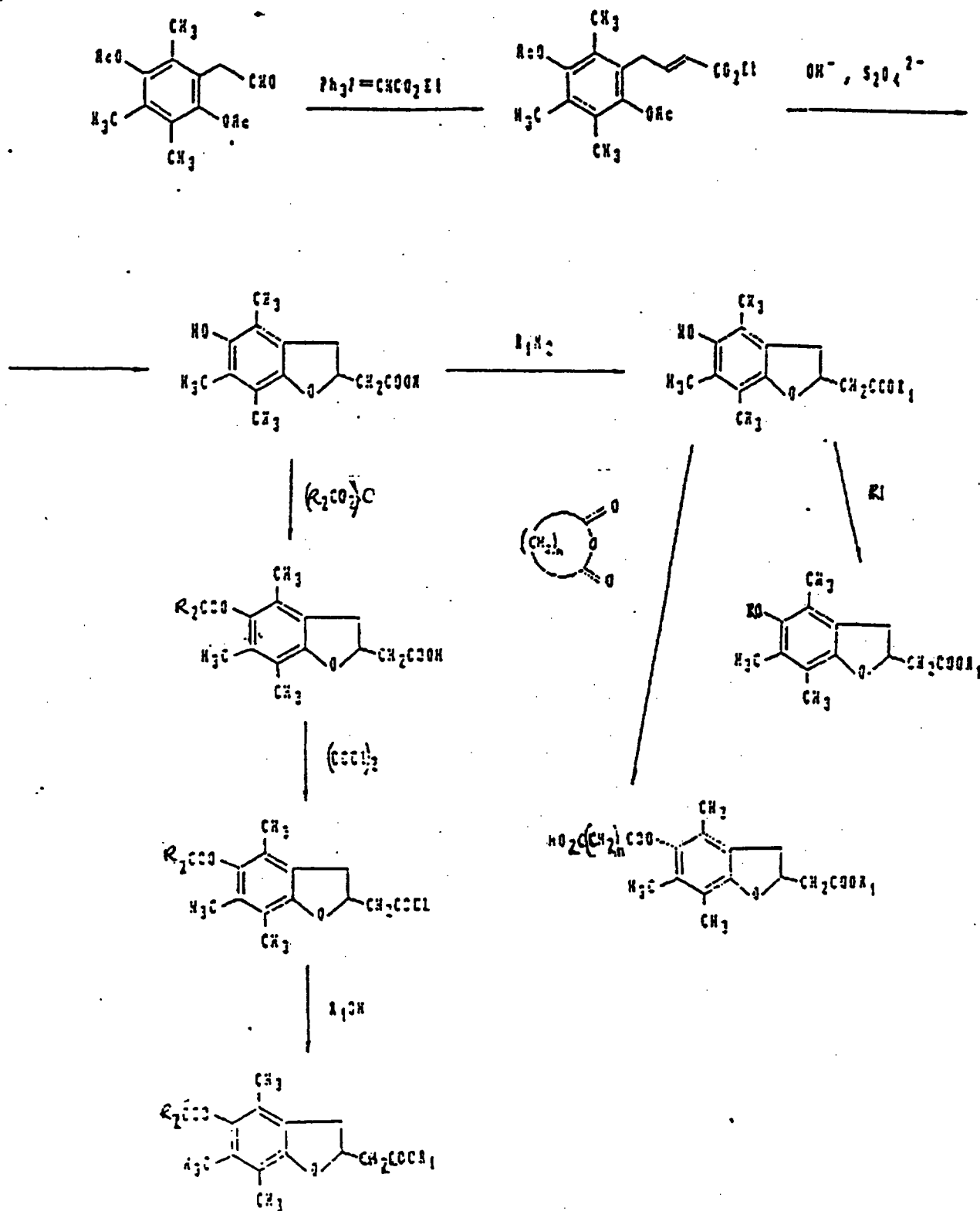
Using as a starting product 2,5 diacetyloxy-3,4,6-trimethylphenylacetaldehyde (prepared according to K.Okamoto et al., Chem. Pharm. Bull. 1982, 30 (8), 2797) from which (RS)-2-(2,3-dihydro-5-hydroxy-4,6,7-trimethylbenzofuranyl) acetic acid may be obtained in two

steps. From the latter, by acylation and alkylation of phenolic hydroxyl and by esterification of the carboxylic group with suitable reagents, all the products described in the present invention can be obtained.

Various preferred features and embodiments of the invention will now be described by way of non-limiting example.

In the first step of the reaction sequence shown in Diagram I, a condensation according to Wittig is carried out between 2,5-diacetyloxy-3,4,6-trimethylphenylacetaldehyde and carboethoxymethyltriphenylphosphorane, dissolving the two compounds in a suitable organic solvent while stirring, then bringing the solution to the boil and refluxing it for a sufficient time. On evaporation of the solvent, ethyl trans-4-(2,5-diacetyloxy-3,4,6-trimethylphenyl)-2-butenate is obtained, which is crystallized by a suitable solvent.

The latter, dissolved in an organic solvent, e.g. acetone, is saponified by treating it with KOH or NaOH, in the presence of sodium hydrosulphite or of another suitable reducing agent to prevent oxidation of the resulting hydroquinone to quinone, then the reaction mixture is refluxed for a sufficient time. The thus formed hydroquinone cyclizes directly to (RS)-2-(2,3-dihydro-5-hydroxy-4,6,7-trimethylbenzofuranyl) acetic acid, which is isolated by extraction with an organic solvent followed by re-extraction with a solution of NaHCO_3 and acidification of the latter. The product obtained is filtered under vacuum and crystallized.



(RS)-2-(2,3-dihydro-5-hydroxy-4,6,7-trimethylbenzofuranyl) acetic acid is acylated to the phenolic hydroxyl by dissolving it under a nitrogen atmosphere in the sufficient amount of an organic base such as pyridine, collidine or toluidine and adding to such solution an acylating agent, e.g. an acid anhydride or an acylic halide. The reaction mixture, diluted with water, is then extracted with an organic solvent after acidification. The alkylation of the same phenolic hydroxyl is carried out in an acetone solution using K_2CO_3 or Na_2CO_3 as base and an alkyl halide.

The esterification of 5-acyl and 5-alkyl derivatives of (RS)-2-(2,3-dihydro-5-hydroxy-4,6,7-trimethylbenzofuranyl) acetic acid is obtained via the acid halide thereof. To obtain the latter, the acid is dispersed in benzene and oxalyl halide is added, the solution is then stirred, for a short period of time, at a suitable temperature (generally $50^\circ C$).

After removing the solvent and washing the residue with toluene, the halide is used directly, without purification, for the subsequent reaction. The esterification, may be carried out in an aprotic organic solvent such as tetrahydrofuran, by adding an alcohol to the halide in the presence of pyridine or of another organic base. The isolation and purification of the final product depends on the nature of the alcohol used for the esterification.

Generally one extraction with organic solvent and one crystallization are sufficient. In some cases it is necessary to use chromatography techniques. It is possible, finally, to esterify directly (RS)-2-(2,3-dihydro-5-hydroxy-4,6,7-trimethylbenzofuranyl) acetic acid by reacting it with an ether solution, or other organic solvent, of a suitable diazoalkane. Once the excess of the latter has been destroyed with acetic acid, the desired product is obtained by simply evaporating the solution and effecting chromatography for purification.

The invention also relates to the use of the substances of formula (I) as mucolytic-mucoregulating and antiinflammatory drugs.

Table I shows, as an example, the effect of the following compounds on mucoproduction:

(RS)-2-(2,3-dihydro-5-acetyloxy-4,6,7-trimethylbenzofuranyl) acetic acid (IRFI 016), (RS)-2-(2,3-dihydro-5-hydroxy-4,6,7-trimethylbenzofuranyl) acetic acid (IRFI 005) and (RS)-2-(2,3-dihydro-5-hydroxy-4,6,7-trimethylbenzofuranyl) acetic acid ethyl ester (IRFI 034).

Table II shows the effects of compound IRFI 016 on mucoproduction in rabbits.

Table III shows the antiinflammatory activity of compound IRFI 016.

TABLE I : MUCOPRODUCTION IN MICE

The method described by Graziani et coll. (Il Farmaco Ed. Pr. 36, 167, 1981) - suitably modified has been followed.

Male albino mice CD 1 (Charles River) weighing 22-24 g. were used.

The amount of red phenol was assessed, injected intraperitoneally, in the bronchial wash liquid, and the values obtained in the treated animals were compared.

The drugs were administered orally (gastric probe).

As comparison drugs, some of the mucolytic/mucoregulating agents most widely known and used in the human therapy have been chosen.

TABLE I

Oral administration. (n=10)

SUBSTANCE	ED ₅₀ mg/kg	SAFETY LIMITS 95%
IRFI 016	151.697	112.602 - 190.692
IRFI 005	61.88	53.534 - 70.232
IRFI 034	44.477	39.132 - 49.821
THIOPRONINE	155.75	134.389 - 176.518
BROMEXINE	177.06	170.872 - 183.252

TABLE II: MUCOPRODUCTION IN RABBITS

The method described by Scuri et Coll. (Boll. Chim. Farm. 119, 181, 1980) was followed.

Male HY rabbits (Charles River) weighing 3-3.5 Kg were used.

The drugs were administered intravenously (auricular vein) and the tracheo-bronchial mucus was collected for 4 hours before (basal) and after pharmaceutical treatment.

As comparison drugs, some of the mucolytic/mucoregulating agents most known and used in the human therapy were selected.

TABLE II

Intravenous administration (n=10)

SUBSTANCE	ED ₅₀ mg/kg	SAFETY LIMITS
IRFI 005	12.443	8.827 - 16.060
IRFI 016	10.547	8.723 - 12.372
N-ACETYLCYSTEINE	17.279	16.990 - 17.568
BROMEXINE	8.395	8.301 - 8.490
SOBREROLE	7.541	7.520 - 7.563

TABLE III: ANTIINFLAMMATORY ACTIVITY

The method by Winter et Coll. (J.Pharmacol.Expl. The. 141, 369, 1963) was used.

Male Wistar rats (Charles River) weighing 120 - 130 g were used.

The influence of the drugs on the carragenine subplantar oedema was studied (0.05 ml of a suspension of 1% carragenine in distilled water).

The drugs were administered orally (gastric probe).

TABLE III

Oral administration (n=5)

SUBSTANCE	DOSAGE mg/kg	ODEMA VOL. (ml) X + ES	VAR.%
CONTROLS	-	0.332 + 0.45	-
IRFI 016	200	0.158 + 0.38	- 52
IRFI 016	100	0.202 + 0.43	- 39
CONTROL	-	0.310 + 0.05	
PHENYLBUTAZONE	100	0.140 + 0.02	- 58

Therefore, according to the present invention compounds of formula I can be used as mucoregulating drugs for the treatment of diseases of the respiratory system characterized by an increase in the consistence and amount of secretion (bronchitis and bronchiolitis, chronic bronchitis, bronchiectasis and complications of asthmatic disease and pulmonary emphysema, acute and chronic pharyngopharyngitis and trachetis, rhinitis and sinusitis with phlogosis of the mucous membrane of the respiratory tract).

For therapeutical use, the compounds of Formula I can be administered orally, topically, parenterally, by inhalation or rectally in formulations containing non-toxic conventional pharmaceutical excipients. The term 'parenteral' herein used includes, for example, subcutaneous, endovenous, intramuscular, intrasternum injections as well as technical infusions.

Pharmaceutical compositions containing the active component can be in a form suitable for oral use, e.g. tablets, aqueous or oily suspensions, dispersible powders or granules, hard or soft capsules, syrups or elixirs. The compositions for oral use can contain one or more sweetening, colouring, aromatizing and preservative agents to make the pharmaceutical preparation convenient and palatable.

The formulations for oral use include tablets wherein the active drug is mixed with non-toxic, pharmaceutically acceptable excipients that may be inert diluents such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating or disintegrating agents such as wheat starch or alginic acid; binding agents such as starch, jellies; lubricating agents such as magnesium stearate, stearic acid or talc.

The tablets can be uncoated or coated in accordance with known techniques, to retard disintegration and absorption in the gastrointestinal tract in order to have a delayed and/or prolonged action.

Aqueous solutions generally contain the active component mixed with suitable excipients. The excipients can be suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone; dispersing or wetting agents. They can contain one or more preservatives e.g. ethyl or n-propyl p-hydroxybenzoate; one or more colouring agents; one or more aromatizing agents; and/or one or more sweeteners.

Oily suspensions can be formulated by suspending the active component in a vegetable or mineral oil; they can contain sweetening and aromatizing agents to make the preparation palatable.

Dispersible powders and granules used for the preparation of an aqueous suspension by addition of water may contain the active component in a mixture with a dispersing or wetting agent, a suspending agent and one or more preservatives.

Pharmaceutical compositions of the present invention can also be in the form of water/oil emulsion. The oily phase can be substituted by a vegetable or mineral oil. The emulsifying agents can be natural gums such as acacia gum or natural phosphatides, e.g. lecithin or natural or synthetic fatty acid esters.

Syrups and elixirs can be formulated with sweetening agents, e.g. glycerol, sorbitol or saccharose. The pharmaceutical compositions can be in the form of aqueous or oily sterile injectable suspensions. The suspensions can be formulated by known techniques using dispersing or wetting agents and known suspending agents. The sterile injectable preparations can be sterile solutions or suspensions injectable in a non-toxic solvent or diluent suitable for parenteral use.

The compounds of Formula I can also be administered rectally in the form of suppositories. These compositions can be prepared by mixing the active component with a suitable non-irritating excipient which is solid at room temperature but liquid at rectal temperature; it melts, therefore, in the rectum and releases the drug. Polyethylenglycols and cocoa butter are suitable for this purpose.

For topical use creams, ointments, gels, solutions, suspensions or other appropriate formulations containing the mucolytic can be prepared. The following examples illustrate the invention without limiting it.

EXAMPLE 1

a) Trans ethyl 4-(2,5-diacetyloxy-3,4,6-trimethylphenyl)-2-butenate

A solution of 2,5-diacetyloxy-3,4,6-trimethylphenylacetaldehyde (69.1 g, prepared according to K.Okamoto et al, Chem.Pharm. Bull. 1982, 30, (8), 2797) and of carbethoxymethyltriphenylphosphorane (145.2 g) is refluxed in dioxane (5.0 l) for 16 hours. The mixture is evaporated under vacuum and the residue is crystallized using ethanol, obtaining 69.2 g of a white crystalline solid. M.P. = 128 - 30°C; IR (KBr): 1750 (CH₃COOAr),

1724 cm^{-1} (COOC_2H_5); $^1\text{H-NMR}$ (CDCl_3): 7.2-6.7. (1H,m), 5.8-5.4 (1H,m), 4.15 (2H,q), 3.5-3.3 (2H,m), 2.30 (3H,s), 2.27 (3H,s), 2.02 (3H,s), 2.00 (6H,s), 1.2 (3H,t).

Elemental analysis for $\text{C}_{19}\text{H}_{24}\text{O}_6$ (M.W. 348.39)

	C%	H%	O%
Eval.	66.09	6.82	27.08
Found	66.17	6.86	26.79

b) (RS)-2-(2,3-dihydro-5-hydroxy-4,6,7-trimethylbenzofuranyl) acetic acid (IRFI 005)

A mixture of trans ethyl 4-(2,5-diacetyloxy-3,4,6-trimethylphenyl)-2-butenate (69.2 g), $\text{Na}_2\text{S}_2\text{O}_4$ (210 g), acetone (850 ml) and 10% KOH (3.35 l) is refluxed for 4 hours. After cooling, the solution is acidified and extracted with ethyl acetate. The organic phase is then washed twice with H_2O and re-extracted with 5% NaHCO_3 . The aqueous phase is acidified and the precipitate is vacuum filtered, dried and crystallized using benzene.

35.5 g is obtained. M.P. = $173-4^\circ\text{C}$; IR (KBr): 3427 (OH), 1709 cm^{-1} (COOH); $^1\text{H-NMR}$ ($\text{DMSO}-d_6$): 12.2 (1H,sb), 7.4(1H,sb) 5.35-4.85 (1H,m), 3.55-2.55 (4H,m), 2.05 (6H,s), 2.00 (3H,s)

Elemental analysis for $\text{C}_{13}\text{H}_{16}\text{O}_4$ (M.W. 236.27)

	C%	H%	O%
Eval.	66.09	6.82	27.08
Found	66.17	6.36	26.79

EXAMPLE 2

(RS)-2-(2,3-dihydro-5-acetyloxy-4,6,7-trimethylbenzofuranyl) acetic acid
(IRFI 016)

A solution of (RS)-2-(2,3-dihydro-5-hydroxy-4,6,7-trimethylbenzofuranyl) acetic acid (see example 1) (3.5 g) in pyridine (15.8 ml) and acetic anhydride (9.5 ml) is stirred under nitrogen atmosphere for 4 hours. To the solution there is added ice (40g) and HCl 6 N until pH2, then the solution is extracted with chloroform

The organic phase is dried and vacuum evaporated. The residue is crystallized using benzene: 3.0 g of a white crystalline solid is obtained. M.P. = 165-6°C; IR (KBr): 1749 (CH₃COOAr), 1706 (cm⁻¹) (COOH); ¹H-NMR (CDCl₃): 10.4 (1H,s), 5.35- 4.85 (1H,m) 3.55 - 2.55 (4H,m), 2.30 (3H,s), 2.05 (3H,s), 2.00 (6H,s).

Elemental analysis for C₁₅H₁₈O₅ (M.W. 278.30)

	C%	H%
Eval:	64.74	6.52
Found	64.74	6.54

EXAMPLE 3

Propionic acid, 5-(2,3-dihydro-2-(RS)-carboxymethyl-4,6,7-trimethylbenzofuranyl) ester

A solution of (RS)-2-(2,3-dihydro-5-hydroxy-4,6,7-trimethylbenzofuranyl) acetic acid (see example 1) (0.5 g) in pyridine (2.3 ml) with addition of propionic anhydride (1.8 ml) is stirred in inert atmosphere for 2 hours. To the solution are added ice (5 g) and HCl 6 N until pH 2: a white solid is thus precipitated. The product is vacuum filtered, dried and crystallized using benzene/heptane. 0.4 g of a white

crystalline solid is obtained. M.P. = 148-50°C; IR (KBr): 1746 (EtCOOAr), 1710 cm^{-1} (COOH); $^1\text{H-NMR}$ (CDCl_3): 11.0 (1H,sb) 5.35- 4.85 (1H,m), 3.35- 2.55 (6H,m), 2.0 (3H,s), 1.9 (6H,s), 1.2 (3H,t,J=14Hz)

Elemental analysis for $\text{C}_{16}\text{H}_{20}\text{O}_5$ (M.W. 292.33)

	C%	H%
Eval.	65.74	6.89
Found	66.01	6.83

EXAMPLE 4

Succinic acid, mono 5-(2,3-dihydro-2-(RS)-carboxymethyl-4,6,7 - trimethylbenzofuranyl) ester

A mixture of (RS)-2-(2,3-dihydro-5-hydroxy-4,6,7-trimethylbenzofuranyl) acetic acid (see example 1) (1.0 g) succinic anhydride (2.5 g) and pyridine (12 ml) is stirred for 4 h at 100°C under an inert atmosphere. The obtained solution is cooled with the addition of H_2O (20 ml) and HCl 6 N until pH 2, and then extracted with chloroform. The organic phase is vacuum evaporated, and the residue is crystallized using benzene. 0.8 g of a white crystalline solid is obtained. M.P. = 186-8°C; IR (KBr):1744 (RCOOAr), 1708 cm^{-1} (COOH); $^1\text{H-NMR}$ (CD_3OD): 5.35- 4.90 (1H,m), 3.4 - 2.5 (8H,m) 2.05 (3H,s), 1.95 (6H,s).

Elemental analysis for $\text{C}_{17}\text{H}_{20}\text{O}_7$ (M.W. 336.34)

	C%	H%
Eval.	60.71	5.99
Found	60.87	5.92

EXAMPLE 5

(RS)-2-(2,3-dihydro-5-hydroxy-4,6,7-trimethylbenzofuranyl) acetic acid, methyl ester

To a suspension of (RS)-2-(2,3-dihydro-5-hydroxy-4,6,7-trimethylbenzofuranyl) acetic acid (see example 1) (1.4 g) in diethyl ether (15 ml) is added dropwise - keeping the mixture temperature at 5°C - an ether solution of diazomethane (prepared as in Org. Synth. Coll. Vol. II, 166), until complete dissolution of the substrate (about 20 ml is necessary). The excess diazomethane is destroyed with acetic acid. The solution is filtered and the filtrate is dried. The residue is purified by column chromatography (SiO₂). 1.4 g of a white crystalline solid is obtained. M.P. = 108 ± 10°C; IR (KBr): 3428 (OH), 1730 cm (COOMe); H-NMR (COC1₃): 6.5 (1H, sb), 5.30-4.75 (1H, m), 3.65 (3H, s), 3.35-2.55 (4H, m), 2.1 (6H, s), 2.0 (3H, s).

Elemental analysis for C₁₄H₁₈O₄ (M.W. 250.29)

	C%	H%
Eval.	67.18	7.25
Found	67.04	7.26

EXAMPLE 6

Succinic acid, mono 5-[2,3-dihydro-2-(RS)-(methoxycarbonyl)methyl-4,6,7-trimethylbenzofuranyl] ester

A mixture of (RS)-2-(2,3-dihydro-5-hydroxy-4,6,7-trimethylbenzofuranyl) acetic acid, methyl ester (see example 5) (0.25 g) and succinic anhydride (0.20 g) in pyridine (1.5 ml) is placed at 100°C under an inert atmosphere for 5 h. The thus obtained solution is cooled with the addition of HCl 2 N until pH 2, and extracted with ethyl acetate. The extracts are washed twice with H₂O, then dried and vacuum

evaporated. The raw residue is crystallized using benzene. 0.26 g white crystalline solid is obtained. M.P. = 154-6°C; IR (KBr): 1741 (COOAr), 1731 (COOMe), 1694 cm^{-1} (COOH); $^1\text{H-NMR}(\text{CDCl}_3)$: 10.5 (1H,sb), 5.35-4.85 (1H,m), 3.7 (3H,s), 3.4-2.6 (8H,m), 2.05 (3H,s), 1.95 (6H,s).

Elemental analysis for $\text{C}_{18}\text{H}_{22}\text{O}_7$ (M.W. 350.37)

	C%	H%
Eval.	61.71	6.33
Found	61.70	6.36

EXAMPLE 7

(RS)-2-(2,3-dihydro)-5-methoxy-4,6,7-trimethylbenzofuranyl) acetic acid, methyl ester

To a solution of (RS)-2-(2,3-dihydro-5-hydroxy-4,6,7-trimethylbenzofuranyl) acetic acid, methyl ester (see example 5) (0.25 g) in acetone (2 ml) is added anhydrous potassium carbonate (0.15 g) and methyl iodide (0.1 ml). The mixture is refluxed for 24 h; after cooling the non-reacted potassium carbonate is filtered away and the filtrate is vacuum concentrated. The residue is subjected to chromatographic column (SiO_2); 60 mg of a white crystalline solid is obtained. M.P. = 44-6°C; IR (KBr): 1740 cm^{-1} (COOMe); $^1\text{H-NMR}(\text{CDCl}_3)$: 5.35 - 4.85 (1H,m), 3.75 (3H,s), 3.65 (3H,s), 3.4 - 2.5 (4H,m), 2.15 (6H,s), 2.05 (3H,s).

Analysis for $\text{C}_{15}\text{H}_{20}\text{O}_4$ (M.W. 264.32)

	C%	H%
Eval.	68.16	7.63
Found	67.92	7.58

EXAMPLE 8

- a) (RS)-2-(2,3-dihydro-5-acetyloxy-4,6,7-trimethylbenzofuranyl)
acetyl chloride

To a suspension of (RS)-2-(2,3-dihydro-5-acetyloxy-4,6,7-trimethylbenzofuranyl) acetic acid (see example 2) (4.4 g) in benzene (36 ml) is added dropwise oxalyl chloride (7 ml) over 30 minutes.

The thus obtained solution is kept under stirring at 50°C for a further 15 minutes. After cooling, the solution is vacuum evaporated and the residue is washed twice with toluene. 4.69 g is obtained. The product is used for the successive reactions without purification IR (KBr): 1804 cm (COC1).

- b) (RS)-2-(2,3-dihydro-5-acetyloxy-4,6,7-trimethylbenzofuranyl)
acetic acid, ethyl ester (IRFI 034)

To a solution of (RS)-2-(2,3-dihydro-5-acetyloxy-4,6,7-trimethylbenzofuranyl) acetyl chloride (1.0 g) in anhydrous tetrahydrofuran (4 ml) is added pyridine (0.4 ml), then absolute ethanol (0.3 ml); the mixture is stirred at room temperature for 1 hour. The suspension is then vacuum evaporated, and H₂O and ethyl acetate is added. The organic phase is dried and evaporated under vacuum. The residue is purified by column chromatography (SiO₂). 0.75 g of white crystalline solid is obtained. M.P. = 76-77.5°C, IR (KBr): 1755 (CH₃COOAr), 1725 (COOC₂H₅); ¹H-NMR (CDCl₃): 5.35- 4.85 (1H,m), 4.2 (2H,q), 3.55- 2.55 (4H,m), 2.3 (3H,s), 2.05(3H,s), 2.00 (6H,s) 1.25 (3H,t).

Elemental analysis for C₁₇H₂₂O₅ (M.W. 306.36)

	C%	H%
Eval.	66.65	7.24
Found	66.40	7.36

EXAMPLE 9

(RS)-2-(2,3-dihydro-5-acetyloxy-4,6,7-trimethylbenzofuranyl) acetic acid, isobutyl ester

The working process is identical to that of example 8. The product is purified by column chromatography (SiO₂). 0.3 g of a white crystalline solid is obtained. M.P. = 44.5 - 45.5°C; IR (KBr): 1761 (CH₃COOAr), 1736 cm⁻¹ (COOR); ¹H-NMR (CDCl₃): 5.35-4.85 (1H,m), 3.9 (2H,d,J=12Hz), 3.45-2.65 (5H,m), 2.3 (3H,s), 2.05 (3H,s), 2.00 (6H,s), 0.9 (6H,d,J=12Hz).

Elemental analysis for C₁₉H₂₆O₅ (M.W. 334.41)

	C%	H%
Eval.	68.24	7.84
Found	68.59	7.85

EXAMPLE 10

(RS)-2-(2,3-dihydro-5-acetyloxy-4,6,7-trimethylbenzofuranyl) acetic acid, n-octyl ester

The working process is identical to that of example 8.

The product is purified by column chromatography (SiO₂). 0.35 g of a white crystalline solid is obtained. M.P. = 42.5°C - 43.5°C; IR (KBr): 1762 (CH₃COOAr), 1737 cm⁻¹ (COOR); ¹H-NMR (CDCl₃): 5.35-4.85 (1H,m), 4.1 (2H,t), 3.55-2.65 (4H,m), 2.3 (3H,s), 2.05 (3H,s), 2.00 (6H,s), 1.6-1.1 (12H,m), 0.85 (3H,m).

Elemental analysis for C₂₃H₃₄O₅ (M.W. 390.52)

	C%	H%
Eval.	70.74	8.77
Found	70.36	8.76

EXAMPLE 11

(RS)-2-(2,3-dihydro-5-acetyloxy-4,6,7-trimethylbenzofuranyl) acetic acid, n-octadecyl ester

The working process is identical to the one of example 8. The product is purified by column chromatography (SiO). 0.3 g of a white crystalline solid is obtained. M.P. = 58-58.5°C; IR (KBr): 1746 (CH₃COOAr), 1723 cm⁻¹ (COOR); ¹H-NMR (CDCl₃): 5.35-4.85 (1H,m), 4.1 (2H,t), 3.35-2.65 (4H,m), 2.3 (3H,s), 2.05 (3H,s), 1.95 (6H,s), 1.5-1.2 (32H,m) 0.8 (3H,m).

Elemental analysis for C₃₃H₅₄O₅ (M.W. 530.79)

	C%	H%
Eval.	74.67	10.25
Found	74.62	10.24

EXAMPLE 12

(RS)-2-(2,3-dihydro-5-acetyloxy-4,6,7-trimethylbenzofuranyl) acetic acid, 2-dimethylamino ethyl ester, chlorohydrate

To a solution of (RS)-2-(2,3-dihydro-5-acetyloxy-4,6,7-trimethylbenzofuranyl) acetyl chloride (see example 8) (0.3 g) in anhydrous tetrahydrofuran (1 ml) there is added N,N-dimethylethanolamine (0.09 ml). The reaction mixture is stirred for 1 h; the obtained precipitate is vacuum filtered, washed with diethyl ether, dried and crystallized by ethyl acetate. 0.25 g of a white crystalline solid is obtained. M.P. = 166-8°C; IR (KBr): 2650 (NH), 1752 (CH₃COOAr), 1742 cm⁻¹ (COOR); ¹H-NMR (CD₃OD): 5.4-4.8 (1H,m), 4.5-4.3 (2H,m), 3.65-2.75 (6H,m), 2.9 (6H,s), 2.3 (3H,s), 2.05 (3H,s), 1.95 (6H,s).

Elemental analysis for $C_{19}H_{28}ClNO_5$ (M.W. 385.89)

	C%	H%	N%
Eval.	59.14	7.31	3.63
Found	58.93	7.38	3.60

EXAMPLE 13

(RS)-2-(2,3-dihydro-5-acetyloxy-4,6,7-trimethylbenzofuranyl) acetic acid,
2-(4-morpholin) ethyl ester, hydrochlorate

To a solution of (RS)-2-(2,3-dihydro-5-acetyloxy-4,6,7-trimethylbenzofuranyl) acetyl chloride (see example 8) (3.4 g) in anhydrous tetrahydrofuran (10 ml) is added 4-(2-hydroxyethyl) morpholine (1.3 ml). After 1 h the resulting precipitate is vacuum filtered. The purification of the product takes place by extraction with diethyl ether of the aqueous solution of the chlorohydrate brought to pH 7 with 5% sodium bicarbonate.

The extracts are dried, vacuum concentrated and treated with diethyl ether saturated with HCl.

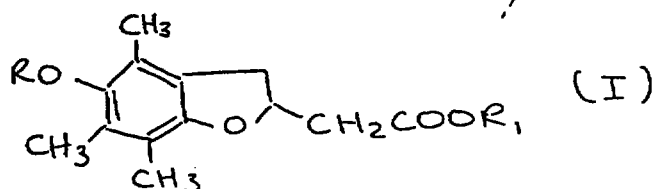
The precipitate is then vacuum filtered, dried and re-crystallised by an ethyl acetate and methanol mixture. 2.8 g of a crystalline solid is obtained. M.P. = 161-3°C; IR (KBr): 2556, 2455 (NH), 1753 (CH_3COOAr), 1738 cm^{-1} (COOR); 1H -NMR (CD_3OD): 4.6-5.4 (1H,m), 4.6-4.35 (2H,t), 4.15-3.75 (4H,t), 3.6-2.6 (10H,m), 2.3 (3H,s), 2.05(3H,s), 1.95 (6H,s).

Elemental analysis for $C_{21}H_{30}ClNO_6$ (M.W. 427.92)

	C%	H%	N%
Eval.	58.94	7.07	3.27
Found			

CLAIMS

1. A compound of formula:

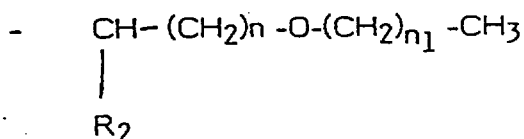


or pharmaceutically acceptable salts thereof, wherein R is:

- hydrogen
- an acyl group, either linear or branched, with 1 to 7 carbon atoms;
- a hemiacyl of a dicarboxylic acid;
- a lower alkyl having 1 to 6 carbon atoms;

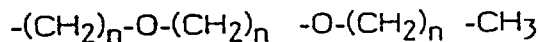
R₁ is:

- hydrogen,
- a linear or branched alkyl group with 1 to 20 carbon atoms;
- an alkyl ether group of the formula:



wherein n and n₁ are independently numbers from 0 to 6 and R₂ is a lower alkyl group,

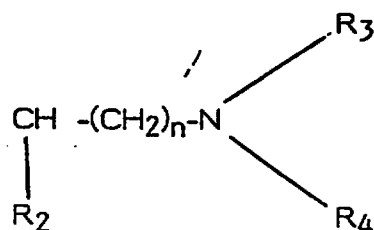
- an alkyl diether group of the formula:



wherein n and n₁ are independently from 1 to 6, and n₂ is a number from 0 to 6,

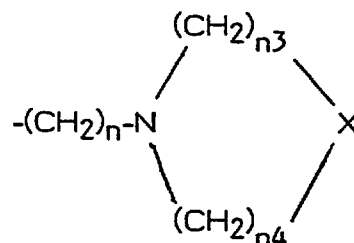


- an alkylamine group of the formula:



wherein n is a number from 0 to 6, R₂ is as previously defined and R₃ and R₄ are independently lower alkyl groups having 1 to 4 carbon atoms; or

- a N-alkylheterocyclic group of the formula:



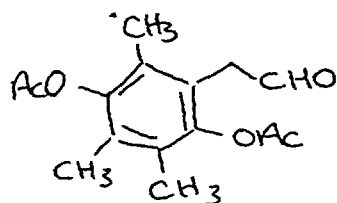
wherein X is CH₂, S, O or NR₂

(where R₂ is as previously defined, n is a number from 1 to 6, n₃ and n₄ are independently numbers from 1 to 3; with the proviso that when R is hydrogen, R₁ is not a C₁ alkyl group.

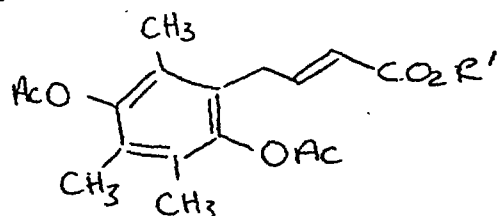
2. A compound according to claim 1, wherein R is an acyl group selected from acetyl, propanoyl, butanoyl and isobutanoyl.
3. A compound according to claim 1, wherein R is a hemisuccinoyl group.
4. A compound according to claim 1, wherein R is a lower alkyl group selected from methyl and ethyl.



5. A compound according to any preceding claim, wherein R_1 is an alkyl group selected from methyl, ethyl, isobutyl, octyl and octadecyl.
6. A compound according to any one of claims 1 to 4, wherein R_1 is dimethylaminoethyl.
7. A compound according to any one of claims 1 to 4 wherein R_1 is a N-alkylheterocyclic group selected from N-ethylmorpholine or N ethyl - N' - methylpiperazine group.
8. A compound according to claim 1 as herein specifically disclosed.
9. A process for preparing a compound of formula (I) according to claim 1, wherein $R=R_1 = H$, comprising reacting a compound of formula:



where Ac is an acetyl group or any other protecting group, with $Ph_3P=CHC(=O)O_2R'$, where R' is an alkyl group, to give a compound of formula:-



which is then saponified and the resulting solution acidified to give (RS)-2-(2,3-dihydro-5-hydroxy-4,6,7-trimethylbenzofuranyl) acetic acid.



10. A process for preparing a compound of formula (1) according to claim 1, wherein $R=R_1=H$, comprising reacting as starting product 2,5-diacetoxy-3,4,6-trimethylphenylacetaldehyde with carboethoxymethyltriphenylphosphorane in an inert solvent to give ethyl trans - 4 - (2,5-diacetoxy-3,4,6-trimethylphenyl)-2-butenate, which is treated with a solution of an alkaline hydroxide to give (RS)-2-(2,3-dihydro-5-hydroxy-4,6,7-trimethylbenzofuranyl) acetic acid.
11. A process according to claim 10, wherein the inert solvent is dioxane.
12. A process for preparing a compound of formula I according to claim 1, wherein R is an acyl group and R_1 hydrogen, comprising acylating (RS)-2-(2,3-dihydro-5-hydroxy-4,6,7-trimethylbenzofuranyl) acetic acid by means of an acid anhydride and an organic base.
13. A process for preparing a compound of formula I according to claim 1 wherein R is hydrogen and R_1 is methyl or ethyl, comprising esterifying (RS)-2-(2,3-dihydro-5-hydroxy-4,6,7-trimethylbenzofuranyl) acetic acid by means of diazomethane or diazoethane.
14. A process for preparing a halide of (RS)-2-(2,3-dihydro-5-hydroxy-4,6,7-trimethylbenzofuranyl) acetic acid, comprising treating a compound prepared according to claim 13 with an oxalyl halide in an inert solvent.
15. A process according to claim 14 wherein the inert solvent is benzene, toluene or xylene.
16. A process for preparing an ester of (RS)-2-(2,3-dihydro-5-hydroxy-4,6,7-trimethylbenzofuranyl) acetic acid, comprising treating an acid halide prepared according to either of claims 14 and 15 with R_1OH , wherein R_1 is as defined in claim 1, in an inert solvent in the presence of an acidity acceptor.



17. A process according to claim 16 wherein the inert solvent is tetrahydrofuran, diethyl ether or dioxane.
18. A process according to either of claims 16 and 17 wherein the acidity acceptor is pyridine or triethylamine.
19. A process for preparing a compound of formula I wherein R is an alkyl group and R₁ methyl or ethyl, comprising treating a compound prepared according to claim 13 with an alkyl halide in an inert solvent in the presence of an acidity acceptor.
20. A process according to claim 19 wherein the inert solvent is acetone.
21. A process according to either of claims 19 and 20 wherein the acidity acceptor is sodium or potassium carbonate.
22. A pharmaceutical composition comprising a compound according to any one of claims 1 to 8 together with a pharmaceutically acceptable carrier or excipient.
23. Use of a compound according to any one of claims 1 to 8 for the manufacture of a medicament for use as a mucoregulator or antiischaemic agent.
24. A compound according to any one of claims 1 to 8 as substantially herein described with reference to the Examples.
25. A pharmaceutical composition according to claim 22 as substantially herein described with reference to the Examples.
26. A process for preparing a compound according to formula I as substantially herein described with reference to the Examples.

