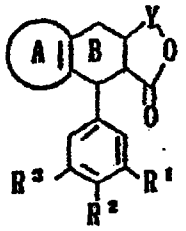
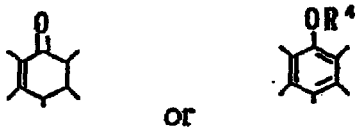
Description

This invention relates to a novel biphenyl derivative, processes for preparing the same and synthetic intermediates thereof. More particularly, it relates to a biphenyl derivative of the formula:



(I)

wherein Ring A is a thiophene or furan ring which may have a substituent selected from formyl group, a C_1-C_4 alkoxy-methyl group and hydroxymethyl group; Ring B is a ring of the formula:

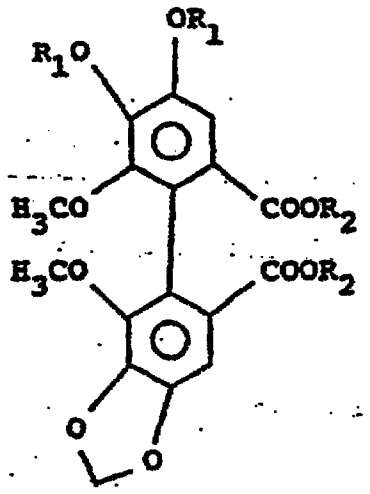


each of R^1 or R^3 is hydrogen atom, a halogen atom or a C_1-C_4 alkoxy group, or R^1 is hydrogen atom, and R^2 and R^3 are combined together to form a C_1-C_4 alkylenedioxy group; R^4 is a C_1-C_4 alkyl group which may have a substituent selected from a C_1-C_4 alkoxy group and a C_1-C_4 alkoxycarbonyl group; Y is methylene group or carbonyl group, or a pharmaceutically acceptable salt thereof.

The liver is an important organ having various functions such as detoxication, various metabolism, storage of nutrients and is acutely or chronically injured by various causes such as virus, drugs, alcohols. These injuries bring about various hepatic diseases such as acute or chronic hepatitis, fatty liver and finally result in hepatocirrhosis. In particular, acute and chronic hepatitis and hepatocirrhosis are characterized by round cell infiltration and mesenchymal reactions such as fibrosis in the liver.

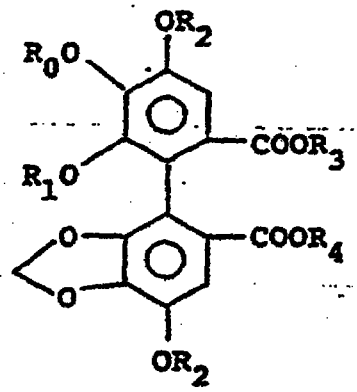
It is hitherto known that Malotilate (Chemical name: diisopropyl 1,3-dithiol-2-ylidenemalonate) increases protein synthesis in the liver and is useful for the therapy of these hepatic diseases [Japanese Patent Publication (unexamined) No. 144734 (1976)]. However, this compound is known to frequently bring about hepatic hypertrophy.

EP-A-0269754 discloses biphenyl derivatives represented by the following formula



wherein R_1 and R_2 stand for a hydrogen atom or a methyl group.

EP-A-0267970 discloses biphenyl derivatives represented by the following formula



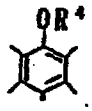
(I)

wherein R_0 and R_1 independently stand for a lower alkyl group or R_0 and R_1 together represent a group O=C<, R_2 stands for an alkyl group having 1 to 3 carbon atoms, and R_3 and R_4 independently stand for a hydrogen atom or a lower alkyl group.

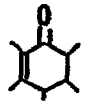
The biphenyl derivatives of the above prior art are effective for remedy of acute hepatitis. These compounds are structurally very different from the compounds of the present invention.

The novel biphenyl derivatives (I) of the present invention and pharmaceutically acceptable salts thereof are useful to alleviate or cure hepatic injuries and also protect the liver from hepatic injuries without hepatic hypertrophy.

Examples of the compound of the present invention include those of the formula (I) in which Ring A is a thiophene or furan ring which may have a substituent selected from formyl group, a C_1-C_4 alkoxy-methyl group and hydroxymethyl group. Among them, pharmaceutically preferred examples include those of the formula (I) in which each of R^1 to R^3 is hydrogen atom, a halogen atom or a C_1-C_4 alkoxy group. More preferred examples include those of the formula (I) in which Ring A is thiophene or furan ring which may be substituted with hydroxymethyl group, R^1 is hydrogen atom or a C_1-C_4 alkoxy group, each of R^2 and R^3 is a C_1-C_4 alkoxy group, and R^4 is a C_1-C_4 alkyl group. Most preferred examples are those of the formula (I) in which Ring A is thiophene ring, Ring B is a ring of the formula:

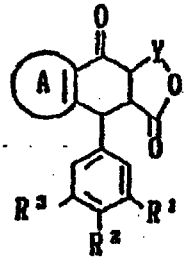


R^1 is hydrogen atom, each of R^2 and R^3 is methoxy group, and R^4 is methyl group, and those of the formula (I) in which Ring A is furan ring which may be substituted with hydroxymethyl group, Ring B is a ring of the formula:



R^1 is hydrogen atom, each of R^2 and R^3 is methoxy group, and Y is methylene group.

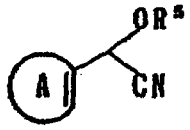
According to the present invention, a biphenyl derivative of the formula:



(I-a)

wherein Ring A, R^1 to R^3 and Y are the same as defined above, can be prepared by the steps of:

[A] reacting a cyanohydrin derivative of the formula:



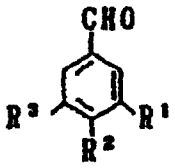
(II)

wherein R^5O is a protected hydroxy group, and Ring A is the same as defined above, with a heterocyclic compound of the formula:



(III)

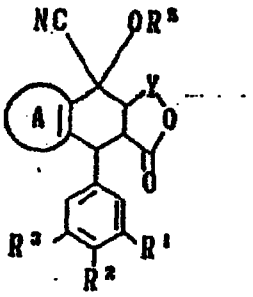
wherein Y is the same as defined above, and an aldehyde compound of the formula:



(IV)

wherein R^1 to R^3 are the same as defined above,

[B] cyclizing the product in the presence of an acid to give a tetrahydrobiphenyl compound of the formula:

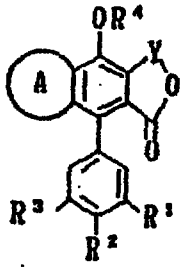


(V)

wherein Ring A, R^1 to R^3, R^5O and Y are the same as defined above, and

[C] treating the compound (V) with a fluorine ion-donor.

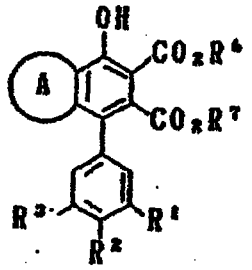
On the other hand, a biphenyl derivative of the formula:



(I-b)

wherein Ring A, R^1 to R^4 and Y are the same as defined above, can be prepared by the steps of:

[D]-(1) subjecting a dicarboxylate compound of the formula:

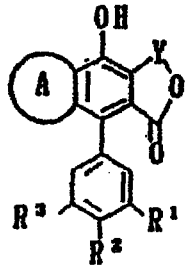


(VI)

wherein each of R^6 and R^7 is a C_1-C_4 alkyl group, and Ring A and R^1 to R^3 are the same as defined above, to reductive lactonization or

-(2) hydrolyzing the dicarboxylate compound (VI), followed by dehydration thereof, and

[E] condensing the resultant hydroxy-biphenyl compound of the formula:



(VII)

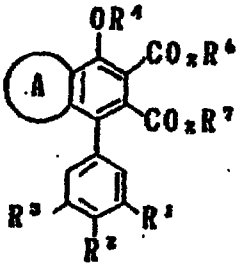
wherein Ring A, R^1 to R^3 and Y are the same as defined above, with a compound of the formula:

$$R^4\text{-}X \qquad \text{(VIII)}$$

wherein X is a leaving group, and R^4 is the same as defined above.

The compound (I-b) may also be prepared by the steps of:

[F] condensing the dicarboxylate compound (VI) with the compound (VIII) to give a dicarboxylate compound of the formula:



(IX)

wherein Ring A, R^1 to R^4, R^6 and R^7 are the same as defined above, and

[G]-(1) subjecting the compound (IX) to reductive lactonization or

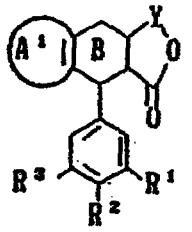
-(2) hydrolyzing the compound (IX), followed by dehydration thereof.

Alternatively, the compound (I-b) may be prepared by

[H] oxidizing the compound (I-a) to give the hydroxybiphenyl compound (VII) and

[I] condensing it with the compound (VIII).

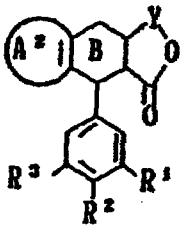
Further, among the compound (I), a biphenyl derivative of the formula:



(I-c)

wherein Ring A^1 is a thiophene or furan ring substituted with hydroxymethyl group or a C_1-C_4 alkoxymethyl group, and Ring B, R^1 to R^3 and Y are the same as defined above, can also be prepared by the step or steps of:

[J] reducing a biphenyl derivative of the formula:



(I-d)

wherein Ring A^2 is a thiophene or furan ring substituted with formyl group, and Ring B, R^1 to R^3 and Y are the same as defined above, and

[K] if required, alkylating the product.

The reaction of the starting compounds (II), (III) and (IV) (i.e., Step [A]) can be carried out in the presence of a base. Any conventional base may be used for this purpose. Preferred base includes, for example, a lithium dialkylamide, phenyl lithium and a lower alkyl lithium. The protecting group (R^5) for the hydroxy group includes any conventional protecting group such as a tri(lower alkyl)silyl group, a diphenyl(lower alkyl)silyl group, a lower alkoxy-lower alkyl group, a lower alkoxy-lower alkoxy-lower alkyl group and a phenyl-lower alkyl group. The reaction is preferably carried out in a solvent such as tetrahydrofuran, diethyl ether, diglyme, hexane, toluene and xylene and under cooling, for example, at a temperature between -80 and -40°C. Said reaction may be carried out by addition of a base to the mixture of the starting compounds (II), (III) and (IV), but it is usually preferred to carry it out by first condensing the cyanohydrin derivative (II) with the heterocyclic compound (III), and then condensing the product with the aldehyde compound (IV).

The subsequent acid treatment (i.e., Step [B]) can be conducted in a conventional manner. Examples of the acid include organic acids such as acetic acid, trifluoroacetic acid, methanesulfonic acid or p-toluenesulfonic acid; inorganic acids such as sulfuric acid. Said acid treatment is preferably carried out in the same solvent as employed in the above- mentioned reaction and at ambient temperature or with heating, for example, at a temperature of 10 to 50°C.

The subsequent treatment of the tetrahydrobiphenyl compound (V) with a fluorine ion-donor (i.e., Step [C]) can be conducted in a conventional manner. Any conventional fluorine ion-donor which can releases fluorine ion in the reaction system can be used for the purpose of the invention. Preferred examples of such fluorine ion-donor include hydrogen fluoride, a mixture of a fluoride (e.g., an alkali metal fluoride, ammonium fluoride, a tetra(lower alkyl)ammonium fluoride) and an organic acid. Said treatment is preferably carried out in a solvent such as methylene chloride or chloroform under cooling or at ambient temperature, for example, at a temperature between -20 to 30 °C.

On the other hand, the reductive lactonization of dicarboxylate compounds (VI) and (IX) (i.e., Step [D]-(1) and [G]-(1)) can be carried out by treating said compound with a reducing agent, and then, if required, treating the product with an acid. The reducing agents include, for example, a borane-complex, an alkali metal borohydride-boron trifluoride complex, an alkali metal borohydride, an alkaline earth metal borohydride and lithium aluminum hydride. The same organic or inorganic acids as mentioned in Step [B] are preferably used in the reaction. These reactions are preferably carried out in a solvent such as a lower alkanol, tetrahydrofuran, ethyl acetate or dioxane and at ambient temperature or with heating, for example, at a temperature between 10 and 100 °C. Concomitantly, when the compound (VI) or (IX) has formyl group on Ring A thereof, such formyl group is simultaneously converted to hydroxy-methyl group during the above-mentioned reductive lactonization.

The hydrolysis and subsequent dehydration of the compounds (VI) and (IX) (i.e., Step [D]-(2) and [G]-(2)) can be conducted in a conventional manner. The hydrolysis is preferably carried out by using a conventional organic or inorganic base such as a tri(lower alkyl)amine, an alkali metal alkoxide or an alkali metal hydroxide. The following dehydration is preferably carried out in the presence of a conventional dehydrating agent such as acetic anhydride, dicyclohexylcarbodiimide, a mixture of p-toluenesulfonyl chloride and pyridine. These reactions are preferably carried out in the same solvent as used in the above-mentioned reductive lactonization and at ambient temperature or with heating, for example, at a temperature between 10 and 100 °C. However, when an excess amount of acetic anhydride is used as the dehydrating agent, said dehydration may be carried out without solvent.

The condensation reaction of the compound (VI) or (VII) with the compound (VIII) (i.e., Step [E] and [F]) can be carried out in the presence or absence of an acid acceptor. Examples of the leaving group [X] of the compound (VIII) include for instance a halogen atom and diazo group. Organic bases such as a tri(lower alkyl)amine, pyridine, an N-(lower alkyl)piperidine and inorganic bases such as an alkali metal carbonate, an alkali metal hydroxide, an alkali metal hydride are preferably used as the acid acceptor. It is preferred to carry out the reactions in a solvent such as N,N-dimethylformamide, tetrahydrofuran, methylene chloride, diethyl ether and dioxane. These reactions preferably proceed at ambient temperature or with ice-cooling or heating, for example, at a temperature between 0 and 100 °C. Concomitantly, when the compound (VI) or (VII) has hydroxymethyl group on Ring A thereof, said hydroxy group may, if required, be protected by a lower alkyl group during the reaction.

The oxidation of the compound (I-a) (i.e., Step [H]) can be conducted in a conventional manner. For example, it can be carried out by reacting the compound (I-a) with a halogenating agent, and then treating the product with an organic base such as a tri(lower alkyl)amine or an inorganic base such as an alkali metal hydroxide, an alkali metal bicarbonate. Any conventional halogenating agent may be used for this purpose, but it is usually preferred to use a transition metal halide (e.g., cupric halide) in the presence of for instance an alkali metal halide. Alternatively, said oxidation may be conducted by treating the product with an oxidizing agent such as selenium dioxide, 2,3-dichloro-5,6-dicyanobenzoquinone. It is preferred to carry out the reactions in a solvent (e.g., acetonitrile, chloroform). These reactions preferably proceed at ambient temperature or with heating, for example, at a temperature between 20 and 85 °C.

The condensation reaction of the thus-obtained hydroxybiphenyl compound (VII) with the compound (VIII) (i.e., Step [I]) can be carried out under the same conditions as in step [E].

The reduction of the compound (I-d) (i.e., Step [J]) can be conducted in a conventional manner, for example, by treating it with a reducing agent. Any conventional reducing agent may be used for the reaction, but it is preferred to use a borane complex, an alkali metal borohydride. The reaction is preferably carried out in a solvent (e.g., a lower alkanol, tetrahydrofuran, diglyme, dioxane and so forth). It is preferred to conduct the reaction under cooling or with warming, for example, at a temperature between 0 and 50 °C.

The alkylation of the thus-obtained compound having hydroxymethyl group on Ring A thereof (i.e., Step [K]) can be carried out by condensing it with a compound (VIII) under the same conditions as in Steps [E] and [F].

Concomitantly, the above-mentioned methods of the present invention may also be applied, if required, with some appropriate modifications. For example, when Ring A of the compound (V) is an unsubstituted thiophene or furan ring, formyl group may be introduced to said compound (V) by , for example, reacting it with dimethylformamide in the presence of a halogenating agent (e.g., phosphorous oxychloride, thionyl chloride).

In the above-mentioned reactions, the starting compounds of the invention may be used either in a free form or in the form of a salt. For example, the compounds (VI) and (VII), and the compounds (II), (V) and (IX) in which Ring A is substituted with a group having hydroxy group are, if required, used for instance in the form of an alkali metal salt, an alkaline earth metal salt and ammonium salt.

The compound (I) of the present invention has excellent pharmacological activities for alleviating or curing various hepatic injuries such as degeneration or necrosis of hepatocytes, fibrosis, accumulation of fat in liver, congestion of liver. The compound (I) also has excellent liver-protecting activities.

Accordingly, the compound (I) of the present invention is useful as a therapeutic or prophylactic agent for hepatic diseases such as acute or chronic hepatitis, fatty liver, hepatic congestion, hepatocirrhosis in warm-blooded animals including human beings. In particular, the compound (I) of the present invention is characterized in that it shows excellent activities in treating or preventing chronic hepatitis or hepatocirrhosis. For example, the compound (I) when administered orally shows excellent curing and/or protecting effects against chronic active hepatitis which are induced by 3-hydroxy-4-pyrone [Experientia, Vol.40, P. 894-896 (1984)]. The compound (I) also suppresses the progress of CCl_4-induced fibrosis in the liver [Pharmacological Reviews, Vol. 19, P.145-208 (1967)], and further shows an excellent therapeutic effect against hepatocirrhosis.

Moreover, the compound (I) of the present invention is low in toxicity and has high safety as a medicine.

The compound (I) is also advantageous in that it can be administered repeatedly for a long period because it causes no substantial hepatic hypertrophy usually observed in the known drugs such as Malotilate.

The biphenyl derivatives (I) can be used for pharmaceutical use either in a free form or in the form of a pharmaceutically acceptable salt. Examples of the pharmaceutically acceptable salts include salts with an organic or inorganic base such as alkali metal salts (e.g., potassium salt, sodium salt), alkaline earth metal salts (e.g., calcium salt) and ammonium salt.

Moreover, the biphenyl derivative (I-a) of the present invention may exist in the form of eight optical isomers due to the three asymmetric carbon atoms contained in Ring B. The present invention includes within its scope either one of these optical isomers and a mixture thereof. If required, diastereoisomers may be converted to each other according to a conventional manner. For example, an isomer of the invention having the (r-5, t-6, c-7)-configuration may be converted to the corresponding (r-5, c-6, t-7)-isomer by treating the former with a base (e.g., triethylamine).

The compound (I) and a pharmaceutically acceptable salt thereof may be administered either orally or parenterally, but it is preferred to administer them orally. They may also be used in the form of pharmaceutical preparations such as tablets, capsules, powders, granules and injections, if necessary, in admixture with a pharmaceutically acceptable carrier, diluent or disintegrant.

The dose of the compound (I) or a pharmaceutically acceptable salt thereof may vary depending on, for instance, the age, body weight and condition of patients, the kind and severity of diseases to be treated, administration route, but it may usually be in the range of about 0.1 to about 500 mg/kg, preferably about 1 to about 300 mg/kg, per day.

Among the starting compounds of the present invention, the cyanohydrin derivative (II) and the dicarboxylate compound (VI) are novel. The compound (II) may be prepared, for example, by reacting an aldehyde compound of the formula:



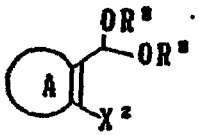
wherein Ring A is the same as defined above, with an alkali metal cyanide and a compound of the formula:

$$R^5\text{-}X^1$$

wherein X^1 is a halogen atom and R^5 is the same as defined above, in the presence of Lewis acid [e.g., zinc (II) iodide].

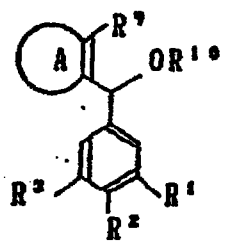
On the other hand, the compound (VI) may be prepared, for example, by the steps of:

(1) reacting an acetal compound of the formula:



wherein R^8 is a lower alkyl group, X^2 is hydrogen atom or bromine atom and Ring A is the same as defined above, with an aldehyde compound (IV) in the presence of an alkyl lithium,

(2) if required, hydrolyzing the product and/or alkylating or acylating the hydroxy group thereof to give a compound of the formula:



wherein R^9 is formyl group or a di(lower alkyl)methyl group, R^{10} is hydrogen atom, a lower alkyl group or a lower alkanoyl group, and Ring A and R^1 to R^3 are the same as defined above, and then

(3) reacting the thus-obtained product with a di(lower alkyl)acetylenedicarboxylate in the presence of an acid (e.g., trifluoroacetic acid, p-toluenesulfonic acid).

Further, when Ring A of the product has no substituent, formyl group may be introduced to said Ring A in a conventional manner.

In this Specification and Claims, relative configuration of each compound is indicated according to IUPAC Nomenclature of Organic Compound (E-2.3.3 and E-2.3.4). And the terms "a lower alkyl group", "a lower alkoxy group" and "a lower alkanoyl group" represent an alkyl group of one to 4 carbon atoms, an alkoxy group of one to 4 carbon atoms and an alkanoyl group of 2 to 5 carbon atoms, respectively.

Experiment

(Protecting effect against carbon tetrachloride(CCl_4)-induced acute liver injury)

Groups of 3 ddY male mice (weight: 28-35 g) were used. Test compounds suspended in 0.5% sodium carboxymethyl-cellulose (CMC-Na) solution were orally given for 4 consecutive days at a dose of 100 mg/kg/day, and CCl_4 was given at a dose of 50 µl/kg [1%(v/v)-olive oil mixture] orally 3 hours after the last administration of test compounds. After a 24 hour fast following the administration of CCl_4, the blood was collected into tubes treated with heparin according to the method described in Journal of Pharmacobio-Dynamics, Vol. 10, P. 599-607(1987). After plasma was separated from the blood of mice, glutamic-pyruvic transaminase (GPT) activity was measured. The protective effect (%) against CCl_4-induced liver injury was estimated according to the following equation.

$$\text{Protective Effect (\%)} = \left[\frac{GPT(CCl_4)-GPT(T)}{GPT(CCl_4)-GPT(C)}\right] X\ 100$$

GPT(T) : the average of GPT activity in the medicated group of mice.

GPT(CCl_4): the average of GPT activity in a group of mice to which a 0.5% CMC-Na solution was administered instead of the test compound solution.

GPT(C) : the average of GPT activity in a group of mice to which a 0.5% CMC-Na solution and olive oil were administered instead of the test compound solution and the CCl_4 solution, respectively.

[List of compounds tested]

No.1: 2, r-5-bis(hydroxymethyl)-4-oxo-t-7-(3,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[b]furan-c-6-carboxylic acid γ-lactone

No.2: 4-oxo-r-5-hydroxymethyl-t-7-(3,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzol[b]furan-c-6-carboxylic acid lactone

No.3: 4-methoxy-7-(3,4-dimethoxyphenyl)benzol[b]thiophen-5,6-dicarboxylic acid anhydride

No.4: 4-methoxy-5-hydroxymethyl-7-(3,4-dimethoxyphenyl)benzo[b]thiophen-6-carboxylic acid lactone

No.5: 4-methoxy-5-hydroxymethyl-7-(3,4-dimethoxyphenyl)benzo[b]furan-6-carboxylic acid lactone

No.6: 4-methoxy-5-hydroxymethyl-7-(4-methoxyphenyl)benzo[b]thiophen-6-carboxylic acid lactone

No.7: 4-methoxymethoxy-5-hydroxymethyl-7-(3,4-dimethoxyphenyl)benzo[b]thiophen-6-carboxylic acid lactone

No.8: 4-ethoxycarbonylmethoxy-5-hydroxymethyl-7-(3,4-dimethoxyphenyl)benzo[b]thiophen-6-carboxylic acid lactone

No.9: 4-methoxy-5-hydroxymethyl-7-(3,4-dichlorophenyl)benzo[b]thiophen-6-carboxylic acid lactone

No.10: 4-methoxy-5-hydroxymethyl-7-(3,4,5-trimethoxyphenyl)benzo[b]thiophen-6-carboxylic acid lactone

No.11: 2-methoxymethyl-4-methoxy-5-hydroxymethyl-7-(3,4-dimethoxyphenyl)benzo[b]thiophen-6-carboxylic acid lactone

The results are shown in the following Table 1.

Table 1

Test Comp. Nos.	Protective Effect (%)
1	56.8
2	79.4
3	63.7
4	55.2
5	28.3
6	28.5
7	24.3
8	28.3
9	22.7
10	31.7
11	22.9

Example 1

(1) 188 g of potassium cyanide, 384 g of tert.-butyldimethylsilyl chloride, 185 g of 3-furylaldehyde and 18 g of zinc iodide are added to 1.5 liters of acetonitrile and the mixture is stirred at ambient temperature for 2 days. 3 liters of diethyl ether are added to the reaction mixture, and the insoluble materials are filtered off. The filtrate is condensed, and the residue is dissolved in diethyl ether. The mixture is washed with water, dried and condensed. The residue is further distilled under reduced pressure to give 416 g of 2-(3-furyl)-2-(tert.-butyldimethylsilyloxy)acetonitrile.

B.p. 90 to 100 °C/133 to 267 Pa (1 to 2 mmHg)

NMR($CDCl_3$, δ): 0.16 (s, 3H), 0.21 (s, 3H), 0.93 (s, 9H), 5.47 (s, 1H), 6.4 - 6.6 (m, 1H), 7.3 - 7.5 (m, 1H), 7.5 -7.6 (m, 1H)

(2) A solution of 267 g of the product obtained in paragraph (1) in 300 ml of toluene, a solution of 97.4 g of 2-oxo-2,5-dihydrofuran in 1.5 liters of toluene and a solution of 192 g of 3,4-dimethoxybenzaldehyde in 300 ml of toluene are added dropwise in this order to a lithium diisopropylamide solution [prepared from 129 g of diisopropylamine and 1.28 mole of n-butyl lithium in hexane-toluene at -78 °C]. 146 ml of acetic acid and one liter of water are further added to the reaction mixture. The organic layer is separated, washed with water, dried and evaporated under reduced pressure to remove the solvent. 560 g of crude 2-oxo-3-(α-hydroxy-3,4-dimethoxy-benzyl)-4-[(3-furyl)(tert.-butyldimethylsilyloxy)cyanomethyl]-2,3,4,5-tetrahydrofuran are obtained.

(3-a) 560 g of the crude product obtained in paragraph (2) are dissolved in one liter of methylene chloride, and 500 ml of trifluoroacetic acid are added thereto. The mixture is allowed to-stand at ambient temperature overnight. The reaction mixture is diluted with one liter of chloroform, washed with water, dried and evaporated to remove the solvent. The residue is recrystallized from diethyl ether to give 304 g of 4-(tert.-butyldimethylsilyloxy)-4-cyano-5-hydroxymethyl-7-(3,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[b]furan-6-carboxylic acid lactone. This product is a mixture of (r-4, c-5, t-6, c-7)-isomer and (r-4, t-5, c-6, t-7)-isomer.

M.p. 152 to 156 °C

(3-b) 560 g of the crude product obtained in paragraph (2) are dissolved in 1.4 liters of dioxane, and 270 ml of methane-sulfonic acid are added thereto. The mixture is stirred at ambient temperature for 3 hours. 4 liters of chloroform are added thereto, and the mixture is washed with water, dried and evaporated to

remove the solvent. The residue is triturated with methanol, and crystalline precipitates are collected by filtration, washed with methanol and dried. 267 g of 4-(tert.-butyldimethylsilyloxy)-4-cyano-5-hydroxymethyl-7-(3,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[b]furan-6-carboxylic acid lactone are obtained as a mixture of (r-4, c-5, t-6, c-7)-isomer and (r-4, t-5, c-6, t-7)-isomer.

The physico-chemical properties of this product are identical with those of the product obtained in paragraph (3-a).

(4) 32.6 g of phosphorus oxychloride are added dropwise to 100 ml of N,N-dimethylformamide under ice-cooling, and the mixture is stirred at ambient temperature for 30 minutes. A solution of 20 g of the product obtained in paragraph (3-a) or (3-b) in 100 ml of N,N-dimethylformamide are added thereto, and the mixture is stirred at 50 to 60 °C for 6 hours. The reaction mixture is poured into ice-water and extracted with ethyl acetate. The extract is washed with water, dried and evaporated to remove the solvent. The residue is purified by silica gel column chromatography [solvent: hexane - chloroform (1 : 10)]. The eluate is evaporated to remove the solvent, and diethyl ether is added to the residue. The crystalline precipitates are collected by filtration. 11.4 g of 2-formyl-4-(tert.-butyldimethylsilyloxy)-4-cyano-5-hydroxymethyl-7-(3,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[b]furan-6-carboxylic acid lactone are obtained as a mixture of (r-4, c-5, t-6, c-7)-isomer and (r-4, t-5, c-6, t-7)-isomer.

M.p. 150 to 154 °C

(5) 6.5 g of the product obtained in paragraph (4) are dissolved in 50 ml of methylene chloride, and 1.18 g of acetic acid and 15.7 ml of a 1M solution of tetra(n-butyl)ammonium fluoride in tetrahydrofuran are added thereto under ice-cooling. Five minutes later, the reaction mixture is washed with water, dried and evaporated to remove the solvent. The residue is added to 100 ml of toluene, and the mixture is refluxed with heating for 3 hours. The reaction mixture is evaporated to remove the solvent, and the residue is purified by silica gel column chromatography [solvent: hexane - ethyl acetate (1 : 1)]. The eluate is condensed, and the residue is recrystallized from a mixture of ethyl acetate and hexane. 3.5 g of 2-formyl-4-oxo-r-5-hydroxymethyl-t-7-(3,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[b]furan-c-6-carboxylic acid lactone are obtained.

M.p. 182 to 184 °C

Example 2

1.0 g of 2-formyl-4-oxo-r-5-hydroxymethyl-t-7-(3,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[b]furan-c-6-carboxylic acid lactone is dissolved in 100 ml of isopropyl alcohol, and 2.0 g of sodium borohydride are added gradually thereto. Then, the mixture is stirred at ambient temperature for 2 hours. Acetic acid is added thereto, and insoluble materials are filtered off. The filtrate is evaporated to remove the solvent, and the residue is dissolved in chloroform. The mixture is washed with water, dried and evaporated to remove the solvent, and the residue is recrystallized from ethyl acetate. 670 mg of 2, r-5-bis(hydroxymethyl)-4-oxo-t-7-(3,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[b]furan-c-6-carboxylic acid γ-lactone are obtained.

M.p. 154 to 156 °C

Example 3

2.06 g of 4-(tert.-butyldimethylsilyloxy)-4-cyano-5-hydroxymethyl-7-(3,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[b]furan-6-carboxylic acid lactone [a mixture of (r-4, c-5, t-6, c-7)-isomer and (r-4, t-5, c-6, t-7)-isomer] and 0.35 ml of acetic acid are dissolved in 20 ml of methylene chloride. 5.3 ml of a 1M solution of tetra(n-butyl)ammonium fluoride in tetrahydrofuran are added dropwise thereto under ice-cooling, and the mixture is stirred at ambient temperature overnight. The reaction mixture is washed with water, dried and evaporated to remove the solvent. The residue is recrystallized from ethyl acetate. 1.23 g of 4-oxo-r-5-hydroxymethyl-t-7-(3,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[b]furan-c-6-carboxylic acid lactone are obtained.

M.p. 165.9 °C

Example 4

(1-a) 23.0 g of 4-(tert.-butyldimethylsilyloxy)-4-cyano-5-hydroxymethyl-7-(3,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[b]furan-6-carboxylic acid lactone [a mixture of (r-4, c-5, t-6, c-7)-isomer and (r-4, t-5, c-6, t-7)-isomer] and 6.9 g of ammonium fluoride are added to a mixture of 207 ml of acetonitrile and 23 ml of water. The mixture is stirred at ambient temperature for 20 hours. The reaction mixture is poured into water, and the crystalline precipitates are collected by filtration, washed with water-methanol and dried. 14.3 g of 4-oxo-r-5-hydroxymethyl-c-7-(3,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[b]furan-t-6-car-

boxylic acid lactone are obtained.

M.p. 210 to 212 °C

(1-b) 200 g of 4-(tert.-butyldimethylsilyloxy)-4-cyano-5-hydroxymethyl-7-(3,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[b]furan-6-carboxylic acid lactone [a mixture of (r-4, c-5, t-6, c-7)-isomer and (r-4, t-5, c-6, t-7)-isomer] and 30.8 g of acetic acid are dissolved in 500 ml of methylene chloride. 448 ml of a 1M tetrahydrofuran solution of tetra(n-butyl)ammonium fluoride are added dropwise thereto at -20 to -10 °C, and the mixture is stirred at -10 °C for 10 minutes. The reaction mixture is poured into diethyl ether, and insoluble materials are filtered off. 92 g of 4-oxo-r-5-hydroxymethyl-c-7-(3,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[b]furan-t-6-carboxylic acid lactone are obtained.

The physico-chemical properties of this product are identical with those of the product obtained in paragraph (1-a).

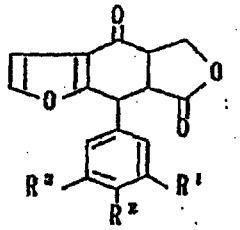
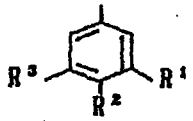
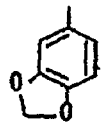
(2) 14.3 g of the product obtained in paragraph (1-a) or (1-b) are suspended in 200 ml of toluene, and 5 ml of triethylamine are added thereto. The mixture is refluxed with heating for 5.5 hours. 5 ml of triethylamine are added to the mixture, and the mixture is further refluxed with heating for 4.5 hours. The reaction mixture is evaporated to remove the solvent, and the residue is recrystallized from ethyl acetate. 12.48 g of 4-oxo-r-5-hydroxymethyl-t-7-(3,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[b]furan-c-6-carboxylic acid lactone are obtained.

The physico-chemical properties of this product are identical with those of the product obtained in Example 3.

Examples 5 and 6

The corresponding starting materials are treated in the same manner as described in either one of Examples 1 to 4 to give the compounds in the following Table 2.

Table 2

Ex. Nos.	 (r-5, c-6, t-7)-isomer	
		Melting points
5		156 to 158 °C
6		116 to 119 °C

Example 7

(1) 224 g of 3-thiophenecarbaldehyde and 265 g of methyl orthoformate are dissolved in 200 ml of methanol. One g of strongly acidic ion-exchange resin Amberlite IR-120(H^+) [manufactured by Rohm & Haas] is added thereto, and the mixture is refluxed with heating for 2 hours. The resin is separated by filtration, and the filtrate is condensed under reduced pressure. The residue is distilled to give 294 g of 3-dimethoxymethylthiophene .

B.p. 65 °C/533Pa(4mmHg)

(2) 10.0 g of the product obtained in paragraph (1) are dissolved in 100 ml of tetrahydrofuran. 45 ml of a 1.55M n-butyl lithium solution in hexane are added thereto under stirring at -70 to -50 °C for about 10 minutes. After the mixture is stirred at -70 to -60 °C for 30 minutes, a solution of 10.5 g of 3,4-dimethoxybenzaldehyde in 50 ml of tetrahydrofuran are added thereto. Said addition is carried out at a temperature of -70 to -50 °C for about 10 minutes. The mixture is stirred at the same temperature for 30 minutes, and then, poured into 300 ml of water. 500 ml of ethyl acetate are added thereto, and an organic layer is separated after shaking. Said organic layer is dried and evaporated under reduced pressure to remove the solvent. The residue is purified by silica gel column chromatography [solvent: hexane - ethyl acetate (2 : 1)]. The eluate is evaporated to remove the solvent. 18.0 g of 3-dimethoxymethyl-2-(α- hydroxy-3,4-dimethox-

ybenzyl)thiophene are obtained as an oil.

(3-a) 1.9 g of boric acid are added to a solution of one g of the product obtained in paragraph (2) in 20 ml of toluene, and the mixture is refluxed with heating. After cooled, the mixture is evaporated to remove the solvent, and 50 ml of ethyl acetate are added to the residue. The mixture is washed with water, dried and evaporated under reduced pressure to remove the solvent. The residue is purified by silica gel column chromatography [solvent: hexane - ethyl acetate (1: 1)], and the eluate is evaporated to remove the solvent. 470 mg of 2-(α-hydroxy-3,4-dimethoxybenzyl)thiophen-3-carbaldehyde are obtained as colorless crystals.

M.p. 90 to 91 °C

(3-b) 6.0 g of sodium hydride are suspended in 300 ml of tetrahydrofuran. A tetrahydrofuran solution containing 81.0 g of the product obtained in paragraph (2) and 18.8 ml of methyl iodide are added thereto successively. The mixture is stirred overnight. Water is added thereto and the mixture is extracted with chloroform. The extract is dried and evaporated under reduced pressure to remove the solvent. The residue is purified by silica gel column chromatography [solvent: hexane - ethyl acetate (1: 1)], and the eluate is condensed. 67.7 g of 3-dimethoxymethyl-2-(α-methoxy-3,4-dimethoxybenzyl)thiophene are obtained as an oil.

NMR($CDCl_3$, δ): 3.23 (s, 3H), 3.30 (s, 3H), 3.47 (s, 3H), 3.84 (s, 6H), 5.44 (s, 1H), 5.68 (s, 1H), 6.73 - 7.38 (m, 5H)

(4) 160 g of the product obtained in paragraph (3-a) are dissolved in 500 ml of methylene chloride. 60 ml of acetic anhydride and 0.5 g of 4-dimethylaminopyridine are added thereto. The mixture is cooled below 10 °C. 97 ml of triethylamine are added dropwise thereto at the same temperature, and the mixture is stirred at ambient temperature for one hour. Water is added to the reaction mixture. The organic layer is separated, and the aqueous layer is further extracted with methylene chloride. Both of the organic layers are combined, washed with aqueous sodium bicarbonate solution and water, dried and evaporated under reduced pressure to remove the solvent. The residue is recrystallized from toluene to give 162 g of 2-(α-acetoxy-3,4-dimethoxybenzyl)thiophen-3-carbaldehyde.

M.p. 91 to 92 °C

(5-a) 10.0 g of the product obtained in paragraph (2) and 4.3 g of dimethyl acetylenedicarboxylate are dissolved in 50 ml of toluene with heating. 0.05 ml of trifluoroacetic acid is added thereto, and the mixture is refluxed for 5 hours. The reaction mixture is evaporated under reduced pressure to remove the solvent. The residue is recrystallized from toluene to give 7.1 g of 4-hydroxy-5,6-bis(methoxycarbonyl)-7-(3,4-dimethoxyphenyl)benzo[b]thiophene as colorless prisms.

M.p. 147 to 148 °C

(5-b) 68.4 g of the product obtained in paragraph (3-a), 35 g of dimethyl acetylenedicarboxylate and 0.5 ml of trifluoroacetic acid are dissolved in 350 ml of toluene. The mixture is refluxed for 2 hours and evaporated under reduced pressure to remove the solvent. The residue is recrystallized from toluene to give 78.2 g of 4-hydroxy-5,6-bis(methoxycarbonyl)-7-(3,4-dimethoxyphenyl)benzo[b]thiophene as colorless prisms.

The physico-chemical properties of this product are identical with those of the product obtained in paragraph (5-a).

(5-c) 60 g of the product obtained in paragraph (4), 34.4 g of dimethyl acetylenedicarboxylate and 0.6 ml of trifluoroacetic acid are dissolved in 300 ml of benzene. The mixture is refluxed with heating for 10 hours. 0.3 ml of trifluoroacetic acid is added thereto, and the mixture is further refluxed for 5 hours. The reaction mixture is evaporated under reduced pressure to remove the solvent, and the residue is recrystallized from toluene. 60.3 g of 4-hydroxy-5,6-bis(methoxycarbonyl)-7-(3,4-dimethoxyphenyl)benzo[b]thiophene are obtained as colorless prisms.

The physico-chemical properties of this product are identical with those of the product obtained in paragraph (5-a).

(5-d) The product obtained in paragraph (3-b) is treated in the same manner as described in either one of (5-a), (5-b) or (5-c). 4-hydroxy-5,6-bis(methoxycarbonyl)-7-(3,4-dimethoxyphenyl)benzo[b]thiophene are obtained as colorless prisms.

The physico-chemical properties of this product are identical with those of the product obtained in paragraph (5-a).

(6) 35.0 g of the product obtained in either one of paragraph (5-a), (5-b), (5-c) or (5-d) are dissolved in 20 ml of N,N-dimethylformamide. The solution is added dropwise to a suspension of 4.17 g of sodium hydride in 100 ml of N,N-dimethylformamide. The mixture is stirred at ambient temperature for one hour. 14.8 g of methyl iodide are added thereto. The mixture is stirred at ambient temperature for 3 hours and evaporated under reduced pressure to remove the solvent. The residue is recrystallized from ethyl acetate to

give 22.6 g of 4-methoxy-5,6-bis(methoxycarbonyl)-7-(3,4-dimethoxyphenyl)benzo[b]thiophene.
M.p. 118 °C

(7) 4.0 g of sodium hydroxide are dissolved in a mixture of 30 ml of ethanol and 30 ml of water. 4.0 g of the product obtained in paragraph (6) are added thereto, and the mixture is refluxed with heating for 5 hours. After cooled down to ambient temperature, the mixture is acidified with diluted hydrochloric acid and extracted with ethyl acetate. The extract is dried and evaporated to remove the solvent. The residue is dried under reduced pressure and dissolved in 15 ml of acetic anhydride. The solution is refluxed with heating for one hour and evaporated under reduced pressure to remove the solvent. The residue is recrystallized from ethyl acetate to give 2.6 g of 4-methoxy-7-(3,4-dimethoxyphenyl)benzo[b]thiophen-5,6-dicarboxylic anhydride
M.p. 201 to 202 °C

Example 8

4-hydroxy-5,6-bis(methoxycarbonyl)-7-(3,4-dimethoxyphenyl)benzo[b]thiophene is treated in the same manner as described in Example 7-(7). The thus-obtained product is treated in the same manner as described in Example 7-(6) to give 4-methoxy-7-(3,4-dimethoxyphenyl)benzo[b]thiophen-5,6-dicarboxylic anhydride.
The physico-chemical properties of this product are identical with those of the product obtained in Example 7-(7).

Example 9

(1) 75.5 g of 4-hydroxy-5,6-bis(methoxycarbonyl)-7-(3,4-dimethoxyphenyl)benzo[b]thiophene are dissolved in 250 ml of tetrahydrofuran. 21.6 ml of 10M borane-dimethylsulfide complex are added dropwise thereto at a temperature below 10°C. The mixture is stirred at 10 °C for one hour. After slowly warmed up to ambient temperature, the mixture is stirred at the same temperature overnight and evaporated under reduced pressure to remove the solvent. 170 ml of methanol and 2 ml of trifluoroacetic acid are added to the residue, and the mixture is refluxed with heating for 12 hours. After the reaction mixture is cooled down to ambient temperature, crystalline precipitates are collected by filtration, washed with methanol and dried with air. 66.6 g of 4-hydroxy-5-hydroxymethyl-7-(3,4-dimethoxyphenyl)benzo[b]thiophen-6-carboxylic acid γ-lactone are obtained as pale yellow crystals.
M.p. 221 to 222 °C

(2) 22.2 g of the product obtained in paragraph (1) are added to a suspension of 1.86 g of sodium hydride in 350 ml of tetrahydrofuran. The mixture is stirred at ambient temperature for 30 minutes. 4.83 g of methyl iodide and 20 ml of N,N-dimethylformamide are added thereto. The mixture is stirred overnight. The reaction mixture is evaporated under reduced pressure to remove the solvent. The residue is recrystallized from toluene to give 18.8 g of 4-methoxy-5-hydroxymethyl-7-(3,4-dimethoxyphenyl)benzo[b]thiophen-6-carboxylic acid γ-lactone.
M.p. 186 °C

Example 10

4-methoxy-5,6-bis(methoxycarbonyl)-7-(3,4-dimethoxyphenyl)benzo[b]thiophene is treated in the same manner as described in Example 9-(1) to give 4-methoxy-5-hydroxymethyl-7-(3,4-dimethoxyphenyl)benzo[b]thiophen-6-carboxylic acid lactone.
The physico-chemical properties of this product are identical with those of the product obtained in Example 9-(2).

Example 11

(1) 20 g of 4-oxo-r-5-hydroxymethyl-t-7-(3,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[b]furan-c-6-carboxylic acid lactone, 54.4 g of cupric bromide and 5.30 g of lithium bromide are dissolved in 300 ml of acetonitrile. The mixture is stirred with heating for 15 hours. The reaction mixture is evaporated under reduced pressure to remove the solvent. Water is added to the residue. The mixture is acidified with hydrochloric acid and extracted with chloroform. The extract is dried and evaporated to remove the solvent. Diethyl ether is added to the residue, and crystalline precipitates are collected by filtration and dried. 11.9 g of 4-hydroxy-5-hydroxymethyl-7-(3,4-dimethoxyphenyl)benzo[b]furan-6-carboxylic acid lactone are obtained.
M.p. 255 °C

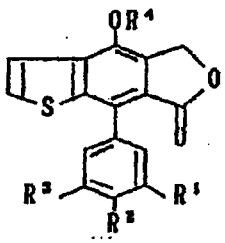
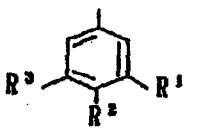
(2) A solution of 2.94 g of the product obtained in paragraph (1) in 10 ml of N,N-dimethylformamide are added dropwise to a suspension of 0.32 g of sodium hydride in 30 ml of N,N-dimethylformamide. The mixture is stirred at ambient temperature for 30 minutes. 1.92 g of methyl iodide are added thereto. The mixture is stirred at ambient temperature for 4 hours and evaporated under reduced pressure to remove the solvent. Water is added to the residue, and the mixture is extracted with chloroform. The extract is dried and evaporated under reduced pressure to remove the solvent. The residue is purified by silica gel column chromatography [solvent: hexane - ethyl acetate (1: 1)]. The eluate is condensed to give 1.65 g of 4-methoxy-5-hydroxymethyl-7-(3,4-dimethoxyphenyl)benzo[b]furan-6-carboxylic acid lactone.

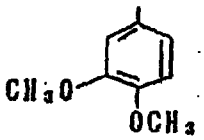
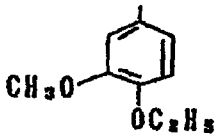
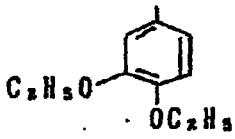
M.p. 214 °C

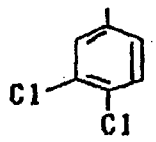
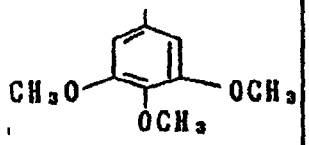
Examples 12 to 21

The corresponding starting materials are treated in the same manner either as described in Example 7-(1) to (5-d) and Example 9 or 10, or as described in Example 3 or 4 and Example 11 to give the compounds shown in the following Table 3.

Table 3

Ex. Nos.			
	R^4		Melting points
12	-CH_3		176 °C
13			183 °C

14	$-C_2H_5$		178 to 179 °C
15	$-(CH_2)_3CH_3$		180 to 182 °C
16	$-CH_2OCH_3$		176 °C
17	$-CH_2CO_2C_2H_5$		151 to 152 °C
18	$-CH_3$		186 to 187 °C
19			165 to 167 °C

20	-CH_3		210 °C
21			170 to 171 °C

Example 22

(1) 16.9 g of 3-dimethoxymethyl-2-(α-methoxy-3,4-dimethoxybenzyl)thiophene are dissolved in 200 ml of tetrahydrofuran. 37.5 ml of 1.6M n-butyl lithium in hexane are added dropwise thereto at -78 °C, and the reaction mixture is warmed up to -30 °C gradually. After the mixture is chilled at -78 °C, 4.3 ml of N,N-dimethylformamide are added thereto. The mixture is stirred for 30 minutes. The reaction mixture is warmed up to ambient temperature. The mixture is acidified with diluted sulfuric acid, stirred for one hour and extracted with chloroform. The extract is washed with aqueous sodium bicarbonate solution and water, dried and evaporated under reduced pressure to remove the solvent. The residue is purified by silica gel column chromatography [solvent: hexane - ethyl acetate (2: 1)], and the eluate is condensed. 14.6 g of 2-(α-methoxy-3,4-dimethoxybenzyl)thiophen-3,5-dicarbaldehyde are obtained as an oil.

NMR($CDCl_3$, δ): 3.40 (s, 3H), 3.86 (s, 6H), 6.05 (s, 1H), 6.78 - 7.12 (m, 3H), 8.02 (s, 1H), 9.86 (s, 1H), 9.99 (s, 1H)

(2) 14.6 g of the product obtained in paragraph (1), 7.4 ml of dimethyl acetylenedicarboxylate and one ml of trifluoroacetic acid are dissolved in 150 ml of benzene. The mixture is refluxed with heating for 20 hours and evaporated under reduced pressure to remove the solvent. The residue is purified by silica gel column chromatography [solvent: hexane - ethyl acetate (2: 1)], and the eluate is condensed. 8.33 g of 4-hydroxy-5,6-bis(methoxycarbonyl)-7-(3,4-dimethoxyphenyl)benzo[b]thiophen-2-carbaldehyde are obtained as an oil.

NMR($CDCl_3$, δ): 3.62 (s, 3H), 3.86 (s, 3H), 3.93 (s, 6H), 6.92 (s, 3H), 8.26 (s, 1H), 9.96 (s, 1H)

(3) 8.33 g of the product obtained in paragraph (2) are dissolved in 50 ml of tetrahydrofuran. 4.5 ml of 10M boranedimethylsulfide complex are added thereto under ice-cooling. The mixture is stirred at ambient temperature overnight and evaporated under reduced pressure to remove the solvent. 30 ml of methanol and catalytic amount of trifluoroacetic acid are added to the residue. The mixture is refluxed with heating for 3 hours and cooled down to ambient temperature. Crystalline precipitates are collected by filtration, washed with methanol and dried with air. 5.75 g of 4-hydroxy-2,5-bis(hydroxymethyl)-7-(3,4-dimethoxyphenyl)benzo[b]thiophen-6-carboxylic acid γ-lactone are obtained.

NMR(d_6-DMSO, δ): 3.75 (s, 3H), 3.93 (s, 3H), 4.63-4.87 (m, 2H), 5.26-5.38 (m, 2H), 5.50-5.85 (m, 1H), 6.93-7.13 (m, 3H), 7.52 (s, 1H)

(4) 1.25 g of the product obtained in paragraph (3), 0.70 g of potassium carbonate and 0.27 ml of methyl iodide are dissolved in 20 ml of N,N-dimethylformamide. The mixture is stirred at ambient temperature for 4 hours and evaporated under reduced pressure to remove the solvent. Water is added to the residue, and the mixture is extracted with chloroform. The extract is dried and evaporated under reduced pressure to remove the solvent. The residue is purified by silica gel column chromatography [solvent: ethyl acetate], and the eluate is condensed. 0.97 g of 2,5-bis(hydroxymethyl)-4-methoxy-7-(3,4-dimethoxyphenyl)benzo[b]thiophen-6-carboxylic acid γ-lactone is obtained.

M.p. 164 °C

Example 23

1.25 g of 4-hydroxy-2,5-bis(hydroxymethyl)-7-(3,4-dimethoxyphenyl)benzo[b]thiophen-6-carboxylic acid γ-lactone are dissolved in 5 ml of N,N-dimethylformamide. Said solution is added dropwise to a suspension of 0.20 g of sodium hydride in 20 ml of N,N-dimethylformamide. The mixture is stirred at ambient temperature for 30 minutes. 1.20 g of methyl iodide are added thereto. The mixture is stirred at ambient temperature for 3 hours and evaporated under reduced pressure to remove the solvent. The water is added to the residue, and the mixture is extracted with chloroform. The extract is dried and evaporated under reduced pressure to remove the solvent. The residue is purified by silica gel column chromatography [solvent: ethyl acetate], and the eluate is condensed. 0.97 g of 2-methoxymethyl-4-methoxy-5-hydroxymethyl-7-(3,4-dimethoxyphenyl)benzo[b]thiophen-6-carboxylic acid lactone is obtained.
M.p. 175 to 176 °C

Example 24

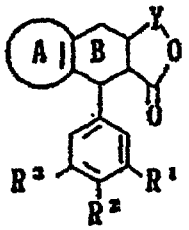
2,5-bis(hydroxymethyl)-4-methoxy-7-(3,4-dimethoxyphenyl)benzo[b]thiophen-6-carboxylic acid γ-lactone is treated in the same manner as described in Example 23. 2-methoxymethyl-4-methoxy-5-hydroxymethyl-7-(3,4-dimethoxyphenyl)benzo[b]thiophen-6-carboxylic acid lactone is obtained.

The physico-chemical properties of this product are identical with those of the product obtained in Example 23.

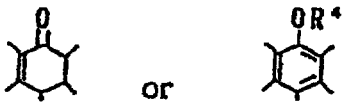
Claims

Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. A biphenyl derivative of the formula



wherein Ring A is a thiophene or furan ring which may have a substituent selected from formyl group, a C_1-C_4 alkoxy-methyl group and hydroxymethyl group; Ring B is a ring of the formula:



each of R^1 to R^3 is hydrogen atom, a halogen atom or C_1-C_4 alkoxy group, or R^1 is hydrogen atom, and R^2 and R^3 are combined together to form a C_1-C_4 alkylenedioxy group; R^4 is a C_1-C_4 alkyl group which may have a substituent selected from a C_1-C_4 alkoxy group and a C_1-C_4 alkoxy-carbonyl group; Y is methylene group or carbonyl group, or a pharmaceutically acceptable salt thereof.

2. A compound as claimed in claim 1, in which each of R^1 to R^3 is hydrogen atom, a halogen atom or a C_1-C_4 alkoxy group.

3. A compound as claimed in claim 2, in which Ring A is thiophene or furan ring which may be substituted with hydroxymethyl group, R^1 is hydrogen atom or a C_1-C_4 alkoxy group, each of R^2 and R^3 is a C_1-C_4 alkoxy group, and R^4 is a C_1-C_4 alkyl group.

4. A compound as claimed in claim 3, in which Ring A is thiophene ring, Ring B is a ring of the formula

Example 23

1.25 g of 4-hydroxy-2,5-bis(hydroxymethyl)-7-(3,4-dimethoxyphenyl)benzo[b]thiophen-6-carboxylic acid γ-lactone are dissolved in 5 ml of N,N-dimethylformamide. Said solution is added dropwise to a suspension of 0.20 g of sodium hydride in 20 ml of N,N-dimethylformamide. The mixture is stirred at ambient temperature for 30 minutes. 1.20 g of methyl iodide are added thereto. The mixture is stirred at ambient temperature for 3 hours and evaporated under reduced pressure to remove the solvent. The water is added to the residue, and the mixture is extracted with chloroform. The extract is dried and evaporated under reduced pressure to remove the solvent. The residue is purified by silica gel column chromatography [solvent: ethyl acetate], and the eluate is condensed. 0.97 g of 2-methoxymethyl-4-methoxy-5-hydroxymethyl-7-(3,4-dimethoxyphenyl)benzo[b]thiophen-6-carboxylic acid lactone is obtained.
M.p. 175 to 176 °C

Example 24

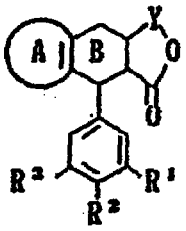
2,5-bis(hydroxymethyl)-4-methoxy-7-(3,4-dimethoxyphenyl)benzo[b]thiophen-6-carboxylic acid γ-lactone is treated in the same manner as described in Example 23. 2-methoxymethyl-4-methoxy-5-hydroxymethyl-7-(3,4-dimethoxyphenyl)benzo[b]thiophen-6-carboxylic acid lactone is obtained.

The physico-chemical properties of this product are identical with those of the product obtained in Example 23.

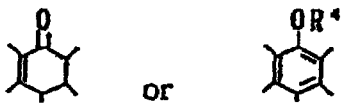
Claims

Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. A biphenyl derivative of the formula



wherein Ring A is a thiophene or furan ring which may have a substituent selected from formyl group, a C_1-C_4 alkoxy-methyl group and hydroxymethyl group; Ring B is a ring of the formula:

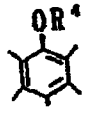


each of R^1 to R^3 is hydrogen atom, a halogen atom or C_1-C_4 alkoxy group, or R^1 is hydrogen atom, and R^2 and R^3 are combined together to form a C_1-C_4 alkylenedioxy group; R^4 is a C_1-C_4 alkyl group which may have a substituent selected from a C_1-C_4 alkoxy group and a C_1-C_4 alkoxy-carbonyl group; Y is methylene group or carbonyl group, or a pharmaceutically acceptable salt thereof.

2. A compound as claimed in claim 1, in which each of R^1 to R^3 is hydrogen atom, a halogen atom or a C_1-C_4 alkoxy group.

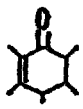
3. A compound as claimed in claim 2, in which Ring A is thiophene or furan ring which may be substituted with hydroxymethyl group, R^1 is hydrogen atom or a C_1-C_4 alkoxy group, each of R^2 and R^3 is a C_1-C_4 alkoxy group, and R^4 is a C_1-C_4 alkyl group.

4. A compound as claimed in claim 3, in which Ring A is thiophene ring, Ring B is a ring of the formula



R^1 is hydrogen atom, each of R^2 and R^3 is methoxy group, and R^4 is methyl group.

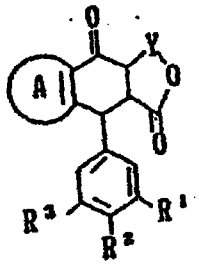
5. A compound as claimed in claim 3, in which Ring A is furan ring which may be substituted with hydroxymethyl group, Ring B is a ring of the formula



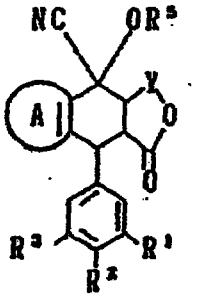
R^1 is hydrogen atom, each of R^2 and R^3 is methoxy group, and Y is methylene group.

6. A pharmaceutical composition which comprises a pharmaceutically effective amount of the compound claimed in either one of claims 1-5 and a pharmaceutically acceptable carrier, diluent or disintegrant.

7. A process for preparing a biphenyl derivative of the formula:

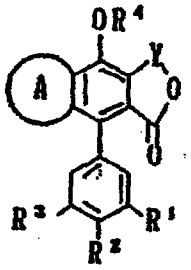


wherein Ring A is a thiophene or furan ring which may have a substituent selected from formyl group, a C_1-C_4 alkoxy-methyl group and hydroxymethyl group; each of R^1 to R^3 is hydrogen atom, a halogen atom or a C_1-C_4 alkoxy group, or R^1 is hydrogen atom, and R^2 and R^3 are combined together to form a C_1-C_4 alkylenedioxy group; Y is methylene group or carbonyl group, or a pharmaceutically acceptable salt thereof, which comprises treating a tetrahydrobiphenyl compound of the formula:

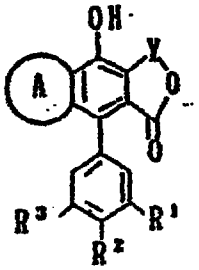


wherein OR^5 is a protected hydroxy group, and Ring A, R^1 to R^3 and Y are the same as defined above, or a salt thereof with a fluorine ion-donor, and, if required, converting the product into a pharmaceutically acceptable salt thereof.

8. A process for preparing a biphenyl derivative of the formula:



wherein Ring A is a thiophene or furan ring which may have a substituent selected from formyl group, a C_1-C_4 alkoxy-methyl group and hydroxymethyl group; each of R^1 to R^3 is hydrogen atom, a halogen atom or a C_1-C_4 alkoxy group, or R^1 is hydrogen atom, and R^2 and R^3 are combined together to form a C_1-C_4 alkylenedioxy group; R^4 is a C_1-C_4 alkyl group which may have a substituent selected from a C_1-C_4 alkoxy group and a C_1-C_4 alkoxy-carbonyl group; Y is methylene group or carbonyl group, or a pharmaceutically acceptable salt thereof, which comprises condensing a hydroxy-biphenyl compound of the formula:

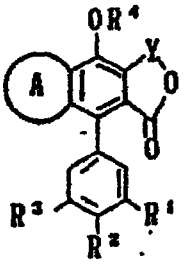


wherein Ring A, R^1 to R^3 and Y are the same as defined above, or a salt thereof with a compound of the formula

$$R^4\text{-}X$$

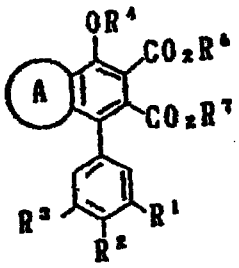
wherein X is a leaving group, and R^4 is the same as defined above, and, if required, converting the product into a pharmaceutically acceptable salt thereof.

9. A process for preparing a biphenyl derivative of the formula:



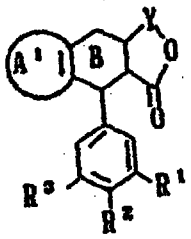
wherein Ring A is a thiophene or furan ring which may have a substituent selected from formyl group, a C_1-C_4 alkoxy-methyl group and hydroxymethyl group; each of R^1 to R^3 is hydrogen atom, a halogen atom or a C_1-C_4 alkoxy group, or R^1 is hydrogen atom, and R^2 and R^3 are combined together to form a C_1-C_4 alkylenedioxy group; R^4 is a C_1-C_4 alkyl group which may have a substituent selected from a C_1-C_4 alkoxy group and a C_1-C_4 alkoxy-carbonyl group; Y is methylene group or carbonyl group, or a pharmaceutically acceptable salt thereof, which comprises either

(1) subjecting a dicarboxylate compound of the formula:

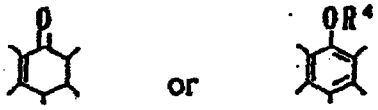


wherein each of R^6 and R^7 is a C_1-C_4 alkyl group, and Ring A and R^1 to R^4 are the same as defined above, or a salt thereof to reductive lactonization or
(2) hydrolyzing the dicarboxylate compound or a salt thereof followed by dehydration, and, if required, converting the product into a pharmaceutically acceptable salt thereof.

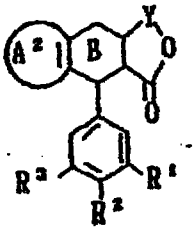
10. A process for preparing a biphenyl derivative of the formula:



wherein Ring A^1 is a thiophene or furan ring substituted with hydroxy-methyl group or a C_1-C_4 alkoxy methyl group; Ring B is a ring of the formula

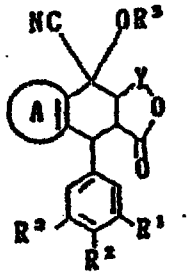


each of R^1 to R^3 is hydrogen atom, a halogen atom or a C_1-C_4 alkoxy group, or R_1 is hydrogen atom, and R^2 and R^3 are combined together to form a C_1-C_4 alkylenedioxy group; R^4 is a-C_1-C_4 alkyl group which may have a substituent selected from a C_1-C_4 alkoxy group and a C_1-C_4 alkoxy-carbonyl group; Y is methylene group or carbonyl group, or a pharmaceutically acceptable salt thereof, which comprises reducing a biphenyl derivative of the formula



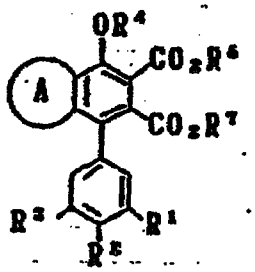
wherein Ring A^2 is a thiophene or furan ring substituted with formyl group, and Ring B, R^1 to R^4 and Y are the same as defined above, or a salt thereof and,
if necessary, alkylating the product, and,
if required, further converting the product into a pharmaceutically acceptable salt thereof.

11. A tetrahydrobiphenyl compound of the formula:



wherein Ring A is a thiophene or furan ring which may have a substituent selected from formyl group, a C_1-C_4 alkoxy-methyl group and hydroxymethyl group; each of R^1 to R^3 is hydrogen atom, a halogen atom or a C_1-C_4 alkoxy group, or R^1 is hydrogen atom, and R^2 and R^3 are combined together to form a C_1-C_4 alkylenedioxy group; OR^5 is a protected hydroxy group; Y is methlyene group or carbonyl group, or a salt thereof.

12. A dicarboxylate compound of the formula:

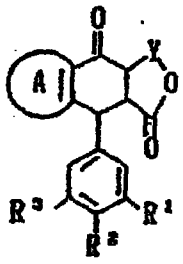


wherein Ring A is a thiophene or furan ring which may have a substituent selected from formyl group, a C_1-C_4 alkoxy-methyl group and hydroxymethyl group; each of R^1 to R^3 is hydrogen atom, a halogen atom or a C_1-C_4 alkoxy group, or R^1 is hydrogen atom, and R^2 and R^3 are combined together to form a C_1-C_4 alkylenedioxy group; R^4 is a C_1-C_4 alkyl group which may have a substituent selected from a C_1-C_4 alkoxy group and a C_1-C_4 alkoxy-carbonyl group; each of R^6 and R^7 is a C_1-C_4 alkyl group, or a salt thereof.

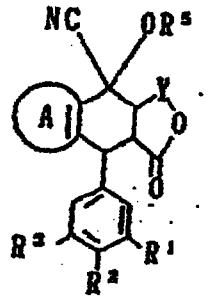
13. The use of a compound according to any of the preceding claims 1-5 for the making of a medicament for hepatic diseases.

Claims for the following Contracting States : ES, GR

1. A process for preparing a biphenyl derivative of the formula:

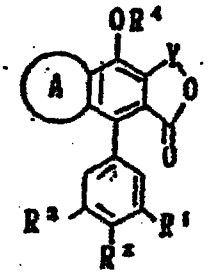


wherein Ring A is a thiophene or furan ring which may have a substituent selected from formyl group, a C_1-C_4 alkoxy-methyl group and hydroxymethyl group; each of R^1 to R^3 is hydrogen atom, a halogen atom or a C_1-C_4 alkoxy group, or R^1 is hydrogen atom, and R^2 and R^3 are combined together to form a C_1-C_4 alkylenedioxy group; Y is methylene group or carbonyl group, or a pharmaceutically acceptable salt thereof, which comprises treating a tetrahydrobiphenyl compound of the formula:

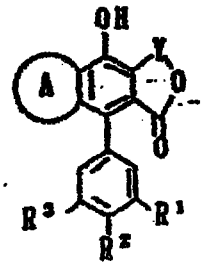


wherein OR^5 is a protected hydroxy group, and Ring A, R^1 to R^3 and Y are the same as defined above, or a salt thereof with a fluorine ion-donor, and, if required, converting the product into a pharmaceutically acceptable salt thereof.

2. A process for preparing a biphenyl derivative of the formula:



wherein Ring A is a thiophene or furan ring which may have a substituent selected from formyl group, a C_1-C_4 alkoxy-methyl group and hydroxymethyl group; each of R^1 to R^3 is hydrogen atom, a halogen atom or a C_1-C_4 alkoxy group, or R^1 is hydrogen atom, and R^2 and R^3 are combined together to form a C_1-C_4 alkylenedioxy group; R^4 is a C_1-C_4 alkyl group which may have a substituent selected from a C_1-C_4 alkoxy group and a C_1-C_4 alkoxy-carbonyl group; Y is methylene group or carbonyl group, or a pharmaceutically acceptable salt thereof, which comprises condensing a hydroxy-biphenyl compound of the formula:

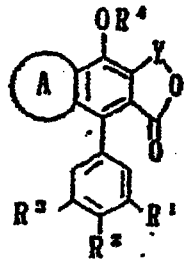


wherein Ring A, R^1 to R^3 and Y are the same as defined above, or a salt thereof with a compound of the formula

$$R^4\text{-}X$$

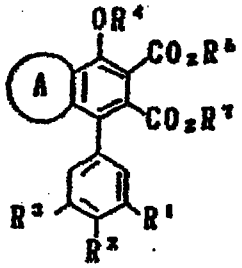
wherein X is a leaving group, and R^4 is the same as defined above, and, if required, converting the product into a pharmaceutically acceptable salt thereof.

3. A process for preparing a biphenyl derivative of the formula:



wherein Ring A is a thiophene or furan ring which may have a substituent selected from formyl group, a C_1-C_4 alkoxy-methyl group and hydroxymethyl group; each of R^1 to R^3 is hydrogen atom, a halogen atom or a C_1-C_4 alkoxy group, or R^1 is hydrogen atom, and R^2 and R^3 are combined together to form a C_1-C_4 alkylenedioxy group; R^4 is a C_1-C_4 alkyl group which may have a substituent selected from a C_1-C_4 alkoxy group and a C_1-C_4 alkoxy-carbonyl group; Y is methylene group or carbonyl group, or a pharmaceutically acceptable salt thereof, which comprises either

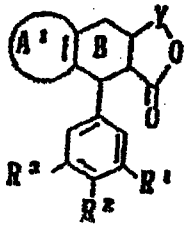
(1) subjecting a dicarboxylate compound of the formula:



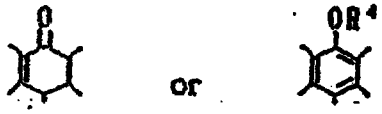
wherein each of R^6 and R^7 is a C_1-C_4 alkyl group, and Ring A and R^1 to R^4 are the same as defined above, or a salt thereof to reductive lactonization or

(2) hydrolyzing the dicarboxylate compound or a salt thereof followed by dehydration, and, if required, converting the product into a pharmaceutically acceptable salt thereof.

4. A process for preparing a biphenyl derivative of the formula:

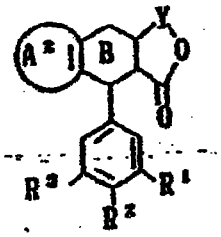


wherein Ring A^1 is a thiophene or furan ring substituted with hydroxy-methyl group or a C_1-C_4 alkoxy methyl group; Ring B is a ring of the formula



each of R^1 to R^3 is hydrogen atom, a halogen atom or a C_1-C_4 alkoxy group, or R_1 is hydrogen atom, and R^2 and R^3 are combined together to form a C_1-C_4 alkylenedioxy group; R^4 is a C_1-C_4 alkyl group which may have a substituent selected from a C_1-C_4 alkoxy group and a C_1-C_4 alkoxy-carbonyl group; Y is methylene group or carbonyl group, or a pharmaceutically acceptable salt thereof, which comprises reducing

a biphenyl derivative of the formula



wherein Ring A^2 is a thiophene or furan ring substituted with formyl group, and Ring B, R^1 to R^4 and Y are the same as defined above, or a salt thereof and,

if necessary, alkylating the product, and,

if required, further converting the product into a pharmaceutically acceptable salt thereof.

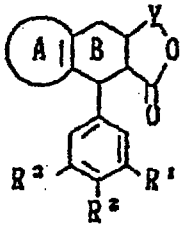
5. The use of a compound obtainable according to a process according to any of the claims 1-4 for the making of a medicament for treating hepatic diseases.

6. A method for preparing a pharmaceutical composition by combining a pharmaceutically effective amount of a biphenyl derivative as defined in any of claims 1-4 with a pharmaceutically acceptable carrier, diluent or disintegrant.

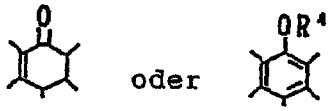
Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Biphenylderivat der Formel



wobei Ring A ein Thiophen- oder Furanring ist, der einen Substituenten, ausgewählt aus Formylgruppe, einer C_1-C_4-Alkoxy-methylgruppe und Hydroxymethylgruppe, haben kann; Ring B ein Ring der Formel



ist, wobei jeder der Reste R^1 bis R^3 Wasserstoffatom, ein Halogenatom oder eine C_1-C_4-Alkoxygruppe ist, oder R^1 Wasserstoffatom ist, und R^2 und R^3 miteinander unter Bildung einer C_1-C_4-Alkylendioxygruppe verbunden sind; R^4 eine C_1-C_4-Alkylgruppe ist, die einen Substituenten, ausgewählt aus einer C_1-C_4-Alkoxygruppe und einer C_1-C_4-Alkoxy-carbonylgruppe haben kann; Y Methylengruppe oder Carbonylgruppe ist, oder ein pharmazeutisch geeignetes Salz davon.

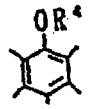
2. Verbindung nach Anspruch 1, wobei jeder der Reste R^1 bis R^3 Wasserstoffatom, ein Halogenatom oder eine C_1-C_4-Alkoxygruppe ist.

3. Verbindung nach Anspruch 2, wobei der Ring A Thiophen- oder Furan-Ring ist, welcher mit Hydroxymethylgruppe substituiert sein kann, R^1 Wasserstoffatom oder eine C_1-C_4-Alkoxygruppe ist, sowohl R^2 wie

* C L M S *

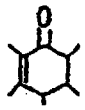
auch R^3 ein C_1-C_4-Alkoxygruppe sind, und R^4 eine C_1-C_4-Alkylgruppe ist.

4. Verbindung nach Anspruch 3, wobei der Ring A Thiophenring ist, Ring B ein Ring der Formel



ist, R^1 Wasserstoffatom ist, sowohl R^2 wie auch R^3 Methoxygruppe sind, und R^4 Methylgruppe ist.

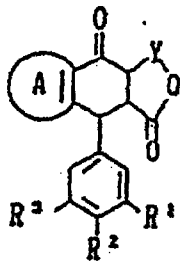
5. Verbindung nach Anspruch 3, wobei Ring A Furanring ist, welcher durch Hydroxymethylgruppe substituiert sein kann, Ring B ein Ring der Formel



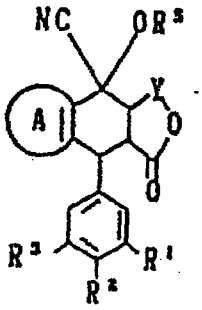
ist, R^1 Wasserstoffatom ist, sowohl R^2 wie auch R^3 Methoxygruppe sind, und Y Methylengruppe ist.

6. Pharmazeutische Zusammensetzung, umfassend eine pharmazeutisch wirksame Menge der in einem der Ansprüche 1 bis 5 beanspruchten Verbindung und einen pharmazeutisch geeigneten Träger, Verdünnungsmittel oder Auflösemittel.

7. Verfahren zum Herstellen eines Biphenylderivats der Formel



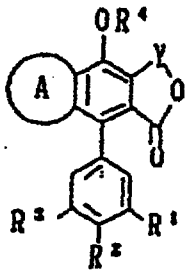
wobei Ring A ein Thiophen- oder Furanring ist, welcher einen Substituenten, ausgewählt aus Formylgruppe, einer C_1-C_4-Alkoxy-methylgruppe und Hydroxymethylgruppe haben kann; jeder der Reste R^1 bis R^3 Wasserstoffatom, ein Halogenatom oder eine C_1-C_4-Alkoxygruppe ist, oder R^1 Wasserstoffatom ist und R^2 und R^3 miteinander unter Bildung einer C_1-C_4-Alkylendioxygruppe verbunden sind; Y Methylengruppe oder Carbonylgruppe ist,
oder eines pharmazeutisch verträglichen Salzes davon, umfassend Behandeln einer Tetrahydrobiphenylverbindung der Formel:



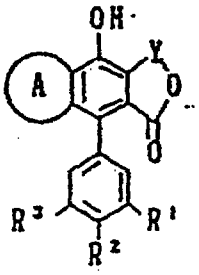
wobei OR^5 eine geschützte Hydroxygruppe ist, und Ring A, R^1 bis R^3 und Y wie zuvor angegeben definiert

sind, oder eines Salzes davon mit einem Fluorionendonor, und, auf Verlangen, Umwandeln des Produkts in ein pharmazeutisch verträgliches Salz davon.

8. Verfahren zum Herstellen eines Biphenylderivats der Formel:



wobei Ring A ein Thiophen- oder Furanring ist, welcher einen Substituenten aus Formylgruppe, einer C_1-C_4-Alkoxy-methylgruppe und Hydroxymethylgruppe haben kann; jeder der Reste R^1 bis R^3 Wasserstoffatom, ein Halogenatom oder eine C_1-C_4-Alkoxygruppe ist, oder R^1 Wasserstoffatom ist, und R^2 und R^3 unter Bildung einer C_1-C_4-Alkylendioxygruppe miteinander verbunden sind; R^4 eine C_1-C_4-Alkylgruppe ist, die einen Substituenten, ausgewählt aus einer C_1-C_4-Alkoxygruppe und einer C_1-C_4-Alkoxy-carbonylgruppe haben kann; Y Methylengruppe oder Carbonylgruppe ist,
oder eines pharmazeutisch verträglichen Salzes davon, umfassend Kondensieren einer Hydroxybiphenylverbindung der Formel:

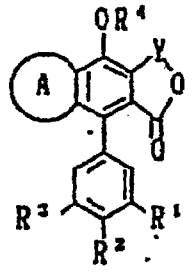


wobei Ring A, R^1 bis R^3 und Y wie zuvor angegeben definiert sind, oder eines Salzes davon mit einer Verbindung der Formel

$$R^4\text{-}X,$$

wobei X eine Abgangsgruppe ist, und R^4 wie zuvor angegeben definiert ist, und gewünschtenfalls Umwandeln des Produktes in ein pharmazeutisch geeignetes Salz davon.

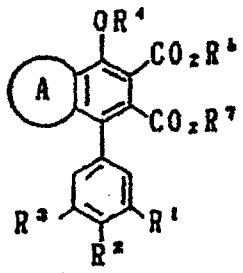
9. Verfahren zum Herstellen eines Biphenylderivats der Formel:



wobei Ring A ein Thiophen- oder Furanring ist, welcher einen Substituenten, ausgewählt aus Formylgruppe, einer C_1-C_4-Alkoxy-methylgruppe und Hydroxymethylgruppe haben kann; jeder der Reste R^1 bis R^3 Wasserstoffatom, ein Halogenatom oder eine C_1-C_4-Alkoxygruppe ist, oder R^1 Wasserstoffatom ist, und R^2 und R^3 miteinander unter Bildung einer C_1-C_4-Alkylendioxygruppe verbunden sind; R^4 eine C_1-C_4-Alkylgruppe ist, die einen Substituenten, ausgewählt aus einer C_1-C_4-Alkoxygruppe und einer C_1-C_4-Alkoxy-

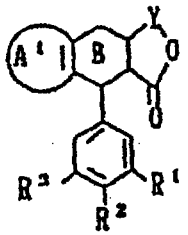
* C L M S *

carbonylgruppe, haben kann; Y Methylengruppe oder Carbonylgruppe ist,
oder eines pharmazeutisch verträglichen Salzes davon, umfassend entweder
(1) reduzierende Lactonisierung einer Dicarboxylatverbindung der Formel:

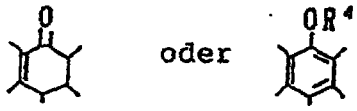


wobei sowohl R^6 wie auch R^7 eine C_1-C_4-Alkylgruppe ist, und Ring A und R^1 bis R^4 wie zuvor angegeben definiert sind, oder eines Salzes davon, oder
(2) Hydrolysieren der Dicarboxylatverbindung oder eines Salzes davon mit anschließender Dehydratisierung und, auf Verlangen, Umwandeln des Produktes in ein pharmazeutisch geeignetes Salz davon.

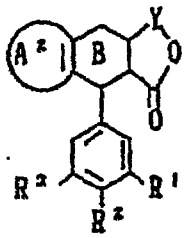
10. Verfahren zum Herstellen eines Biphenylderivats der Formel:



wobei Ring A^1 ein Thiophen- oder Furanring ist, der mit Hydroxy-methylgruppe oder einer C_1-C_4-Alkoxy-methylgruppe substituiert ist; Ring B ein Ring der Formel



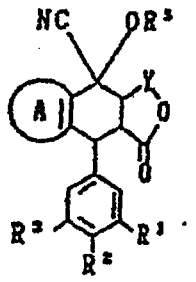
ist, wobei jeder der Reste R^1 bis R^3 Wasserstoffatom, ein Halogenatom oder eine C_1-C_4-Alkoxygruppe ist, oder R^1 Wasserstoffatom ist, und R^2 und R^3 unter Bildung einer C_1-C_4-Alkylendioxygruppe miteinander verbunden sind; R^4 eine C_1-C_4-Alkylgruppe ist, die einen Substituenten, ausgewählt aus einer C_1-C_4-Alkoxygruppe und einer C_1-C_4-Alkoxy-carbonylgruppe, haben kann; Y Methylengruppe oder Carbonylgruppe ist,
oder eines pharmazeutisch verträglichen Salzes davon, umfassend
Reduzieren eines Biphenylderivats der Formel



wobei Ring A^2 ein Thiophen- oder Furanring ist, der durch Formylgruppe substituiert ist, und Ring B, R^1

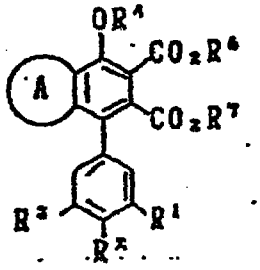
bis R^4 und Y wie zuvor angegeben definiert sind, oder eines Salzes davon, und, erforderlichenfalls, Alkylieren des Produktes, und, auf Verlangen, zusätzliches Umwandeln des Produktes in ein pharmazeutisch geeignetes Salz davon.

11. Tetrahydrobiphenylverbindung der Formel:



wobei Ring A ein Thiophen- oder Furanring ist, der einen Substituenten, ausgewählt aus Formylgruppe, einer C_1-C_4-Alkoxy-methylgruppe und Hydroxymethylgruppe, haben kann; jeder der Reste R^1 bis R^3 Wasserstoffatom, ein Halogenatom oder eine C_1-C_4-Alkoxygruppe ist, oder R^1 Wasserstoffatom ist und R^2 und R^3 miteinander unter Bildung einer C_1-C_4-Alkylendioxygruppe verbunden sind; OR^5 eine geschützte Hydroxygruppe ist; Y Methylengruppe oder Carbonylgruppe ist, oder ein Salz davon.

12. Dicarboxylatverbindung der Formel:

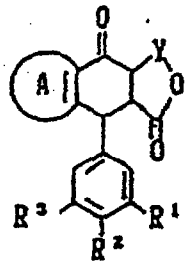


wobei Ring A ein Thiophen- oder Furanring ist, der einen Substituenten, ausgewählt aus Formylgruppe, einer C_1-C_4-Alkoxy-methylgruppe und Hydroxymethylgruppe, haben kann; jeder der Reste R^1 bis R^3 Wasserstoffatom, ein Halogenatom oder eine C_1-C_4-Alkoxygruppe ist, oder R^1 Wasserstoffatom ist und R^2 und R^3 miteinander unter Bildung einer C_1-C_4-Alkylendioxygruppe verbunden sind; R^4 eine C_1-C_4-Alkylgruppe ist, die einen Substituenten, ausgewählt aus einer C_1-C_4-Alkoxygruppe und einer C_1-C_4-Alkoxy-carbonylgruppe, haben kann; sowohl R^6 wie auch R^7 eine C_1-C_4-Alkylgruppe sind, oder ein Salz davon.

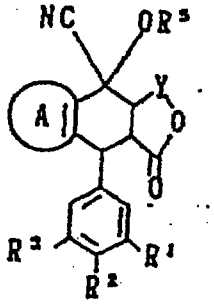
13. Verwendung einer Verbindung nach einem der vorhergehenden Ansprüche 1 bis 5 für die Herstellung eines Arzneimittels für die Behandlung von Lebererkrankungen.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zum Herstellen eines Biphenylderivats der Formel:

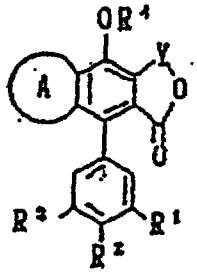


wobei Ring A ein Thiophen- oder Furanring ist, der einen Substituenten, ausgewählt aus Formylgruppe, einer C_1-C_4-Alkoxy-methylgruppe und Hydroxymethylgruppe, haben kann; jeder der Reste R^1 bis R^3 ist Wasserstoffatom, ein Halogenatom oder eine C_1-C_4-Alkoxygruppe, oder R^1 ist Wasserstoffatom und R^2 und R^3 sind unter Bildung einer C_1-C_4-Alkylendioxygruppe miteinander verbunden; Y ist Methylengruppe oder Carbonylgruppe, oder eines pharmazeutisch verträglichen Salzes davon, umfassend Behandeln einer Tetrahydrobiphenylverbindung der Formel:

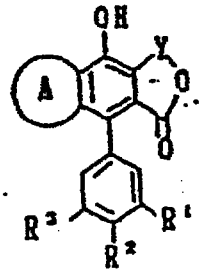


wobei OR^5 eine geschützte Hydroxygruppe ist, und Ring A, R^1 bis R^3 und Y wie zuvor angegeben definiert sind, oder eines Salzes davon mit einem Fluorionendonor, und, auf Verlangen, Umwandeln des Produktes in ein pharmazeutisch verträgliches Salz davon.

2. Verfahren zum Herstellen eines Biphenylderivats der Formel:



wobei Ring A ein Thiophen- oder Furanring ist, der einen Substituenten, ausgewählt aus Formylgruppe, einer C_1-C_4-Alkoxy-methylgruppe und Hydroxymethylgruppe, haben kann; jeder der Reste R^1 bis R^3 Wasserstoffatom, ein Halogenatom oder eine C_1-C_4-Alkoxygruppe ist, oder R^1 Wasserstoffatom ist, und R^2 und R^3 miteinander unter Bildung einer C_1-C_4-Alkylendioxygruppe verbunden sind; R^4 eine C_1-C_4-Alkylgruppe ist, die einen Substituenten, ausgewählt aus einer C_1-C_4-Alkoxygruppe und einer C_1-C_4-Alkoxycarbonylgruppe, haben kann; Y Methylengruppe oder Carbonylgruppe ist,
oder eines pharmazeutisch verträglichen Salzes davon, umfassend Kondensieren einer Hydroxybiphenylverbindung der Formel:

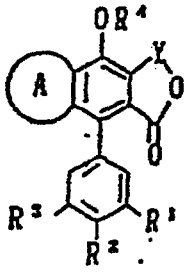


wobei Ring A, R^1 bis R^3 und Y wie zuvor angegeben definiert sind, oder eines Salzes davon mit einer Verbindung der Formel

$$R^4\text{-}X,$$

wobei X eine Abgangsgruppe ist, und R^4 wie zuvor angegeben definiert ist, und gewünschtenfalls Umwandeln des Produktes in ein pharmazeutisch geeignetes Salz davon.

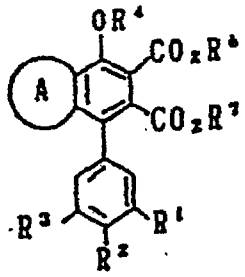
3. Verfahren zum Herstellen eines Biphenylderivats der Formel:



wobei Ring A ein Thiophen- oder Furanring ist,
welcher einen Substituenten, ausgewählt aus Formylgruppe, einer C_1-C_4-Alkoxy-methylgruppe und Hydroxymethylgruppe haben kann; jeder der Reste R^1 bis R^3 Wasserstoffatom, ein Halogenatom oder eine C_1-C_4-Alkoxygruppe ist, oder R^1 Wasserstoffatom ist, und R^2 und R^3 miteinander unter Bildung einer C_1-C_4-Alkylendioxygruppe verbunden sind; R^4 eine C_1-C_4-Alkylgruppe ist, die einen Substituenten, ausgewählt aus einer C_1-C_4-Alkoxygruppe und einer C_1-C_4-Alkoxy-carbonylgruppe, haben kann; Y Methylengruppe oder Carbonylgruppe ist,

oder eines pharmazeutisch verträglichen Salzes davon, umfassend entweder

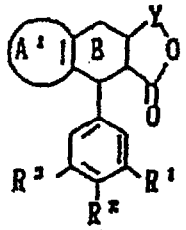
(1) reduzierende Lactonisierung einer Dicarboxylatverbindung der Formel:



wobei sowohl R^6 wie auch R^7 eine C_1-C_4-Alkylgruppe ist, und Ring A und R^1 bis R^4 wie zuvor angegeben definiert sind, oder eines Salzes davon, oder

(2) Hydrolysieren der Dicarboxylatverbindung oder eines Salzes davon mit anschließender Dehydratisierung und, auf Verlangen, Umwandeln des Produktes in ein pharmazeutisch geeignetes Salz davon.

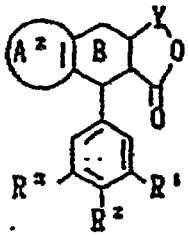
4. Verfahren zum Herstellen eines Biphenylderivats der Formel:



wobei Ring A^1 ein Thiophen- oder Furanring ist, der mit Hydroxy-methylgruppe oder einer C_1-C_4-Alkoxy-methylgruppe substituiert ist; Ring B ein Ring der Formel



ist, wobei jeder der Reste R^1 bis R^3 Wasserstoffatom, ein Halogenatom oder eine C_1-C_4-Alkoxygruppe ist, oder R^1 Wasserstoffatom ist, und R^2 und R^3 unter Bildung einer C_1-C_4-Alkylendioxygruppe miteinander verbunden sind; R^4 eine C_1-C_4-Alkylgruppe ist, die einen Substituenten, ausgewählt aus einer C_1-C_4-Alkoxygruppe und einer C_1-C_4-Alkoxy-carbonylgruppe, haben kann; Y Methylengruppe oder Carbonylgruppe ist,
oder eines pharmazeutisch verträglichen Salzes davon, umfassend
Reduzieren eines Biphenylderivats der Formel



wobei Ring A^2 ein Thiophen- oder Furanring ist, der durch Formylgruppe substituiert ist, und Ring B, R^1 bis R^4 und Y wie zuvor angegeben definiert sind, oder eines Salzes davon, und, erforderlichenfalls, Alkylieren des Produktes, und, auf Verlangen, zusätzliches Umwandeln des Produktes in ein pharmazeutisch geeignetes Salz davon.

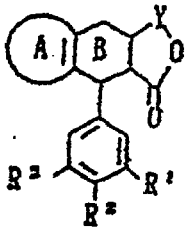
5. Verwendung einer gemäß einem Verfahren nach einem der Ansprüche 1 bis 4 erhältlichen Verbindung zum Herstellen eines Medikamentes zum Behandeln von Leberkrankheiten.

6. Verfahren zum Herstellen einer pharmazeutischen Zusammensetzung durch Verbinden einer pharmazeutisch wirksamen Menge eines Biphenylderivats, wie in einem der Ansprüche 1 bis 4 definiert, mit einem pharmazeutisch geeigneten Träger, Verdünnungsmittel oder Auflösungsmittel.

Revendications

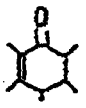
Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Dérivé biphénylique de formule :

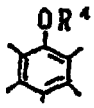


(I)

dans laquelle le cycle A est un cycle thiophène ou furanne qui peut porter un substituant choisi parmi les groupes formyle, (alcoxy en C_1-C_4)méthyle et hydroxyméthyle, le cycle B est un cycle de formule :



ou

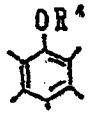


chacun des symboles R^1 à R^3 représente un atome d'hydrogène ou d'halogène ou un groupe alcoxy en C_1-C_4, ou bien R^1 représente un atome d'hydrogène et R^2 et R^3 forment, réunis ensemble, un groupe alkylènedioxy en C_1-C_4, R^4 représente un groupe alkyle en C_1-C_4 pouvant porter un substituant choisi parmi les groupes alcoxy en C_1-C_4 et (alcoxy en C_1-C_4)-carbonyle, et Y représente un groupe méthylène ou un groupe carbonyle,
ainsi qu'un sel pharmaceutiquement acceptable d'un tel composé.

2. Composé conforme à la revendication 1, dans lequel chacun des symboles R^1 à R^3 représente un atome d'hydrogène, un atome d'halogène ou un groupe alcoxy en C_1-C_4.

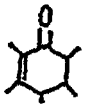
3. Composé conforme à la revendication 2, dans lequel le cycle A est un cycle thiophène ou furanne qui peut être substitué par un groupe hydroxyméthyle, R^1 représente un atome d'hydrogène ou un groupe alcoxy en C_1-C_4, chacun des symboles R^2 et R^3 représente un groupe alcoxy en C_1-C_4, et R^4 représente un groupe alkyle en C_1-C_4.

4. Composé conforme à la revendication 3, dans lequel le cycle A est un cycle thiophène, le cycle B est un cycle de formule :



R^1 représente un atome d'hydrogène, chacun des symboles R^2 et R^3 représente un groupe méthoxy et R^4 représente un groupe méthyle.

5. Composé conforme à la revendication 3, dans lequel le cycle A est un cycle furanne qui peut être substitué par un groupe hydroxyméthyle, le cycle B est un cycle de formule :

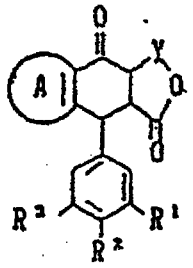


R^1 représente un atome d'hydrogène, chacun des symboles R^2 et R^3 représente un groupe méthoxy et Y représente un groupe méthylène.

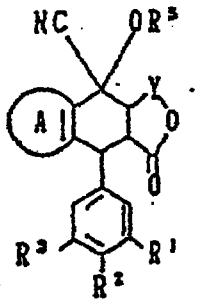
6. Composition pharmaceutique qui contient une quantité pharmaceutiquement efficace d'un composé conforme à l'une quelconque des revendications 1 à 5, ainsi qu'un véhicule, diluant ou désintégrant phar-

maceutiquement acceptable.

7. Procédé de préparation d'un dérivé biphénylique de formule :

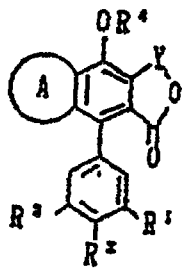


dans laquelle le cycle A est un cycle thiophène ou furanne qui peut porter un substituant choisi parmi un groupe formyle, un groupe (alcoxy en C_1-C_4)méthyle et un groupe hydroxyméthyle, chacun des symboles R^1 à R^3 représente un atome d'hydrogène, un atome d'halogène ou un groupe alcoxy en C_1-C_4, ou bien R^1 représente un atome d'hydrogène et R^2 et R^3 forment ensemble un groupe alkylènedioxy en C_1-C_4, et Y représente un groupe méthylène ou un groupe carbonyle,
ou d'un sel pharmaceutiquement acceptable d'un tel dérivé, qui comprend le traitement d'un composé tétrahydrobiphénylique de formule :



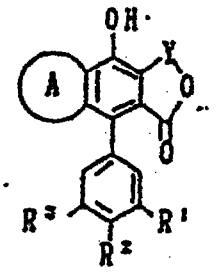
dans laquelle OR^5 représente un groupe hydroxy protégé et le cycle A, les symboles R^1 à R^3 et Y ont les mêmes significations que celles données ci-dessus,
ou d'un sel d'un tel composé avec un donneur d'ions fluor, et si nécessaire, la conversion du produit en un sel pharmaceutiquement acceptable de celui-ci.

8. Procédé de préparation d'un dérivé biphénylique de formule :



dans laquelle le cycle A est un cycle thiophène ou furanne qui peut porter un substituant choisi parmi un groupe formyle, un groupe (alcoxy en C_1-C_4)méthyle et un groupe hydroxyméthyle, chacun des symboles R^1 à R^3 représente un atome d'hydrogène, un atome d'halogène ou un groupe alcoxy en C_1-C_4, ou bien R^1 représente un atome d'hydrogène et R^2 et R^3 forment ensemble un groupe alkylènedioxy en C_1-C_4, R^4 représente un groupe alkyle en C_1-C_4 qui peut porter un substituant choisi parmi un groupe alcoxy en C_1-C_4 et un groupe (alcoxy en C_1-C_4)carbonyle, et Y représente un groupe méthylène ou un groupe carbonyle,
ou d'un sel pharmaceutiquement acceptable d'un tel composé, qui comprend la condensation d'un compo-

sé hydroxybiphénylique de formule :

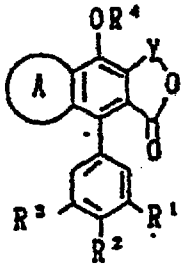


dans laquelle le cycle A, les symboles R^1 à R^3 et Y ont les mêmes définitions que celles données ci-dessus, ou d'un sel d'un tel composé avec un composé de formule :

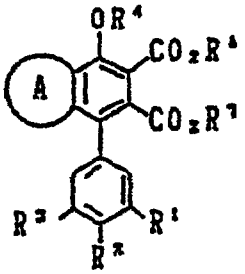
$$R^4\text{-}X$$

dans laquelle X représente un groupe partant et R^4 a la même définition que celle donnée ci-dessus, et, si nécessaire, la conversion du produit et un sel pharmaceutiquement acceptable de celui-ci.

9. Procédé de préparation d'un dérivé biphénylique de formule :

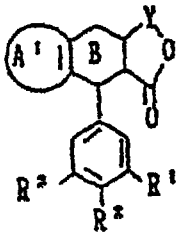


dans laquelle le cycle A est un cycle thiophène ou furanne qui peut porter un substituant choisi parmi un groupe formyle, un groupe (alcoxy en C_1-C_4)méthyle et un groupe hydroxyméthyle, chacun des symboles R^1 à R^3 représente un atome d'hydrogène, un atome d'halogène ou un groupe alcoxy en C_1-C_4, ou bien R^1 représente un atome d'hydrogène et R^2 et R^3 forment ensemble un groupe alkylènedioxy en C_1-C_4, R^4 représente un groupe alkyle en C_1-C_4 qui peut porter un substituant choisi parmi un groupe alcoxy en C_1-C_4 et un groupe (alcoxy en C_1-C_4)-carbonyle, et Y représente un groupe méthylène ou un groupe carbonyle,
ou d'un sel pharmaceutiquement acceptable .d'un tel composé, qui comporte :
(1) soit le fait de soumettre un composé dicarboxylate de formule :

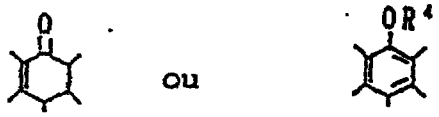


dans laquelle chacun des symboles R^6 et R^7 représente un groupe alkyle en C_1-C_4 et le cycle A et les symboles R^1 à R^4 ont les mêmes définitions que celles données ci-dessus,
ou un sel d'un tel composé à une lactonisation réductrice ;
(2) soit l'hydrolyse du composé dicarboxylate ou d'un sel de celui-ci, suivie d'une déshydratation ;
et si nécessaire la conversion du produit en un sel pharmaceutiquement acceptable de celui-ci.

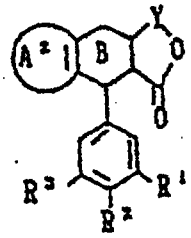
10. Procédé de préparation d'un dérivé biphénylique de formule :



dans laquelle le cycle A^1 représente un cycle thiophène ou furanne substitué par un groupe hydroxyméthyle ou un groupe (alcoxy en C_1-C_4)méthyle, le cycle B représente un cycle de formule :

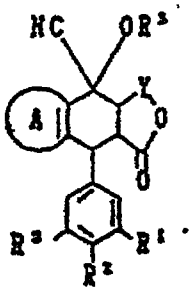


chacun des symboles R^1 à R^3 représente un atome d'hydrogène ou d'halogène ou un groupe alcoxy en C_1-C_4, ou bien R^1 représente un atome d'hydrogène et R^2 et R^3 forment, réunis ensemble, un groupe alkylènedioxy en C_1-C_4, R^4 représente un groupe alkyle en C_1-C_4 pouvant porter un substituant choisi parmi les groupes alcoxy en C_1-C_4 et (alcoxy en C_1-C_4)-carbonyle, et Y représente un groupe méthylène ou un groupe carbonyle,
ou d'un sel pharmaceutiquement acceptable d'un tel composé, qui comprend la réduction d'un dérivé biphénylique de formule :



dans laquelle le cycle A^2 représente un cycle thiophène ou furanne substitué par un groupe formyle, et le cycle B, les symboles R^1 à R^4 et Y ont les mêmes définitions que celles données ci-dessus,
ou d'un sel d'un tel dérivé, et, si nécessaire, l'alkylation du produit, et, si nécessaire, la conversion ultérieure du produit en un sel pharmaceutiquement acceptable de celui-ci.

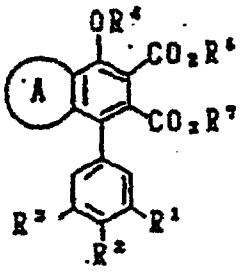
11. Composé tétrahydrobiphénylique de formule :



dans laquelle le cycle A est un cycle thiophène ou furanne qui peut porter un substituant choisi parmi un groupe formyle, un groupe (alcoxy en C_1-C_4)méthyle et un groupe hydroxyméthyle, chacun des symboles R^1 à R^3 représente un atome d'hydrogène, un atome d'halogène ou un groupe alcoxy en C_1-C_4, ou bien R^1 représente un atome d'hydrogène et R^2 et R^3 forment ensemble un groupe alkylènedioxy en C_1-C_4, OR^5 représente un groupe hydroxy protégé, et Y représente un groupe méthylène ou un groupe carbonyle,

ou un sel d'un tel composé.

12. Composé dicarboxylate de formule :

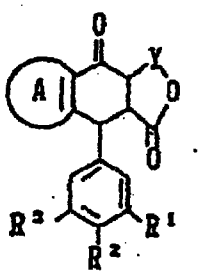


dans laquelle le cycle A est un cycle thiophène ou furanne qui peut porter un substituant choisi parmi un groupe formyle, un groupe (alcoxy en C_1-C_4)méthyle et un groupe hydroxyméthyle, chacun des symboles R^1 à R^3 représente un atome d'hydrogène, un atome d'halogène ou un groupe alcoxy en C_1-C_4, ou bien R^1 représente un atome d'hydrogène et R^2 et R^3 forment ensemble un groupe alkylènedioxy en C_1-C_4, R^4 représente un groupe alkyle en C_1-C_4 qui peut porter un substituant choisi parmi un groupe alcoxy en C_1-C_4 et un groupe (alcoxy en C_1-C_4)-carbonyle, et chacun des symboles R^6 et R^7 représente un groupe alkyle en C_1-C_4,
ou sel d'un tel composé.

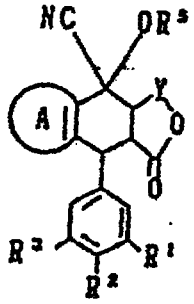
13. Utilisation d'un composé conforme à l'une quelconque des revendications précédentes 1 à 5, pour la fabrication d'un médicament pour les maladies du foie.

Revendications pour les Etats contractants suivants : ES, GR

1. Procédé de préparation d'un dérivé biphénylique de formule :

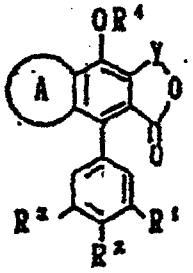


dans laquelle le cycle A est un cycle thiophène ou furanne qui peut porter un substituant choisi parmi un groupe formyle, un groupe (alcoxy en C_1-C_4)méthyle et un groupe hydroxyméthyle, chacun des symboles R^1 à R^3 représente un atome d'hydrogène, un atome d'halogène ou un groupe alcoxy en C_1-C_4, ou bien R^1 représente un atome d'hydrogène et R^2 et R^3 forment ensemble un groupe alkylènedioxy en C_1-C_4, et Y représente un groupe méthylène ou un groupe carbonyle,
ou d'un sel pharmaceutiquement acceptable d'un tel dérivé, qui comprend le traitement d'un composé tétrahydrobiphénylique de formule :

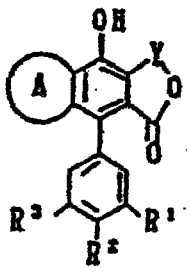


dans laquelle OR^5 représente un groupe hydroxy protégé et le cycle A, les symboles R^1 à R^3 et Y ont les mêmes significations que celles données ci-dessus,
ou d'un sel d'un tel composé avec un donneur d'ions fluor, et si nécessaire, la conversion du produit en un sel pharmaceutiquement acceptable de celui-ci.

2. Procédé de préparation d'un dérivé biphénylique de formule :



dans laquelle le cycle A est un cycle thiophène ou furanne qui peut porter un substituant choisi parmi un groupe formyle, un groupe (alcoxy en C_1-C_4)méthyle et un groupe hydroxyméthyle, chacun des symboles R^1 à R^3 représente un atome d'hydrogène, un atome d'halogène ou un groupe alcoxy en C_1-C_4, ou bien R^1 représente un atome d'hydrogène et R^2 et R^3 forment ensemble un groupe alkylènedioxy en C_1-C_4, R^4 représente un groupe alkyle en C_1-C_4 qui peut porter un substituant choisi parmi un groupe alcoxy en C_1-C_4 et un groupe (alcoxy en C_1-C_4)-carbonyle, et Y représente un groupe méthylène ou un groupe carbonyle,
ou d'un sel pharmaceutiquement acceptable d'un tel composé, qui comprend la condensation d'un composé hydroxybiphénylique de formule :

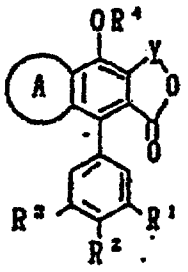


dans laquelle le cycle A, les symboles R^1 à R^3 et Y ont les mêmes définitions que celles données ci-dessus, ou d'un sel d'un tel composé avec un composé de formule :

$$R^4\text{-}X$$

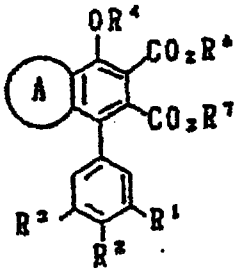
dans laquelle X représente un groupe partant et R^4 a la même définition que celle donnée ci-dessus, et, si nécessaire, la conversion du produit en un sel pharmaceutiquement acceptable de celui-ci.

3. Procédé de préparation d'un dérivé biphénylique de formule :



dans laquelle le cycle A est un cycle thiophène ou furanne qui peut porter un substituant choisi parmi un groupe formyle, un groupe (alcoxy en C_1-C_4)méthyle et un groupe hydroxyméthyle, chacun des symboles R^1 à R^3 représente un atome d'hydrogène, un atome d'halogène ou un groupe alcoxy en C_1-C_4, ou bien R^1 représente un atome d'hydrogène et R^2 et R^3 forment ensemble un groupe alkylènedioxy en C_1-C_4, R^4 représente un groupe alkyle en C_1-C_4 qui peut porter un substituant choisi parmi un groupe alcoxy en C_1-C_4 et un groupe (alcoxy en C_1-C_4)-carbonyle, et Y représente un groupe méthylène ou un groupe carbonyle,
ou d'un sel pharmaceutiquement acceptable d'un tel composé, qui comporte :

(1) soit le fait de soumettre un composé dicarboxylate de formule :

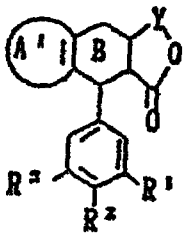


dans laquelle chacun des symboles R^6 et R^7 représente un groupe alkyle en C_1-C_4 et le cycle A et les symboles R^1 à R^4 ont les mêmes définitions que celles données ci-dessus,
ou un sel d'un tel composé à une lactonisation réductrice ;

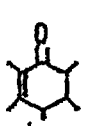
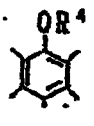
(2) soit l'hydrolyse du composé dicarboxylate ou d'un sel de celui-ci, suivie d'une déshydratation ;

et si nécessaire la conversion du produit en un sel pharmaceutiquement acceptable de celui-ci.

4. Procédé de préparation d'un dérivé biphénylique de formule :



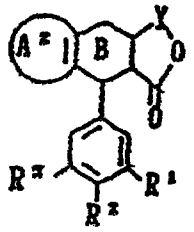
dans laquelle le cycle A^1 représente un cycle thiophène ou furanne substitué par un groupe hydroxyméthyle ou un groupe (alcoxy en C_1-C_4)méthyle, le cycle B représente un cycle de formule :

 ou 

chacun des symboles R^1 à R^3 représente un atome d'hydrogène ou d'halogène ou un groupe alcoxy en

* C L M S *

C_1-C_4, ou bien R^1 représente un atome d'hydrogène et R^2 et R^3 forment, réunis ensemble, un groupe alkylènedioxy en C_1-C_4, R^4 représente un groupe alkyle en C_1-C_4 pouvant porter un substituant choisi parmi les groupes alcoxy en C_1-C_4 et (alcoxy en C_1-C_4)-carbonyle, et Y représente un groupe méthylène ou un groupe carbonyle,
ou d'un sel pharmaceutiquement acceptable d'un tel composé, qui comprend la réduction d'un dérivé biphénylique de formule :



dans laquelle le cycle A^2 représente un cycle thiophène ou furanne substitué par un groupe formyle, et le cycle B, les symboles R^1 à R^4 et Y ont les mêmes définitions que celles données ci-dessus,
ou d'un sel d'un tel dérivé, et, si nécessaire, l'alkylation du produit, et, si nécessaire, la conversion ultérieure du produit en un sel pharmaceutiquement acceptable de celui-ci.

5. Utilisation d'un composé que l'on peut obtenir selon un procédé conforme à l'une quelconque des revendications 1 à 4, pour la fabrication d'un médicament destiné au traitement de maladies du foie.

6. Procédé de préparation d'une composition pharmaceutique, par combinaison d'une quantité pharmaceutiquement efficace d'un dérivé biphénylique tel que défini dans l'une quelconque des revendications 1 à 4, avec un véhicule, diluant ou désintégrant pharmaceutiquement acceptable.