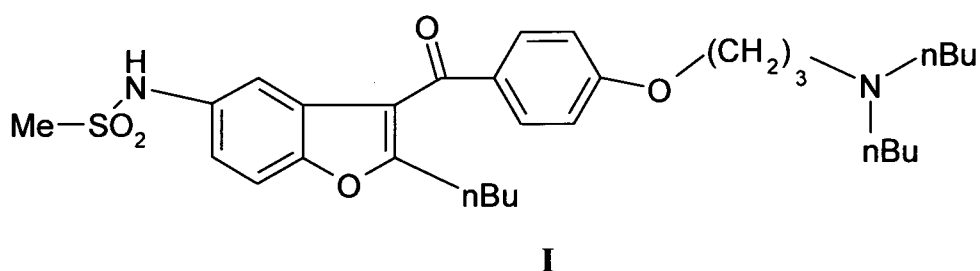


PROCESS FOR THE PREPARATION OF DRONEDARONE

This invention relates to a novel process for the preparation of N-[2-n-butyl-3-{4-
[(3-di-n-butylamino)-propoxy]-benzoyl}-1-benzofuran-5-yl]-methane-sulfonamide
5 (dronedarone) and its pharmaceutically acceptable salts and to the novel
intermediates used in this process.

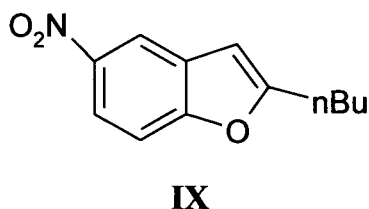


10

Dronedarone of the formula **I** is useful in the treatment of certain
pathological changes of the cardiovascular system, first of all in the treatment of
angina pectoris, high blood pressure, arrhythmia and insufficient cerebral blood
15 flow (EP 0471609 B1).

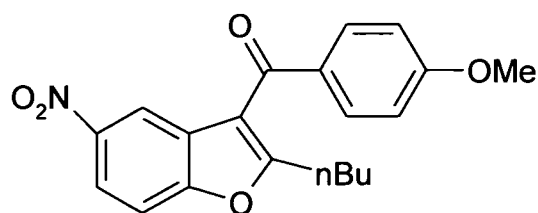
Presently several methods for the preparation of Dronedarone of the formula
I are known. In one of the prior art methods (EP 0471609 B1) the 2-n-butyl-5-nitro-
benzofuran of formula **IX**

20

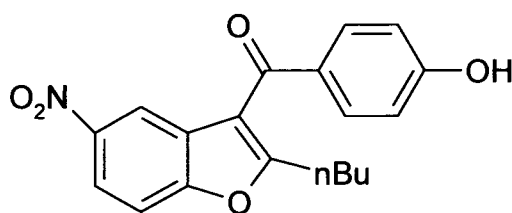


is reacted with anisoyl chloride under Friedel-Crafts conditions, and by heating the
25 resulting 2-n-butyl-3-(4-methoxy-benzoyl)-5-nitro-benzofuran of formula **X**

2

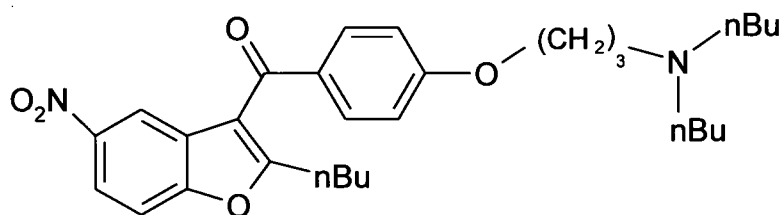
**X**

in the presence of aluminum chloride

**XI**

the 2-n-butyl-3-(4-hydroxy-benzoyl)-5-nitro-benzofuran of formula **XI** is obtained.

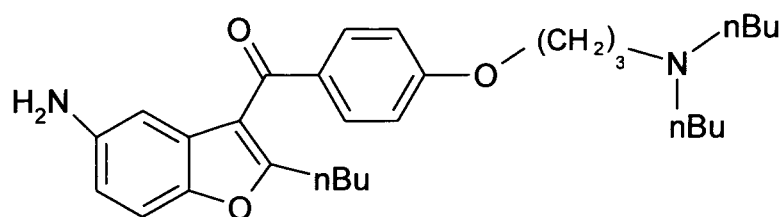
Utilization of this reaction step in industrial scale, however, involves
 10 difficulties, since the compound of formula **X** is mutagenic, and aluminum chloride
 is harmful for the health. Reaction of the resulting compound of formula **XI** with
 di-n-butylamino-propyl chloride gives the 2-n-butyl-3-[4-(3-di-n-butylamino-
 propoxy)-benzoyl]-5-nitro-benzofuran of formula **XII**

**XII**

which on reduction with platinum oxide catalyst gives the 5-amino-2-n-butyl-3-[4-
 (3-di-n-butylamino-propoxy)-benzoyl]-benzofuran of formula **XIII**.

20

3

**XIII**

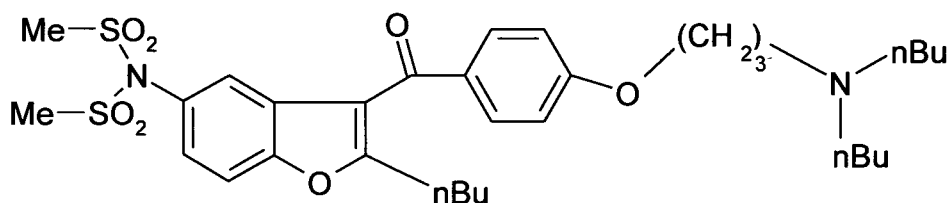
Finally, mesylation the compound of formula **XIII** results dronedarone of formula **I**.

5

This is a linear synthesis, where the parts of the desired molecule are built up stepwise, using more and more complicated molecules in the consecutive steps, which is economically unfavourable.

In the last step, the selective mesylation of the amino group of the compound of formula **XIII** is difficult, the double mesylated 2-n-butyl-3-[(di-n-butylamino-3-propoxy)-benzoyl]-5-bis-(methylsulfonamido)-benzofuran derivative of formula **II** is also formed and it appears beside the dronedarone of formula **I**.

10

**II**

15

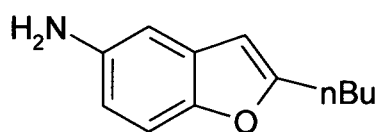
According to the literature, this process, after purification by column chromatography, results in 61.6% yield, but the process is complicated, not suitable for industrial application.

20

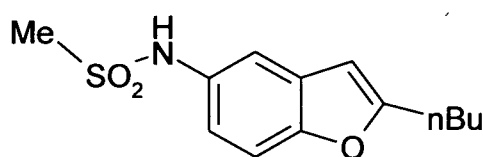
Another process for the preparation of dronedarone is described in patent application of publication number WO 02/48132. This super-convergent route consists of the following steps:

25 The 5-amino-2-n-butyl-benzofuran of formula **XIV**

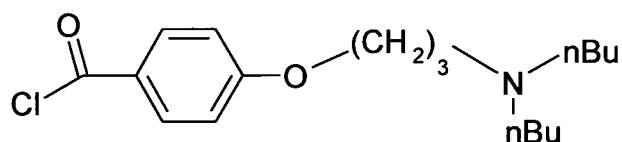
4

**XIV**

is mesylated and the resulting 2-n-butyl-5-methylsulfonamido-benzofuran of
 5 formula **XV**

**XV**

10 is reacted under Friedel-Crafts conditions with the hydrochloride salt of the 4-[3-(di-n-butylamino)propoxy]-benzoyl chloride of formula **VIII**



15

VIII

to obtain the hydrochloride salt of dronedarone of formula **I**.

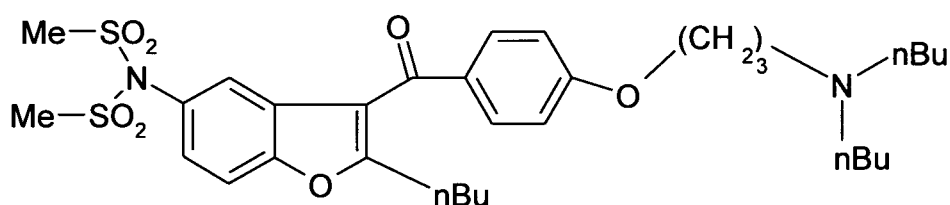
20 In this method the sequence of the reaction steps is changed, the reduction and the mesylation steps are at the beginning of the synthesis.

This method is very simple and economical as regards the number of the reaction steps. Its drawback is, however, that in the last step the hydrochloride salt of dronedarone is obtained in a rather contaminated form. This can be explained by the presence of the dibutylamino-propyl group in the Friedel-Crafts reaction. In the
 25 examples of WO02/48132 the yield is 90%, during the purification steps at first the

raw dronedarone hydrochloride salt, then following treatment with hydrogen chloride solution in isopropanol, the purified dronedarone hydrochloride salt is obtained (90%). It means that the yield of the raw dronedarone hydrochloride is 90 % and then the purification step has a yield of 90 %. Another drawback of the method is that the reactants used in the Friedel-Crafts reaction and the obtained by-products are insoluble in water, thus they cannot be removed from the system by aqueous washing.

Our aim was to work out a novel method for the preparation of dronedarone and its pharmaceutically acceptable salts, which method avoids the above mentioned disadvantages of known processes and it is economical and industrially applicable.

We have found that if one methylsulfonyl group of the 2-n-butyl-3-[(di-n-butylamino-3-propoxy)-benzoyl]-5-bis-(methylsulfonamido)-benzofuran of formula II



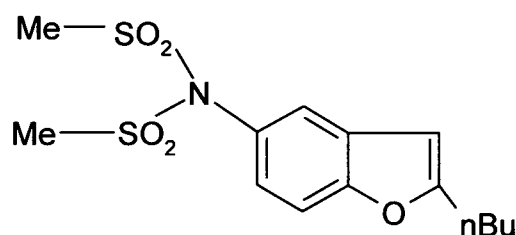
II

is selectively cleaved, then dronedarone of formula I is obtained in good yield and in appropriate purity.

According to our invention the cleavage of one of the methylsulfonyl groups of the compound of formula II is performed in an alcoholic solvent or in the mixture of alcoholic solvents, in the presence of an alkali alcoholate. As for

alcoholic solvent, methanol, ethanol or the mixture of them can be used. As for alkali alcoholate, sodium methylate, potassium methylate, sodium ethylate or potassium ethylate can be applied.

- 5 In one embodiment of the process according to our invention, the 2-n-butyl-5-bis-(methylsulfonamido)-benzofuran of the formula **III**

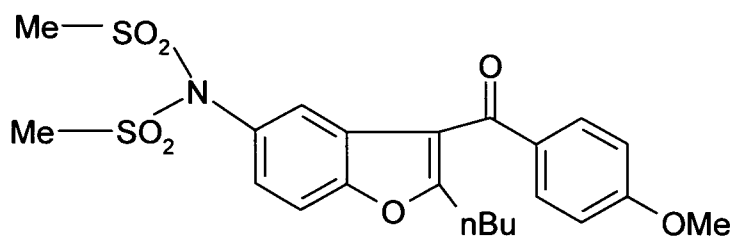


10

III

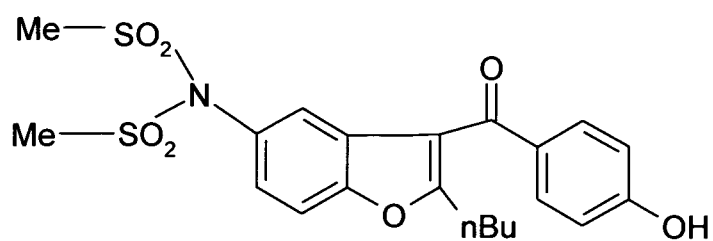
is reacted under Friedel Crafts conditions with anisoyl chloride, and the resulting 2-n-butyl-5-bis-(methylsulfonamido)-3-(4-methoxy-benzoyl)-benzofuran of formula **VII**

15

**VII**

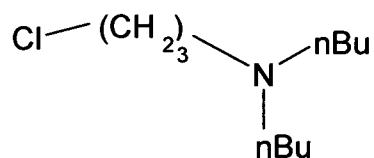
- is demethylated, and the thus obtained 2-n-butyl-3-(4-hydroxy-benzoyl)-5-bis-(methylsulfonamido)-benzofuran of formula **VI**
- 20

7



VI

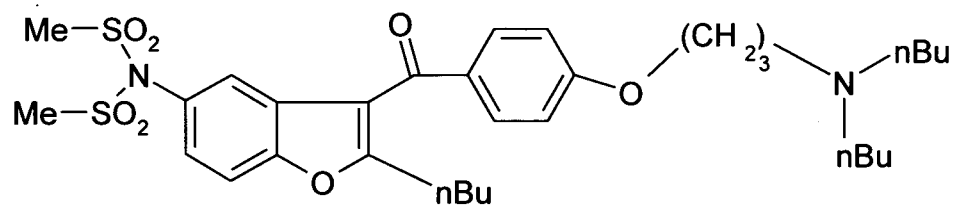
5 is reacted with the 3-di-n-butylamino-propyl chloride of formula V



V

10

and from the resulting 2-n-butyl-3-[(di-n-butylamino-3-propoxy)-benzoyl]-5-bis-(methylsulfonamido)-benzofuran of formula II

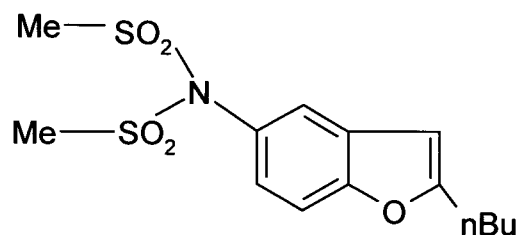


II

15

one of the methylsulfonyl groups is selectively cleaved by the method described
20 above.

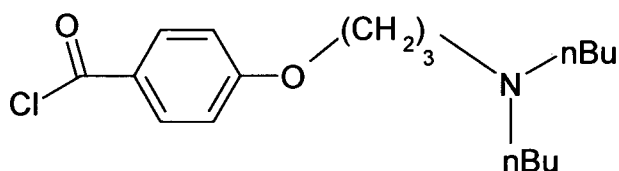
In another embodiment of the process according to the invention, the 2-n-butyl-5-(bis-methylsulfonamido)-benzofuran of formula **III**



5

III

is reacted under Friedel-Crafts conditions with the hydrochloride of the 4-(3-di-n-butylamino-propoxy)-benzoic acid of formula **VIII**

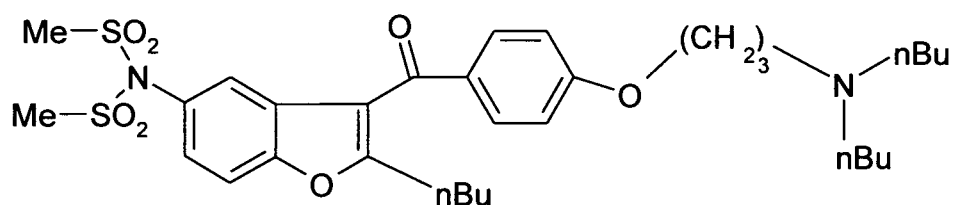


10

VIII

and from the thus obtained 2-n-butyl-3-[(di-n-butylamino-3-propoxy)-benzoyl]-5-bis-(methylsulfonamido)-benzofuran of formula **II**

15

**II**

20

one of the methylsulfonyl groups is selectively cleaved by the method described above.

According to our invention the reaction of the compound of formula **III** with anisoyl chloride is carried out in an inert organic solvent or in the mixture of inert organic solvents. As for inert organic solvent, halogenated organic solvents (dichloromethane, dichloroethane, chlorobenzene) are applied.

- 5 The reaction of the compound of formula **III** with anisoyl chloride is carried out in the presence of Lewis acid. As Lewis acid, iron(III) chloride or aluminum chloride are applied, in maximum 5 equivalent amount.

The demethylation reaction of the compound of formula **VII** is carried out in an inert organic solvent or in the mixture of inert organic solvents. As for inert
10 organic solvent, halogenated organic solvents (dichloromethane, dichloroethane, chlorobenzene) are applied.

The demethylation reaction of the compound of formula **VII** is carried out in the presence of Lewis acid. As for Lewis acid, iron(III) chloride or aluminum chloride is applied.

- 15 The demethylation reaction of the compound of formula **VII** is carried out at a temperature between 20-100 °C.

The reaction of the compounds of the formulae **V** and **VI** is carried out in an organic solvent or in the mixture of organic solvents. As for organic solvent, alcohols of lower carbon atom number (methanol, ethanol) or ketones of lower
20 carbon atom number (acetone, methyl ethyl ketone) are applied.

The reaction of the compounds of formulae **V** and **VI** is performed in the presence of an acid binder of basic character. As for acid binder of basic character, inorganic carbonates are used.

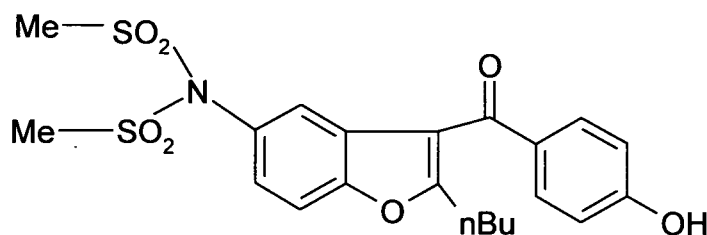
- 25 The reaction of the compounds of formulae **V** and **VI** is carried out at a temperature around the boiling point of the applied solvent or solvent mixture.

The reaction of the compounds of formulae **III** and **VIII** is carried out in an inert organic solvent or in the mixture of inert organic solvents. As for inert organic solvent, halogenated organic solvents (dichloromethane, dichloroethane,
30 chlorobenzene) are applied.

The reaction of the compounds of formulae **III** and **VIII** is carried out in the presence of Lewis acid. As for Lewis acid, iron(III) chloride or aluminum chloride is applied.

5 Preparation of the 2-n-butyl-3-[(di-n-butylamino-3-propoxy)-benzoyl]-5-bis-(methylsulfonamido)-benzofuran of formula **II** and of the 2-n-butyl-5-bis-(methylsulfonamido)-benzofuran of formula **III** from 2-n-butyl-5-nitro-benzofuran are known from the literature (EP 0471609 B1, Example 35. and Example 70.

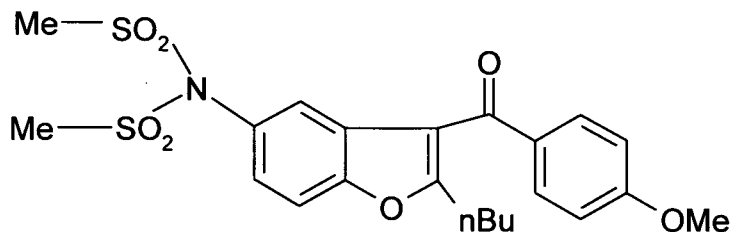
10 The 2-n-butyl-3-(4-hydroxy-benzoyl)-5-bis-(methylsulfonamido)-benzofuran of formula **VI**



15 **VI**

and

the 2-n-butyl-5-bis-(methylsulfonamido)-3-(4-methoxy-benzoyl)-benzofuran of formula **VII**



20 **VII**

are novel compounds, they are not known from the literature.

The following examples demonstrate further details of the invention – without limiting the claims of the Applicant to the Examples.

Example 1.

5 N-[2-n-butyl-3-{4-[(3-di-n-butylamino)-propoxy]-benzoyl}-1-benzofuran-5-yl]-methane-sulfonamide (I)

To 7g of 2-n-butyl-3-[(di-n-butylamino)-3-propoxy]-4-benzoyl]-5-bis-(methylsulfonamido)-benzofuran (II) the solution prepared from 5 g sodium and
10 170 ml abs. ethanol is added. The reaction mixture is boiled for 30 minutes, then evaporated under reduced pressure. To the residue 30 ml of dichloromethane and 50 ml of water are added and the mixture is stirred for 20 minutes. The phases are separated. The organic phase is washed with 20 ml of water and evaporated.

Product: oil (yield: 97.9%). Purity (HPLC): 93.1%.

15 The product is purified through its oxalate salt (yield: 90.3%). Purity (HPLC): 99.5%.

¹H NMR(DMSO): 0.8-0.9 ppm (m, 9H); 1.2-1.5 ppm (m, 10H); 1.67 ppm (5', 2H); 1.87 ppm (5', 2H); 2.38 ppm (t, J=7.2Hz, 4H); 2.57 ppm (m, 2H); 2.81 ppm (t, J=7.5Hz, 2H); 2.91 ppm (s, 3H); 4.15 ppm (t, J=6.2Hz, 2H); 7.09 (d, J=8.8Hz, 2H);
20 7.24 ppm (dd, J=8.9; 2.2Hz, 1H); 7.34 ppm (d, J=2.1Hz, 1H); 7.65 ppm (d, J=8.8Hz, 1H); 7.81 ppm (d, J=8.8Hz, 2H).

Example 2.

25 N-[2-n-butyl-3-{4-[(3-di-n-butylamino)-propoxy]-benzoyl}-1-benzofuran-5-yl]-methane-sulfonamide (I)

The process according to Example 1. is performed, with the difference that methanol is used, instead of ethanol.

30 Yield of the purified product: 88.6%. Purity (HPLC): 99.7%.

Example 3.

N-[2-n-butyl-3-{4-[(3-di-n-butylamino)-propoxy]-benzoyl}-1-benzofuran-5-yl]-methane-sulfonamide (I)

5

The process according to Example 1. is performed, with the difference that potassium is used instead of sodium.

Yield of the purified product: 88.9%. Purity (HPLC): 99.5%.

10

Example 4.

N-[2-n-butyl-3-{4-[(3-di-n-butylamino)-propoxy]-benzoyl}-1-benzofuran-5-yl]-methane-sulfonamide (I)

15

To 22 g of the unpurified dronedarone (I) which contains 4% of the bis-methanesulfonamido compound (II), 0.8 g of sodium metal dissolved in 220 ml of abs. ethanol is added. The reaction mixture is boiled for 30 minutes, then evaporated. To the residue 140 ml of water and 80 ml of dichloromethane are added and the reaction mixture is stirred for 20 minutes. The phases are separated, the dichloromethane phase is evaporated. The crude dronedarone (I) is purified through its oxalate salt.

20

Yield of the purified product: 93.5%. Purity (HPLC): 99.4%.

Example 5.

25

2-n-butyl-5-bis-(methylsulfonamido)-3-(4-methoxy-benzoyl)-benzofuran (VII)

30

4 g of 2-n-butyl-5-bis-(methylsulfonamido)-benzofuran (III) and 2.29 g of anisoyl chloride are dissolved under stirring in 20 ml of dichloromethane. The solution is cooled to 5-10°C and at this temperature 2.16 g of iron(III) chloride is

added in four portions, in a period of 15 minutes. The mixture is heated to 20°C and stirred at that temperature for 1 hour. The reaction mixture is then heated to 40°C and at this temperature 30 ml of water is added to it in 30 minutes. The phases are separated at this temperature. The dichloromethane phase is washed with 10 ml of water, 2 x 10 ml of 5% aqueous sodium hydrogen carbonate solution and 2 x 10 ml of water. The dichloromethane phase is evaporated.

Product: oil (yield: 95.98%). Purity (HPLC): 99.0%.

¹H NMR (DMSO-d₆): 7.86 ppm (d, J=8.6Hz, 2H); 7.80 ppm (d, J=8.7Hz, 1H); 7.55 ppm (d, J= 1.9Hz, 1H); 7.51 ppm (dd, J= 8.7Hz, 2.0Hz, 1H); 7.12 ppm (d, J=8.7Hz, 2H); 3.9 ppm (s, 3H); 3.53 ppm (s, 6H); 2.84 ppm (t, J= 7.4Hz, 2H); 1.7 ppm (5', J= 7.3Hz, 2H); 1.27 ppm (6', J=7.4 Hz, 2H); 0.83 ppm (t, J= 7.4Hz, 3H).

Molecular mass: [M+H]⁺ calculated: 480.1151 Da; [M+H]⁺ measured: 480.1142 Da.

Example 6.

15

2-n-butyl-3-(4-hydroxy-benzoyl)-5-bis-(methylsulfonamido)-benzofuran (VI)

5.3 g of 2-n-butyl-5-bis-(methylsulfonamido)-3-(4-methoxy-benzoyl)-benzofuran (VII) is dissolved in 12 ml of chlorobenzene. The solution is then added at 64-66°C to the suspension made of 4.44 g of aluminum chloride and 17 ml of chlorobenzene, so that half of the amount of the solution is added in 30 minutes and the other half in 3 hours. After the addition the mixture is stirred at 64-66°C for 4 hours and at that temperature 25 ml of water is added in 10 minutes. The phases are still hot separated. The chlorobenzene phase is stirred at 65°C with 3 x 25 ml of water, the phases are separated and the organic phase is evaporated.

25

Product: oil (yield: 94.0%). Purity (HPLC) 99.0%.

¹H NMR(DMSO): 0.84 ppm (t, J=7.4Hz, 3H); 1.27 ppm (6', J=7.3Hz, 2H); 1.70 ppm (5', J=7.4Hz, 2H); 2.85 ppm (t, J=7.3Hz, 2H); 3.53 ppm (s, 6H); 6.93 ppm (s,

J=8.5Hz, 2H); 7.50 ppm (dd, J=8.6Hz, 1.8Hz, 1H); 7.54 ppm (d, J=1.9Hz, 1H); 7.77 ppm (d, J=8.5Hz, 2H); 7.79 ppm (d, J=8.7Hz, 1H); 10.54 ppm (s, 1H)

Molecular mass: $[M+H]^+$ calculated: 466.0994 Da; $[M+H]^+$ measured: 466.1001 Da.

5 **Example 7.**

2-n-butyl-3-(4-hydroxy-benzoyl)-5-bis-(methylsulfonamido)-benzofuran
(VI)

10 The process according to Example 6 is performed with the difference that dichloroethane is used as solvent.

Yield of the product: 97.0%. Purity (HPLC): 99.1%.

Example 8.

15

2-n-butyl-3-[(di-n-butylamino-3-propoxy)-4-benzoyl]-5-bis-
(methylsulfonamido)- benzofuran (II)

20 2 g of 2-n-butyl-3-(4-hydroxy-benzoyl)-5-bis-(methylsulfonamido)-benzofuran (V) and 0.88 g of (3-di-n-butylamino)-propyl chloride are dissolved in 16 ml of methyl ethyl ketone. 1.75 g of potassium carbonate is added to the solution and the reaction mixture is boiled for 8 hours. The inorganic salts are filtered off, washed with 16 ml of methyl ethyl ketone. The solvent is removed by evaporation.

25 Product: oil (2.56 g, yield: 93.5%) Purity (HPLC): 99.1%

^1H NMR (DMSO-d₆): 7.87 ppm (d, J=8.8Hz, 2H); 7.81 ppm (d, J=8.8Hz, 1H); 7.53 ppm (d, J=2.3Hz, 1H); 7.52 ppm (dd, J=8.8; 2.3Hz, 1H); 7.12 ppm (d, J=8.8Hz, 2H); 4.21pp (w, 2H); 3.53 ppm (s, 6H); 3.26 ppm (w, 2H); 3.03 ppm (w, 4H); 2.84 ppm (t, J=7.5Hz, 2H); 2.19 ppm (w, 2H); 1.70 ppm (5', J=7.4Hz, 2H); 1.68 ppm (w,

4H); 1.36 ppm (6', J=7.0Hz, 4H); 1.27 ppm (6', J=7.3Hz, 2H); 0.94 ppm (t, J=7.2Hz, 6H); 0.84 ppm (t, J=7.4Hz, 3H)

Example 9.

2-n-butyl-3-[(di-n-butylamino-3-propoxy)-4-benzoyl]-5-bis-(methylsulfonamido)-benzofuran (II)

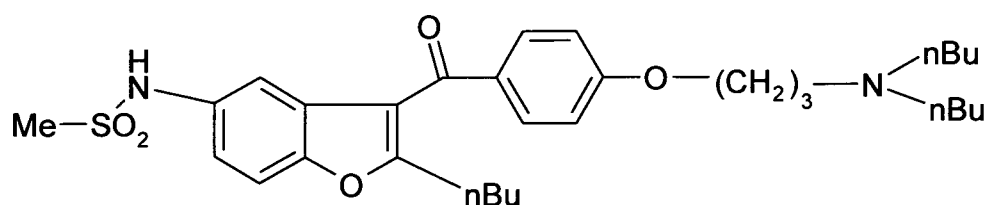
2 g of 2-n-butyl-5-bis-(methylsulfonamido)-benzofuran (III) is dissolved in 10 ml of dichloromethane and to the solution 1.8 g of the hydrochloride of 4-(di-n-butylamino-propoxy)benzoyl chloride (VIII) is added. The mixture is cooled to 5°C and in four portions, in 15 minutes 0.93 g of iron(III) chloride is added. The reaction mixture is heated to 20°C and stirred at that temperature for 1 hour, then heated to 35-40°C and 16 ml of water is added to it. After stirring for 30 minutes the phases are separated. The dichloromethane phase is washed at 35-40°C with 6 ml of water, 2 x 6 ml of 5% aqueous sodium hydrogen carbonate solution and 2 x 60 ml of water. The dichloromethane is removed by evaporation.

Product: oil (3.5 g yield: 95.2%). Purity: (HPLC) 89.2%

The product is identical with the compound prepared in Example 8.

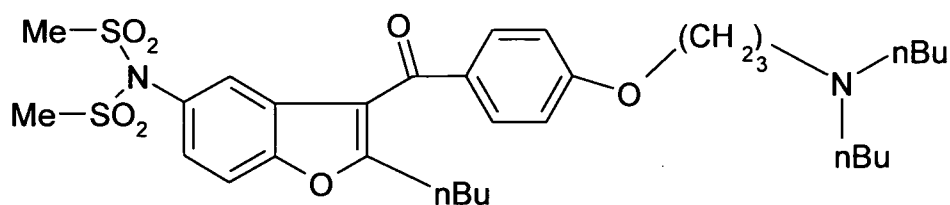
Claims

1. Process for the preparation of N-[2-n-butyl-3-{4-[(3-dibutylamino)-propoxy]-benzoyl}-1-benzofuran-5-yl]-methane-sulfonamide of formula I



I

- and its pharmaceutically acceptable salts, **characterized in that** one of the methylsulfonyl groups of the 2-n-butyl-3-[(di-n-butylamino-3-propoxy)-benzoyl]-5-bis-(methylsulfonylamido)-benzofuran of formula II



II

15

is selectively cleaved and if desired, the resulting compound of formula I is transformed into its salt.

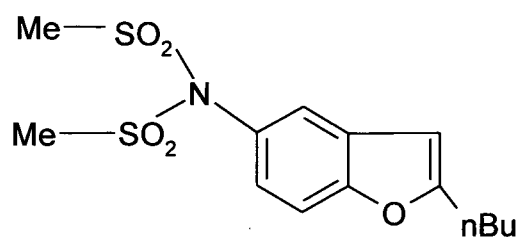
2. Process as defined in claim 1, **characterized in that** the reaction is carried out in an organic solvent or in the mixture of organic solvents.

3. Process as defined in any of claims 1-2, **characterized in that** the reaction is carried out in the presence of alkali alcoholate.

4. Process as defined in any of claims 1-3, **characterized in that**

25

a) the 2-n-butyl-5-bis-(methylsulfonamido)-benzofuran of formula **III**



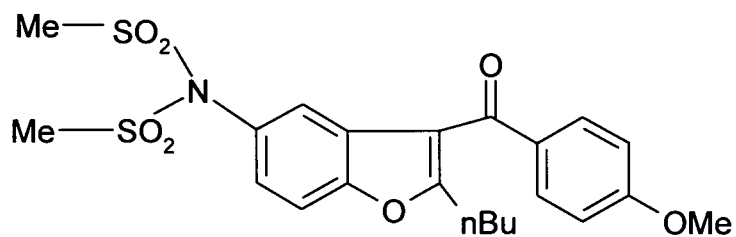
5

III

is reacted with anisoyl chloride in the presence of a Lewis acid,
and

b) the resulting 2-n-butyl-5-bis-(methylsulfonamido)-3-(4-methoxy-benzoyl)-benzofuran of formula **VII**

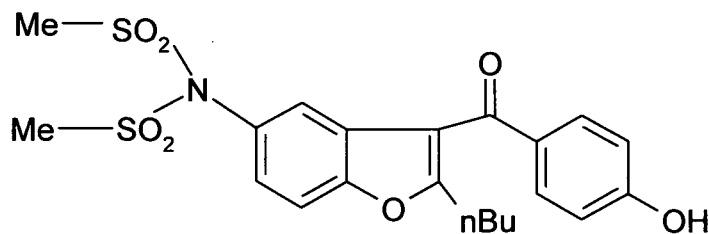
10

**VII**

is demethylated, and

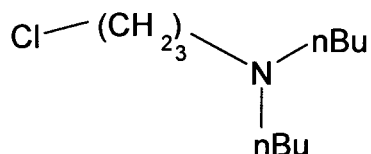
c) the resulting 2-n-butyl-3-(4-hydroxy-benzoyl)-5-bis-(methylsulfonamido)-benzofuran of formula **VI**

15

**VI**

20

is reacted with 3-(di-n-butyl-amino)-propyl-chloride of formula V

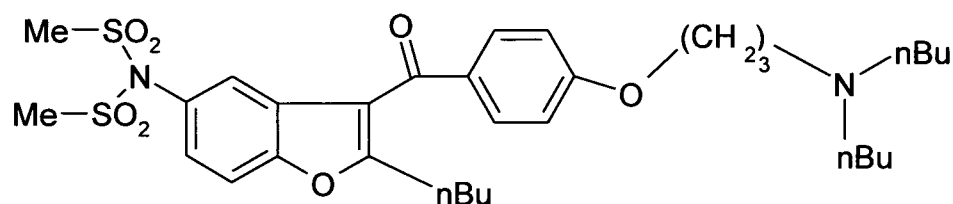


V

and

d) one of the methylsulfonyl groups of the resulting 2-n-butyl-3-[(di-n-butylamino-3-propoxy)-benzoyl]-5-bis-(methylsulfonamido)-benzofuran of formula

II



II

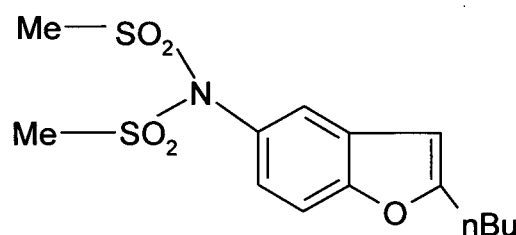
is selectively cleaved and if desired, the thus obtained compound of formula I is transformed into its salt.

5. Process according to reaction step b) of claim 4, characterized in that the reaction is performed in the presence of a Lewis acid.

6. Process according to reaction step b) of claim 4, characterized in that the reaction is carried out in an inert organic solvent or in the mixture of inert organic solvents.

7. Process according to reaction step b) of claim 4, characterized in that the reaction is carried out at a temperature between 20-100 °C.

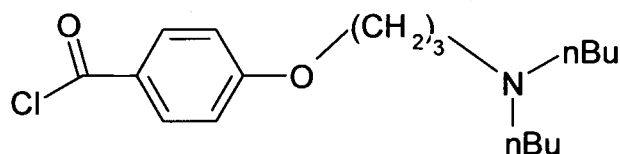
8. Process according to claim 10, **characterized in that** the reaction is carried out at a temperature around the boiling point of the applied solvent or solvent mixture.
- 5 9. Process according to reaction step c) of claim 4, **characterized in that** the reaction is carried out in an inert organic solvent or in the mixture of inert organic solvents.
- 10 10. Process according to reaction step c) of claim 4, **characterized in that** the reaction is carried out in the presence of an acid binder of basic character.
11. Process according to any of claims 1-3, **characterized in that**
a) the 2-n-butyl-5-bis-(methylsulfonamido)-benzofuran of formula **III**



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III

is reacted in the presence of a Lewis acid with the hydrochloride of the 4-(3-di-n-butylamino-propoxy)-benzoyl chloride of formula **VIII**

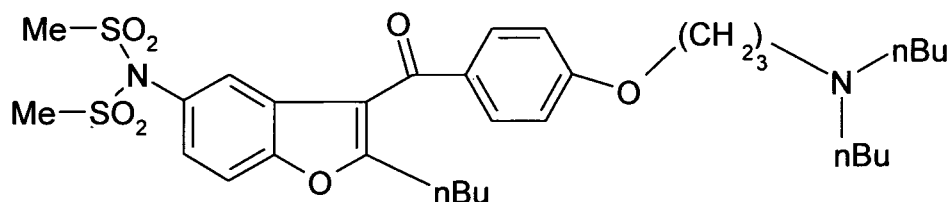


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VIII

and

b) from the resulting 2-n-butyl-3-[(di-n-butylamino-3-propoxy)-benzoyl]-5-bis-(methylsulfonamido)-benzofuran of formula II



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II

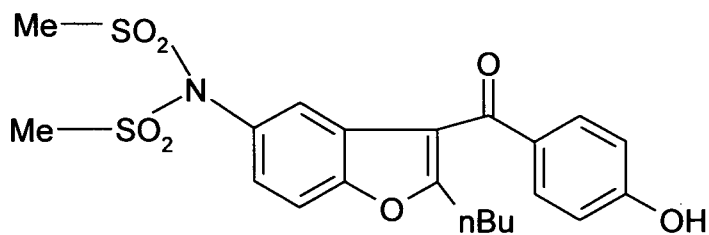
one of the methylsulfonyl groups is selectively cleaved, and if desired, the thus obtained compound of formula I is transformed into its salt.

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12. Process according to reaction step a) of claims 4-11 or according to claim 5, characterized in that iron(III) chloride or aluminium(III) chloride is used as Lewis acid.

13. Process according to reaction step a) of claim 4 or claim 12, characterized in that the reaction is carried out in an inert organic solvent or in the mixture of inert organic solvents.

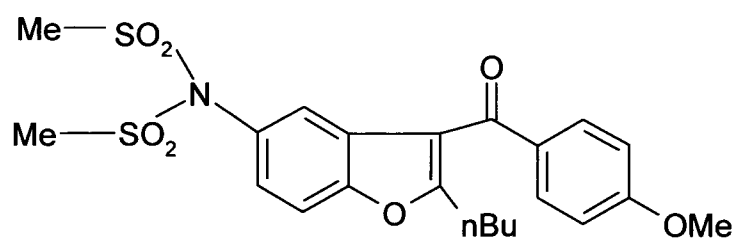
14. The 2-n-butyl-3-(4-hydroxy-benzoyl)-5-bis-(methylsulfonamido)-benzofuran of formula VI



VI

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15. The 2-n-butyl-5-bis-(methylsulfonamido)-3-(4-methoxy-benzoyl)-benzofuran of formula **VII**

**VII**

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