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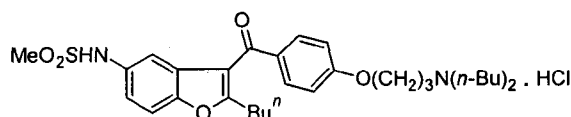
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(54) Title: PROCESS FOR *N*-[2-*n*-BUTYL-3-[4-[3-(DI-*n*-BUTYLAMINO) PROPOXY]ENZOYL]BENZOFURAN-5-YL]METHANESULFONAMIDE HYDROCHLORIDE

(I)

(57) Abstract: The present invention provides a process for preparing compound of formula (I),

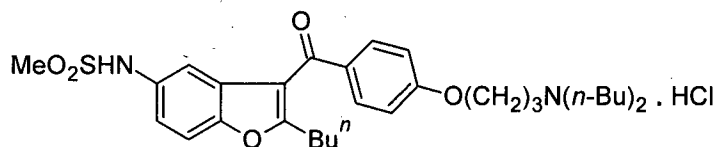
**PROCESS FOR *N*-[2-*n*-BUTYL-3-[4-[3-(DI-*n*-BUTYLAMINO)PROPOXY]BENZOYL]BENZOFURAN-5-YL]METHANESULFONAMIDE
HYDROCHLORIDE**

5 RELATED APPLICATIONS

This application claims the benefit of Indian Patent Application No. 667/MUM/ 2011 filed on March 10, 2011 which is hereby incorporated by reference.

FIELD OF INVENTION

The present invention relates to a process for the preparation of dronedarone
10 hydrochloride, a compound of formula (I).

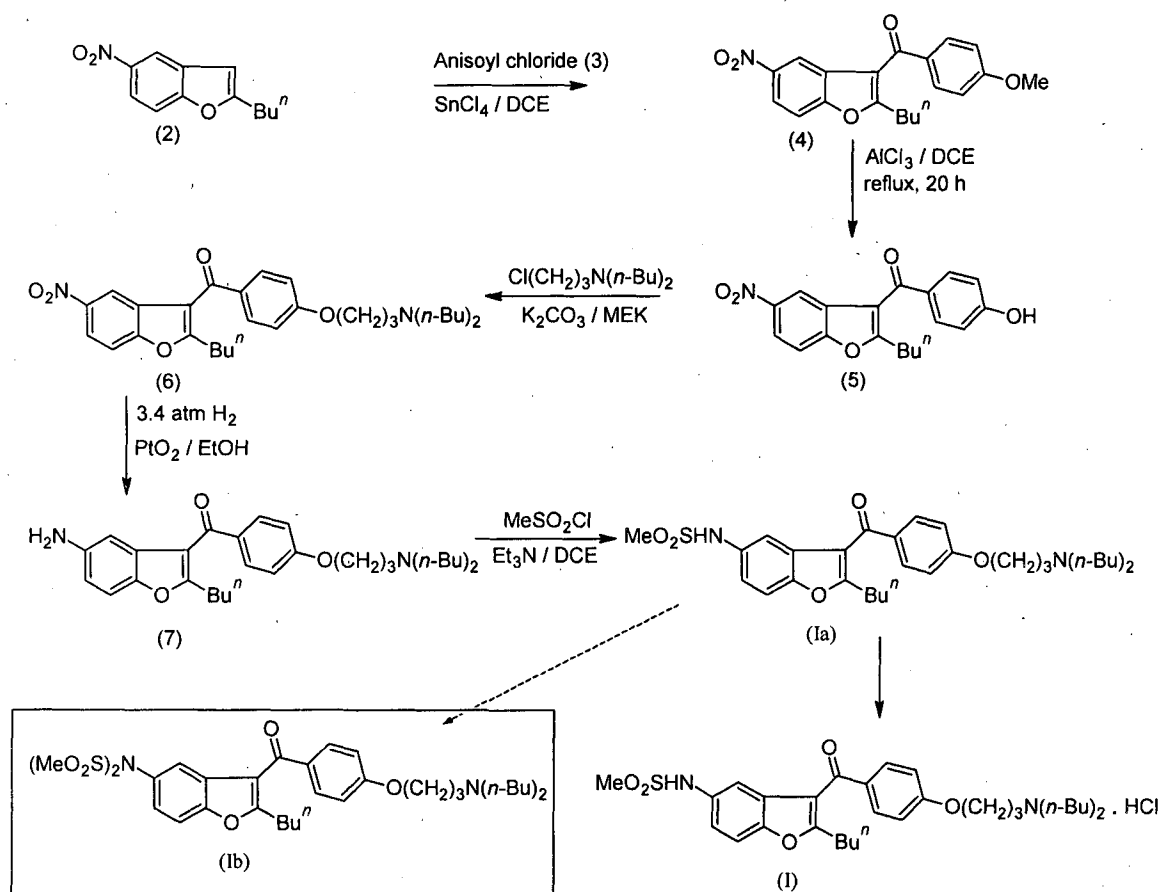


formula (I)

BACKGROUND OF THE INVENTION

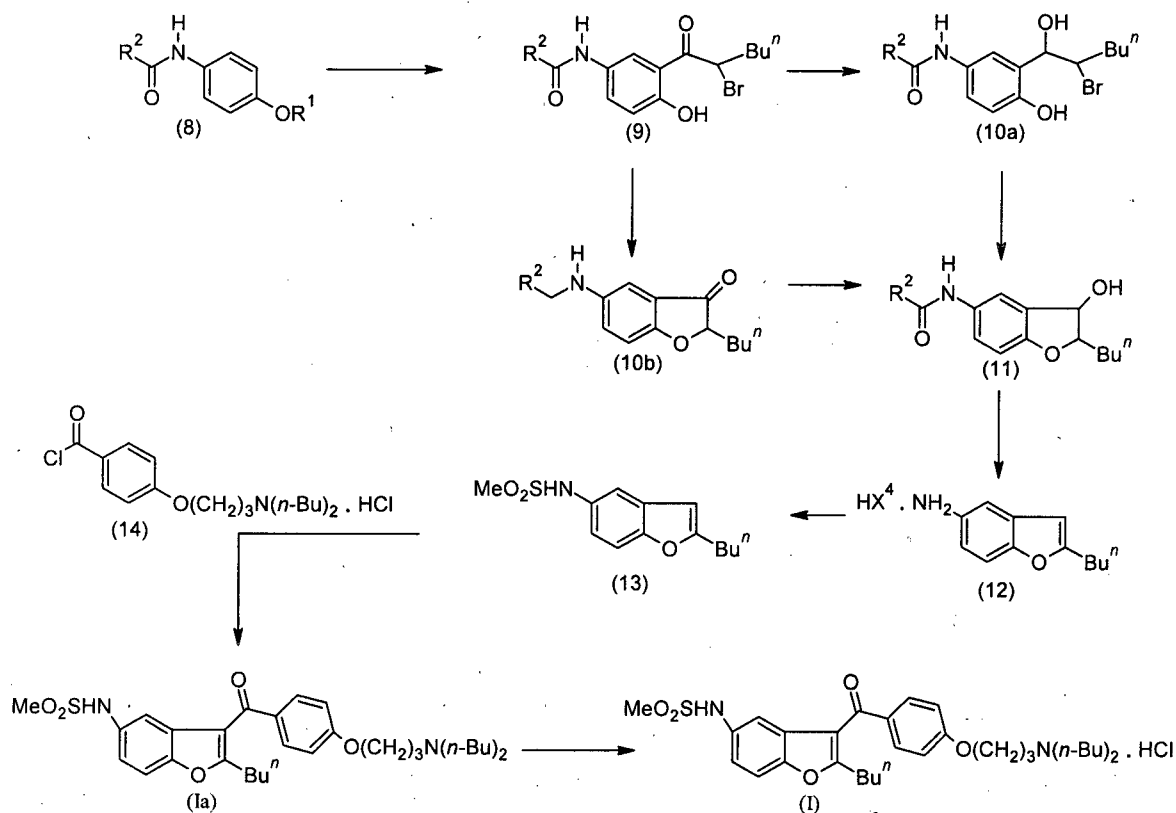
Dronedarone hydrochloride, *N*-[2-*n*-butyl-3-[4-[3-(di-*n*-butylamino)propoxy]benzoyl]-
15 benzofuran-5-yl]methanesulfonamide hydrochloride, having the formula (I), is a drug for the treatment of arrhythmia. The various methods for the preparation of dronedarone hydrochloride and/or its intermediates are disclosed in US 5,223,510, US 6,555,697, US 6,828,448, US 6,846,936, US 6,855,842, US 6,984,741, US 7,312,345, WO 2007/140989, WO 2010/132511 and US 2010/292319.

- US 5,223,510 (the '510 patent) discloses the preparation of various benzofurans, benzothiophenes, indoles, and indolizines as cardiovascular agents, including the synthesis of *N*-[2-*n*-butyl-3-[4-[3-(di-*n*-butylamino)propoxy]benzoyl]benzofuran-5-yl]methanesulfonamide hydrochloride (dronedarone hydrochloride) as depicted in
- 5 Scheme 1. The '510 patent discloses the synthesis of dronedarone by Friedel-Crafts acylation of 2-*n*-butyl-5-nitrobenzofuran (2) with anisoyl chloride (3) in presence of SnCl₄ to give 3-(4-methoxybenzoyl)-5-nitrobenzofuran (4) which on demethylation followed by etherification with 1-chloro-3-(di-*n*-butylamino)propane gave 2-butyl-3-[4-[(3-di-*n*-butylamino)propoxy]benzoyl]-5-nitrobenzofuran (6). The reduction of the
- 10 nitro group by platinum oxide to obtain the arylamine of formula (7) followed by *N*-methanesulfonylation using methanesulfonyl chloride gave *N*-[2-*n*-butyl-3-[4-[3-(di-*n*-butylamino)propoxy]benzoyl]benzofuran-5-yl]methanesulfonamide (Ia) (dronedarone base) which was then converted to its hydrochloride salt (I) (dronedarone hydrochloride) by treatment with HCl in diethyl ether.
- 15 In our hands, the sulfonamidation of the arylamine of formula (7) with methanesulfonyl chloride to dronedarone base (Ia) under the conditions described in the '510 patent invariably generated the undesired bis-sulfonamide impurity of formula (Ib) (Scheme 1) to an extent of ~5-10%. In order to obtain pure dronedarone base free from the bis-sulfonamide impurity (Ib), either column chromatography or
- 20 extensive recrystallization is required.



Scheme 1

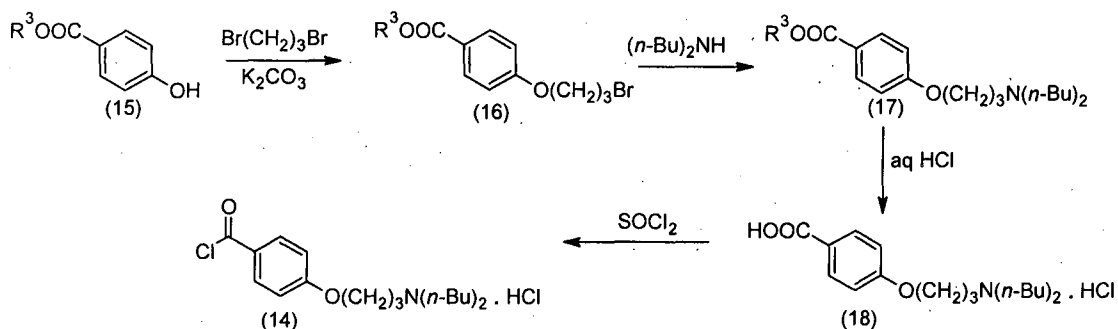
US 7,312,345 (the '345 patent) discloses the preparation of dronedarone
 5 hydrochloride as depicted in Scheme 2.



Scheme 2

The reaction is carried out by reacting *N*-(alkoxyphenyl)acylamide (8) with 2-bromohexanoyl chloride or bromide under Friedel-Crafts reaction conditions to form compound (9) which is optionally converted to 2-*n*-butyl-5-benzofuranamine free base or salt (12) via intermediate (10a) or (10b) and (11). Reaction of 2-*n*-butyl-5-benzofuranamine free base or salt with methanesulfonyl chloride gave *N*-(2-*n*-butyl-5-benzofuran-5-yl)methanesulfonamide (13). Friedel-Crafts acylation of *N*-(2-*n*-butyl-5-benzofuran-5-yl)methanesulfonamide (13) with 4-[(3-di-*n*-butylamino)propoxy]-benzoyl chloride hydrochloride (14) gave dronedarone base (Ia) which was then converted to its hydrochloride salt (I) using HCl in ethyl acetate.

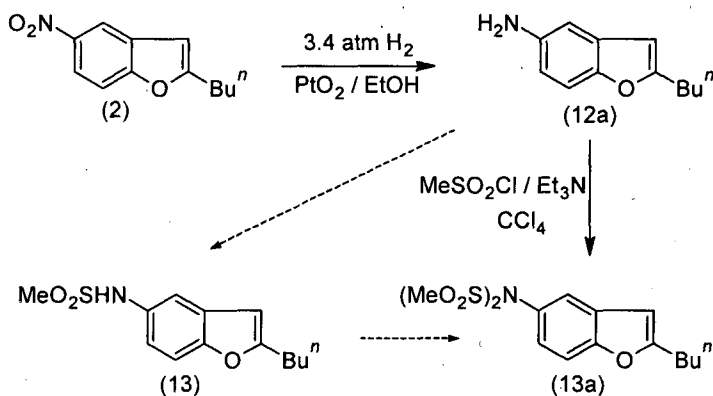
The preparation of the intermediate, 4-[(3-di-*n*-butylamino)propoxy]benzoyl chloride hydrochloride (14) for the preparation of dronedarone, is also reported in the '345 patent and is depicted in Scheme 3.



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Scheme 3

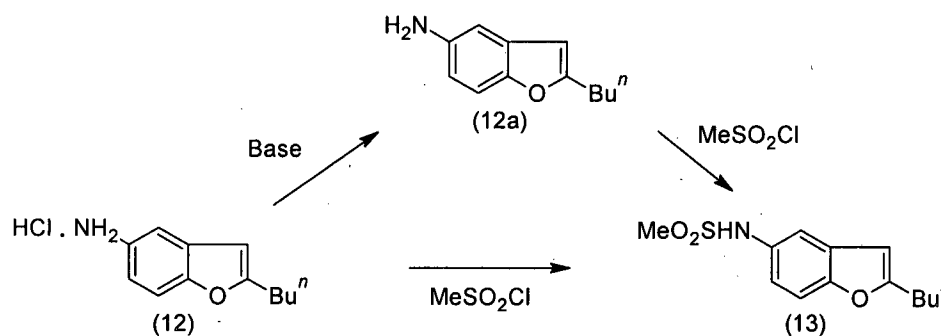
The '510 patent discloses the catalytic reduction (3.4 atm H₂/PtO₂/EtOH) of 2-*n*-butyl-5-nitrobenzofuran (2) to 2-*n*-butyl-5-benzofuranamine free base (12a), which on reaction with methanesulfonyl chloride in the presence of triethylamine as acid scavenger and carbon tetrachloride as a solvent gave *N*-(2-*n*-butylbenzofuran-5-yl)-*N*-(methylsulfonyl)methanesulfonamide (13a) instead of *N*-(2-*n*-butylbenzofuran-5-yl)methanesulfonamide (13) as depicted in Scheme 4.



Scheme 4

It has also been reported that in the preparation of *N*-(2-*n*-butylbenzofuran-5-yl)methanesulfonamide (13), it is difficult to drive the conversion of 2-*n*-butyl-5-benzofuranamine (12a) to completion in the presence of a base without the formation of a substantial quantity of *N*-(2-*n*-butylbenzofuran-5-yl)-*N*-(methylsulfonyl)methanesulfonamide (13a). In order to optimize the conversion of 2-*n*-butyl-5-benzofuranamine (12a) to the desired compound (13) it is necessary to stop the reaction when only partial conversion of the aryl amine has been achieved. This however leads to reduced yields.

This may be one of the reason as to why in the '345 patent the preparation of *N*-(2-*n*-butylbenzofuran-5-yl)methanesulfonamide (13) the sulfamidation reaction using methanesulfonyl chloride is carried out using either the hydrochloride salt of 2-*n*-butyl-5-benzofuranamine (12) or its *in situ* generated free base (12a), as depicted in Scheme 5.



Scheme 5

The process for dronedarone hydrochloride as described in the '345 patent is quite tedious (Schemes 2 & 3), and uses chromatography for the purification of dronedarone base (formula Ia).

On the other hand, the process described in the '510 patent suffers from several drawbacks as listed below:

- It uses toxic solvents dichloroethane (DCE) and carbon tetrachloride
- Uses expensive platinum oxide for the reduction of the nitro compound of formula (6) to the amine of formula (7).
- Mesylation of amine of formula (7) to dronedarone base of formula (Ia) (Scheme 1) invariably generates the bis-sulfonamide impurity of formula (Ib).
- The dronedarone base (formula Ia) is purified by column chromatography, which is tedious for commercial scale preparations.
- The purified free base is converted to its hydrochloride salt in a separate step by treating with HCl in diethyl ether. Diethyl ether is a flammable solvent and is unfriendly for commercial scale preparation.
- The overall yields for dronedarone hydrochloride are low.

US 6,846,936 (the '936 patent) discloses the process for the preparation of 2-*n*-butyl-3-[4-[3-(di-*n*-butylamino)propoxy]benzoyl]-5-nitrobenzofuran (6) using 4-[3-(di-*n*-butylamino)propoxy]benzoyl chloride (14) and 2-*n*-butyl-5-nitrobenzofuran (2) in presence of FeCl₃ which on reduction (3.4 atm H₂/PtO₂/EtOH) followed by treatment with methanesulfonyl chloride in the presence of triethylamine gave dronedarone base. The '936 patent also uses expensive PtO₂ for the reduction of nitro group to amino function. Besides, purification of dronedarone free base is performed once again by tedious column chromatography giving product with purity of only 96% purity. As in the '510 patent, dronedarone hydrochloride is prepared from dronedarone base using HCl in diethyl ether which is a highly flammable solvent.

US 6,828,448 (the '448 patent) discloses a process for the preparation of 2-*n*-butyl-5-(methanesulfonamido)benzofuran (13) by reduction of 2-*n*-butyl-5-nitrobenzofuran (2) (25 bar H₂, PtO₂, 60°C, EtOH) and sulfonylation with methanesulfonyl chloride

and subsequent reaction with 4-[3-(di-*n*-butylamino)propoxy]benzoyl chloride hydrochloride (14) gave dronedarone hydrochloride. The '448 patent also uses expensive PtO₂ for the reduction of nitro group to the corresponding amino function. Besides, a solvent mixture comprising of THF and MTBE is used for the mesylation
5 of the amine of formula (7) rendering tedious the recovery of the solvents. Like in the other prior art processes described *vide supra*, the salt formation to dronedarone hydrochloride is carried out in a separate step.

WO 2007/140989 discloses a process for preparation of the intermediate 2-*n*-butyl-3-(4-methoxybenzoyl)-5-nitrobenzofuran (4) by reaction of 2-*n*-butyl-5-nitrobenzofuran
10 (2) with 4-methoxybenzoyl chloride (3) in the presence of FeCl₃. However, the conversion of this intermediate of formula (4) to dronedarone hydrochloride is once again as per the '510 patent, with all the drawbacks as mentioned *vide supra*.

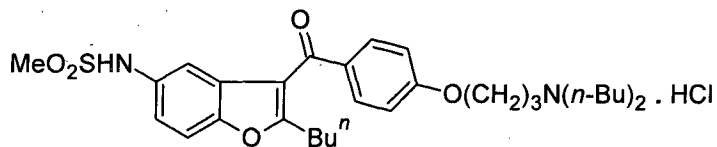
As described above, each of the reported prior art methods for the synthesis of dronedarone hydrochloride suffer from intrinsic disadvantages such as the use of
15 expensive catalyst, hazardous solvent(s), impurity issues, tedious purification steps etc.

There is thus a need for a simple, efficient and a commercially viable process which provides dronedarone hydrochloride in high yields and with high purity without the drawbacks of the prior art processes.

20 The present invention overcomes the drawbacks of the prior art processes and provides an efficient commercially viable process for the preparation of dronedarone hydrochloride (I). Further, the dronedarone hydrochloride produced with the present process has high purity and is completely free of the bis-sulfonamide impurity. The product obtained conforms to ICH grade purity specifications for bulk drugs, which
25 requires that known impurity should not be more than 0.15% and unknown impurity should not be more than 0.10%.

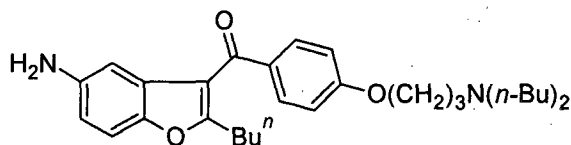
SUMMARY OF THE INVENTION

The present invention relates to a process for preparing compound of formula (I),



formula (I)

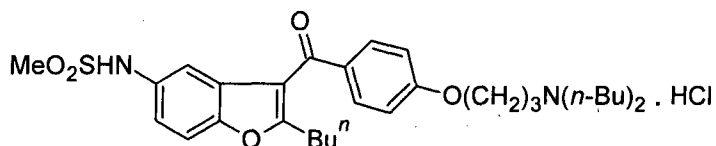
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formula (7)

comprising, heating compound of formula (7) with mesyl chloride in absence of a base in a hydrocarbon solvent or an ether or a halogenated solvent.

- 10 The present invention also relates to a process for the preparation of dronedarone hydrochloride, a compound of formula (I),

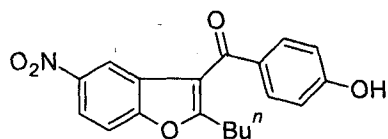


formula (I)

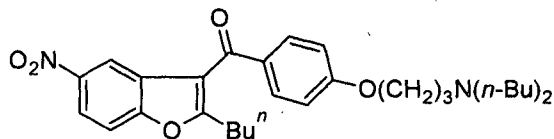
comprising,

- 15 a) reacting compound of formula (5) with 1-chloro-3-(di-*n*-butylamino)propane in a biphasic system comprising an aqueous phase containing an inorganic

base, an organic phase and a phase transfer catalyst to give compound of formula (6),

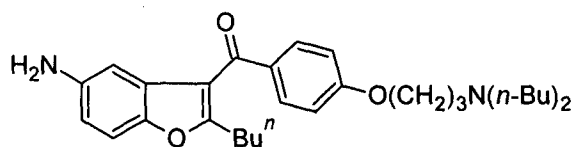


formula (5)



formula (6)

- 5 b) hydrogenating compound of formula (6) using palladium on charcoal or Raney nickel as catalyst, in a protic solvent or an aprotic solvent or a mixture thereof, to obtain compound of formula (7),

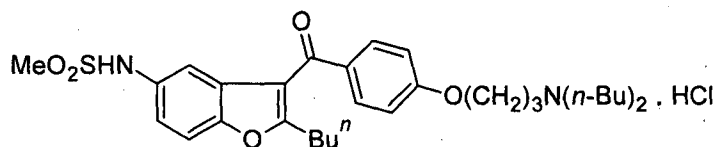


formula (7)

- 10 c) heating compound of formula (7) with mesyl chloride in the absence of a base in a hydrocarbon solvent or an ether or a halogenated solvent to obtain compound of formula (I).

DETAILED DESCRIPTION OF THE INVENTION

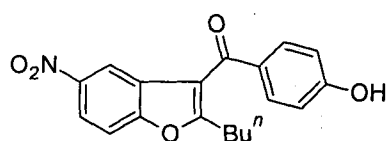
The present invention relates to a process for the preparation of dronedarone
15 hydrochloride, a compound of formula (I),



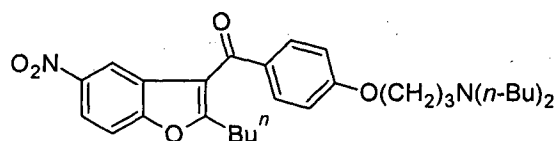
formula (I)

comprising,

- a) reacting compound of formula (5) with 1-chloro-3-(di-*n*-butylamino)propane in a biphasic system comprising an aqueous phase containing an inorganic base, an organic phase and a phase transfer catalyst to give compound of formula (6),

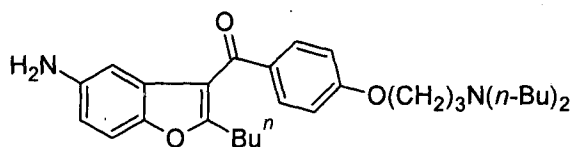


formula (5)



formula (6)

- b) hydrogenating compound of formula (6) using palladium on charcoal or Raney nickel as catalyst in a protic solvent or an aprotic solvent, or a mixture thereof, to obtain compound of formula (7),

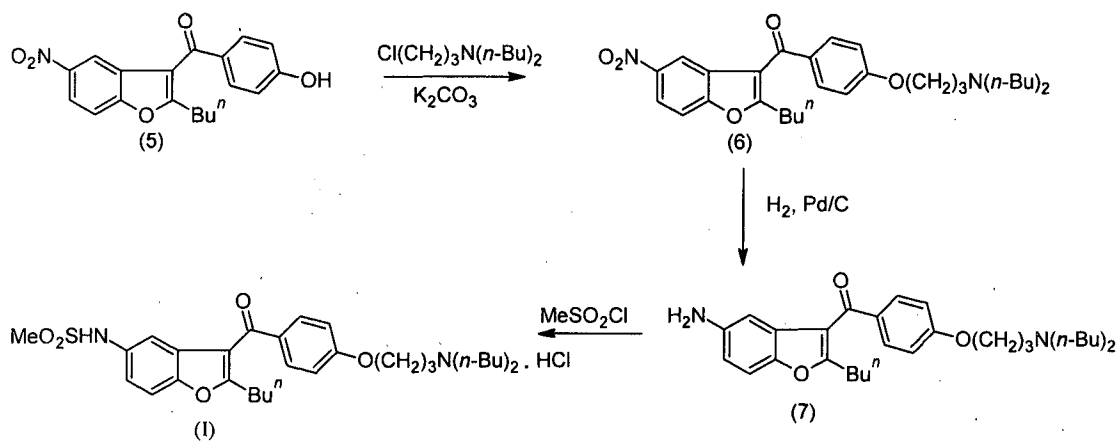


formula (7)

- c) heating compound of formula (7) with mesyl chloride in the absence of a base in a hydrocarbon solvent or an ether or a halogenated solvent to obtain compound of formula (I).

The present invention relates to a process for the preparation of dronedarone hydrochloride, a compound of formula (I) as depicted in Scheme 6. The compound of formula (5) is reacted with 1-chloro-3-(di-*n*-butylamino)propane in a biphasic system comprising an aqueous phase containing an inorganic base such as an hydroxide, carbonate or bicarbonate of an alkaline earth metal, an organic phase comprising of a

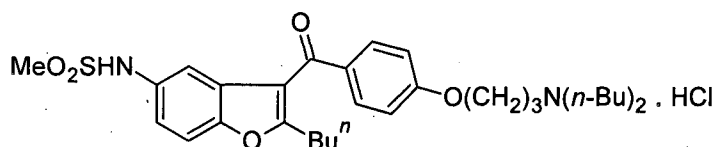
water immiscible solvent chosen from the group selected from a saturated hydrocarbon, an aromatic hydrocarbon, an ether or a halogenated solvent, and a phase transfer catalyst selected from a quaternary ammonium or phosphonium salt to give compound of formula (6). The compound of formula (6) is hydrogenated using
 5 palladium on charcoal or Raney nickel as catalyst in a protic solvent or an aprotic solvent, or a mixture thereof to obtain compound of formula (7), isolated optionally as an acid addition salt. The compound of formula (7) is heated with mesyl chloride in the absence of a base in a hydrocarbon solvent to obtain dronedarone hydrochloride of formula (I).



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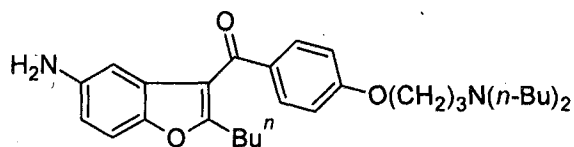
Scheme 6

In one preferred embodiment the present invention provides a process for preparing compound of formula (I),



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formula (I)



formula (7)

comprising, heating compound of formula (7) with mesyl chloride in absence of a base in a hydrocarbon solvent or an ether or a halogenated solvent.

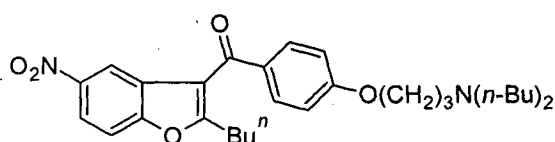
- 5 In another preferred embodiment the present invention provides a process for preparing compound of formula (I), substantially free of the bis-sulfonamide impurity of formula (Ib).

In yet another preferred embodiment, the present invention provides a process for preparing compound of formula (I), wherein the reaction of formula (7) with mesyl
10 chloride is carried out at temperature of 40-120°C, preferably at 80-85°C.

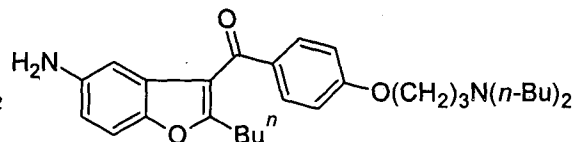
In yet another preferred embodiment the present invention provides a process for preparing compound of formula (I), wherein the reaction of formula (7) with mesyl chloride is carried out in a hydrocarbon solvent selected from a saturated hydrocarbon containing 2 to 10 carbon atoms such as pentane, hexane, heptanes etc, or an
15 substituted or unsubstituted aromatic hydrocarbon such as benzene, toluene etc, ether such as diethyl ether, ethyl methyl ether etc or halogenated solvents such as dichloromethane, dichloroethane etc.

In yet another preferred embodiment the present invention provides a process for preparing compound of formula (I), wherein the reaction of formula (7) with mesyl
20 chloride is carried out in a hydrocarbon solvent selected from a saturated hydrocarbon or an aromatic hydrocarbon, most preferably the solvent is toluene.

In yet another preferred embodiment the present invention provides a process for preparing compound of formula (7),



formula (6)



formula (7)

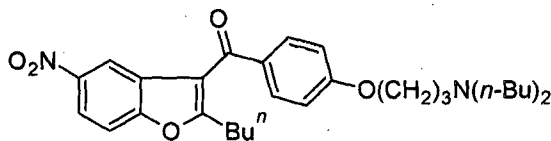
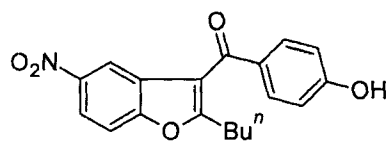
comprising, hydrogenating compound of formula (6) using palladium on charcoal or Raney nickel as catalyst, in a protic solvent or an aprotic solvent or a mixture to
5 obtain compound of formula (7) or its salt.

In yet another preferred embodiment the present invention provides a process for preparing compound of formula (7), wherein the hydrogenation of compound of formula (6) is performed using palladium on charcoal or Raney nickel as catalyst, preferably the hydrogenation catalyst is palladium on charcoal.

10 In yet another preferred embodiment the present invention provides a process for preparing compound of formula (7), wherein the hydrogenation reaction is carried out in a protic solvent or an aprotic solvent, or a mixture thereof, wherein the protic solvent is an alcohol, preferably methanol, ethanol or 2-propanol, and the aprotic solvent is dichloromethane. Most preferably the hydrogenation is carried out in 2-
15 propanol.

In yet another preferred embodiment the present invention provides a process for preparing the dioxalate salt of compound of formula (7).

In yet another preferred embodiment the present invention provides a process for preparing compound of formula (6),



20

formula (5)**formula (6)**

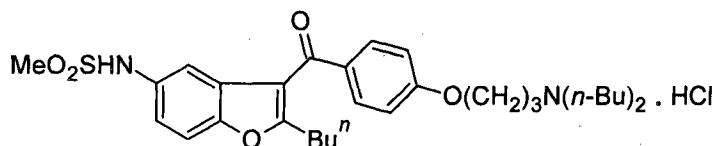
comprising, reacting compound of formula (5) with 1-chloro-3-(di-*n*-butylamino)propane in a biphasic system comprising an aqueous phase containing an inorganic base, an organic phase and a phase transfer catalyst.

- 5 In another preferred embodiment, the present invention provides a process for preparing compound of formula (6), wherein inorganic base used is selected from hydroxide, carbonate or bicarbonate of an alkaline earth metal, preferably the inorganic base is sodium hydroxide.

- 10 In yet another preferred embodiment the present invention provides a process for preparing compound of formula (6), wherein the phase transfer catalyst used is a quaternary ammonium salt, preferably the phase transfer catalyst is selected from methyl-*N,N,N*-trialkyl(C_8 - C_{10})ammonium chlorides viz. Adogens, most preferably *N*-methyl-*N,N,N*-trioctylammonium chloride (Adogen[®] 464).

- 15 In yet another preferred embodiment the present invention provides a process for preparing compound of formula (6), wherein the organic phase used comprises of a water immiscible solvent selected from the group comprising of a saturated hydrocarbon, an aromatic hydrocarbon, an ether, or a halogenated solvent, preferably the water immiscible solvent is dichlormethane.

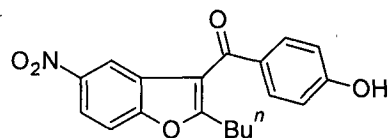
- 20 In one preferred embodiment the present invention provides a process for preparing compound of formula (I),

**formula (I)**

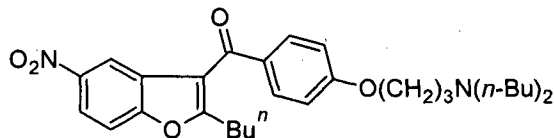
comprising,

- (a) reacting compound of formula (5) with 1-chloro-3-(di-*n*-butylamino)propane in a biphasic system comprising an aqueous phase containing an inorganic base, an organic phase and a phase transfer catalyst to give compound of formula (6),

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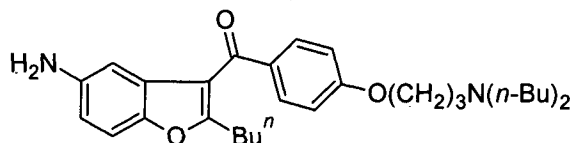
formula (5)



formula (6)

- (b) hydrogenating compound of formula (6) using palladium on charcoal or Raney nickel as catalyst in a protic solvent or an aprotic solvent, or a mixture thereof, to obtain compound of formula (7),

10



formula (7)

- (c) heating compound of formula (7) with mesyl chloride in absence of a base in a hydrocarbon solvent or an ether or a halogenated solvent to obtain compound of formula (I).

- 15 In another preferred embodiment, the present invention provides a process for preparing compound of formula (I), wherein inorganic base used in step (a) is selected from hydroxide, carbonate or bicarbonate of an alkaline earth metal, preferably the inorganic base is sodium hydroxide.

- In yet another preferred embodiment the present invention provides a process for
20 preparing compound of formula (I), wherein the phase transfer catalyst used in step

(a) is a quaternary ammonium salt, preferably the phase transfer catalyst is selected from methyl-*N,N,N*-trialkyl(C₈-C₁₀)ammonium chlorides viz. Adogens, most preferably *N*-methyl-*N,N,N*-trioctylammonium chloride (Adogen[®] 464).

5 In yet another preferred embodiment the present invention provides a process for preparing compound of formula (I), wherein the organic phase used in step (a) comprises of a water immiscible solvent selected from the group comprising of a saturated hydrocarbon, an aromatic hydrocarbon, an ether, or a halogenated solvent, preferably the water immiscible solvent is dichloromethane.

10 In yet another preferred embodiment the present invention provides a process for preparing compound of formula (I), wherein the hydrogenation of compound of formula (6) in step (b) is performed using palladium on charcoal or Raney nickel as catalyst, preferably the hydrogenation catalyst is palladium on charcoal.

15 In yet another preferred embodiment the present invention provides a process for preparing compound of formula (I), wherein the hydrogenation reaction in step (b) is carried out in a protic solvent or an aprotic solvent, or a mixture thereof, wherein the protic solvent is an alcohol, preferably methanol, ethanol or 2-propanol, and the aprotic solvent is dichloromethane. Most preferably the hydrogenation in step (b) is carried out in 2-propanol.

20 In yet another preferred embodiment the present invention the compound of formula (7) is isolated directly from the hydrogenated mixture as a dioxalate salt.

In yet another preferred embodiment the present invention provides a process for preparing compound of formula (I), wherein the reaction of formula (7) with mesyl chloride in step (c) is carried out at temperature of 40-120°C, preferably at 80-85°C.

25 In yet another preferred embodiment the present invention provides a process for preparing compound of formula (I), wherein the reaction of formula (7) with mesyl

chloride in step (c) is carried out in a hydrocarbon solvent selected from a saturated hydrocarbon or an aromatic hydrocarbon, most preferably the solvent is toluene.

In yet another preferred embodiment the present invention provides a process for preparing compound of formula (I), free of the bis-sulfonamide impurity of formula
5 (Ib).

EXPERIMENTAL:

The examples that follow do not limit the scope of the present invention and are included as illustrations:

Example-1:

10 2-*n*-Butyl-3-[4-[(3-di-*n*-butylamino)propoxy]benzoyl]-5-nitrobenzofuran (6)

To a suspension of 10 g (0.03 mole) of 2-*n*-butyl-3-(4-hydroxybenzoyl)-5-nitrobenzofuran in 50 ml dichloromethane was added 60 ml of 15% aqueous sodium hydroxide solution, 7.2 g (0.04 mole) of 1-chloro-3-(di-*n*-butylamino)propane and 0.2 g (2.0% w/w) of Adogen[®] 464. The mixture was stirred at r.t. for 24 hours, an
15 additional 0.1 g (1% w/w) of Adogen[®] 464 was added and the stirring continued for further 24 hours. The mixture was settled and the product enriched organic layer was separated. The aqueous layer was extracted once with methylene chloride, the combined organic layers were washed with DM water and concentrated under vacuum to obtain residue of 2-*n*-butyl-3-[4-[3-di-*n*-butylamino)propoxy]benzoyl]-5-
20 nitrobenzofuran (6) as a gummy mass.

Example -2:

2-*n*-Butyl-3-[4-[(3-di-*n*-butylamino)propoxy]benzoyl]-5-aminobenzofuran (7), as dioxalate salt

The above residue (example 1) of 2-*n*-butyl-3-[4-[3-di-*n*-butylamino)propoxy]-benzoyl]-5-nitrobenzofuran (6) was dissolved in 2-propanol, 1.6 g (10% palladium on carbon, 50% wet) was added and the mixture was hydrogenated for 24 hours at r.t. After completion of reaction the catalyst was filtered and 7.7 g (0.07 mole) oxalic acid dihydrate was added. The resulting suspension was stirred at r.t. for 2 hours, The solid was filtered and dried to afford 15 g 2-*n*-butyl-3-[4-[3-(di-*n*-butylamino)propoxy]-benzoyl]-5-aminobenzofuran (7) as a dioxalate salt.

Example -3:

***N*-[2-*n*-butyl-3-[4-[3-(di-*n*-butylamino)propoxy]benzoyl]benzofuran-5-yl]-methanesulfonamide hydrochloride (dronedarone hydrochloride)**

2-*n*-butyl-3-[4-[3-di-*n*-butylamino)propoxy]benzoyl]-5-aminobenzofuran dioxalate salt 10 g, was suspended in water and pH adjusted to 10 with liquor ammonia. The free base obtained was extracted into toluene (50ml). To the toluene extract was added 2.1 g (0.018 mole) methanesulfonyl chloride at r.t. The mixture was heated at 80-85°C for 2 hour and concentrated under vacuum at 50-55°C. The residue was dissolved in dichloromethane and washed with DM water. The dichloromethane layer was concentrated and degassed to obtain dronedarone hydrochloride devoid of bis-sulfonamide impurity (by UPLC analysis). Recrystallization from acetone provided dronedarone hydrochloride with purity >99.5% and free from any bis-sulfonamide impurity.

The scope of present invention is not limited by the description, examples and suggested uses described herein, and modifications can be made without departing from the spirit of invention.

Example -4:

Manufacture of dronedarone hydrochloride on plant scale

To a suspension of 2-*n*-butyl-3-(4-hydroxybenzoyl)-5-nitrobenzofuran (50 kg, 147.34 mole) in dichloromethane (250 lit) (in 1KL SS reactor) were charged sequentially 15% aqueous sodium hydroxide solution (300 lit), 1-chloro-3-di-*n*-butylaminopropane (36 kg, 176.03 mole) and Adogen[®] 464 (1.0 kg). The mixture was stirred at r.t. for 24 hours and then charged a second lot of Adogen[®] 464 (0.5 kg), and stirring was continued for further 24 hours and then kept for layer separation. The product enriched methylene chloride layer was separated and the aqueous layer was extracted with methylene chloride. Combined methylene chloride layers were washed with DM water and concentrated under vacuum to obtain residue of 2-*n*-Butyl-3-[4-(3-di-*n*-butylaminopropoxy)benzoyl]-5-nitrobenzofuran.

To the above residue of 2-*n*-Butyl-3-[4-(3-di-*n*-butylaminopropoxy)benzoyl]-5-nitrobenzofuran was charged isopropyl alcohol (300 lit), stirred to get a clear solution and then charged 10% w/w palladium on carbon, (3.65 kg, 50% wet). Hydrogenation was performed at r.t. for 24 hours at 1 to 1.5 kg/ sq.cm pressure (1KL SS autoclave). The catalyst was filtered and to the clear filtrate was charged oxalic acid dihydrate (38.5 kg, 305.55 mole). The resulting suspension was stirred at r.t. for 2 hours, filtered and dried to obtain 2-*n*-butyl-3-[4-(3-di-*n*-butylaminopropoxy)benzoyl]-5-aminobenzofuran dioxalate salt (75 kg).

The above obtained 2-*n*-butyl-3-[4-(3-di-*n*-butylaminopropoxy)benzoyl]-5-aminobenzofuran dioxalate salt (65 kg) was converted to its free base by treatment with alkali and extracted into toluene. To the solution of the free base in toluene (325 lit) was charged methanesulfonyl chloride (13.7 kg, 119.59 mole) at r.t. then heated to 80-85°C and stirred for 2 hour (0.5KL GLR). Toluene was completely stripped off and the resulting residue was dissolved in methylene chloride to get a clear solution. The solution was washed with DM water and the solvent was completely stripped off.

The resulting residue was recrystallized from acetone to obtain dronedarone hydrochloride (40 kg); purity (by UPLC) was 99.8%, conformed to ICH specifications and was free of the bis-sulfonamide impurity.

Example 5:

5 UPLC analytical method for detection of bis-sulfonamide impurity

Buffer solution: Transfer 1.2g of ammonium dihydrogen orthophosphate in 1000ml of Milli Q water. Add 5 ml of triethylamine and adjust the pH of this solution to 3.5 ± 0.1 with orthophosphoric acid.

Mobile phase-A: Prepare mobile phase-A by mixing 450 volumes of buffer solution and 50 volumes of acetonitrile. Filter through 0.22 μ filter paper and degas prior to use.

Mobile phase-B: Prepare mobile phase-B by mixing 150 volumes of buffer solution, 250 volumes of acetonitrile and 100 volumes of methanol. Filter through 0.22 μ filter paper and degas prior to use.

15 Diluent: Mix Mobile phase A and Mobile phase B in the ratio of 50:50 as diluent. Filter through 0.22 μ filter paper and degas prior to use.

Standard solution: Transfer 1.0 ml of standard stock solution to a 10 ml volumetric flask and dilute upto the mark with diluent.

20 System suitability solution: Transfer accurately weighed about 10 mg of Dronedarone hydrochloride WS and 1.0 ml of standard stock solution to a 10 ml volumetric flask. Dissolve in and dilute up to mark with diluent

Test Solution: Transfer about 25 mg of sample, accurately weighed, to a 25 ml volumetric flask. Dissolve in and dilute up to mark with diluent.

Chromatographic system: Use a suitable Ultra Performance Liquid Chromatograph (UPLC) with the following conditions.

Column	Acquity UPLC BEH shield RP 18 (150 x 2.1) mm, 1.7 μ
Flow rate	0.4 ml/min.
Wavelength	215 nm.
Run time	30 min.
Injection volume	1 μ l
Sample cooler	15°C
Column oven	45°C
Sampling Rate	20points/sec

The system is also equipped to deliver the two phases in a programmed manner as shown in the following below table,

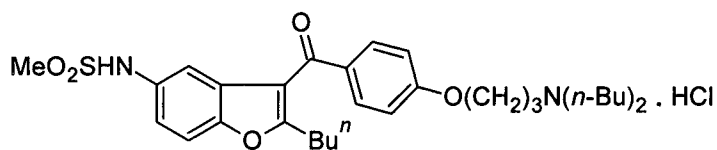
Time (min)	% Mobile phase-A	% Mobile phase-B
0	60	40
21	20	80
27	20	80
27.1	60	40
30	60	40

Procedure: Inject 1 μ l of diluent into the chromatographic system and record the chromatograms up to 30 min. Inject 1 μ l of system suitability solution into the chromatographic system and record the chromatograms up to 30 min. Inject 1 μ l of standard solution six times and calculate the mean and %RSD of each peak. The %RSD of each peak should be less than 10%. Inject 1 μ l test solution into the system and record the chromatograms up to 30 min.

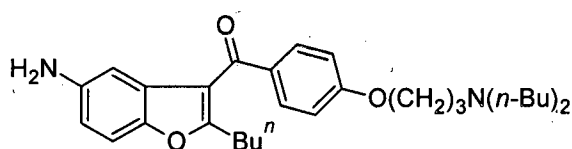
Dronedarone hydrochloride prepared according to the process of the present invention did not show a peak for bis-sulfonamide impurity at a relative retention time of 1.09 when tested according to the above method (LoD & LoQ for bis-sulfonamide impurity are 0.0042% & 0.0083% respectively), however this impurity was found in
5 dronedarone hydrochloride when prepared according to the prior art.

We Claim;

1. A process for preparing compound of formula (I),



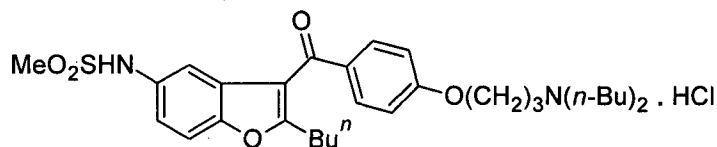
formula (I)



formula (7)

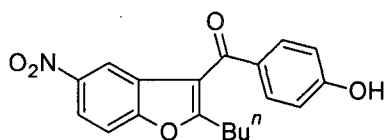
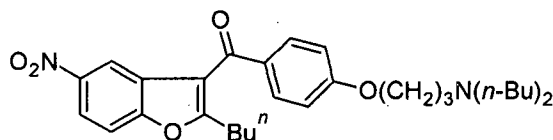
comprising, heating compound of formula (7) with mesyl chloride in absence of a base in a hydrocarbon solvent or an ether or a halogenated solvent.

2. The process according to claim 1, wherein the reaction is carried out at temperature of 40-120°C.
3. The process according to claim 2, wherein the reaction is carried out at temperature of 80-85°C.
4. The process according to claim 1, wherein the hydrocarbon solvent selected from a saturated hydrocarbon or an aromatic hydrocarbon.
5. The process according to claim 4, wherein the hydrocarbon solvent is toluene.
6. A process according to claim 1, for the preparation of compound of formula (I),

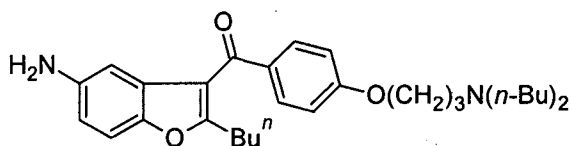
**formula (I)**

comprising,

- 5 a) reacting compound of formula (5) with 1-chloro-3-(di-*n*-butylamino)-propane in a biphasic system comprising an aqueous phase containing an inorganic base, an organic phase and a phase transfer catalyst to give compound of formula (6),

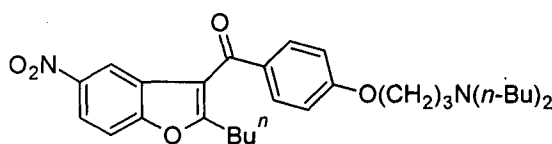
**formula (5)****formula (6)**

- 10 b) hydrogenating compound of formula (6) in presence of palladium on charcoal or Raney nickel as catalyst in a protic solvent or an aprotic solvent, or a mixture thereof, to obtain compound of formula (7),

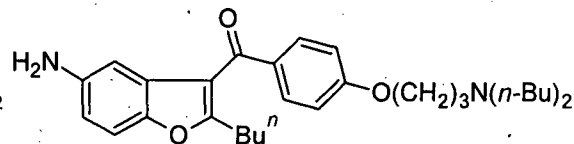
**formula (7)**

- 15 c) heating compound of formula (7) with mesyl chloride in the absence of a base in a hydrocarbon solvent or an ether or a halogenated solvent to obtain compound of formula (I).

7. A process for preparing compound of formula (7),

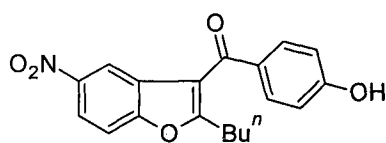


formula (6)

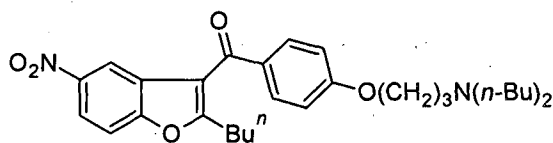


formula (7)

- 5 comprising, hydrogenating compound of formula (6) in presence of palladium on charcoal or Raney nickel as catalyst, in a protic solvent or an aprotic solvent or a mixture thereof to obtain compound of formula (7) and optionally isolating it as a salt.
8. The process according to claim 7, wherein the hydrogenation of compound of formula (6) is carried out in presence of palladium on charcoal.
- 10 9. The process according to claim 7, wherein the protic solvent is an alcohol, selected from methanol, ethanol or 2-propanol, and the aprotic solvent is dichloromethane.
10. The process according to claim 9, wherein the protic solvent is 2-propanol.
11. A process according to claim 7, for preparation of dioxalate salt of compound of formula (7).
- 15 12. A process for preparing compound of formula (6),



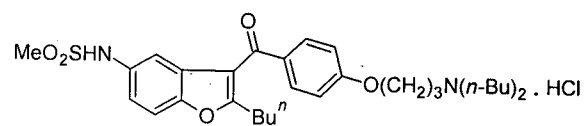
formula (5)



formula (6)

comprising, reacting compound of formula (5) with 1-chloro-3-(di-*n*-butylamino)propane in a biphasic system comprising an aqueous phase containing an inorganic base, an organic phase and a phase transfer catalyst.

- 5 13. The process according to claim 12, wherein inorganic base is selected from hydroxide, carbonate or bicarbonate of an alkaline earth metal.
14. The process according to claim 13, wherein inorganic base is sodium hydroxide.
15. The process according to claim 12, wherein the phase transfer catalyst is a quaternary ammonium salt, selected from methyl-*N,N,N*-trialkyl(C₈-C₁₀)ammonium chlorides viz. Adogens.
- 10 16. The process according to claim 15, wherein the phase transfer catalyst is *N*-methyl-*N,N,N*-trioctylammonium chloride (Adogen[®] 464).
17. The process according to claim 12, wherein the organic phase comprises of a water immiscible solvent selected from the group comprising of a saturated hydrocarbon, an aromatic hydrocarbon, an ether, or a halogenated solvent.
- 15 18. The process according to claim 17, wherein the water immiscible solvent is a halogenated solvent.
19. The process according to claim 18, wherein the water immiscible solvent is dichloromethane.
- 20 20. A compound of formula (I), prepared according to claim 1.



formula (I).