SYNTHETIC METHODS FOR SPIRO-OXINDOLE COMPOUNDS

CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefit under 35 U.S.C. § 119(e) of U.S. Provisional Patent Application No. 61/251,335, filed October 14, 2009. This application is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

The present invention is directed to improved methods of preparing certain spiro-oxindole compounds as well as various intermediates involved therein. In particular, this invention is directed to methods of preparing spiro-oxindole compounds, and their pharmaceutically acceptable salts, which are useful in treating sodium channel-mediated diseases or conditions, such as pain, as well as other diseases and conditions associated with the mediation of sodium channels.

BACKGROUND OF THE INVENTION

Sodium channels play a diverse set of roles in maintaining normal and pathological states, including the long recognized role that voltage gated sodium channels play in the generation of abnormal neuronal activity and neuropathic or pathological pain. Damage to peripheral nerves following trauma or disease can result in changes to sodium channel activity and the development of abnormal afferent activity including ectopic discharges from axotomised afferents and spontaneous activity of sensitized intact nociceptors. These changes can produce long-lasting abnormal hypersensitivity to normally innocuous stimuli, or allodynia. Examples of neuropathic pain include, but are not limited to, post-herpetic neuralgia, trigeminal neuralgia, diabetic neuropathy, chronic lower back pain, phantom limb pain, and pain resulting from cancer and chemotherapy, chronic pelvic pain, complex regional pain syndrome and related neuralgias.

There have been some advances in treating neuropathic pain symptoms by using medications, such as gabapentin, and more recently pregabalin, as short-term, first-line treatments. However, pharmacotherapy for neuropathic pain has generally had limited success with little response to commonly used pain reducing drugs, such as NSAIDS and opiates. Consequently, there is still a considerable need to explore novel treatment modalities.

There remain a limited number of potent effective sodium channel blockers with a minimum of adverse events in the clinic. There is also an unmet medical need to treat neuropathic pain and other sodium channel associated pathological states effectively and without adverse side effects.

PCT Published Patent Application No. WO 2006/110917, PCT Published Patent Application No. WO 2010/45251 and PCT Patent Application No. PCT/US2010/040187 discloses certain spiro-oxindole compounds. These compounds are disclosed therein as being useful for the treatment of sodium channel-mediated diseases, preferably diseases related to pain, central nervous conditions such as epilepsy, anxiety, depression and bipolar disease; cardiovascular conditions such as arrhythmias, atrial fibrillation and ventricular fibrillation; neuromuscular conditions such as restless leg syndrome; neuroprotection against stroke, neural trauma and multiple sclerosis; and channelopathies such as erythromelalgia and familial rectal pain syndrome.

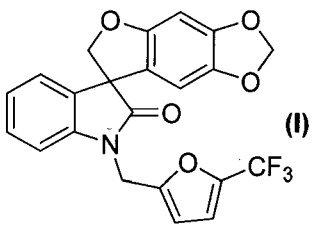
Methods of preparing these compounds and pharmaceutical compositions containing them are also disclosed in PCT Published Patent Application No. WO 2006/110917, PCT Published Patent Application No. WO 2010/45251 and PCT Patent Application No. PCT/US2010/040187.

There exists, therefore, a need for improved methods of preparing certain spiro-oxindole compounds.

SUMMARY OF THE INVENTION

The present invention is directed to methods of preparing certain spiro-oxindole compounds as single stereoisomers or single enantiomers, or mixtures thereof, or as pharmaceutically acceptable salts thereof. These compounds are useful in treating sodium channel-mediated diseases and conditions, such as pain.

Accordingly, in one aspect, this invention is directed to a method of preparing a compound of formula (I):



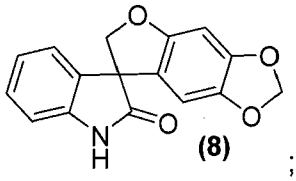
(I)

;

or a pharmaceutically acceptable salt thereof, as a single stereoisomer or enantiomer

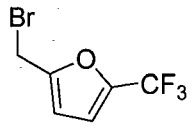
or a mixture thereof;

wherein the method comprises treating a compound of formula (8):



(8) ;

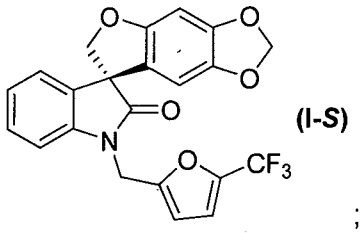
or a pharmaceutically acceptable salt thereof, with a compound of formula (9):



(9) ;

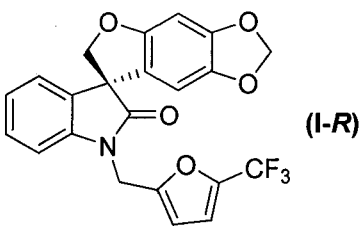
or a pharmaceutically acceptable salt thereof, under suitable conditions to provide the compound of formula (I), or a pharmaceutically acceptable salt thereof, as a single stereoisomer or enantiomer or a mixture thereof.

In another aspect, this invention is directed to a method of preparing a compound of formula (I-*S*):



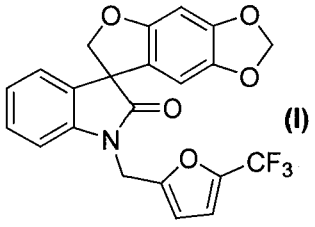
(I-*S*) ;

or a pharmaceutically acceptable salt thereof, and a compound of formula (I-*R*):



(I-*R*) ;

or a pharmaceutically acceptable salt thereof, wherein the method comprises resolving a compound of formula (I):

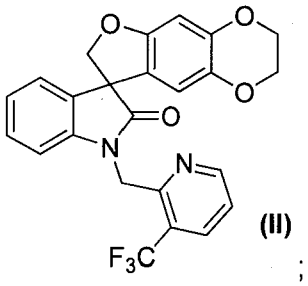


(I)

;

or a pharmaceutically acceptable salt thereof, as a single stereoisomer or enantiomer or a mixture thereof; under suitable conditions to yield a compound of formula (I-*S*), or a pharmaceutically acceptable salt thereof, and a compound of formula (I-*R*), or a pharmaceutically acceptable salt thereof.

In another aspect, this invention is directed to a method of preparing a compound of formula (II):

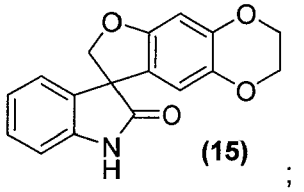


(II)

;

or a pharmaceutically acceptable salt thereof, as a single stereoisomer or enantiomer or a mixture thereof;

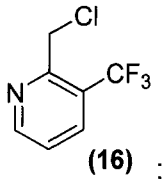
wherein the method comprises treating a compound of formula (15):



(15)

;

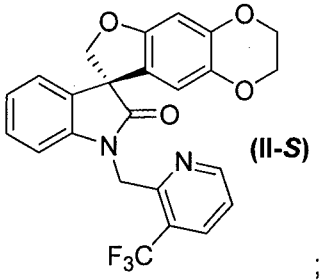
or a pharmaceutically acceptable salt thereof, with a compound of formula (16):



(16) ;

or a pharmaceutically acceptable salt thereof, under suitable conditions to provide the compound of formula (II), or a pharmaceutically acceptable salt thereof, as a single stereoisomer or enantiomer or a mixture thereof.

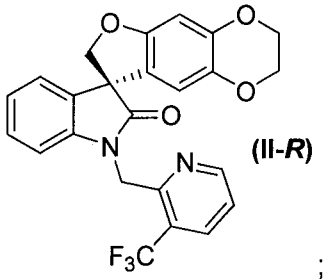
In another aspect, this invention is directed to a method of preparing a compound of formula (II-*S*):



(II-*S*)

;

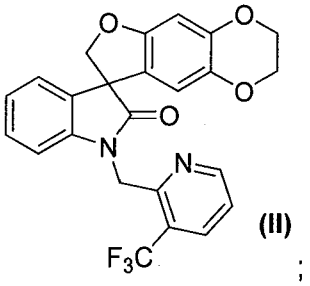
or a pharmaceutically acceptable salt thereof, and a compound of formula (II-*R*):



(II-*R*)

;

or a pharmaceutically acceptable salt thereof, wherein the method comprises resolving a compound of formula (II):



(II)

;

or a pharmaceutically acceptable salt thereof, as a single stereoisomer or enantiomer or a mixture thereof; under suitable conditions to yield a compound of formula (II-*S*), or a pharmaceutically acceptable salt thereof, and a compound of formula (II-*R*), or a pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

As used in the specification and appended claims, unless specified to the

contrary, the following terms have the meaning indicated:

"Amino" refers to the $-NH_2$ substituent.

"Cyano" refers to the –CN substituent.

"Hydroxyl" refers to the –OH substituent.

"Imino" refers to the =NH substituent.

"Nitro" refers to the $-NO_2$ substituent.

"Oxo" refers to the =O substituent.

"Trifluoromethyl" refers to the $-CF_3$ substituent.

"Analgesia" refers to an absence of pain in response to a stimulus that would normally be painful.

"Allodynia" refers to a condition in which a normally innocuous sensation, such as pressure or light touch, is perceived as being extremely painful.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

"Mammal" includes humans and both domestic animals such as laboratory animals and household pets, (*e.g.*, cats, dogs, swine, cattle, sheep, goats, horses, and rabbits), and non-domestic animals such as wildelife and the like.

"Pharmaceutically acceptable salt" includes both acid and base addition salts.

"Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as, but are not limited to, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as, but not limited to, acetic acid, 2,2-dichloroacetic acid, adipic acid, alginic acid, ascorbic acid, aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, camphoric acid, camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, gluconic acid, glucuronic acid, glutamic acid, glutaric acid, 2-oxo-glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, isobutyric acid, lactic acid, lactobionic acid, lauric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, mucic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, propionic acid,

pyroglutamic acid, pyruvic acid, salicylic acid, 4-aminosalicylic acid, sebacic acid, stearic acid, succinic acid, tartaric acid, thiocyanic acid, *p*-toluenesulfonic acid, trifluoroacetic acid, undecylenic acid, and the like.

"Pharmaceutically acceptable base addition salt" refers to those salts which retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Salts derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Preferred inorganic salts are the ammonium, sodium, potassium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as ammonia, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, diethanolamine, ethanolamine, deanol, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, benethamine, benzathine, ethylenediamine, glucosamine, methylglucamine, theobromine, triethanolamine, tromethamine, purines, piperazine, piperidine, *N*-ethylpiperidine, polyamine resins and the like. Particularly preferred organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline and caffeine.

"Treating" or "treatment" as used herein covers the treatment of the disease or condition of interest in a mammal, preferably a human, having the disease or condition of interest, and includes:

(i) preventing the disease or condition from occurring in a mammal, in particular, when such mammal is predisposed to the condition but has not yet been diagnosed as having it;

(ii) inhibiting the disease or condition, *i.e.*, arresting its development;

(iii) relieving the disease or condition, *i.e.*, causing regression of the disease or condition; or

(iv) relieving the symptoms resulting from the disease or condition, *i.e.*, relieving pain without addressing the underlying disease or condition.

As used herein, the terms "disease" and "condition" may be used interchangeably or may be different in that the particular malady or condition may not have a known causative agent (so that etiology has not yet been worked out) and it is

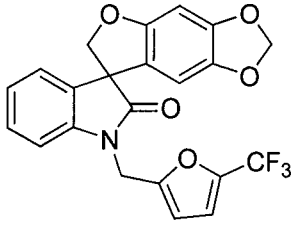
therefore not yet recognized as a disease but only as an undesirable condition or syndrome, wherein a more or less specific set of symptoms have been identified by clinicians.

The compounds prepared herein may contain one or more asymmetric centres and may thus give rise to enantiomers that may be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)- or, as (D)- or (L)- for amino acids. The present invention is meant to include all such possible enantiomers, as well as their racemic and optically pure forms. Optically active (+) and (-), (*R*)- and (*S*)-, or (D)- and (L)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, for example, chromatography and fractional crystallisation, or by the techniques disclosed herein. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC).

A "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures, which are not interchangeable. The present invention contemplates various stereoisomers and mixtures thereof and includes "enantiomers", which refers to two stereoisomers whose molecules are nonsuperimposeable mirror images of one another.

The chemical naming protocol and structure diagrams used herein are a modified form of the I.U.P.A.C. nomenclature system, using the ACD/Name Version 9.07 software program, wherein the compounds of the invention are named herein as derivatives of the central core structure, *i.e.*, the 2-oxindole structure. For complex chemical names employed herein, a substituent group is named before the group to which it attaches. For example, cyclopropylethyl comprises an ethyl backbone with cyclopropyl substituent. In chemical structure diagrams, all bonds are identified, except for some carbon atoms, which are assumed to be bonded to sufficient hydrogen atoms to complete the valency.

Thus, for example, a compound of formula (I):



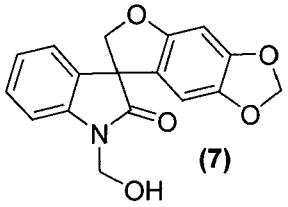
(I)

is named herein as 1'-{[5-(trifluoromethyl)-2-furyl]methyl}spiro[furo[2,3-*f*][1,3]benzodioxole-7,3'-indol]-2'(1'*H*)-one.

EMBODIMENTS OF THE INVENTION

Of the various aspects of the invention set forth above in the Summary of the Invention, certain embodiments of the methods disclosed herein are preferred.

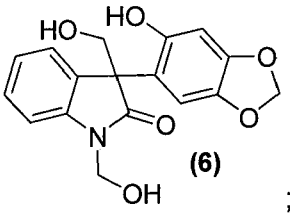
Of the method of preparing a compound of formula (I), as set forth above in the Summary of the Invention, or a pharmaceutically acceptable salt thereof, as a single stereoisomer or enantiomer or a mixture thereof, one embodiment is the method which further comprises the preparation of a compound of formula (8), or a pharmaceutically acceptable salt thereof, wherein a compound of formula (7):



(7) ;

or a pharmaceutically acceptable salt thereof, is treated with a base under suitable conditions to form the compound of formula (8), or a pharmaceutically acceptable salt thereof.

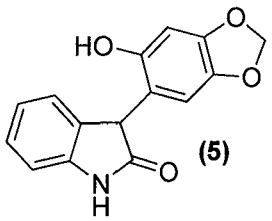
Of this embodiment, another embodiment is a method which further comprises the preparation of the compound of formula (7), or a pharmaceutically acceptable salt thereof, wherein a compound of formula (6):



(6) ;

or a pharmaceutically acceptable salt thereof, is treated under standard Mitsunobu reaction conditions to form a compound of formula (5), or a pharmaceutically acceptable salt thereof.

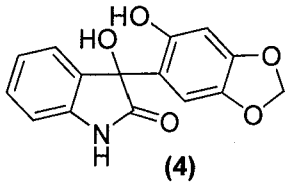
Of this embodiment, another embodiment is a method which further comprises the preparation of the compound of formula (6), or a pharmaceutically acceptable salt thereof, wherein a compound of formula (5):



(5) ;

or a pharmaceutically acceptable salt thereof, is treated with an aldehyde under suitable conditions to form the compound of formula (6), or a pharmaceutically acceptable salt thereof.

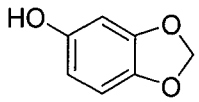
Of this embodiment, another embodiment is a method which further comprises the preparation of the compound of formula (5), or a pharmaceutically acceptable salt thereof, wherein a compound of formula (4):



(4) ;

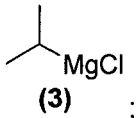
or a pharmaceutically acceptable salt thereof, is treated under suitable conditions to form the compound of formula (5), or a pharmaceutically acceptable salt thereof.

Of this embodiment, another embodiment is a method which further comprises the preparation of the compound of formula (4), or a pharmaceutically acceptable salt thereof, wherein a compound of formula (2):



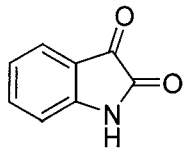
(2) ;

or a pharmaceutically acceptable salt thereof, is treated with a Grignard reagent of formula (3):



(3) ;

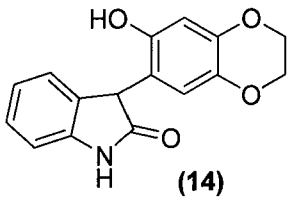
under suitable conditions to form an intermediate product; and the intermediate product is then reacted with a compound of formula (1):



(1) ;

or a pharmaceutically acceptable salt thereof, under suitable conditions to form the compound of formula (4), or a pharmaceutically acceptable salt thereof.

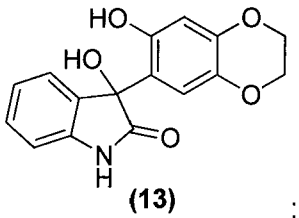
Of the method of preparing a compound of formula (II), as set forth above in the Summary of the Invention, or a pharmaceutically acceptable salt thereof, as a single stereoisomer or enantiomer or a mixture thereof, one embodiment is the method which further comprises the preparation of a compound of formula (15), or a pharmaceutically acceptable salt thereof, wherein a compound of formula (14):



(14) ;

or a pharmaceutically acceptable salt thereof, is treated with an alkylating agent under suitable conditions to form the compound of formula (15), or a pharmaceutically acceptable salt thereof.

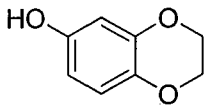
Of this embodiment, another embodiment is a method which further comprises the preparation of the compound of formula (14), or a pharmaceutically acceptable salt thereof, wherein a compound of formula (13):



(13) ;

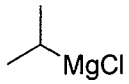
or a pharmaceutically acceptable salt thereof, is treated under suitable conditions to form the compound of formula (14), or a pharmaceutically acceptable salt thereof.

Of this embodiment, another embodiment is a method which further comprises the preparation of the compound of formula (13), or a pharmaceutically acceptable salt thereof, wherein a compound of formula (12):



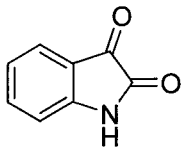
(12) ;

is reacted with a Grignard reagent of formula (3):



(3) ;

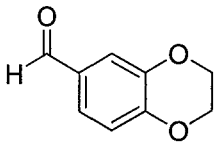
under suitable conditions to form an intermediate product; and then the intermediate product is reacted with a compound of formula (1):



(1) ;

or a pharmaceutically acceptable salt thereof, under suitable conditions to form the compound of formula (13), or a pharmaceutically acceptable salt thereof.

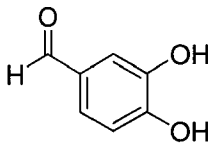
Of this embodiment, another embodiment is a method which further comprises the preparation of the compound of formula (12), or a pharmaceutically acceptable salt thereof, wherein a compound of formula (11):



(11) ;

is treated with an oxidizing agent under suitable conditions to form the compound of formula (12), or a pharmaceutically acceptable salt thereof.

Of this embodiment, another embodiment is a method which further comprises the preparation of the compound of formula (11), wherein a compound of formula (10):



(10) ;

is treated with a suitable alkylating reagent under suitable conditions to form the compound of formula (11).

Specific embodiments of the methods of the invention, including the suitable conditions for each of the above described steps, are described in more detail below in the Methods of the Invention.

METHODS OF THE INVENTION

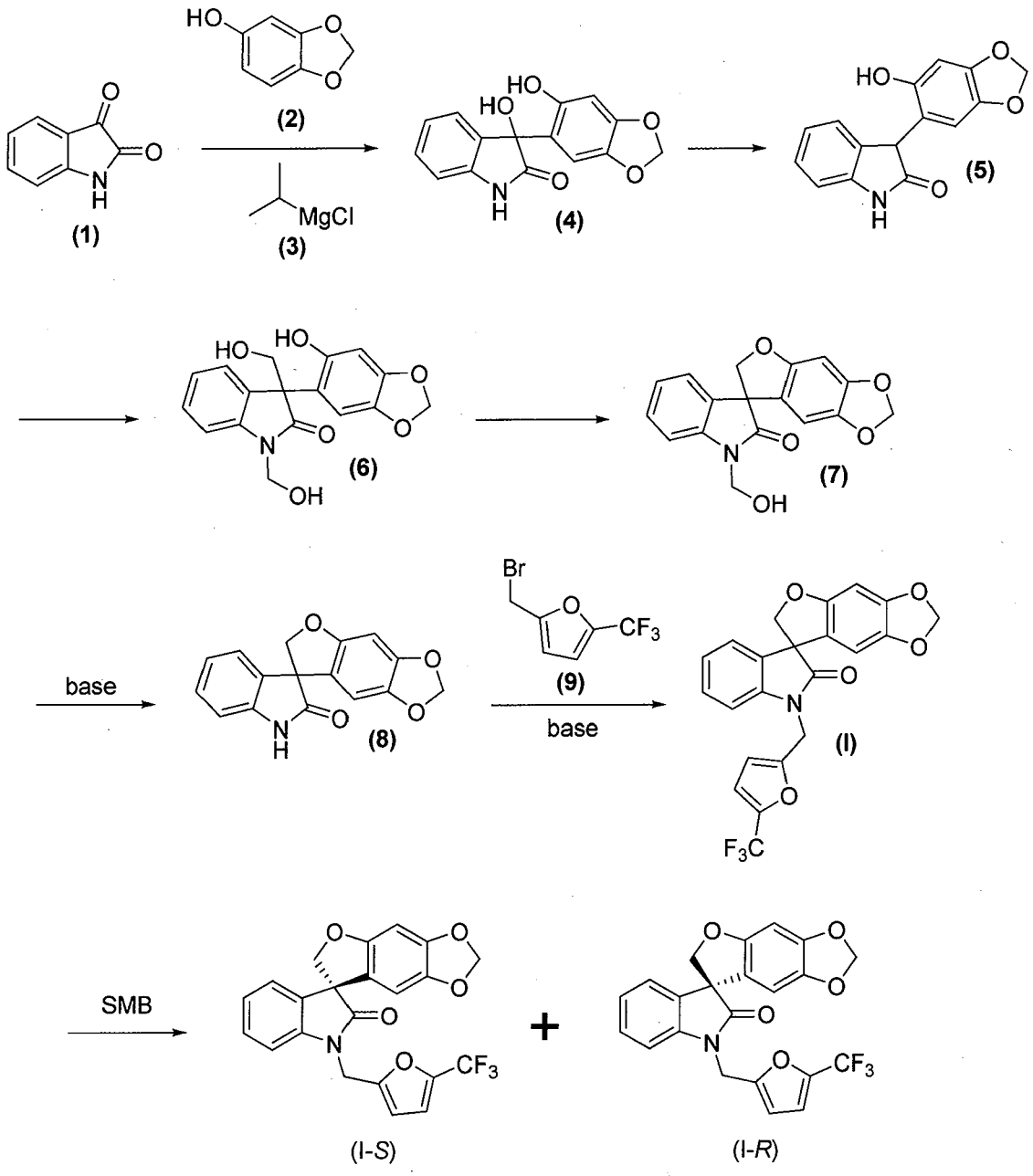
The methods of the invention are directed to methods of preparing compounds of formulae (I) and (II) and the compounds of formulae (I-*S*), (I-*R*), (II-*S*) and/or (II-*R*), as described herein, or pharmaceutically acceptable salts thereof.

In general, starting components may be obtained from sources such as Sigma Aldrich, Lancaster Synthesis, Inc., Maybridge, Matrix Scientific, TCI, and Fluorochem USA, etc. or synthesized according to sources known to those skilled in the art (see, *e.g.*, Smith, M.B. and J. March, *Advanced Organic Chemistry: Reactions*, Mechanisms, and Structure, 5th edition (Wiley, December 2000)) or prepared as described herein or by the methods disclosed in PCT Published Patent Application No. WO 2006/110917, PCT Published Patent Application No. WO 2010/45251 and PCT Patent Application No. PCT/US2010/040187.

Preparation of Compounds of Formulae (I), (I-*S*) and (I-*R*)

Compounds of formulae (I), (I-*S*) and (I-*R*) are prepared as described below in Reaction Scheme 1:

REACTION SCHEME 1



Compounds of formula (1), formula (2), formula (3) and formula (9) are commercially available, or can be prepared by methods known to one skill in the art.

In general, compounds of formula (I), (I-*S*) and (I-*R*) are prepared by the method disclosed above in Reaction Scheme 1 by first reacting a compound of formula (2) with a suitable Grignard reagent (such as that of formula (3)) under suitable conditions, such as at a temperature of between about -25 °C and about 25 °C, preferably at about 0 °C, to allow for the formation of a magnesium halide intermediate

product. This intermediate product undergoes nucleophilic addition with the keto-carbonyl group of the isatin compound of formula (1) under suitable conditions, such as in a solvent, preferably, but not limited to, tetrahydrofuran or dichloromethane, to afford the oxindole compound of formula (4).

The removal of the hydroxyl group at the C-3 position of the oxindole ring in the compound of formula (4) is achieved by treating the compound of formula (4) under suitable conditions, such as treatment with a silane reagent, such as triethylsilane, in the presence of an acid, such as, but not limited to, trifluoroacetic acid, to yield the compound of formula (5). The removal of the hydroxyl group can also be achieved by treating the compound of formula (4) under suitable conditions, such as treatment with $SOCl_2/NEt_3$, followed by reduction of the resulting intermediate with Zn dust, to give the compound of formula (5). Alternatively, the removal can be achieved by treating the compound of formula (4) with hydriodic acid to give the compound of formula (5).

The compound of formula (5) is then treated under suitable conditions, such as treatment with a base, preferably, but not limited to, diisopropylamine, diisopropylethyl amine, lithium diisopropylamide, lithium hydroxide or sodium hydroxide, followed by reaction with formaldehyde or paraformaldehyde, to yield the hydroxymethyl intermediate compound of formula (6).

Intramolecular cyclization of the compound of formula (6) to yield the compound of formula (7) is achieved by treating the compound of formula (6) to standard Mitsunobu reaction conditions, such as the employment of a phosphine reagent, preferably, but not limited to, triphenylphosphine or tributylphosphine, and an azo reagent, preferably, but not limited to, diethyl azodicarboxylate, diisopropyl azodicarboxylate, di-*tert*-butyl azodicarboxylate or tetramethyl diazenedicarboxamide, in a solvent, preferably, but not limited to, tetrahydrofuran, dichloromethane or ethyl acetate. The resulting compound of formula (7) can be isolated from the reaction mixture by standard isolation techniques or used directly in the next step without being isolated from the reaction mixture.

Alternatively, intramolecular cyclization is achieved by treating the compound of formula (6) with a suitable *bis*-electrophile such as, but not limited to, chloroiodomethane in the presence of a base such as, but not limited to, cesium carbonate in a suitable solvent such as, but not limited to, *N,N*-dimethylformamide or methyl ethyl ketone to provide a compound of formula (8).

The removal of the hydroxymethyl group on the nitrogen of the compound of formula (7) is achieved by treating the compound of formula (7) with a base, preferably,

but not limited to, sodium hydroxide, lithium hydroxide or ammonium hydroxide, under suitable conditions to provide a compound of formula (8), which can be isolated from the reaction mixture by standard isolation techniques.

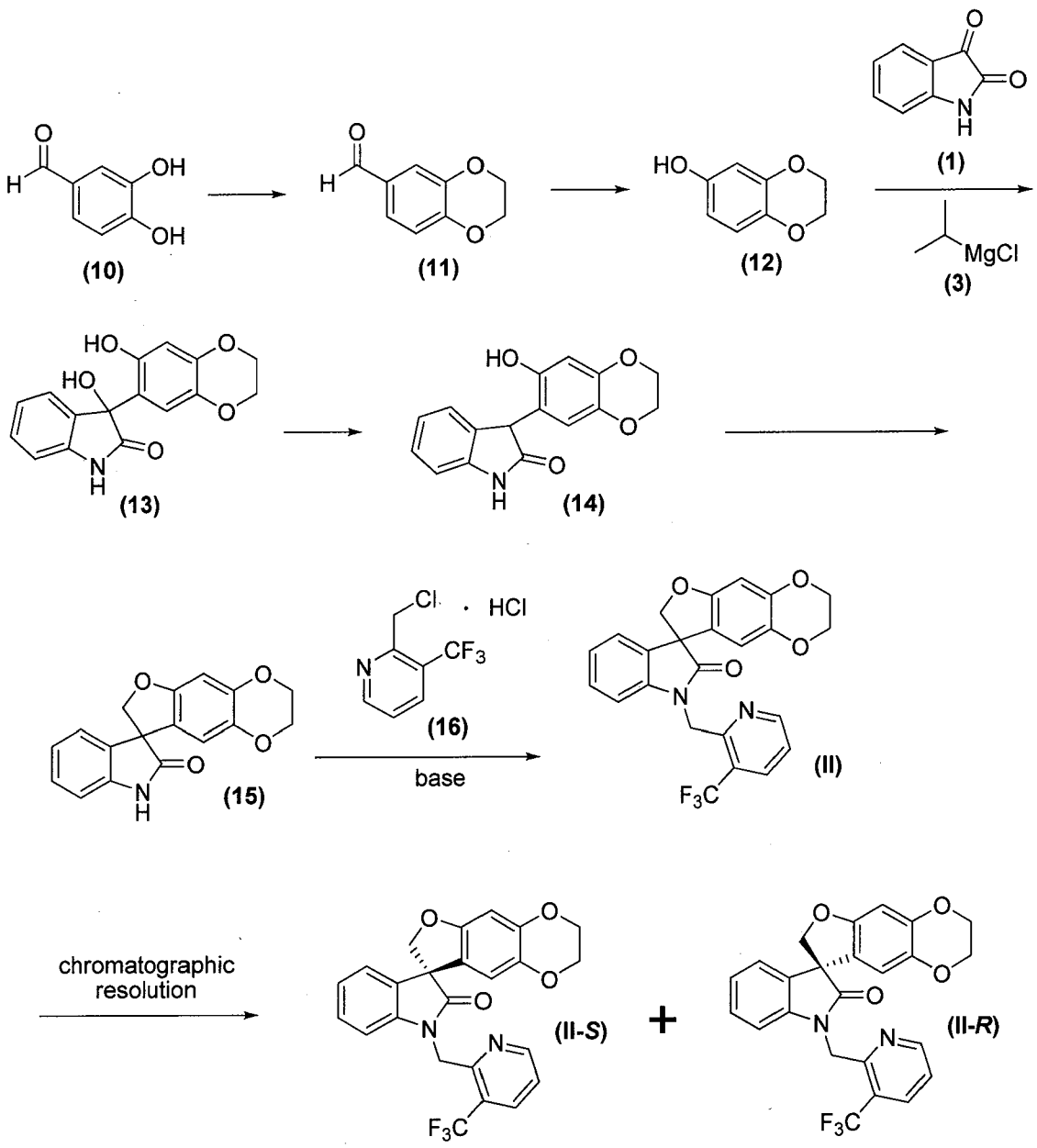
The compound of formula (8) is then reacted with an electrophile of formula (9) under suitable conditions, such as in the presence of a base, preferably, but not limited to, sodium hydride, cesium carbonate or sodium hydroxide, in a solvent, preferably, but not limited to, *N*,*N*-dimethylformamide, acetonitrile, tetrahydrofuran or acetone, to yield the compound of formula (I), which can be isolated from the reaction mixture by standard isolation techniques.

The compound of formula (I) can be resolved into the (*S*)-enantiomer (*i.e.*, the compound of formula (I-*S*)) and the corresponding (*R*)-enantiomer (*i.e.*, the compound of formula (I-*R*)) under suitable conditions, for example, by chiral chromatographic separation such as, but not limited to, simulated moving bed chromatography or chiral HPLC.

Preparation of Compounds of Formulae (II), (II-*S*) and (II-*R*)

Compounds of formula (II), (II-*S*) and (II-*R*) are prepared as described below in Reaction Scheme 2:

REACTION SCHEME 2



Compounds of formula (10), formula (11), formula (12), formula (1), formula (3) and formula (16) are commercially available, or can be prepared by methods known to one of skill in the art.

In general, compounds of formulae (II), (II-*S*) and (II-*R*) are prepared by the method disclosed above in Reaction Scheme 2 by first heating a dihydroxyaldehyde of formula (10) with a suitable *bis*-alkylating reagent such as, but not limited to, 1,2-dibromoethane in the presence of a base such as, but not limited to, potassium carbonate in a solvent such as, but not limited to, acetone to provide a compound of

formula (11).

Compounds of formula (12) are prepared by treatment of a compound of formula (11) with an oxidizing agent such as, but not limited to, 3-chloroperoxybenzoic acid in the presence of a base such as, but not limited to, sodium bicarbonate in a suitable solvent such as, but not limited to, dichloromethane, followed by treatment with water and a base such as, but not limited to, sodium hydroxide to provide a compound of formula (12).

The compound of formula (12) is then treated with a suitable Grignard reagent such as, but not limited to, the Griganrd reagent of formula (3) under suitable conditions, such as at a temperature of between about -25 °C and about 25 °C, preferably at about 0 °C, to form a phenyloxymagnesium halide intermediate product which is then reacted with the compound of formula (1) under suitable conditions, such as in a polar non-protic solvent, preferably, but not limited to, dichloromethane or tetrahydrofuran, to afford the oxindole compound of formula (13).

The removal of the hydroxyl group at the C-3 position of the oxindole compound of formula (13) is achieved by treating the compound of formula (13) under suitable conditions, such as treatment with a silane reagent, preferably, but not limited to, triethylsilane, in the presence of an acid, preferably, but not limited to, trifluoroacetic acid, to produce the compound of formula (14). The removal of the hydroxyl group at C-3 position of the oxindole compound of formula (13) can also be achieved by first treating the compound of formula (13) with $SOCl_2/NEt_3$, then reducing the resulting intermediate with Zn dust to give the compound of formula (14). Alternatively, the removal can be achieved by treating the compound of formula (13) with hydriodic acid to give the compound of formula (14).

Intramolecular cyclization is achieved by treating the compound of formula (14) with a *bis*-alkylating agent, preferably, but not limited to, chloroiodomethane, under suitable conditions, such as in the presence of a base, preferably, but not limited to, cesium carbonate, to produce the compound of formula (15), which is isolated from the reaction mixture by standard isolation techniques.

The compound of formula (15) is then reacted with an electrophile of formula (16) under suitable conditions, such as in the presence of a base, preferably, but not limited to, sodium hydride, cesium carbonate or sodium hydroxide, in a solvent, preferably, but not limited to, *N*,*N*-dimethylformamide, acetonitrile, tetrahydrofuran, 1,4-dioxane or acetone, to yield the compound of formula (II), which can be isolated from the reaction mixture by standard isolation techniques.

The compound of formula (II) may be chromatographically resolved into the (*S*)-enantiomer (*i.e.*, the compound of formula (II-*S*)) and the corresponding (*R*)-enantiomer (*i.e.*, the compound of formula (II-*R*)) by simulated moving bed chromatography using a suitable chiral stationary phase such as, but not limited to, ChiralPAK®-IC and a suitable mobile phase such as, but not limited to, dichloromethane/acetone.

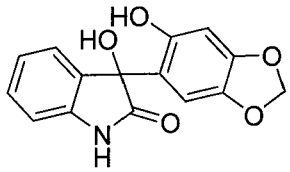
All of the compounds described above as being prepared which may exist in free base or acid form may be converted to their pharmaceutically acceptable salts by treatment with the appropriate inorganic or organic base or acid. Salts of the compounds prepared above may be converted to their free base or acid form by standard techniques. It is understood that all polymorphs, amorphous forms, anhydrates, hydrates, solvates and salts of the compounds of formula (I) and (II) are intended to be within the scope of the invention. Furthermore, all compounds of formula (I) and (II) which contain an acid or an ester group can be converted to the corresponding ester or acid, respectively, by methods known to one skilled in the art or by methods described herein.

The following specific Synthetic Preparations (for the preparation of starting materials and intermediates) and Synthetic Examples (for the preparation of the compounds of formula (I) and formula (II) by the methods of the invention) are provided as a guide to assist in the practice of the invention, and are not intended as a limitation on the scope of the invention. Where one or more NMR's are given for a particular compound, each NMR may represent a single stereoisomer, a non-racemic mixture of stereoisomers or a racemic mixture of the stereoisomers of the compound.

SYNTHETIC PREPARATION 1

Synthesis of 3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2*H*-indol-2-one

Compound of formula (4)



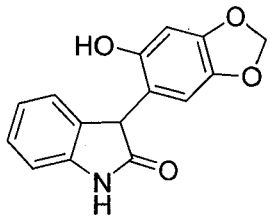
A 630 L reactor was charged with sesamol (42.6 kg, 299 mol). Tetrahydrofuran (400 kg) was added and the resultant solution was cooled to 1 °C over 42 minutes. Isopropylmagnesium chloride (2 M solution in tetrahydrofuran, 173 kg, 337 mol) was

added over 2 h such that the internal temperature was kept between 0 and 4 °C. Once the addition was complete, the internal temperature was lowered to -5 °C and isatin (37.9 kg, 250 mol) was added in four portions. The reaction mixture was stirred for 2.75 h at 1 to 3 °C. A 1000 L reactor was charged with ammonium chloride (72 kg), followed by deionized water (356 kg). The mixture was stirred at 15 °C until the solid had completely dissolved and the resultant solution was cooled to 1 °C over 1 h. The contents of the 630 L reactor were transferred to the 1000 L reactor over 1 h such that the internal temperature remained between 3 and 4 °C. The 630 L reactor was rinsed with toluene (133 kg) and the rinse solution added to the 1000 L reactor. The contents of the 1000 L reactor were allowed to warm to 20-25 °C over 29 minutes and were stirred for a further 15 minutes. The stirring was stopped and the contents of the reactor held at 25 °C for 15 minutes, allowing the phases to separate. The aqueous phase was removed and a solution of sodium chloride (42 kg) in deionized water (218 kg) was added over 25 minutes at an internal temperature of 22-24 °C. The stirring was stopped and the mixture held at 25 °C for 1 h, allowing the phases to separate. The organic phase was degassed for 0.5 h with nitrogen and toluene (89 kg) was added. A 300 mbar vacuum was applied to the reactor and the reactor's external temperature was set to 50-60 °C. Volatile components of the mixture were removed by distillation over a period of 12 h such that 670 L of distillate were collected. The reactor's external temperature was set to 20-25 °C. An orange precipitate was deposited upon cooling. Toluene (114 kg) was added and the suspension stirred for 10 minutes. The solid was collected by filtration, washed with *tert*-butyl methyl ether (171 kg) and heptane (85 kg) and dried at 55-60 °C under a reduced pressure of 170 to 4 mbar over a period of 10.5 h to afford 3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2*H*-indol-2-one (73.5 kg, quantitative yield) as a pale pink solid: purity (HPLC-UV at 300 nm) 99.3% a/a; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.18 (s, 1H), 9.08 (s, 1H), 7.21-7.07 (m, 2H), 6.88-6.74 (m, 3H), 6.38 (br s, 1H), 6.23 (s, 1H), 5.92 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 178.4, 148.4, 146.6, 143.0, 139.4, 133.2, 128.6, 123.8, 121.1, 120.1, 109.0, 106.8, 100.8, 97.4, 75.1.

SYNTHETIC PREPARATION 2

Synthesis of 3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2*H*-indol-2-one

Compound of formula (5)

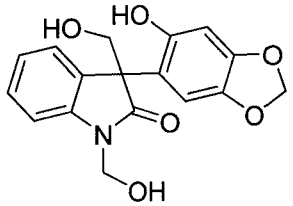


A 1600 L reactor was charged with 3-hydroxy-3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2*H*-indol-2-one (113.1 kg, 396 mol), evacuated and filled with nitrogen. Trifluoroacetic acid (679 kg) was added in two portions over 20 minutes and the internal temperature was lowered to 10 °C over 1 h. Triethylsilane (69.2 kg, 595 mol) was added over 2 h 05 min at 10-11 °C and the mixture was stirred for a further 0.5 h at 10-11 °C. A 1000 L reactor was charged with heptane (524 kg) and *tert*-butyl methyl ether (63 kg). The contents of the 1000 L reactor were transferred to the 1600 L reactor over 13 minutes at an internal temperature of 10-11 °C. The resultant yellow-orange suspension was allowed to warm to 23 °C over 1 h. The solid was collected by filtration, washed with heptane (464 kg) followed by *tert*-butyl methyl ether (57 kg) and dried at 50 °C under a reduced pressure of 58 to 7 mbar over a period of 25 h to afford 3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2*H*-indol-2-one (82.8 kg, 75%) as an off-white solid: purity (HPLC-UV at 300 nm) 98.0% a/a; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.40 (s, 1H), 9.25 (s, 1H), 7.17-7.10 (m, 1H), 6.95-6.81 (m, 3H), 6.55 (s, 1H), 6.43 (s, 1H), 5.92-5.85 (m, 2H), 4.66 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 177.9, 150.1, 146.6, 142.7, 139.6, 130.9, 127.4, 123.8, 121.2, 115.9, 109.5, 109.0, 100.7, 97.8, 55.0.

SYNTHETIC PREPARATION 3

Synthesis of 3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-*bis*(hydroxymethyl)-1,3-dihydro-2*H*-indol-2-one

Compound of formula (6)

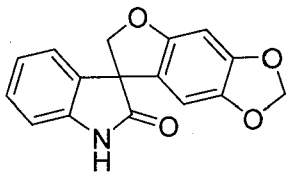


A 1000 L reactor was charged with 3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-dihydro-2*H*-indol-2-one (56.3 kg, 209 mol), followed by paraformaldehyde (25.4 kg, 847 mol) and deionized water (285 kg). The reaction mixture was cooled to an internal temperature of 5 °C over 25 minutes and a 30% by weight aqueous solution of sodium hydroxide (113 kg, 847 mol) was added at 5 °C over 40 minutes. The reaction mixture was stirred for 1 h at 5 °C. A second 1000 L reactor was charged with deionized water (260 kg) and 32% hydrochloric acid (124 kg). The contents of the first reactor were added to the contents of the second reactor at 1 °C over 80 minutes. The first reactor was rinsed with deionized water (35 kg) and the rinse solution transferred to the second reactor. The resultant suspension was stirred for at 1 °C for 1 h and the solid was collected by filtration, washed with a mixture of concentrated hydrochloric acid (11 kg) and water (20 kg) and dried at 55-60 °C under a reduced pressure of 50 to 6 mbar over a period of 24 h to afford 3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-*bis*(hydroxymethyl)-1,3-dihydro-2*H*-indol-2-one (69.8 kg, 99%) as a pale brown solid: purity (HPLC-UV at 230 nm) 95.4% a/a; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.06 (s, 1H), 7.17-6.84 (m, 5H), 6.19-6.10 (m, 2H), 5.86 (s, 2H), 5.12-4.92 (m, 3H), 4.11-4.06 (m, 1H), 3.79-3.73 (m, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 179.0, 150.5, 146.7, 143.9, 139.9, 132.6, 127.4, 124.0, 121.9, 118.2, 108.7, 108.6, 101.1, 98.0, 65.4, 63.2, 56.2.

SYNTHETIC PREPARATION 4

Synthesis of spiro[furo[2,3-*f*][1,3]benzodioxole-7,3'-indol]-2'(1'*H*)-one

Compound of formula (8)



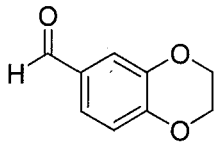
A 1000 L reactor was charged with 3-(6-hydroxy-1,3-benzodioxol-5-yl)-1,3-*bis*(hydroxymethyl)-1,3-dihydro-2*H*-indol-2-one (65.0 kg, 197 mol), followed by tetrahydrofuran (586 kg). The resultant solution was cooled to -4 °C over 20 minutes and tri-*n*-butylphosphine (40.0 kg, 197 mol) was added over 6 minutes, followed by a solution of diisopropyl azodicarboxylate (44.8 kg, 197 mol) in tetrahydrofuran (75 kg) over 125 minutes such that the internal temperature remained below 0 °C. The reaction mixture was stirred at -3 °C for a further 25 minutes and the contents of the reactor were transferred to a 2500 L reactor. The 1000 L reactor was rinsed with tetrahydrofuran (16 kg) and the rinse solution added to the 2500 L reactor. A 25% by

weight solution of ammonia in water (118 kg) was added at -3 to -2 °C over 30 minutes. The reaction mixture was allowed to warm to 25 °C over 1.25 h and was stirred for a further 2 h. Deionized water (650 kg) and ethyl acetate (585 kg) were added and the mixture was warmed to 40 °C over 40 minutes. After stirring for a further 15 minutes, the stirring was stopped and the phases were allowed to separate for 1 h. The aqueous phase was removed and deionized water (650 kg) was added. The mixture was stirred for 15 minutes at 40 °C. The stirring was stopped and the phases were allowed to separate for 1 h. The aqueous phase was removed and deionized water (325 kg) was added. The mixture was partially concentrated by distillation under reduced pressure at an internal temperature of 21-39 °C and a pressure of 382 to 98 mbar until 950 L of distillate had been collected over a period of 4.5 h. Methanol (1600 kg) was added and the mixture heated to 60 °C over 35 minutes. The mixture was partially concentrated by distillation under reduced pressure at an internal temperature of 32-58 °C and a pressure of 530 to 170 mbar until 1260 L of distillate had been collected over a period of 9.33 h. The resultant suspension was allowed to cool to 22 °C over 2 h and was stirred for a further 6 h. The solid was collected by filtration, washed with a mixture of methanol (34 kg) and deionized water (17 kg) and dried at 55-60 °C under a reduced pressure of 50 to 3 mbar over a period of 31 h to afford 35.8 kg of a brown solid, which was transferred to a 400 L reactor. Methanol (163 kg) was added and the resultant suspension was stirred for 0.5 h. The mixture was heated to reflux over a period of 35 minutes and was heated at reflux for a further 15 minutes. Deionized water (33 kg) was added and the mixture was heated at reflux for 155 minutes. The suspension was filtered while hot and the filter cake was washed with a mixture of methanol (22 kg) and deionized water (11 kg) and dried at 55-60 °C under a reduced pressure of 50 to 4 mbar over a period of 8 h to afford spiro[furo[2,3-*f*][1,3]benzodioxole-7,3'-indol]-2'(1'*H*)-one (30.44 kg, 49%) as a pale brown solid: purity (HPLC-UV at 230 nm) 89.4%; MS (ES+) *m/z* 282.3 (M + 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ10.56 (s, 1H), 7.27-6.92 (m, 4H), 6.67 (s, 1H), 6.26 (s, 1H), 5.93 (s, 2H), 4.79-4.64 (m, 2H).

SYNTHETIC PREPARATION 5

Synthesis of 2,3-dihydro-1,4-benzodioxine-6-carbaldehyde

Compound of formula (11)



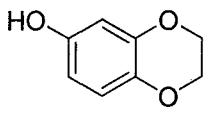
A 2000 L reactor was charged with acetone (404.5 kg), followed by potassium carbonate (256 kg, 1852 mol) and 1,2-dibromoethane (241.5 kg, 1298 mol). The mixture was heated at reflux. A 500 L reactor was charged with acetone (606 kg) and 3,4-dihydroxybenzalhdehyde (128 kg, 926 mol). The contents of the 500 L reactor were added to the 2000 L reactor at a rate of 150-180 kg/h while the reaction temperature was maintained at 50-60 °C. The reaction mixture was stirred at 54-60 °C for 12 h, was cooled to 20 °C and was filtered through a 500 L Nutsche filter. The filter cake was washed with acetone (2 × 202 kg). The filtrate and acetone washes were combined in a 2000 L reactor and the resultant solution was concentrated to dryness under reduced pressure at a temperature < 40 °C. To the residue was added ethyl acetate (683 kg) and the resultant solution was washed with a 5% by weight aqueous solution of potassium carbonate (256 kg). The mixture was stirred for 0.5 h, allowed to settle for 0.5 h and the aqueous phase was removed. This washing procedure was repeated three times in total. The organic phase was temporarily set aside into drums. A 2000 L reactor was charged with the combined aqueous washes, followed by ethyl acetate (113.9 kg). The mixture was stirred for 0.5 h, allowed to settle for 0.5 h and the aqueous phase was removed. The organic phase from the drums was added to the reactor followed by a 28% by weight aqueous solution of sodium chloride (192 kg). The mixture was stirred for 0.5 h, allowed to settle for 0.5 h and the aqueous phase was removed. The organic phase was concentrated under reduced pressure at a temperature < 45 °C until the mixture's ethyl acetate content was below 10% (as determined by gas chromatography). Petroleum ether (268.8 kg) was added to the residue at a rate of 80-90 kg/h while the mixture was maintained at a temperature of 35-45 °C. The mixture was cooled to 5 °C over 3 h and held at this temperature for a further 1 h, during which time a precipitate was deposited. The resultant slurry was filtered through a centrifugal filter and dried to afford 2,3-dihydro-1,4-benzodioxine-6-carbaldehyde (111.4 kg, 73%) as an off-white solid: purity (HPLC-UV at 230 nm)

99.3%.

SYNTHETIC PREPARATION 6

Synthesis of 2,3-dihydro-1,4-benzodioxin-6-ol

Compound of formula (12)



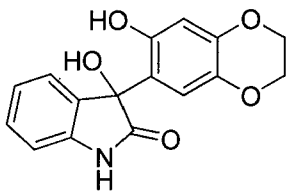
A 2000 L reactor was charged with dichloromethane (1303.4 kg) followed by 2,3-dihydro-1,4-benzodioxine-6-carbaldehyde (98.0 kg, 597 mol) and stirred until a homogeneous solution was obtained. 3-Chloroperoxybenzoic acid (144.3 kg, 836 mol) was added. The mixture was heated to reflux at a rate of 8-10 °C/h, heated at reflux for a further 6 h and allowed to cool to 20 °C. The resultant suspension was filtered through a 500 L Nutsche filter and the filter cake was washed with dichloromethane (391 kg). The filtrate and wash solution were transferred to a 2000 L reactor. A 7% by weight aqueous solution of sodium bicarbonate (212.7 kg) was added and the mixture was stirred for 0.5 h. The stirring was stopped and the phases were allowed to separate over 0.5 h. The aqueous layer was removed. The aqueous sodium bicarbonate washing procedure was repeated three times in total. The organic phase was concentrated to dryness under reduced pressure at a temperature < 30 °C. Methanol (116.1 kg) was added and the resultant mixture was cooled to 0 °C. A 15.5% by weight aqueous solution of sodium hydroxide (234.3 kg) was added at a rate of 30-40 kg/h such that the mixture's temperature was maintained between 0-10 °C. The mixture was stirred at this temperature for a further 2.25 h and the pH of the mixture was adjusted to 6-7 by the addition of 4 N hydrochloric acid (266.5 kg) such that the mixture's temperature was maintained between 0-10 °C. The mixture was allowed to warm to ambient temperature and was extracted three times in total with methyl *tert*-butyl ether (145 kg for each extraction) by stirring for 0.5 h, stopping the stirring and allowing the phases to separate for 0.5 h. The combined organic extracts were washed three times in total with a 7% aqueous solution of sodium bicarbonate (212.7 kg for each wash) by stirring for 0.5 h, stopping the stirring, allowing the phases to separate for 0.5 h and removing the aqueous phase. The organic phase was then washed with a 30% by weight aqueous solution of sodium chloride (212.7 kg) by stirring for 0.5 h, stopping the stirring, allowing the phases to separate for 0.5 h and

removing the aqueous phase. The organic phase was concentrated to dryness under reduced pressure at a temperature < 45 °C. Tetrahydrofuran (170 kg) was added and the resultant solution concentrated to dryness under reduced pressure at a temperature < 45 °C. Further tetrahydrofuran (17.1 kg) was added and the resultant solution concentrated to dryness under reduced pressure at a temperature < 45 °C. Tetrahydrofuran (122.5 kg) was added to afford a brown-red solution of 2,3-dihydro-1,4-benzodioxin-6-ol (86.3 kg, 95%) in tetrahydrofuran which was carried forward without further purification: purity (HPLC-UV at 220 nm) 95.7%.

SYNTHETIC PREPARATION 7

Synthesis of 3-hydroxy-3-(7-hydroxy-2,3-dihydro-1,4-benzodioxin-6-yl)-1,3-dihydro-2*H*-indol-2-one

Compound of formula (13)



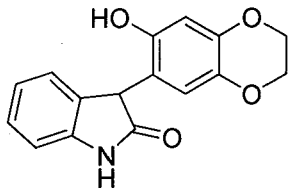
A 1000 L reactor was charged with tetrahydrofuran (296.8 kg). The tetrahydrofuran was heated at reflux for 1 h and allowed to cool to ambient temperature. Magnesium (15.0 kg, 625 mol), iodine (19.5 g, catalytic amount) and bromoethane (147.0 g, catalytic amount) were added at a temperature of 15-30 °C. The resultant mixture was heated at 50-55 °C for 0.5 h and 2-chloropropane (4.5 kg, 57 mol) was added, followed by a 2 M solution of isopropylmagnesium chloride in tetrahydrofuran (7.6 kg, catalytic amount). 2-Chloropropane (39.2 kg, 500 mol) was added at a rate of 8-10 kg/h such that the temperature of the reaction mixture was maintained between 55-70 °C. The reaction mixture was heated at 58-68 °C for 3 h, allowed to cool to ambient temperature and was stirred for a further 4 h. A 2000 L reactor was charged with a solution of 2,3-dihydro-1,4-benzodioxin-6-ol (86.3 kg, 567 mol) in tetrahydrofuran (122.5 kg), followed by further tetrahydrofuran (804.1 kg). The resultant solution was cooled to 0 °C and the contents of the 1000 L reactor were added to the 2000 L reactor at a rate of 30-50 kg/h such that the temperature of the reaction mixture was maintained between 0-5 °C. The 1000 L reactor was rinsed three times with tetrahydrofuran (5 kg for each rinse) and the rinse solutions were added to the 2000 L reactor. The reaction mixture was stirred at 7-13 °C for 1 h and was cooled

to -5 °C. Isatin (69.5 kg, 472.5 mol) was added in three equal portions over 0.5 h and the mixture stirred for 0.5 h at -5-0 °C. The reaction mixture was heated at 50-55 °C for 7.5 h and was allowed to cool to ambient temperature. A 5000 L reactor was charged with water (576.9 kg) and ammonium chloride (118.2 kg). The resultant solution was cooled to 0-5 °C. The contents of the 2000 L reactor were added to the 5000 L reactor at a rate of 300-500 kg/h such that the temperature of the mixture was maintained between 0-5 °C. The mixture was stirred at 15-25 °C for 0.5 h and the stirring was stopped. The phases were allowed to separate for 1 h and the aqueous phase was removed. A 27% by weight aqueous solution of sodium chloride (69.6 kg) was added and the mixture stirred for 0.5 h. The stirring was stopped, the phases were allowed to separate for 1 h and the aqueous layer was removed. The aqueous sodium chloride wash procedure was repeated two times in total. The organic phase was transferred to a 2000 L reactor and was concentrated under reduced pressure at a temperature of 45-55 °C. Toluene (302.3 kg) was added to the residue at a rate of 90-130 kg/h and at a temperature of 45-50 °C. The resultant mixture was cooled to 15 °C at a rate of 8-10 °C/h and stirred for at 10-15 °C for a further 1 h. The resultant slurry was filtered through a centrifugal filter and the filter cake was washed with water (69.5 kg) and dried at 45-50 °C to afford 3-hydroxy-3-(7-hydroxy-2,3-dihydro-1,4-benzodioxin-6-yl)-1,3-dihydro-2*H*-indol-2-one (130.8 kg, 93%) as an off-white solid: purity (HPLC-UV at 210 nm) 99.7%.

SYNTHETIC PREPARATION 8

Synthesis of 3-(7-hydroxy-2,3-dihydro-1,4-benzodioxin-6-yl)-1,3-dihydro-2*H*-indol-2-one

Compound of formula (14)



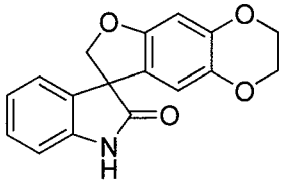
A 2000 L reactor was charged with dichloromethane (489.4 kg), followed by 3-hydroxy-3-(7-hydroxy-2,3-dihydro-1,4-benzodioxin-6-yl)-1,3-dihydro-2*H*-indol-2-one (92.0 kg, 307 mol) in four 23 kg portions over 1 h. The resultant solution was stirred at ambient temperature for 1 h and triethylsilane (107.2 kg, 921 mol) was added. The mixture was cooled to -5 °C and trifluoroacetic acid (105.1 kg, 921 mol) was added at

a rate of 25-30 kg/h such that the temperature of the reaction mixture remained below 0 °C. The mixture was stirred at -5-0 °C for 2.5 h, warmed to 18-20 °C, stirred for a further 6.5 h and concentrated to dryness under reduced pressure at a temperature <30 °C. Methyl *tert*-butyl ether (139.8 kg) was added to the residue at 15-20 °C and the mixture concentrated to near-dryness under reduced pressure at a temperature <35 °C. The mixture was filtered in a centrifugal filter and a 2000 L reactor was charged with the filter cake, followed by methanol (72.7 kg). The mixture was stirred at 10-15 °C for 0.5 h and filtered in a centrifugal filter. The filter cake was dried under reduced pressure at 40-50 °C to afford 3-(7-hydroxy-2,3-dihydro-1,4-benzodioxin-6-yl)-1,3-dihydro-2*H*-indol-2-one (68.0 kg, 78%) as a colorless solid: purity (HPLC-UV at 254 nm) 99.3%.

SYNTHETIC PREPARATION 9

Synthesis of 2,3-dihydrospiro[furo[2,3-*g*][1,4]benzodioxine-8,3'-indol]-2'(1'*H*)-one

Compound of formula (15)



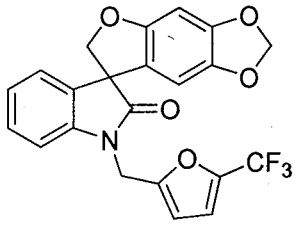
A 2000 L stainless steel crystallizer was charged with *N,N*-dimethylformamide (113.7 kg) and tetrahydrofuran (1070.9 kg). The contents were cooled to 0-5 °C and 3-(7-hydroxy-2,3-dihydro-1,4-benzodioxin-6-yl)-1,3-dihydro-2*H*-indol-2-one (12.0 kg, 42.4 mol) was added, followed by cesium carbonate (30.4 kg, 93.3 mol). A solution of chloroiodomethane (9.4 kg, 53.7 mol) in *N,N*-dimethylformamide (16.9 kg) was added at a rate of 39.5 kg/h such that the temperature of the reaction mixture was maintained between 0 and 5 °C. The reaction mixture was stirred at 0-5 °C for 2 h and heated at 20-25 °C for 18.5 h. The mixture was filtered and the filter cake was suspended in tetrahydrofuran (26.4 kg) and filtered again. The combined filtrates were combined and concentrated to a volume of 110 L under reduced pressure at a temperature < 60 °C. The mixture was cooled to 20-25 °C and purified water (1200.8 kg) was added at a rate of 343.1 kg/h. The mixture was cooled to 0-5 °C and filtered. The filter cake was suspended in water (310.5 kg), filtered and dried at a temperature < 60 °C until the water content was 10.6% by weight by Karl-Fisher titration. A 200 L reactor

was charged with tetrahydrofuran (98.0 kg). The partially-dried filter cake (~11.0 kg) was added to the 200 L reactor by means of a solid addition funnel. The mixture was heated at reflux for 4.5 h, cooled to 10-15 °C and stirred for 3.5 h at 10-15 °C. The mixture was filtered and the filter cake was washed with cold (0-5 °C) tetrahydrofuran (2 × 10.7 kg) and dried in a tray dryer at a temperature < 55 °C to afford 2,3-dihydrospiro[furo[2,3-*g*][1,4]benzodioxine-8,3'-indol]-2'(1'*H*)-one (6.88 kg, 63%) as a pale yellow solid: purity (HPLC-UV at 210 nm) 98.3%; mp > 250 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.58 (br s, 1H), 7.26-7.19 (m, 1H), 7.09 (d, J = 7.2 Hz, 1H), 6.99-6.90 (m, 2H), 6.47 (s, 1H), 6.16 (s, 1H), 4.74, 4.60 (ABq, J_{AB} = 9.2 Hz, 2H), 4.20-4.07 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 178.4, 154.7, 144.0, 141.8, 137.8, 132.6, 128.7, 123.8, 122.3, 121.5, 111.1, 109.8, 98.7, 79.5, 64.2, 63.6, 57.7; MS (ES+) *m/z* 295.9 (M + 1).

SYNTHETIC EXAMPLE 1

Synthesis of 1'-{[5-(trifluoromethyl)-2-furyl]methyl}spiro[furo[2,3-*f*][1,3]benzodioxole-7,3'-indol]-2'(1'*H*)-one

Compound of formula (I)



A 100 L reactor was charged with spiro[furo[2,3-*f*][1,3]benzodioxole-7,3'-indol]-2'(1'*H*)-one (6.03 kg, 19.5 mol), followed by cesium carbonate (16.02 kg, 48.7 mol). Acetone (48.8 kg) was added and the resultant suspension was heated to reflux over 1 h. 2-Bromomethyl-5-(trifluoromethyl)furan (4.92 kg, 21.2 mol) was added by means of an addition funnel over a period of 2 h while the reaction mixture was maintained at reflux. The reaction mixture was stirred at reflux for a further 2 h and the acetone was removed by distillation at atmospheric pressure until 37 L of distillate had been collected. Toluene (48.8 kg) was added and the distillation was continued, first at atmospheric pressure then under reduced pressure until 37 L of distillate had been collected. Toluene (36.9 kg) was added and the distillation was continued at 54-55 °C and a pressure of 150-180 mbar until 37 L of distillate had been collected. The contents of the 100 L reactor were allowed to cool to 25 °C and toluene (40.9 kg) was

added. The contents of the 100 L reactor were transferred to a 200 L reactor and deionized water (48.8 kg) was added. The stirred mixture was warmed to 39 °C, the stirring was stopped and the phases were allowed to separate for 11 h. The lower phase was removed and the remaining toluene phase was subjected to distillation at 55-64 °C under a reduced pressure of 100 mbar until 18 L of distillate had been collected. The resultant solution was diluted with toluene to a total volume of 98 L. The contents of the 200 L reactor were passed through a chromatography column packed with silica gel (20 kg) and toluene (40 kg). The column was eluted with toluene such that ten 30 kg fractions were collected. The column was washed with acetone (100 kg). Fractions 2 through 10 were successively transferred to a 200 L reactor as a distillation under reduced pressure was proceeding. The contents of the reactor were adjusted with toluene to a volume of 50 L and the solution was heated to 79 °C. Heptane (85 kg) was added over 15 minutes and the mixture was cooled to 10 °C over a period of 3 h. Crystallization started at an internal temperature of 56 °C. The solid was collected by filtration, washed with a mixture of heptane (10.2 kg) and toluene (5.1 kg) and dried at 45-50 °C under a reduced pressure of 50 mbar over a period of 15 h to afford 1'-{[5-(trifluoromethyl)-2-furyl]methyl}spiro[furo[2,3-*f*][1,3]benzodioxole-7,3'-indol]-2'(1'*H*)-one (6.08 kg, 73%) as a colorless solid: purity (HPLC-UV at 230 nm) 99.6%; mp 139–141 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-6.97 (m, 5H), 6.72 (d, J = 3.3 Hz, 1H), 6.66 (s, 1H), 6.07 (s, 1H), 5.90-5.88 (m, 2H), 5.05, 4.86 (ABq, J_{AB} = 16.1 Hz, 2H), 4.91 (d, J = 9.0 Hz, 1H), 4.66 (d, J = 9.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9, 155.7, 153.5, 148.8, 142.2, 141.9, 140.8, 140.2, 139.7, 139.1, 132.1, 129.2, 124.7, 124.1, 123.7, 121.1, 120.1, 117.6, 114.5, 114.4, 110.3, 109.7, 103.0, 101.9, 93.8, 80.0, 57.8, 36.9; MS (ES+) *m/z* 430.2 (M + 1), 452.2 (M + 23); Calc'd for $C_{22}H_{14}F_3NO_5$: C, 61.54%; H, 3.29%; N, 3.26%; Found: C, 61.51%; H, 3.29%; N, 3.26%.

SYNTHETIC EXAMPLE 2

Resolution of Compound of Formula (I) by Chiral HPLC

The compound of formula (I) was resolved into the compound of formula (I-*S*) and the compound of formula (I-*R*) by chiral HPLC under the following conditions:

Column:	Chiralcel ® OJ-RH; 20 mm I.D. × 250 mm, 5 mic; Lot: OJRH CJ-EH001 (Daicel Chemical Industries, Ltd)
Eluent:	Acetonitrile/Water (60/40, v/v, isocratic)
Flow rate:	10 mL/min

Run time: 60 min

Loading: 100 mg of compound of formula (I) in 1 mL of acetonitrile

Temperature: Ambient

Under the above chiral HPLC conditions, the compound of formula (I-*R*), *i.e.*, (*R*)-1'-{[5-(trifluoromethyl)furan-2-yl]methyl}spiro[furo[2,3-*f*][1,3]-benzodioxole-7,3'-indol]-2'(1'*H*)-one, was isolated as the first fraction as a white solid; ee (enantiomeric excess) >99% (analytical OJ-RH, 55% acetonitrile in water); mp 103-105 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.32-6.99 (m, 5H), 6.71 (d, J = 3.4 Hz, 1H), 6.67 (s, 1H), 6.05 (s, 1H), 5.89 (d, J = 6.2 Hz, 2H), 5.13, 5.02 (ABq, J_{AB} = 16.4 Hz, 2H), 4.82, 4.72 (ABq, J_{AB} = 9.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 155.9, 152.0, 149.0, 142.4, 142.0, 141.3, 132.0, 129.1, 123.9, 120.6, 119.2, 117.0, 112.6, 109.3, 108.9, 103.0, 101.6, 93.5, 80.3, 58.2, 36.9; MS (ES+) *m/z* 430.2 (M + 1), $[\alpha]_D$ –17.46° (*c* 0.99, DMSO). The compound of formula (I-*S*), *i.e.*, (*S*)-1'-{[5-(trifluoromethyl)furan-2-yl]methyl}spiro-[furo[2,3-*f*][1,3]benzodioxole-7,3'-indol]-2'(1'*H*)-one, was isolated as the second fraction as a white solid; ee > 99% (analytical OJ-RH, 55% acetonitrile in water); mp 100-102 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.32-6.99 (m, 5H), 6.71 (d, J = 3.4 Hz, 1H), 6.67 (s, 1H), 6.05 (s, 1H), 5.89 (d, J = 6.3 Hz, 2H), 5.12, 5.02 (ABq, J_{AB} = 16.4 Hz, 2H), 4.82, 4.72 (ABq, J_{AB} = 9.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 155.9, 152.0, 149.0, 142.4, 142.0, 141.3, 132.0, 129.1, 123.9, 120.6, 119.2, 117.0, 112.6, 109.3, 108.9, 103.0, 101.6, 93.5, 80.3, 58.2, 36.9; MS (ES+) *m/z* 430.2 (M + 1), $[\alpha]_D$ +14.04° (*c* 0.99, DMSO).

SYNTHETIC EXAMPLE 3

Resolution of Compound of Formula (I) by SMB Chromatography

The compound of formula (I) was resolved into the compound of formula (I-*S*) and the compound of formula (I-*R*) by SMB chromatography under the following conditions:

Extract: 147.05 mL/min

Raffinate: 86.13 mL/min

Eluent: 183.18 mL/min

Feed: 50 mL/min

Recycling: 407.88 mL/min

Run Time: 0.57 min

Temperature: 25 °C

Pressure: 55 bar

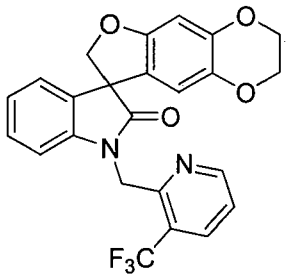
The feed solution (25 g of compound of formula (I) in 1.0 L of mobile phase (25:75 (v:v) mixture of acetonitrile /methanol)) was injected continuously into the SMB system (Novasep Licosep Lab Unit), which was equipped with eight identical columns in 2-2-2-2 configuration containing 110 g (per column, 9.6 cm, 4.8 cm I.D.) of ChiralPAK-AD as stationary phase. The first eluting enantiomer (the compound of formula (I-*R*)) was contained in the raffinate stream and the second eluting enantiomer (the compound of formula (I-*S*)) was contained in the extract stream. The characterization data of the compound of formula (I-*R*) and the compound of formula (I-*S*) obtained from the SMB resolution were identical to those obtained above utilizing chiral HPLC.

The compound of formula (I) was resolved into the compound of formula (I-*R*) and the compound of formula (I-*S*) on a Waters preparative LCMS autopurification system. The first-eluting enantiomer from the chiral column was brominated (at a site well-removed from the stereogenic centre) to give the corresponding 5'-bromo derivative, which was subsequently crystallized to generate a single crystal suitable for X-ray crystallography. The crystal structure of this brominated derivative of the first-eluting enantiomer was obtained and its absolute configuration was found to be the same as the compound of formula (1-*R*). Hence, the second-eluting enantiomer from the chiral column is the compound of formula (1-*S*). Moreover, the material obtained from the extract stream of the SMB resolution had a specific optical rotation of the same sign (positive, *i.e.* dextrorotatory) as that of the material obtained from the aforementioned LC resolution.

SYNTHETIC EXAMPLE 4

Synthesis of 1'-{[3-(trifluoromethyl)pyridin-2-yl]methyl}-2,3-dihydrospiro[furo[2,3-*g*][1,4]benzodioxine-8,3'-indol]-2'(1'*H*)-one

Compound of formula (II)



A 160 L reactor was charged with 1,4-dioxane (43 L) at ambient temperature

followed by 2,3-dihydrospiro[furo[2,3-*g*][1,4]benzodioxine-8,3'-indol]-2'(1'*H*)-one (6.80 kg, 23 mol). To the resultant suspension was added cesium carbonate (18.7 kg, 58 mol) and the mixture was heated to 82 °C over 72 minutes. A container was rinsed with 1,4-diozane (7 L) and used for the addition of 2-(Chloromethyl)-3-(trifluoromethyl)pyridine hydrochloride (5.88 kg, 25 mol) portionwise over 35 minutes. The temperature of the reaction mixture was increased to 100 °C over 43 minutes and the mixture stirred at 100 °C for 3 h, cooled to 20 °C over 90 minutes and stirred for a further 16 h. Deionized water (40 L) and dichloromethane (40 L) were added and the resultant mixture stirred at 22 °C for 12 minutes. The stirring was stopped and the phases were allowed to separate for 21 minutes. The aqueous and organic phases were separated into drums. A 160 L reactor was charged with the aqueous phase and dichloromethane (41 L) was added. The mixture was stirred at 19 °C for 10 minutes, the stirring was stopped and the phases were allowed to separate for 10 minutes. The aqueous phase was removed and the organic phase from the previous step was transferred from the drum to the reactor. Deionized water (40 L) was added and the mixture stirred at 22 °C for 10 minutes. The stirring was stopped and the phases were allowed to separate for 43 minutes. The aqueous phase was removed and the organic phase concentrated to dryness under a reduced pressure of 712-97 mbar at 19-38 °C. To the residue was added methanol (56 L) over 19 minutes. The resultant suspension was cooled to 3 °C over 64 minutes and stirred for 98 minutes. The mixture was filtered and the filter cake washed with cold (0 °C) methanol (14 L) and dried under a reduced pressure of 90-9 mbar at 21-46 °C for 10.5 h to obtain 1'-{[3-(trifluoromethyl)pyridin-2-yl]methyl}-2,3-dihydrospiro[furo[2,3-*g*][1,4]benzodioxine-8,3'-indol]-2'(1'*H*)-one (8.00 kg, 81%) as an off-white solid: purity (HPLC-UV) 99.8%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67-8.63 (m, 1H), 8.01-7.96 (m, 1H), 7.35-7.28 (m, 1H), 7.22-7.13 (m, 2H), 7.05-6.98 (m, 1H), 6.63 (s, 1H), 6.62-6.58 (m, 1H), 6.49 (s, 1H), 5.42, 5.14 (ABq, J_{AB} = 17.3 Hz, 2H), 5.00, 4.74 (ABq, J_{AB} = 8.9 Hz, 2H), 4.22-4.10 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.3, 155.3, 152.5, 144.6, 142.4, 138.4, 134.3 (q, $^3J_{C\text{-}F}$ = 5.2 Hz), 132.8, 128.7, 124.4, (q, $^2J_{C\text{-}F}$ = 32.6 Hz), 123.9 (q, $^1J_{C\text{-}F}$ = 273.3 Hz), 123.8, 123.4, 122.2, 121.7, 112.6, 108.6, 99.2, 80.2, 64.6, 64.0, 58.3, 42.3 (q, $^4J_{C\text{-}F}$ = 3.3 Hz); MS (ES+) *m/z* 454.8 (M + 1).

SYNTHETIC EXAMPLE 5

Resolution of Compound of Formula (II) by SMB Chromatography

The compound of formula (II) was resolved into the compound of formula (II-*S*) and the compound of formula (II-*R*) by SMB chromatography under the following conditions:

Extract:	182.67 mL/min
Raffinate:	67.44 mL/min
Eluent:	224.11 mL/min
Feed:	26.0 mL/min
Recycling:	420 mL/min
Run Time:	1.05 min
Temperature:	25 °C
Pressure:	50-55 bar

The feed solution (68.4 g of compound of formula (II) in 1.0 L of mobile phase (97:3 (v:v) mixture of dichloromethane/acetone)) was injected continuously into the SMB system (Novasep Licosep Lab Unit), which was equipped with eight identical columns in 2-2-2-2 configuration containing 110 g (per column, 10.0 cm, 4.8 cm I.D.) of ChiralPAK®-IC as stationary phase. The compound of formula (II-*R*) was contained in the raffinate stream and the compound of formula (I-*S*) was contained in the extract stream.

A total of 10.62 kg of the compound of formula (II) were processed by SMB chromatography using the above conditions. All extract fractions with a chiral purity (HPLC) > 99.0 a/a were pooled, concentrated to a volume of 26 L under reduced pressure and transferred to a 100 L reactor. The solution was further concentrated under a reduced pressure of 700-590 mbar at 26-37 °C until 13 L of distillate had been collected. Methanol (25 L) was added and the mixture concentrated under a reduced pressure of 650-360 mbar at 30-38 °C until 15 L of distillate had been collected. The mixture was cooled to 20 °C and methanol (15 L) was added. The mixture was concentrated under a reduced pressure of 650-320 mbar at 20-39 °C until 15 L of distillate had been collected and was cooled to 1 °C over 53 minutes and stirred for a further 70 minutes. The suspension was filtered and the filter cake was washed with cold (0 °C) methanol (9 L) and dried at ambient temperature under a flow of nitrogen gas for 15.5 h. The solid was further dried at a reduced pressure of 40-1 mbar at 50 °C for 195 minutes to afford the compound of formula (II-*S*), *i.e.*, (*S*)-1'-{[3-

(trifluoromethyl)pyridin-2-yl]methyl}-2,3-dihydrospiro[furo[2,3-*g*][1,4]benzodioxine-8,3'-indol]-2'(1'*H*)-one (3.62 kg) as a colorless solid: purity (HPLC-UV) 100%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67-8.63 (m, 1H), 8.01-7.96 (m, 1H), 7.35-7.28 (m, 1H), 7.22-7.13 (m, 2H), 7.05-6.98 (m, 1H), 6.63 (s, 1H), 6.62-6.58 (m, 1H), 6.49 (s, 1H), 5.42, 5.14 (ABq, J_{AB} = 17.3 Hz, 2H), 5.00, 4.74 (ABq, J_{AB} = 8.9 Hz, 2H), 4.22-4.10 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.3, 155.3, 152.5, 144.6, 142.4, 138.4, 134.3 (q, $^3J_{C-F}$ = 5.2 Hz), 132.8, 128.7, 124.4, (q, $^2J_{C-F}$ = 32.6 Hz), 123.9 (q, $^1J_{C-F}$ = 273.3 Hz), 123.8, 123.4, 122.2, 121.7, 112.6, 108.6, 99.2, 80.2, 64.6, 64.0, 58.3, 42.3 (q, $^4J_{C-F}$ = 3.3 Hz); MS (ES+) *m/z* 454.8 (M + 1); $[\alpha]_D$ +45.1° (*c* 2.02, DMSO); ee (CHIRALPAK IC, dichloromethane/acetone 97/3 (v/v)) 100%.

The compound of formula (II-*R*), *i.e.*, (*R*)-1'-{[3-(trifluoromethyl)pyridin-2-yl]methyl}-2,3-dihydrospiro[furo[2,3-*g*][1,4]benzodioxine-8,3'-indol]-2'(1'*H*)-one, was isolated from the raffinate by standard procedures.

BIOLOGICAL ASSAYS

In order that the invention described herein may be more fully understood, the following biological assay is set forth to demonstrate the utility of the compounds prepared herein. It should be understood that this example is for illustrative purposes only and is not to be construed as limiting this invention in any manner.

BIOLOGICAL EXAMPLE 1

Guanidine Influx Assay (*in vitro* assay)

This example describes an *in vitro* assay for testing and profiling test agents against human or rat voltage-gated sodium channels stably expressed in cells of either an endogenous or heterologously expressed origin. The assay is also useful for determining the IC_{50} of a voltage-gated sodium channel modulating (preferably blocking) compound. The assay is based on the guanidine influx assay described by Reddy, N.L., *et al.*, *J. Med. Chem.* (1998), 41(17):3298-302.

The guanidine influx assay is a radiotracer flux assay used to determine ion flux activity of voltage-gated sodium channels in a high-throughput microplate-based format., The assay uses ^{14}C-guanidine hydrochloride in combination with various known voltage-gated sodium channel modulators that produce maintained influx, to assay the potency of test agents. Potency is determined by an IC_{50} calculation. Selectivity is determined by comparing potency of the compound for the voltage-gated sodium channel of interest to its potency against other voltage-gated sodium channels

(also called 'selectivity profiling').

Each of the test agents is assayed against cells that express the voltage-gated sodium channels of interest. Voltage-gated sodium channels are characterized as TTX sensitive or insensitive. This property is useful when evaluating the activities of a voltage-gated sodium channel of interest when it resides in a mixed population with other voltage-gated sodium channels. The following Table 1 summarizes cell lines useful in screening for a certain voltage-gated sodium channel activity in the presence or absence of TTX.

TABLE 1

CELL LINE	mRNA Expression	Functional Characterization
CHO-K1 (Chinese Hamster Ovary; recommended host cell line) ATTC accession number CCL-61	• $Na_V1.4$ expression has been shown by RT-PCR • No other Na_V expression has been detected	• The 18- to 20-fold increase in [^{14}C] guanidine influx was completely blocked using TTX. ($Na_V1.4$ is a TTX sensitive channel)
L6 (rat myoblast cell) ATTC Number CRL-1458	• Expression of $Na_V1.4$ and 1.5	• The 10- to 15-fold increase in [^{14}C] guanidine influx was only partially blocked by TTX at 100 nM ($Na_V1.5$ is TTX resistant)
SH-SY5Y (Human neuroblastoma) ATTC Number CRL-2266	• Published Expression of $Na_V1.9$ and $Na_V1.7$ (Blum *et al.*)	• The 10- to 16-fold increase in [^{14}C] guanidine influx above background was partially blocked by TTX ($Na_V1.9$ is TTX resistant)
SK-N-BE2C (a human neuroblastoma cell line ATCC Number CRL-2268)	• Expression of $Na_V1.8$	• Stimulation of BE2C cells with pyrethroids results in a 6-fold increase in [^{14}C] guanidine influx above background. • TTX partially blocked influx ($Na_V1.8$ is TTX resistant)
PC12 (rat pheochromocytoma) ATTC Number CRL-1721	• Expression of $Na_V1.2$ and $Na_V1.7$	• The 8- to 12-fold increase in [^{14}C] guanidine influx was completely blocked using TTX. ($Na_V1.2$ and $Na_V1.7$ are TTX sensitive channels)

CELL LINE	mRNA Expression	Functional Characterization
HEK293 (human embryonic kidney) ATTC Number CRL-1573	• Expression of $hNa_V1.7$	• $Na_V1.7$ is a TTX sensitive channel. The TTX IC_{50} in the functional Guanidinium assay is 8 nM.

It is also possible to employ immortalized cell lines that heterologously express voltage-gated sodium channels. Cloning, stable transfection and propagation of such cell lines are known to those skilled in the art (see, for example, Klugbauer, N, *et al.*, *EMBO J.* (1995), 14(6):1084-90; and Lossin, C., *et al.*, *Neuron* (2002), 34, pp. 877-884).

Cells expressing the voltage-gated sodium channel of interest are grown according to the supplier or in the case of a recombinant cell in the presence of selective growth media such as G418 (Gibco/Invitrogen). The cells are disassociated from the culture dishes with an enzymatic solution (1X) Trypsin/EDTA (Gibco/Invitrogen) and analyzed for density and viability using haemocytometer (Neubauer). Disassociated cells are washed and resuspended in their culture media then plated into Poly-D-Lysine coated Scintiplates (Perkin Elmer) (approximately 100,000 cells/ well) and incubated at 37 °C/5% CO_2 for 20-24 hours. After an extensive wash with Low sodium HEPES-buffered saline solution (LNHBSS) (150 mM Choline Chloride, 20 nM HEPES (Sigma), 1 mM Calcium Chloride, 5 mM Potassium Chloride, 1 mM Magnesium Chloride, 10 mM Glucose) the test agents are diluted with LNHBSS and then added to each well at the desired concentration. (Varying concentrations of test agent may be used). The activation/radiolabel mixture contains an alkaloid such as veratridine or Aconitine (Sigma) or a pyrethroid such as deltamethrin, venom from the scorpion *Leiurus quinquestriatus hebraeus* (Sigma) and ^{14}C-guanidine hydrochloride (ARC) to measure flux through the voltage-gated sodium channels.

After loading the cells with test agent and activation/radiolabel mixture, the Poly-D-Lysine coated Scintiplates are incubated at ambient temperature. Following the incubation, the Poly-D-Lysine coated Scintplates are extensively washed with LNHBSS supplemented with Guanidine (Sigma). The Poly-D-Lysine coated Scintiplates are dried and then counted using a Wallac MicroBeta TriLux (Perkin-Elmer Life Sciences). The ability of the test agent to block voltage-gated sodium channel activity is determined by comparing the amount of ^{14}C-guanidine present inside the

cells expressing the different voltage-gated sodium channels. Based on this data, a variety of calculations, as set out elsewhere in this specification, may be used to determine whether a test agent is selective for a particular voltage-gated sodium channel.

The IC_{50} value of a test agent for a specific voltage-gated sodium channel may be determined using the above general method. The IC_{50} may be determined using a 3, 8, 10, 12 or 16 point curve in duplicate or triplicate with a starting concentration of 1, 5 or 10 μM diluted serially with a final concentration reaching the sub-nanomolar, nanomolar and low micromolar ranges. Typically the mid-point concentration of test agent is set at 1 μM, and sequential concentrations of half dilutions greater or smaller are applied (*e.g.*, 0.5 μM; 5 μM and 0.25 μM; 10 μM and 0.125 μM; 20 μM etc.). The IC_{50} curve is calculated using the 4 Parameter Logistic Model or Sigmoidal Dose-Response Model formula (fit = (A+((B-A)/(1+((C/x)^D))))).

The fold selectivity, factor of selectivity or multiple of selectivity, is calculated by dividing the IC_{50} value of the test voltage-gated sodium channel by the reference voltage-gated sodium channel, for example, $Na_V1.5$.

Accordingly, the compounds prepared by the methods disclosed herein demonstrated voltage-gated sodium channel blocking activity against $hNa_V1.7$ as set forth below in Table 2:

TABLE 2

Compound	Chemical Name	IC_{50} (μM)
(I)	1'-{[5-(trifluoromethyl)furan-2-yl]methyl}spiro[furo[2,3-*f*][1,3]benzodioxole-7,3'-indol]-2'(1'*H*)-one	0.007
(I-*R*)	(*R*)-1'-{[5-(trifluoromethyl)furan-2-yl]methyl}spiro[furo[2,3-*f*][1,3]benzodioxole-7,3'-indol]-2'(1'*H*)-one	4.200
(I-*S*)	(*S*)-1'-{[5-(trifluoromethyl)furan-2-yl]methyl}spiro[furo[2,3-*f*][1,3]benzodioxole-7,3'-indol]-2'(1'*H*)-one	0.003
(II)	1'-{[3-(trifluoromethyl)pyridin-2-yl]methyl}-2,3-dihydrospiro[furo[2,3-*g*][1,4]benzodioxine-8,3'-indol]-2'(1'*H*)-one	0.015
(II-*S*)	(*S*)-1'-{[3-(trifluoromethyl)pyridin-2-yl]methyl}-2,3-dihydrospiro[furo[2,3-*g*][1,4]benzodioxine-8,3'-indol]-2'(1'*H*)-one	0.005

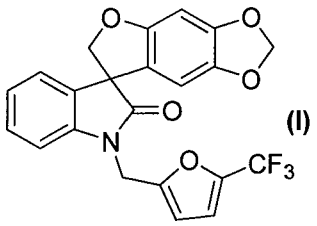
* * * * *

All of the U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the Application Data Sheet are incorporated herein by reference, in their entireties.

Although the foregoing invention has been described in some detail to facilitate understanding, it will be apparent that certain changes and modifications may be practiced within the scope of the appended claims. Accordingly, the described embodiments are to be considered as illustrative and not restrictive, and the invention is not to be limited to the details given herein, but may be modified within the scope and equivalents of the appended claims.

WHAT IS CLAIMED IS

1. A method of preparing a compound of formula (I):

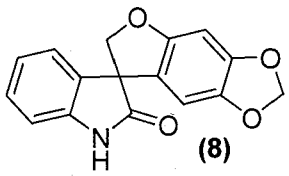


(I)

;

or a pharmaceutically acceptable salt thereof, as a single stereoisomer or enantiomer or a mixture thereof;

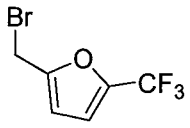
wherein the method comprises treating a compound of formula (8):



(8)

;

or a pharmaceutically acceptable salt thereof, with a compound of formula (9):

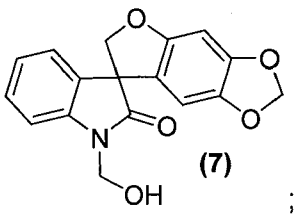


(9)

;

or a pharmaceutically acceptable salt thereof, under suitable conditions to provide the compound of formula (I), or a pharmaceutically acceptable salt thereof, as a single stereoisomer or enantiomer or a mixture thereof.

2. The method of Claim 1 further comprising a preparation of the compound of formula (8), wherein the method comprises treating a compound of formula (7):

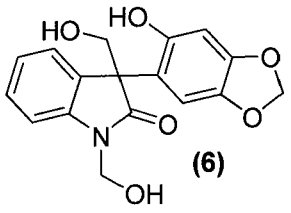


(7)

;

or a pharmaceutically acceptable salt thereof, with a base under suitable conditions to form the compound of formula (8), or a pharmaceutically acceptable salt thereof.

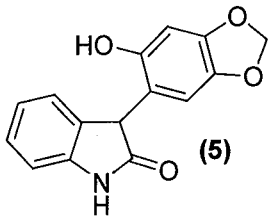
3. The method of Claim 2 further comprising a preparation of the compound of formula (7), wherein the method comprises treating a compound of formula (6):



(6) ;

or a pharmaceutically acceptable salt thereof, under standard Mitsunobu reaction conditions to form the compound of formula (7), or a pharmaceutically acceptable salt thereof.

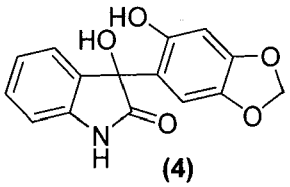
4. The method of Claim 3 further comprising a preparation of the compound of formula (6), wherein the method comprises treating a compound of formula (5):



(5) ;

or a pharmaceutically acceptable salt thereof, with an aldehyde under suitable conditions to form the compound of formula (6), or a pharmaceutically acceptable salt thereof.

5. The method of Claim 4 further comprising a preparation of the compound of formula (5), wherein the method comprises treating a compound of formula (4):

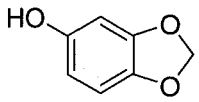


(4) ;

or a pharmaceutically acceptable salt thereof, under suitable conditions to form the compound of formula (5), or a pharmaceutically acceptable salt thereof.

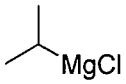
6. The method of Claim 5 further comprising a preparation of the compound of formula (4), wherein the method comprises:

a) reacting a compound of formula (2):



(2) ;

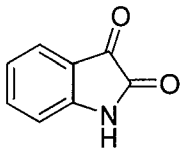
or a pharmaceutically acceptable salt thereof, with a Grignard reagent of formula (3):



(3) ;

under suitable conditions to form an intermediate product; and

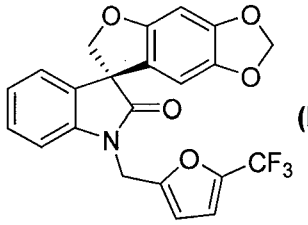
b) reacting the intermediate product of a) with a compound of formula (1):



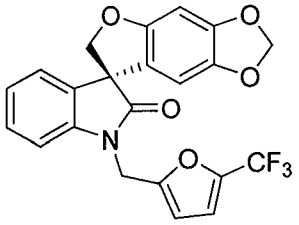
(1) ;

or a pharmaceutically acceptable salt thereof, under suitable conditions to form the compound of formula (4), or a pharmaceutically acceptable salt thereof.

7. The method of Claim 1 further comprising resolving the compound of formula (I), or a pharmaceutically acceptable salt thereof, under suitable conditions, to yield a compound of formula (I-*S*):

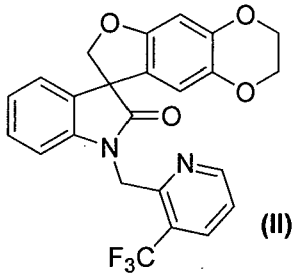

(I-*S*)
;

or a pharmaceutically acceptable salt thereof, and a compound of formula (I-*R*):

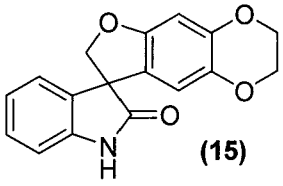

(I-*R*)
;

or a pharmaceutically acceptable salt thereof.

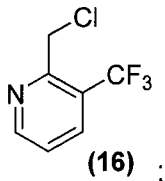
8. A method of preparing a compound of formula (II):


(II)
;

or a pharmaceutically acceptable salt thereof, as a single stereoisomer or enantiomer or a mixture thereof;
wherein the method comprises treating a compound of formula (15):


(15)
;

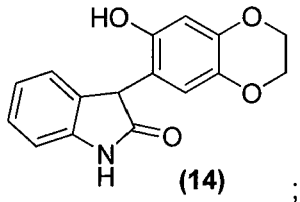
or a pharmaceutically acceptable salt thereof, with a compound of formula (16):



(16) ;

or a pharmaceutically acceptable salt thereof, under suitable conditions to provide the compound of formula (II), or a pharmaceutically acceptable salt thereof, as a single stereoisomer or enantiomer or a mixture thereof.

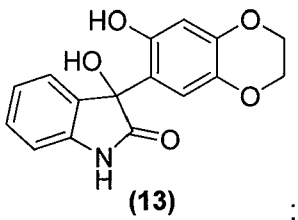
9. The method of Claim 8 further comprising a preparation of the compound of formula (15), or a pharmaceutically acceptable salt thereof, wherein the method comprises treating a compound of formula (14):



(14) ;

or a pharmaceutically acceptable salt thereof, with an alkylating agent under suitable conditions to form the compound of formula (15), or a pharmaceutically acceptable salt thereof.

10. The method of Claim 9 further comprising a preparation of the compound of formula (14), or a pharmaceutically acceptable salt thereof, wherein the method comprises treating a compound of formula (13):

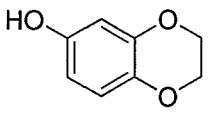


(13) ;

or a pharmaceutically acceptable salt thereof, under suitable conditions to form the compound of formula (14), or a pharmaceutically acceptable salt thereof.

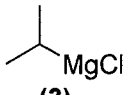
11. The method of Claim 10 further comprising a preparation of the compound of formula (13), or a pharmaceutically acceptable salt thereof, wherein the method comprises:

a) reacting a compound of formula (12):



(12) ;

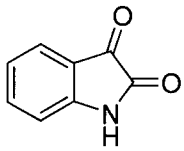
with a Grignard reagent of formula (3):



(3) ;

under suitable conditions to form an intermediate product; and

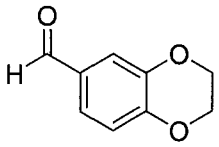
b) reacting the intermediate product of a) with a compound of formula (1):



(1) ;

or a pharmaceutically acceptable salt thereof, under suitable conditions to form the compound of formula (13), or a pharmaceutically acceptable salt thereof.

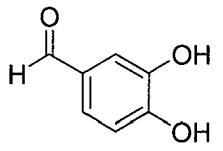
12. The method of Claim 11 further comprising a preparation of the compound of formula (12), or a pharmaceutically acceptable salt thereof, wherein the method comprises treating a compound of formula (11):



(11) ;

with an oxidizing agent under suitable conditions to form the compound of formula (12), or a pharmaceutically acceptable salt thereof.

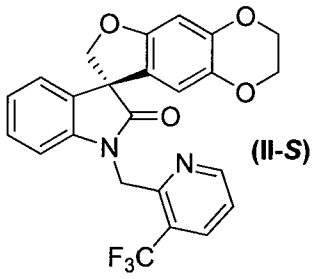
13. The method of Claim 12 further comprising a preparation of the compound of formula (11), wherein the method comprises treating a compound of formula (10):



(10) ;

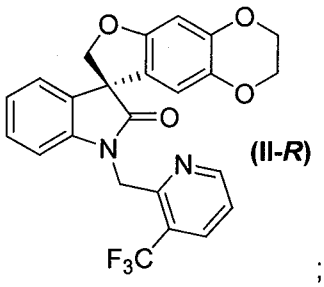
with a suitable alkylating reagent under suitable conditions to form the compound of formula (11).

14. The method of Claim 8 further comprising resolving a compound of formula (II) under suitable conditions to yield a compound of formula (II-*S*):



(II-*S*) ;

or a pharmaceutically acceptable salt thereof; and a compound of formula (II-*R*):



(II-*R*) ;

or a pharmaceutically acceptable salt thereof.