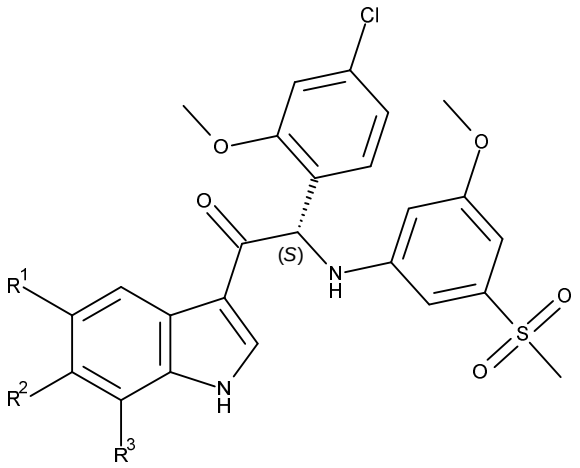
Claims

1. A process for the preparation of a compound of formula (I)



(I)

wherein R^1 is H, R^2 is F and R^3 is H or CH_3,

R^1 is H, CH_3 or F, R^2 is OCH_3 and R^3 is H and

R^1 is H, R^2 is OCH_3 and R^3 is CH_3,

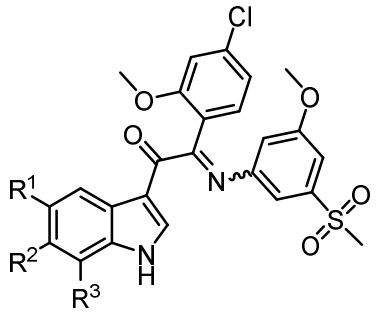
R^1 is CH_3, R^2 is F and R^3 is H,

R^1 is CF_3 or OCF_3, R^2 is H and R^3 is H,

R^1 is OCF_3, R^2 is OCH_3 and R^3 is H and

R^1 is OCF_3, R^2 is H and R^3 is CH_3;

characterized by hydrogenation of compound of formula (III)

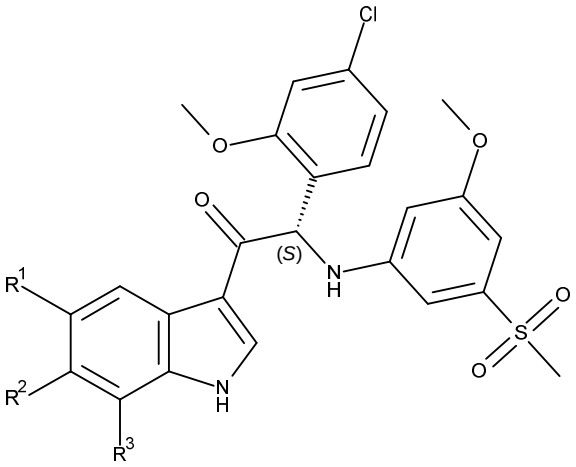


(III)

wherein the hydrogenation is performed in the presence of a combination of a catalyst and a chiral ligand.

2. The process according to claim 1 wherein the catalyst is bis(norbornadiene)-rhodium(I)tetrafluoroborate and the chiral ligand is **(***S*)-1-[(RP)-2-(diphenyl-phosphino)ferrocenyl]ethyldi-tert-butylphosphine.

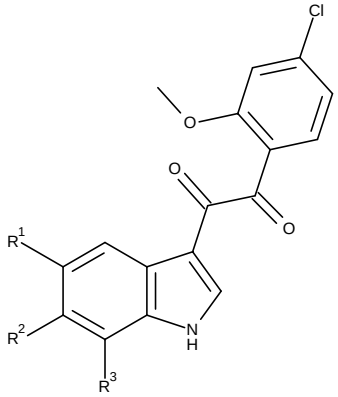
3. A process for the preparation of a compound of formula (I)



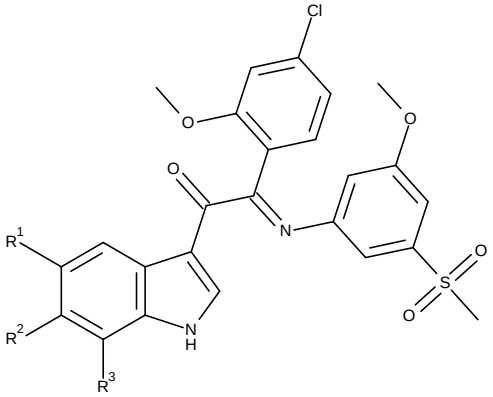
(I)

comprising the steps of:

a) reacting a compound of formula (II) with 3-methoxy-5-methylsulfonyl-aniline to produce a compound of formula (III); and



(II)



(III)

b) hydrogenation of compound of formula (III) to produce compound of formula (I);

wherein:

R^1 is H, R^2 is F and R^3 is H or CH_3,

R^1 is H, CH_3 or F, R^2 is OCH_3 and R^3 is H and

R^1 is H, R^2 is OCH_3 and R^3 is CH_3,

R^1 is CH_3, R^2 is F and R^3 is H,

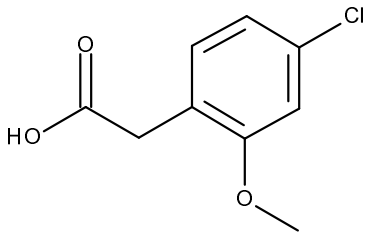
R^1 is CF_3 or OCF_3, R^2 is H and R^3 is H,

R^1 is OCF_3, R^2 is OCH_3 and R^3 is H and

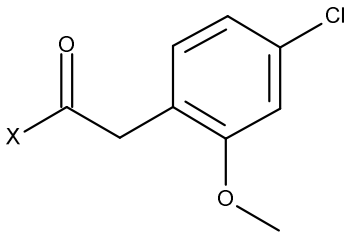
R^1 is OCF_3, R^2 is H and R^3 is CH_3.

4. The process according to claim 3 wherein the compound of formula (II) is prepared by a method comprising the steps of:

i) converting 2-(4-chloro-2-methoxy-phenyl)acetic acid (IX) into a compound of formula (Xa), wherein X is Cl or Br;

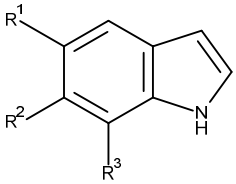


(IX)

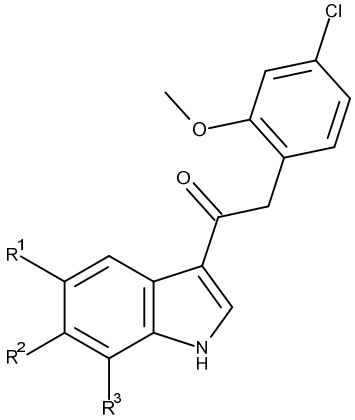


(Xa)

ii) reacting a compound of formula (Xa) with a compound of formula (XI) to produce a compound of formula (XII);



(XI)



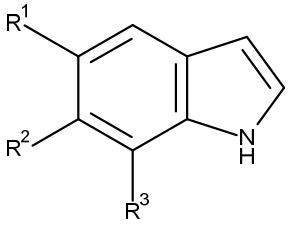
(XII)

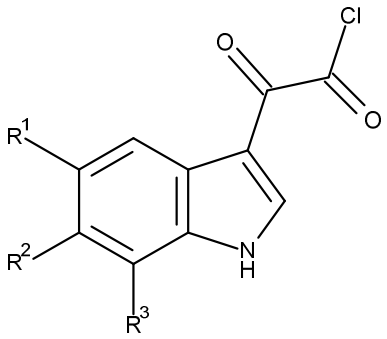
iii) contacting compound of formula (XII) with an oxidizing agent to produce a compound of formula (II);

wherein R^1, R^2 and R^3 are as defined in claim 3.

5. The process according to claim 3 wherein the compound of formula (II) is prepared by a method comprising the steps of:

i) reacting a compound of formula (XI) with oxalyl chloride to produce a compound of formula (XIII);





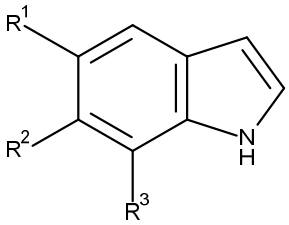
(XI) (XIII)

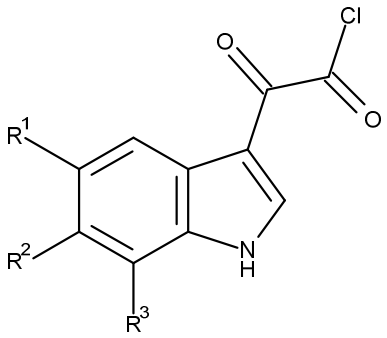
ii) contacting compound of formula (XIII) with a compound selected from the group comprising: (4-chloro-2-methoxyphenyl)magnesium bromide, (4-chloro-2-methoxyphenyl)magnesium chloride, (4-chloro-2-methoxyphenyl)magnesium iodide, (4-chloro-2-methoxyphenyl)Zinc bromide, (4-chloro-2-methoxyphenyl)Zinc chloride or (4-chloro-2-methoxyphenyl)Zinc iodide, to afford a compound of formula (II);

wherein R^1, R^2 and R^3 are as defined in claim 3.

6. The process according to claim 3 wherein the compound of formula (II) is prepared by a method comprising the steps of:

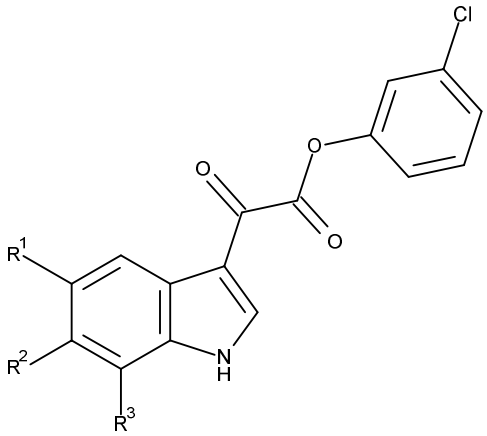
i) reacting a compound of formula (XI) with oxalyl chloride to produce a compound of formula (XIII);





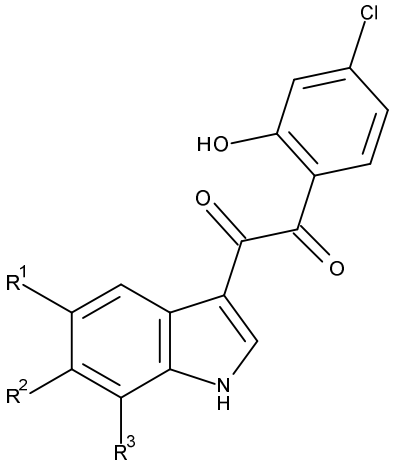
(XI) (XIII)

ii) reacting compound of formula (XIII) with 3-chlorophenol to produce a compound of formula (XVI);



(XVI)

iii) submitting compound of formula (XVI) to acidic conditions to afford compound of formula (XVII);



(XVII)

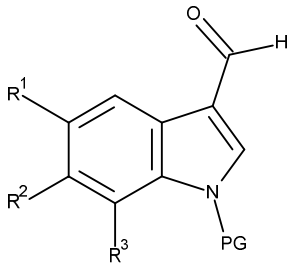
iv) methylation of the compound of formula (XVII) to afford compound of formula (II);

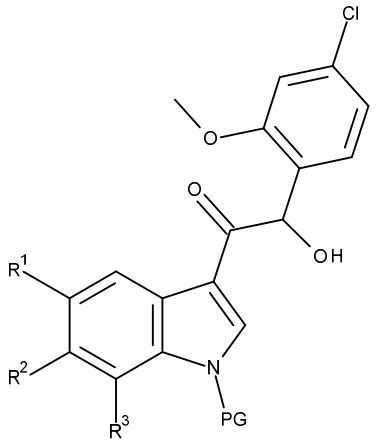
wherein R^1, R^2 and R^3 are as defined in claim 3.

7. The process according to claim 3 wherein the compound of formula (II) is prepared by a method comprising the steps of:

i) reacting 4-chloro-2-methoxybenzaldehyde with a compound of formula (XVIII) to afford a compound of formula (XIX), wherein PG is a protecting group preferably selected from the group comprising benzyl, methyl, acetyl,

tosyl; and





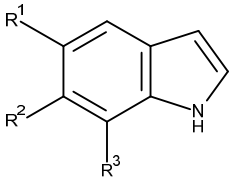
(XVIII) (XIX)

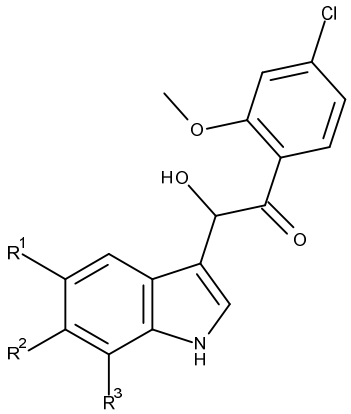
ii) contacting compound of formula (XIX) with an oxidizing agent to produce compound of formula (II);

wherein R^1, R^2 and R^3 are as defined in claim 3.

8. The process according to claim 3 wherein the compound of formula (II) is prepared by a method comprising the steps of:

i) reacting 1-(4-chloro-2-methoxy-phenyl)-2,2-dihydroxy-ethanone with a compound of formula (XI) to afford a compound of formula (XX);





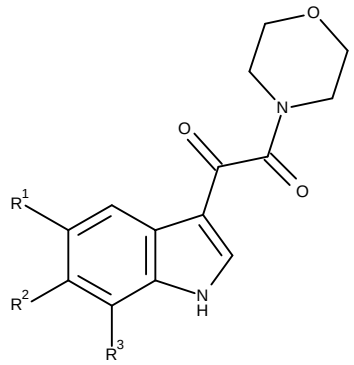
(XI) (XX)

ii) reacting a compound of formula (XX) with an oxidizing agent to afford compound of formula (II);

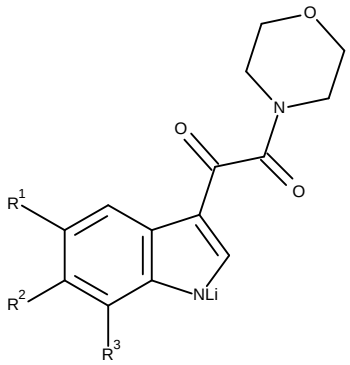
wherein R^1, R^2 and R^3 are as defined in claim 3.

9. The process according to claim 3 wherein the compound of formula (II) is prepared by a method comprising the steps of:

i) reacting a compound of formula (XXV) with a base selected from LiOtBu, LiHMDS, LiOEt, LiOMe and LiOH to produce a compound of formula (XXVI);



(XXV)



(XXVI)

ii) reacting compound of formula (XXVI) with 4-chloro-2-methoxyphenyl magnesium halide or with (4-chloro-2-methoxyphenyl)Lithium to produce compound of formula (II), preferably wherein the halide is Br, Cl or I;

wherein R^1, R^2 and R^3 are as defined in claim 3.

10. The process according to any one of claims 3-9, wherein the step of reacting a compound of formula (II) with 3-methoxy-5-methylsulfonyl-aniline to produce a compound of formula (III) is be performed in the presence of at least one reagent selected from the group comprising p-TsOH, MSA, TFA, dichloroacetic acid (DCA), saccharin, $Ca(OTf)_2$, $ZnBr_2$ $Zn(OTf)_2$, $TiCl_4$, $Ti(i\text{-}PrO)_4$, $Ti(EtO)_4$, $FeCl_3$, CuBr, $ZnCl_2$,TfOH and $Ba(OTf)_2$.

11. The process according to any one of claims 3 to 10, wherein the step of hydrogenating the compound of formula (III) to produce a compound of formula (I) is performed in the presence of a combination of bis(norbornadiene)rhodium(I) tetrafluoroborate and **(***S***)**-1-[(RP)-2-(diphenylphosphino)ferrocenyl]ethyldi-tert-butylphosphine.

12. The process according to any one of claims 3 to 10, wherein the step of hydrogenating the compound of formula (III) to produce a compound of formula (I) is performed in

the presence of a combination of the ruthenium catalyst $Ru(COD)(TFA)_2$ and the ligand (S)-DM-SEGPHOS.

13. The process according to any one of claims 3 to 12 wherein R^1 is OCF_3, R^2 is H and R_3 is H.