(DIPEA) to obtain 5-hydroxy-2-(isoindolin-2-ylmethyl)-4*H*-pyran-4-one (III) followed by reaction with (1-(methylsulfonyl)piperidin-4-yl)methyl methane sulfonate (V) in dimethylformamide (DMF) in the presence of potassium carbonate base. The compound of formula (1A) is recovered from the reaction mixture by addition of water, extracting with EtOAc and evaporating to dryness followed by purification by column chromatography.

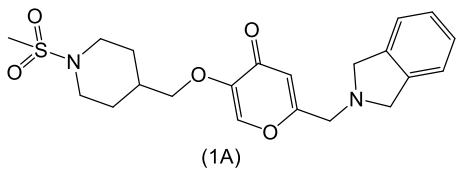
The above mentioned process has several drawbacks. The yield of the first step for obtaining compound of formula (III) is poor, not higher than about 36 %, and large volumes of solvent is needed. The final step suffers from the need to evaporate the solvent to dryness for obtaining the brownish crude product, which needs to be purified by column chromatography leading to poor yield. The process does not provide the possibility of crystallization the end product directly from the solvent.

Thus, there is a need for a more practical and economical process that is suitable for the manufacture of compound (1A) and intermediates thereof in the large scale.

Summary ~~of the invention~~

It has now been found that the compound of formula (1A) and its intermediates can be prepared using a process, which is more practical, economical and suitable for use in a large scale. In particular, the compound of formula (1A) and intermediates thereof can be obtained in significantly higher yields and with lower solvent volumes. Moreover, the compound of formula (1A) is obtained as a high purity and low colored product directly by crystallization without the need of purification by chromatography.

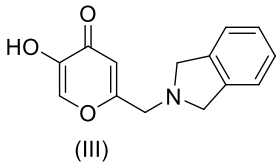
Thus, the present ~~invention~~disclosure provides a process for the preparation of a compound of formula (1A) or a pharmaceutically acceptable salt thereof



(1A)

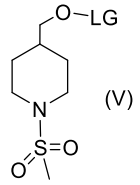
comprising the steps of either

a) reacting a compound of formula (III)



(III)

with a compound of formula (V),



(V)

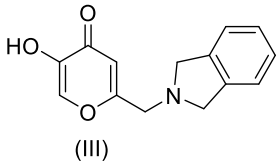
wherein LG is a leaving group selected from a mesyl or a tosyl group,
in sulfolane in the presence of cesium carbonate;

b) adding acetone and water to the mixture; and

c) isolating the compound of formula (1A), and optionally converting it to its pharmaceutically acceptable salt;

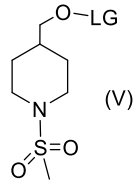
or

a') reacting a compound of formula (III)



(III)

with a compound of formula (V),



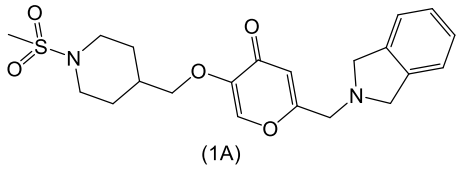
(V)

wherein LG is a leaving group selected from a mesyl or a tosyl group,
in dimethyl sulfoxide or dimethyl formamide at an elevated temperature in the presence of cesium carbonate and tris[2-(2-methoxyethoxy)ethyl]amine);

b') adding isopropanol and water to the mixture; and

c') isolating the compound of formula (1A), and optionally converting it to its pharmaceutically acceptable salt.

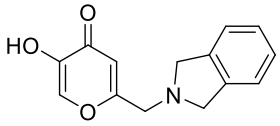
In one aspect, the present disclosure provides a process for the preparation of a compound of formula (1A) or a pharmaceutically acceptable salt thereof



(1A)

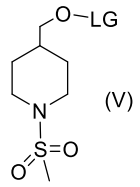
comprising the steps of either

a) reacting a compound of formula (III)



(III)

with a compound of formula (V)



(V)

wherein LG is a leaving group selected from a mesyl or a tosyl group,

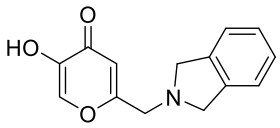
in sulfolane in the presence of cesium carbonate;

b) adding acetone and water to the mixture; and

c) isolating the compound of formula (1A), and optionally converting it to its pharmaceutically acceptable salt;

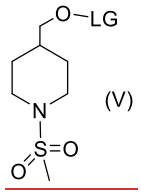
or

a') reacting a compound of formula (III)



(III)

with a compound of formula (V)



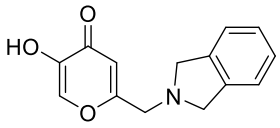
(V)

wherein LG is a leaving group selected from a mesyl or a tosyl group,
in dimethyl sulfoxide or dimethyl formamide in the presence of cesium carbonate and tris[2-(2-methoxyethoxy)ethyl]amine);

b') adding isopropanol and water to the mixture; and

c') isolating the compound of formula (1A), and optionally converting it to its pharmaceutically acceptable salt.

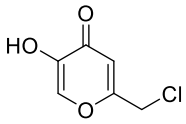
In another aspect, the present ~~invention~~disclosure provides a process for the preparation of a compound of formula (III)



(III)

comprising the steps of either

a) reacting a compound of formula (II)



(II)

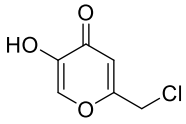
with isoindoline hydrochloride in water in the presence of potassium hydroxide;

b) transferring the reaction mixture of step a) into a mixture of acetone and acetic acid; and

c) isolating the compound of formula (III);

or

a') reacting a compound of formula (II)



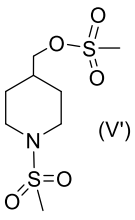
(II)

with isoindoline hydrochloride in dimethyl sulfoxide in the presence of N,N-diisopropylethylamine;

b') adding acetonitrile and water to the mixture; and

c') isolating the compound of formula (III).

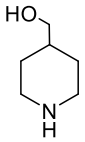
In still another aspect, the present ~~invention~~disclosure provides a process for the preparation of a compound of formula (V')



(V')

comprising the steps of

a) reacting a compound of formula (IV)



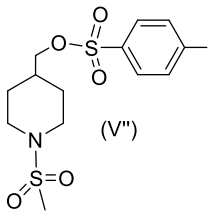
(IV)

with methanesulfonyl chloride in acetonitrile-pyridine solvent;

b) adding water and acetic acid to the mixture; and

c) isolating the compound of formula (V').

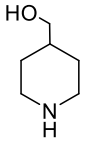
In still another aspect, the present ~~invention~~disclosure provides a process for the preparation of a compound of formula (V'')



(V")

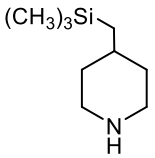
comprising the steps of

a) reacting a compound of formula (IV)



(IV)

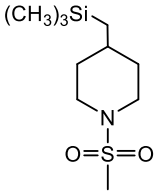
with chlorotrimethylsilane to obtain compound of formula (IVb)



(IVb)

;

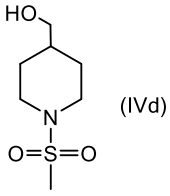
b) reacting the compound of formula (IVb) with methanesulfonyl chloride to obtain a compound of formula (IVc)



(IVc)

;

c) treating the compound of formula (IVc) with p-toluenesulfonic acid in the presence of methanol to obtain a compound of formula (IVd)

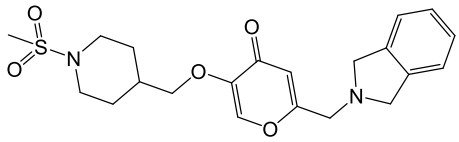


(IVd)

; and

d) reacting the compound of formula (IVd) with p-toluenesulfonyl chloride to obtain the compound of formula (V'').

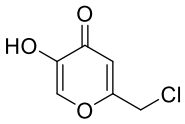
~~In still another aspect, the~~The present ~~invention~~disclosure provides a process for the preparation of a compound of formula (1A) or a pharmaceutically acceptable salt thereof



(1A)

comprising the steps of either

a) reacting a compound of formula (II)



(II)

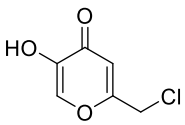
with isoindoline hydrochloride in water in the presence of potassium hydroxide;

b) transferring the reaction mixture of step a) into a mixture of acetone and acetic acid; and

c) isolating the compound of formula (III);

or

a') reacting a compound of formula (II)



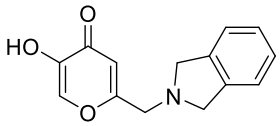
(II)

with isoindoline hydrochloride in dimethyl sulfoxide in the presence of N,N-diisopropylethylamine;

b') adding acetonitrile and water to the mixture; and

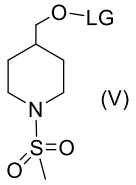
c') isolating the compound of formula (III);

d) either reacting a compound of formula (III)



(III)

with a compound of formula (V)



(V)

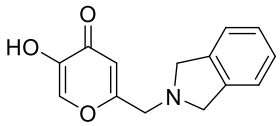
wherein LG is a leaving group selected from a mesyl or a tosyl group,
in sulfolane in the presence of cesium carbonate;

e) adding acetone and water to the mixture; and

f) isolating the compound of formula (1A), which is optionally converted to its pharmaceutically acceptable salt;

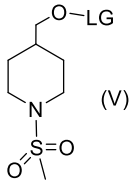
or

d') reacting a compound of formula (III)



(III)

with a compound of formula (V)



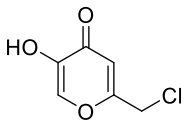
(V)

wherein LG is a leaving group selected from a mesyl or a tosyl group,
in dimethyl sulfoxide or dimethyl formamide at an elevated temperature in the presence of cesium carbonate and tris[2-(2-methoxyethoxy)ethyl]amine);

e') adding isopropanol and water to the mixture; and

f') isolating the compound of formula (1A), which is optionally converted to its pharmaceutically acceptable salt.

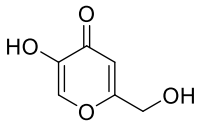
In another aspect, the present disclosure provides a process for the preparation of a compound of formula (II)



(II)

comprising the steps of

a) reacting a compound of formula (I)



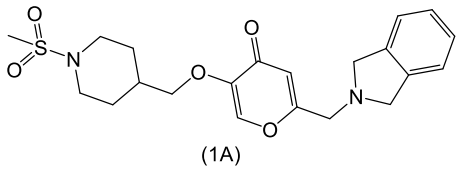
(I)

with thionyl chloride in acetonitrile;

b) adding water; and

c) isolating the compound of formula (II).

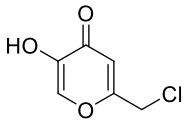
In another aspect, the present disclosure provides a process for the preparation of a compound of formula (1A) or a pharmaceutically acceptable salt thereof



(1A)

comprising the steps of either

a) reacting a compound of formula (II)



(II)

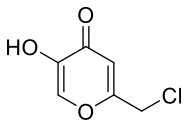
with isoindoline hydrochloride in water in the presence of potassium hydroxide;

b) transferring the reaction mixture of step a) into a mixture of acetone and acetic acid; and

c) isolating the compound of formula (III);

or

a') reacting a compound of formula (II)



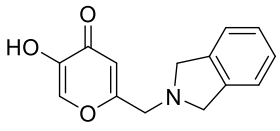
(II)

with isoindoline hydrochloride in dimethyl sulfoxide in the presence of N,N-diisopropylethylamine;

b') adding acetonitrile and water to the mixture; and

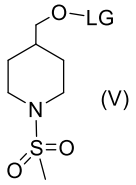
c') isolating the compound of formula (III);

d) either reacting a compound of formula (III)



(III)

with a compound of formula (V)



(V)

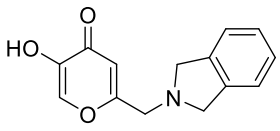
wherein LG is a leaving group selected from a mesyl or a tosyl group,
in sulfolane in the presence of cesium carbonate;

e) adding acetone and water to the mixture; and

f) isolating the compound of formula (1A), and optionally converting it to its pharmaceutically acceptable salt;

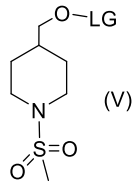
or

d') reacting a compound of formula (III)



(III)

with a compound of formula (V)



(V)

wherein LG is a leaving group selected from a mesyl or a tosyl group,
in dimethyl sulfoxide or dimethyl formamide in the presence of cesium carbonate and tris[2-(2-methoxyethoxy)ethyl]amine);

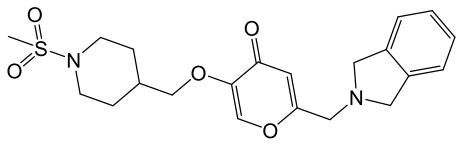
e') adding isopropanol and water to the mixture; and

f') isolating the compound of formula (1A), and optionally converting it to its pharmaceutically acceptable salt.

Detailed description of the invention

Claims

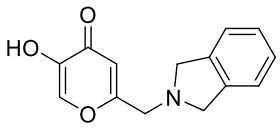
1. A process for the preparation of a compound of formula (1A) or a pharmaceutically acceptable salt thereof



(1A)

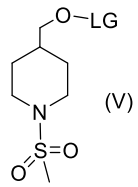
comprising the steps of either

a) reacting a compound of formula (III)



(III)

with a compound of formula (V)



(V)

wherein LG is a leaving group selected from a mesyl or a tosyl group,

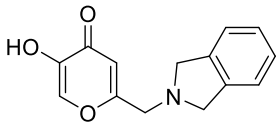
in sulfolane in the presence of cesium carbonate;

b) adding acetone and water to the mixture; and

c) isolating the compound of formula (1A), and optionally converting it to its pharmaceutically acceptable salt;

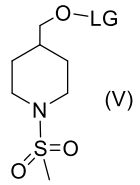
or

a') reacting a compound of formula (III)



(III)

with a compound of formula (V)



(V)

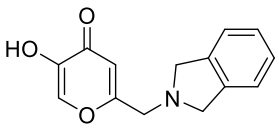
wherein LG is a leaving group selected from a mesyl or a tosyl group,
in dimethyl sulfoxide or dimethyl formamide in the presence of cesium carbonate and tris[2-(2-methoxyethoxy)ethyl]amine);

b') adding isopropanol and water to the mixture; and

c') isolating the compound of formula (1A), and optionally converting it to its pharmaceutically acceptable salt.

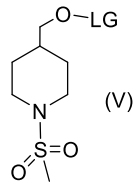
2. A process according to claim 1 comprising the steps of

a) reacting a compound of formula (III)



(III)

with a compound of formula (V)



(V)

wherein LG is a leaving group selected from a mesyl or a tosyl group,
in sulfolane in the presence of cesium carbonate;

b) adding acetone and water to the mixture; and

c) isolating the compound of formula (1A), and optionally converting it to its pharmaceutically acceptable salt.

3. A process according to any one of the preceding claims, wherein the reaction temperature at step a) is from about 70 to about 90 °C.

4. A process according to any one of the preceding claims, wherein step b) is carried out by adding acetone followed by water.

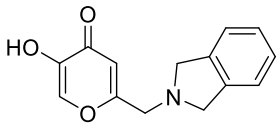
5. A process according to any one of the preceding claims, wherein the ratio acetone to water at step b) is from about 1:1 to about 1:3 per volume.

6. A process according to any one of the preceding claims, wherein the temperature after step b) is from about 45 °C to about 60 °C.

7. A process according to any one of the preceding claims, wherein before step c) the mixture is cooled to a temperature form about 5 °C to about 25 °C.

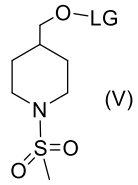
8. A process according to claim 1 comprising the steps of

a') reacting a compound of formula (III)



(III)

with a compound of formula (V)



(V)

wherein LG is a leaving group selected from a mesyl or a tosyl group,
in dimethyl sulfoxide or dimethyl formamide in the presence of cesium carbonate and tris[2-(2-methoxyethoxy)ethyl]amine);

b') adding isopropanol and water to the mixture; and

c') isolating the compound of formula (1A), and optionally converting it to its pharmaceutically acceptable salt.

9. A process according to claim 8 wherein step a') is carried out in dimethyl sulfoxide.

10. A process according to claim 8 or 9, wherein the reaction temperature at step a') is from about 50 °C to about 70 °C.

11. A process according to any one of claims 8-10, wherein step b') is carried out by adding isopropanol followed by water.

12. A process according to any one of claims 8-11, wherein the ratio of isopropanol to water at step b') is from about 1:1 to about 1:3 per volume.

13. A process according to any one of claims 9-12, wherein before step c') the mixture is cooled to a temperature which is form about 5 to about 25 °C.

14. A process according to claim 8, wherein step a') is carried out in dimethyl formamide.

15. A process according to claim 14, wherein the reaction temperature at step a') is from about 65 °C to about 75 °C.

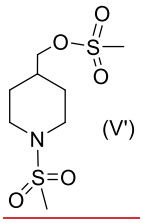
16. A process according to claims 14 or 15, wherein step b') is carried out by adding isopropanol followed by water.

17. A process according to any one of claims 14-16, wherein the ratio of isopropanol to water at step b') is from about 1:1 to about 1:3 per volume.

18. A process according to any one of claims 14-17, wherein the temperature after step b') is from about 40 °C to about 60 °C.

19. A process according to any one of claims 14-18, wherein before step c') the mixture is cooled to a temperature which is form about 10 °C to about 30 °C.

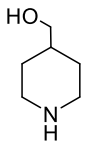
20. A process for the preparation of a compound of formula (V')



(V')

comprising the steps of

a) reacting a compound of formula (IV)



(IV)

with methanesulfonyl chloride in acetonitrile-pyridine solvent;

b) adding water and acetic acid to the mixture; and

c) isolating the compound of formula (V').

21. A process according to claim 20, wherein the reaction temperature at step a) is from about 25 °C to about 50 °C.

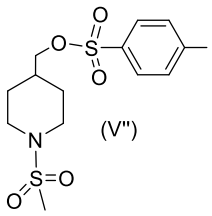
22. A process according to claim 20 or 21, wherein the ratio of acetonitrile to pyridine at step a) is from about 1:2 to about 2:1 per volume.

23. A process according to any one of claims 20-22, wherein step b) is carried out by adding water followed by acetic acid.

24. A process according to any one of claims 20-23, wherein the ratio of water to acetic acid at step b) is from about 5:1 to about 10:1 per volume.

25. A process according to any one of claims 20-24, wherein before step c) the mixture is cooled to a temperature which is form about -10 to about 10 °C.

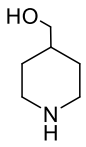
26. A process for the preparation of a compound of formula (V'')



(V'')

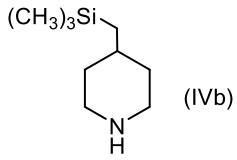
comprising the steps of

a) reacting a compound of formula (IV)



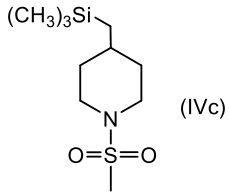
(IV)

with chlorotrimethylsilane to obtain compound of formula (IVb)



(IVb);

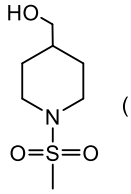
b) reacting the compound of formula (IVb) with methanesulfonyl chloride to obtain a compound of formula (IVc)



(IVc)

;

c) treating the compound of formula (IVc) with p-toluenesulfonic acid in the presence of methanol to obtain a compound of formula (IVd)



(IVd)

; and

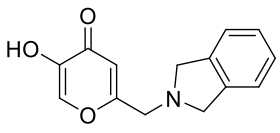
d) reacting the compound of formula (IVd) with p-toluenesulfonyl chloride to obtain the compound of formula (V'').

27. A process according to claim 26, wherein step a) is carried out in the presence of 1,1,3,3-tetramethylguanidine.

28. A process according to claim 26 or 27, wherein step b) is carried out in the presence of N-methylmorpholine.

29. A process according to any one of claims 26-28, wherein step d) is carried out in the presence of pyridine.

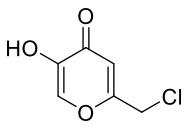
~~20~~30. A process for the preparation of a compound of formula (III)



(III)

comprising the steps of either

a) reacting a compound of formula (II)



(II)

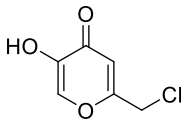
with isoindoline hydrochloride in water in the presence of potassium hydroxide;

b) transferring the reaction mixture of step a) into a mixture of acetone and acetic acid; and

c) isolating the compound of formula (III);

or

a') reacting a compound of formula (II)



(II)

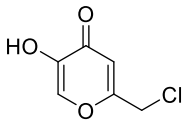
with isoindoline hydrochloride in dimethyl sulfoxide in the presence of N,N-diisopropylethylamine;

b') adding acetonitrile and water to the mixture; and

c') isolating the compound of formula (III).

~~21~~31. A process according to claim ~~20~~ 30 comprising the steps of

a) reacting a compound of formula (II)



(II)

with isoindoline hydrochloride in water in the presence of potassium hydroxide;

b) transferring the reaction mixture of step a) into a mixture of acetone and acetic acid; and

c) isolating the compound of formula (III).

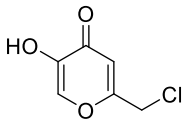
~~22~~32. A process according to claim ~~21~~31, wherein the reaction temperature at step a) is from about 0 °C to about 20 °C.

~~23~~33. A process according to claim ~~21~~ 31 or ~~22~~32, wherein the ratio of acetone to acetic acid at step b) is from about 10:1 to about 6:1 per volume.

~~24~~34. A process according to any one of claims ~~21~~31-~~23~~33, wherein the temperature after step b) is from about 30 °C to about 40 °C.

~~25~~35. A process according to claim ~~20~~ 30 comprising the steps of

a') reacting a compound of formula (II)



(II)

with isoindoline hydrochloride in dimethyl sulfoxide in the presence of N,N-diisopropylethylamine;

b') adding acetonitrile and water to the mixture; and

c') isolating the compound of formula (III).

~~26~~36. A process according to claim ~~25~~35, wherein the reaction temperature at step a') is from about 40 °C to about 60 °C.

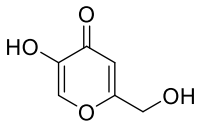
~~27~~37. A process according to claim ~~25~~ 35 or ~~26~~36, wherein the ratio of acetonitrile to water at step b') is from about 1:1 to about 1:3 per volume.

~~28~~38. A process according to any one of claims ~~25~~35-~~27~~37, wherein step b') further comprises addition of acetic acid.

~~29~~39. A process according to any one of claims ~~25~~35-~~28~~38, wherein the temperature after step b') is from about 40 °C to about 60 °C.

~~30~~40. A process according to any one of claims ~~25~~35-~~29~~39, wherein before step c') the mixture is cooled to a temperature which is form about 10 °C to about 30 °C.

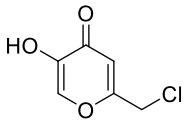
~~31~~41. A process according to any one of claims ~~20~~ 30 to ~~30~~40, wherein the compound of formula (II) is prepared by reacting a compound of formula (I)



(I)

with thionyl chloride in acetonitrile, adding water, and isolating the compound of formula (II).

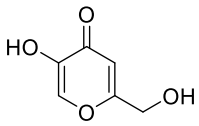
~~32~~42. A process for the preparation of a compound of formula (II)



(II)

comprising the steps of

a) reacting a compound of formula (I)



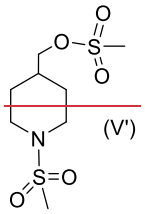
(I)

with thionyl chloride in acetonitrile;

b) adding water; and

c) isolating the compound of formula (II).

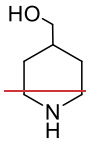
~~33. A process for the preparation of a compound of formula (V')~~



~~(V')~~

~~comprising the steps of~~

~~a) reacting a compound of formula (IV)~~



~~(IV)~~

~~with methanesulfonyl chloride in acetonitrile-pyridine solvent;~~

~~b) adding water and acetic acid to the mixture; and~~

~~c) isolating the compound of formula (V').~~

~~34. A process according to claim 33, wherein the reaction temperature at step a) is from about 25 °C to about 50 °C.~~

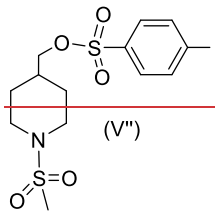
~~35. A process according to claim 33 or 34, wherein the ratio of acetonitrile to pyridine at step a) is from about 1:2 to about 2:1 per volume.~~

~~36. A process according to any one of claims 33-35, wherein step b) is carried out by adding water followed by acetic acid.~~

~~37. A process according to any one of claims 33-36, wherein the ratio of water to acetic acid at step b) is from about 5:1 to about 10:1 per volume.~~

~~38. A process according to any one of claims 33-37, wherein before step c) the mixture is cooled to a temperature which is form about -10 to about 10 °C.~~

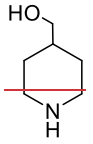
~~39. A process for the preparation of a compound of formula (V'')~~



(V'')

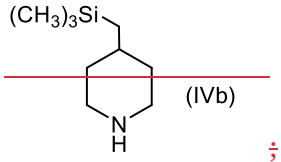
~~comprising the steps of~~

~~a) reacting a compound of formula (IV)~~



(IV)

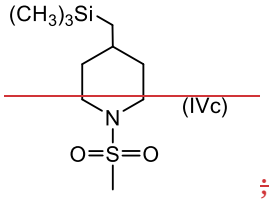
~~with chlorotrimethylsilane to obtain compound of formula (IVb)~~



(IVb)

~~;~~

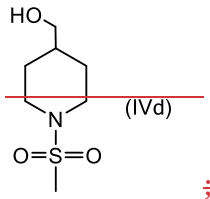
~~b) reacting the compound of formula (IVb) with methanesulfonyl chloride to obtain a compound of formula (IVc)~~



(IVc)

~~;~~

~~c) treating the compound of formula (IVc) with p-toluenesulfonic acid in the presence of methanol to obtain a compound of formula (IVd)~~



(IVd)

; and

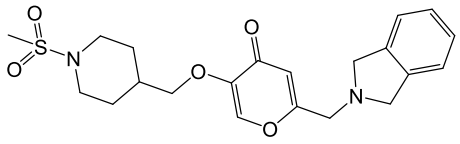
d) reacting the compound of formula (IVd) with p-toluenesulfonyl chloride to obtain the compound of formula (V'').

40. A process according to claim 39, wherein step a) is carried out in the presence of 1,1,3,3-tetramethylguanidine.

41. A process according to claim 39 or 40, wherein step b) is carried out in the presence of N-methylmorpholine.

42. A process according to any one of claims 39-41, wherein step d) is carried out in the presence of pyridine.

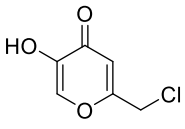
43. A process for the preparation of a compound of formula (1A) or a pharmaceutically acceptable salt thereof



(1A)

comprising the steps of either

a) reacting a compound of formula (II)



(II)

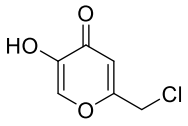
with isoindoline hydrochloride in water in the presence of potassium hydroxide;

b) transferring the reaction mixture of step a) into a mixture of acetone and acetic acid; and

c) isolating the compound of formula (III);

or

a') reacting a compound of formula (II)



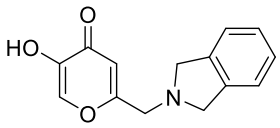
(II)

with isoindoline hydrochloride in dimethyl sulfoxide in the presence of N,N-diisopropylethylamine;

b') adding acetonitrile and water to the mixture; and

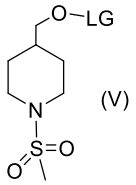
c') isolating the compound of formula (III);

d) either reacting a compound of formula (III)



(III)

with a compound of formula (V)



(V)

wherein LG is a leaving group selected from a mesyl or a tosyl group,

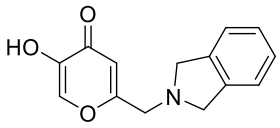
in sulfolane in the presence of cesium carbonate;

e) adding acetone and water to the mixture; and

f) isolating the compound of formula (1A), and optionally converting it to its pharmaceutically acceptable salt;

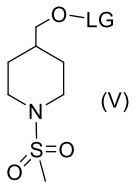
or

d') reacting a compound of formula (III)



(III)

with a compound of formula (V)



(V)

wherein LG is a leaving group selected from a mesyl or a tosyl group,

in dimethyl sulfoxide or dimethyl formamide in the presence of cesium carbonate and tris[2-(2-methoxyethoxy)ethyl]amine);

e') adding isopropanol and water to the mixture; and

f') isolating the compound of formula (1A), and optionally converting it to its pharmaceutically acceptable salt.