US-B-6,677,349 describes imidazoquinoline and tetrahydroimidazoquinoline compounds that contain sulfonamide functionality at the 1-position. The compounds are said to be useful as immunomodulators.

US-A-2003/0144283 and WO-A-00/76505 describe imidazoquinoline and tetrahydroimidazoquinoline compounds that contain amide functionality at the 1-position. The compounds are said to be useful as immunomodulators.

WO-A-2005/051324 describes imidazoquinoline, pyridine and naphthyridine ring systems substituted in 1-position with oxime or a special N-oxide functionality. The compounds are said to be useful as immunomodulators.

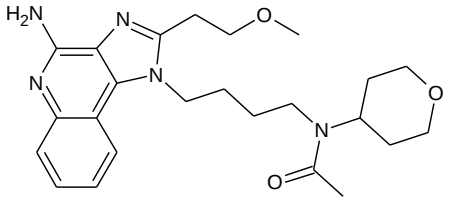
WO-A-2009/118296 describes imidazoquinoline compounds. The compounds are described as toll-like receptor agonist/TLR7 activators.

N-(4-(4-amino-2-(2-methoxyethyl)-1H-imidazo[4,5-c]quinolin-1-yl)butyl)-N-(tetrahydro-2H-pyran-4-yl)acetamide and a process for its preparation are disclosed in PCT/EP2018/073470, which is hereby incorporated by reference.

The present disclosure provides a novel process for the preparation of N-(4-(4-amino-2-(2-methoxyethyl)-1H-imidazo[4,5-c]quinolin-1-yl)butyl)-N-(tetrahydro-2H-pyran-4-yl)acetamide or a solvate or salt thereof that employs novel intermediates.

Summary

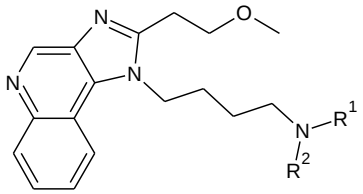
The present disclosure provides a process for synthesizing N-(4-(4-amino-2-(2-methoxyethyl)-1H-imidazo[4,5-c]quinolin-1-yl)butyl)-N-(tetrahydro-2H-pyran-4-yl)acetamide, or a solvate or salt thereof, as further described in the following. Said compound is an agonist or activator for TLR7 and may serve as cytokine inducing substance. Said compound has the following chemical formula (I):



(I)

The process comprises the following steps:

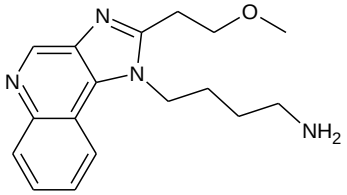
a) providing a compound of formula (3):



(3)

or a solvate or salt thereof, wherein each of R^1 and R^2 is independently selected from the group consisting of -H and an amino protecting group, and at least one of R^1 and R^2 is an amino protecting group;

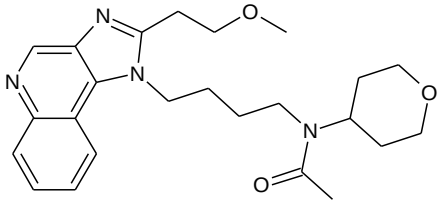
b) reacting the compound of formula (3) or a solvate or salt thereof with one or more reagents to remove the amino protecting group(s) at position R^1 and R^2 to give a compound of formula (4):



(4)

or a solvate or salt thereof;

c) reacting the compound of formula (4) or a solvate or salt thereof with one or more reagents for introducing (i) a tetrahydropyranyl group and (ii) an acetyl group to give a compound of formula (5):

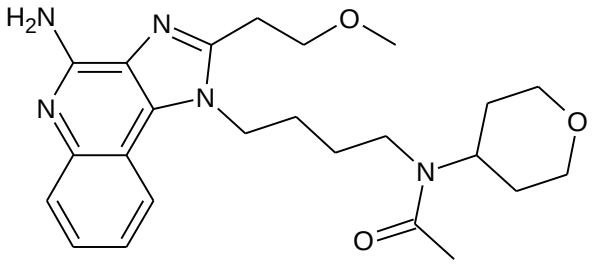


(5)

or a s solvate or salt thereof; and

d) subjecting the compound of formula (5) or a solvate or salt thereof to an oxidative amination reaction to give the compound of formula (I) or a solvate or salt thereof. Preferred examples of the process are specified below, in the claims, and in any one of Figures 1A to 1H, 2A to 2D, 3A to 3G, 4A to 4H, 5A to 5E, and 6A to 6D.

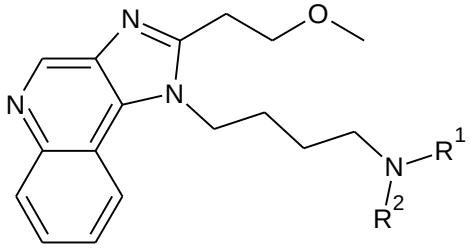
In one aspect, the present disclosure provides a process for synthesizing a compound having the formula (I):



(I)

or a solvate or salt thereof, the process comprising the following steps:

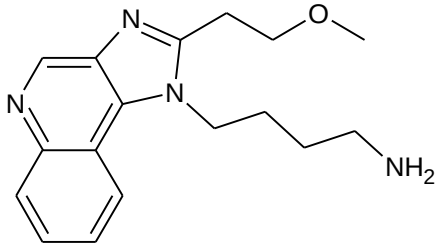
a) providing a compound of formula (3):



(3)

or a solvate or salt thereof, wherein each of R^1 and R^2 is independently selected from the group consisting of -H and an amino protecting group, and at least one of R^1 and R^2 is an amino protecting group;

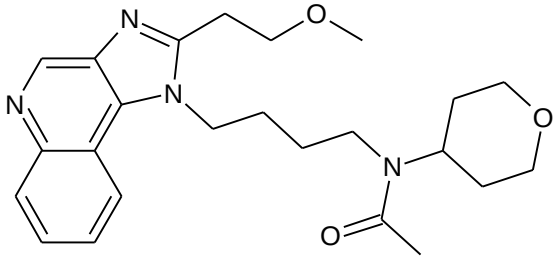
b) reacting the compound of formula (3) or a solvate or salt thereof with one or more reagents to remove the amino protecting group(s) at position R^1 and R^2 to give a compound of formula (4):



(4)

or a solvate or salt thereof;

c) reacting the compound of formula (4) or a solvate or salt thereof with one or more reagents for introducing (i) a tetrahydropyranyl group and (ii) an acetyl group to give a compound of formula (5):

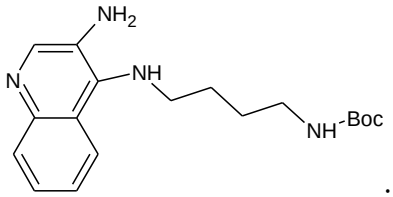
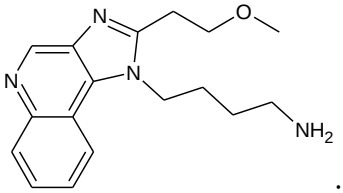
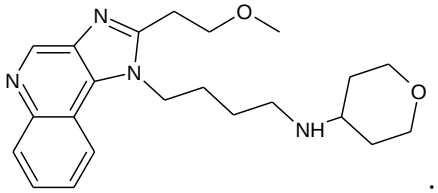
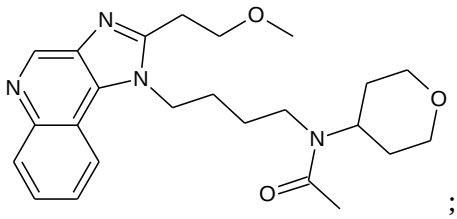


(5)

or a solvate or salt thereof; and

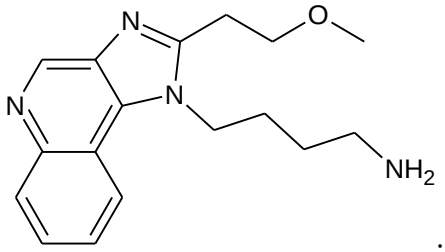
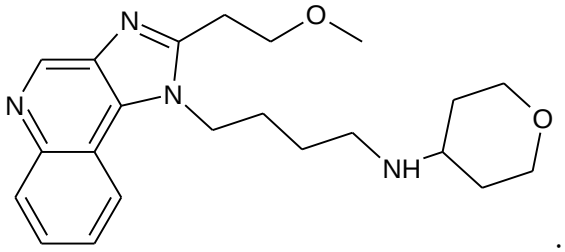
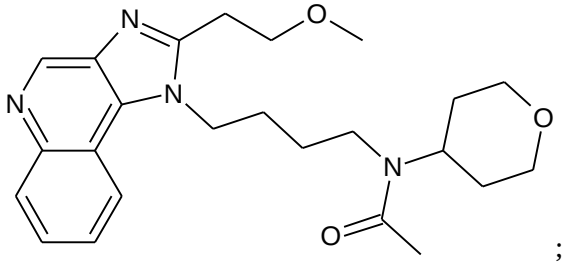
d) subjecting the compound of formula (5) or a solvate or salt thereof to an oxidative amination reaction to give the compound of formula (I) or a solvate or salt thereof.

The disclosure also provides a compound selected from the group consisting of:

and a solvate or salt thereof. These compounds are intermediates useful in the process provided.

In another aspect, the present disclosure provides a compound selected from the group consisting of:

and a solvate or salt thereof.

In a third aspect, the present disclosure provides a use of a compound of the disclosure for synthesizing a compound of formula (I).

Brief description of the Figures

Figures 1A to 1H show preferred embodiments of the process of the present invention. Substituents (e.g., R^1, R^2, R^{10}) and abbreviations (e.g., THP, PTSA) referred to in Figures 1A to 1H have the same meaning as specified in the description.

Figures 2A to 2D show preferred embodiments of step a) of the process of the present invention.

Figures 3A to 3G show preferred embodiments of step b) of the process of the present invention.

Figures 4A to 4H show preferred embodiments of step c) of the process of the present invention.

Figures 5A to 5E show preferred embodiments of step d) of the process of the present invention.

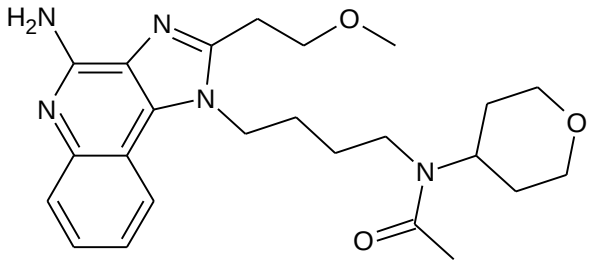
Figures 6A to 6D show preferred embodiments of steps (precipitation and/or crystallization) which may be performed after step d) of the process of the present invention.

Figure 7 shows a spectrum (^{1}H NMR, D_2O, 400 MHz) for the compound of formula (4) as fumaric acid addition salt obtained by the process of the present invention.

Figure 8 shows a chromatogram (HPLC) for the compound of formula (4) as fumaric acid addition salt (designated as SC 103439) obtained by the process of the present invention.

Claims

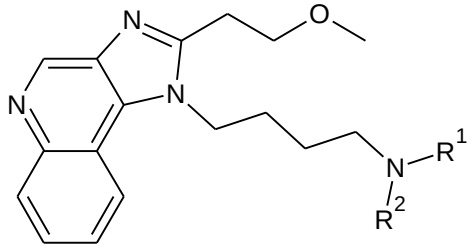
1. A process for synthesizing a compound having the formula (I):



(I)

or a solvate or salt thereof, the process comprising the following steps:

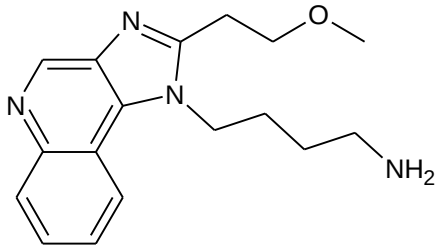
a) providing a compound of formula (3):



(3)

or a solvate or salt thereof, wherein each of R^1 and R^2 is independently selected from the group consisting of -H and an amino protecting group, and at least one of R^1 and R^2 is an amino protecting group;

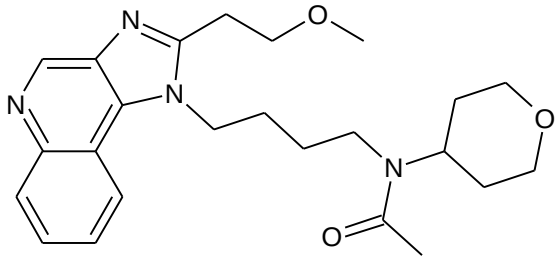
b) reacting the compound of formula (3) or a solvate or salt thereof with one or more reagents to remove the amino protecting group(s) at position R^1 and R^2 to give a compound of formula (4):



(4)

or a solvate or salt thereof;

c) reacting the compound of formula (4) or a solvate or salt thereof with one or more reagents for introducing (i) a tetrahydropyranyl group and (ii) an acetyl group to give a compound of formula (5):



(5)

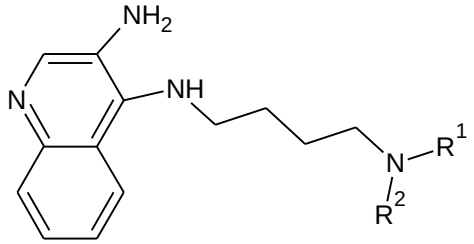
or a solvate or salt thereof; and

d) subjecting the compound of formula (5) or a solvate or salt thereof to an oxidative amination reaction to give the compound of formula (I) or a solvate or salt thereof.

2. The process of claim 1, further comprising the step of (i) precipitating the compound of formula (4) or a solvate or salt thereof before step c); (ii) precipitating the compound of formula (5) or a solvate or salt thereof before step d); and/or (iii) precipitating the compound of formula (I) or a solvate or salt thereof after step d).

3. The process of claim 1 or 2, wherein each of R^1 and R^2 is independently selected from the group consisting of -H, tert-butyloxycarbonyl (Boc), 9-fluorenylmethyloxy carbonyl (Fmoc), benzyloxycarbonyl (Cbz), tosylate (Ts), benzyl (Bn), allyloxycarbonyl (Alloc), trityl (Trt), dimethoxytrityl (DMT), and monomethoxytrityl (MMT).

4. The process of any one of claims 1 to 3, wherein step a) comprises reacting a compound of formula (1):



(1)

or a solvate or salt thereof with $HOOC(CH_2)_2OCH_3$ (formula (2)) or a derivative thereof to give a compound of formula (3) or a solvate or salt thereof.

5. The process of claim 4, wherein the derivative of formula (2) is (i) selected from the group consisting of carboxylic acid halides, orthoesters, and 1,1-dialkoxyalkyl alkanoates; and/or (ii) an orthoester, preferably an orthoester having the formula $(R^{10}O)_3C(CH_2)_2OCH_3$, wherein each R^{10} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl.

6. The process of claim 4 or 5, wherein the reaction of the compound of formula (1) with the compound of formula (2) is performed (i) in a solvent, such as an aromatic solvent; (ii) in the presence of an acid; (iii) at a suitable temperature, such as between 0°C and 120°C, e.g., at the reflux temperature of the solvent, if present; and/or (iv) for a sufficient amount of time, such as 30 min to 10 h.

7. The process of any one of claims 1 to 6, wherein step b) is performed (i) in a solvent, such as an aromatic solvent, e.g., the solvent used in step a); (ii) at a suitable temperature, such as between 0°C and 40°C; and/or (iii) for a sufficient amount of time, such as 30 min to 5 h.

8. The process of any one of claims 1 to 7, wherein each of R^1 and R^2 is independently selected from the group consisting of -H and tert-butyloxycarbonyl (Boc) and the one or more reagents to remove the amino protecting group(s) in step b) are selected from the group consisting of trifluoroacetic acid (TFA), HCl, CH_3SO_3H, and $(H_3C)_3SiCl$ (TMSCl), wherein preferably, after the reaction of the compound of formula (3) or a solvate or salt thereof with one or more reagents to remove the amino protecting group(s), step b) further comprises adding a base.

9. The process of any one of claims 1 to 8, wherein the one or more reagents for introducing a tetrahydropyranyl group in step c) are tetrahydropyranone and a reducing agent, such as tetrahydropyranone and a borohydride.

10. The process of any one of claims 1 to 9, wherein in step c) the reaction of the compound of formula (4) or a solvate or salt thereof with one or more reagents for introducing a tetrahydropyranyl group is performed (i) in a solvent, such as a halogenated organic solvent; (ii) in the presence of an acid; (iii) at a suitable temperature, such as between -20°C and 40°C; and/or (iv) for a sufficient amount of time, such as 5 h to 24 h.

11. The process of any one of claims 1 to 10, wherein the one or more reagents for introducing an acetyl group in step c) are selected from acetic anhydride and acetic halides.

12. The process of any one of claims 1 to 11, wherein in step c) the reaction of the compound of formula (4) or a solvate or salt thereof with one or more reagents for introducing an acetyl group is performed (i) in a solvent, such as a halogenated organic solvent; (ii) at a suitable temperature, such as between 0°C and 50°C; and/or (iii) for a sufficient amount of time, such as 6 h to 48 h.

13. The process of any one of claims 1 to 12, wherein step d) comprises reacting the compound of formula (5) or a solvate or salt thereof with first (i) an oxidation agent, and then with (ii) an acylating agent and an aminating agent.

14. The process of claim 13, wherein the oxidation agent is selected from oxidation agents capable of forming N-oxides, such as 3-chloroperoxybenzoic acid, and the oxidation reaction is preferably performed (i) in a solvent, such as a halogenated organic solvent; (ii) at a suitable temperature, such as between -10°C and 40°C; and/or (iii) for a sufficient amount of time, such as 30 min to 12 h.

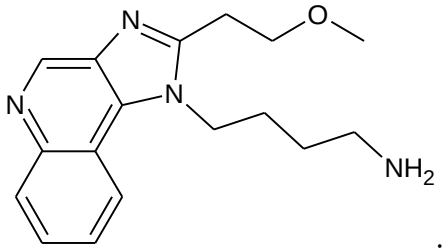
15. The process of claim 13 or 14, wherein the acylating agent is selected from the group consisting of alkysulfonyl halides and arylsulfonyl halides, such as methanesulfonyl chloride, benzenesulfonyl chloride, or p-toluenesulfonyl chloride, and the reaction with the acylating agent is preferably performed (i) in a solvent, such as a halogenated organic solvent; (ii) at a suitable temperature, such as between -10°C and 40°C; and/or (iii) for a sufficient amount of time, such as 30 min to 12 h.

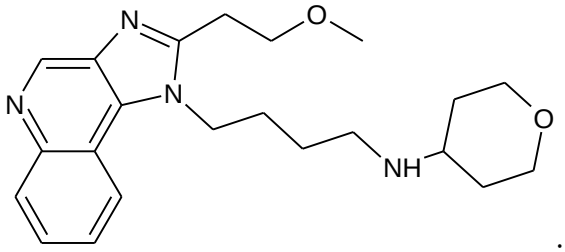
16. The process of any one of claims 13 to 15, wherein the aminating agent is selected from the group consisting of ammonia and its salts, such as aqueous NH_3, ammonium hydroxide, ammonium carbonate, ammonium bicarbonate, or ammonium phosphate, and the reaction with the aminating agent is preferably performed (i) in a solvent, such as a halogenated organic solvent; (ii) at a suitable temperature, such as between -10°C and 40°C; and/or (iii) for a sufficient amount of time, such as 30 min to 12 h.

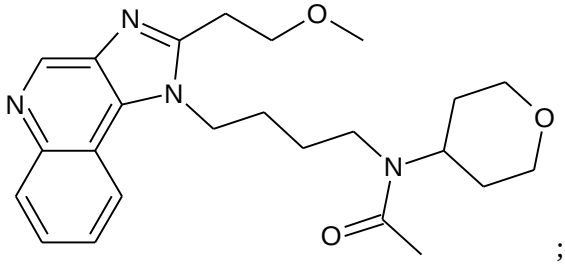
17. The process of any one of claims 1 to 16, wherein after step d) the process further comprises crystallizing the compound of formula (I) or a solvate or salt thereof, preferably from an alcoholic solvent.

18. The process of any one of claims 1 to 17, wherein one or more of steps a) to d) are performed in a chromatography-free manner.

19. A compound selected from the group consisting of:



;


;


;

and a solvate or salt thereof.

20. Use of a compound of claim 19 for synthesizing a compound of formula (I).