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(54) Title: PROCESSES FOR THE PREPARATION OF 1,2,3,5,6,7-HEXAHYDRO-S-INDACENE DERIVATIVES

(57) Abstract: The present invention relates to intermediates and processes useful for preparing 1-ethyl-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)piperidine-4-sulfonamide and salts thereof. The present invention further relates to 1-ethyl-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)piperidine-4-sulfonamide and salts thereof when prepared by such processes and to associated pharmaceutical compositions and uses for the treatment and prevention of medical disorders and diseases, most especially by NLRP$_3$ inhibition.

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PROCESSES FOR THE PREPARATION OF 1,2,3,5,6,7-HEXAHYDRO-S-INDACENE DERIVATIVES

Field of the Invention

The present invention relates to intermediates and processes useful for preparing 1-ethyl-*N*-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)piperidine-4-sulfonamide and salts thereof. The present invention further relates to 1-ethyl-*N*-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)piperidine-4-sulfonamide and salts thereof when prepared by such processes and to associated pharmaceutical compositions and uses for the treatment and prevention of medical disorders and diseases, most especially by NLRP3 inhibition.

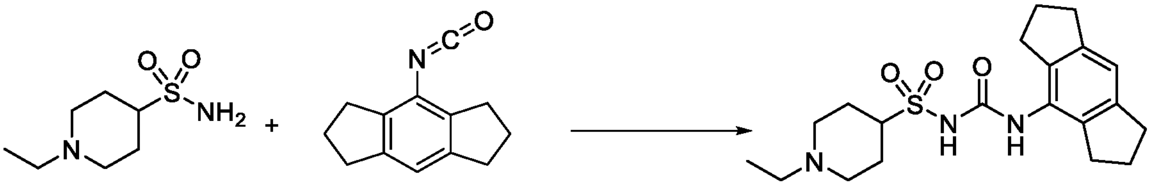
Background

1-Ethyl-*N*-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)piperidine-4-sulfonamide is disclosed in WO 2019/008025 A1 as an NLRP3 inhibitor (see Example 6). However, there is a need to provide improved processes for preparing 1-ethyl-*N*-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)piperidine-4-sulfonamide and salts thereof. In particular, there is a need to provide efficient processes that are suitable for large scale synthesis and which, for example, avoid multiple, complex and partially low yielding chemical steps and overall atom inefficient synthesis.

There is also a need to provide 1-ethyl-*N*-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)piperidine-4-sulfonamide and salts thereof at a higher yield compared to prior art processes, especially on a large scale. Further, for large-scale industrialization, greener synthesis routes, reduced solvent waste, and improved safety are also of concern. The present invention solves the aforementioned problems. Furthermore, the present invention can be implemented in both batch or continuous methods.

Summary of the Invention

The invention provides a process of preparing compound (C) or a salt thereof, comprising the step of contacting compound (A) with compound (B) in the presence of a solvent and a base, to obtain compound (C) or a salt thereof.



(A) (B) (C)
(7) (13) (14)

Unless stated otherwise, any reference to an element is to be considered a reference to all isotopes of that element. Thus, for example, unless stated otherwise any reference to hydrogen is considered to encompass all isotopes of hydrogen including deuterium and tritium.

Unless stated otherwise, any reference to a compound or group is to be considered a reference to all tautomers of that compound or group.

In an embodiment of the present invention, the solvent for contacting compound (A) with compound (B) is selected from toluene, anisole, cyclopentylmethylether, ethylbenzene, isopropyl acetate, isobutyl acetate, 2-methyl tetrahydrofuran, water, *t*-butanol, ethyl acetate, methyl acetate, xylene, tetrahydrofuran dimethyl sulfoxide, acetonitrile, *t*-butyl methyl ether, *N*-methyl pyrrolidine, *N*-ethyl pyrrolidone, heptane, cyclohexane, acetone, or any combination thereof.

In a further embodiment of the present invention, the solvent for contacting compound (A) with a compound (B) is selected from toluene, anisole, ethylbenzene and xylene.

In a further embodiment of the present invention, the solvent for contacting compound (A) with a compound (B) is selected from 2-methyl thetrahydrofuran and tehrahydrofuran.

In a further embodiment of the present invention, the solvent for contacting compound (A) with a compound (B) is dimethyl sulfoxide.

In a further embodiment of the present invention, the solvent for contacting compound (A) with compound (B) is toluene or toluene in combination with water, t-butanol, tetrahydrofuran, dimethyl sulfoxide or acetonitrile.

In a further embodiment of the present invention, the solvent for contacting compound (A) with compound (B) is toluene and tetrahydrofuran.

In a further embodiment of the present invention, the base for contacting compound (A) with compound (B) is selected from potassium tert-butoxide, potassium hydroxide or any other basic potassium salt.

In a further embodiment of the present invention, the base for contacting compound (A) with compound (B) is selected from potassium *tert*-butoxide or potassium hydroxide.

In a further embodiment of the present invention, the base for contacting compound (A) with compound (B) is potassium tert-butoxide.

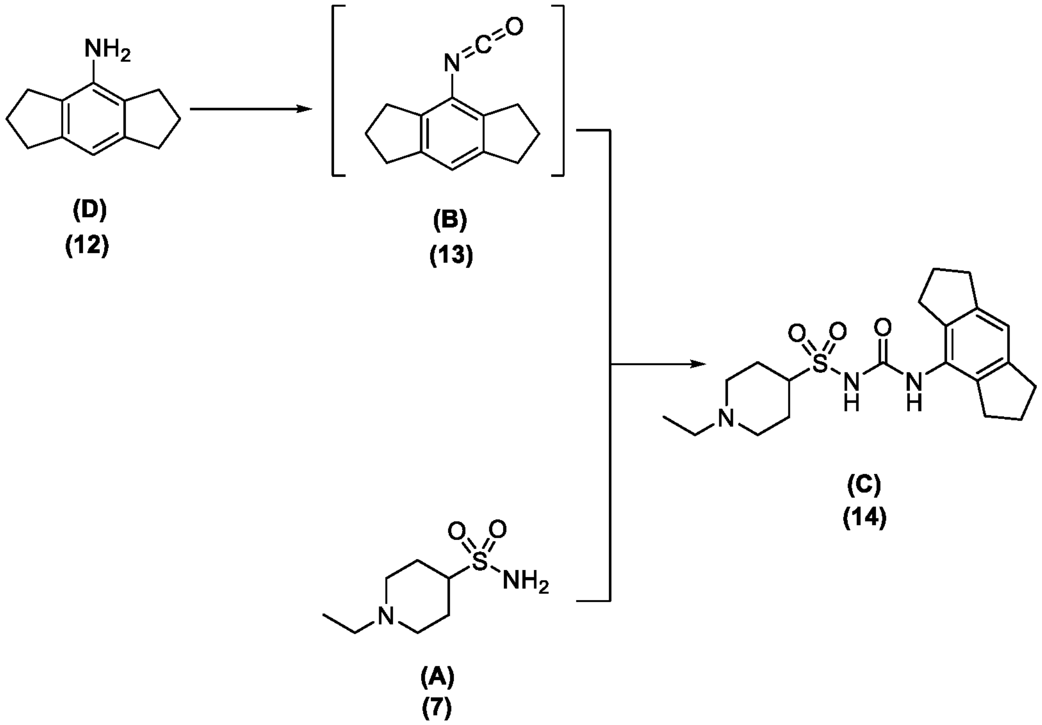
An embodiment of the present invention provides a process of preparing a salt of compound (C), such as a cationic salt. Typically the salt is pharmaceutically acceptable.

For the purposes of this invention, a “cationic salt” of 1-ethyl-*N*-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)piperidine-4-sulfonamide is a salt formed between a protic acid functionality (such as a urea proton) of the compound by the loss of a proton and a suitable cation. Suitable cations include, but are not limited to lithium, sodium, potassium, magnesium, calcium and ammonium. The salt may be a mono-, or di- salt. Preferably the salt is a mono- or di-lithium, sodium, potassium, magnesium, calcium or ammonium salt. More preferably the salt is a mono- or di-sodium salt or a mono- or di-potassium salt. More preferably the salt is a mono- or di-potassium salt, more preferably still the salt is a mono-potassium salt.

Advantageously, where a cationic salt of 1-ethyl-*N*-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)piperidine-4-sulfonamide (Compound (C)) is desired, the cation of the salt is provided by the conjugate acid of the base. For example, one embodiment of the first aspect of the invention provides a process of preparing an alkali metal or an alkali earth metal salt of 1-ethyl-*N*-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)piperidine-4-sulfonamide (C), comprising the step of contacting 1-ethyl-4-piperidinesulfonamide (A) with a 1,2,3,5,6,7-hexahydro-*s*-indacene derivative (B) or (B') in the presence of a solvent and an alkali metal or an alkali earth metal alkoxide, to obtain the alkali metal or alkali earth metal salt of 1-ethyl-*N*-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)-carbamoyl)-piperidine-4-sulfonamide, wherein the alkali metal or alkali earth metal of the salt is the same as the alkali metal or alkali earth metal of the alkoxide. Typically in such an embodiment, the alkali metal or alkali earth metal alkoxide is an alkali metal or an alkali earth metal tertiary butoxide.

In an embodiment of the present invention, the salt of 1-ethyl-*N*-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)piperidine-4-sulfonamide (C) is purified by recrystallisation or reprecipitation. For example, the crude salt of 1-ethyl-*N*-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)piperidine-4-sulfonamide (C) may be dissolved in a first solvent to obtain a first mixture, optionally the mixture may be filtered, and the salt of the 1-ethyl-*N*-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)-carbamoyl)piperidine-4-sulfonamide (C) may be precipitated by the addition of a second solvent, optionally with cooling. Typically, the first solvent is a polar protic solvent such as methanol. Typically, the second solvent is a polar aprotic solvent such as acetonitrile.

A further aspect of the invention provides a process of preparing compound (C) or a salt thereof, comprising the step of contacting compound (A) with compound (B) in the presence of a solvent and a base, to obtain compound (C) or a salt thereof, wherein compound (B) is obtained from compound (D):



In an embodiment of the present invention, compound (C) is isolated using an antisolvent.

In a further aspect of the present invention, compound (C) is isolated using an antisolvent, wherein the antisolvent is selected from acetonitrile, any alcohol or water.

In an embodiment of the present invention, compound (C) is isolated using a wash solvent.

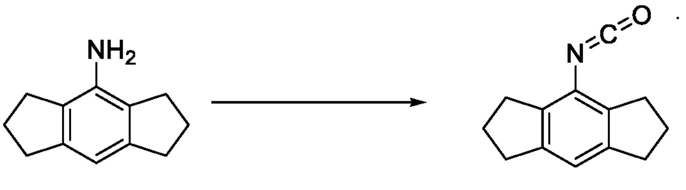
In a further aspect of the present invention, compound (C) is isolated using a wash solvent, wherein the wash solvent is selected from tetrahydrofuran, toluene, dimethylsulfoxide, or acetonitrile.

A second aspect of the invention provides 1-ethyl-*N*-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)piperidine-4-sulfonamide (Compound (C)) or a salt thereof, prepared by a process of the first aspect of this invention.

In one embodiment, the second aspect of the invention provides an alkali metal or an alkali earth metal salt of 1-ethyl-*N*-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-piperidine-4-sulfonamide. Typically, the second aspect of the invention provides a potassium salt of 1-ethyl-*N*-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-piperidine-4-sulfonamide. Most typically, the second aspect of the invention provides a mono-potassium salt of 1-ethyl-*N*-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-piperidine-4-sulfonamide.

In an embodiment of the present invention, compound (B) is prepared by a process according to the third aspect of the invention.

A third aspect of the invention provides a process of preparing a compound (B), the process comprising the step wherein compound (D) is converted into compound (B):



(D)
(12)

(B)
(13)

Accordingly, in one embodiment of the third aspect of the invention, there is provided a process of preparing compound (B), the process comprising the step of converting compound (D) into compound (B) using a reaction mixture of compound (D) with phosgene, triphosgene, carbonyldiimidazole, or di-tert-butyl dicarbonate in the presence of a base and a solvent.

In a further embodiment of the third aspect of the invention, the solvent is selected is selected from toluene, anisole, cyclopentylmethylether, ethylbenzene, isopropyl acetate, isobutyl acetate, 2-methyl tetrahydrofuran, water, ethyl acetate, methyl acetate, xylene, tetrahydrofuran or dimethyl sulfoxide, acetonitrile, *t*-butyl methyl ether, diethyl ether, dichloromethane, 1,2-dichloroethane, chloroform, *N*-methyl pyrrolidine, *N*-ethyl pyrrolidone, heptane, cyclohexane or any combination thereof, and the base is a tertiary amine, such as *N,N*-diisopropylethylamine, triethylamine, or tributylamine or the base is an inorganic base such as potassium carbonate, potassium hydroxide, or sodium carbonate.

In a further embodiment of the third aspect of the invention, the solvent is selected from toluene or toluene in combination with water, acetonitrile, or tetrahydrofuran, and the base is selected from *N,N*-diisopropylethylamine, trimethylamine, tributylamine, potassium carbonate, potassium hydroxide, or sodium carbonate.

In a further embodiment of the third aspect of the invention, the solvent is toluene and/or water, and the base is *N,N*-diisopropylethylamine, trimethylamine or potassium carbonate.

In a further embodiment of the third aspect of the invention, the solvent is toluene and the base is *N,N*-diisopropylethylamine or potassium carbonate.

In a further embodiment of the third aspect of the invention, the solvent is toluene and the base is potassium carbonate.

In a further embodiment of the third aspect of the invention, the solvent is toluene and the base is *N,N*-diisopropylethylamine.

Toluene and potassium carbonate, or toluene and N,N-diisopropylethylamine, provide an advantage over using THF (tetrahydrofuran) and TEA (triethylamine), as was used previously (EGGLER J F ET AL: Journal of Labelled Compounds and Radiopharmaceuticals, vol. 45, no. 9, 2002, pages 785-794, XP002264662), due to the proposed process above involving less time and energy for workup because of the elimination of the need to evaporate or perform a silica gel filtration. Therefore the process here is a less intensive process than that previously reported.

In another embodiment of the third aspect of the invention, there is provided a process of preparing compound (B) , the process comprising the step of converting compound (D) into compound (B), wherein the reaction mixture is washed using an aqueous solution to obtain compound (B) in an organic solvent.

An embodiment of the present invention provides a process to obtain compound (C) wherein compound (B) is obtained according to the third aspect of the invention.

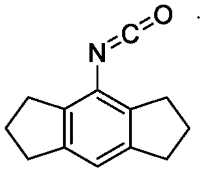
An embodiment of the present invention provides a process to obtain compound (C) according to the first aspect of the invention, wherein compound (B) is obtained according to the third aspect of the invention.

In an embodiment of the present invention, compound (B) is prepared by a batch process or in a continuous mode.

In an embodiment of the present invention, compound (B) is prepared in a continuous mode.

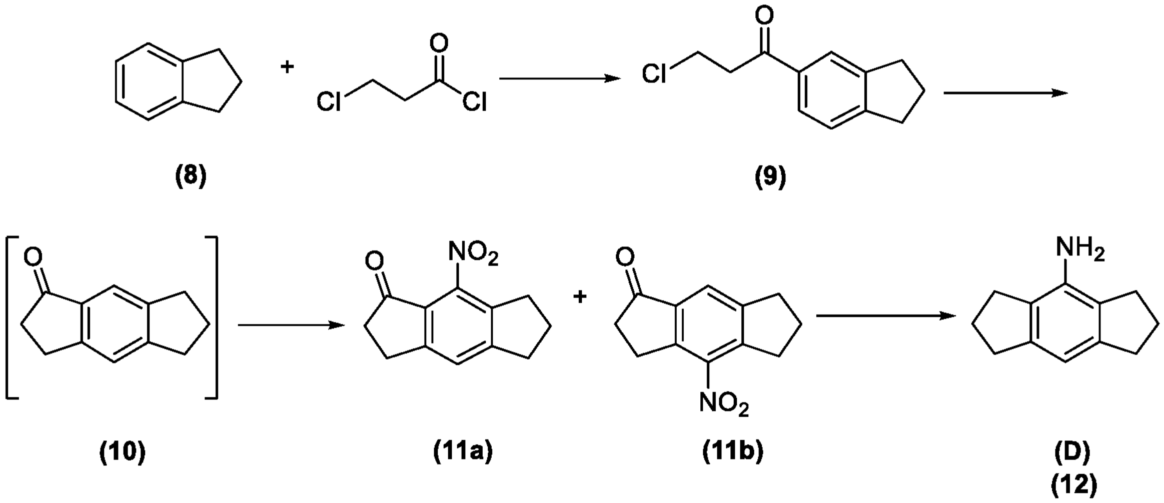
In an embodiment of the present invention, the process to obtain compound (B) and compound (C) are telescoped.

A fourth aspect of the invention provides compound (B):



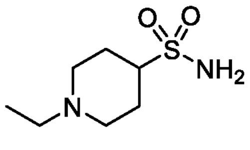
(B)
(13)

In one embodiment of the third aspect of the invention, compound (D) is prepared by a process comprising the following steps:



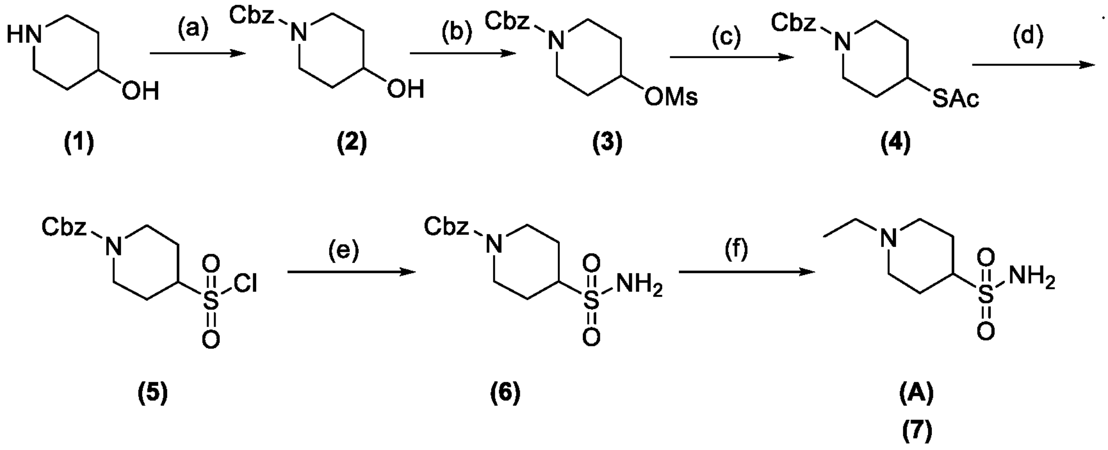
The process for the preparation of compound (D) may be as described in WO 2020/079207 A1, the contents of which are incorporated herein by reference in their entirety.

In one embodiment, the process of the fifth aspect of the invention is a process for preparing compound (A) or a salt thereof:



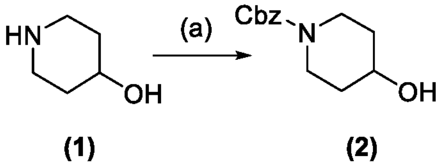
(A)
(7)

A fifth aspect of the invention provides a process for the preparation of compound (A), prepared by a process comprising the following steps:



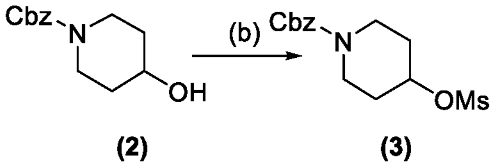
wherein Cbz is carboxybenzyl/benzyloxycarbonyl, OMs is methanesulfonate, and SAc is acetylthio.

In an exemplary embodiment of the fifth aspect of the invention, the reaction step (a) comprises contacting compound (1) with benzyl chloroformate to obtain N-carboxybenzyl-4-hydroxy piperidine compound (2):



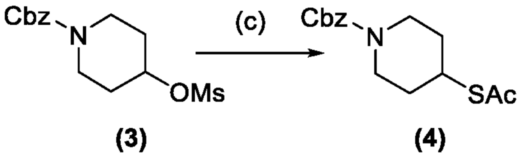
Typically in such an embodiment, compound (1) is contacted with the benzyl chloroformate in the presence of a base and a solvent.

In an exemplary embodiment of the fifth aspect of the invention, the reaction step (b) comprises contacting compound (2) with mesyl chloride to obtain compound (3):



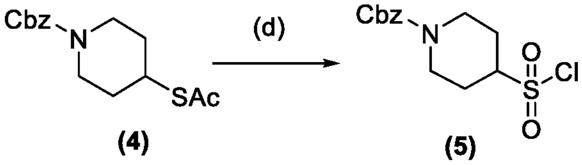
Typically in such an embodiment, the compound (2) is contacted with mesyl chloride in the presence of a tertiary amine base such as triethylamine and a polar aprotic solvent such as dichloromethane.

In an exemplary embodiment of the fifth aspect of the invention, the reaction step (c) comprises contacting compound (3) with $MeCOS^-$ in a solvent to obtain compound (4):



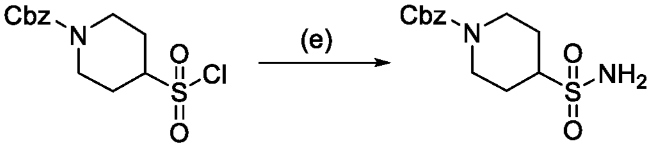
Typically in such an embodiment, the $MeCOS^-$ is generated in situ by the reaction of MeCOSH with a base such as cesium carbonate. Typically in such an embodiment, the solvent is *N,N*-dimethylformamide.

In an exemplary embodiment of the fifth aspect of the invention, the reaction step (d) comprises contacting compound (4) with a chlorinating agent to obtain compound (5):



Typically in such an embodiment, the chlorinating agent is N-chlorosuccinimide. Typically in such an embodiment, the compound (4) is contacted with the chlorinating agent in the presence of acetic acid and water.

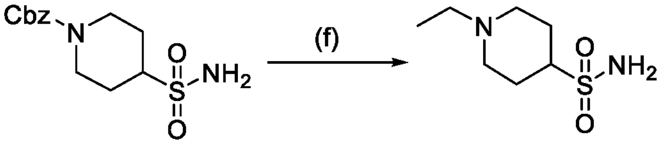
In an exemplary embodiment of the fifth aspect of the invention, the reaction step (e) comprises contacting compound (5) with ammonia to obtain compound (6):



(5) **(6)**

Typically in such an embodiment, the compound (5) is contacted with ammonia in the presence of a polar aprotic solvent such as dichloromethane.

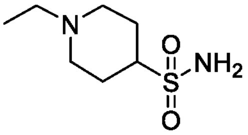
In an exemplary embodiment of the fifth aspect of the invention, the reaction step (f) comprises contacting compound (6) with acetonitrile or acetaldehyde in the presence of a catalyst and hydrogen gas, to obtain compound (A):



(6) **(A)**
(7)

Typically in such an embodiment, the compound (6) is contacted with acetonitrile in the presence of a catalyst and hydrogen gas. Typically, the catalyst is a palladium catalyst such as palladium hydroxide on carbon.

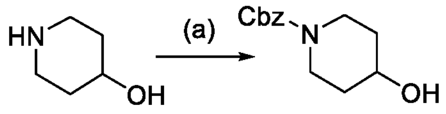
In one specific embodiment of the fifth aspect of the present invention, there is provided a process of preparing compound (A) or a salt thereof:



(A)
(7)

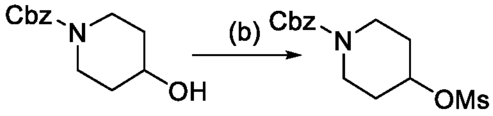
comprising the steps:

(a) converting compound (1) to compound (2):



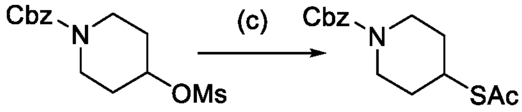
(1) **(2)**

(b) converting compound (2) to compound (3):



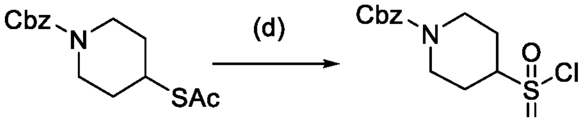
(2) **(3)**

(c) converting compound (3) to compound (4):



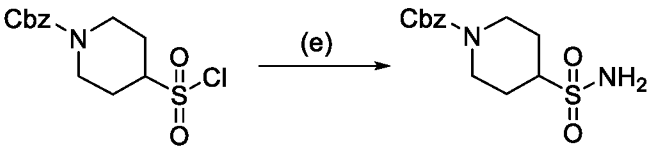
(3) **(4)**

(d) converting compound (4) to compound (5):



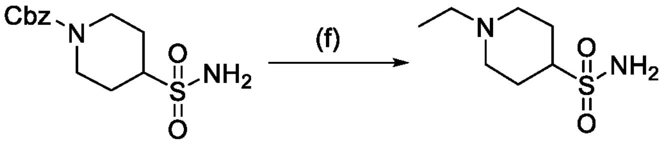
(4) **(5)**

(e) converting compound (5) to compound (6)



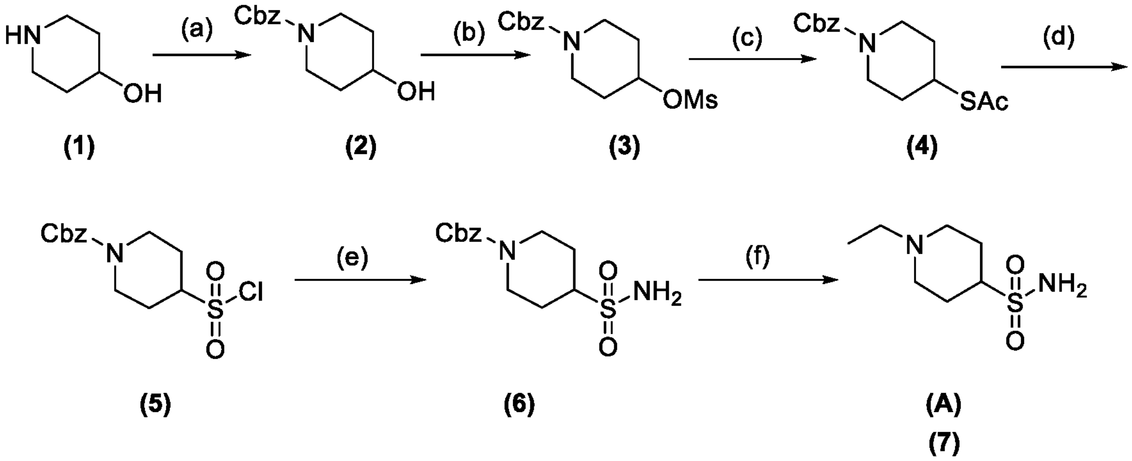
(5) **(6)**

(f) and converting compound (6) to compound (A):



(6) **(A)** **(7)**

In one specific embodiment of the fifth aspect of the present invention, there is provided a process of preparing compound (A) or a salt thereof via the following steps:



wherein Cbz is carboxybenzyl/benzyloxycarbonyl, OMs is methanesulfonate, and SAc is acetylthio.

An embodiment of the present invention provides a process to obtain compound (C) wherein compound (A) is obtained according to the fifth aspect of the invention.

The compounds used in and provided by the present invention can be used both, in their free base form and their acid addition salt form. For the purposes of this invention, a “salt” of a compound of the invention includes an acid addition salt. Acid addition salts are preferably pharmaceutically acceptable, non-toxic addition salts with suitable acids, including but not limited to inorganic acids such as hydrohalogenic acids (for example, hydrofluoric, hydrochloric, hydrobromic or hydroiodic acid) or other inorganic acids (for example, nitric, perchloric, sulfuric or phosphoric acid); or organic acids such as organic carboxylic acids (for example, propionic, butyric, glycolic, lactic, mandelic, citric, acetic, benzoic, salicylic, succinic, malic or hydroxysuccinic, tartaric, fumaric, maleic, hydroxymaleic, mucic or galactaric, gluconic, pantothenic or pamoic acid), organic sulfonic acids (for example, methanesulfonic, trifluoromethanesulfonic, ethanesulfonic, 2-hydroxyethanesulfonic, benzenesulfonic, toluene-p-sulfonic, naphthalene-2-sulfonic or camphorsulfonic acid) or amino acids (for example, ornithinic, glutamic or aspartic acid). The acid addition salt may be a mono-, di-, tri- or multi-acid addition salt. A preferred salt is a hydrohalogenic, sulfuric, phosphoric or organic acid addition salt. A preferred salt is a hydrochloric acid addition salt.

Where a compound of the invention includes a quaternary ammonium group, typically the compound is used in its salt form. The counter ion to the quaternary ammonium group may be any pharmaceutically acceptable, non-toxic counter ion. Examples of suitable counter ions include the conjugate bases of the protic acids discussed above in relation to acid addition salts.

The compounds used in and provided by the present invention can also be used both, in their free acid form and their salt form. For the purposes of this invention, a “salt” of a compound of the present invention includes one formed between a protic acid functionality (such as a carboxylic acid group or a urea group) of a compound of the present invention and a suitable cation. Suitable cations include, but are not limited to lithium, sodium, potassium, magnesium, calcium and ammonium. The salt may be a mono-, di-, tri- or multi-salt. Preferably the salt is a mono- or di-lithium, sodium, potassium, magnesium, calcium or ammonium salt. More preferably the salt is a mono- or di-sodium salt or a mono- or di-potassium salt.

Preferably, any salt is a pharmaceutically acceptable non-toxic salt. However, in addition to pharmaceutically acceptable salts, other salts are included in the present invention, since they have potential to serve as intermediates in the purification or preparation of other, for example, pharmaceutically acceptable salts, or are useful for identification, characterisation or purification of the free acid or base.

The compounds and/or salts used in and provided by the present invention may be anhydrous or in the form of a hydrate (e.g. a hemihydrate, monohydrate, dihydrate or trihydrate) or other solvate. Such other solvates may be formed with common organic solvents, including but not limited to, alcoholic solvents e.g. methanol, ethanol or isopropanol.

The compounds, salts and solvates used in and provided by the present invention may contain any stable isotope including, but not limited to ^{12}C, ^{13}C, ^{1}H, ^{2}H (D), ^{14}N, ^{15}N, ^{16}O, ^{17}O, ^{18}O, ^{19}F and ^{127}I, and any radioisotope including, but not limited to ^{11}C, ^{14}C, ^{3}H (T), ^{13}N, ^{15}O, ^{18}F, ^{123}I, ^{124}I, ^{125}I and ^{131}I.

Unless stated otherwise, the compounds, salts and solvates used in and provided by the present invention may be in any polymorphic or amorphous form.

A sixth aspect of the present invention provides a pharmaceutical composition comprising the compound (C) or the salt thereof of the second aspect of the invention, and a pharmaceutically acceptable excipient.

Conventional procedures for the selection and preparation of suitable pharmaceutical formulations are described in, for example, “Aulton’s Pharmaceutics - The Design and Manufacture of Medicines”, M. E. Aulton and K. M. G. Taylor, Churchill Livingstone Elsevier, 4th Ed., 2013. Pharmaceutically acceptable excipients including adjuvants, diluents or carriers that may be used in the pharmaceutical compositions of the invention, are those conventionally employed in the field of pharmaceutical formulation.

A seventh aspect of the present invention provides compound (C) or the salt thereof of the second aspect of the invention, or the pharmaceutical composition of the sixth aspect of the invention, for use in medicine, and/or for use in the treatment or prevention of a disease, disorder or condition.

Most especially, where compound (C) is used in the treatment or prevention of a disease, disorder and condition, the compound (C) acts as an NLRP3 inhibitor.

In one embodiment, the disease, disorder or condition to be treated or prevented is selected from:

(i) inflammation;
(ii) an auto-immune disease;
(iii) cancer;
(iv) an infection;
(v) a central nervous system disease;
(vi) a metabolic disease;
(vii) a cardiovascular disease;
(viii) a respiratory disease;
(ix) a liver disease;
(x) a renal disease;
(xi) an ocular disease;
(xii) a skin disease;
(xiii) a lymphatic condition;
(xiv) a psychological disorder;
(xv) pain; and
(xvi) any disease where an individual has been determined to carry a germline or somatic non-silent mutation in NLRP3.

Typically, the treatment or prevention of the disease, disorder or condition comprises the administration of the compound (C) or the salt thereof of the second aspect of the invention, or the pharmaceutical composition of the sixth aspect of the invention, to a subject.

Any of the medicaments employed in the present invention can be administered by oral, parenteral (including intravenous, subcutaneous, intramuscular, intradermal, intratracheal, intraperitoneal, intraarticular, intracranial and epidural), airway (aerosol), rectal, vaginal or topical (including transdermal, buccal, mucosal and sublingual) administration.

Typically, the mode of administration selected is that most appropriate to the disorder, disease or condition to be treated or prevented.

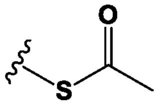
An eighth aspect of the invention provides a method of inhibiting NLRP3, the method comprising the use of the compound (C) or the salt thereof of the second aspect of the invention, or the pharmaceutical composition of the sixth aspect of the invention, to inhibit NLRP3.

For the avoidance of doubt, insofar as is practicable any embodiment of a given aspect of the present invention may occur in combination with any other embodiment of the same aspect of the present invention. In addition, insofar as is practicable it is to be understood that any preferred, typical or optional embodiment of any aspect of the present invention should also be considered as a preferred, typical or optional embodiment of any other aspect of the present invention.

Examples

All solvents, reagents and compounds were purchased and used without further purification unless stated otherwise.

Abbreviations

Cbz:	carboxybenzyl/benzyloxycarbonyl
SAc:	acetylthio 
GC:	gas chromatography
HPLC:	high performance liquid chromatography
THF:	tetrahydrofuran

MTBE:	methyl tertiary butyl ether
DCM:	dichloromethane
DMF:	dimethylformamide
TEA:	triethylamine
HDPE:	high density polyethylene
NMT:	No more than
Vol:	volumes
AKX reagent:	AQUAMICRON® AKX

% a/a: (area under peak of compound (a) / combined area under peaks of compound (a) and all other components) x 100

Experimental Methods

NMR Methods:
NMR spectra were obtained on Bruker AV 400MHz spectrometer (model: Advance IIID) operated at room temperature (25°C).

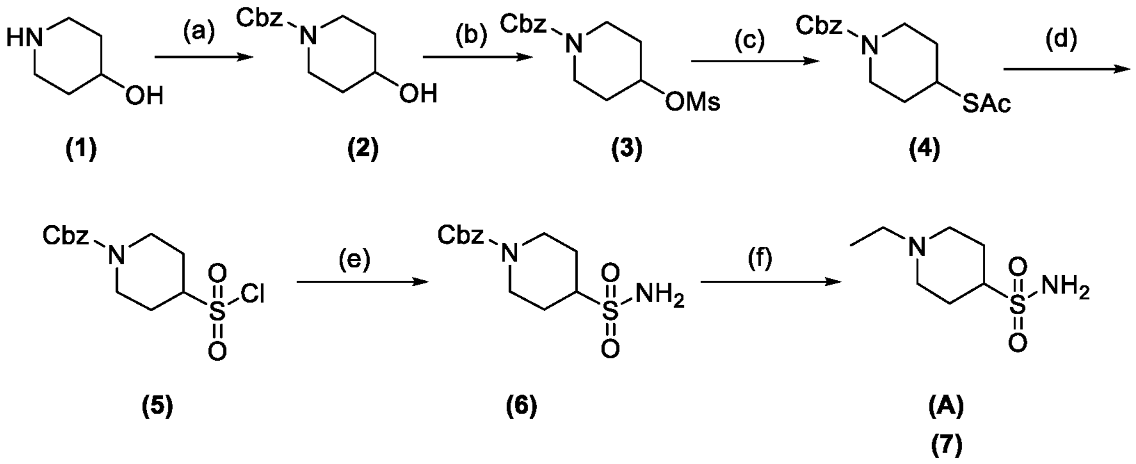
GC Methods:
GC analysis was conducted on one of the following machines: Agilent 7890, 6890, or Agilent 6890N with ALS injector.

KF Methods:
Coulometric KF (Karl Fischer) titration was run using AKX reagent on Mitsubishi CA-20 or Predicta OM1000.

Synthesis Examples

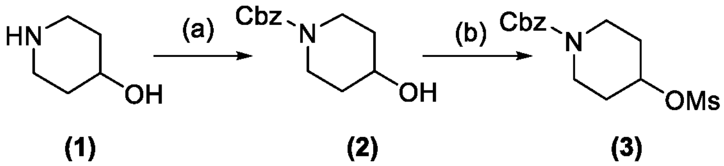
1-ethyl-4-piperidinesulfonamide (7)

1-ethyl-4-piperidinesulfonamide (7) was prepared according to the reaction sequence illustrated in reaction scheme 1.



Scheme 1. 1-ethyl-4-piperidinesulfonamide (7) synthesis

Reaction scheme 1 – step (a) and (b)



4-hydroxy piperidine (1) (46.0 Kg) was charged into the reactor at 25 to 30°C. 1,4-dioxane (226.0 L) was charged to the reactor at 25 to 30°C. The reaction mixture was stirred for 5-10 minutes and then cooled to 15 to 20°C. A 2N NaOH solution (prepared by mixing NaOH (18.4 Kg) with cold purified water (230.0 L) at 25 to 30°C in a separate reactor) was slowly charged to the reaction mixture at 15 to 25°C. The reaction mixture was stirred for 5-10 minutes. 50% benzyl chloroformate in toluene (147.2 L) was slowly added over a period of 1-2 hours to the reaction mixture. The temperature was raised to 25 to 30°C and stirred for 1-2 hours.

Purified water (230.0 L) was added to the reaction mixture and the reaction mixture was stirred for 10-15 min at 25 to 30°C. MTBE (230.0 L) was charged into the reactor at 30 to 35°C. The reaction mixture was stirred for 15-20 minutes at 25 to 30°C and then allowed to settle for 20-30 minutes. The organic layer (OL-1) and aqueous layer (AL-1) were separated into different containers and AL-1 was charged back into the reactor. MTBE (230.0 L) was charged into the reactor at 25 to 30°C. The reaction mixture was stirred for 15-20 minutes at 25 to 30°C and then allowed to settle for 20-30 minutes. The organic layer (OL-2) and aqueous layer (AL-2) were separated into different containers. OL-1 and OL-2 were combined and charged into the reactor at 25 to 30°C. Purified water (138.0 L) was charged to the reactor at 25 to 30°C. The reaction mixture was stirred for 15-20 minutes at 25 to 30°C and then allowed to settle for 20-30 minutes. The aqueous layer (AL-3) was separated from the organic layer (OL-3).

10% NaCl solution (prepared by adding NaCl (13.80 Kg) to purified water (138.0 L) in a reactor at 25 to 30°C with stirring) was charged to OL-3 at 25 to 30°C. The reaction mixture was stirred for 15-20 minutes at 25 to 30°C and then allowed to settle for 20-30 minutes. The organic layer (OL-4) and aqueous layer (AL-4) were separated into different containers. OL-4 was dried with sodium sulfate (23.0 Kg). OL-4 was filtered through a Buchner funnel and washed with MTBE (46.0 L). OL-4 was distilled down to 46-92 L at 40 to 45°C under vacuum (650mmHg). The vacuum was released and DCM (138.0 L) was charged to the mixture and the mixture was co-distilled 35 to 40°C under vacuum to 46-92 L. The mixture was cooled to 25 to 30°C and the vacuum was released. DCM (552.0 L) was charged to the mixture at 25 to 30°C and the mixture was stirred for 5-10 minutes. The reaction mixture was cooled to 20 to 25°C. TEA (127.8 L) was added at 20 to 25°C. The reaction mixture was cooled to -5 to 5°C.

Methane sulfonyl chloride (67.62 Kg) was slowly charged at -5 to 5°C over a period of 1-2 hours. The reaction mixture was raised to 25 to 30°C and stirred for 1-2 hours at 25 to 30°C.

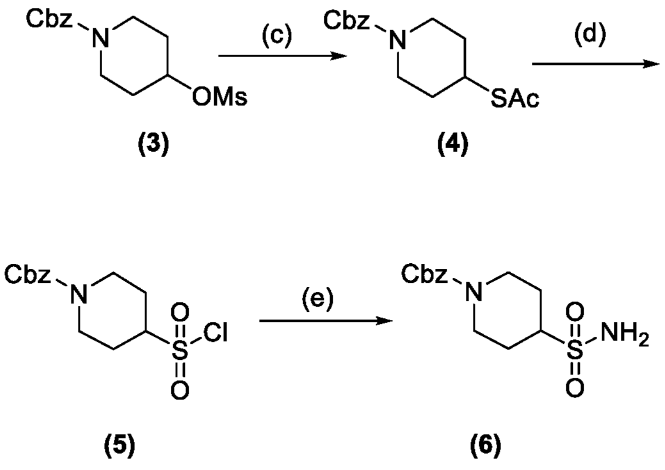
The unwanted salts were filtered, washed with DCM (92.0 L) at 25 to 30°C and sucked dry completely under vacuum at 25 to 30°C. The filtrate was charged into a reactor at 25 to 30°C. 10% sodium bicarbonate solution (prepared by adding sodium bicarbonate (23.0 Kg) to purified water (230.0 L) at 25 to 30°C) was charged to the filtrate at 25 to 30°C. The reaction mixture was stirred for 15-20 minutes at 25 to 30°C and then allowed to settle for 20-30 minutes. The organic layer (OL-5) and aqueous layer (AL-5) were separated into different containers and OL-5 was charged back into the reactor at 25 to 30°C.

Purified water (230.0 L) was charged into the reactor at 25 to 30°C. The reaction mixture was stirred for 15-20 minutes at 25 to 30°C and then allowed to settle for 20-30 minutes. The organic layer (OL-6) and aqueous layer (AL-6) were separated into different containers and OL-6 was charged back into the reactor at 25 to 30°C. 10% sodium chloride solution (prepared by adding sodium chloride (11.50 Kg) to the purified water (230.0 L) at 25 to 30°C) was charged to the reactor at 25 to 30°C. The reaction mixture was stirred for 15-20 minutes at 25 to 30°C and then allowed to settle for 20-30 minutes.

The organic layer (OL-7) and aqueous layer (AL-7) were separated into different containers. OL-7 was dried with sodium sulfate (23.0 Kg). OL-7 was filtered through a Buchner funnel and washed with DCM (46.0 L). OL-7 was distilled down to 46-92 L at 40 to 45°C under vacuum (650mmHg). The vacuum was released and ethyl acetate (92.0 L) was charged to the mixture and the mixture was co-distilled 40 to 45°C under vacuum to 46-92 L. The mixture was cooled to 30 to 40°C and the vacuum was released. Ethyl acetate (115.0 L) was charged to the mixture at 30 to 40°C and the mixture was stirred for 10-15 minutes at 30 to 35°C. Hexane (1150.0 L) was slowly charged to the mixture at 30 to 35°C and the mixture was stirred for 2-3 hours at 25 to 30°C. The solid was filtered on a nutsche filter under vacuum, washed with hexane (92.0 L) at 25 to 30°C and sucked dry completely under vacuum at 25 to 30°C. The solid material was dried in a vacuum oven at 30 to 35°C for 6-8 hours, delumping the material every 3-4 hours.

Final product: benzyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate
Off white colour (solid)
Output: 121.87 Kg
Yield: 85.5 %
HPLC purity: 94.7 %
^{1}H NMR: ($CDCl_3$ 400MHz): δ 1.82-1.86(m, 2H), δ 1.96-1.97(m, 2H), δ 3.03(s, 3H), δ 3.41-3.45(m, 2H) δ 3.72-3.78(m, 2H), δ 4.88-4.92(m, 1H) δ 5.13(s, 2H), δ 7.26-7.37(m, 5H)

Reaction scheme 1 – step (c, d, e)



DMF was charged in to a clean and dry four neck reactor (equipped with a mechanical stirrer, nitrogen inlet, thermo pocket and reflux condenser) under nitrogen atmosphere and heated to reflux at 60 to 65°C for 20-30 min. The temperature was reduced to 25 to 30°C, the refluxed DMF was unloaded and the reactor was dried under nitrogen and vacuum.

Benzyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (3) (29.0 Kg) was charged to the reactor at 25 to 30°C. DMF (145.0 L) was charged to the reactor at 25 to 30°C. The reaction mixture was stirred for 5-10 minutes, cooled to 15 to 20°C and then allowed to settle for 20-30 minutes.

Cesium carbonate 44.95 Kg was charged to the reactor at 15 to 25°C. The reaction mixture was stirred for 5-10 minutes. Thioacetic acid 10.56 Kg was charged at 15 to 25°C. The reaction mixture was raised to 45 to 50°C and stirred for 24 hours.

The reaction mixture was cooled to 25 to 30°C. The unwanted salts were filtered through a Buchner funnel under vacuum at 25 to 30°C, washed with ethyl acetate (145.0 L) and sucked dry completely under vacuum at 25 to 30°C. The filtrate was charged back to the reactor at 25 to 30°C and cooled to 15 to 20°C. Purified water (145.0 L) was charged to the reactor at 15-25°C and the reaction mixture was stirred for 5-10 minutes. Ethyl acetate (145.0 L) was charged to the reactor at 25 to 30°C. The reaction mixture was stirred for 15-20 minutes at 25 to 30°C and allowed to settle for 20-30 minutes.

The organic layer (OL-1) and aqueous layer (AL-1) were separated into different containers. AL-1 was charged into the reactor at 25 to 30°C. Ethyl acetate (145.0 L) was charged at 25 to 30°C. The reaction mixture was stirred for 15-20 minutes at 25 to 30°C and allowed to settle for 20-30 minutes.

The organic layer (OL-2) and aqueous layer (AL-2) were separated into different containers. OL-1 and OL-2 were combined and charged into the reactor at 25 to 30°C.

A 10% $NaHCO_3$ solution (prepared by adding sodium bicarbonate (14.50 Kg) to purified water (145.0 L) at 25 to 30°C and stirring well to mix) was charged to the reactor at 25 to 30°C. The reaction mixture was stirred for 15-20 minutes at 25 to 30°C and allowed to settle for 20-30 minutes.

The organic layer (OL-3) and aqueous layer (AL-3) were separated into different containers. OL-3 was charged into the reactor at 25 to 30°C. 10% NaCl solution (prepared by adding NaCl (14.50 Kg) to purified water (145 L) at 25 to 30°C and stirring well to mix) was charged to the reactor at 25 to 30°C. The reaction mixture was stirred for 15-20 minutes at 25 to 30°C and allowed to settle for 20-30 minutes.

The organic layer (OL-4) and aqueous layer (AL-4) were separated into different containers. OL-4 was dried with sodium sulfate (14.50 Kg), filtered through a Buchner funnel and washed with ethyl acetate (29.0 L). The filtrate was distilled completely in the reactor until no drops at 45 to 50°C under vacuum (650mmHg). The vacuum was released and the mixture was cooled to 25 to 30°C.

Acetic acid (377.0 L) was charged at 25 to 30°C to the reactor. The reaction mixture was stirred for 5-10 minutes at 25 to 30°C. Purified water (37.7 L) was charged at 25 to 30°C. The reaction mixture was stirred for 5-10 minutes at 25 to 30°C and then cooled to 17 to 25°C. N-chlorosuccinimide (33.64 Kg) was slowly added portion wise for 1-2 hours at 18 to 25°C. The reaction mixture was stirred for 1 hour at 25 to 30°C.

The reaction mixture was cooled to 15 to 20°C. Purified water (377.0 L) was added to the reaction mixture at 15 to 20°C and the reaction mixture was stirred for 5-10 minutes at 25 to 30°C. DCM (145.0 L) was charged to the reactor at 25 to 30°C. The reaction mixture was stirred for 10-15 minutes at 25 to 30°C and allowed to settle for 20-30 minutes. The organic layer (OL-5) and aqueous layer (AL-5) were separated into different containers. AL-5 was charged to the reactor. DCM (145.0 L) was charged to the reactor at 25 to 30°C. The reaction mixture was stirred for 10-15 minutes at 25 to 30°C and allowed to settle for 20-30 minutes.

The organic layer (OL-6) and aqueous layer (AL-6) were separated into different containers. OL-5 and OL-6 were combined and charged into the reactor at 25 to 30°C. Purified water (145.0 L) was charged to the reactor at 25 to 30°C. The reaction mixture was stirred for 5-10 minutes at 25 to 30°C and allowed to settle for 25-30 minutes.

The organic layer (OL-7) and aqueous layer (AL-7) were separated into different containers. OL-7 was charged to the reactor. Part one of a 2% sodium bicarbonate solution (prepared by adding sodium bicarbonate (8.70 Kg) with purified water (435.0 L) and dividing into three equal volume parts) was charged to the reactor at 25 to 30°C. The reaction mixture was stirred for 5-10 minutes at 25 to 30°C and allowed to settle for 25-30 minutes.

The organic layer (OL-8) and aqueous layer (AL-8) were separated into different containers. OL-8 was charged to the reactor. Part two of the above 2% sodium bicarbonate solution was charged to the reactor at 25 to 30°C. The reaction mixture was stirred for 5-10 minutes at 25 to 30°C and allowed to settle for 25-30 minutes.

The organic layer (OL-9) and aqueous layer (AL-9) were separated into different containers. OL-9 was charged to the reactor. Part three of the above 2% sodium bicarbonate solution was charged to the RBF at 25 to 30°C. The reaction mixture was stirred for 5-10 minutes at 25 to 30°C and allowed to settle for 25-30 minutes.

The organic layer (OL-10) and aqueous layer (AL-10) were separated into different containers. OL-10 was dried with sodium sulfate (14.50 Kg), filtered at 25 to 30°C, and washed with DCM (29.0 L). The filtrate was charged to RBF at 25 to 30°C.

The reaction mixture was cooled to -40 to -30°C and purged with ammonia gas for 2-3 hours. The temperature was raised to 25 to 30°C and stirred for 10-12 hours at 25 to 30°C.

The unwanted salts were filtered under vacuum at 25 to 30°C, washed with DCM (14.50 L) and sucked dry completely. The filtrate was charged into a clean and dried reactor at 25 to 30°C and dried with sodium sulfate (14.50 Kg). The mixture was filtered at 25 to 30°C and the sodium sulfate was washed with DCM (14.50 L). The mixture was charged through a 0.2 micron filter cartridge into a clean and dried reactor and distilled under vacuum at 35 to 40°C down to 29-58 L.

The vacuum was released and the reaction mixture was cooled to 25 to 30°C. Ethyl acetate (58.0 L) was charged to the reactor at 25 to 30°C and the mixture was distilled under vacuum at 35 to 40°C down to 29-58 L. The vacuum was released and the

reaction mixture was cooled to 25 to 30°C. Ethyl acetate (72.5 L) was charged to the reactor at 25 to 30°C and the mixture was stirred for 30 min at 25 to 30°C. Hexane (36.25 L) was charged to the reactor at 25 to 30°C and the mixture was stirred for 1-2 hours at 25 to 30°C. The solid was filtered under vacuum at 25 to 30°C, washed with hexane (58.0 L) and sucked dry completely.
Output: 11.0 Kg
Yield: 39.85 %
HPLC purity: 90.5 %

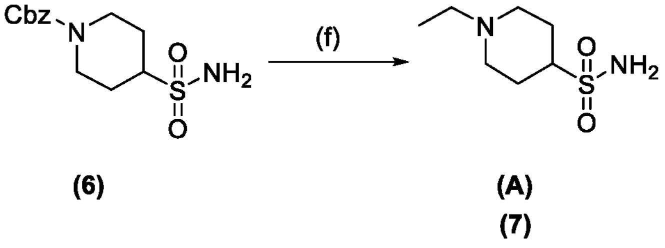
Purification

Wet material (6) (53.95 Kg) was charged into a clean and dry reactor at 25 to 30°C. DCM (580 L) was charged at 25 to 30°C and the mixture was stirred for 5-10 minutes at 25 to 30°C. Methanol (25.0 L) was charged at 25 to 30°C and the mixture was stirred for 5-10 minutes at 25 to 30°C. Neutral alumina (174.0 Kg) was charged at 25 to 30°C and the mixture was stirred for 1 hour at 25 to 30°C. The neutral alumina was filtered at 25 to 30°C. The salts were washed with DCM (150.0 L). The filtrate was charged in to a clean and dried reactor at 25 to 30°C. Hexane (1050 L) was charged at 25 to 30°C and the mixture was stirred for 1-2 hours at 25 to 30°C. The precipitate was filtered under vacuum at 25 to 30°C, washed with hexane (116.0 L) and sucked dry completely. The wet material was dried under vacuum at 30 to 35°C for 6-8 hours with delumping every 3 hours).

Final product: 1-(benzyloxycarbonyl)-4-piperidinesulfonamide

White colour (solid powder)
Output: 41.60 Kg
Yield: 41.80 %
HPLC purity: 96.1 %
^{1}H NMR: (DMSO 400MHz): δ 1.41-1.51(m, 2H), δ 1.99-2.01(m, 2H), δ 2.50-286(m, 2H), δ 3.022-3.05(m, 1H) δ 4.08-4.11(m, 2H), δ 5.75(s, 2H) δ 6.78(s, 2H), δ 7.40-7.30(m, 5H)

Reaction scheme 1 – step (f)



1-(benzyloxycarbonyl)-4-piperidinesulfonamide (6) (21.85 Kg) was charged to a vessel which was then purged with nitrogen. Acetonitrile (free of propionitrile) (109.8 Kg) and purified water (65.0 L) were charged to the vessel and the temperature was adjusted to 15 to 25°C. The vessel was vacuum / nitrogen purged three times at 15 to 25°C and then charged with palladium hydroxide on carbon (20 wt%; 50% water) (0.455 Kg). The vessel was vacuum / nitrogen purged three times at 15 to 25°C. The vessel was vacuum / hydrogen purged three times at 15 to 25°C and maintained under an atmosphere of hydrogen (ca.1 bar absolute). The reaction mixture was stirred until complete.

The vessel was vacuum / nitrogen purged three times at 15 to 25°C and then charged with palladium hydroxide on carbon (20 wt%; 50% water) (2.265 Kg) at 15 to 25°C. The vessel was vacuum / nitrogen purged three times at 15 to 25°C. The vessel was vacuum / hydrogen purged three times at 15 to 25°C and maintained under an atmosphere of hydrogen (ca.1 bar absolute).The reaction mixture was stirred at 15 to 25°C until complete.

The reaction mixture was stirred at 15 to 25°C until complete.

Once the reaction was deemed complete by GC, the vessel was purged with nitrogen and the reaction mixture was filtered through a 1 μm filter at 15 to 25°C to remove the catalyst. The filter cake was twice washed with pre-mixed purified water and acetonitrile at 15 to 25°C.

The filtrate was charged with decolourising charcoal (activated) (4.40 Kg) and stirred at 15 to 25°C for at least 60 minutes (target 60 to 120 minutes). The mixture was filtered through a 1 µm filter at 15 to 25°C to remove the charcoal. The filter cake was washed twice with pre-mixed purified water and acetonitrile at 15 to 25°C. The filtrate was charged with SiliaMetS Thiol 40-63 µm 60Å (4.515 Kg) and stirred at 15 to 25°C for at least 60 minutes (target 60 to 120 minutes). The mixture was filtered through a 0.6µm filter at 15 to 25°C to remove SiliaMetS Thiol. The filter cake was twice washed with pre-mixed purified water and acetonitrile at 15 to 25°C.

The filtrate was charged to a vessel and adjusted to 50 to 60°C, concentrated under reduced pressure at 50 to 60°C to ca 110 L. n-Butanol (89.8 Kg) was charged at 50 to 60°C and the mixture was concentrated under reduced pressure at 50 to 60°C to ca 110 L. n-Butanol (86.9 Kg) was charged at 50 to 60°C and the mixture was concentrated under reduced pressure at 50 to 60°C to ca 110 L. n-Butanol (88.4 Kg) was charged at 50 to 60°C and the mixture was concentrated under reduced pressure at 50 to 60°C to ca 90 L.

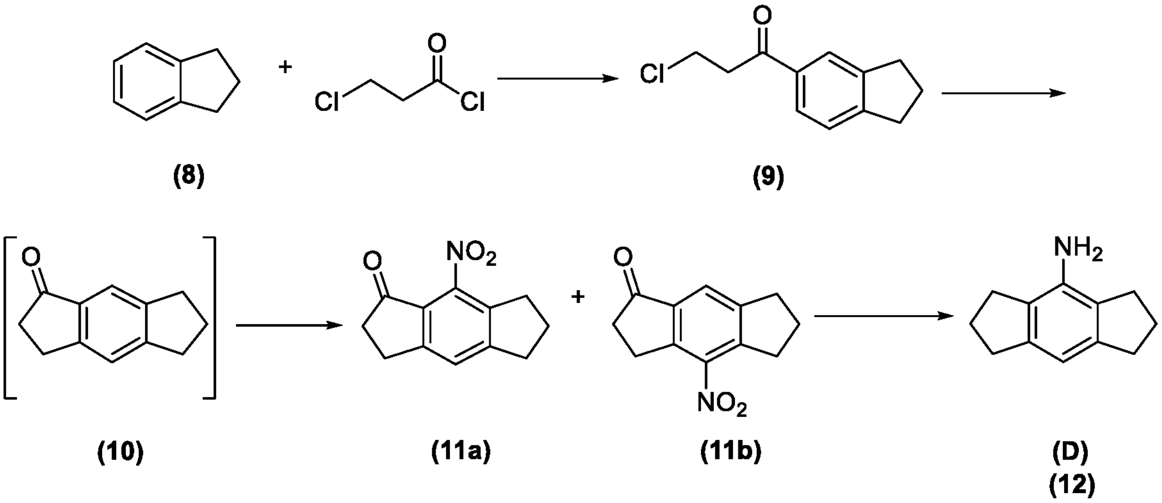
The temperature was adjusted to 15 to 25°C and ethyl acetate (98.6 Kg) was charged at 15 to 25°C. The reaction mixture was cooled to -2 to +2°C over at least 60 minutes (target 60 to 120 minutes). The mixture was stirred at -2 to 2°C for at least 4 hours (target 4 to 6 hours). The solid was filtered on 20µm filter cloth at -2 to 2°C and washed twice with ethyl acetate, (38.1 Kg and 39.9Kg) at -2 to 2°C.

The solid was dried at up to 60°C under a flow of nitrogen until the n-butanol content was ≤0.5%w/w and ethyl acetate content was ≤0.5%w/w (measured by ^1H NMR spectroscopy). The dried weight of the solid 1-ethyl-4-piperidinesulfonamide (7) was measured and assayed using 1H NMR spectroscopy.

Final Product: 1-ethyl-4-piperidinesulfonamide
Output: 12.00 Kg
Yield: 85 %
GC purity: 99.7 %
NMR purity: 98.7 %
^1H NMR: (DMSO) 0.95 (t), 1.55(dq), 1.80 (app t), 1.95 (app d), 2.30 (q), 2.75 (m), 2.90 (app d)

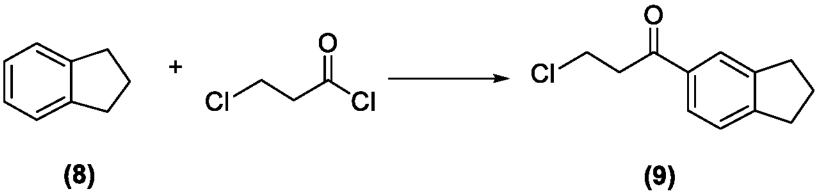
1,2,3,5,6,7-hexahydro-s-indacen-4-amine (12)

1,2,3,5,6,7-hexahydro-s-indacen-4-amine (12) was prepared according to the reaction sequence illustrated in Reaction Scheme 2.



Scheme 2. Synthesis of 1,2,3,5,6,7-hexahydro-s-indacen-4-amine (12)

Reaction scheme 2 - step (a)



DCM (385 L) and $AlCl_3$ (99.86 Kg) were charged at 25 to 30°C under a nitrogen atmosphere into a reactor clean and dry glass-lined reactor. The reaction mixture was cooled to -10°C.

3-chloropropanoyl chloride (90.99 Kg) was added slowly at -10 to -5°C under a nitrogen atmosphere. The reaction mixture was maintained for 30 minutes at 10°C under a nitrogen atmosphere. 2,3-dihydro-*1H*-indene (8) (77.00 Kg was then added slowly to the reaction mixture at -10 to -5°C under nitrogen atmosphere.

The reaction mixture was maintained for 2 hours at 10 to 15°C.

After completion of the reaction, the reaction mixture was added slowly to a 6 N hydrochloric acid solution (prepared from water (308 L) and conc. hydrochloric acid (308 L)) at 0 to 10°C. DCM (231 L) was added and the reaction mixture temperature was raised to 30 to 35°C. The reaction mixture was stirred at 30 to 35°C for 30 minutes and allowed to settle at 30 to 35°C for 30 minutes. The layers were separated and the organic layer (OL-1) was kept aside. DCM (231 L) was charged to the aqueous layer at 25 to 30°C. The reaction mixture was stirred at 25 to 30°C for 30 minutes and allowed to settle at 25 to 30°C for 30 minutes. The layers were separated (aqueous layer (AL-1) and organic layer (OL-2)) and AL-1 was kept aside. OL-1 and OL-2 were combined at 25 to 30°C. Demineralised water (385 L) was added to the combined organic layers. The reaction mixture was stirred at 25 to 30°C for 30 minutes and allowed to settle at 25 to 30°C for 30 minutes. The layers were separated (aqueous layer (AL-2) and organic layer (OL-3)) and AL-2 was kept aside.

10 % Saturated sodium bicarbonate solution (prepared from demineralised water (385 L) and sodium bicarbonate (38.5 Kg)) was charged to OL-3 at 25 to 30°C. The reaction mixture was stirred at 25 to 30°C for 30 minutes and allowed to settle at 25 to 30°C for 30 minutes. The layers were separated (aqueous layer (AL-3) and organic layer (OL-4)) and AL-3 was kept aside. OL-4 was dried over anhydrous Na_2SO_4 (38.5 Kg) and the anhydrous Na_2SO_4 was washed with DCM (150 L) at 25 to 30°C.

The solvent was distilled under vacuum at below 35 to 40°C until 5 % remained. n-hexane (308 L) was charged to the reaction mixture at 35 to 40°C and the solvent was distilled completely at 35 to 40°C until no condensate drops were formed. N-hexane (150 L) was charged to the reaction mixture at 35 to 40°C and the reaction mixture was cooled to 5 to 10°C and maintained at 5 to 10°C for 30 minutes.

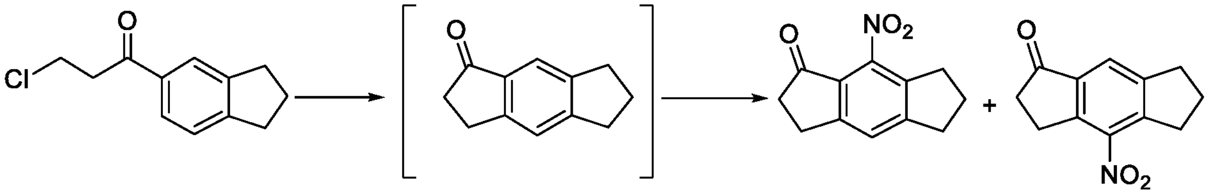
The solid product was filtered, washed with cooled hexane (77 L), and dried in a hot air oven at 40 to 45°C for 6 hours to afford the product.

Final Product: 3-chloro-1-(2,3-dihydro-*1H*-inden-5-yl)propan-1-one (9)

Output: 120.5 Kg
Yield: 88.63 %
HPLC purity: 99.3 %
Moisture content: 0.09 %

^{1}H NMR: (500 MHz, CDCl3): δ 7.81 (S, 1H), 7.76 (d, 1H), 7.31(d, 1H), 3.93 (t, 2H), 3.45 (t, 2H), 2.97 (t, 4H), 2.15 (q, 2H)

Reaction scheme 2 – step (b) and step (c)



(9) **(10)** **(11a)** **(11b)**

Sulfuric acid (300.0 L) was charged at 25 to 30°C into a 2.0 KL clean and dry glass-lined reactor. 3-chloro-1-(2,3-dihydro-*1H*-inden-5-yl)propan-1-one (9) (60.0 Kg) was charged lot wise at 25 to 30°C and the reaction mixture was maintained for 30 minutes at 25 to 30°C. The reaction mixture was slowly heated to 65 to 70°C and maintained at 65 to 70°C for 24 hours. The absence of 3-chloro-1-(2,3-dihydro-*1H*-inden-5-yl)propan-1-one (9) was confirmed by HPLC (Limit: ≤ 1.0 %).

Then the reaction mixture was cooled to 0 to 5°C. A nitration mixture*1 was added slowly at 0 to 5°C and the reaction mixture was maintained at 0 to 5°C for 1 hour. The reaction mixture was maintained at 0 to 5°C.

Demineralised water (900.0 L) was charged at 25 to 30°C into a 2.0 KL clean and dry glass-lined reactor. The water was cooled to 0 to 5°C. The reaction mixture was added slowly added to the reactor at 0 to 5°C. Toluene (480.0 L) was added and the temperature was raised to 30 to 35°C. The reaction mixture was maintained at 30 to 35°C for 30 minutes and allowed to settle at 30 to 35°C for 30 minutes. The reaction mixture was filtered through a Celite® bed (prepared with Celite® (6.0 Kg) and toluene (30.0 L)). The Celite® bed was washed with toluene (60.0 L). The solid was filtered and sucked dry for 30 min.

The reaction mixture was charged to a 2.0 KL clean and dry glass-lined reactor. The reaction mixture was allowed to settle at 30 to 35°C for 30 minutes. The layers were separated (aqueous layer (AL-1) and organic layer (OL-1)) and OL-1 was kept aside.

Toluene (60.0 L) was charged to AL-1. The reaction mixture was stirred at 35 to 40°C for 30 minutes and allowed to settle at 35 to 40°C for 30 minutes. The layers were separated (aqueous layer (AL-2) and organic layer (OL-2)) and OL-2 was kept aside. OL-1 and OL-2 were combined to form OL-3.

A 5 % saturated sodium bicarbonate solution (prepared from demineralised water (300.0 L) and sodium bicarbonate (15.0 Kg)) was slowly charged to OL-3 at 30 to 35°C. The reaction mixture was stirred at 35 to 40°C for 30 minutes and allowed to settle at 35 to 40°C for 30 minutes. The reaction mixture was filtered through a Celite® bed (prepared with Celite® (6.0 Kg) and demineralised water (60.0 L)). The Celite® bed was washed with toluene (60.0 L).

The reaction mixture was charged to a 3.0 KL clean and dry glass-lined reactor. The reaction mixture was allowed to settle at 30 to 35°C for 30 minutes. The layers were separated (aqueous layer (AL-3) and organic layer (OL-4)) and OL-4 was kept aside.

Toluene (60.0 L) was charged to AL-3. The layers were separated (aqueous layer (AL-4) and organic layer (OL-5)) and OL-5 was kept aside. OL-4 and OL-5 were combined to form OL-6. Brine solution (prepared from demineralised water (300.0 L) and sodium chloride (12.0 Kg) at 25 to 30°C. The reaction mixture was stirred at 30 to 35°C for 30 minutes and allowed to settle at 30 to 35°C for 30 minutes. The layers were separated (aqueous layer (AL-5) and organic layer (OL-7)) and OL-7 was kept aside. OL-7 was dried over anhydrous Na_2SO_4 (9.0 Kg) and the anhydrous Na_2SO_4 was washed with toluene (30.0 L) at 25 to 30°C. The solvent was distilled under vacuum at below 40 to 45°C until 5 % remained. Methanol (60.0 L) was charged to the reaction mixture at 40 to 45°C and down to 60 L of reaction mass.

Methanol (120.0 L) was charged to the reaction mixture at 40 to 45°C and the reaction mixture was cooled to 5 to 10°C and maintained at 5 to 10°C for 30 minutes. The solid product was filtered, washed with cooled methanol (30.0 L), and dried in a hot air oven at 40 to 45°C for 6 hours to afford the product.

*1: To prepare the nitration mixture, sulfuric acid (27.0 L) was charged at 25 to 30°C into a 160 L clean and dry glass-lined reactor. The reaction mixture was cooled to 0 to

5°C. Nitric acid (27.0 L) at 0 to 5°C was added slowly and the reaction mixture was maintained for 30 minutes at 0 to 5°C to afford the nitration mixture.

Final Product: 8-nitro-1,2,3,5,6,7-hexahydro-s-indacen-1-one (11a) and 4-nitro-1,2,3,5,6,7-hexahydro-s-indacen-1-one (11b)

Combined Output (11a+11b): 38.87 Kg

Combined Yield (11a+11b): 62.24 %

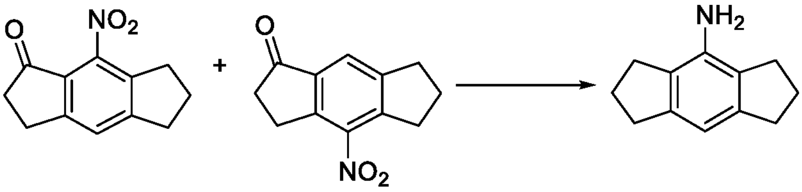
Weight ratio (11a:11b): 9:1

HPLC purity: 95.9%

Moisture content: 0.19%

^{1}H NMR: (500 MHz, $CDCl_3$):δ7.44(S, 1H), 2.21(m, 2H), 2.78 (t, 2H), 3.02 (m, 4H), 3.13 (t, 2H)

Reaction scheme 2 – step (d)



(11a) (11b) (D)
(12)

A mixture of 8-nitro-1,2,3,5,6,7-hexahydro-s-indacen-1-one (11a) and 4-nitro-1,2,3,5,6,7-hexahydro-s-indacen-1-one (11b) (9:1 ratio; 27.0 Kg) at 25 to 30°C was charged into a 600 L clean and dry pressure reactor.

Methanol (270 L) was charged at 25 to 30°C. Methane sulfonic acid (14.3 Kg) was slowly charged at 25 to 30°C and the reaction mixture was maintained for 30 minutes. 15 % $Pd(OH)_2$ slurry (60 % wet)^{*2} was added.

The reaction mixture was degassed under vacuum and filled with an argon atmosphere (0.5 Kg) three times. The reaction mixture was degassed under vacuum and filled with

a hydrogen atmosphere (0.5 Kg) three times. Then the reaction mixture was stirred under hydrogen pressure (100 Psi) at room temperature for 32 hours.
After completion of the reaction, the reaction mixture was cooled to 25 to 30°C. The reaction mixture was degassed under vacuum and filled with nitrogen atmosphere (0.5 Kg) three times.

The reaction mixture was filtered through a candy filter to remove $Pd(OH)_2$, followed by a micro filter and the bed was washed with methanol (54 L). 95 % of the solvent was distilled off under vacuum at below 45 to 50°C. Demineralised water (135 L) was charged into the reaction mixture at 25 to 30°C and maintained for 30 minutes. The reaction mixture was cooled to 5-10°C. The pH was adjusted to about 9-10 with 2 N aqueous NaOH solution (prepared from NaOH (6.48 Kg) and demineralised water (81 L)) and the reaction mixture was stirred for 30 minutes. Then toluene (135 L) was charged to the reaction mixture and the reaction mixture was stirred for 30 minutes. The reaction mixture was stirred for a further 30 minutes, whilst bringing the temperature up to 25 to 30°C. The reaction mixture was allowed to settle for 30 minutes, whilst the temperature was maintained at 25 to 30°C.

The reaction mixture was filtered through a Celite® bed (prepared with Celite® (5.4 Kg) and toluene (13.5 L). The Celite® bed was washed with toluene (54 L).

The layers were separated (aqueous layer (AL-1) and organic layer (OL-1)) and OL-1 was kept aside. Toluene (54 L) was added to AL-1 at 25 to 30°C. The reaction mixture was stirred at 25 to 30°C for 30 minutes and allowed to settle at 25 to 30°C for 30 minutes. The layers were separated (aqueous layer (AL-2) and organic layer (OL-2)) and AL-2 was kept aside. Toluene (54 L) was added to AL-1 at 25 to 30°C. A brine solution (prepared with demineralised water (135 L) and sodium chloride (54 Kg)) was charged to the combined organic layers (OL-1 and OL-2) at 25 to 30°C. The reaction mixture was stirred at 25 to 30°C for 30 minutes and allowed to settle at 25 to 30°C for 30 minutes.

The layers were separated (aqueous layer (AL-3) and organic layer (OL-3)) and AL-3 was kept aside. Charcoal (1.3 Kg) was added to OL-3 and the temperature was raised to 35-40°C and maintained at 35 to 40°C for 30 minutes. The reaction mixture was filtered through a Celite® bed (prepared with Celite® (5.4 Kg) and toluene (54 L)) at 35 to 40°C. The Celite® bed was washed with toluene (54 L). The organic layer was dried over anhydrous Na_2SO_4 (13.5 Kg). The Na_2SO_4 was washed with toluene (27 L).

The solvent was distilled under vacuum at below 35 to 40°C until 5 % remained. Methanol (40.5 L) was charged to the reaction mixture at 35 to 40°C and distilled until 5 % remained. Methanol (97.2 L) and water (10.8 L) were charged to the reaction mixture at 35 to 40°C. The reaction mixture was heated to 50 to 55°C, stirred for 1 hour at 50 to 55°C, slowly cooled to 0 to 5°C and maintained at 0 to 5°C for 30 minutes.

The solid product was filtered and washed with cold methanol (13.5 L), and dried in a hot air oven at 40 to 45°C for 6 hours to afford the product.

*2: To prepare the 15 % $Pd(OH)_2$ slurry, 20 % $Pd(OH)_2$ on carbon (60 % wet; 4.05 Kg) was added to methanol (27 L).

Final product: 1,2,3,5,6,7-hexahydro-s-indacen-4-amine (12)
Output: 11.3 Kg
Yield: 41.85 %
HPLC purity: 98.1 %
Moisture content: 0.10
^1H NMR: (400 MHz, DMSO-d_6): δ 6.38 (S, 1H), 4.45 (S, 2H), 2.75 (t, 4H), 2.58 (t, 4H), 1.98 (t, 4H).

Purification (A) of 1,2,3,5,6,7-hexahydro-s-indacen-4-amine (12)
1,2,3,5,6,7-Hexahydro-s-indacen-4-amine (12) (54.5 Kg) was charged at 25 to 30°C into a 250 L clean and dry reactor. Toluene (27.2 L) was charged at 25 to 30°C and the reaction mixture was stirred at 25 to 30°C for 30 minutes. Methanol (163 L) was charged to the reaction mixture at 25 to 30°C. The reaction mixture was stirred at 25 to 30°C for 30 minutes, cooled to -5 to 0°C, and stirred at -5 to 0°C for 30 minutes. The solid product was filtered, washed with cold methanol (54.5 L), and dried at 40 to 45°C for 6 hours.

Final Product: 1,2,3,5,6,7-hexahydro-s-indacen-4-amine (12)
Output: 40.5 Kg

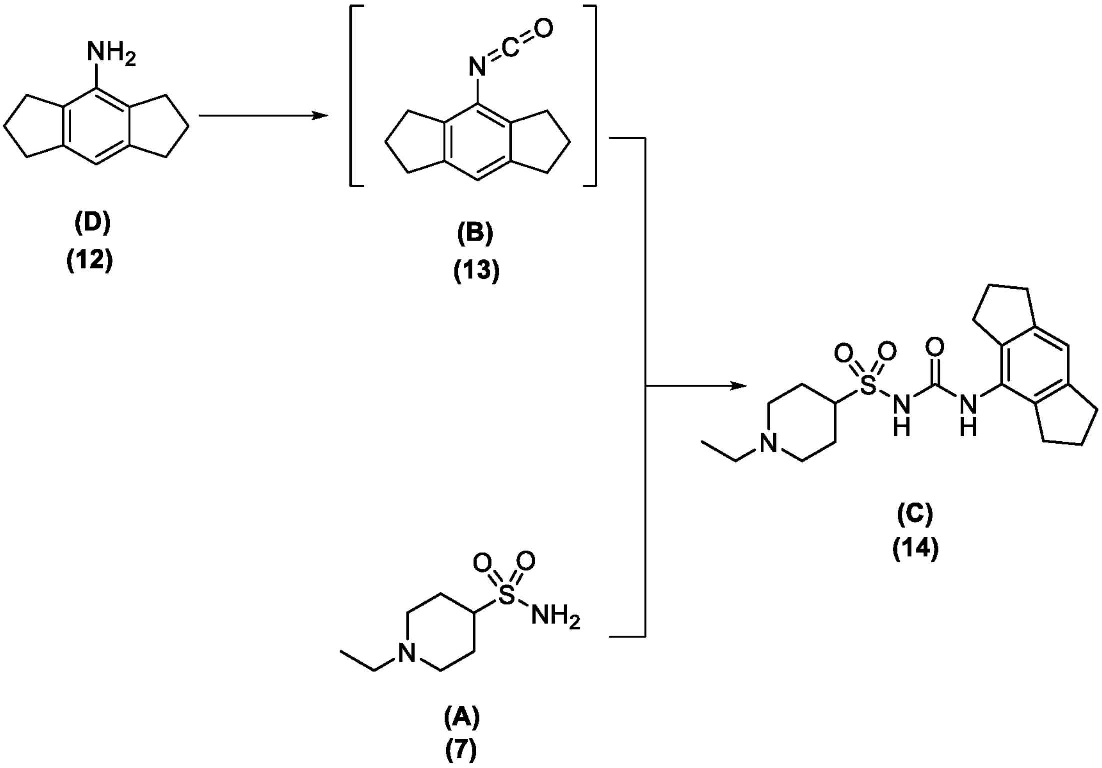
Yield: 74.31 %

HPLC purity: 99.5 %

Moisture content: 0.3 %

^{1}H NMR: (400 MHz, DMSO-d_6): δ 6.33 (s, 1H), 4.53 (s, 2H), 2.72 (t, 4H), 2.57 (t, 4H), 1.98 (t, 4H).

1-Ethyl-*N*-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)piperidine-4-sulfonamide (potassium salt) (14)



Reaction scheme 3. Synthesis of (14)

1,2,3,5,6,7-hexahydro-s-indacen-4-amine-isocyanate (13) preparation in a batch mode:

1,2,3,5,6,7-hexahydro-s-indacen-4-amine (**12**) (1.00 g, 1.00 equiv) was dissolved in toluene (9.60 g) in a 50 mL reactor at 10 – 20 °C. *N,N*-diisopropylethylamine (2.25 g, 3.00 equiv) was added followed by the 20wt% phosgene solution (4.28 g, 1.50 equiv) over 3 minutes and the formed suspension was further stirred for 30 minutes at 10 – 20 °C. The reaction mixture was washed with saturated $NaHCO_3$ solution (5.0 mL) and water

(5.0 mL). The layers were separated to give 1,2,3,5,6,7-hexahydro-s-indacen-4-amine-isocyanate in toluene (OL-1, ca. 20 mL, contains 1,2,3,5,6,7-hexahydro-s-indacen-4-amine (12) (5.77 mmol). The obtained solution OL-1 is used in the next step (Coupling of indacenamine-isocyanate (12) with 1-ethyl-4-piperidinesulfonamide (7)) to yield (14) in ca. 80% overall yield.

1,2,3,5,6,7-hexahydro-s-indacen-4-amine-isocyanate (13) preparation in a flow mode:

Feed solutions preparation:

Feed solution A: 1,2,3,5,6,7-hexahydro-s-indacen-4-amine (**12**) (43.31 g) was dissolved in toluene (206.69 g) to give a 0.90 M solution.

Feed solution B: Potassium carbonate (103.5 g) was dissolved in water (950 g) to give a 0.75 M solution.

Feed A (0.70 mL/min, 1.10 equiv), 20 % w/w phosgene solution toluene (0.45 mL/min, 1.50 equiv) and Feed B solution (2.35 mL/min, 3.10 equiv) was dosed simultaneously at 0 to 10 °C (Internal temperature) in a reactor 1 (ca. 25 mL). Residence time in reactor 1 is 5 – 10 minutes. The biphasic solution from reactor 1 is continuously pumped out and layers are separated continuously to give organic layer (OL-1) with 1,2,3,5,6,7-hexahydro-s-indacen-4-amine isocyanate (**13**) and aqueous layer (AL-1) that is directed to the waste. Organic layer OL-1 is collected over 81 minutes at steady state to afford ca. 90 mL of 1,2,3,5,6,7-hexahydro-s-indacen-4-amine (12) (51 mmol). The obtained solution OL-1 is used in the next step.

Coupling of indacenamine-isocyanate (12) with 1-ethyl-4-piperidinesulfonamide (7):

1-ethyl-4-piperidinesulfonamide (7) (8.88 g, 46 mmol, 1.0 equiv) was charged to a vessel. Tetrahydrofuran (62.52 g) was charged to the vessel and the mixture was adjusted to 20 to 25°C. The mixture was stirred for at least 20 minutes at 20 to 25°C until clumps disappeared and homogenous suspension was formed. Potassium *tert*-butoxide (1.05 M, 43.98 mL, 46 mmol) was charged to the vessel over 90 to 120 minutes, maintaining the temperature at 20 to 25°C and the mixture stirred for 2 to 4 hours at 20 to 25°C to give a thick, white suspension.

The organic layer OL-1 containing 1,2,3,5,6,7-hexahydro-s-indacen-4-amine -isocyanate (**13**) (51 mmol of 1,2,3,5,6,7-hexahydro-s-indacen-4-amine (**12**) , ca. 90 mL) prepared in a batch or a flow mode was added to the formed white suspension in toluene over 2 hours by keeping 20 – 25 °C. The reaction mixture quickly became a well stirrable suspension and at the end of addition a slightly turbid brown solution. The reaction mixture was stirred further 1 – 2 h at 20 to 25°C. The water content was analysed by KF and conversion of 1,2,3,5,6,7-hexahydro-s-indacen-4-amine confirmed by LC/MS or HPLC analysis (typically > 95%). Optionally a clear filtration via Celite layer (G3 filter) is performed. Water (4.44 g, 0.5 V) was added to the reaction mixture at 25 to 40 °C dropwise over 2 hours. Solids started to crystallize at about 0.5 – 1 wt% water content. At the end of dosing a suspension was formed. The reaction mixture was cooled to 0 to 5 °C (IT) over 1 h and stirred further for 16 h at 0 to 5 °C. Solids were filtered through a G3 filter and washed with toluene/THF (1/1 by volume, 44.4 mL) mixture.

The solid was dried at up to 50°C, 10 – 20 mbar under a flow of nitrogen over 12 h. The dried weight of the crude solid was measured, identified and analysed using ^{1}H NMR spectroscopy and HPLC.

Final Product: 1-ethyl-*N*-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)-carbamoyl)piperidine-4-sulfonamide (potassium salt) (14)

Output: ca. 16.0 g
Yield: ca. 80 %
NMR purity: >97%
HPLC purity: >99%

Recrystallization of 1-ethyl-*N*-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)-carbamoyl)piperidine-4-sulfonamide (potassium salt) (14)

Crude 1-ethyl-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)piperidine-4-sulfonamide (potassium salt) (14) (15.00 g) was charged to a reaction vessel.

Methanol (33.55 g) was charged to the vessel followed by acetonitrile (33.55 g) and the temperature was adjusted to 15 to 25°C as required with stirring for 10 to 20 minutes (until a homogeneous cloudy solution with no lumps of solid present was formed). The solution was filtered through a 1 µm filter at 15 to 25°C. The filter was washed with methanol/acetonitrile mixture (7.59 g) at 15 to 25°C and further acetonitrile (64.0 g) was added followed by seed crystals (0.138 g) of (14) in acetonitrile (ca. 1 g). Supsension was formed.

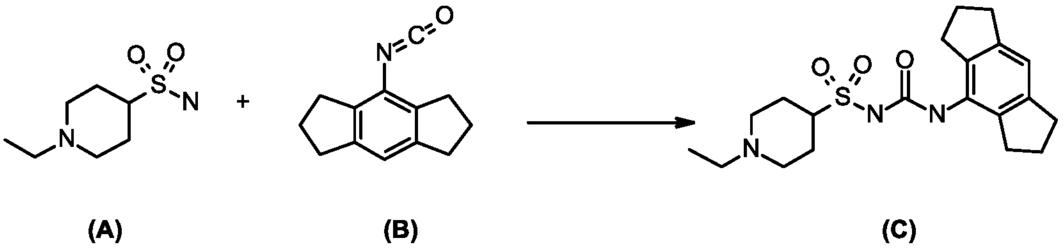
The solution was concentrated to ca. 122 mL at 25 to 35°C. Acetonitrile (54.32 g) was charged to the mixture and the solution was concentrated to ca. 122 L at 25 to 35°C. Acetonitrile (52.53 g) was charged to the mixture and the mixture was concentrated to ca. 122 mL at ≤ 35°C. The mixture was analysed for residual methanol content. Pass criterion ≤ 0.3% w/w methanol. Acetonitrile (53.45 g) was charged to the vessel and the temperature was adjusted to 15 to 25°C. The slurry was aged for at least 1 hour (target 1 to 2 hours) at 15 to 25°C and then filtered over 20 µm cloth at 15 to 25°C. The filter cake was twice washed with acetonitrile (43.39 g) at 15 to 25°C. The solid was dried at up to 50°C under a flow of nitrogen to yield 13.75 g (92%) of the white solid.

Final Product: 1-ethyl-*N*-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)-carbamoyl)piperidine-4-sulfonamide (potassium salt) (14)

Output: 13.75 g
Yield: 92 %
HPLC purity: 99.7 %

Claims

1. A process of preparing compound (C) or a salt thereof, comprising the step of contacting compound (A) with compound (B) in the presence of a solvent and a base, to obtain compound (C) or a salt thereof



2. The process of claim 1, wherein the solvent for contacting compound (A) with compound (B) is selected from toluene, anisole, cyclopentyl methyl ether, ethylbenzene, isopropyl acetate, isobutyl acetate, 2-methyl tetrahydrofuran, water, *t*-butanol, ethyl acetate, methyl acetate, xylene, tetrahydrofuran dimethyl sulfoxide, acetonitrile, *t*-butyl methyl ether, *N*-methyl pyrrolidine, *N*-ethyl pyrrolidone, heptane, cyclohexane, acetone, or any combination thereof.

3. The process of claim 1 or 2, wherein the solvent for contacting compound (A) with compound (B) is toluene or toluene in combination with water, *tert*-butanol, tetrahydrofuran, dimethyl sulfoxide or acetonitrile.

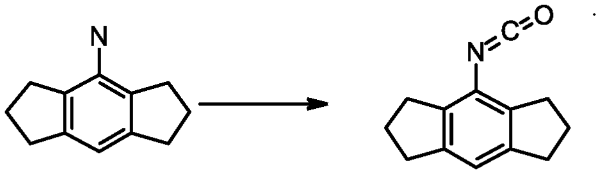
4. The process of any one of claims 1 to 3, wherein the solvent for contacting compound (A) with compound (B) is toluene and tetrahydrofuran

5. The process of any one of claims 1 to 4, wherein the base for contacting compound (A) with compound (B) is selected from potassium *tert*-butoxide, potassium hydroxide or any other basic potassium salt.

6. The process of any one of claims 1 to 5, wherein the base for contacting compound (A) with compound (B) is selected from potassium *tert*-butoxide or potassium hydroxide.

7. The process of any one of claims 1 to 6, wherein the base for contacting compound (A) with compound (B) is potassium *tert*-butoxide.

8. A process of preparing compound (B) wherein compound (D) is converted into compound (B):



(D) **(B)**

9. The process according to 8, wherein compound (D) is converted into compound B using a reaction mixture of compound (D) with phosgene, triphosgene, carbonyldiimidazole, or di-tert-butyl dicarbonate in the presence of a base and a solvent.

10. The process of claim 9, wherein

the solvent is selected from toluene, anisole, cyclopentylmethylether, ethylbenzene, isopropyl acetate, isobutyl acetate, 2-methyl tetrahydrofuran, water, ethyl acetate, methyl acetate, xylene, tetrahydrofuran or dimethyl sulfoxide, acetonitrile, t-butyl methyl ether, diethyl ether, dichloromethane, 1,2-dichloroethane, chloroform, *N*-methyl pyrrolidine, *N*-ethyl pyrrolidone, heptane, cyclohexane or any combination thereof; and

the base is a tertiary amine, such as *N,N*-diisopropylethylamine, triethylamine, or tributylamine or the base is an inorganic base such as potassium carbonate, potassium hydroxide, or sodium carbonate.

11. The process of claim 9 or claim 10, wherein

the solvent is selected from toluene or toluene in combination with water, acetonitrile, or tetrahydrofuran; and

the base is selected from *N,N*-diisopropylethylamine, trimethylamine, tributylamine, potassium carbonate, potassium hydroxide, or sodium carbonate.

12. The process of any one of claims 9 to 11, wherein the solvent is toluene and/or water, and the base is *N,N*-diisopropylethylamine, trimethylamine or potassium carbonate.

13. The process of any one of claims 9 to 12, wherein the solvent is toluene and the base is N,N-diisopropylethylamine or potassium carbonate.

14. The process of any one of claims 8 to 13, wherein the reaction mixture is washed using an aqueous solution to yield compound (B) in an organic solvent.

15. The process of any one of claims 1 to 7, wherein compound (B) is prepared by a process according to any one of claims 8 to 14.

16. The process of any one of claims 8 to 15, wherein compound (B) is prepared by a batch process or in a continuous mode.

17. The process of any one of claims 8 to 15, wherein the process is performed in a continuous mode.

18. The process of any one of claims 1 to 7, wherein compound (C) is isolated using an antisolvent.

19. The process of claim 18, wherein the antisolvent is selected from acetonitrile, any alcohol or water.

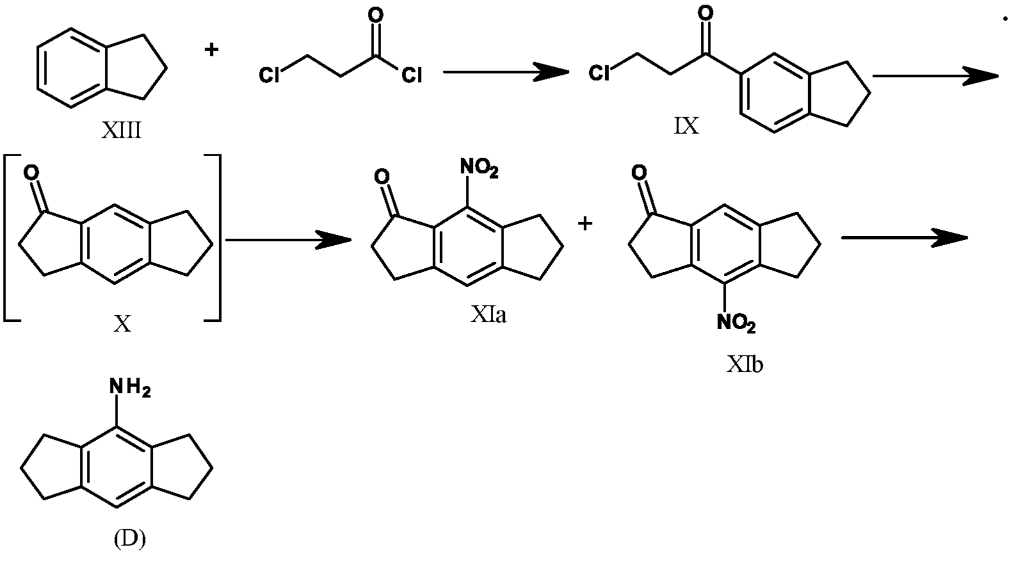
20. The process of any one of claims 1 to 7, wherein compound (C) is isolated using a wash solvent.

21. The process of claim 20, wherein the wash solvent is selected from tetrahydrofuran, toluene, dimethylsulfoxide, or acetonitrile.

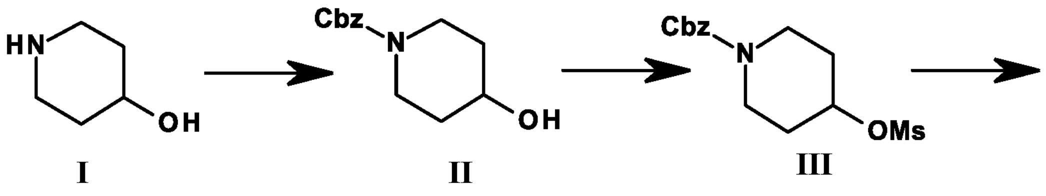
22. The process of any one of claims 15 to 17, wherein the process to obtain compound (B) and compound (C) are telescoped.

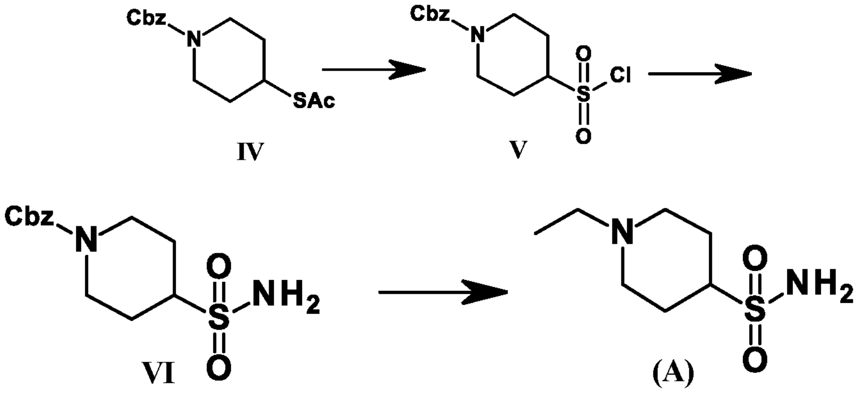
23. Compound (C) or a salt thereof, prepared by a process according to any one of claims 1 to 7, or 18 to 22.

24. A process according to any one of claims 8 to 17, wherein compound (D) is prepared via the following steps:



25. A process according to any one of claims 1 to 7, or 18 to 22, or 24 wherein compound (A) is prepared via the following steps:





wherein Cbz is carboxybenzyl/benzyloxycarbonyl, OMs is methanesulfonate, and SAc is acetylthio.

26. A pharmaceutical composition comprising Compound (C) or the salt thereof of claim 23, and a pharmaceutically acceptable excipient.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2023/053410

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D211/54 C07C263/10
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2019/008025 A1 (INFLAZOME LTD [IE]) 10 January 2019 (2019-01-10) cited in the application preparation of intermediate A14 on page 122; claims 16-18; example 6 ----- -/--	1-3,5-9, 15-26

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search 24 July 2023	Date of mailing of the international search report 28/07/2023
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Grassi, Damian

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EGGLER J F ET AL: "Synthesis of covalent (14C)-labeled diarylsulfonylurea (DASU) inhibitors of the processing and release of IL-1", JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMACEUTICALS, JOHN WILEY & SONS LTD, GB, vol. 45, no. 9, 1 August 2002 (2002-08-01), pages 785-794, XP002264662, ISSN: 0362-4803, DOI: 10.1002/JLCR.602	8-10
Y	Scheme 2, page 791, preparation of non-labelled (3) -----	1-3,5-7, 15
Y	WO 2021/111351 A1 (CADILA HEALTHCARE LTD [IN]) 10 June 2021 (2021-06-10) pages 19-20 -----	1-3,5-7, 15
Y	US 2017/304272 A1 (OR YAT SUN [US] ET AL) 26 October 2017 (2017-10-26) paragraph [0147] -----	1-3,5-7, 15
Y	US 2012/245144 A1 (HEFFRON TIMOTHY [US] ET AL) 27 September 2012 (2012-09-27) paragraphs [0806] - [0808] -----	25
Y	WO 2007/050522 A1 (VERTEX PHARMA [US]; MARTINBOROUGH ESTHER [US] ET AL.) 3 May 2007 (2007-05-03) pages 48-52 -----	25
Y	EP 3 272 739 A1 (NODTHERA LTD [GB]) 24 January 2018 (2018-01-24) page 33 -----	24
Y	WO 2019/034686 A1 (INFLAZOME LTD [IE]) 21 February 2019 (2019-02-21) pages 127-129 page 113 -----	25
Y	FRANK J. URBAN ET AL: "Novel Synthesis of 1-(1,2,3,5,6,7-Hexahydro- s -indacen-4-yl)-3-[4-(1-hydroxy-1-methyl-ethyl)-furan-2-sulfonyl]urea, an Anti-inflammatory Agent", SYNTHETIC COMMUNICATIONS, vol. 33, no. 12, 1 July 2003 (2003-07-01), pages 2029-2043, XP055306651, US ISSN: 0039-7911, DOI: 10.1081/SCC-120021029 page 2034 -----	24

-/--

7

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98/32733 A1 (PFIZER [US]; DOMBROSKI MARK ANTHONY [US]; EGGLER JAMES FREDERICK [US]) 30 July 1998 (1998-07-30) pages 40-41 pages 19,24 -----	8-14
Y	CROWLEY P J ET AL: "SYNTHESIS OF SOME ARYLSULFUR PENTAFLUORIDE PESTICIDES AND THEIR RELATIVE ACTIVITIES COMPARED TO THE TRIFLUOROMETHYL ANALOGUES", CHIMIA INTERNATIONAL JOURNAL FOR CHEMISTRY, SCHWEIZERISCHE CHEMISCHE GESELLSCHAFT, CH, vol. 58, no. 3, 1 January 2004 (2004-01-01), pages 138-142, XP009070673, ISSN: 0009-4293, DOI: 10.2533/000942904777678172 Scheme 2 -----	8-14
Y	US 2014/378475 A1 (BATT DOUGLAS G [US] ET AL) 25 December 2014 (2014-12-25) page 74, Intermediate 44B -----	8-14

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2023/053410

Box No. II **Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III **Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4, 13, 23, 26

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims;; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 4, 23, 26(completely); 1-3, 5-7, 15-22, 24, 25(partially)

   Process of claim 1 involving toluene, anisole, ethylbenzene or xylene as solvent and claims 23 and 26.

   \---

2. claims: 1-3, 5-7, 15-22, 24, 25(all partially)

   Process of claim 1 involving cyclopentyl methyl ether or t-butyl methyl ether as solvent.

   \---

3. claims: 1-3, 5-7, 15-22, 24, 25(all partially)

   Process of claim 1 involving isopropyl acetate, isobutyl acetate, ethyl acetate or methyl acetate as solvent.

   \---

4. claims: 1-3, 5-7, 15-22, 24, 25(all partially)

   Process of claim 1 involving 2-methyl tetrahydrofuran or tetrahydrofuran as solvent.

   \---

5. claims: 1-3, 5-7, 15-22, 24, 25(all partially)

   Process of claim 1 involving water or t-butanol as solvent.

   \---

6. claims: 1-3, 5-7, 15-22, 24, 25(all partially)

   Process of claim 1 involving dimethyl sulfoxide as solvent.

   \---

7. claims: 1-3, 5-7, 15-22, 24, 25(all partially)

   Process of claim 1 involving acetonitrile as solvent.

   \---

8. claims: 1-3, 5-7, 15-22, 24, 25(all partially)

   Process of claim 1 involving N-methyl pyrrolidine or N-ethyl pyrrolidone as solvent.

   \---

9. claims: 1-3, 5-7, 15-22, 24, 25(all partially)

   Process of claim 1 involving heptane or cyclohexane as solvent.

   \---

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

10. claims: 1-3, 5-7, 15-22, 24, 25(all partially)

Process of claim 1 involving acetone as solvent.

---

11. claims: 13(completely); 8-12, 14, 16, 17, 24, 25(partially)

Process of claim 8 involving toluene, anisole, ethylbenzene or xylene as solvent (the group is not unitary).

---

12. claims: 8-12, 14, 16, 17, 24, 25(all partially)

Process of claim 8 involving cyclopentyl methyl ether, 2-methyl tetrahydrofuran, tetrahydrofuran, t-butyl methyl ether or diethyl ether as solvent.

---

13. claims: 8-12, 14, 16, 17, 24, 25(all partially)

Process of claim 8 involving isopropyl acetate, isobutyl acetate, ethyl acetate or methyl acetate as solvent.

---

14. claims: 8-12, 14, 16, 17, 24, 25(all partially)

Process of claim 8 involving water as solvent.

---

15. claims: 8-12, 14, 16, 17, 24, 25(all partially)

Process of claim 8 involving dimethyl sulfoxide as solvent.

---

16. claims: 8-12, 14, 16, 17, 24, 25(all partially)

Process of claim 8 involving acetonitrile as solvent.

---

17. claims: 8-12, 14, 16, 17, 24, 25(all partially)

Process of claim 8 involving dichloromethane, 1,2-dichloroethane or chloroform as solvent.

---

18. claims: 8-12, 14, 16, 17, 24, 25(all partially)

Process of claim 8 involving N-methyl pyrrolidine or N-ethyl pyrrolidone as solvent.

---

19. claims: 8-12, 14, 16, 17, 24, 25(all partially)

Process of claim 8 involving heptane or cyclohexane as solvent.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

INTERNATIONAL SEARCH REPORT

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PCT/EP2023/053410

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Information on patent family members

International application No
PCT/EP2023/053410

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(19)国家知识产权局

(12)发明专利申请

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(51)Int.Cl.
C07D 211/54(2006.01)
C07C 263/10(2006.01)

权利要求书3页 说明书23页

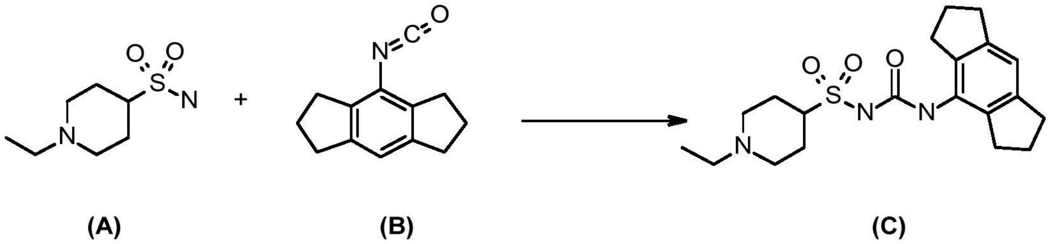
(54)发明名称

用于制备1,2,3,5,6,7-六氢-s-二环戊二烯并苯衍生物的方法

(57)摘要

本发明涉及可用于制备1-乙基-N-((1,2,3,5,6,7-六氢-s-二环戊二烯并苯-4-基)氨基甲酰基)哌啶-4-磺酰胺及其盐的中间体和方法。本发明进一步涉及通过此类方法制备的1-乙基-N-((1,2,3,5,6,7-六氢-s-二环戊二烯并苯-4-基)氨基甲酰基)哌啶-4-磺酰胺及其盐,并且涉及相关的药物组合物以及用于治疗和预防、尤其是通过NLRP$_3$抑制来治疗和预防医学疾患和疾病的用途。

1.一种制备化合物(C)或其盐的方法,所述方法包括在溶剂和碱存在下使化合物(A)与化合物(B)接触以获得化合物(C)或其盐的步骤



。

2.根据权利要求1所述的方法,其中用于使化合物(A)与化合物(B)接触的所述溶剂选自甲苯、苯甲醚、环戊基甲醚、乙苯、乙酸异丙酯、乙酸异丁酯、2-甲基四氢呋喃、水、叔丁醇、乙酸乙酯、乙酸甲酯、二甲苯、四氢呋喃、二甲基亚砜、乙腈、叔丁基甲醚、N-甲基吡咯烷、N-乙基吡咯烷酮、庚烷、环已烷、丙酮或其任意组合。

3.根据权利要求1或2所述的方法,其中用于使化合物(A)与化合物(B)接触的所述溶剂为甲苯、或者甲苯与水、叔丁醇、四氢呋喃、二甲基亚砜或乙腈的组合。

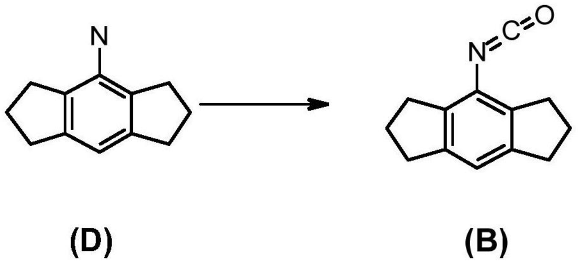
4.根据权利要求1至3中任一项所述的方法,其中用于使化合物(A)与化合物(B)接触的所述溶剂为甲苯和四氢呋喃。

5.根据权利要求1至4中任一项所述的方法,其中用于使化合物(A)与化合物(B)接触的所述碱选自叔丁醇钾、氢氧化钾或任何其他碱性钾盐。

6.根据权利要求1至5中任一项所述的方法,其中用于使化合物(A)与化合物(B)接触的所述碱选自叔丁醇钾或氢氧化钾。

7.根据权利要求1至6中任一项所述的方法,其中用于使化合物(A)与化合物(B)接触的所述碱为叔丁醇钾。

8.一种制备化合物(B)的方法,其中将化合物(D)转化为化合物(B):



。

9.根据权利要求8所述的方法,其中在碱和溶剂存在下,使用化合物(D)与光气、三光气、羰基二咪唑或二碳酸二叔丁酯的反应混合物来将化合物(D)转化为化合物B。

10.根据权利要求9所述的方法,其中

所述溶剂选自甲苯、苯甲醚、环戊基甲醚、乙苯、乙酸异丙酯、乙酸异丁酯、2-甲基四氢呋喃、水、乙酸乙酯、乙酸甲酯、二甲苯、四氢呋喃或二甲基亚砜、乙腈、叔丁基甲醚、二乙醚、二氯甲烷、1,2-二氯乙烷、氯仿、N-甲基吡咯烷、N-乙基吡咯烷酮、庚烷、环已烷或其任意组合;并且

所述碱为叔胺,诸如N,N-二异丙基乙胺、三乙胺或三丁胺,或者所述碱为无机碱,诸如碳酸钾、氢氧化钾或碳酸钠。

11.根据权利要求9或权利要求10所述的方法,其中

所述溶剂选自甲苯、或者甲苯与水、乙腈或四氢呋喃的组合；并且

所述碱选自N,N-二异丙基乙胺、三甲胺、三丁胺、碳酸钾、氢氧化钾或碳酸钠。

12.根据权利要求9至11中任一项所述的方法，其中所述溶剂为甲苯和/或水，并且所述碱为N,N-二异丙基乙胺、三甲胺或碳酸钾。

13.根据权利要求9至12中任一项所述的方法，其中所述溶剂为甲苯，并且所述碱为N,N-二异丙基乙胺或碳酸钾。

14.根据权利要求8至13中任一项所述的方法，其中使用水溶液洗涤所述反应混合物以获得在有机溶剂中的化合物(B)。

15.根据权利要求1至7中任一项所述的方法，其中化合物(B)是通过根据权利要求8至14中任一项所述的方法制备的。

16.根据权利要求8至15中任一项所述的方法，其中化合物(B)是通过分批法或以连续方式制备的。

17.根据权利要求8至15中任一项所述的方法，其中所述方法是以连续方式进行的。

18.根据权利要求1至7中任一项所述的方法，其中使用反溶剂分离化合物(C)。

19.根据权利要求18所述的方法，其中所述反溶剂选自乙腈、任何醇或水。

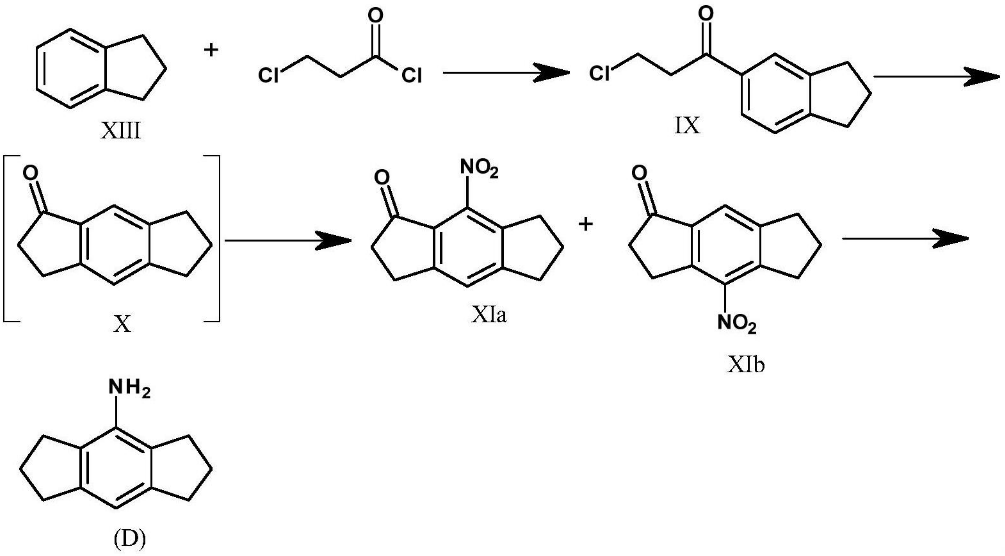
20.根据权利要求1至7中任一项所述的方法，其中使用洗涤溶剂分离化合物(C)。

21.根据权利要求20所述的方法，其中所述洗涤溶剂选自四氢呋喃、甲苯、二甲基亚砜或乙腈。

22.根据权利要求15至17中任一项所述的方法，其中获得化合物(B)和化合物(C)的方法是经叠嵌的。

23.一种化合物(C)或其盐，其通过根据权利要求1至7或18至22中任一项所述的方法制备。

24.根据权利要求8至17中任一项所述的方法，其中化合物(D)经由以下步骤制备：



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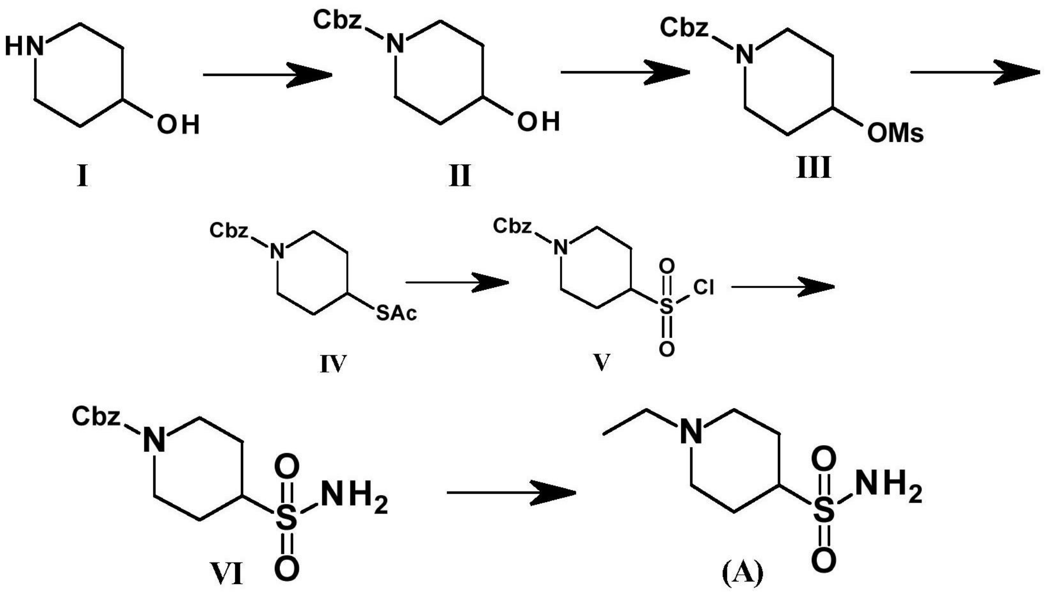
25.根据权利要求1至7、或18至22、或24中任一项所述的方法，其中化合物(A)经由以下步骤制备：



,

其中Cbz为羧基苄基/苄氧基羰基,OMs为甲烷磺酸根,并且SAc为乙酰基硫基。

26.一种药物组合物,其包含根据权利要求23所述的化合物(C)或其盐、以及药用赋形剂。

用于制备1,2,3,5,6,7-六氢-s-二环戊二烯并苯衍生物的方法

技术领域

[0001] 本发明涉及可用于制备1-乙基-N-((1,2,3,5,6,7-六氢-s-二环戊二烯并苯-4-基)氨基甲酰基)哌啶-4-磺酰胺及其盐的中间体和方法。本发明进一步涉及通过此类方法制备的1-乙基-N-((1,2,3,5,6,7-六氢-s-二环戊二烯并苯-4-基)氨基甲酰基)哌啶-4-磺酰胺及其盐,并且涉及相关的药物组合物以及用于治疗和预防、尤其是通过NLRP3抑制来治疗和预防医学病症和疾患的用途。

背景技术

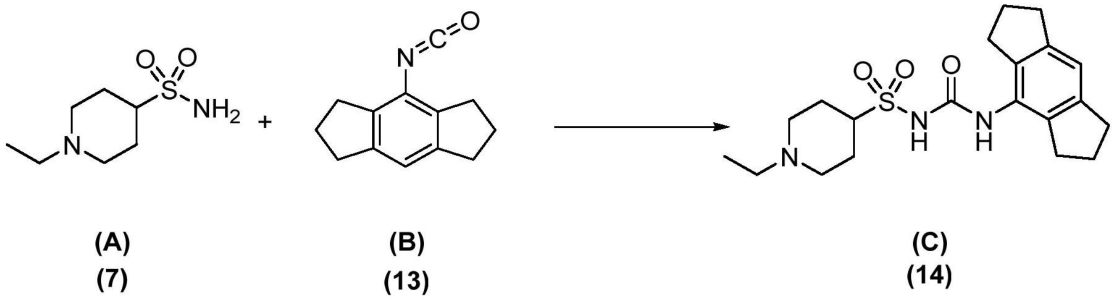
[0002] 1-乙基-N-((1,2,3,5,6,7-六氢-s-二环戊二烯并苯-4-基)氨基甲酰基)哌啶-4-磺酰胺在WO 2019/008025 A1中公开作为NLRP3抑制剂(参见实例6)。然而,需要提供用于制备1-乙基-N-((1,2,3,5,6,7-六氢-s-二环戊二烯并苯-4-基)氨基甲酰基)哌啶-4-磺酰胺及其盐的改善的方法。具体地,需要提供适用于大规模合成并且例如避免多个复杂且部分低产率的化学步骤以及整体原子低效合成的有效方法。

[0003] 还需要与现有技术方法相比以较高的产量提供,尤其是大规模地提供1-乙基-N-((1,2,3,5,6,7-六氢-s-二环戊二烯并苯-4-基)氨基甲酰基)哌啶-4-磺酰胺及其盐。此外,对于大规模工业化,更绿色的合成路线、减少溶剂浪费和改善安全性也值得关注。本发明解决了上述问题。此外,本发明可以以分批法或连续方法实施。

发明内容

[0004] 本发明提供了一种制备化合物(C)或其盐的方法,其包括在溶剂和碱的存在下使化合物(A)与化合物(B)接触以获得化合物(C)或其盐的步骤。

[0005]



[0006] 除非另有说明,否则对元素的任何引用均被视为对该元素的所有同位素的引用。因此,例如,除非另有说明,否则对氢的任何引用均被认为涵盖氢的所有同位素,包括氘和氚。

[0007] 除非另有说明,对化合物或基团的任何引用均被视为对该化合物或基团的所有互变异构体的引用。

[0008] 在本发明的一个实施例中,用于使化合物(A)与化合物(B)接触的溶剂选自甲苯、苯甲醚、环戊基甲基醚、乙苯、乙酸异丙酯、乙酸异丁酯、2-甲基四氢呋喃、水、叔丁醇、乙酸

乙酯、乙酸甲酯、二甲苯、四氢呋喃、二甲基亚砜、乙腈、叔丁基甲基醚、N-甲基吡咯烷、N-乙基吡咯烷酮、庚烷、环已烷、丙酮或其任意组合。

[0009] 在本发明的另一实施方案中,用于使化合物(A)与化合物(B)接触的溶剂选自甲苯、苯甲醚、乙苯和二甲苯。

[0010] 在本发明的另一实施方案中,用于使化合物(A)与化合物(B)接触的溶剂选自2-甲基四氢呋喃和四氢呋喃。

[0011] 在本发明的另一实施方案中,用于使化合物(A)与化合物(B)接触的溶剂是二甲基亚砜。

[0012] 在本发明的另一实施方案中,用于使化合物(A)与化合物(B)接触的溶剂为甲苯、或者甲苯与水、叔丁醇、四氢呋喃、二甲亚砜或乙腈的组合。

[0013] 在本发明的另一实施方案中,用于使化合物(A)与化合物(B)接触的溶剂是甲苯和四氢呋喃。

[0014] 在本发明的另一实施方案中,用于使化合物(A)与化合物(B)接触的碱选自叔丁醇钾、氢氧化钾或任何其他碱性钾盐。

[0015] 在本发明的另一实施方案中,用于使化合物(A)与化合物(B)接触的碱选自叔丁醇钾或氢氧化钾。

[0016] 在本发明的另一实施方案中,用于使化合物(A)与化合物(B)接触的碱是叔丁醇钾。

[0017] 本发明的一个实施方案提供了一种制备化合物(C)的盐、诸如阳离子盐的方法。典型地该盐是药用的。

[0018] 为了本发明的目的,1-乙基-N-((1,2,3,5,6,7-六氢-s-二环戊二烯并苯-4-基)氨基甲酰基)哌啶-4-磺酰胺的“阳离子盐”是化合物的质子酸官能团(诸如尿素质子)通过失去质子与合适的阳离子之间形成的盐。合适的阳离子包括但不限于锂、钠、钾、镁、钙和铵。该盐可为单盐、或二盐。优选地,该盐是单锂盐或二锂盐、钠盐、钾盐、镁盐、钙盐或铵盐。更优选地,该盐是单钠盐或二钠盐或者单钾盐或二钾盐。更优选地,该盐是单钾盐或二钾盐,还更优选地,该盐是单钾盐。

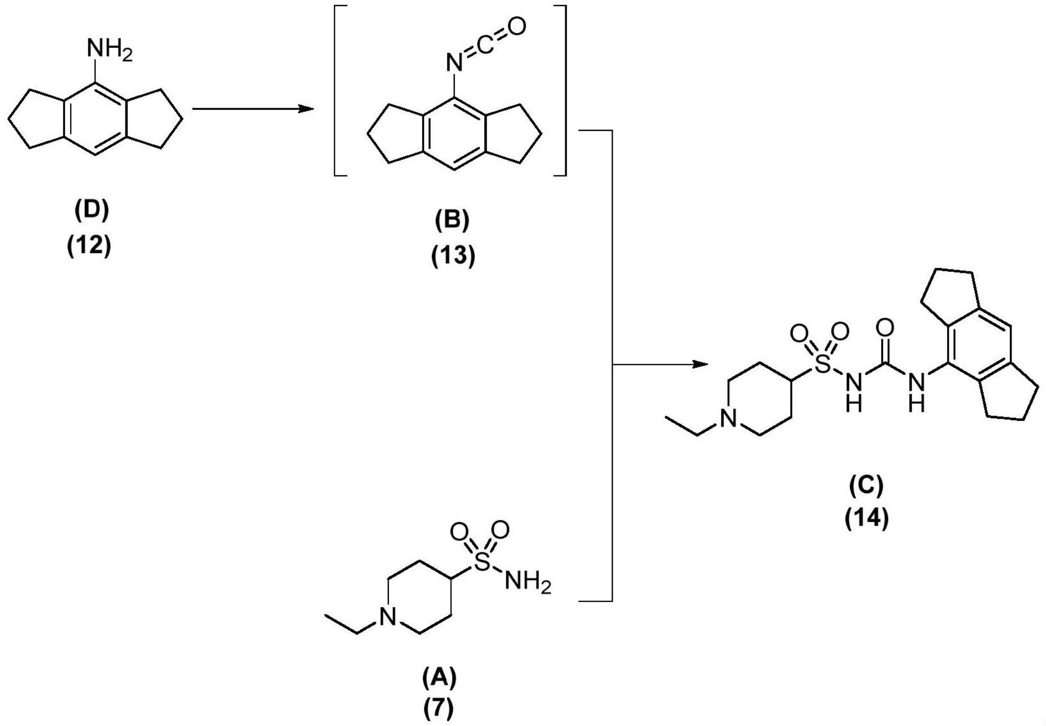
[0019] 有利地,其中需要1-乙基-N-((1,2,3,5,6,7-六氢-s-二环戊二烯并苯-4-基)氨基甲酰基)哌啶-4-磺酰胺(化合物(C))的阳离子盐时,盐的阳离子由碱的共轭酸提供。例如,本发明的第一方面的一个实施方案提供了一种制备1-乙基-N-((1,2,3,5,6,7-六氢-s-二环戊二烯并苯-4-基)氨基甲酰基)哌啶-4-磺酰胺(C)的碱金属盐或碱土金属盐的方法,该方法包括如下步骤:使1-乙基-4-哌啶磺酰胺(A)与1,2,3,5,6,7-六氢-s-二环戊二烯并苯衍生物(B)或(B’)在溶剂和碱金属醇盐或碱土金属醇盐的存在下接触,以获得1-乙基-N-((1,2,3,5,6,7-六氢-s-二环戊二烯并苯-4-基)-氨基甲酰基)-哌啶-4-磺酰胺的碱金属盐或碱土金属盐,其中盐的碱金属或碱土金属与醇盐的碱金属或碱土金属相同。典型地在此类实施方案中,碱金属醇盐或碱土金属醇盐是碱金属叔丁醇盐或碱土金属叔丁醇盐。

[0020] 在本发明的一个实施方案中,1-乙基-N-((1,2,3,5,6,7-六氢-s-二环戊二烯并苯-4-基)氨基甲酰基)哌啶-4-磺酰胺(C)的盐通过重结晶或再沉淀纯化。例如,可以将1-乙基-N-((1,2,3,5,6,7-六氢-s-二环戊二烯并苯-4-基)氨基甲酰基)哌啶-4-磺酰胺(C)的粗盐溶解在第一溶剂中以获得第一混合物,任选地可以过滤该混合物,并且1-乙基-N-((1,2,

3,5,6,7-六氢-s-二环戊二烯并苯-4-基)-氨基甲酰基)哌啶-4-磺酰胺(C)的盐可以通过添加第二溶剂、任选地在冷却下沉淀。典型地，第一溶剂是极性质子溶剂，诸如甲醇。典型地，第二溶剂是极性非质子溶剂，诸如乙腈。

[0021] 本发明的另一方面提供了一种制备化合物(C)或其盐的方法，其包括在溶剂和碱的存在下使化合物(A)与化合物(B)接触以获得化合物(C)或其盐的步骤，其中化合物(B)由化合物(D)获得：

[0022]



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[0023] 在本发明的一个实施方案中，使用反溶剂分离化合物(C)。

[0024] 在本发明的另一方面，使用反溶剂分离化合物(C)，其中反溶剂选自乙腈、任何醇或水。

[0025] 在本发明的一个实施方案中，使用洗涤溶剂分离化合物(C)。

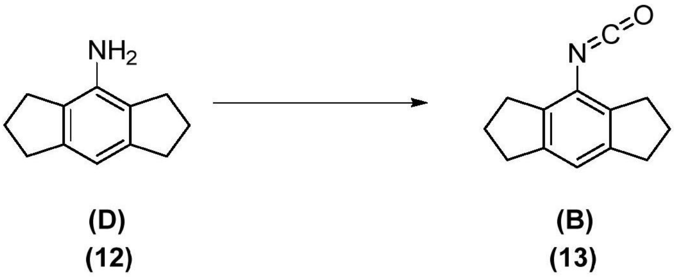
[0026] 在本发明的另一方面，使用洗涤溶剂分离化合物(C)，其中所述洗涤溶剂选自四氢呋喃、甲苯、二甲基亚砜或乙腈。

[0027] 本发明的第二方面提供了1-乙基-N-((1,2,3,5,6,7-六氢-s-二环戊二烯并苯-4-基)氨基甲酰基)哌啶-4-磺酰胺(化合物(C))或其盐，其通过本发明的第一方面的方法制备。

[0028] 在一个实施方案中，本发明的第二方面提供1-乙基-N-((1,2,3,5,6,7-六氢-s-二环戊二烯并苯-4-基)氨基甲酰基)-哌啶-4-磺酰胺的碱金属盐或碱土金属盐。典型地，本发明的第二方面提供1-乙基-N-((1,2,3,5,6,7-六氢-s-二环戊二烯并苯-4-基)氨基甲酰基)-哌啶-4-磺酰胺的钾盐。最典型地，本发明的第二方面提供1-乙基-N-((1,2,3,5,6,7-六氢-s-二环戊二烯并苯-4-基)氨基甲酰基)-哌啶-4-磺酰胺的单钾盐。

[0029] 在本发明的一个实施方案中，化合物(B)通过根据本发明的第三方面的方法制备。

[0030] 本发明的第三方面提供了一种制备化合物(B)的方法，该方法包括将化合物(D)转化为化合物(B)的步骤：

[0031] 

(D)
(12)　(B)
(13)　。

[0032]　因此,在本发明第三方面的一个实施方案中,提供了一种制备化合物(B)的方法,该方法包括在碱和溶剂的存在下,使用化合物(D)与光气、三光气、羰基二咪唑或二碳酸二叔丁酯的反应混合物,将化合物(D)转化为化合物(B)的步骤。

[0033]　在本发明的第三方面的另一实施方案中,该溶剂选自甲苯、苯甲醚、环戊基甲基醚、乙苯、乙酸异丙酯、乙酸异丁酯、2-甲基四氢呋喃、水、乙酸乙酯、乙酸甲酯、二甲苯、四氢呋喃或二甲基亚砜、乙腈、叔丁基甲基醚、二乙醚、二氯甲烷、1,2-二氯乙烷、氯仿、N-甲基吡咯烷、N-乙基吡咯烷酮、庚烷、环己烷或其任意组合,且该碱为叔胺,诸如N,N-二异丙基乙胺、三乙胺或三丁胺,或者该碱是无机碱,诸如碳酸钾、氢氧化钾或碳酸钠。

[0034]　在本发明的第三方面的另一实施方案中,该溶剂选自甲苯、或者甲苯与水、乙腈或四氢呋喃的组合,并且该碱选自N,N-二异丙基乙胺、三甲胺、三丁胺、碳酸钾、氢氧化钾或碳酸钠。

[0035]　在本发明的第三方面的另一实施方案中,该溶剂为甲苯和/或水,并且该碱为N,N-二异丙基乙胺、三甲胺或碳酸钾。

[0036]　在本发明的第三方面的另一实施方案中,该溶剂是甲苯并且该碱是N,N-二异丙基乙胺或碳酸钾。

[0037]　在本发明的第三方面的另一实施方案中,该溶剂是甲苯并且该碱是碳酸钾。

[0038]　在本发明的第三方面的另一实施方案中,该溶剂是甲苯并且该碱是N,N-二异丙基乙胺。

[0039]　甲苯和碳酸钾,或甲苯和N,N-二异丙基乙胺提供了优于使用THF(四氢呋喃)和TEA(三乙胺)的优势,如先前所用(EGGLER J F等人:Journal ofLabelled Compounds and Radiopharmaceuticals,第45卷,第9期,2002年,第785-794页,XP002264662),这是由于上述提出的方法因消除了蒸发或进行硅胶过滤的需要而涉及较少的后处理时间和能量。因此,这里的方法比先前报道的方法强度低。

[0040]　在本发明第三方面的另一实施方案中,提供了一种制备化合物(B)的方法,该方法包括将化合物(D)转化为化合物(B)的步骤,其中使用水溶液洗涤反应混合物以获得在有机溶剂中的化合物(B)。

[0041]　本发明的一个实施方案提供了一种获得化合物(C)的方法,其中化合物(B)是根据本发明的第三方面获得的。

[0042]　本发明的一个实施方案提供了根据本发明的第一方面获得化合物(C)的方法,其中化合物(B)是根据本发明的第三方面获得的。

[0043]　在本发明的一个实施方案中,化合物(B)是通过分批法或连续方式制备的。

[0044]　在本发明的一个实施方案中,化合物(B)是以连续方式制备的。

[0045]　在本发明的一个实施方案中,获得化合物(B)和化合物(C)的方法是经叠嵌的。

[0046] 本发明的第四方面提供了化合物(B)：

[0047] 

(B)
(13)

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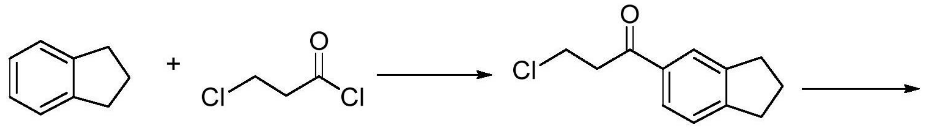
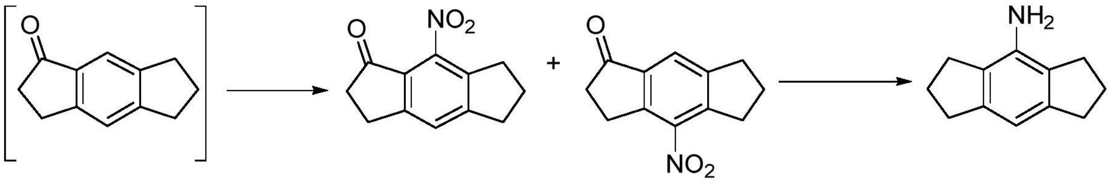
[0048] 在本发明的第三方面的一个实施方案中,化合物(D)由包括以下步骤的方法制备：



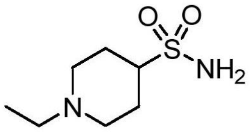
(8) **(9)**

[0049] 

(10) **(11a)** **(11b)** **(D)**
(12)

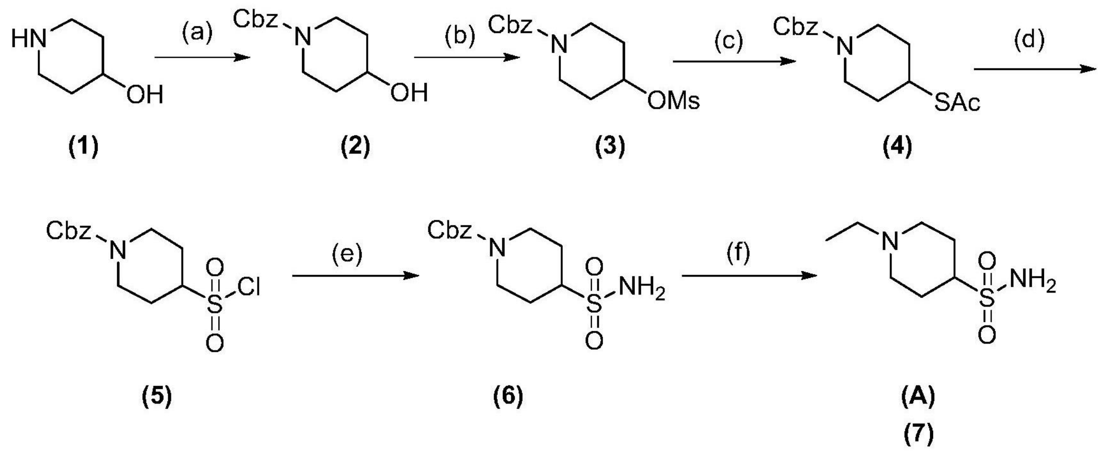
[0050] 用于制备化合物(D)的方法可如WO 2020/079207 A1中所述,其内容通过引用整体并入本文。

[0051] 在一个实施方案中,本发明的第五方面的方法是用于制备化合物(A)或其盐的方法：

[0052] 

(A)
(7)

[0053] 本发明的第五方面提供了一种制备化合物(A)的方法,该化合物通过包括以下步骤的方法制备：

[0054] 

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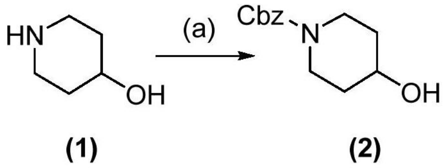
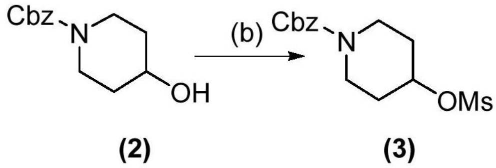
[0055] 其中Cbz为羧基苄基/苄氧基羰基，OMs为甲烷磺酸根，并且SAc为乙酰基硫基。

[0056] 在本发明的第五方面的示例性实施方案中，反应步骤(a)包括使化合物(1)与氯甲酸苄酯接触以获得N-羧基苄基-4-羟基哌啶化合物(2)：

[0057] 

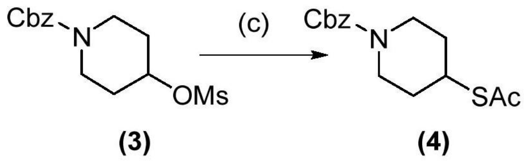
[0058] 典型地在此类实施方案中，化合物(1)在碱和溶剂的存在下与氯甲酸苄酯接触。

[0059] 在本发明的第五方面的示例性实施方案中，反应步骤(b)包括使化合物(2)与甲磺酰氯接触以获得化合物(3)：

[0060] 

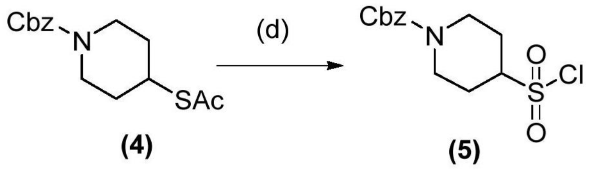
[0061] 典型地在此类实施方案中，化合物(2)在叔胺碱(诸如三乙胺)和极性非质子溶剂(诸如二氯甲烷)的存在下与甲磺酰氯接触。

[0062] 在本发明的第五方面的示例性实施方案中，反应步骤(c)包括使化合物(3)与$MeCOS^-$在溶剂中接触以获得化合物(4)：

[0063] 

[0064] 典型地在此类实施方案中，$MeCOS^-$通过MeCOSH与碱(诸如碳酸铯)的反应原位产生。典型地在此类实施方案中，溶剂是N,N-二甲基甲酰胺。

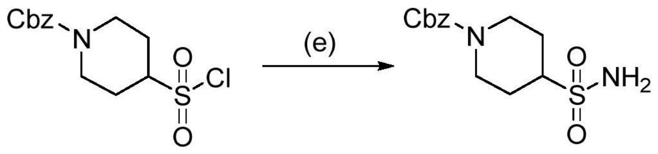
[0065] 在本发明的第五方面的示例性实施方案中，反应步骤(d)包括使化合物(4)与氯化剂接触以获得化合物(5)：

[0066] 

[0067]　典型地在此类实施方案中,氯化剂是N-氯代琥珀酰亚胺。典型地在此类实施方案中,化合物(4)在乙酸和水的存在下与氯化剂接触。

[0068]　在本发明的第五方面的示例性实施方案中,反应步骤(e)包括使化合物(5)与氨接触以获得化合物(6):

[0069]

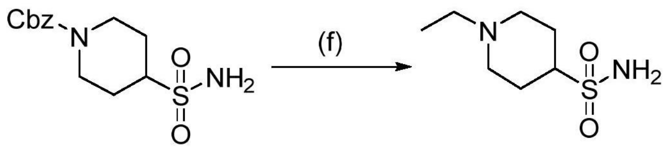


(5)　　　　(6)

[0070]　典型地在此类实施方案中,化合物(5)在极性非质子溶剂(诸如二氯甲烷)的存在下与氨接触。

[0071]　在本发明的第五方面的示例性实施方案中,反应步骤(f)包括在催化剂和氢气的存在下使化合物(6)与乙腈或乙醛接触,以获得化合物(A):

[0072]

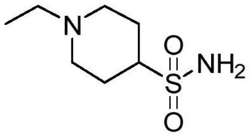


(6)　　　　(A)
(7)

[0073]　典型地在此类实施方案中,化合物(6)在催化剂和氢气的存在下与乙腈接触。典型地,催化剂是钯催化剂,诸如碳载氢氧化钯。

[0074]　在本发明的第五方面的一个具体实施方案中,提供了一种制备化合物(A)或其盐的方法:

[0075]

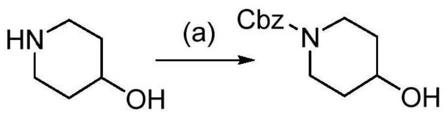


(A)
(7)

[0076]　包括以下步骤:

[0077]　(a)将化合物(1)转化为化合物(2):

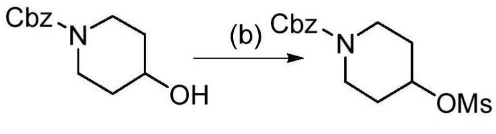
[0078]



(1)　　　　(2)

[0079]　(b)将化合物(2)转化为化合物(3):

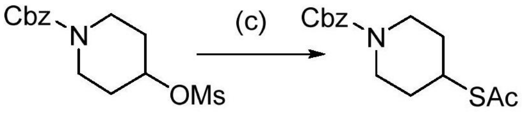
[0080]



(2)　　　　(3)

[0081]　(c)将化合物(3)转化为化合物(4)：

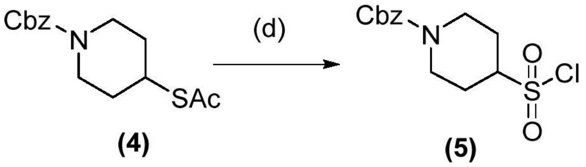
[0082]



(3)　**(4)**

[0083]　(d)将化合物(4)转化为化合物(5)：

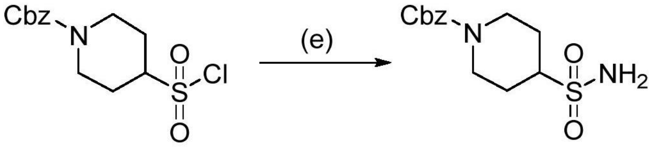
[0084]



(4)　**(5)**

[0085]　(e)将化合物(5)转化为化合物(6)

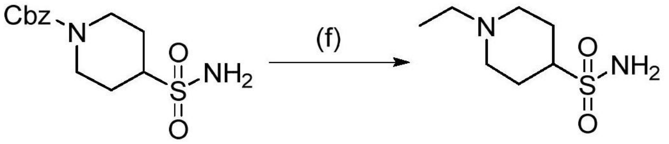
[0086]



(5)　**(6)**

[0087]　(f)以及，将化合物(6)转化为化合物(A)：

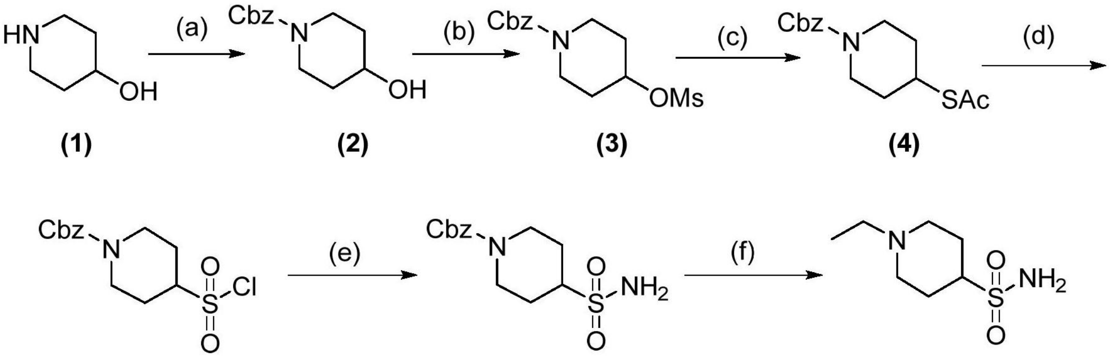
[0088]



(6)　**(A)**
(7)

[0089]　在本发明的第五方面的一个具体实施方案中，提供了一种制备化合物(A)或其盐的方法，其经由以下步骤进行：

[0090]



(1)　**(2)**　**(3)**　**(4)**

(5)　**(6)**　**(A)**
(7)

[0091]　其中Cbz为羧基苄基/苄氧基羰基，OMs为甲烷磺酸根，并且SAc为乙酰基硫基。

[0092]　本发明的一实施方案提供了一种获得化合物(C)的方法，其中化合物(A)是根据本发明的第五方面获得的。

[0093]　本发明中使用和提供的化合物既能以其游离碱形式使用，又能以其酸加成盐形式使用。为了本发明的目的，本发明的化合物的“盐”包括酸加成盐。酸加成盐优选地是与合适

的酸的、药用的、无毒的加成盐，所述酸包括但不限于：无机酸诸如氢卤酸（例如，氢氟酸、氢氯酸、氢溴酸或氢碘酸）或其他无机酸（例如，硝酸、高氯酸、硫酸或磷酸）；或者有机酸诸如有机羧酸（例如，丙酸、丁酸、乙醇酸、乳酸、扁桃酸、柠檬酸、乙酸、苯甲酸、水杨酸、琥珀酸、苹果酸或羟基丁二酸、酒石酸、富马酸、马来酸、羟基马来酸、粘酸或半乳糖二酸、葡萄糖酸，泛酸或双羟萘酸）、有机磺酸（例如，甲磺酸、三氟甲磺酸、乙磺酸、2-羟基乙磺酸、苯磺酸、对甲苯磺酸、2-萘磺酸或樟脑磺酸）或氨基酸（例如，鸟氨酸、谷氨酸或天冬氨酸）。酸加成盐可为单酸加成盐、二酸加成盐、三酸加成盐或多酸加成盐。优选的盐是盐酸加成盐、硫酸加成盐、磷酸加成盐或有机酸加成盐。优选的盐是氢氯酸加成盐。

[0094] 当本发明的化合物包含季铵基团时，典型地该化合物以其盐形式使用。季铵基团的抗衡离子可为任何药用的、无毒的抗衡离子。合适的抗衡离子的实例包括上面关于酸加成盐讨论的质子酸的共轭碱。

[0095] 本发明中使用和提供的化合物也可以以其游离酸形式和盐形式使用。为了本发明的目的，本发明的化合物的“盐”包括在本发明的化合物的质子酸官能团（诸如甲酸基团或脲基团）与合适的阳离子之间形成的盐。合适的阳离子包括但不限于锂、钠、钾、镁、钙和铵。该盐可为单盐、二盐、三盐或多盐。优选地，该盐是单锂盐或二锂盐、钠盐、钾盐、镁盐、钙盐或铵盐。更优选地，该盐是单钠盐或二钠盐或者单钾盐或二钾盐。

[0096] 优选地，任何盐是药用的无毒盐。然而，除了药用盐之外，其他盐也包括在本发明中，因为它们有可能充当纯化或制备其他例如药用盐的中间体，或者用于鉴定、表征或纯化游离酸或碱。

[0097] 本发明中使用和提供的化合物和/或盐可为无水的或水合物（例如半水合物、一水合物、二水合物或三水合物）或其他溶剂化物的形式。此类其他溶剂化物可以用常见的有机溶剂形成，包括但不限于醇溶剂，例如甲醇、乙醇或异丙醇。

[0098] 本发明中使用且提供的化合物、盐和溶剂化物可含有任何稳定的同位素，包括但不限于^{12}C、^{13}C、^{1}H、^{2}H(D)、^{14}N、^{15}N、^{16}O、^{17}O、^{18}O、^{19}F以及^{127}I；以及任何放射性同位素，包括但不限于^{11}C、^{14}C、^{3}H(T)、^{13}N、^{15}O、^{18}F、^{123}I、^{124}I、^{125}I以及^{131}I。

[0099] 除非另有说明，本发明中使用和提供的化合物、盐和溶剂化物可为任何多晶型或无定形形式。

[0100] 本发明的第六方面提供了一种药物组合物，其包含本发明的第一方面的化合物(C)以及药用赋形剂。

[0101] 用于选择和制备合适的药物制剂的常规程序描述于例如，“Aulton’sPharmaceutics-The Design and Manufacture of Medicines”，M.E.Aulton和K.M.G.Taylor，Churchill Livingstone Elsevier，第4版，2013年。可以用于本发明的药物组合物中的药用赋形剂，包括佐剂、稀释剂或载体，是药物制剂的领域中常规采用的那些。

[0102] 本发明的第七方面提供本发明的第二方面的化合物(C)或其盐，或者本发明的第六方面的药物组合物，其用于药物中，和/或用于治疗或预防疾病、疾患或病症。

[0103] 最特别地，当化合物(C)用于治疗或预防疾病、疾患和病症时，化合物(C)充当NLRP3抑制剂。

[0104] 在一个实施方案中，待治疗或预防的疾病、紊乱或病症选自以下：

[0105] (i)炎症；

[0106] (ii)自身免疫性疾病;

[0107] (iii)癌症;

[0108] (iv)感染;

[0109] (v)中枢神经系统疾病;

[0110] (vi)代谢疾病;

[0111] (vii)心血管疾病;

[0112] (viii)呼吸道疾病;

[0113] (ix)肝脏疾病;

[0114] (x)肾脏疾病;

[0115] (xi)眼部疾病;

[0116] (xii)皮肤疾病;

[0117] (xiii)淋巴病症;

[0118] (xiv)心理紊乱;

[0119] (xv)疼痛;以及

[0120] (xvi)已确定个体携带NLRP3中种系或体细胞非沉默突变的任何疾病。

[0121] 通常,疾病、疾患或病症的治疗或预防包括向受试者施用本发明的第二方面的化合物(C)或其盐、或本发明的第六方面的药物组合物。

[0122] 本发明中采用的任何药物可以通过口服、胃肠外(包括静脉内、皮下、肌内、皮内、气管内、腹膜内、关节内、颅内和硬膜外)、气道(气雾剂)、直肠、阴道或局部(包括经皮、口腔、粘膜和舌下)施用。

[0123] 典型地,所选择的施用的模式是最适合待治疗或预防的紊乱、疾病或病症的模式。

[0124] 本发明的第八方面提供了一种抑制NLRP3的方法,该方法包括使用本发明的第二方面的化合物(C)或其盐、或本发明的第六方面的药物组合物以抑制NLRP3。

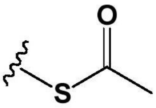
[0125] 为了避免疑问,在可行的范围内,本发明的给定方面的任何实施方案可以与本发明的相同方面的任何其他实施方案组合出现。另外,在可行的范围内,应当理解,本发明的任何方面的任何优选的、典型的或可选的实施方案也应当被认为是本发明的任何其他方面的优选的、典型的或可选的实施方案。

[0126] 实例

[0127] 除非另有说明,所有溶剂、试剂和化合物均购买并使用而无需进一步纯化。

[0128] 缩写

[0129] Cbz:羧基苄基/苄氧羰基

[0130] SAc:乙酰硫基 

[0131] GC:气相色谱法

[0132] HPLC:高效液相色谱法

[0133] THF:四氢呋喃

[0134] MTBE:甲基叔二丁醚

[0135] DCM:二氯甲烷

[0136] DMF：二甲基甲酰胺

[0137] TEA：三乙胺

[0138] HDPE：高密度聚乙烯

[0139] NMT：不多于

[0140] Vol：体积

[0141] AKX试剂：AQUAMICRON®AKX

[0142] %a/a:(化合物(a)的峰下面积/化合物(a)和所有其他组分的组合的峰下面积)x100

[0143] 实验方法

[0144] NMR方法:

[0145] NMR谱在于室温(25℃)操作的Bruker AV 400MHz光谱仪(型号:Advance IIID)上获得。

[0146] GC方法:

[0147] GC分析在以下机器中的一者上进行:配备ALS进样器的Agilent7890、6890或Agilent 6890N。

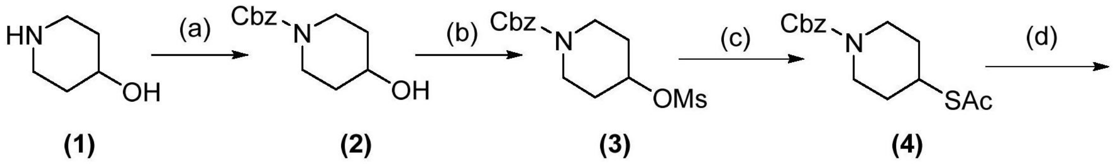
[0148] KF方法:

[0149] 使用AKX试剂在Mitsubishi CA-20或Predicta OM1000上进行库仑KF(卡尔费休)滴定。

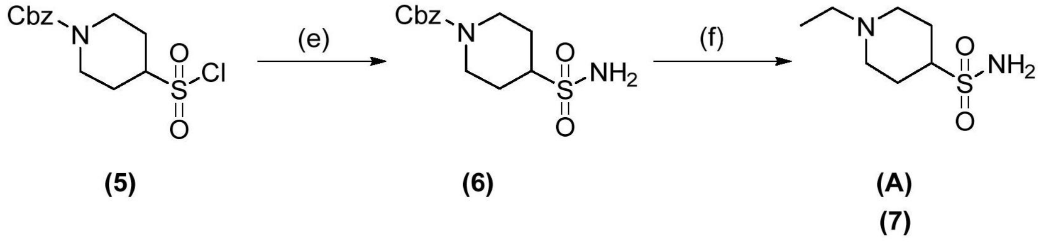
[0150] 合成实例

[0151] <u>1-乙基-4-哌啶磺酰胺(7)</u>

[0152] 根据反应方案1所示的反应顺序制备1-乙基-4-哌啶磺酰胺(7)。



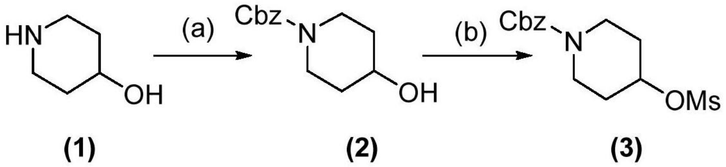
[0153]



[0154] 方案1.1-乙基-4-哌啶磺酰胺(7)合成

[0155] 反应方案1-步骤(a)和(b)

[0156]



[0157] 将4-羟基哌啶(1)(46.0Kg)在25至30℃下装入至反应器中。将1,4-二噁烷(226.0L)在25至30℃下装入至反应器中。将反应混合物搅拌5-10分钟,并且然后冷却至15

至20℃。将2N NaOH溶液(通过在25至30℃下在单独的反应器中将NaOH(18.4Kg)与冷纯化水(230.0L)混合来制备)在15至25℃下缓慢装入至反应混合物。将反应混合物搅拌5-10分钟。将50％氯甲酸苄酯的甲苯溶液(147.2L)历经1-2小时缓慢添加至反应混合物。将温度升高至25至30℃并且搅拌1-2小时。

[0158] 将纯化水(230.0L)加入至反应混合物并且将反应混合物在25至30℃下搅拌10-15min。将MTBE(230.0L)在30至35℃下装入反应器中。将反应混合物在25至30℃下搅拌15-20分钟,并且然后静置20-30分钟。将有机层(OL-1)和水层(AL-1)分离到不同的容器中并且将AL-1装回到反应器中。将MTBE(230.0L)在25至30℃下装入至反应器中。将反应混合物在25至30℃下搅拌15-20分钟,并且然后静置20-30分钟。将有机层(OL-2)和水层(AL-2)分离到不同的容器中。将OL-1和OL-2组合并且在25至30℃下装入至反应器中。将纯化水(138.0L)在25至30℃下装入至反应器中。将反应混合物在25至30℃下搅拌15-20分钟,并且然后静置20-30分钟。将水层(AL-3)从有机层(OL-3)分离。

[0159] 将10％ NaCl溶液(通过在反应器中将NaCl(13.80Kg)在25至30℃下搅拌添加至纯化水(138.0L)中来制备)在25至30℃下装入至OL-3中。将反应混合物在25至30℃下搅拌15-20分钟,并且然后静置20-30分钟。将有机层(OL-4)和水层(AL-4)分离到不同的容器中。用硫酸钠(23.0Kg)干燥OL-4。通过布氏漏斗过滤OL-4并且用MTBE(46.0L)洗涤。OL-4在真空(650mmHg)下的40至45℃下向下蒸馏至46-92L。释放真空并且将DCM(138.0L)装入至混合物,并且将混合物在真空下的35至40℃下共蒸馏至46-92L。将混合物冷却至25至30℃并且释放真空。将DCM(552.0L)在25至30℃下装入至混合物并且将混合物搅拌5-10分钟。将反应混合物冷却至20至25℃。在20至25℃下加入TEA(127.8L)。将反应混合物冷却至-5至5℃。

[0160] 在-5至5℃下历经1-2小时缓慢装入甲磺酰氯(67.62Kg)。将反应混合物升高至25至30℃并且在25至30℃下搅拌1-2小时。

[0161] 过滤出不需要的盐,在25至30℃下用DCM(92.0L)洗涤并且在25至30℃下的真空下完全吸干。在25至30℃下将滤液装入至反应器中。将10％碳酸氢钠溶液(通过将碳酸氢钠(23.0Kg)在25至30℃下添加至纯化水(230.0L)来制备)在25至30℃下装入至滤液。将反应混合物在25至30℃下搅拌15-20分钟,并且然后静置20-30分钟。将有机层(OL-5)和水层(AL-5)分离到不同的容器中并且在25至30℃下将OL-5装回至反应器中。

[0162] 将纯化水(230.0L)在25至30℃下装入至反应器中。将反应混合物在25至30℃下搅拌15-20分钟,并且然后静置20-30分钟。将有机层(OL-6)和水层(AL-6)分离到不同的容器中并且在25至30℃下将OL-6装回至反应器中。将10％氯化钠溶液(通过将氯化钠(11.50Kg)在25至30℃下加入至纯化水(230.0L)来制备)在25至30℃下装入至反应器。将反应混合物在25至30℃下搅拌15-20分钟,并且然后静置20-30分钟。

[0163] 将有机层(OL-7)和水层(AL-7)分离到不同的容器中。用硫酸钠(23.0Kg)干燥OL-7。通过布氏漏斗过滤OL-7并且用DCM(46.0L)洗涤。OL-7在真空(650mmHg)下的40至45℃下向下蒸馏至46-92L。释放真空并且将乙酸乙酯(92.0L)装入至混合物,并且将混合物在真空下的40至45℃下共蒸馏至46-92L。将混合物冷却至30至40℃并且释放真空。将乙酸乙酯(115.0L)在30至40℃下装入至混合物,并且将混合物在30至35℃下搅拌10-15分钟。在30至35℃下将己烷(1150.0L)缓慢装入至混合物,并且将混合物在25至30℃下搅拌2-3小时。将固体在真空下在吸滤器上过滤,在25至30℃下用己烷(92.0L)洗涤并且在25至30℃下在真

空下完全吸干。将固体材料在真空烘箱中在30至35℃下干燥6-8小时,每3-4小时将材料粉碎一次。

[0164] 最终产物:4-((甲基磺酰基)氧基)哌啶-1-甲酸苄酯

[0165] 灰白色(固体)

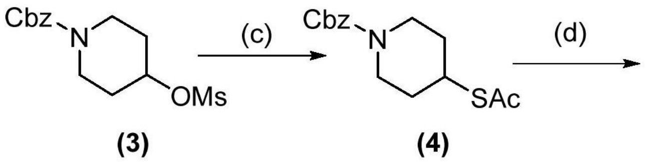
[0166] 输出:121.87Kg

[0167] 收率:85.5%

[0168] HPLC纯度:94.7%

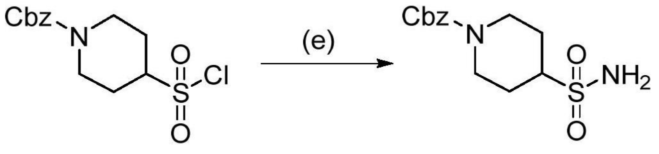
[0169] ^{1}H NMR:(CDCl$_3$ 400MHz):δ1.82-1.86(m,2H),δ1.96-1.97(m,2H),δ3.03(s,3H),δ3.41-3.45(m,2H)δ3.72-3.78(m,2H),δ4.88-4.92(m,1H)δ5.13(s,2H),δ7.26-7.37(m,5H)

[0170] 反应方案1-步骤(c、d、e)



(3) (4)

[0171]



(5) (6)

[0172] 将DMF在氮气气氛下装入至清洁且干燥的四颈反应器(配备有机械搅拌器、氮气入口、热袋和回流冷凝器)中,并且在60至65℃下加热至回流20-30min。将温度降低至25至30℃,卸载回流的DMF并将反应器在氮气和真空下干燥。

[0173] 将4-((甲基磺酰基)氧基)哌啶-1-甲酸苄酯(3)(29.0Kg)在25至30℃下装入至反应器。将DMF(145.0L)在25至30℃下装入至反应器。将反应混合物搅拌5-10分钟,冷却至15至20℃,并且然后静置20-30分钟。

[0174] 将44.95Kg碳酸铯在15至25℃下装入至反应器。将反应混合物搅拌5-10分钟。在15至25℃下装入10.56Kg硫代乙酸。将反应混合物升温至45至50℃并搅拌24小时。

[0175] 将反应混合物冷却至25至30℃。在25至30℃下真空下通过布氏漏斗过滤不需要的盐,用乙酸乙酯(145.0L)洗涤并且在25至30℃下真空下完全吸干。将滤液在25至30℃下装回至反应器并且冷却至15至20℃。将纯化水(145.0L)在15-25℃下装入至反应器并且将反应混合物搅拌5-10分钟。将乙酸乙酯(145.0L)在25至30℃下装入至反应器。将反应混合物在25至30℃下搅拌15-20分钟并且静置20-30分钟。

[0176] 将有机层(OL-1)和水层(AL-1)分离到不同的容器中。将AL-1在25至30℃下装入至反应器中。在25至30℃下装入乙酸乙酯(145.0L)。将反应混合物在25至30℃搅拌15-20分钟并且静置20-30分钟。

[0177] 将有机层(OL-2)和水层(AL-2)分离到不同的容器中。将OL-1和OL-2组合并且在25至30℃下装入至反应器中。

[0178] 将10% NaHCO$_3$溶液(通过将碳酸氢钠(14.50Kg)在25至30℃下装入至纯化水

(145.0L)并且充分搅拌混合来制备)在25至30℃下装入至反应器。将反应混合物在25至30℃下搅拌15-20分钟并且静置20-30分钟。

[0179] 将有机层(OL-3)和水层(AL-3)分离到不同的容器中。将OL-3在25至30℃下装入至反应器中。将10% NaCl溶液(通过将NaCl(14.50Kg)在25至30℃下加入至纯化水(145L)并且充分搅拌混合来制备)在25至30℃下装入至反应器。将反应混合物在25至30℃下搅拌15-20分钟并且静置20-30分钟。

[0180] 将有机层(OL-4)和水层(AL-4)分离到不同的容器中。将OL-4用硫酸钠(14.50Kg)干燥,通过布氏漏斗过滤并且用乙酸乙酯(29.0L)洗涤。将滤液在反应器中完全蒸馏,直到在真空(650mmHg)下在45至50℃下没有滴落。释放真空并将混合物冷却至25至30℃。

[0181] 将乙酸(377.0L)在25至30℃下装入至反应器。将反应混合物在25至30℃下搅拌5-10分钟。在25至30℃下装入纯化水(37.7L)。将反应混合物在25至30℃下搅拌5-10分钟,并且然后冷却至17至25℃。在18至25℃下经1-2小时缓慢分批加入N-氯代琥珀酰亚胺(33.64Kg)。将反应混合物在25至30℃下搅拌1小时。

[0182] 将反应混合物冷却至15至20℃。将纯化水(377.0L)在15至20℃下加入至反应混合物,并且将反应混合物在25至30℃下搅拌5-10分钟。将DCM(145.0L)在25至30℃下装入至反应器。将反应混合物在25至30℃下搅拌10-15分钟并且静置20-30分钟。将有机层(OL-5)和水层(AL-5)分离到不同的容器中。将AL-5装入至反应器。将DCM(145.0L)在25至30℃下装入至反应器。将反应混合物在25至30℃下搅拌10-15分钟并且静置20-30分钟。

[0183] 将有机层(OL-6)和水层(AL-6)分离到不同的容器中。将OL-5和OL-6组合并且在25至30℃下装入至反应器中。将纯化水(145.0L)在25至30℃下装入至反应器。将反应混合物在25至30℃下搅拌5-10分钟并且静置25-30分钟。

[0184] 将有机层(OL-7)和水层(AL-7)分离到不同的容器中。将OL-7装入至反应器。将2%碳酸氢钠溶液(通过添加碳酸氢钠(8.70Kg)和纯化水(435.0L)并且分成等体积的三份来制备)的第一部分在25至30℃下装入至反应器。将反应混合物在25至30℃下搅拌5-10分钟并且静置25-30分钟。

[0185] 将有机层(OL-8)和水层(AL-8)分离到不同的容器中。将OL-8装入至反应器。将上述2%碳酸氢钠溶液的第二部分在25至30℃下装入至反应器。将反应混合物在25至30℃下搅拌5-10分钟并且静置25-30分钟。

[0186] 将有机层(OL-9)和水层(AL-9)分离到不同的容器中。将OL-9装入至反应器。将上述2%碳酸氢钠溶液的第三部分在25至30℃下装入至反应器。将反应混合物在25至30℃下搅拌5-10分钟并且静置25-30分钟。

[0187] 将有机层(OL-10)和水层(AL-10)分离到不同的容器中。将OL-10用硫酸钠(14.50Kg)干燥,在25至30℃下过滤,并且用DCM(29.0L)洗涤。将滤液在25至30℃下装入至反应器。

[0188] 将反应混合物冷却至-40至-30℃并且用氨气吹扫2-3小时。将温度升高至25至30℃并且在25至30℃下搅拌10-12小时。

[0189] 在25至30℃下在真空下过滤不需要的盐,用DCM(14.50L)洗涤并且完全吸干。将滤液在25至30℃下装入至干净并且干燥的反应器中并且用硫酸钠(14.50Kg)干燥。将混合物在25至30℃下过滤并且用DCM(14.50L)洗涤硫酸钠。将混合物通过0.2微米滤筒装入干净并

且干燥的反应器中,并且在35至40℃下在真空下向下蒸馏至29-58L。

[0190] 释放真空并且将反应混合物冷却至25至30℃。将乙酸乙酯(58.0L)在25至30℃下装入至反应器,并且将混合物在35至40℃下在真空下向下蒸馏至29-58L。释放真空并且将反应混合物冷却至25至30℃。将乙酸乙酯(72.5L)在25至30℃下装入至反应器并且将混合物在25至30℃下搅拌30min。将己烷(36.25L)在25至30℃下装入至反应器,并且将混合物在25至30℃下搅拌1-2小时。在25至30℃下在真空下过滤固体,用己烷(58.0L)洗涤并且完全吸干。

[0191] 输出:11.0Kg

[0192] 收率:39.85%

[0193] HPLC纯度:90.5%

[0194] 纯化

[0195] 将湿材料(6)(53.95Kg)在25至30℃下装入至干净并且干燥的反应器中。在25至30℃下装入DCM(580L)并且将混合物在25至30℃下搅拌5-10分钟。在25至30℃下装入甲醇(25.0L)并且将混合物在25至30℃下搅拌5-10分钟。在25至30℃下装入中性氧化铝(174.0Kg)并且将混合物在25至30℃下搅拌1小时。在25至30℃下过滤中性氧化铝。用DCM(150.0L)洗涤盐。将滤液在25至30℃下装入至干净并且干燥的反应器中。在25至30℃下装入己烷(1050L)并且将混合物在25至30℃下搅拌1-2小时。在25至30℃下在真空下过滤沉淀物,用己烷(116.0L)洗涤并且完全吸干。将湿材料在30至35℃下在真空下干燥6-8小时,每3小时粉碎一次。

[0196] 最终产物:1-(苄基氧基羰基)-4-哌啶磺酰胺

[0197] 白色(固体粉末)

[0198] 输出:41.60Kg

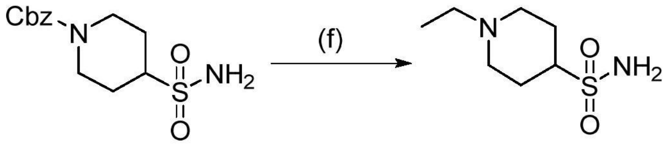
[0199] 收率:41.80%

[0200] HPLC纯度:96.1%

[0201] ^{1}H NMR:(DMSO 400MHz):δ1.41-1.51(m,2H),δ1.99-2.01(m,2H),δ2.50-286(m,2H),δ3.022-3.05(m,1H)δ4.08-4.11(m,2H),δ5.75(s,2H)δ6.78(s,2H),δ7.40-7.30(m,5H)

[0202] 反应方案1步骤(f)

[0203]



(6)　　(A)
(7)

[0204] 将1-(苄基氧基羰基)-4-哌啶磺酰胺(6)(21.85Kg)装入至容器,然后用氮气吹扫。将乙腈(不含丙腈)(109.8Kg)和纯化水(65.0L)装入至容器并且将温度调节至15至25℃。在15至25℃下对容器进行真空/氮气吹扫三次,并且然后装入有碳载氢氧化钯(20wt%;50%水)(0.455Kg)。在15至25℃下对容器进行真空/氮气吹扫三次。在15至25℃下对容器进行真空/氢气吹扫三次并且保持在氢气气氛下(约1巴绝对压力)。搅拌反应混合物直至完全。

[0205] 在15至25℃下对容器进行真空/氮气吹扫三次,并且然后在15至25℃下装入有碳载氢氧化钯(20wt%;50%水)(2.265Kg)。在15至25℃下对容器进行真空/氮气吹扫三次。在

15至25℃下对容器进行真空/氢气吹扫三次并且保持在氢气气氛下(约1巴绝对压力)。将反应混合物在15至25℃下搅拌直至完全。

[0206] 在15至25℃下搅拌反应混合物直至完全。

[0207] 一旦GC确认反应完成,就用氮气吹扫容器,并且在15至25℃下通过1μm过滤器过滤反应混合物以去除催化剂。将滤饼用预混合的纯化水和乙腈在15至25℃下洗涤两次。

[0208] 滤液装入有脱色炭(活化的)(4.40Kg)并且在15至25℃下搅拌至少60分钟(目标60至120分钟)。在15至25℃下将混合物通过1μm过滤器过滤以去除木炭。将滤饼用预混合的纯化水和乙腈在15至25℃下洗涤两次。滤液装入有SiliaMetS硫醇40-63μm 60Å(4.515Kg)并且在15至25℃下搅拌至少60分钟(目标60至120分钟)。在15至25℃下将混合物通过0.6μm过滤器过滤以去除SiliaMetS硫醇。将滤饼用预混合的纯化水和乙腈在15至25℃下洗涤两次。

[0209] 将滤液装入至容器并且调节至50至60℃,在50至60℃下减压浓缩至约110L。在50至60℃下装入正丁醇(89.8Kg)并且将混合物在50至60℃下减压浓缩至约110L。在50至60℃下装入正丁醇(86.9Kg)并且将混合物在50至60℃下减压浓缩至约110L。在50至60℃下装入正丁醇(88.4Kg)并且将混合物在50至60℃下减压浓缩至约90L。

[0210] 将温度调节至15至25℃并且在15至25℃下装入乙酸乙酯(98.6Kg)。历经至少60分钟(目标60至120分钟)将反应混合物冷却至-2至+2℃。将混合物在-2至2℃下搅拌至少4小时(目标4至6小时)。在-2至2℃下将固体在20μm滤布上过滤并且在-2至2℃下用乙酸乙酯(38.1Kg和39.9Kg)洗涤两次。

[0211] 将固体在氮气流下在高达60℃下干燥直至正丁醇含量≤0.5%w/w并且乙酸乙酯含量≤0.5%w/w(通过^{1}H NMR光谱测量)。使用1H NMR光谱测量并且分析固体1-乙基-4-哌啶磺酰胺(7)的干燥重量。

[0212] 最终产物:1-乙基-4-哌啶磺酰胺

[0213] 输出:12.00Kg

[0214] 收率:85%

[0215] GC纯度:99.7%

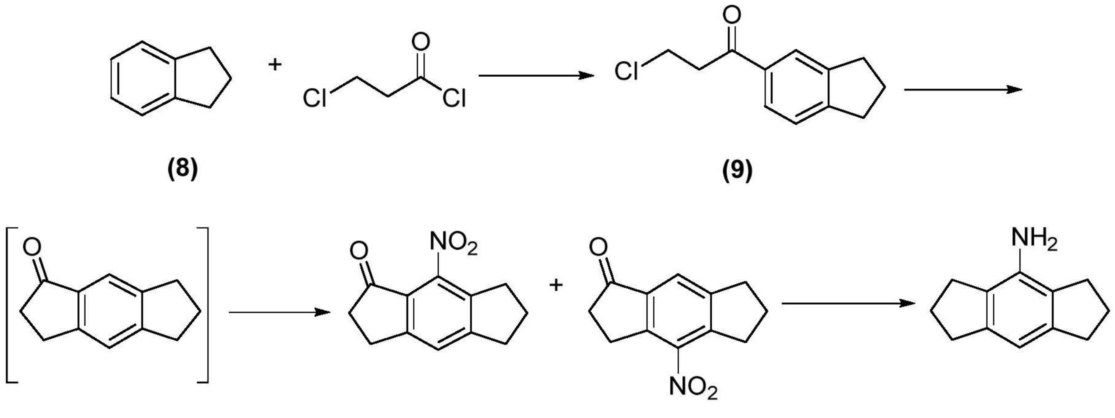
[0216] NMR纯度:98.7%

[0217] ^{1}H NMR:(DMSO)0.95(t),1.55(dq),1.80(app t),1.95(app d),2.30(q),2.75(m),2.90(app d)

[0218] 1,2,3,5,6,7-六氢-s-二环戊二烯并苯-4-胺(12)

[0219] 根据反应方案2所示的反应顺序制备1,2,3,5,6,7-六氢-s-二环戊二烯并苯-4-胺(12)。

[0220]



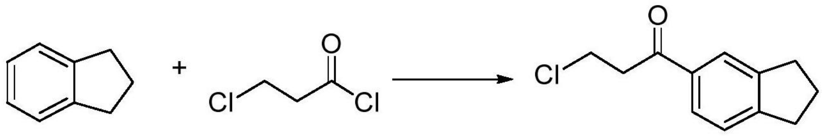
(8)　(9)

(10)　(11a)　(11b)　(D) (12)

[0221]　方案2.1,2,3,5,6,7-六氢-s-二环戊二烯并苯-4-胺(12)的合成

[0222]　反应方案2-步骤(a)

[0223]



(8)　(9)

[0224]　将DCM(385L)和AlCl$_3$(99.86Kg)在25至30℃下在氮气气氛下装入至反应器、即干净并且干燥的搪玻璃反应器中。将反应混合物冷却至-10℃。

[0225]　在-10至-5℃下在氮气气氛下缓慢加入3-氯丙酰氯(90.99Kg)。将反应混合物在氮气气氛下在10℃下保持30分钟。然后在氮气气氛下在-10至-5℃下将2,3-二氢-1H-茚(8)(77.00Kg)缓慢加入至反应混合物。

[0226]　将反应混合物在10至15℃下保持2小时。

[0227]　反应完成后,将反应混合物在0至10℃下缓慢加入至6N氢氯酸溶液(由水(308L)和浓氢氯酸(308L)制备)中。加入DCM(231L)并且将反应混合物温度升高至30至35℃。将反应混合物在30至35℃下搅拌30分钟并且使其在30至35℃下静置30分钟。分离各层并且将有机层(OL-1)放在一边。在25至30℃下将DCM(231L)装入至水层。将反应混合物在25至30℃下搅拌30分钟并且使其在25至30℃下静置30分钟。分离各层(水层(AL-1)和有机层(OL-2))并且将AL-1放在一边。OL-1和OL-2在25至30℃下混合。将软化水(385L)加入至组合的有机层。将混合物在25至30℃下搅拌30分钟,并且在25至30℃下静置30分钟。分离各层(水层(AL-2)和有机层(OL-3))并且将AL-2放在一边。

[0228]　将10％饱和碳酸氢钠溶液(由软化水(385L)和碳酸氢钠(38.5Kg)制备)在25至30℃下装入至OL-3。将反应混合物在25至30℃下搅拌30分钟并且使其在25至30℃下静置30分钟。分离各层(水层(AL-3)和有机层(OL-4))并且将AL-3放在一边。将OL-4经无水Na$_2$SO$_4$(38.5Kg)干燥并且在25至30℃下用DCM(150L)洗涤无水Na$_2$SO$_4$。

[0229]　在低于35至40℃下在真空下蒸馏溶剂,直至剩余5％。将正己烷(308L)在35至40℃下装入至反应混合物中,并在35至40℃下将溶剂完全蒸馏直至不形成冷凝滴。将正-己烷(150L)在35至40℃下装入至反应混合物,并且将反应混合物冷却至5至10℃并且在5至10℃下保持30分钟。

[0230] 过滤固体产物，用冷却的已烷(77L)洗涤，并且在40至45℃的热风烘箱中干燥6小时以得到产物。

[0231] 最终产物：3-氯-1-(2,3-二氢-1H-茚-5-基)丙-1-酮(9)

[0232] 输出：120.5Kg

[0233] 收率：88.63％

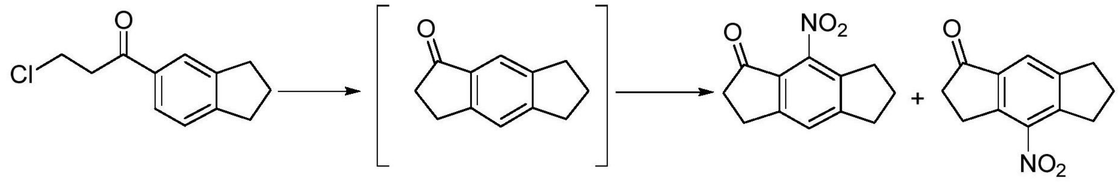
[0234] HPLC纯度：99.3％

[0235] 水分含量：0.09％

[0236] ^{1}H NMR：(500MHz,CDC13)：δ7.81(S,1H),7.76(d,1H),7.31(d,1H),3.93(t,2H),3.45(t,2H),2.97(t,4H),2.15(q,2H)

[0237] 反应方案2-步骤(b)和步骤(c)

[0238]



(9) (10) (11a) (11b)

[0239] 将硫酸(300.0L)在25至30℃下装入至2.0KL干净并且干燥的玻璃衬里反应器中。在25至30℃下分批装入3-氯-1-(2,3-二氢-1H-茚-5-基)丙-1-酮(9)(60.0Kg)并且将反应混合物在25至30℃下保持30分钟。将反应混合物缓慢加热至65至70℃并且在65至70℃下保持24小时。通过HPLC证实不存在3-氯-1-(2,3-二氢-1H-茚-5-基)丙-1-酮(9)(限值：≤1.0％)。

[0240] 然后将反应混合物冷却至0至5℃。在0至5℃下缓慢添加硝化混合物^{*1}，并且将反应混合物在0至5℃下保持1小时。将反应混合物保持在0至5℃下。

[0241] 将软化水(900.0L)在25至30℃下装入至2.0KL干净并且干燥的玻璃衬里反应器中。将水冷却至0至5℃。将反应混合物在0至5℃下缓慢加入至反应器。加入甲苯(480.0L)并且将温度升高至30至35℃。将反应混合物在30至35℃下保持30分钟并且在30至35℃下静置30分钟。将反应混合物通过硅藻土®床(用硅藻土®(6.0Kg)和甲苯(30.0L)制备)过滤。用甲苯(60.0L)洗涤硅藻土®床。过滤固体并且吸干30min。

[0242] 将反应混合物装入至2.0KL干净并且干燥的玻璃衬里反应器。将反应混合物在30至35℃下搅拌30分钟。分离各层(水层(AL-1)和有机层(OL-1))并且将OL-1放在一边。将甲苯(60.0L)装入至AL-1。将混合物在35至40℃下搅拌30分钟，并且在35至40℃下静置30分钟。分离各层(水层(AL-2)和有机层(OL-2))并且将OL-2放在一边。OL-1和OL-2组合以形成OL-3。

[0243] 将5％饱和碳酸氢钠溶液(由软化水(300.0L)和碳酸氢钠(15.0Kg)制备)在30至35℃下缓慢装入至OL-3。将反应混合物在35至40℃下搅拌30分钟并且使其在35至40℃下静置30分钟。将反应混合物通过硅藻土®床(用硅藻土®(6.0Kg)和软化水(60.0L)制备)过滤。用甲苯(60.0L)洗涤硅藻土®床。

[0244] 将反应混合物装入至3.0KL干净并且干燥的玻璃衬里反应器。将反应混合物在30至35℃下搅拌30分钟。分离各层(水层(AL-3)和有机层(OL-4))并且将OL-4放在一边。

[0245] 将甲苯(60.0L)装入至AL-3。分离各层(水层(AL-4)和有机层(OL-5))并且将OL-5放在一边。OL-4和OL-5组合以形成OL-6。盐水溶液(由软化水(300.0L)和氯化钠(12.0Kg)在25至30℃下制备。将反应混合物在30至35℃下搅拌30分钟并且在30至35℃下静置30分钟。分离各层(水层(AL-5)和有机层(OL-7))并且将OL-7放在一边。将OL-7用无水Na_2SO_4(9.0Kg)干燥,并且在25至30℃下用甲苯(30.0L)洗涤无水Na_2SO_4。在低于40至45℃下在真空下蒸馏溶剂,直至剩余5%。在40至45℃下将甲醇(60.0L)装入至反应混合物并且减少至60L的反应物料。

[0246] 在40至45℃下将甲醇(120.0L)装入至反应混合物,并且将反应混合物冷却至5至10℃并且在5至10℃下保持30分钟。过滤固体产物,用冷却的甲醇(30.0L)洗涤,并且在40至45℃的热风烘箱中干燥6小时以得到产物。

[0247] *1:为了制备硝化混合物,将硫酸(27.0L)在25至30℃下装入至160L干净并且干燥的搪玻璃反应器中。将反应混合物冷却至0至5℃。在0至5℃下缓慢加入硝酸(27.0L)并且将反应混合物在0至5℃下保持30分钟以提供硝化混合物。

[0248] 最终产物:8-硝基-1,2,3,5,6,7-六氢-s-二环戊二烯并苯-1-酮(11a)和4-硝基-1,2,3,5,6,7-六氢-s-二环戊二烯并苯-1-酮(11b)

[0249] 组合输出(11a+11b):38.87Kg

[0250] 组合收益(11a+11b):62.24%

[0251] 重量比(11a:11b):9:1

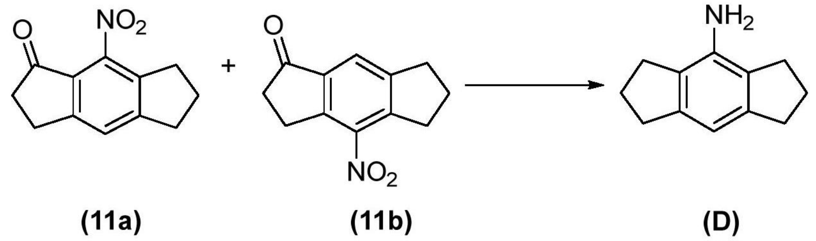
[0252] HPLC纯度:95.9%

[0253] 水分含量:0.19%

[0254] ^1H NMR:(500MHz,$CDCl_3$):δ7.44(S,1H),2.21(m,2H),2.78(t,2H),3.02(m,4H),3.13(t,2H)

[0255] 反应方案2-步骤(d)

[0256]



(11a) (11b) (D)
(12)

[0257] 将8-硝基-1,2,3,5,6,7-六氢-s-二环戊二烯并苯-1-酮(11a)和4-硝基-1,2,3,5,6,7-六氢-s-二环戊二烯并苯-1-酮(11b)(9:1比例;27.0Kg)在25至30℃下装入至600L干净并且干燥的压力反应器中。

[0258] 在25至30℃下装入甲醇(270L)。在25至30℃下缓慢装入甲磺酸(14.3Kg)并且将反应混合物保持30分钟。添加15% $Pd(OH)_2$浆料(60%湿)^{*2}。

[0259] 将反应混合物在真空下脱气并且充入氩气气氛(0.5Kg)三次。将反应混合物在真空下脱气并且充入氢气气氛(0.5Kg)三次。然后,在室温下将反应混合物在氢气气氛(100Psi)下搅拌32小时。

[0260] 反应完成后,将反应混合物冷却至25至30℃。将反应混合物在真空下脱气并且充入氮气气氛(0.5Kg)三次。

[0261] 将反应混合物通过糖果过滤器过滤以去除Pd(OH)$_2$,然后通过微滤器过滤并且用甲醇(54L)洗涤床。在低于45至50℃的真空下蒸馏掉95%的溶剂。在25至30℃下将软化水(135L)装入至反应混合物中并且保持30分钟。将反应混合物冷却至5-10℃。用2N NaOH水溶液(由NaOH(6.48Kg)和软化水(81L)制备)将pH调节至约9-10,并且将反应混合物搅拌30分钟。然后将甲苯(135L)装入至反应混合物并且将反应混合物搅拌30分钟。将反应混合物再搅拌30分钟,同时使温度达到25至30℃。让反应混合物静置30分钟,同时将温度保持在25至30℃。

[0262] 将反应混合物通过**硅藻土**®床(用**硅藻土**®(5.4Kg)和甲苯(13.5L)制备)过滤。用甲苯(54L)洗涤**硅藻土**®床。

[0263] 分离各层(水层(AL-1)和有机层(OL-1))并且将OL-1放在一边。在25至30℃下将甲苯(54L)加入至AL-1。将反应混合物在25至30℃下搅拌30分钟并且使其在25至30℃下静置30分钟。分离各层(水层(AL-2)和有机层(OL-2))并且将AL-2放在一边。在25至30℃下将甲苯(54L)加入至AL-1。在25至30℃下将盐水溶液(用软化水(135L)和氯化钠(54Kg)制备)装入至合并的有机层(OL-1和OL-2)。将反应混合物在25至30℃下搅拌30分钟并且使其在25至30℃下静置30分钟。

[0264] 分离各层(水层(AL-3)和有机层(OL-3))并且将AL-3放在一边。将木炭(1.3Kg)加入至OL-3并且将温度升高至35至40℃并且在35至40℃下保持30分钟。在35至40℃下将反应混合物通过**硅藻土**®床(用**硅藻土**®(5.4Kg)和甲苯(54L)制备)过滤。用甲苯(54L)洗涤**硅藻土**®床。有机层经无水Na_2SO_4(13.5Kg)干燥。用甲苯(27L)洗涤Na_2SO_4。

[0265] 在低于35至40℃下在真空下蒸馏溶剂,直至剩余5%。在35至40℃下将甲醇(40.5L)装入至反应混合物并且蒸馏直至剩余5%。在35至40℃下将甲醇(97.2L)和水(10.8L)装入至反应混合物。将反应混合物加热至50至55℃,在50至55℃下搅拌1小时,缓慢冷却至0至5℃并且在0至5℃下保持30分钟。

[0266] 将固体产物过滤并且用冷甲醇(13.5L)洗涤,并且在40至45℃的热风烘箱中干燥6小时以得到产物。

[0267] *2:为了制备15% Pd(OH)$_2$浆料,将碳载20% Pd(OH)$_2$(60%湿;4.05Kg)加入至甲醇(27L)。

[0268] 最终产物:1,2,3,5,6,7-六氢-s-二环戊二烯并苯-4-胺(12)

[0269] 输出:11.3Kg

[0270] 收率:41.85%

[0271] HPLC纯度:98.1%

[0272] 水分含量:0.10

[0273] ^{1}H NMR:(400MHz,DMSO-d_6):δ6.38(S,1H),4.45(S,2H),2.75(t,4H),2.58(t,4H),1.98(t,4H)。

[0274] 1,2,3,5,6,7-六氢-s-二环戊二烯并苯-4-胺(12)的纯化(A)

[0275] 将1,2,3,5,6,7-六氢-s-二环戊二烯并苯-4-胺(12)(54.5Kg)在25至30℃下装入至250L干净并且干燥的反应器中。在25至30℃下装入甲苯(27.2L)并且将反应混合物在25至30℃下搅拌30分钟。在25至30℃下将甲醇(163L)装入至反应混合物。将反应混合物在25

至30℃下搅拌30分钟，冷却至-5至0℃，并且在-5至0℃下搅拌30分钟。过滤固体产物，用冷甲醇(54.5L)洗涤，并且在40至45℃下干燥6小时。

[0276] 最终产物:1,2,3,5,6,7-六氢-s-二环戊二烯并苯-4-胺(12)

[0277] 输出:40.5Kg

[0278] 收率:74.31%

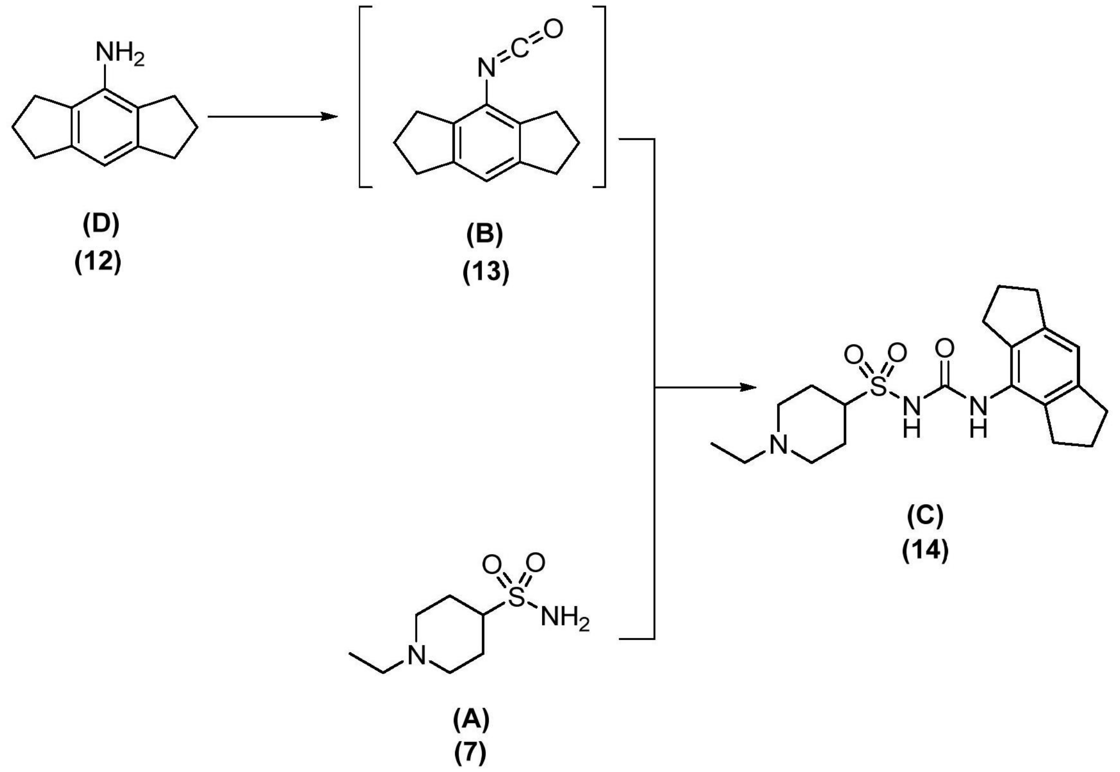
[0279] HPLC纯度:99.5%

[0280] 水分含量:0.3%

[0281] ^{1}H NMR:(400MHz,DMSO-d_6):δ6.33(s,1H),4.53(s,2H),2.72(t,4H),2.57(t,4H),1.98(t,4H)。

[0282] 1-乙基-N-((1,2,3,5,6,7-六氢-s-二环戊二烯并苯-4-基)氨基甲酰基)哌啶-4-磺酰胺(钾盐)(14)

[0283]



[0284] 反应方案3(14)的合成:

[0285] 以分批方式制备的1,2,3,5,6,7-六氢-s-二环戊二烯并苯-4-胺-异氰酸酯(13):

[0286] 将1,2,3,5,6,7-六氢-s-二环戊二烯并苯-4-胺(12)(1.00g,1.00当量)在50mL反应器中于10-20℃下溶解于甲苯(9.60g)中。加入N,N-二异丙基乙胺(2.25g,3.00当量)，然后在3分钟内加入20wt%光气溶液(4.28g,1.50当量)，并将形成的悬浮液在10-20℃下进一步搅拌30分钟。将反应混合物用饱和$NaHCO_3$溶液(5.0mL)和水(5.0mL)洗涤。分离各层，得到1,2,3,5,6,7-六氢-s-二环戊二烯并苯-4-胺-异氰酸酯的甲苯溶液(OL-1,约20mL,含有1,2,3,5,6,7-六氢-s-二环戊二烯并苯-4-胺(12)(5.77mmol))。将获得的溶液OL-1用于下一步骤(二环戊二烯并苯胺-异氰酸酯(12)与1-乙基-4-哌啶磺酰胺(7)的偶合)，产生约80%总产率的(14)。

[0287] 以流动方式制备1,2,3,5,6,7-六氢-s-二环戊二烯并苯-4-胺-异氰酸酯(13):

[0288] 进料溶液的制备：

[0289] 进料溶液A：将1,2,3,5,6,7-六氢-s-二环戊二烯并苯-4-胺(12)(43.31g)溶解在甲苯(206.69g)中，得到0.90M溶液。

[0290] 进料溶液B：将碳酸钾(103.5g)溶解在水(950g)中，得到0.75M溶液。

[0291] 进料A(0.70mL/min，1.10当量)、20％w/w光气甲苯溶液(0.45mL/min，1.50当量)和进料B溶液(2.35mL/min，3.10当量)在0至10℃(内部温度)下同时给入反应器1(约25mL)中。在反应器1中的停留时间为5-10分钟。将来自反应器1的双相溶液连续泵出并连续分离各层，得到含有1,2,3,5,6,7-六氢-s-二环戊二烯并苯-4-胺异氰酸酯(13)的有机层(OL-1)和引导至废料的水层(AL-1)。在稳态下在81分钟内收集有机层OL-1，得到约90mL的1,2,3,5,6,7-六氢-s-二环戊二烯并苯-4-胺(12)(51mmol)。将获得的溶液OL-1用于下一步。

[0292] 二环戊二烯并苯胺-异氰酸酯(12)与1-乙基-4-哌啶磺酰胺(7)的偶联：

[0293] 将1-乙基-4-哌啶磺酰胺(7)(8.88g，46mmol，1.0当量)装入至容器。将四氢呋喃(62.52g)装入到容器中并将混合物调节至20至25℃。将混合物在20至25℃下搅拌至少20分钟，直至团块消失并形成均匀悬浮液。将叔丁醇钾(1.05M，43.98mL，46mmol)在90至120分钟内装入到容器中，将温度保持在20至25℃，并将混合物在20至25℃搅拌2至4小时，得到浓稠的白色悬浮液。

[0294] 将以分批或流动方式制备的含有1,2,3,5,6,7-六氢-s-二环戊二烯并苯-4-胺-异氰酸酯(13)的有机层OL-1(51mmol的1,2,3,5,6,7-六氢-s-二环戊二烯并苯-4-胺(12)，约90mL)通过保持在20-25℃经2小时添加到形成的白色甲苯悬浮液中。反应混合物很快变成可充分搅拌的悬浮液，并且在添加结束时变成稍微混浊的棕色溶液。将反应混合物在20至25℃下再搅拌1-2小时。通过KF分析水含量，并通过LC/MS或HPLC分析确认1,2,3,5,6,7-六氢-s-二环戊二烯并苯-4-胺的转化率(典型的>95％)。任选地，通过硅藻土层(G3过滤器)进行澄清过滤。在25至40℃下经2小时将水(4.44g，0.5V)逐滴添加到反应混合物中。固体在约0.5-1wt％含水量时开始结晶。给料结束时形成悬浮液。经1小时将反应混合物冷却至0至5℃(IT)并在0至5℃下进一步搅拌16小时。通过G3过滤器过滤固体并用甲苯/THF(按体积计1/1，44.4mL)混合物洗涤。

[0295] 将固体在高达50℃、10-20毫巴的氮气流下干燥12小时。使用^{1}HNMR光谱和HPLC测量、鉴定和分析粗固体的干燥重量。

[0296] 最终产物：1-乙基-N-((1,2,3,5,6,7-六氢-s-二环戊二烯并苯-4-基)-氨基甲酰基)哌啶-4-磺酰胺(钾盐)(14)

[0297] 输出：约16.0g

[0298] 产量：约80％

[0299] NMR纯度：＞97％

[0300] HPLC纯度：＞99％

[0301] 1-乙基-N-((1,2,3,5,6,7-六氢-s-二环戊二烯并苯-4-基)-氨基甲酰基)哌啶-4-磺酰胺(钾盐)(14)的重结晶

[0302] 将粗1-乙基-N-((1,2,3,5,6,7-六氢-s-二环戊二烯并苯-4-基)氨基甲酰基)哌啶-4-磺酰胺(钾盐)(14)(15.00g)装入至反应容器。将甲醇(33.55g)、随后是乙腈(33.55g)装入至容器，根据需要将温度调节至15至25℃，同时搅拌10至20分钟(直至形成不存在固体

块的均匀混浊溶液)。在15至25℃下将溶液通过1μm过滤器过滤。在15至25℃下用甲醇/乙腈混合物(7.59g)洗涤过滤器,并进一步添加乙腈(64.0g),随后添加在乙腈(约1g)中的(14)的晶种(0.138g)。形成悬浮液。

[0303] 将溶液在25至35℃下浓缩至约122mL。将乙腈(54.32g)装入至该混合物并将溶液在25至35℃下浓缩至约122L。将乙腈(52.53g)装入至该混合物并将该混合物在≤35℃下浓缩至约122mL。分析混合物的残余甲醇含量。通过标准≤0.3%w/w甲醇。将乙腈(53.45g)装入至容器并且将温度调节至15至25℃。将浆料在15至25℃下老化至少1小时(目标1至2小时),然后在15至25℃下用20μm布过滤。将滤饼在15至25℃下用乙腈(43.39g)洗涤两次。在高达50℃在氮气流下干燥固体,产生13.75g(92%)的白色固体。

[0304] 最终产物:1-乙基-N-((1,2,3,5,6,7-六氢-s-二环戊二烯并苯-4-基)-氨基甲酰基)哌啶-4-磺酰胺(钾盐)(14)

[0305] 输出:13.75g

[0306] 收率:92%

[0307] HPLC纯度:99.7%。