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(71) Applicant: **AYALA PHARMACEUTICALS INC.**
[US/US]; 1007 North Orange Street, 4th Floor, Wilmington,
Delaware 19802 (US).

(72) Inventors: **CIMARUSTI, Christopher M.**; 350 White
Horse Pike, Clementon, New Jersey 08021 (US). **LA-
HOTI, Anandkumar Madanlal**; 206, Laxmi Arcade, Laxmi
Ganga Enclave, Pipeline Road, Hyderabad 500067 (IN).
DARAM, Madan Raja Gopal Reddy; 2-6 Ambapuram,
Kurnool District, Ambapuram 518598 (IN).

(74) Agent: **COHEN, Mark S.** et al.; PEARL COHEN ZEDEK
LATZER BARATZ LLP, 7 Times Square, 19th Floor, New
York, New York 10036 (US).

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(54) Title: METHODS OF PREPARING CHIRAL BENZODIAZEPINONE DERIVATIVES

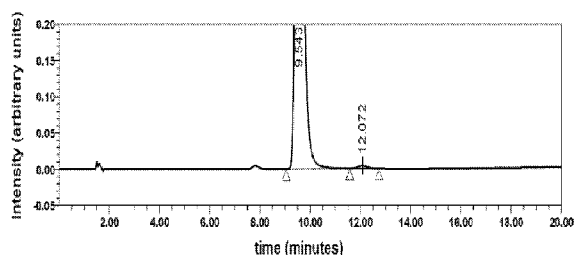
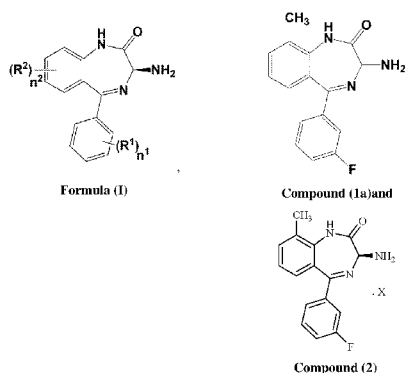


Figure 1

(57) Abstract: The present invention provides methods of preparing compound of Formula (I), wherein the compounds are represented by the structure of Formula (I) wherein: R^1 each is independently F, Cl, Br, I, OCH_3 , CN or NO_2 ; R^2 each is independently identical or different C_1 - C_5 alkyl; n^1 is an integer between 1 and 5; and n^2 is an integer between 1 and 4. In addition, the present invention provides a compound represented by the following structures: Compound (1a) and Compound (2), wherein X comprises: chloride, acetate, adipate, alginate, ascorbate, aspartate, benzoate, benzenesulfonate, bisulfate, borate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydroiodide, maleate, 2-hydroxyethanesulfonate, lactate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, salicylate, succinate, sulfate, sulfonate, tartrate, thiocyanate, toluenesulfonate, or undecanoate salt, or any combination thereof.

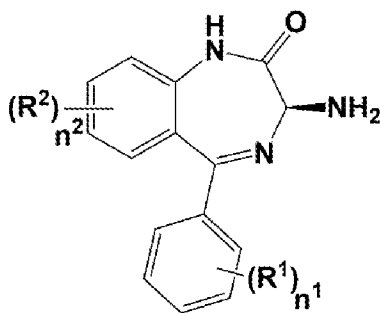
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METHODS OF PREPARING CHIRAL BENZODIAZEPINONE DERIVATIVES

FIELD OF THE INVENTION

[001] The present invention provides methods of preparing compound of Formula (I), as well as other compounds derived therefrom, wherein the compounds are represented by the structure of Formula (I):

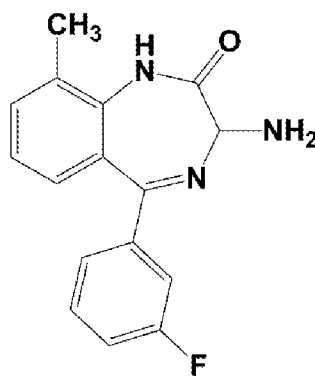


Formula (I)

wherein:

- 10 R^1 each is independently F, Cl, Br, I, OCH_3 , CN or NO_2 ;
 R^2 each is independently identical or different C_1 - C_5 alkyl;
 n^1 is an integer between 1 and 5; and
 n^2 is an integer between 1 and 4.

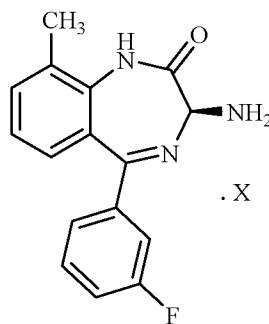
[002] In addition, the present invention provides a compound represented by the following structure:



Compound (1a),

its pharmaceutically acceptable salts, or a combination thereof.

[003] In addition, the present invention provides a compound represented by the following structure:

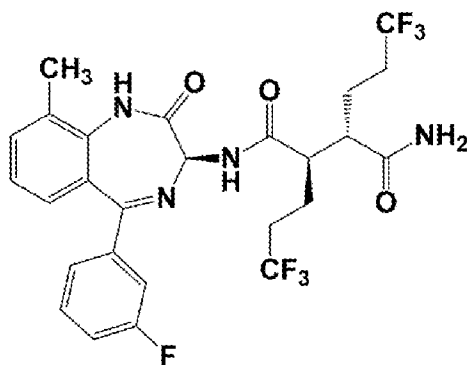
**Compound (2),**

wherein X comprises:

- chloride, acetate, adipate, alginate, ascorbate, aspartate, benzoate, benzenesulfonate, bisulfate,
 5 borate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate,
 dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate,
 heptanoate, hexanoate, hydroiodide, maleate, 2-hydroxyethanesulfonate, lactate,
 methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, pectinate, persulfate, 3-
 phenylpropionate, phosphate, picrate, pivalate, propionate, salicylate, succinate, sulfate, sulfonate,
 10 tartrate, thiocyanate, toluenesulfonate, or undecanoate salt, or any combination thereof.

BACKGROUND OF THE INVENTION

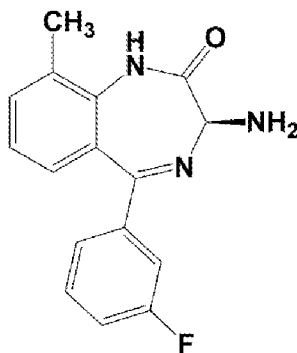
- [004] Benzodiazepinone compounds are useful as pharmaceutically active ingredients in the
 pharmaceutical and fine chemical industries. For example, the gamma-secretase inhibitor (GSI)
 15 (2R,3S)-N-[(3S)-5-(3-Fluorophenyl)-9-methyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl]-
 2,3-bis(3,3,3-trifluoropropyl)succinimide:



- is showing promising results in current clinical trials for the treatment of various cancers,
 particularly cancers with defects in Notch regulation (see US Patent 9,273,014, incorporated herein
 20 by reference).

[005] Since (2R,3S)-N-[(3S)-5-(3-Fluorophenyl)-9-methyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl]-2,3-bis(3,3,3-trifluoropropyl)succinimide is chiral, an efficient and diastereoselective preparation of the chiral compound in a pure form is needed.

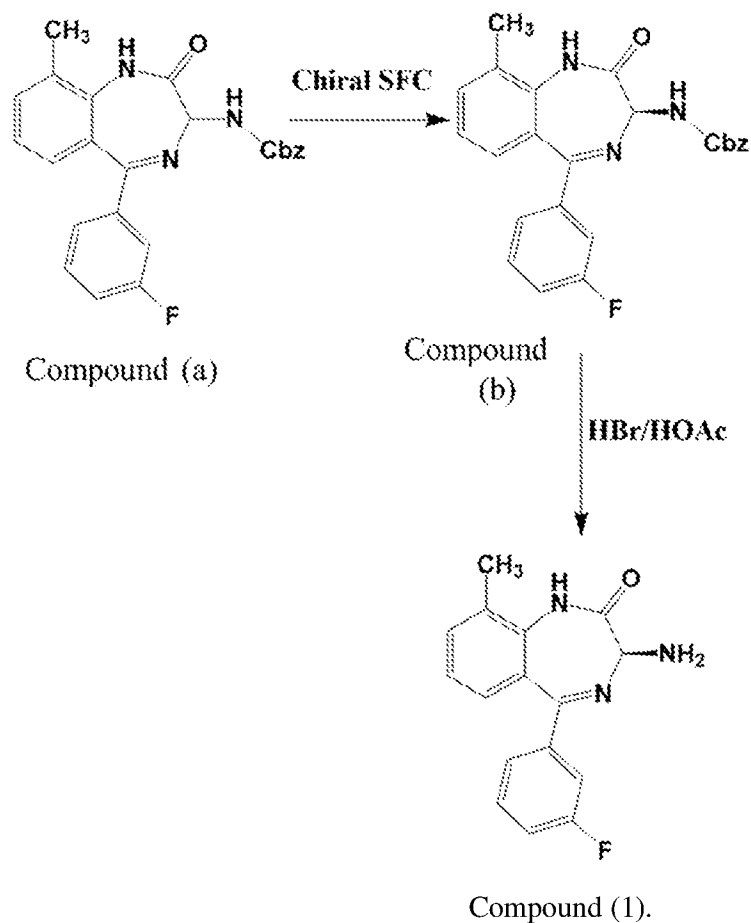
[006] US Patent 9,273,014 discloses a precursor to (2R,3S)-N-[(3S)-5-(3-Fluorophenyl)-9-methyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl]-2,3-bis(3,3,3-trifluoropropyl)succinimide, which is a compound represented by the following structure:



Compound (1).

In US Patent 9,273,014, Compound (1) is prepared as described in Scheme 1 below. In brief, Compound (a) is resolved using chiral Supercritical Fluid Chromatography (SFC) to form chiral Compound (b); which is then hydrolyzed to produce Compound (1). However, chiral chromatographic methods, such as SFC and High-Performance Liquid Chromatography (HPLC), are expensive, time-consuming and tedious methods of producing chiral compounds. In addition, these methods have a theoretical yield of only 50 %.

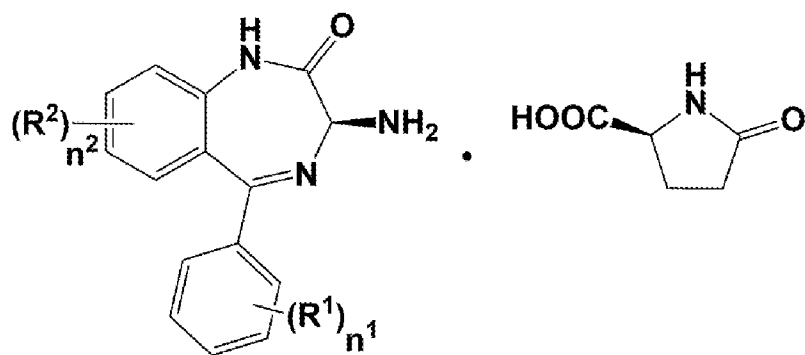
Scheme 1: Preparation of Compound (3) using chiral SFC conditions.



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SUMMARY OF THE INVENTION

[007] In one embodiment, the present invention provides a method of preparing the compound of Formula (Ib),



Formula (Ib)

10

wherein:

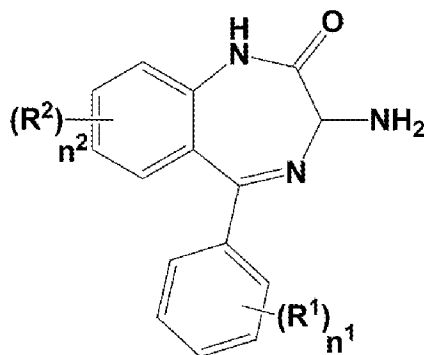
R^1 each is independently Cl, F, Br, I, OCH_3 , CN or NO_2 ;

R^2 each is independently identical or different C_1 - C_5 alkyl;

n^1 is an integer between 1 and 5; and

5 n^2 is an integer between 1 and 4;

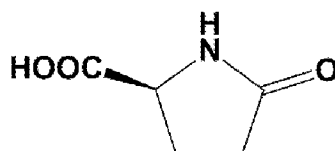
comprising the step of reacting the compound of Formula (Ia)



Formula (Ia)

with L-pyroglutamic acid (L-PGA),

10

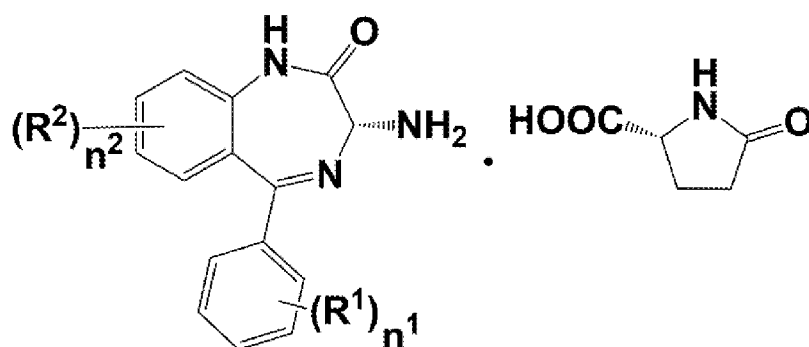


L-pyroglutamic acid (L-PGA),

in the presence of solvent with or without catalyst to obtain a compound of Formula (Ib).

[008] In another embodiment, the present invention provides a method of preparing the

15 compound of Formula (Id),



Formula (Id)

wherein

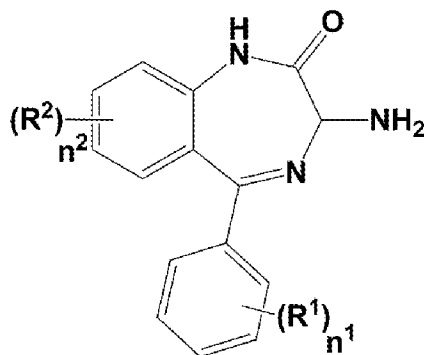
R^1 each is independently Cl, F, Br, I, OCH_3 , CN or NO_2 ;

R^2 each is independently identical or different C_1 - C_5 alkyl;

n^1 is an integer between 1 and 5; and

5 n^2 is an integer between 1 and 4;

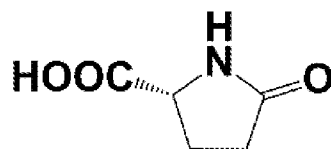
comprising the step of reacting the compound of Formula (Ia)



Formula (Ia)

with D-pyroglutamic acid (D-PGA),

10

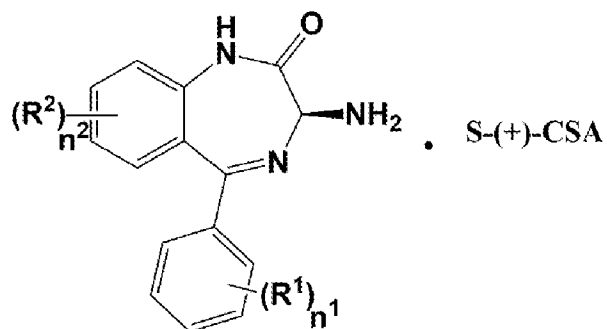


D-pyroglutamic acid (D-PGA)

in the presence of solvent and with or without catalyst to obtain a compound of Formula (Ib).

[009] In another embodiment, the present invention provides a method of preparing the

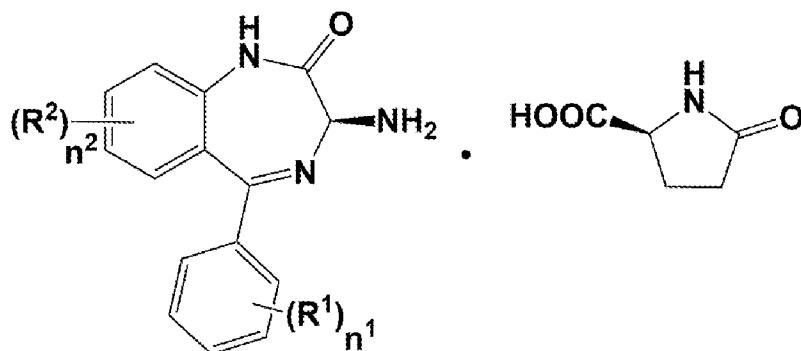
15 compound of Formula (Ic),



Formula (Ic)

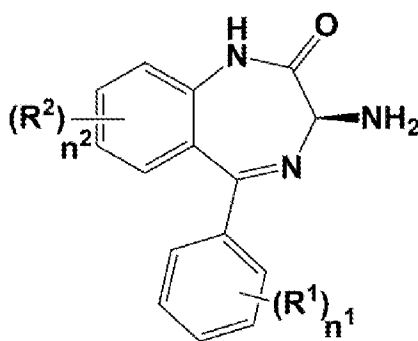
comprising the steps of:

a) reacting the compound of Formula (Ib):



Formula (Ib)

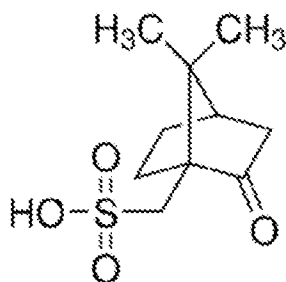
with a base and solvent to provide a compound of Formula (I); and



Formula (I)

b) reacting the compound of Formula (I) with

S (+) camphor sulfonic acid (CSA):



to provide a compound of Formula (Ic),

wherein

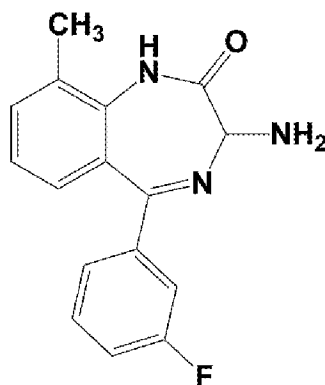
R^1 each is independently Cl, F, Br, I, OCH_3 , CN or NO_2 ;

R^2 each is independently identical or different C_1 - C_5 alkyl;

n^1 is an integer between 1 and 5; and

n^2 is an integer between 1 and 4.

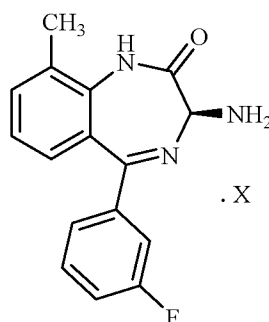
[0010] In another embodiment, the present invention provides a compound represented by the following structure:



Compound (1a),

its pharmaceutically acceptable salts, or a combination thereof wherein the salt comprises chloride, acetate, adipate, alginate, ascorbate, aspartate, benzoate, benzenesulfonate, bisulfate, borate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydroiodide, maleate, 2-hydroxyethanesulfonate, lactate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, salicylate, succinate, sulfate, sulfonate, tartrate, thiocyanate, toluenesulfonate or undecanoate salt or any combination thereof.

[0011] In another embodiment, the present invention provides a compound represented by the following structure:



Compound (2),

wherein X comprises: chloride, acetate, adipate, alginate, ascorbate, aspartate, benzoate, benzenesulfonate, bisulfate, borate, butyrate, citrate, camphorate, camphorsulfonate,

cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydroiodide, maleate, 2-hydroxyethanesulfonate, lactate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, salicylate, succinate, sulfate, sulfonate, tartrate, thiocyanate, toluenesulfonate, or undecanoate salt, or any combination thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] **Figure 1** depicts an HPLC chromatogram, showing the chiral purity of Compound (1b).

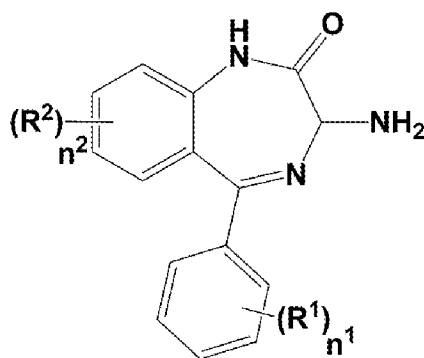
[0013] **Figure 2** depicts an HPLC chromatogram, showing the chiral purity of Compound (1c).

DETAILED DESCRIPTION OF THE PRESENT INVENTION

[0014] In the following detailed description, numerous specific details are set forth in order to provide a thorough understanding of the invention. However, it will be understood by those skilled in the art that the present invention may be practiced without these specific details. In other instances, well-known methods, procedures, and components have not been described in detail so as not to obscure the present invention.

Method of Preparing Compounds of Formula (I) and Salts thereof

[0015] In one embodiment, the present invention provides a method of preparing a compound of Formula (Iz), comprising the step of reacting a compound of Formula (Ia):

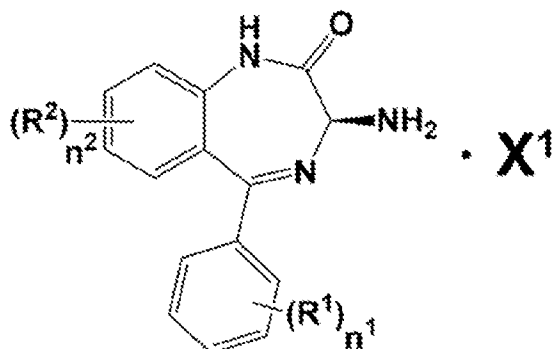


Formula (Ia)

with

X¹

to provide a compound of Formula (Iz):



Formula (Iz),

wherein

X^1 is a chiral salt;

R^1 each is independently F, Cl, Br, I, OCH_3 , CN or NO_2 ;

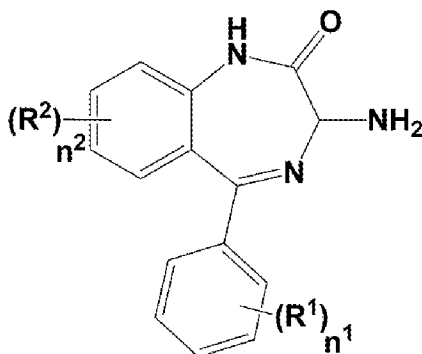
R^2 each is independently identical or different C_1 - C_5 alkyl;

n^1 is an integer between 1 and 5; and

n^2 is an integer between 1 and 4.

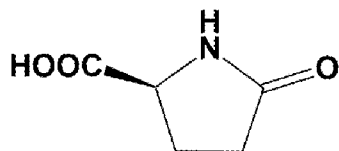
In one embodiment, the chiral salt comprises L-pyroglutamic acid (L-PGA), L-Aspartic acid, L-Leucine, S-Mandelic acid, N-Acetyl-L-Tyrosine, N-Acetyl-L-Valine, S(+)-CSA (camphor sulfonic acid) and L-Glutamic acid. Each possibility represents a separate embodiment of the invention.

[0016] In another embodiment, the present invention provides a method of preparing a compound of Formula (Ib), comprising the step of reacting a compound of Formula (Ia):



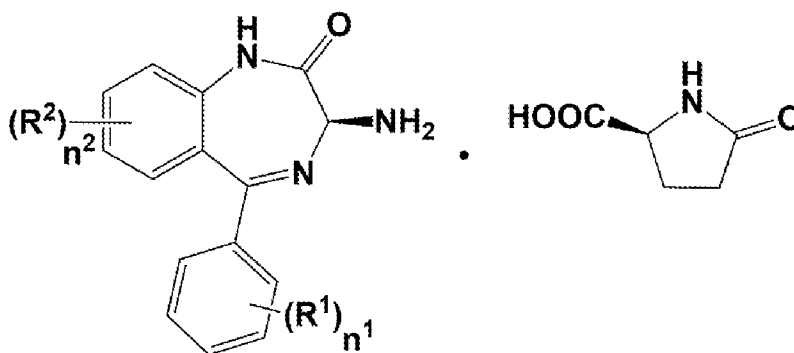
Formula (Ia)

with



L-pyroglutamic acid (**L-PGA**),

5 to provide a compound of Formula (Ib):



Formula (Ib),

10 wherein

R^1 each is independently F, Cl, Br, I, OCH_3 , CN or NO_2 ;

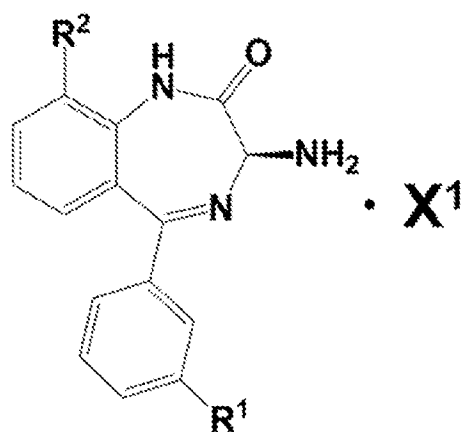
R^2 each is independently identical or different C_1 - C_5 alkyl;

n^1 is an integer between 1 and 5; and

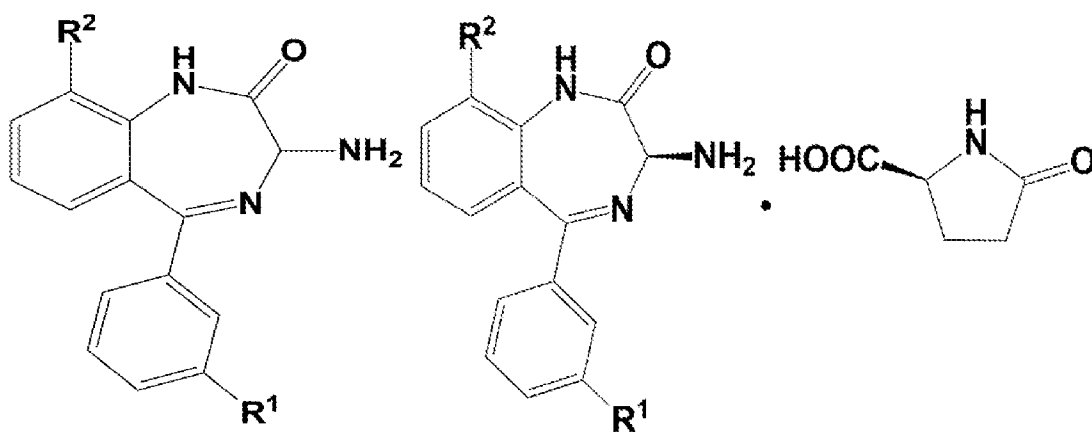
n^2 is an integer between 1 and 4.

15 Each possibility represents a separate embodiment of the invention.

[0017] In one embodiment, the compounds of Formulas (Iz), (Ia) and (Ib) are represented by the compounds of Formulas (Iz-1), (Ia-1) and (Ib-1), respectively:



Formula (Iz-1) ;



5

Formula (Ia-1)

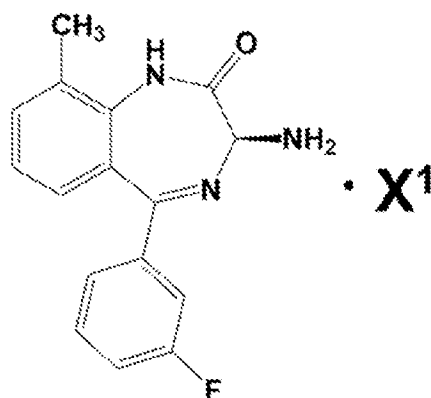
; and

Formula (Ib-1)

.

Each possibility represents a separate embodiment of the invention.

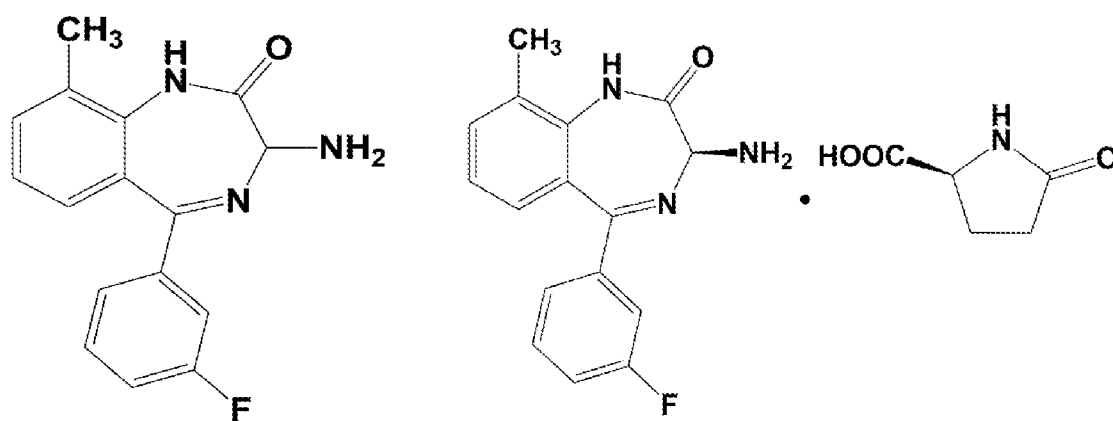
[0018] In another embodiment, the compounds of Formulas (Iz), (Ia) and (Ib) are represented by Compounds (1z), (1a) and (1b), respectively, having the following structures:



Compound (1z)

;

10



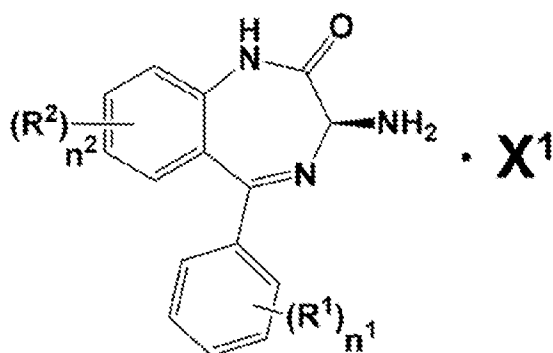
Compound (1a)

and

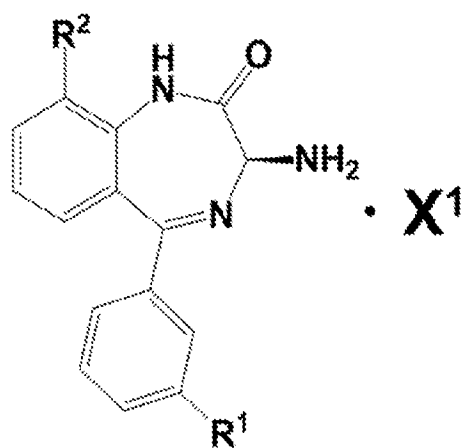
Compound (1b)

- 5 Each possibility represents a separate embodiment of the invention.

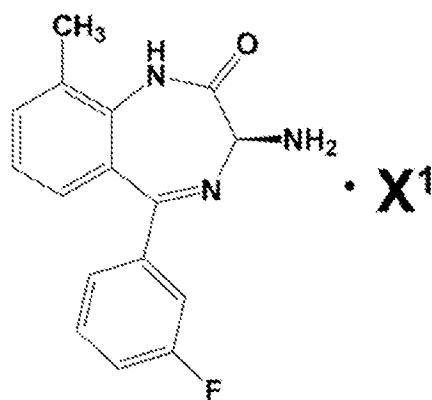
[0019] In another embodiment, the present invention provides a method of preparing a compound of Formula (I), (I-1) or Compound (1), comprising the step of reacting said compound of Formula (Iz), (Iz-1) or (1z):



Formula (Iz),

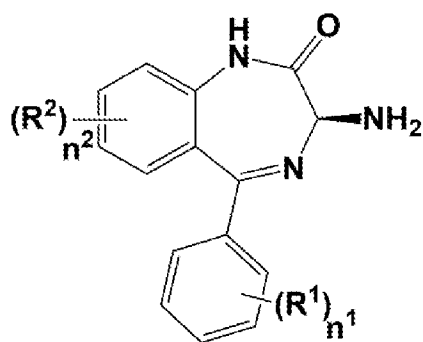


Formula (Iz-1) or

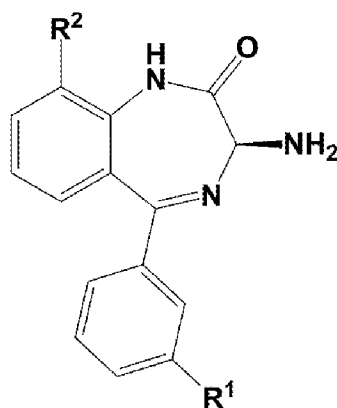


Compound (1z),

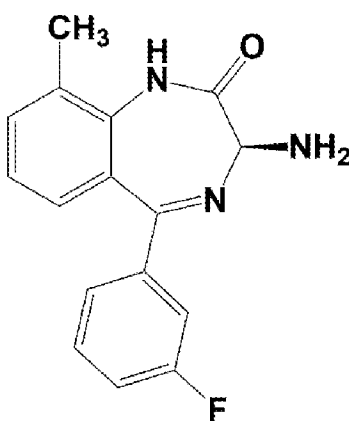
with a base to provide a compound of Formula (I), (I-1) or Compound (1), respectively:



Formula (I),



Formula (I-1) or



Compound (1),

5

wherein

X^1 is selected from L-pyroglutamic acid (**L-PGA**), L-Aspartic acid, L-Leucine, S-Mandelic acid, N-Acetyl-L-Tyrosine, N-Acetyl-L-Valine, S(+)-CSA (camphor sulfonic acid) and L-Glutamic acid;

10

R^1 each is independently F, Cl, Br, I, OCH_3 , CN or NO_2 ;

R^2 each is independently identical or different C_1 - C_5 alkyl;

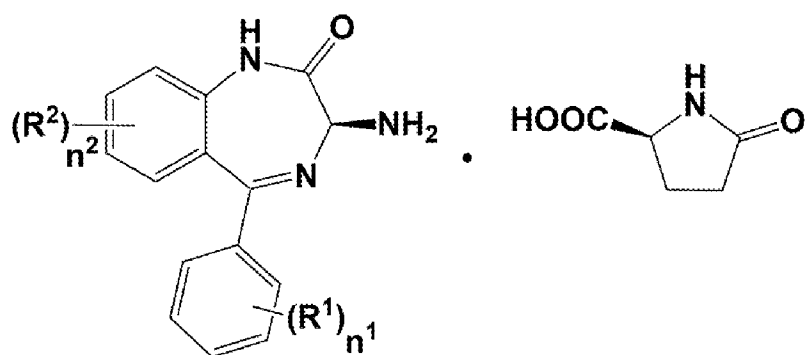
n^1 is an integer between 1 and 5; and

n^2 is an integer between 1 and 4.

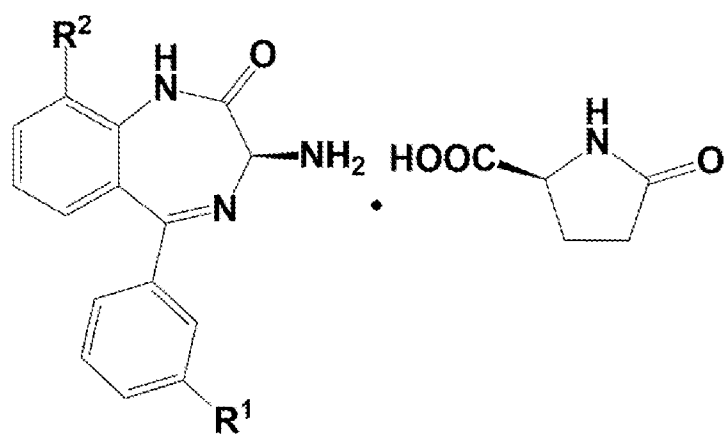
Each possibility represents a separate embodiment of the invention.

15

[0020] In another embodiment, the present invention provides a method of preparing a compound of Formula (I), (I-1) or Compound (1), comprising the step of reacting said compound of Formula (Ib), (Ib-1) or (1b):

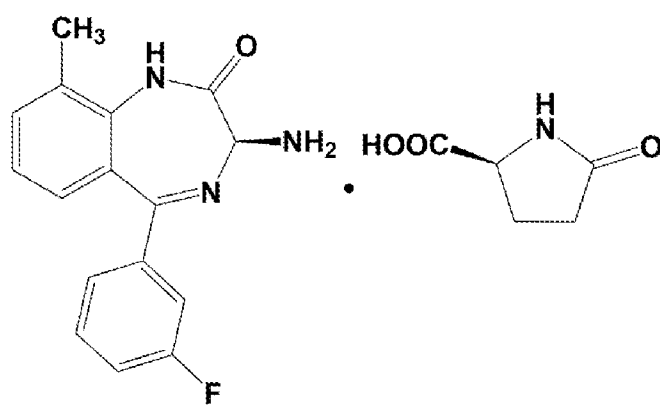


Formula (Ib),



5

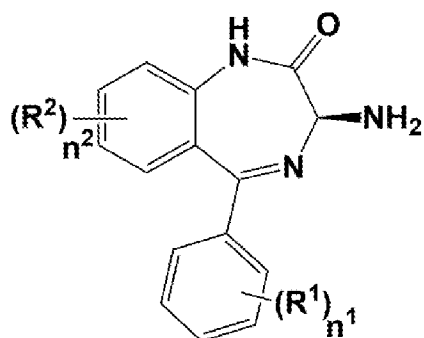
Formula (Ib-1) or



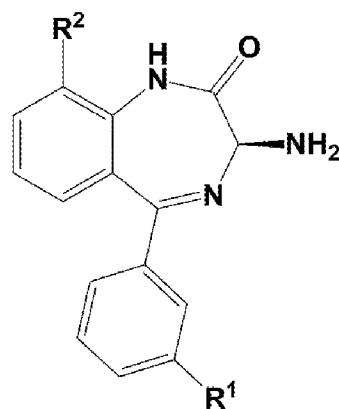
Compound (1b),

10

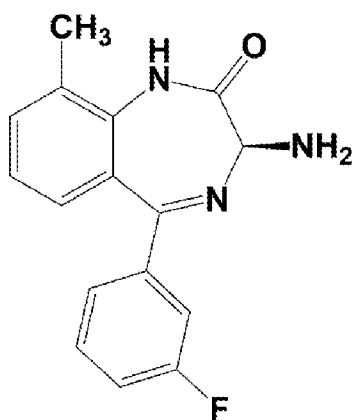
with a base to provide a compound of Formula (I), (I-1) or Compound (1), respectively:



Formula (I),



Formula (I-1) or



Compound (1),

wherein

R¹ each is independently F, Cl, Br, I, OCH₃, CN or NO₂;

R² each is independently identical or different C₁-C₅ alkyl;

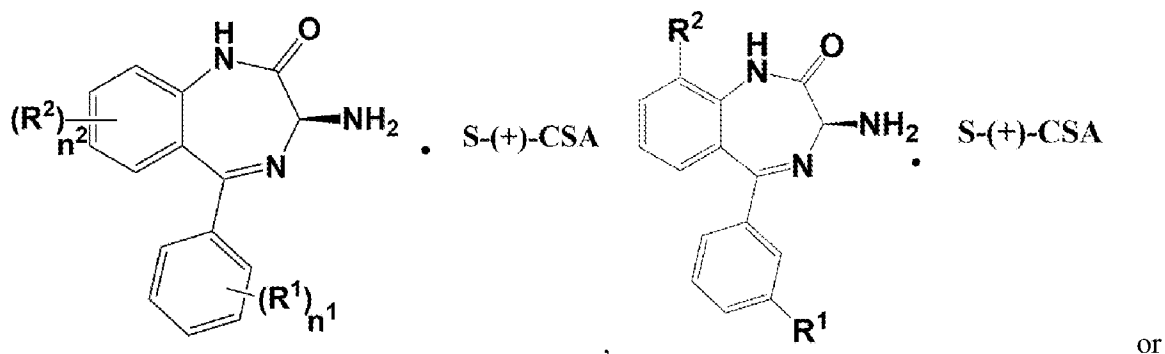
n¹ is an integer between 1 and 5; and

n² is an integer between 1 and 4.

Each possibility represents a separate embodiment of the invention.

[0021] In another embodiment, the method further comprises the step of converting the free-base compound of Formula (I), (I-1) or Compound (1) to its pharmaceutically acceptable salt via e.g. addition of the respective acid, for example hydrochloric acid to this compound to get the chloride salt. In another embodiment, the salt is chloride, acetate, adipate, alginate, ascorbate, aspartate, benzoate, benzenesulfonate, bisulfate, borate, butyrate, citrate, camphorate, pyroglutamate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, maleate, 2-hydroxyethanesulfonate, lactate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, salicylate, succinate, sulfate, sulfonate, tartrate, thiocyanate, toluenesulfonate, or undecanoate salt, or any combination thereof. Each possibility represents a separate embodiment of the invention.

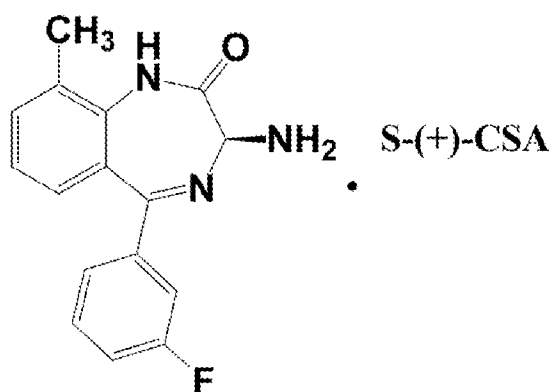
[0022] Surprisingly, L-PGA was the most successful of the chiral acids of X¹ in the resolution of racemic Compound (1a) and provision of a pure Compound (1). In another embodiment, the CSA (camphor sulfonic acid) salt of the S(+) enantiomer of Formula (Ia),(Ia-1) or Compound (1a) (represented by Formula (Ic), (Ic-1a) or Compound (1c); see below) was formed upon reacting the compound represented by Formula (Ib),(Ib-1) or Compound (1b) (structures as provided hereinabove) with base, followed by reaction with S(+)CSA. The formed S(+) CSA salt (represented by the structures of Formula (Ic), (Ic-1) or Compound (1c)) was obtained in high chiral purities, of above 99%, above 99.1%, above 99.2%, above 99.3%, above 99.4%, above 99.5%, above 99.6% or above 99.7%. In one embodiment, the chiral purity of the CSA salts (represented by e.g. Formula (Ic)) is higher than the chiral purity of the PGA salts (represented by e.g. Formula (Ib)). In another embodiment, the chiral purity of the CSA salts is lower, similar or equal to the chiral purity of the PGA salts. Each possibility represents a separate embodiment of the invention.



Formula (Ic)

Formula (Ic-1)

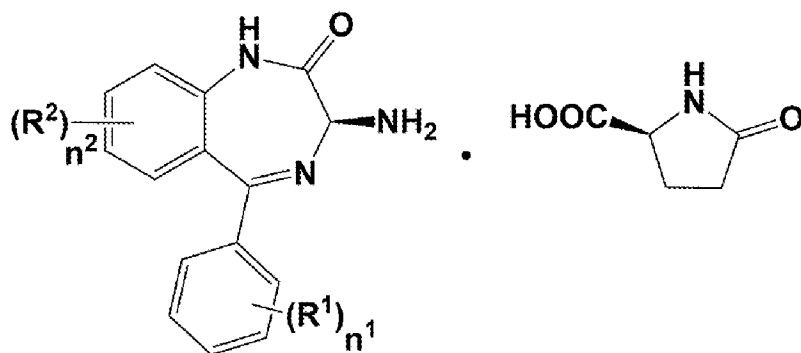
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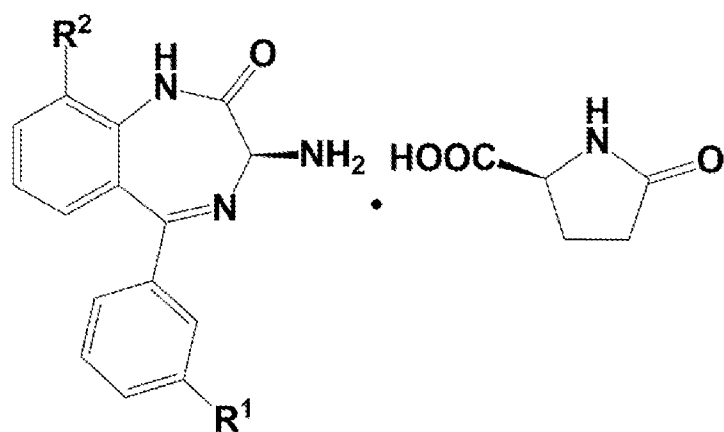
Compound (1c)

[0023] In another embodiment, the present invention provides a method of preparing a compound
 10 of Formula (Ic), (Ic-1) or Compound (1c), comprising the steps of:

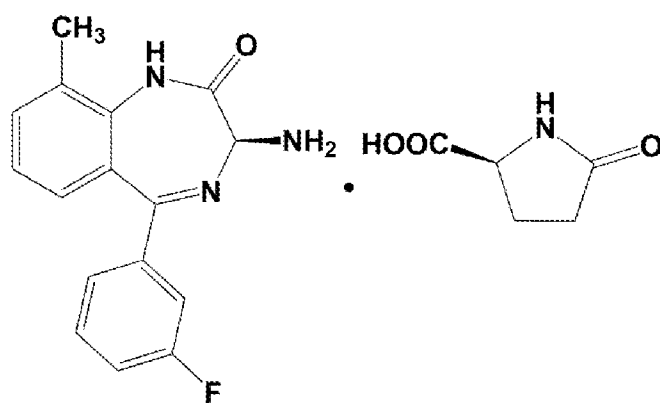
a) reacting said compound of Formula (Ib), (Ib-1) or (1b):



Formula (Ib),

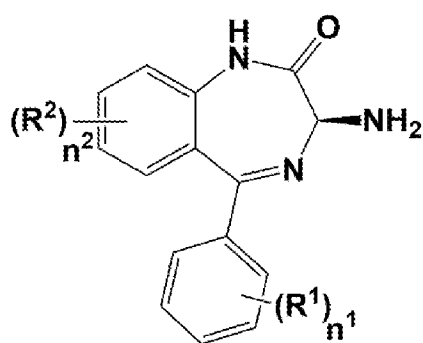


Formula (Ib-1) or

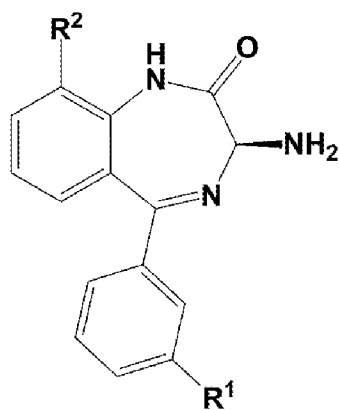


Compound (1b),

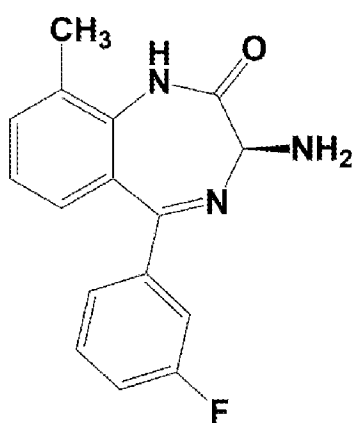
with a base to provide a compound of Formula (I), (I-1) or Compound (1), respectively:



Formula (I),

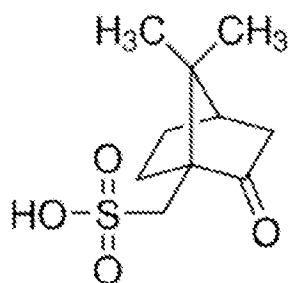


Formula (I-1) or

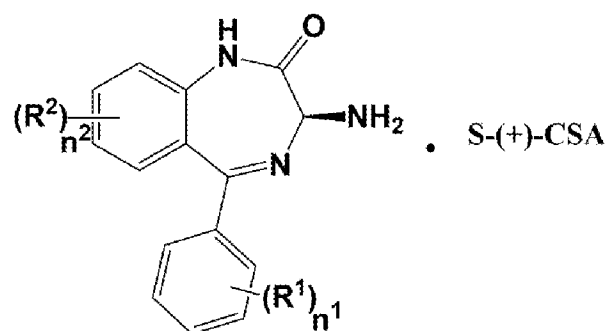


Compound (1); and

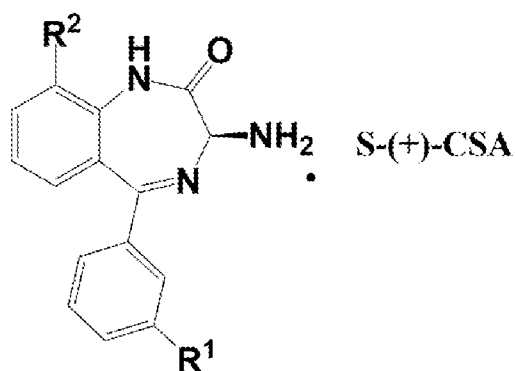
5 b) reacting S (+) CSA:



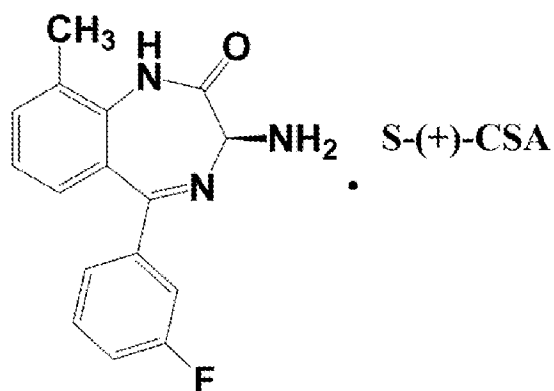
with the compound of Formula (I), (I-1) or Compound (1), to provide a compound of Formula (Ic), (Ic-1) or Compound (1c), respectively:



Formula (Ic),



Formula (Ic-1) or



Compound (1c)

wherein

R^1 each is independently F, Cl, Br, I, OCH_3 , CN or NO_2 ;

R^2 each is independently identical or different C_1 - C_5 alkyl;

n^1 is an integer between 1 and 5; and

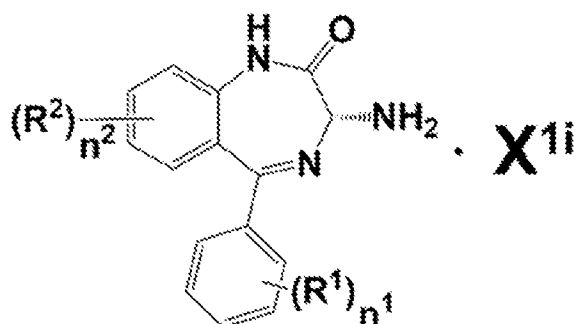
n^2 is an integer between 1 and 4.

Each possibility represents a separate embodiment of the invention.

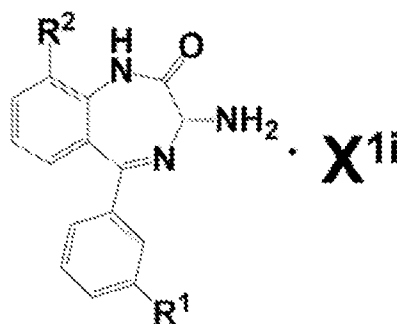
[0024] In another embodiment, the present invention provides a method of preparing a compound of Formula (I), (I-1) or Compound (1), comprising the step of reacting said compound of Formula (Ic), (Ic-1) or Compound (1c) with a base as described hereinabove for the method with Formula (Ib), (Ib-1) or Compound (1b).

[0025] In this regard, it should be noted that reaction of the racemic compound (represented by the structure of Formula (Ia), Formula (Ia-1) or Compound (1a)) with the chiral CSA in the methods of the present invention does not lead to resolution of the racemic compound. Instead, chiral CSA is replacing the chiral PGA within the chiral salt (the compound represented by Formula (Ib), (Ib-1) or Compound (1b)), via *in-situ* formation of chiral amine free-base.

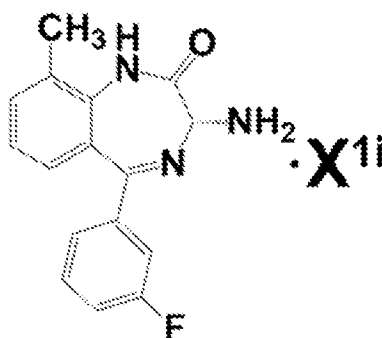
[0026] In some embodiments, reacting the compound represented by Formula (Ia), (Ia-1) or Compound (1a) with the acid with the inverse chirality (e.g. D-PGA instead of L-PGA) in the method according to the invention as described hereinabove leads to the formation of the enantiomeric salt of the compound represented by Formula (Ib), (Ib-1) or Compound (1b). This compound is represented by the structure of Formula (Izi), (Izi-1a) or Compound (1zi):



Formula (Izi)



Formula (Izi-1)



Compound (1zi),

wherein

X^{1i} is selected from D-pyroglutamic acid (D-PGA), D-Aspartic acid, D-Leucine, R-Mandelic acid, N-Acetyl-D-Tyrosine, N-Acetyl-D-Valine, R(-)CSA (camphor sulfonic acid) and D-Glutamic acid;

R^1 each is independently F, Cl, Br, I, OCH_3 , CN or NO_2 ;

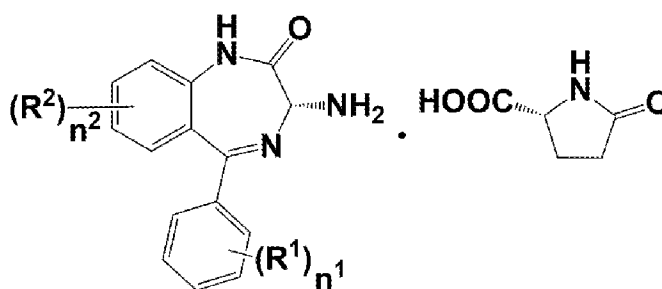
R^2 each is independently identical or different C_1 - C_5 alkyl;

n^1 is an integer between 1 and 5; and

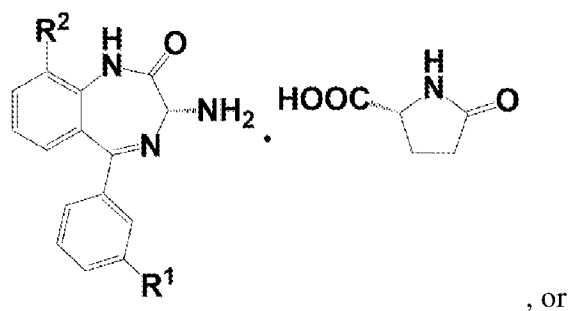
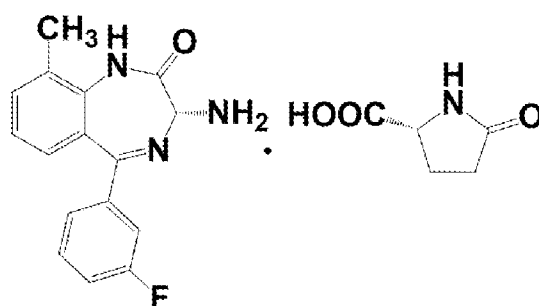
n^2 is an integer between 1 and 4.

Each possibility represents a separate embodiment of the invention.

[0027] In some embodiments, reacting the compound represented by Formula (Ia), (Ia-1) or Compound (1a) with D-PGA instead of L-PGA in the method according to the invention as described hereinabove leads to the formation of the enantiomeric salt of the compound represented by Formula (Ib), (Ib-1) or Compound (1b). This compound is represented by the structure of Formula (Id), (Id-1a) or Compound (1d):



Formula (Id)

**Formula (Id-1)****Compound (1d).**

Each possibility represents a separate embodiment of the invention.

10 [0028] In some embodiments, the methods of preparing the compound of Formula (Iz), (Izi), (Iz-1), (Izi-1) or Compound (1z) or (1zi) further comprise a step of adding an anti-solvent to the reaction mixture, following quenching of the reaction; and reacting this mixture with the anti-solvent, where Formula (Iz), (Izi), (Iz-1), (Izi-1) or Compound (1z) or (1zi) are as defined hereinabove. In one embodiment, the methods comprise the steps of:

- 15 a. reacting a compound of Formula (Ia), (Ia-1) or Compound (1a) with X^1 or X^{1i} to provide a compound of Formula (Iz), (Izi), (Iz-1), (Izi-1) or Compound (1z) or (1zi);
- b. quenching the reaction of step (a);
- c. adding an anti-solvent to the reaction mixture of step (b); and
- d. reacting the mixture of step (b) with the anti-solvent,

20 wherein Formulas (Ia), (Ia-1), (Iz), (Izi), (Iz-1), (Izi-1) and Compounds (1a), (1z) and (1zi) are as defined hereinabove.

[0029] In some embodiments, the methods of preparing the compound of Formula (Ib), (Ib-1) or Compound (1b) further comprise a step of adding an anti-solvent to the reaction mixture, following

quenching of the reaction; and reacting this mixture with the anti-solvent, where Formulas (Ib), (Ib-1) and Compound (1b) are as defined hereinabove. In one embodiment, the methods comprise the steps of:

- a. reacting a compound of Formula (Ia), (Ia-1) or Compound (1a) with L-pyroglutamic acid (L-PGA) to provide a compound of Formula (Ib), (Ib-1) or Compound (1b);
- b. quenching the reaction of step (a);
- c. adding an anti-solvent to the reaction mixture of step (b); and
- d. reacting the mixture of step (b) with the anti-solvent,

wherein Formulas (Ia), (Ia-1), (Ib), (Ib-1), and Compounds (1a) and (1b) are as defined hereinabove.

[0030] In some embodiments, the methods of preparing the compound of Formula (Iz), (Izi), (Iz-1), (Izi-1) or Compound (1z) or (1zi) further comprise the step of adding an anti-solvent and a catalyst to the reaction mixture and reacting the mixture with the anti-solvent and the catalyst, where Formula (Iz), (Izi), (Iz-1), (Izi-1) or Compound (1z) or (1zi) are as defined hereinabove. In one embodiment, the methods comprise the steps of:

- a. reacting a compound of Formula (Ia), (Ia-1) and Compound (1a) with X^1 or X^{1i} for a period of time, to provide a compound of Formula (Iz), (Izi), (Iz-1), (Izi-1) or Compound (1z) or (1zi);
- b. adding a catalyst to the reaction mixture of step (a) and reacting the reaction mixture of step (a) with the catalyst for additional period of time;
- c. quenching the reaction of step (b);
- d. adding an anti-solvent to the reaction mixture of step (c); and
- e. reacting the mixture of step (c) with the anti-solvent,

where Formulas (Ia), (Ia-1), (Iz), (Izi), (Iz-1), (Izi-1) and Compounds (1a), (1z) and (1zi) are as defined hereinabove.

[0031] In some embodiments, the methods of preparing the compound of Formula (Ib), (Ib-1) and Compound (1b) further comprise the step of adding an anti-solvent and a catalyst to the reaction mixture and reacting the mixture with the anti-solvent and the catalyst, where Formulas (Ib), (Ib-1) and Compound (1b) are as defined hereinabove. In one embodiment, the methods comprise the steps of:

- a. reacting a compound of Formula (Ia), (Ia-1) and Compound (1a) with L-pyroglutamic acid (L-PGA) for a period of time, to provide a compound of Formula (Ib), (Ib-1) and Compound (1b);

- b. adding a catalyst to the reaction mixture of step (a) and reacting the reaction mixture of step (a) with the catalyst for additional period of time;
- c. quenching the reaction of step (b);
- d. adding an anti-solvent to the reaction mixture of step (c); and
- 5 e. reacting the mixture of step (c) with the anti-solvent,

where Formulas (Ia), (Ia-1), (Ib), (Ib-1), and Compounds (1a) and (1b) are as defined hereinabove. [0032] In one embodiment, the anti-solvent is cyclohexane, heptane, hexane or petroleum ether. In one embodiment, the quenching is done via cooling to 25-35°C. Each possibility represents a separate embodiment of the invention.

10 [0033] In one embodiment, the yield of the desired chiral salt (e.g. compound of Formula (Iz), (Ib), (Id) or (Izi), Compound (1z), (1b), (1d), or (1zi)) is less than 50%. In one further embodiment, the yield of the desired chiral salt (e.g. compound of Formula (Iz), (Ib), (Id) or (Izi), Compound (1z), (1b), (1d), or (1zi)) is more than 50%. In another embodiment, the yield is more than 55%. In another embodiment, the yield is more than 60%. In another embodiment, the yield is more than 65%. In another embodiment, the yield is more than 70%. In another embodiment, the yield is more than 75%. In another embodiment, the yield is more than 80%. In another embodiment, the yield is more than 85%. In another embodiment, the yield is more than 90%. In another embodiment, the yield is more than 95%. In another embodiment, the yield is more than 99%. In some embodiments, when the yield of the desired chiral salt (e.g. compound of Formula (Iz), (Ib), (Id), or (Izi), Compound (1z), (1b), (1d), or (1zi)) is less than 50%, the reaction is said to proceed by a chiral resolution mechanism. Chiral resolution is found (e.g. Dale, J. A. et al. *J. Org. Chem.* 1969, **34** (9): 2543–2549) when e.g. a racemic mixture is reacted with a chiral acid/base to provide a chiral salt in a maximum of 50% yield from the initial racemic mixture (one stereoisomer of the chiral salt precipitate in the solution and the other one, of the other enantiomer within the racemate, dissolves within or does not form at all). In some embodiments, when the yield of the desired chiral salt (e.g. compound of Formula (Iz), (Ib), (Id) or (Iz), Compound (1z), (1b), (1d), or (1zi)) is more than 50%, the reaction is via dynamic kinetic resolution (DKR) (Pellisier et al. *Tetrahedron* 2003, **59**, 8291-8327). With DKR, when a racemic mixture is reacted with a chiral acid/base to provide a chiral salt, and the yield is higher than 50%, at least part of the opposite, non-desired enantiomer (within the racemic mixture), is dynamically converted (i.e. epimerized) into the desired enantiomer during the process. In one embodiment, DKR occurs in the absence of a catalyst. In another embodiment, DKR occurs in the presence of a catalyst. In one embodiment, the catalyst is an aldehyde catalyst. In another embodiment, the catalyst is benzaldehyde,

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25
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salicylaldehyde, 3,5-dichlorosalicylaldehyde or p-nitrobenzaldehyde. Each possibility represents a separate embodiment of the invention.

[0034] In another embodiment, the period of time and the additional period of time of steps (a) and (b), respectively, are each independently between 0.5 and 48 hours. In another embodiment, the period or additional period of time is 1-3, 3-5, 5-10, 10-24 or 24-48 hours. Each possibility represents a separate embodiment of the invention.

[0035] In one embodiment, Example 2 provides one method for preparing Compound (1).

[0036] In some embodiments, the methods as described herein produce a chiral compound or salt of e.g. Formula (I), (Ib), (Iz), (Ic), (Id), or (Izi) with a chiral purity of greater than 99%. In another embodiment, the chiral purity is above 99.4%. In another embodiment, the chiral purity is above 99.5%. Each possibility represents a separate embodiment of the invention.

[0037] In some embodiments, the base used within the methods of the present invention comprises an inorganic or organic base or any combination thereof. In one embodiment, the inorganic base comprises: an alkali metal hydroxide, an alkali metal hydride, an alkali metal alkoxide, an alkali metal carboxylate, an alkali metal carbonate or bicarbonate or any combination thereof. In another embodiment, non-limiting examples of alkali metal hydroxides comprise: lithium hydroxide, sodium hydroxide, potassium hydroxide, or a combination thereof. In another embodiment, non-limiting examples of alkali metal hydrides comprise: sodium hydride, potassium hydride, or a combination thereof. In another embodiment, non-limiting examples of alkali metal alkoxides comprise: sodium methoxide, sodium ethoxide, lithium methoxide, lithium ethoxide, sodium tert-butoxide, potassium tert-butoxide, sodium tert-pentoxide, potassium tert-pentoxide, or a combination thereof. In another embodiment, non-limiting examples of alkali metal carboxylates comprise: sodium formate, potassium formate, sodium acetate, potassium acetate, or a combination thereof. In another embodiment, non-limiting examples of alkali metal carbonates or bicarbonates comprise: sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, or a combination thereof. In one embodiment, the organic base comprises: a primary amine, a secondary amine, an aromatic amine, a tertiary amine or any combination thereof. In another embodiment, non-limiting examples of the amines comprise: triethylamine, tributylamine, diisopropylethylamine, diethylamine, N-methylmorpholine, pyridine, 4-(N,N-dimethylamino)pyridine, N,N-dimethylaniline, N,N-diethylaniline, dicyclohexylamine, ethanolamine, diethanolamine, triethanolamine, procaine, or a combination thereof. In another embodiment, the alkali metal bicarbonate is sodium bicarbonate. In another embodiment, the alkali

metal bicarbonate is aqueous or non-aqueous sodium bicarbonate. Each possibility represents a separate embodiment of the invention.

[0038] In some embodiments, a solvent is used within the methods of the present invention. In one embodiment, the solvent comprises an alcoholic solvent, an ester solvent, an ether solvent, a hydrocarbon solvent, a polar aprotic solvent, a ketone solvent, a chlorinated solvent, a nitrile solvent, a polar solvent or any combination thereof. In another embodiment, non-limiting examples of alcoholic solvents include: methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, or a combination thereof. In another embodiment, non-limiting examples of ester solvents include: ethyl acetate, methyl acetate, isopropyl acetate, or a combination thereof. In another embodiment, non-limiting examples of ether solvents include: tetrahydrofuran, diethyl ether, methyl tert-butyl ether, or a combination thereof. In another embodiment, non-limiting examples of hydrocarbon solvents include: toluene, hexane, heptane, cyclohexane, or a combination thereof. In another embodiment, non-limiting examples of polar aprotic solvents include: dimethyl acetamide, dimethyl formamide, dimethyl sulfoxide, or a combination thereof. In another embodiment, non-limiting examples of ketone solvents include: acetone, methyl ethyl ketone, methyl isobutyl ketone, or a combination thereof. In another embodiment, non-limiting examples of chlorinated solvents include: methylene chloride, chloroform, ethylene dichloride, or a combination thereof. In another embodiment, non-limiting examples of nitrile solvents include: acetonitrile, propionitrile, or a combination thereof. In another embodiment, non-limiting examples of polar solvents include water. In another embodiment, the solvent is ethanol. In another embodiment, the solvent is isopropyl acetate. In another embodiment, when a solvent such as water is used for example in the basification step within the methods described hereinabove, the product (e.g. compound of Formula (I), (I-1) or Compound (1)) is isolated directly via for example filtration. In another embodiment, basification step using aqueous base (e.g. KHCO_3 (aq)) is done in the presence of non-aqueous solvent such as methylene chloride, and then the non-aqueous solvent is evaporated following separation thereof from the product (e.g. compound of Formula (I), (I-1) or Compound (1)). Each possibility represents a separate embodiment of the invention.

[0039] In another embodiment, the methods of the present invention include use of a catalyst. In another embodiment, a catalyst is optionally used (i.e. may or may not be used) in the chiral salt formation step (providing a compound of Formula (Ib), (Ib-1), (Iz), (Iz-1), (Ic), (Ic-1), (Id), (Id-1), (Izi), (Izi-1) or Compound (1b), (1z), (1c), (1d) or (1zi)). In another embodiment, the catalyst is an aromatic aldehyde catalyst. In another embodiment, the catalyst is benzaldehyde, salicylaldehyde, 3,5-dichlorosalicylaldehyde, p-nitrobenzaldehyde, or any combination thereof. In another

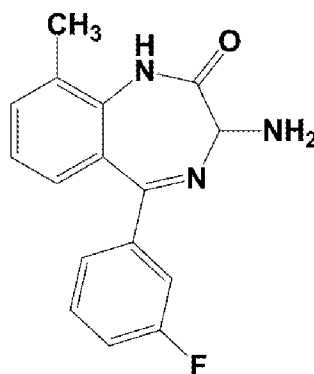
embodiment, the catalyst is 3,5-dichlorosalicylaldehyde. In another embodiment, 0.001 to 1.0 mole equivalents of the catalyst compared to the compound of Formula (Ia), (Ia-1) or Compound (1a) are used. In another embodiment, 0.03 mole equivalents of catalyst are used compared to the compound of Formula (Ia), (Ia-1) or Compound (1a). Each possibility represents a separate
5 embodiment of the invention.

[0040] Without being bound by any mechanism or theory, it is contemplated that the anti-solvent and/or catalyst in the methods of the present invention provides higher yield and/or purity of the provided chiral acid salts (e.g. the compound of Formula (Iz), (Ib), (Izi), (Iz-1), (Ib-1) or Compound (1z), (1zi) or (1b)).

[0041] In another embodiment, the reactions within the methods of the present invention (e.g. salt formation step and/or basification to provide the chiral product) are conducted at a temperature of between -5 - 100°C. In another embodiment, the temperature range is between 60-65°C. In another embodiment, the temperature range is between 0-45°C. In another embodiment, the temperature range is between -5 - 45°C. In another embodiment, the temperature range is between 5-10°C. In
15 another embodiment, the temperature range is between -5 - 35°C. In another embodiment, the temperature range is between 0 - 35°C. In another embodiment, the temperature is 60°C. In another embodiment, the temperature range is between 0 - 100°C. In another embodiment, the salt formation step is conducted at between -5 - 35°C or between 60-65°C. In another embodiment, the basification to provide the chiral product is conducted at between 0-45°C or 5-10°C. Each
20 possibility represents a separate embodiment of the invention.

Compounds (1a)-(1d)

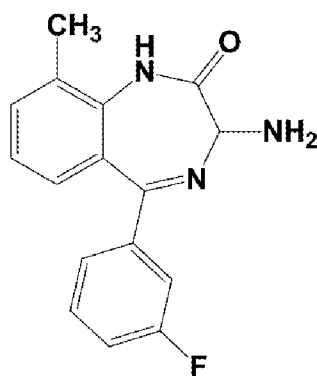
[0042] In another embodiment, the present invention provides a compound represented by the following structure:



Compound (1a)

and/or any pharmaceutically acceptable salts thereof.

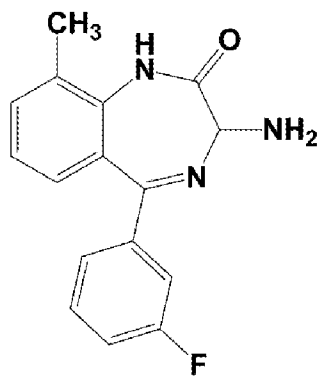
[0043] In another embodiment, the present invention provides a compound represented by the following structure:



Compound (1a)

5 and any pharmaceutically acceptable salts thereof.

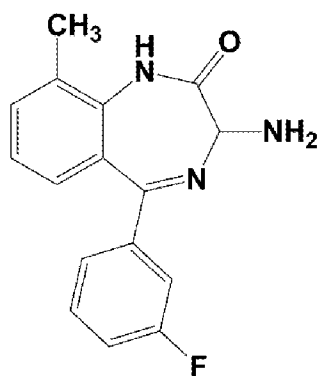
[0044] In another embodiment, the present invention provides a compound represented by the following structure:



Compound (1a)

10 or any pharmaceutically acceptable salts thereof.

[0045] In another embodiment, the present invention provides a compound represented by the following structure:

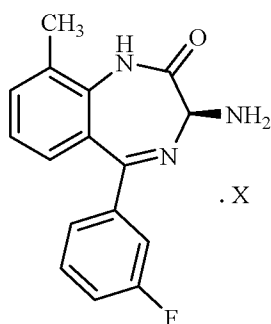


Compound (1a),

a pharmaceutically acceptable salt thereof, or a combination thereof.

[0046] In another embodiment, the present invention provides a mixture or combination comprising a) Compound (1a) in its free base form and b) Compound (1a) in its pharmaceutically acceptable salt form, wherein Compound (1a) is as described hereinabove.

[0047] In another embodiment, the present invention provides a compound represented by the structure of Compound (2):



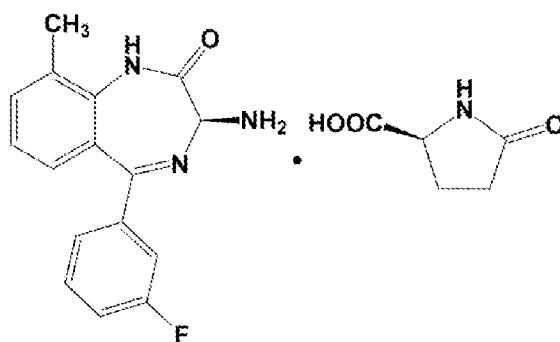
Compound (2),

wherein X comprises: chloride, acetate, adipate, alginate, ascorbate, aspartate, benzoate, benzenesulfonate, bisulfate, borate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydroiodide, maleate, 2-hydroxyethanesulfonate, lactate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, salicylate, succinate, sulfate, sulfonate, tartrate, thiocyanate, toluenesulfonate, or undecanoate salt, or any combination thereof.

[0048] In one embodiment, a compound as described herein, which, in one embodiment, is Compound (1a), is a free base. In another embodiment, the compound is in a pharmaceutically acceptable salt form. In one embodiment, a free base comprises a compound in which the amine moiety of the compound (NH₂) is not protonated. In one embodiment, a pharmaceutically acceptable salt form comprises a compound in which the amine moiety of the compound (NH₂) is protonated, and the whole compound is positively charged. In one embodiment, a counter anion is used to balance the charges. In another embodiment, Compound (1a) is in a chloride, acetate, adipate, alginate, ascorbate, aspartate, benzoate, benzenesulfonate, bisulfate, borate, butyrate, citrate, camphorate, pyroglutamate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, maleate, 2-

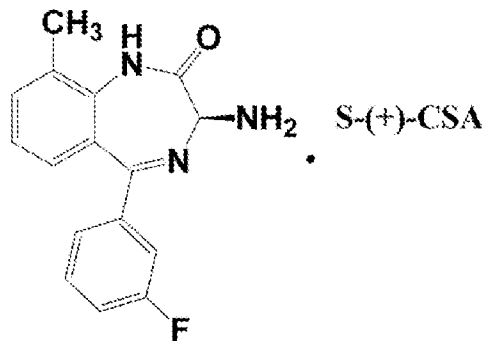
hydroxyethanesulfonate, lactate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, salicylate, succinate, sulfate, sulfonate, tartrate, thiocyanate, toluenesulfonate, or undecanoate salt form, or any combination thereof. Each possibility represents a separate embodiment of the invention.

[0049] In another embodiment, the present invention provides a compound represented by the following structure:



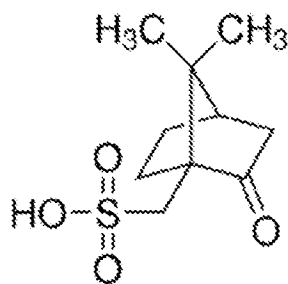
Compound (1b)

[0050] In another embodiment, the present invention provides a compound represented by the following structure:



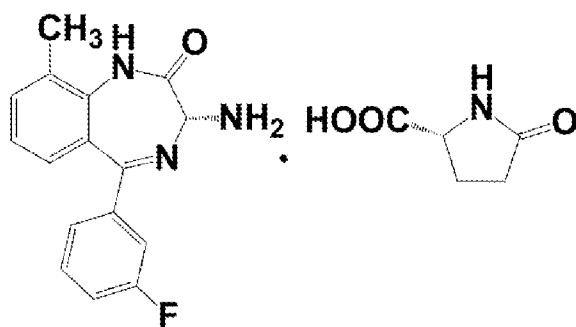
Compound (1c)

wherein S-(+)-camphorsulfonic acid (CSA) is



CSA

[0051] In another embodiment, the present invention provides a compound represented by the following structure:



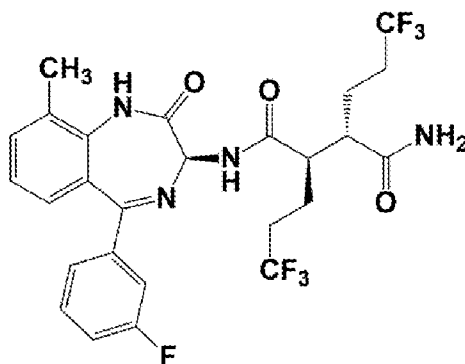
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Compound (1d).

Each possibility represents a separate embodiment of the invention.

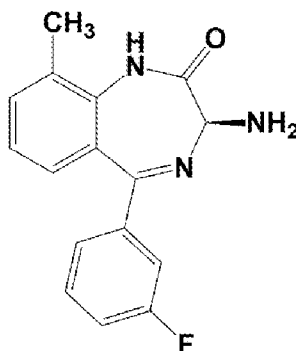
[0052] In some embodiments, the present invention provides Compounds (1a)-(1c) for use as intermediates in the preparation of (2R,3S)-N-[(3S)-5-(3-Fluorophenyl)-9-methyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl]-2,3-bis(3,3,3-trifluoropropyl)succinimide, presented below:

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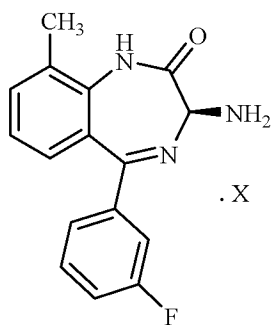
[0053] In one embodiment, the chiral Compound (1) is prepared from Compounds (1a)-(1c), using the methods of the present invention, as detailed below in “Method of Preparing Compound of Formula (I) and Salts thereof.”

15



Compound (1)

[0054] In one embodiment, the chiral Compound (2) is prepared from Compounds (1a)-(1c), using the methods of the present invention, as detailed below in “Method of Preparing Compound of Formula (I) and Salts thereof.”



Compound (2)

[0055] The preparation of (2R,3S)-N-[(3S)-5-(3-Fluorophenyl)-9-methyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl]-2,3-bis(3,3,3-trifluoropropyl)succinimide from Compound (1) is further detailed in US 9,273,014, incorporated herein by reference in its entirety.

Definitions

[0056] In some embodiments, each R^1 is independently F, Cl, Br, I, OCH_3 , CN or NO_2 . In one embodiment, when n^1 is greater than 1, each R^1 is identical or different. Each possibility represents a separate embodiment of the invention.

[0057] In some embodiments, each R^2 is independently C_1 - C_5 alkyl. In one embodiment, the term “alkyl” refers to either branched and straight chain saturated aliphatic hydrocarbon groups containing, for example, from 1 to 12 carbon atoms, from 1 to 6 carbon atoms, and from 1 to 5 carbon atoms. Examples of alkyl groups include, but are not limited to, methyl (Me), ethyl (Et),

propyl (e.g., n-propyl and i-propyl), butyl (e.g., n-butyl, i-butyl, sec-butyl, and t-butyl), and pentyl (e.g., n-pentyl, isopentyl, neopentyl), n-hexyl, 2-methylpentyl, 2-ethylbutyl, 3-methylpentyl, and 4-methylpentyl. When numbers appear in a subscript after the symbol “C”, the subscript defines with more specificity the number of carbon atoms that a particular group may contain. For example, “C₁₋₅ alkyl” denotes straight and branched chain alkyl groups with one to five carbon atoms. Each possibility represents a separate embodiment of the invention.

[0058] In some embodiments, n¹ is an integer between 1 and 5. In one embodiment, n¹ is 1, 2, 3, 4 or 5. Each possibility represents a separate embodiment of the invention.

[0059] In some embodiments, n² is an integer between 1 and 4. In one embodiment, n¹ is 1, 2, 3 or 4. Each possibility represents a separate embodiment of the invention.

[0060] The term “reacting” within the context of the present invention is defined as provision of one or more conditions (e.g. heating, refluxing) which are sufficient for reactants to react chemically.

[0061] In some embodiments, when the following moiety is found within a compound as described hereinabove (e.g. compounds represented by the structures of Formulas (Ib), (Id), (Ib-1), (Id-1) and Compounds (1b) and (1d)):



It is to be understood that at least part of the moiety can be represented by the following ion pair structure:



[0062] In some embodiments, when the following moiety is found within a compound as described hereinabove (e.g. compounds represented by the structures of Formulas (Ic), (Ic-1) and Compound (1c)):



It is to be understood that at least part of the moiety can be represented by the following ion pair structure:



In one embodiment, all (or almost all, e.g. above 99%) of the amine is protonated and all (or almost all, e.g. above 99%) of the carboxylic acid/sulfonic acid is deprotonated within the above structure/embodiment. In some embodiments, the notation “” means “any moiety”.

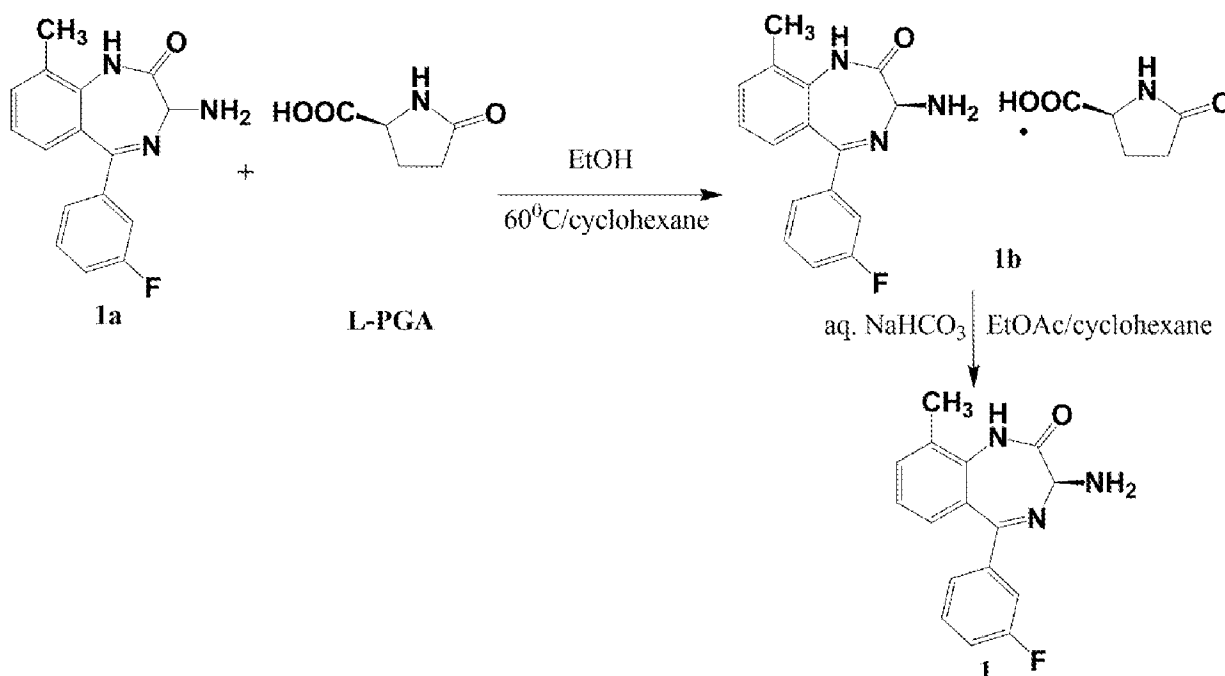
- 5 [0063] The following examples are presented in order to more fully illustrate the preferred embodiments of the invention. They should in no way, however, be construed as limiting the broad scope of the invention.

EXAMPLES

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EXAMPLE 1

Synthesis of Compound (1) – Method A



- 15 [0064] Compound (1a) (0.5 g, 1.0 eq; see synthesis thereof below) was dissolved in EtOH (10 mL, 20 vol) and stirred for 10 min at 25-35°C. L-pyrroglutamic acid or (S)-(-)-2-Pyrroldione-5-carboxylic acid (0.23 g, 1.0 eq) was added (clear solution followed by solid precipitation was observed at 25-35°C), and the contents were heated to 60-65°C, stirred for 1.0 h and subsequently cooled to 25-35°C. Cyclohexane (20 mL, 40 vol) was then added, the solid precipitate was filtered and washed with cyclohexane (5 mL, 10 vol), and the washed solid was dried at 45°C to obtain
- 20 Compound (1b) (0.5 g; 68.4% yield from (1a)). The chiral HPLC purity of Compound (1b) was

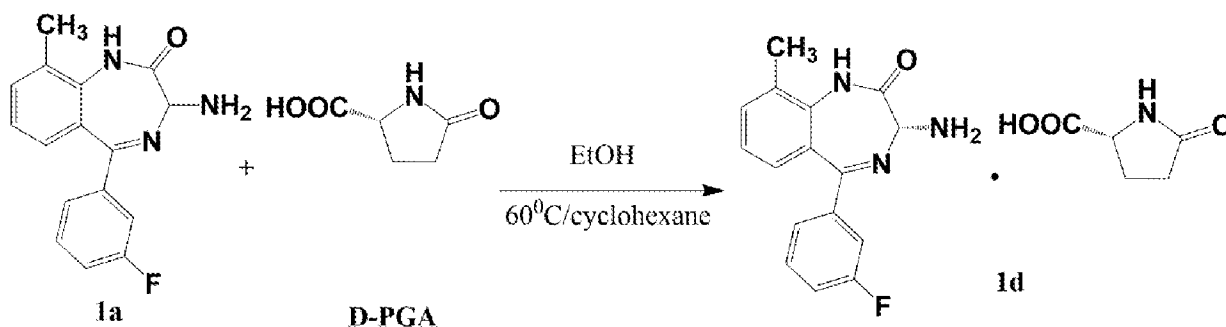
99.4% and of the other isomer was 0.6% (Figure 1). The chiral purity was measured using HPLC with: column of ChiralPack OJ-RH (50 x 4.6 mm, 5 μ m), mobile phase of 10mM ammonium acetate in water:acetonitrile (80:20), pH 7.5 adjusted with ammonium hydroxide, methanol diluent, 1.2 ml/minute flow and isocratic gradient. Retention time of Compound (1b) was 9.54 minutes under these conditions. When 0.5 g of Compound (1a) were used, 0.5 g of Compound (1b) were obtained; when 2 g of Compound (1a) were used, 1.72 g of Compound (1b) were obtained; and when 5 g of Compound (1a) were used, 4.5 g of Compound (1b) were obtained.

[0065] 0.5 gr Compound (1b) was dissolved in water (5 mL, 10 vol), and the pH was adjusted to 8.0-8.5 with 10% NaHCO₃ solution at 25-35°C. The aqueous layer was extracted with EtOAc (270 mL). The combined organic layers were dried over Na₂SO₄, filtered, and the organic layer was distilled-off under vacuum at 30-35°C. To the dried organic layer cyclohexane was added (5 mL, 10 vol), and the resulting solution was stirred for 12 h. The resulting precipitate was filtered and washed with cyclohexane (2.5 mL, 5.0 vol) and subsequently dried at 50-55°C for 16 h to get 0.2g of Compound (1) as the S isomer of Compound (1a). When 0.2 g of Compound (1b) were used, 0.13 g of Compound (1) were obtained.

[0066] The resolution of Compound (1a) using Pyroglutamic acid in ethanol provided an excellent separation of R & S isomers due to the difference in solubility of the diastereomeric salts formed. The S-isomer of Compound (1a), i.e. Compound (1) - was isolated with >99.4% chiral purity after treatment of the diastereomeric salt of the S-isomer with aqueous NaHCO₃.

EXAMPLE 2

Synthesis of Compound (1d)



[0067] Compound (1a) (500 mg, 1.0 eq.) was dissolved in EtOH (10 ml), stirred for 10 min. Next, D-pyrogutamic acid (D-PGA; 0.228 gr, 1.0 eq) was added, and the contents were heated to 60-65°C and then stirred for 1.0 hr, followed by cooling to 25-35°C. Cyclohexane (20 mL) was subsequently added, and the resulting mixture was stirred for 1.0 h at 25-35°C and filtered. The

obtained solid was washed with cyclohexane and dried at 50-55°C to get Compound (1d) at a yield of 0.43 gr/59.1%.

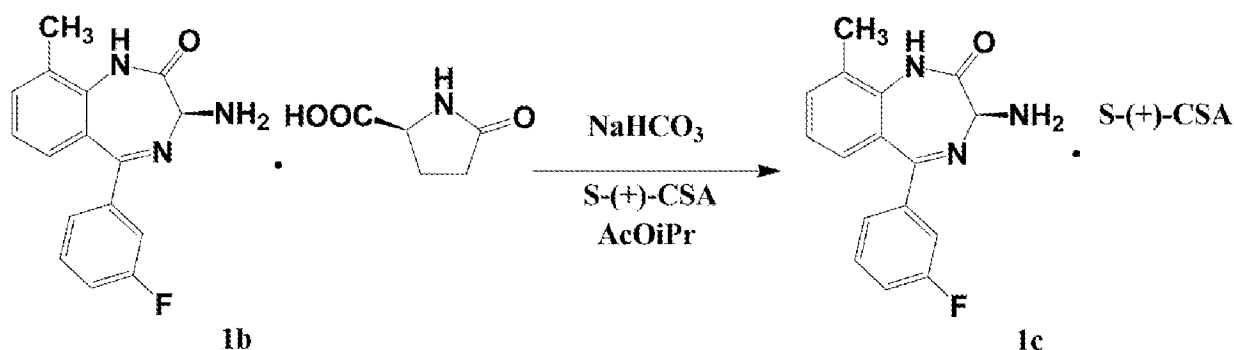
EXAMPLE 3

Non-PGA Salts Did Not Resolve Compound (1a)

[0068] L-Aspartic acid, L-Leucine, S-Mandelic acid, N-Acetyl-L-Tyrosine, N-Acetyl-L-Valine, S-(+)-CSA (camphor sulfonic acid) and L-Glutamic acid were used in similar manner as L-PGA was used in Method A of Example 1. L-Aspartic acid, L-Leucine and N-acetyl-L-Tyrosine did not form a salt with Compound (1a). N-Acetyl-L-Valine, S (+) CSA and L-Glutamic acid salt formation was observed with Compound (1a) but no resolution (50:50 mix. of R:S isomers) was observed by chiral HPLC after isolation of salt.

EXAMPLE 4

Synthesis of Compound (1c)



[0069] 1.0 gr (1.0 eq.) of Compound (1b) was dissolved in water (10 vol), and the pH was adjusted to 8.0-8.5 with 5% NaHCO₃ solution (0.5 gr, 0.5 w/w% 10 vol) at 25-35°C. The mixture was stirred for 30 min. AcOiPr (40 ml) was added, and the resulting mixture was stirred for 30 min followed by separation of both layers. The aqueous layer was extracted with AcOiPr (15 ml). The combined organic layers were dried over NaSO₄ (2.0 g), filtered and washed with AcOiPr (5 ml), and then the filtrate was dissolved into Round Bottom Flask (RBF). S-CSA (0.56 gr/1.0 eq.) was added into RBF, and the resulting mixture was stirred for 4h. The resultant solid was filtered, and the compound was washed with AcOiPr (5.0 ml) and dried at 60-65°C for 16h. The yield of Compound (1c) was 0.95 gr/60.8 %, and chiral purity was 99.88%. When upscaling the reaction by a factor of five (i.e. employing 5.0 eq. (5.0 gr) of Compound (1b) and using corresponding amounts of other reagents/solvents) – a 75% yield of Compound (1c) was achieved, having an HPLC chiral purity of 99.64% (Figure 2). Chiral purity was measured using HPLC, with: column of ChiralPack

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OJ-RH (50 x 4.6 mm, 5 μ m), mobile phase of 10mM ammonium acetate in water: acetonitrile (80:20), pH 7.5 adjusted with ammonium hydroxide, methanol diluent, 1.0 ml/minute flow and isocratic gradient. Retention time of Compound (1c) was 8.03 minutes under these conditions.

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EXAMPLE 5

Synthesis of Compound (1) – Method B (cyclohexane addition)

[0070] Example 1 was repeated using a modified procedure for preparing Compound (1b):

2.0 gr Compound (1a) (1.0 eq.) was dissolved in EtOH (10 ml), and the solution was stirred for 10 min. Then, L-pyroglutamic acid (0.91 gr, 1.0 eq) was added, and the contents were heated to 60-65°C and stirred for 8.0 hr, followed by cooling to 25-35°C. Cyclohexane (80 ml) was then added, and the resulting mixture was stirred for 12 h at 25-35°C and filtered. The obtained solid was washed with cyclohexane (80 ml) and dried at 50-55°C to produce Compound (1b) at a yield of 1.72 gr/59.1%. Compound (1) was prepared from Compound (1b) as in Example 1.

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EXAMPLE 6

Synthesis of Compound (1) – Method C (3,5-dichlorosalicylaldehyde addition)

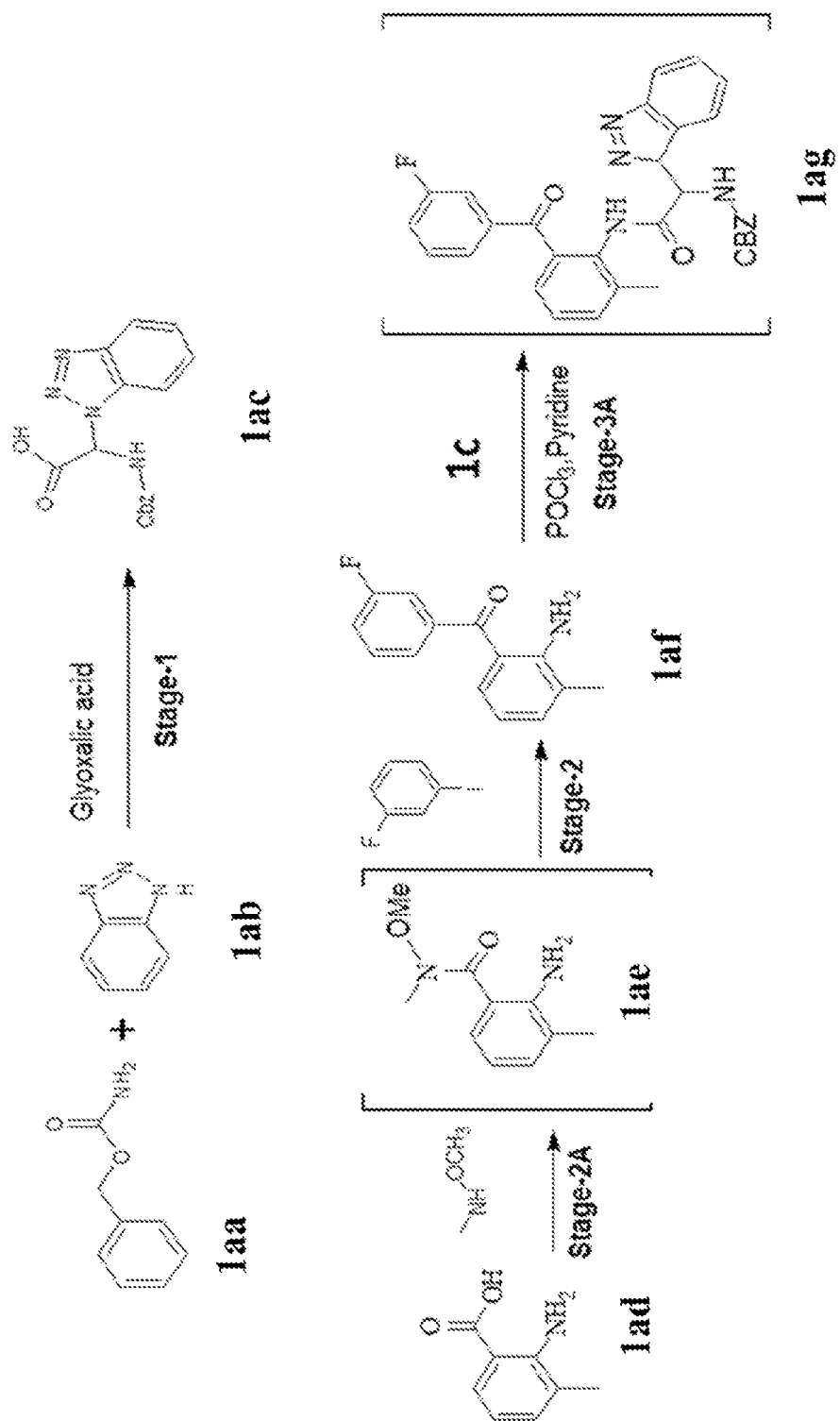
[0071] Example 1 was repeated using a modified procedure for the preparation of Compound (1b):

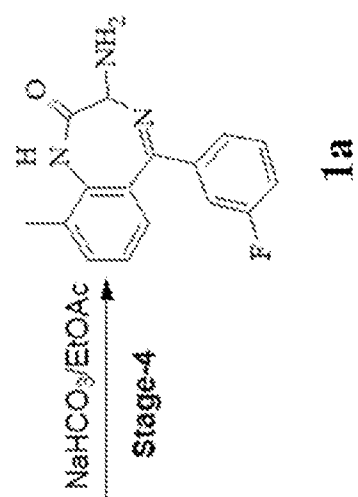
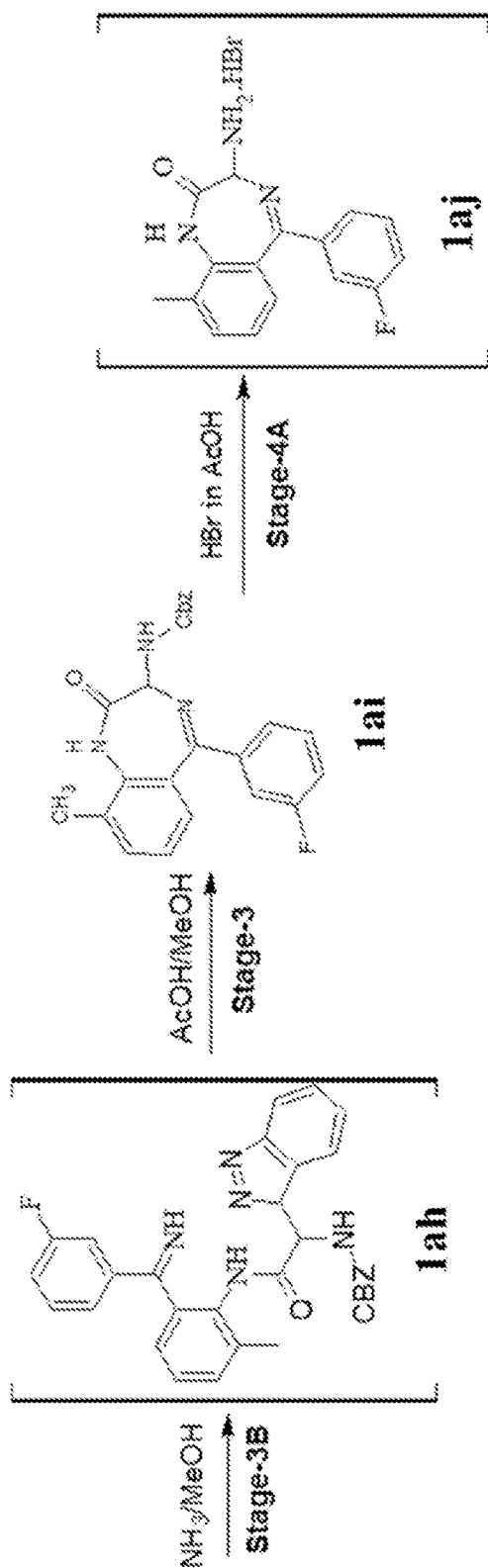
2.0 gr Compound (1a) (1.0 eq.) was dissolved in EtOH (40 ml), and the solution was stirred for 10 min. Then, L-pyroglutamic acid (0.91 gr, 1.0 eq) was added, and the contents were heated to 60-65°C and stirred for 4.0 hr. Then 3,5-Dichoro salicylaldehyde (0.03 eq) was added, and the contents were maintained for 4.0hr at 60-65°C followed by cooling to 25-35°C. Cyclohexane (80 ml) was then added. The resulting mixture was stirred for 12 h at 25-35°C and filtered. The obtained solid was washed with cyclohexane (80 ml) and dried at 50-55°C to produce Compound (1b) at a yield of 2.38 gr/79.9%. Compound (1) was prepared from Compound (1b) as in Example 1.

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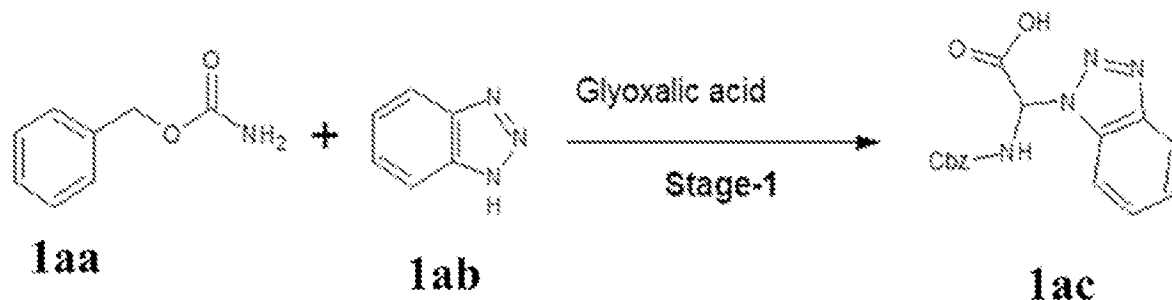
EXAMPLE 7

Synthesis of Compound (1a)



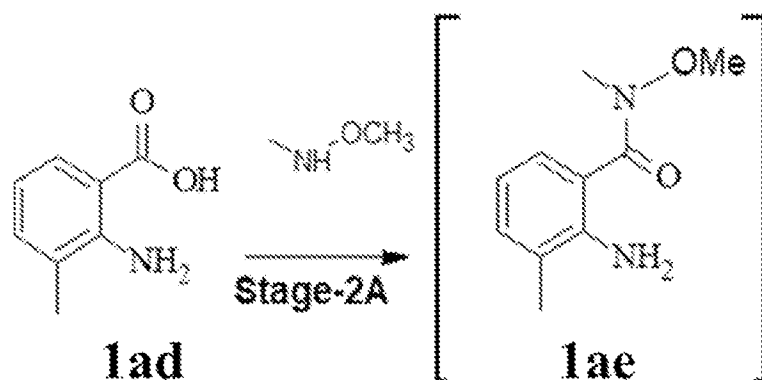


Stage 1



[0072] The experiment was performed at 150 g scale: 150 gr (1 eq.) 1ab, 200.3 gr (1.05 eq.) 1aa, 144.2 gr (1.25 eq.) glyoxalic acid and 4.5 L toluene were mixed at 55-60°C for 6 hr. The progress of the reaction was monitored by TLC. Starting material was present around 2-3% after 4 hrs. After the reaction was completed, the mixture was cooled to 25-30°C, and purified water (10 vol) was added. The resulting mixture was stirred for 1.0 hr, and the contents were filtered. The obtained slurry was washed with water (15 vol) followed by a toluene (5 vol) & MTBE (10 vol) wash. Subsequently, the slurry was dried in a vacuum oven at 70-75°C, with a yield of 375 gr/91.3 % with purity of 97.11% (HPLC).

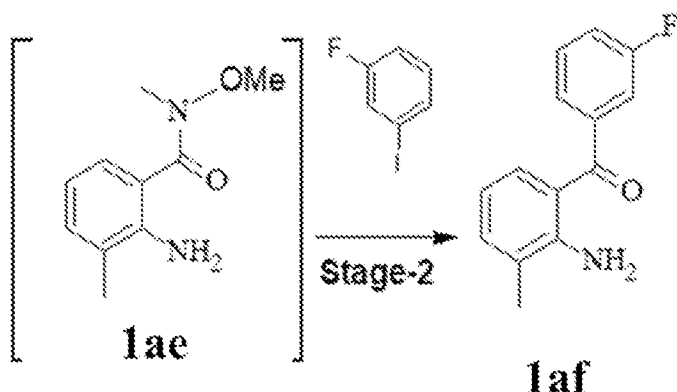
Stage 2A



[0073] The experiment was performed at 10 g scale: 10 gr (1 eq.) 1ad, 12.9 gr (2.0 eq.) methoxymethylamine, 23.3 gr (1.1 eq.) TBTU, 40.1 ml (3.4 eq.) DIPEA and 100ml THF were mixed at 25-35°C for 8 hr. Progress of the reaction was monitored by TLC and starting material was present ~ below 1.0% after 8 hrs. After completion of the reaction, 10% aq NaHCO₃ solution (10 vol) were added, the mixture was stirred for 30 min, then isopropyl acetate (10 vol) was added and the resulting mixture was stirred for 30 min. Both layers were separated.

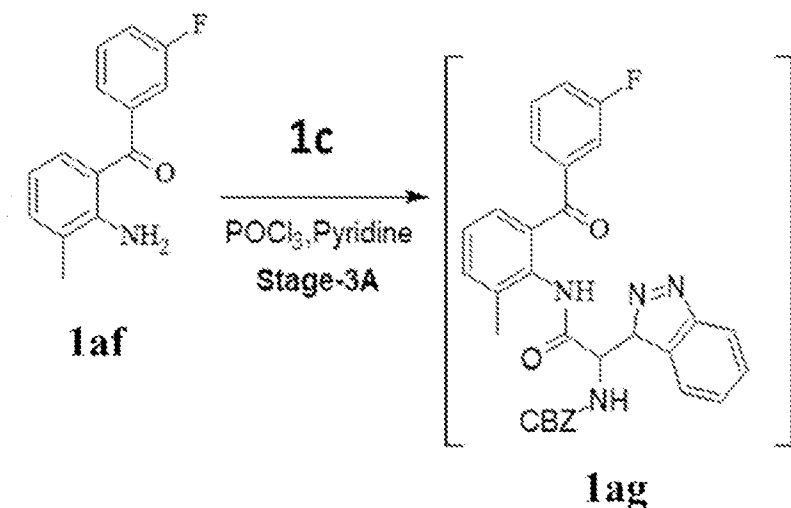
The organic layer was washed with 10% aq NaHCO₃ solution (2 x 5 vol), water (5 vol) and brine solution (5 vol) and then it was dried over Na₂SO₄, filtered and concentrated under vacuum to get compound which was confirmed by HNMR and mass. Yield was 13.1 gr.

5 Stage 2



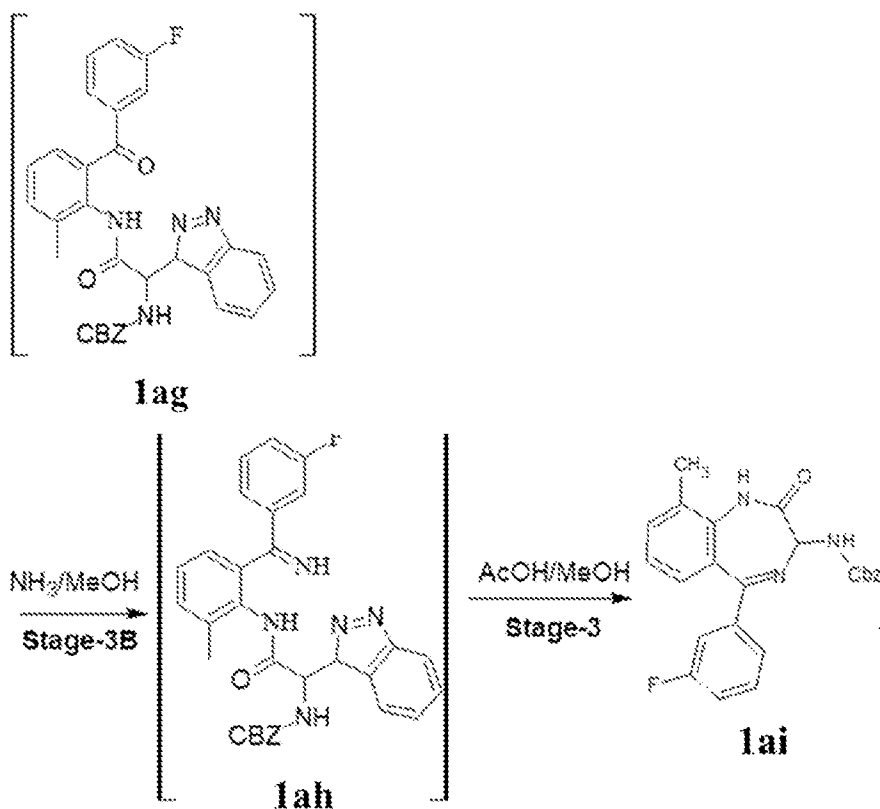
[0074] The experiment was performed at 13 g scale: 13 gr (1 eq.) 1ae, 51.9 gr (3.5 eq.) 3-fluoro-1-iodo-benzene, 93.5 ml (3.5 eq.) 2.5M n-BuLi, 104ml THF were mixed at (-78) – (-73)°C for 1 hr. Progress of the reaction was monitored by TLC and starting material was present ~ below 1.0% after 1 hr. After completion of the reaction, 20% aq Ammonium chloride (13 vol) were added, the mixture was stirred for 30 min and then ethyl acetate (7 vol) was added and the resulting mixture was stirred for 30 min. Both layers were separated. The organic layer was washed with saturated brine solution (5 vol), dried over Na₂SO₄, filtered and concentrated under vacuum to get crude compound which was confirmed by ¹H NMR and mass spectrometry. Yield was 9.5 gr / 53.7%.

Stage 3A



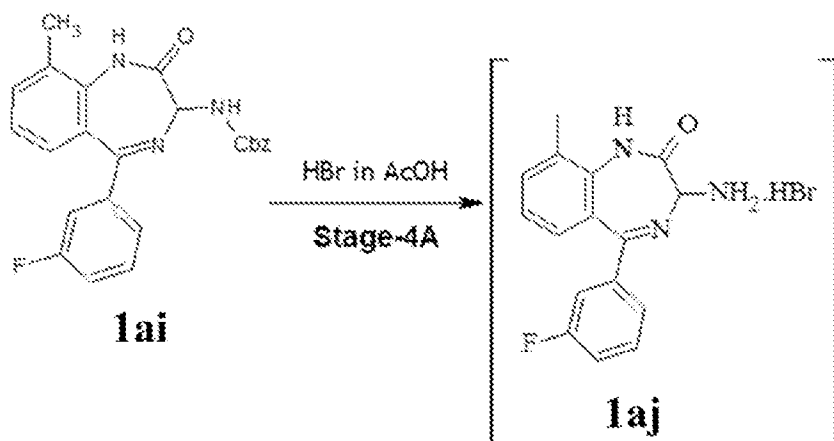
[0075] The experiment was performed at 9 g scale: 9 gr (1 eq.) **1af**, 13.2 gr (1.2 eq.) **1c**, 6.2 gr
 5 (1.2 eq.) POCl_3 , 18 ml (2.0 eq.) pyridine and 45 ml THF were mixed at $(-345) - (-30)^\circ\text{C}$ for
 0.25 hr, then at $0-15^\circ\text{C}$ for 1 hr. After completion of the reaction, the reaction mass was
 quenched with ice cold water (5 vol), stirred for 30 min, then Ethyl acetate (10 vol) was added
 and resulting mixture was stirred for 30 min. Both layers were separated. The organic layer
 was washed with 1N HCl solution (10 vol), water (10 vol), 10% sodium bicarbonate solution
 10 (10 vol), water (10 vol), and saturated brine solution (4 vol) and then the resulting mixture was
 dried over Na_2SO_4 , filtered and concentrated under vacuum. Subsequently, IPA (5 vol) was
 added to get the compound, which was confirmed by ^1H NMR and Mass. Yield was 16 gr/88%.

Stage 3B and 3



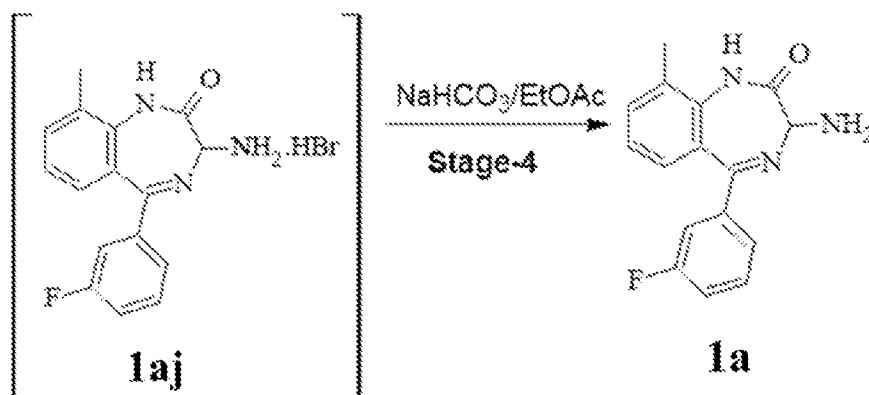
- 5 [0076] The experiment was performed at 15 g scale of 1ag. NH_3 gas purging in Methanol (6.0 vol) for 1h at 0-5°C and after the ammonia gas purging reaction, resulting mixture was distilled of the solvent upto 4.0 vol and 5-6 vol Methanol were added and co-distilled upto 3-4 vol. Acetic acid (4.0 vol) was added to the organic layer and the solution was stirred for 16h at 25-30°C. Following reaction completion, solvent was distilled up to 4.0 vol and the mixture was
- 10 cooled to 25-30°C and then IPA (6.0 vol) and water (6.0 vol) were added, followed by filtration of the solid which was washed with a mixture of IPA (6.0 vol) and purified water (10.0 vol). The product was analyzed and the yield was 7.5 gr/53%.

Stage 4A



[0077] The Experiment was performed at 7 g scale: 7 gr (1 eq.) Compound (**1ai**), 35 ml (5 vol) HBr in AcOH, and 175 ml MTBE were mixed at 25-35°C for 1-2 hrs. Progress of the reaction was monitored by TLC and the starting material was absent after 1 hr. After completion of the reaction, MTBE (15.0 vol) was added, the mixture was stirred for 2h, the contents were filtered and the slurry was washed with MTBE (10 vol), vacuum dried for 1hr and dried at 45-50°C to get Compound (**1aj**) at yield of 6.0 gr/98%.

Stage 4



[0078] The experiment was performed at 90 g scale of 1aj. Compound (1aj) was dissolved in water (10 vol) and the pH was adjusted to 8.0-8.5 with 10% NaHCO₃ solution (5.0 vol) at 25-35°C. After pH adjustment a heterogenous mixture was observed. The contents were stirred

for 2.0 h at 25-35°C, filtered and washed with purified water (5.0 vol) and suck dried under vacuum. The wet material was extracted with EtOAc (1.0 vol) at 25-35°C for 30 min and the compound was filtered and washed with EtOAc (1.0 vol) and dried at 50-55°C for 16h. Yield was 52 gr/85.2%.

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EXAMPLE 8

A dynamic kinetic resolution study of Compound (1a)

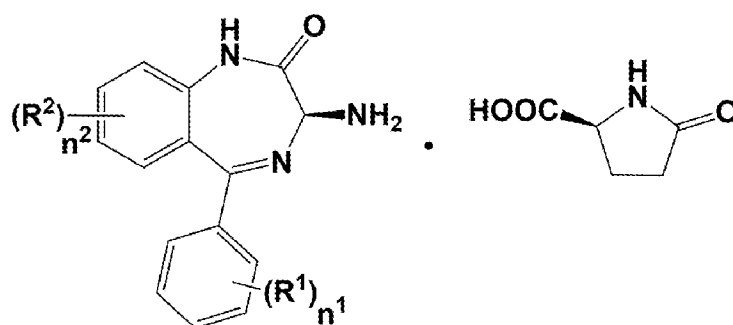
[0079] Compound (1a) is converted to the S isomer (Compound (1)) in one step (with high yield and high chiral purity) using catalytic amounts of benzaldehyde, salicylaldehyde, 3,5-dichlorosalicylaldehyde or p-nitrobenzaldehyde and a solvent such as cyclohexane/EtOH or other appropriate solvent system.

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CLAIMS

What is claimed is:

1. A method of preparing the compound of Formula (Ib),



Formula (Ib)

wherein

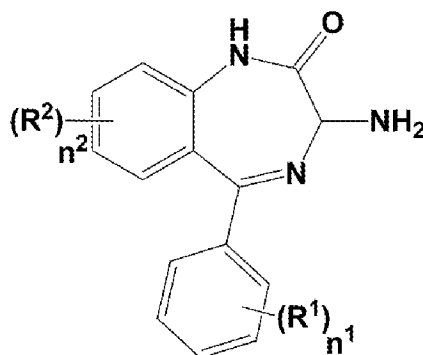
R^1 each is independently Cl, F, Br, I, OCH_3 , CN or NO_2 ;

R^2 each is independently identical or different C_1 - C_5 alkyl;

n^1 is an integer between 1 and 5; and

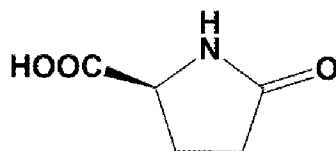
n^2 is an integer between 1 and 4;

comprising the step of: reacting the compound of Formula (Ia)



Formula (Ia)

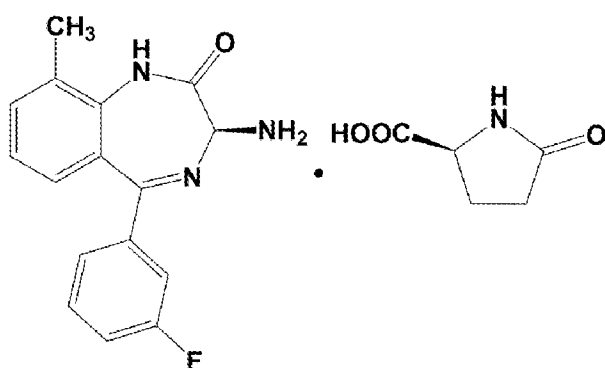
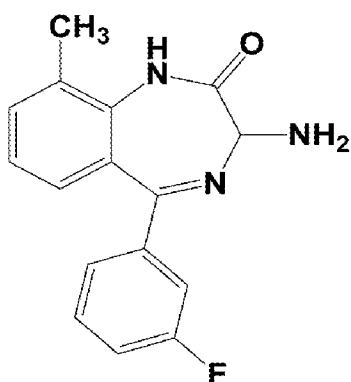
with L-pyroglutamic acid (L-PGA),



L-pyroglutamic acid (L-PGA),

in the presence of solvent and with or without catalyst to obtain a compound of Formula (Ib).

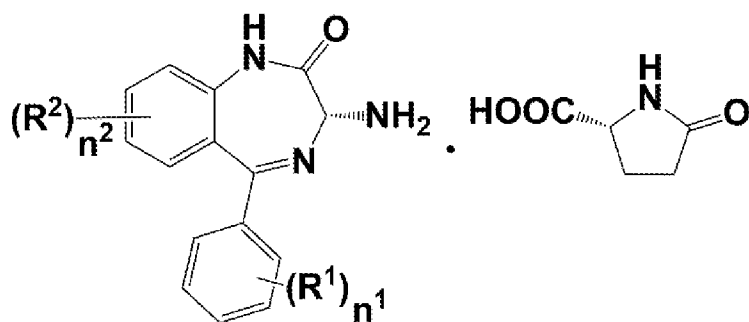
- 5 2. The method according to claim 1, wherein the compound of Formula (Ia) is represented by Compound (1a) and the compound of Formula (Ib) is represented by Compound (1b):



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Compound (1a) and Compound (1b).

3. The method of claim 1, wherein the yield of the compound of Formula (Ib) is greater than 50%.
4. A method of preparing the compound of Formula (Id),



Formula (Id)

wherein

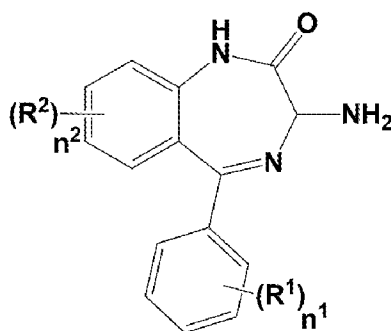
R^1 each is independently Cl, F, Br, I, OCH_3 , CN or NO_2 ;

5 R^2 each is independently identical or different C_1 - C_5 alkyl;

n^1 is an integer between 1 and 5; and

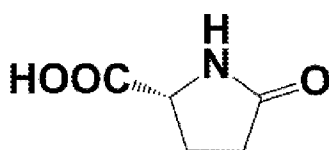
n^2 is an integer between 1 and 4;

comprising the steps of: reacting the compound of Formula (Ia)



Formula (Ia)

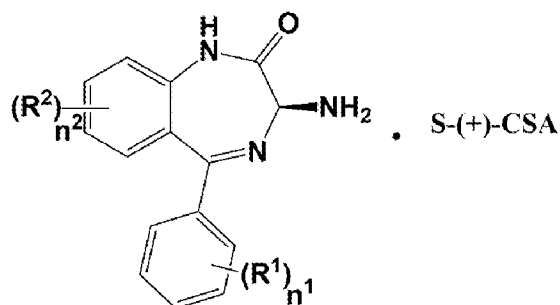
10 with D-pyroglutamic acid (D-PGA),



D-pyroglutamic acid (D-PGA)

15 in the presence of solvent and with or without catalyst to obtain a compound of Formula (Ib).

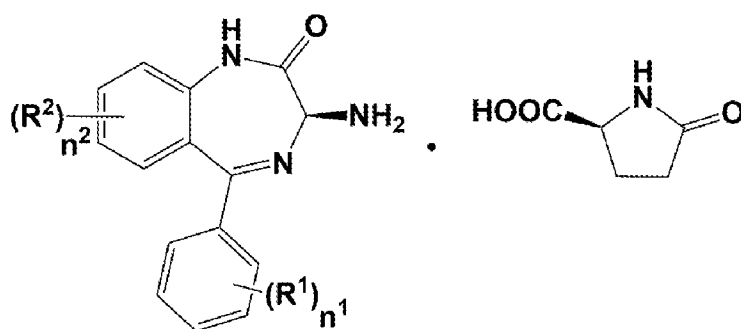
5. The method of claim 4, wherein the yield of the compound of Formula (Id) is greater than 50%.
6. The method according to any one of claims 1-5, wherein the catalyst comprises benzaldehyde, salicylaldehyde, 3,5-dichlorosalicylaldehyde, p-nitrobenzaldehyde or any combination thereof.
7. The method according to claim 6, wherein the catalyst comprises 3,5-dichlorosalicylaldehyde.
8. The method according to any one of claims 1-7, wherein 0.001 to 1.0 mole equivalents of the catalyst compared to the compound of Formula (Ia) are used.
9. The method according to claim 8, wherein 0.03 mole equivalents of the catalyst compared to the compound of Formula (Ia) are used.
10. The method according to any one of claims 1-9, wherein the solvent comprises an alcoholic solvent; an ester solvent; an ether solvent; an hydrocarbon solvent; a polar aprotic solvent; a ketone solvent; a chloro solvent; a nitrile solvent; a polar solvent; or any combination thereof.
11. The method according to claim 10, wherein the alcoholic solvent is ethanol.
12. The method according to any one of claims 1-11, wherein the reaction is conducted at a temperature between 0-100 °C.
13. The method according to claim 12, wherein the temperature is between 60-65 °C.
14. A method of preparing the compound of Formula (Ic),



Formula (Ic)

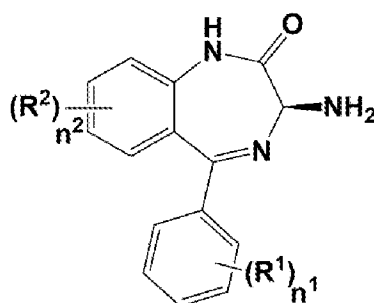
comprising the steps of:

- a) reacting the compound of Formula (Ib):



Formula (Ib)

with a base and solvent to provide a compound of Formula (I); and

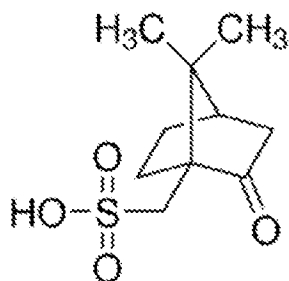


Formula (I)

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b) reacting the compound of Formula (I) with

S (+) camphor sulfonic acid (CSA):



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to provide a compound of Formula (Ic),

wherein

R^1 each is independently Cl, F, Br, I, OCH_3 , CN or NO_2 ;

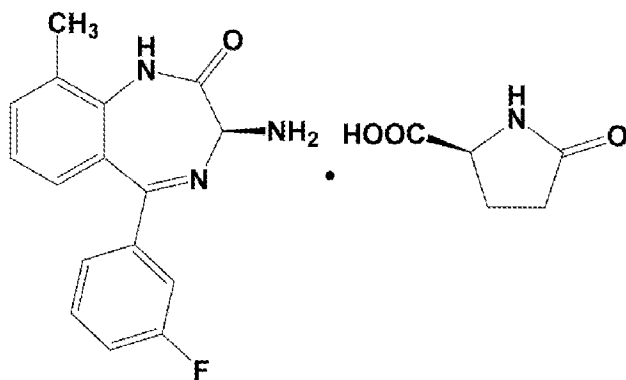
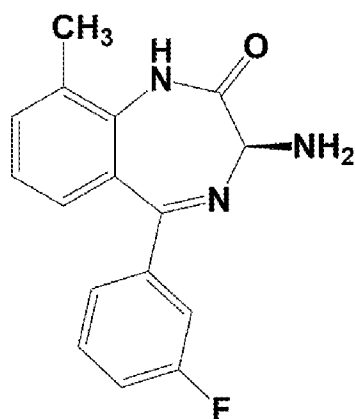
R^2 each is independently identical or different C_1 - C_5 alkyl;

n^1 is an integer between 1 and 5; and

15

n^2 is an integer between 1 and 4.

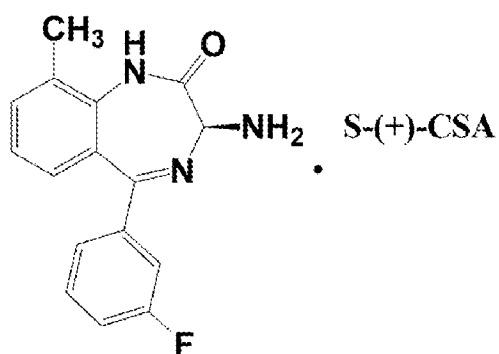
15. The method according to claim 14, wherein the compound of Formula (I) is represented by Compound (1); the compound of Formula (Ib) is represented by Compound (1b); and the compound of Formula (Ic) is represented by Compound (1c):



Compound (1);

Compound (1b);

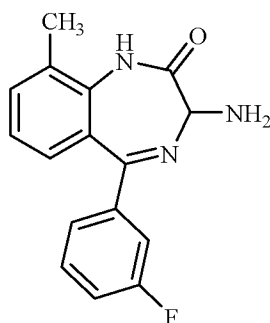
and



Compound (1c).

16. The method according to any one of claims 14-15, wherein the base comprises an inorganic base, an organic base, or any combination thereof.

17. The method according to claim 16, wherein the inorganic base comprises: an alkali metal hydroxide; an alkali metal hydride; an alkali metal alkoxide; an alkali metal carboxylate; an alkali metal carbonate, bicarbonate, or any combination thereof.
18. The method according to claim 17, wherein the alkali metal carbonate is sodium bicarbonate.
19. The method according to any of claims 16-18, wherein the organic base comprises: a primary amine, a secondary amine, an aromatic amine, a tertiary amine, or any combination thereof.
20. The method according to any one of claims 14-19, wherein the solvent comprises an alcoholic solvent; an ester solvent; an ether solvent; an hydrocarbon solvent; a polar aprotic solvent; a ketone solvent; a chloro solvent; a nitrile solvent; a polar solvent; or any combination thereof.
21. The method according to claim 20, wherein the ester solvent is isopropyl acetate.
22. The method according to any one of claims 14-21, wherein the reaction of step (a) is conducted at a temperature between 0-45 °C.
23. The method according to claim 22, wherein the temperature range is between 5-10 °C.
24. The method according to any one of claims 1-23, wherein the chiral purity of the compound of Formula (I), (Ib), (Ic) or (Id) is greater than 99%.
25. The method according to claim 24, wherein the chiral purity is greater than 99.5%.
26. A compound represented by the following structure:

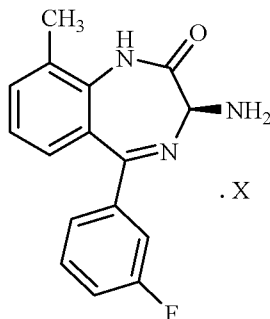


Compound (1a),

a pharmaceutically acceptable salt thereof, or a combination thereof, wherein said salt comprises chloride, acetate, adipate, alginate, ascorbate, aspartate, benzoate, benzenesulfonate, bisulfate, borate, butyrate, citrate, camphorate, D-10-camphor sulfonate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate,

heptanoate, hexanoate, hydroiodide, maleate, 2-hydroxyethanesulfonate, lactate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, salicylate, succinate, sulfate, sulfonate, tartrate, thiocyanate, toluenesulfonate or undecanoate salt or any combination thereof.

27. A compound represented by the following structure:



Compound (2),

wherein X comprises: chloride, acetate, adipate, alginate, ascorbate, aspartate, benzoate, benzenesulfonate, bisulfate, borate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydroiodide, maleate, 2-hydroxyethanesulfonate, lactate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, salicylate, succinate, sulfate, sulfonate, tartrate, thiocyanate, toluenesulfonate, or undecanoate salt, or any combination thereof.

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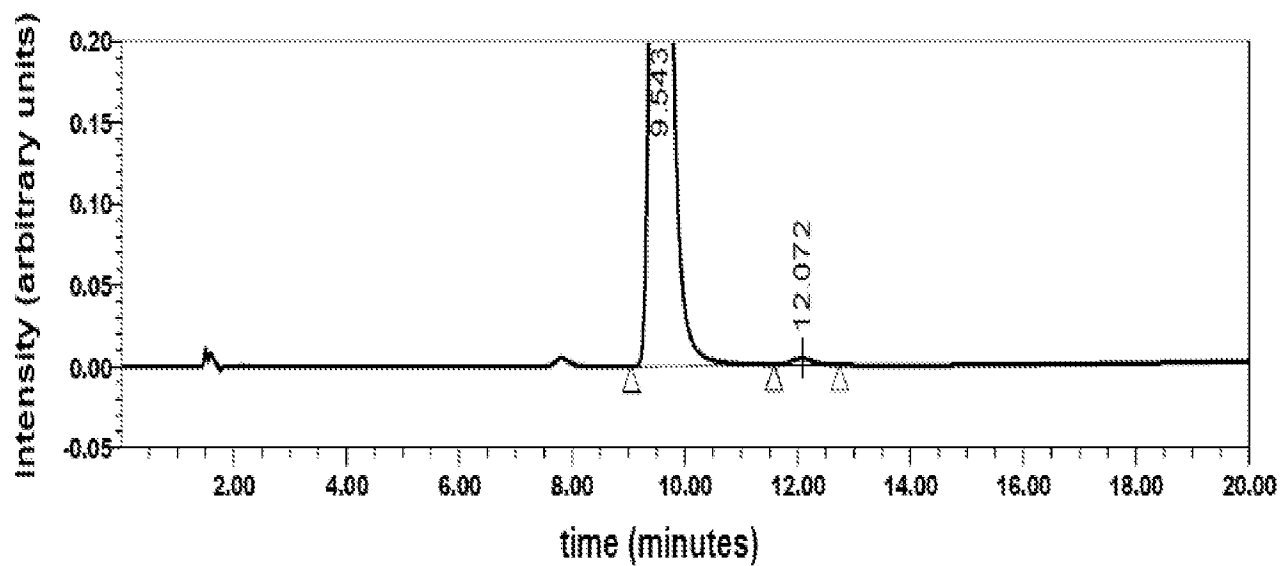


Figure 1

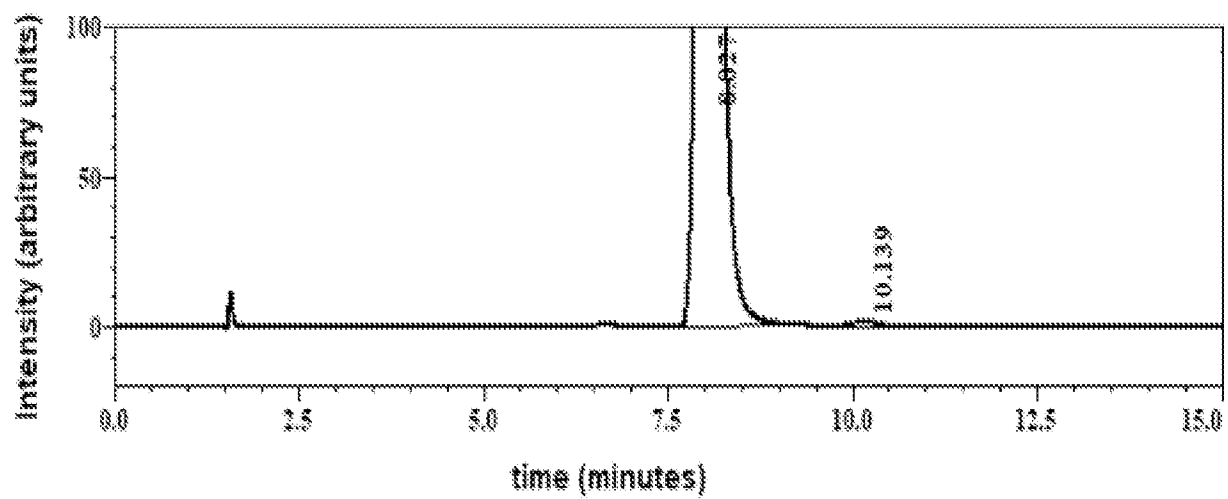


Figure 2

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2021/018137

A. CLASSIFICATION OF SUBJECT MATTER IPC (20210101) C07D 243/18, C07D 243/26 CPC (20130101) C07D 243/18, C07D 243/26 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) IPC (20210101) C07D 243/18, C07D 243/26 CPC (20130101) C07D 243/18, C07D 243/26 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) See extra sheet.		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2014047392 A1 (SQUIBB BRISTOL MYERS CO. [US]) 27 Mar 2014 (2014/03/27) page 50, intermediate B-1	26
Y		1-27
X	WO 2014047374 A1 (SQUIBB BRISTOL MYERS CO. [US]) 27 Mar 2014 (2014/03/27) page 107, intermediate B10	26
Y		1-27
X	WO 2014047372 A1 (SQUIBB BRISTOL MYERS CO. [US]) 27 Mar 2014 (2014/03/27) page 84, intermediate B-1	26
Y		1-27
☒ 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 "D" document cited by the applicant in the international application "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 31 May 2021		Date of mailing of the international search report 01 Jun 2021
Name and mailing address of the ISA: Israel Patent Office Technology Park, Bldg.5, Malcha, Jerusalem, 9695101, Israel Email address: pctoffice@justice.gov.il		Authorized officer NAHAMANI Moshe Telephone No. 972-73-3927144

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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.
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Y		1-27
Y	CN 105439939 A (SICHUAN HENGKANG TECH DEV CO LTD) 30 Mar 2016 (2016/03/30) paragraph [0006]; paragraph [0016]; claims 1 and 3-5	1-27
Y	WO 2010073253 A1 (NATCO PHARMA LTD. [IN]) 01 Jul 2010 (2010/07/01) page 6, example 1; claims 1-2	1-13,24,25
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Y	EP 3162793 A1 (AMOREPACIFIC CORP. [KR]) - 03 May 2017 03 May 2017 (2017/05/03) claims 1, 5, 10, 15 and 18-19	14-27

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International application No.

PCT/US2021/018137

B. FIELDS SEARCHED:

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

Databases consulted: PATENTSCOPE, USPTO, Eponline, Esp@cenet, Google Patents, CAPLUS, REGISTRY, EPODOC, PubMed, Google Scholar

Search terms used: L-pyroglutamic acid; L-PGA; LPGA; gamma-secretase inhibitor; GSI; Benzodiazepinone; (+)-beta-Camphorsulfonic acid, (1S)-(+)-Camphor-10-sulfonic acid, (1S)-(+)-10-Camphorsulfonic acid, CSA; Notch regulation; cancer; chiral auxiliaries; chiral resolution; Chiral Resolving Reagents