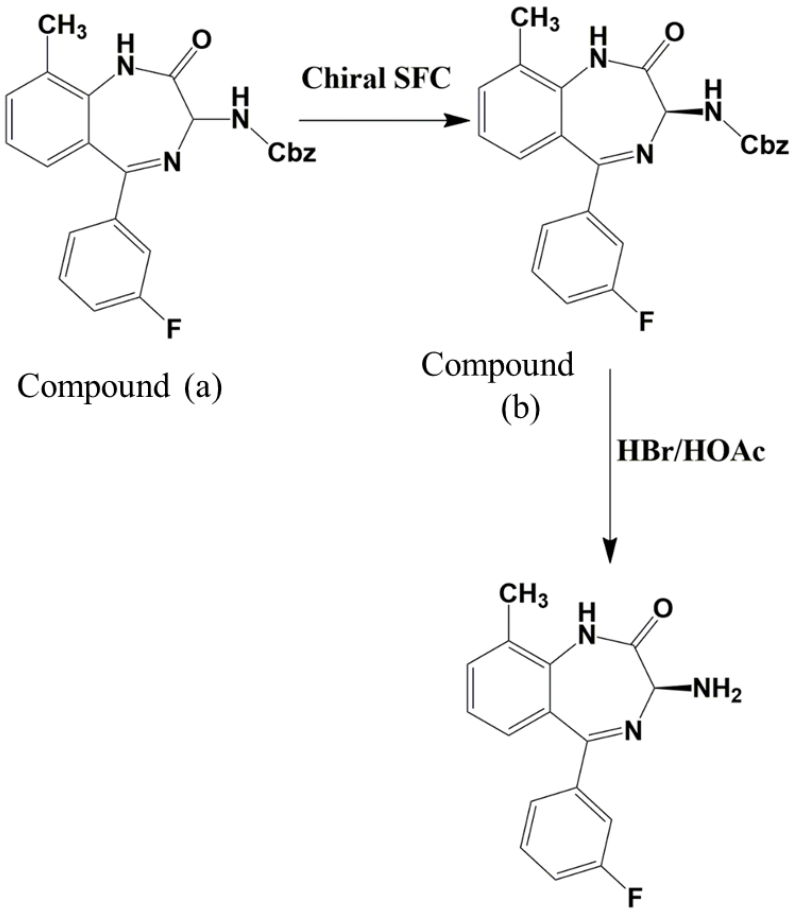
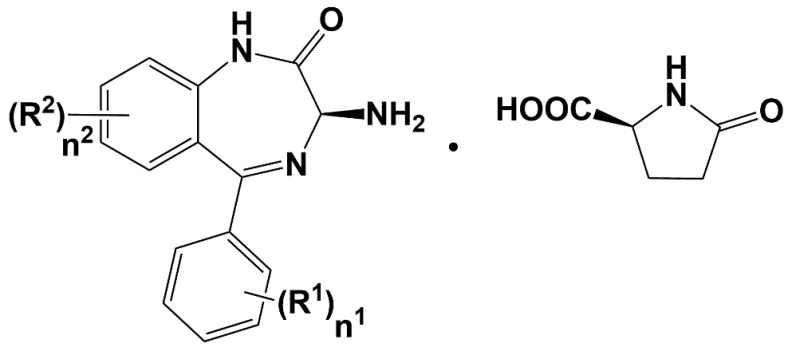
Scheme 1: Preparation of Compound (3) using chiral SFC conditions.



SUMMARY ~~OF THE INVENTION~~

[006a] In one aspect of the present disclosure, there is provided a method of preparing the compound of Formula (Ib),



Formula (Ib)

wherein

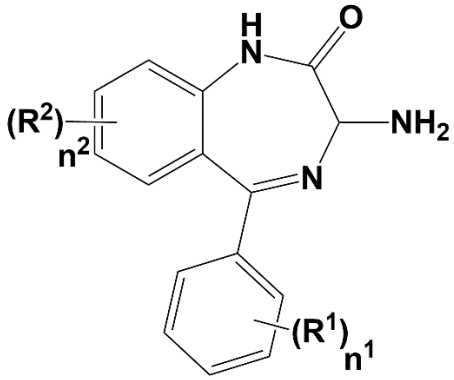
R^1 each is independently Cl, F, Br, I, OCH_3, CN or NO_2;

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

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

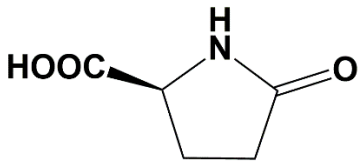
n^2 is an integer between 1 and 4;

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



Formula (Ia)

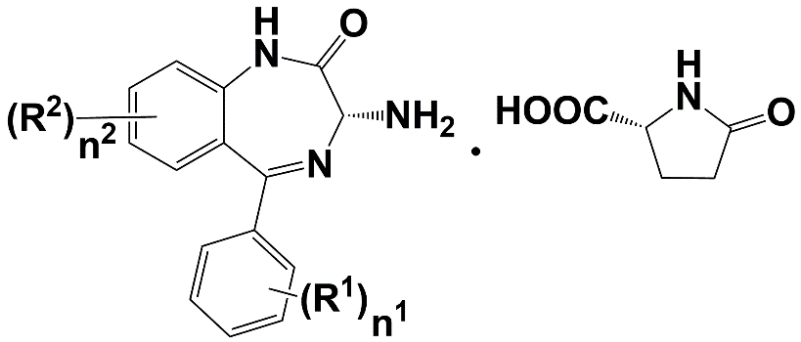
with L-pyroglutamic acid (L-PGA),



L-pyroglutamic acid (L-PGA),

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

[006b] In another aspect of the present disclosure, there is provided a method of preparing the compound of Formula (Id),



Formula (Id)

wherein

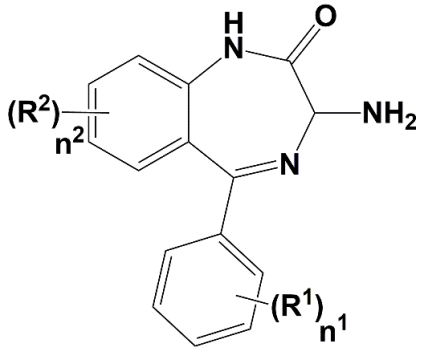
R^1 each is independently Cl, F, Br, I, OCH_3, CN or NO_2;

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

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

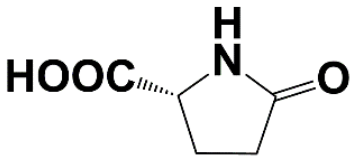
n^2 is an integer between 1 and 4;

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



Formula (Ia)

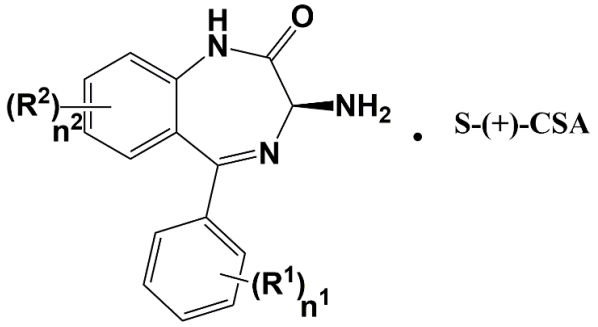
with D-pyroglutamic acid (D-PGA),



D-pyroglutamic acid (D-PGA)

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

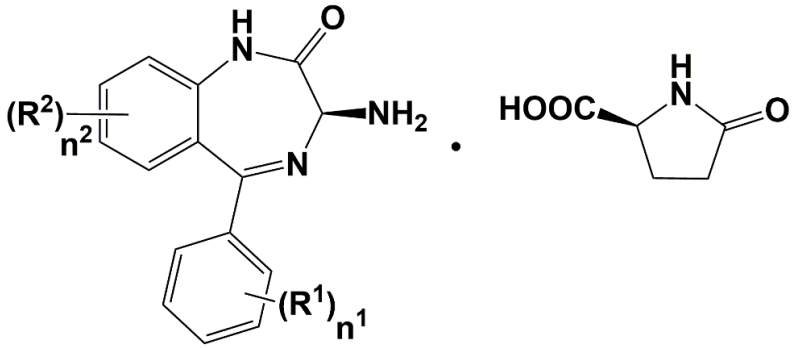
[006c] In a further aspect of the present disclosure, there is provided a method of preparing the compound of Formula (Ic),



Formula (Ic)

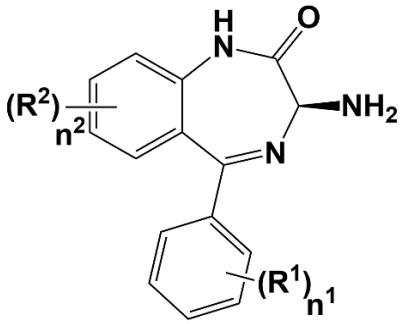
comprising the steps of:

a) reacting the compound of Formula (Ib):



Formula (Ib)

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

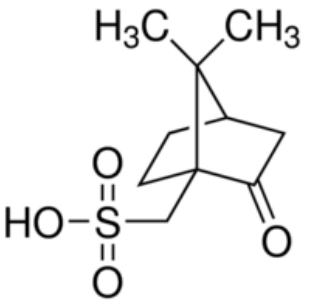


.

Formula (I)

b) reacting the compound of Formula (I) with

S (+) camphor sulfonic acid (CSA):



,

to provide a compound of Formula (Ic),

wherein

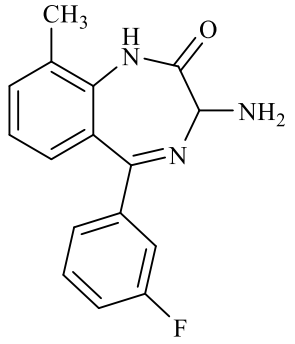
R^1 each is independently Cl, F, Br, I, OCH_3, CN or NO_2;

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.

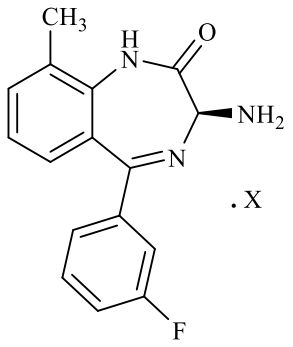
[006d] In another aspect of the present disclosure, there is provided a compound represented by the following structure:



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.

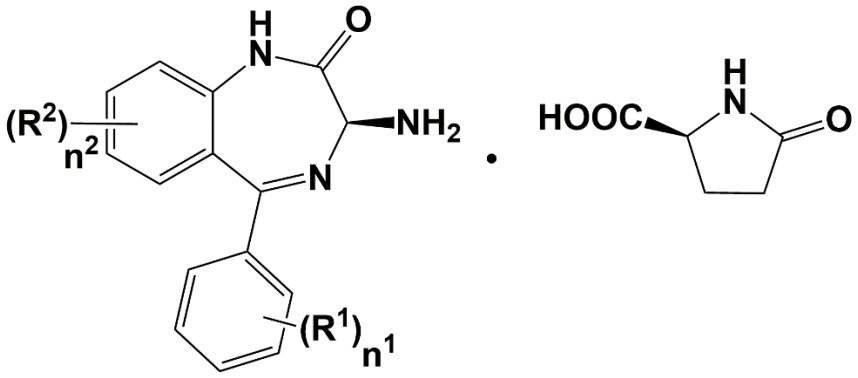
[006e] In a further aspect of the present disclosure, there is provided a compound represented by the following structure:



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.

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



Formula (Ib)

wherein:

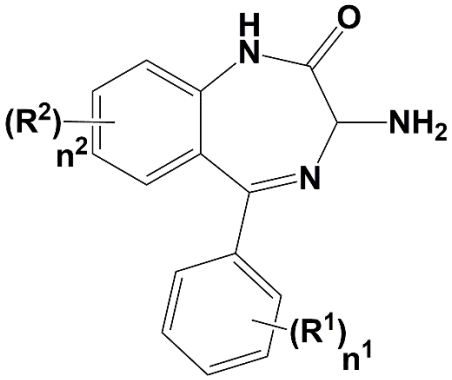
R^1 each is independently Cl, F, Br, I, OCH_3, CN or NO_2;

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

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

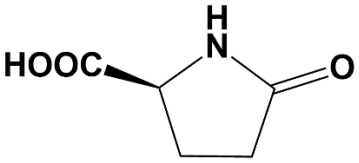
n^2 is an integer between 1 and 4;

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



Formula (Ia)

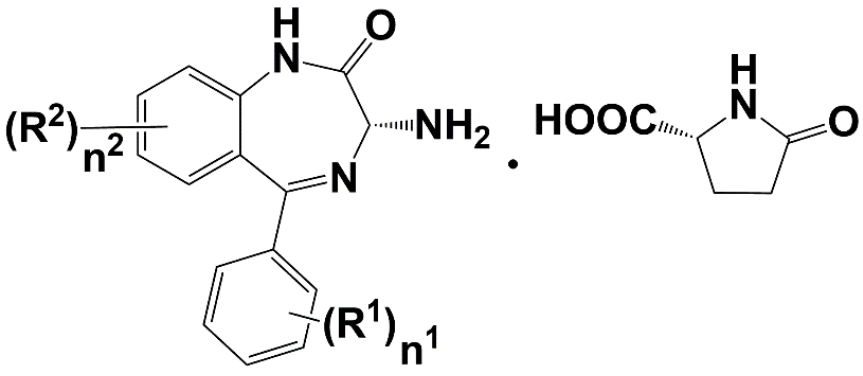
with L-pyroglutamic acid (L-PGA),



L-pyroglutamic acid (L-PGA),

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

[008] In another ~~embodiment~~example, the present ~~invention~~disclosure provides a method of preparing the compound of Formula (Id),



Formula (Id)

wherein

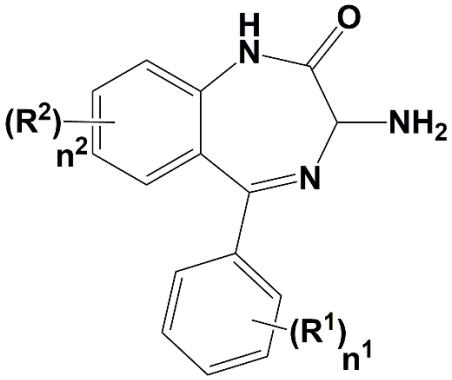
R^1 each is independently Cl, F, Br, I, OCH_3, CN or NO_2;

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

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

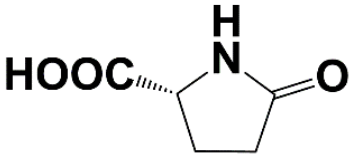
n^2 is an integer between 1 and 4;

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



Formula (Ia)

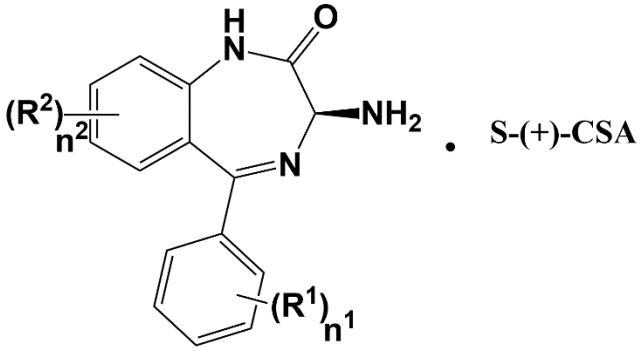
with D-pyroglutamic acid (D-PGA),



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~~example, the present ~~invention~~disclosure provides a method of preparing the compound of Formula (Ic),

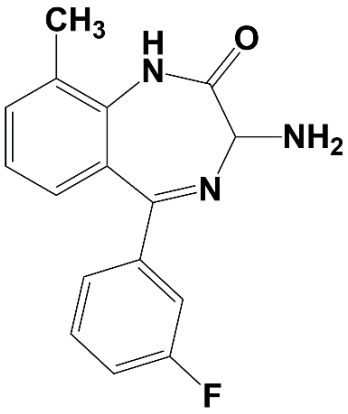


Formula (Ic)

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

n^2 is an integer between 1 and 4.

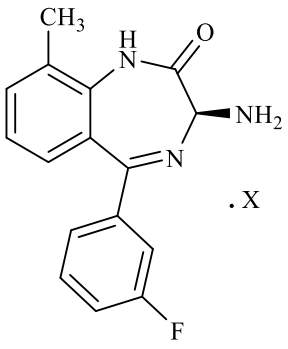
[0010] In another ~~embodiment~~example, the present ~~invention~~disclosure provides a compound represented by the following structure:



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~~example, the present ~~invention~~disclosure 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,