PROCESSES FOR PREPARING DIHYDROPYRIMIDINE DERIVATIVES AND INTERMEDIATES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to Chinese Patent Application Serial No. 201310636920.8, filed with the State Intellectual Property Office of China on November 27, 2013; and Chinese Patent Application Serial No. 201410121009.8, filed with the State Intellectual Property Office of China on March 27, 2014, both of which are hereby incorporated by reference in their entireties and for all purposes as if specifically and fully set forth herein.

FIELD

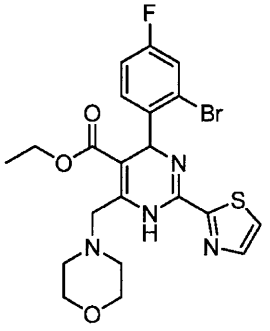
[0002] The invention refers to a chemical medicine field. Specifically, the invention relates to processes for preparation of optically pure dihydropyrimidine derivatives and optically pure dihydropyrimidine intermediates thereof.

BACKGROUND

[0003] The hepatitis B virus belongs to the family of hepadnaviridae. It can cause acute and/or persistent or progressive chronic diseases. Many other clinical manifestations in the pathological morphology can also be caused by HBV—in particular chronic hepatitis, cirrhosis and hepatocellular carcinoma. Additionally, coinfection with hepatitis D virus may have adverse effects on the progress of the disease.

[0004] The conventional medicaments approved to be used for treating chronic hepatitis are interferon and lamivudine. However, the interferon has just moderate activity but has an adverse side reaction. Although lamivudine has good activity, its resistance develops rapidly during the treatment and relapse effects often appear after the treatment has stopped. The IC50 value of lamivudine (3-TC) is 300 nM (*Science*, 2003, 299, 893-896).

[0005] PCT Publication No. WO2008154817 discloses a series of compounds used for preventing, managing, treating or lessening a viral disease in a patient, particularly HBV infection or a related disease. The patent also provides the processes for preparation of specific compounds, such as 4-(*R*,*S*)-ethyl 4-(2-bromo-4-fluorophenyl)-6-(morpholinomethyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate as shown in Formula (Ib).



(Ib),

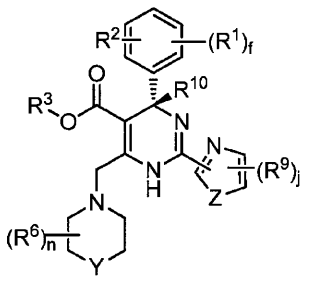
[0006] PCT Publication No. WO2008009210 discloses a series of optically pure compounds , which used for

preventing, managing, treating or lessening an acute or chronic viral disease in a patient, particularly an acute or chronic HBV disease. The patent also provides the processes for preparation of specific compounds, such as (*R*)-ethyl 4-(2-chloro-4-fluorophenyl)-6-methyl-2-(thiazol-2-yl)-1,4- dihydropyrimidine-5-carboxylate.

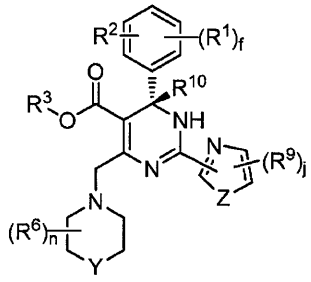
[0007] Dihydropyrimidine derivatives can be prepared by several methods described in prior arts, such as patents WO1999054329, WO2008154817, WO2001068641, WO2010069147, and so on. But the process of preparation of optically pure dihydropyrimidine compounds described herein has not been yet be published.

SUMMARY

[0008] The invention refers to a process for preparing a dihydropyrimidine compound having Formula (I), or a tautomer thereof having Formula (Ia),



(I) or



(Ia),

wherein each R^1 and R^2 is independently F, Cl, or Br;

R^3 is C_{1-4} alkyl;

Z is -O-, -S-, $-S(=O)_t$, or $-N(R^4)$-;

Y is -O-, -S-, $-S(=O)_t$-, $-(CH_2)_q$-, or $-N(R^5)$-;

each t and q is independently 0, 1, or 2;

each of R^4 and R^5 is independently H or C_{1-4} alkyl;

each R^6 is independently H, deuterium, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, amino, C_{1-4} alkylamino, C_{1-4} alkoxy, nitro, triazolyl, tetrazyl, $-(CR^7R^{7a})_m$-OH, $-S(=O)_qOR^{8a}$, $-(CR^7R^{7a})_m-S(=O)_qN(R^{8a})_2$, $-(CR^7R^{7a})_t-N(R^{8a})_2$, $-(CR^7R^{7a})_m-C(=O)O-R^8$, $-(CR^7R^{7a})_m-C(=O)O-(CR^7R^{7a})_m-OC(=O)O-R^8$, $-(CR^7R^{7a})_m-C(=O)O-(CR^7R^{7a})_m-OC(=O)-R^8$, $-(CR^7R^{7a})_m-C(=O)O-(CR^7R^{7a})_m-C(=O)O-R^8$, $-(CR^7R^{7a})_m-OC(=O)-R^8$ or $-(CR^7R^{7a})_m-C(=O)-N(R^8R^{8a})$;

each R^{7a} and R^7 is independently H, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, $-(CH_2)_m$-OH, or $-(CH_2)_m-C(=O)O-R^8$; or R^{7a} and R^7, together with the carbon atom to which they are attached, form a C_{3-6} cycloalkyl group, C_{2-9} heterocyclyl goup, or -(C=O)-;

each R^8 and R^{8a} is independently H, C_{1-4} alkyl, amino-C_{1-4}-alkyl, C_{1-4} alkoxy, C_{1-6} alkyl-$S(=O)_q$-, C_{6-10} aryl, C_{1-9} heteroaryl, C_{3-6} cycloalkyl, C_{2-9} heterocyclyl, C_{6-10} aryl-C_{1-6}-alkyl, C_{1-9} heteroaryl-C_{1-6}-alkyl, C_{3-6} cycloalkyl-C_{1-4}-alkyl, C_{2-9} heterocyclyl-C_{1-6}-alkyl, C_{2-9} heterocyclyl-$S(=O)_q$-, C_{1-9} heteroaryl-$S(=O)_q$-, C_{3-6} cycloalkyl-$S(=O)_q$-, C_{6-10} aryl-$S(=O)_q$-, $-(CH_2)_m$-OH, $-(CH_2)_m-C(=O)O-(CH_2)_m$-H, or $-(CH_2)_m-OC(=O)-(CH_2)_m$-H;

each R^9 is independently H, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkylthio, C_{3-6} cycloalkyl,

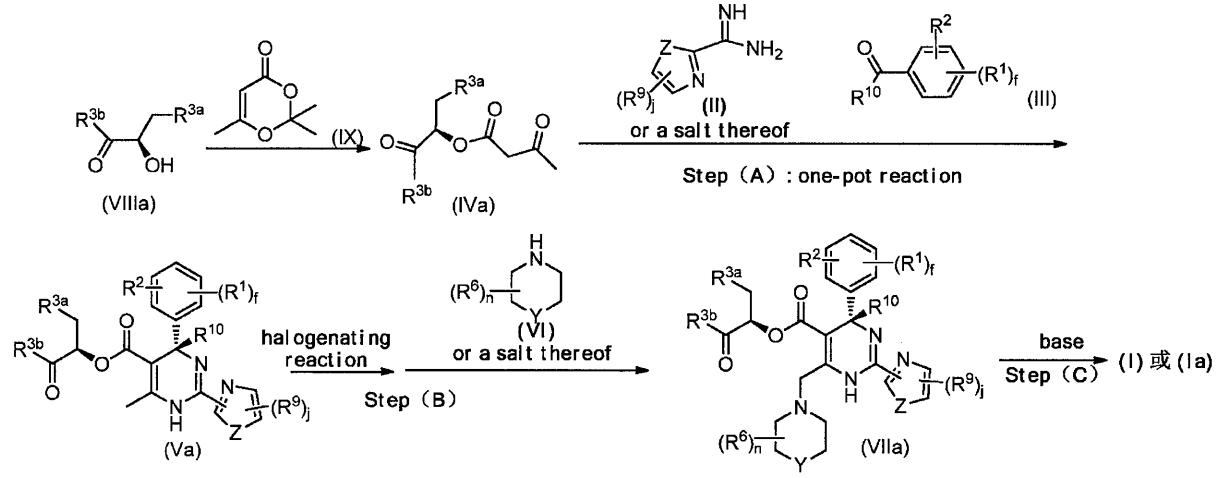
$-(CR^7R^{7a})_m-C(=O)-N(R^8R^{8a})$, or $-(CR^7R^{7a})_m-C(=O)O-R^8$;

R^{10} is H or deuterium;

n is 0, 1, 2, 3, 4, or 5; each m is independently 0, 1, 2, 3, or 4; f is 1, 2, 3, or 4; and j is 0, 1, or 2.

[0009] Two preparation methods of a dihydropyrimidine compound having Formula (I) or a tautomer thereof having Formula (Ia) are depicted in the following schemes,

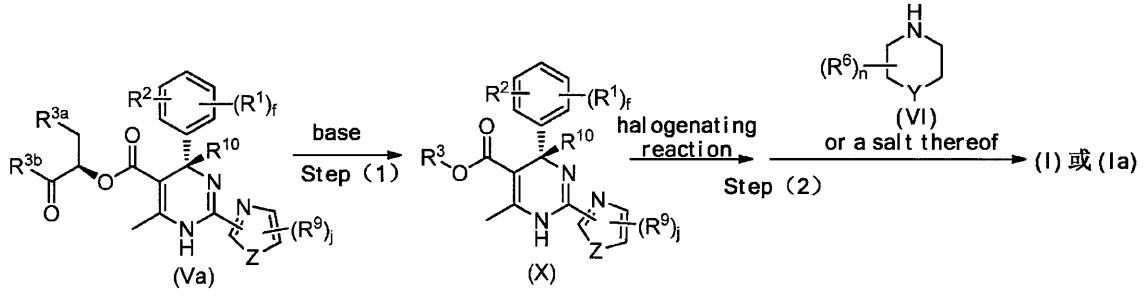
Scheme 1



(Method one)

[0010] A dihydropyrimidine compound having Formula (I), or a tautomer thereof having Formula (Ia) can be prepared by a general synthetic procedure illustrated through method one in Scheme 1, wherein R^1, R^2, Z, R^9, j, f, R^6, n, Y and R^{10} are as defined herein; wherein R^{3a} is H or C_{1-3} alkyl; R^{3b} is methoxy or ethoxy. The method one comprises the following steps of: reacting a compound (VIIIa) with a compound (IX) to obtain a compound (IVa); step (A): reacting a compound (II) or a salt thereof with a compound (III) and the compound (IVa) to obtain a compound (Va) (according to some embodiments of the present invention, the reaction of the step (A) may be an one-pot reaction); step (B): halogenating the compound (Va) to form a halide; and then reacting the halide with a compound (VI), or a salt thereof to obtain a compound (VIIa); step (C): forming a compound (I) or compound (Ia) from the compound (VIIa) in the presence of a base (according to some embodiments of the present invention, the reaction of the step (C) may be a transesterification).

Scheme 2



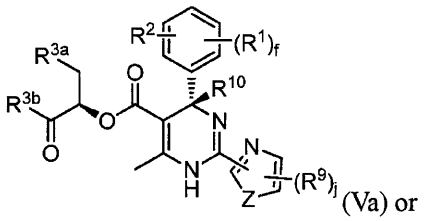
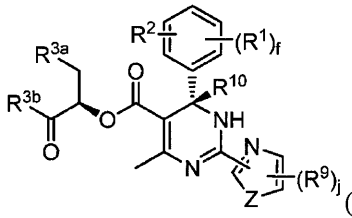
(Method two)

[0011] A dihydropyrimidine compound having Formula (I), or a tautomer thereof having Formula (Ia) can

be prepared by a general synthetic procedure illustrated through method two in Scheme 2, wherein R^1, R^2, Z, R^9, j, f, R^6, n, Y, R^{10}, R^{3a} and R^{3b} are as defined herein. The method two comprises the following steps of: step (1): reacting the compound (Va) in the presence of a base to obtain a compound (X) (according to some embodiments of the present invention, the reaction of the step (1) may be a transesterification); step (2): halogenating the compound (X) to form a halide; and then reacting the halide with a compound (VI) or a salt thereof to obtain a compound (I) or compound (Ia).

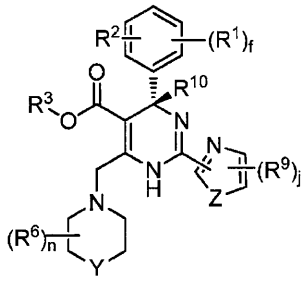
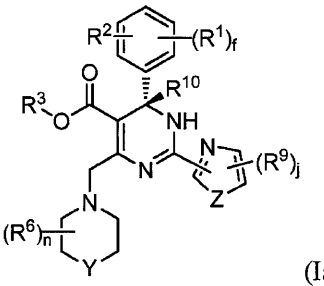
[0012] The method one depicted in scheme 1 and the method two depicted in scheme 2 comprises introducing a new chiral center to the mother nucleus of the compound, and splitting the diastereomers based on the difference in the solubility of the diastereomers; at last, removing the new chiral center from the mother nucleus through transesterification, then a compound may be obtained and in some embodiments of the present invention, the obtained compound may be optically pure. These methods have advantages of convenient work-up, high optical purity of product, and high yield. In addition, the processes of the invention have cheap raw material, mild reaction conditions, simplified operational procedure, controlled safely and they are suited for industrial production.

[0013] The present invention also refers to an intermediate comprising a dihydropyrimidine compound having Formula (Va), or a tautomer thereof having Formula (Va1), or a salt thereof, or a combination thereof,


(Va) or

(Va1),

wherein each R^1, R^2, f, Z, R^9, j, R^{10}, R^{3a} and R^{3b} is as defined herein.

[0014] In one aspect, provided herein is a process for preparing a dihydropyrimidine compound having Formula (I), or a tautomer thereof having Formula (Ia) (such as the method one depicted in scheme 1)


(I) or

(Ia),

wherein each R^1 and R^2 is independently F, Cl, or Br;

R^3 is C_{1-4} alkyl;

Z is -O-, -S-, -S(=O)$_t$-, or -N(R^4)-;

Y is -O-, -S-, -S(=O)$_t$-, -(CH_2)$_q$-, or -N(R^5)-;

each t and q is independently 0, 1, or 2;

each of R^4 and R^5 is independently H, or C_{1-4} alkyl;

each R^6 is independently H, deuterium, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, amino, C_{1-4} alkylamino, C_{1-4} alkoxy, nitro, triazolyl, tetrazyl, $-(CR^7R^{7a})_m-OH$, $-S(=O)_qOR^{8a}$, $-(CR^7R^{7a})_m-S(=O)_qN(R^{8a})_2$, $-(CR^7R^{7a})_t-N(R^{8a})_2$, $-(CR^7R^{7a})_m-C(=O)O-R^8$, $-(CR^7R^{7a})_m-C(=O)O-(CR^7R^{7a})_m-OC(=O)O-R^8$, $-(CR^7R^{7a})_m-C(=O)O-(CR^7R^{7a})_m-OC(=O)-R^8$, $-(CR^7R^{7a})_m-C(=O)O-(CR^7R^{7a})_m-C(=O)O-R^8$, $-(CR^7R^{7a})_m-OC(=O)-R^8$, or $-(CR^7R^{7a})_m-C(=O)-N(R^8R^{8a})$;

each R^{7a} and R^7 is independently H, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, $-(CH_2)_m-OH$, or $-(CH_2)_m-C(=O)O-R^8$; or R^{7a} and R^7, together with the carbon atom to which they are attached, form a C_{3-6} cycloalkyl group, C_{2-9} heterocyclyl goup, or -(C=O)-;

each R^8 and R^{8a} is independently H, C_{1-4} alkyl, amino-C_{1-4}-alkyl, C_{1-4} alkoxy, C_{1-6} alkyl-$S(=O)_q$-, C_{6-10} aryl, C_{1-9} heteroaryl, C_{3-6} cycloalkyl, C_{2-9} heterocyclyl, C_{6-10} aryl-C_{1-6}-alkyl, C_{1-9} heteroaryl-C_{1-6}-alkyl, C_{3-6} cycloalkyl-C_{1-4}-alkyl, C_{2-9} heterocyclyl-C_{1-6}-alkyl, C_{2-9} heterocyclyl-$S(=O)_q$-, C_{1-9} heteroaryl-$S(=O)_q$-, C_{3-6} cycloalkyl-$S(=O)_q$-, C_{6-10} aryl-$S(=O)_q$-, $-(CH_2)_m-OH$, $-(CH_2)_m-C(=O)O-(CH_2)_m-H$, or $-(CH_2)_m-OC(=O)-(CH_2)_m-H$;

each R^9 is independently H, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkylthio, C_{3-6} cycloalkyl, $-(CR^7R^{7a})_m-C(=O)-N(R^8R^{8a})$, or $-(CR^7R^{7a})_m-C(=O)O-R^8$;

R^{10} is H or deuterium;

n is 0, 1, 2, 3, 4, or 5;

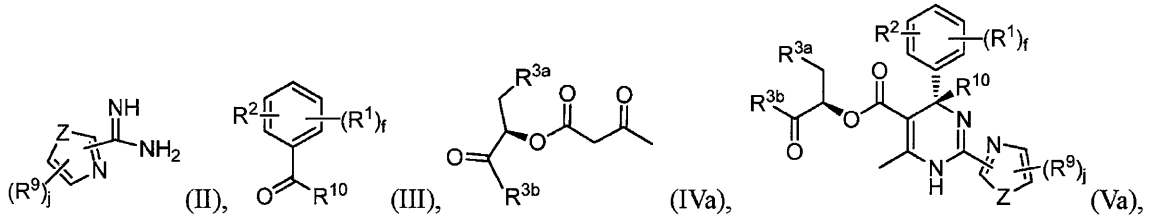
each m is independently 0, 1, 2, 3, or 4;

f is 1, 2, 3, or 4;

j is 0, 1, or 2;

wherein the process comprises the steps of:

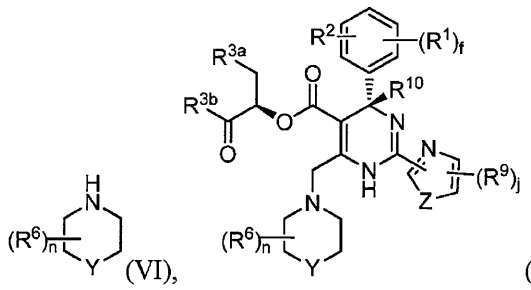
step (A): reacting an amidine compound of Formula (II), or a salt thereof with an aldehyde compound of Formula (III) and a compound of Formula (IVa) to obtain a compound (Va) (according to some embodiments of the present invention, the reaction of step (A) may be an one-pot reaction),



(II), (III), (IVa), (Va),

wherein R^{3b} is methoxy or ethoxy; R^{3a} is H or C_{1-3} alkyl;

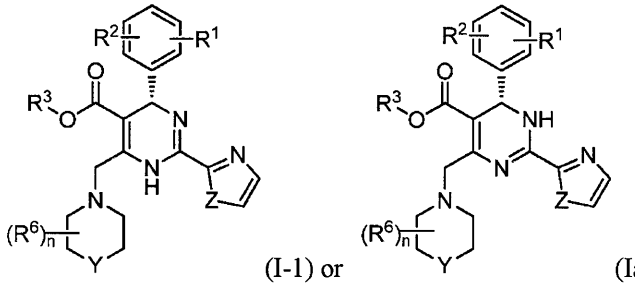
step (B): halogenating the compound of Formula (Va) to form a halide; and then reacting the halide with a compound of Formula (VI), or a salt thereof to obtain a compound of Formula (VIIa),



(VI), (VIIa); and

step (C): forming the compound of Formula (I) or Formula (Ia) from the compound of Formula (VIIa) by means of a transesterification, and the transesterification may be carried out in the presence of a base.

[0015] In some embodiments, the dihydropyrimidine compound having Formula (I-1), or a tautomer thereof having Formula (Ia-1),



(I-1) or (Ia-1),

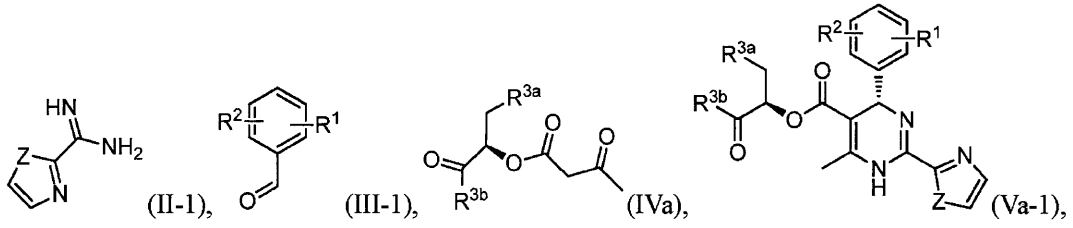
wherein, each R^6 is independently H, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, amino, C_{1-4} alkylamino, C_{1-4} alkoxy, nitro, triazolyl, tetrazyl, $-(CR^7R^{7a})_m-OH$, $-S(=O)_qOR^{8a}$, $-(CR^7R^{7a})_m-S(=O)_qN(R^{8a})_2$, $-(CR^7R^{7a})_t-N(R^{8a})_2$, $-(CR^7R^{7a})_m-C(=O)O-R^8$, $-(CR^7R^{7a})_m-C(=O)O-(CR^7R^{7a})_m-OC(=O)O-R^8$, $-(CR^7R^{7a})_m-C(=O)O-(CR^7R^{7a})_m-OC(=O)-R^8$, $-(CR^7R^{7a})_m-C(=O)O-(CR^7R^{7a})_m-C(=O)O-R^8$, $-(CR^7R^{7a})_m-OC(=O)-R^8$, or $-(CR^7R^{7a})_m-C(=O)-N(R^8R^{8a})$;

each R^{7a} and R^7 is independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, $-(CH_2)_m-OH$, or $-(CH_2)_m-C(=O)O-R^8$; and

each R^1, R^2, R^3, Z, n, Y, m, q, R^{8a}, t and R^8 is as defined herein;

[0016] According to embodiments of present invention, the method one for preparing the dihydropyrimidine compound having Formula (I-1), or a tautomer thereof having Formula (Ia-1) comprises the steps of:

step (A) reacting an amidine compound of Formula (II-1), or a salt thereof with an aldehyde compound of Formula (III-1) and the compound of Formula (IVa) to obtain a compound (Va-1) (according to some embodiments of the present invention, the reaction of the step (A) may be an one-pot reaction).

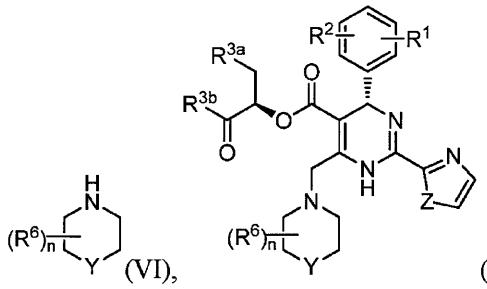


(II-1), (III-1), (IVa), (Va-1),

wherein R^{3a} and R^{3b} are as defined in Formula (Va-1) disclosed herein;

step (B): halogenating the compound of Formula (Va-1) to form a halide; and then reacting the halide with

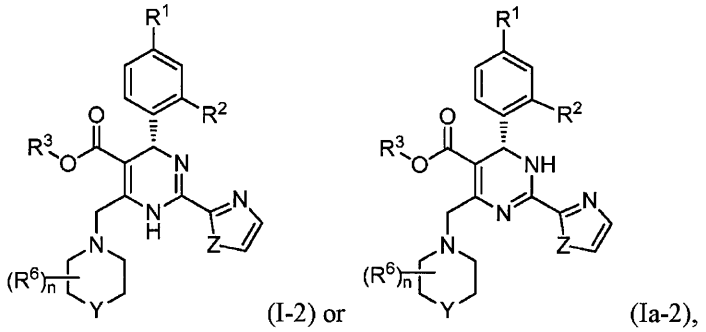
a compound of Formula (VI) or a salt thereof to obtain a compound of Formula (VIIa-1),



(VI), (VIIa-1); and

step (C): forming the compound of Formula (I-1) or Formula (Ia-1) from the compound of Formula (VIIa-1) by means of a transesterification, wherein the transesterification may be carried out in the presence of a base.

[0017] In some embodiments, the dihydropyrimidine compound having Formula (I-2), or a tautomer thereof having Formula (Ia-2),

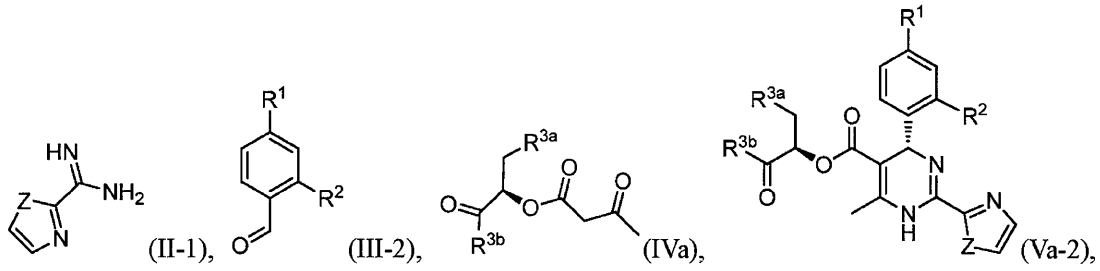


(I-2) or (Ia-2),

wherein R^1 is F or Cl; and R^2 is Cl or Br; R^3, Z, n, R^6 and Y are as defined herein;

[0018] According to embodiments of present invention, the method one for preparing the dihydropyrimidine compound having Formula (I-2), or a tautomer thereof having Formula (Ia-2) comprises the steps of:

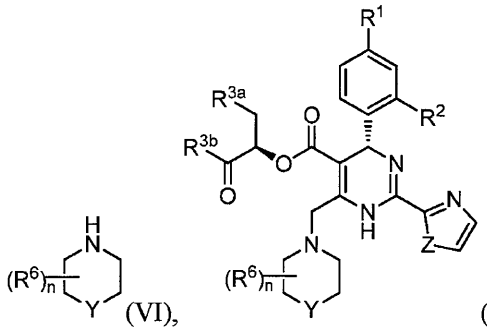
step (A): reacting an amidine compound of Formula (II-1), or a salt thereof with an aldehyde compound of Formula (III-2) and the compound of Formula (IVa) to obtain a compound (Va-2) (according to some embodiments of the present invention, the reaction of the step (A) may be an one-pot reaction),



(II-1), (III-2), (IVa), (Va-2),

wherein R^{3a} and R^{3b} are as defined in Formula (Va-1) disclosed herein;

step (B): halogenating the compound of Formula (Va-2) to form a halide; and then reacting the halide with a compound of Formula (VI), or a salt thereof to obtain a compound of Formula (VIIa-2),



(VI), (VIIa-2); and

step (C): forming the compound of Formula (I-2) or Formula (Ia-2) from the compound of Formula (VIIa-2) by means of a transesterification, wherein the transesterification may be carried out in the presence of a base.

[0019] According to embodiments of present invention, in the method one disclosed herein, in some embodiments, the R^3 is methyl, ethyl, propyl, isopropyl, *tert*-butyl, or butyl; Z is -O-, -S-, or -$N(CH_3)$-; Y is -O-, -S-, -$S(=O)_2$, or -$(CH_2)_q$-; each R^6 is independently H, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, amino, C_{1-4} alkylamino, C_{1-4} alkoxy, nitro, triazolyl, tetrazyl, -$(CR^7R^{7a})_m$-OH, -$(CR^7R^{7a})_m$-$C(=O)O$-R^8, -$(CR^7R^{7a})_t$-$N(R^{8a})_2$, -$S(=O)_qOR^{8a}$, -$(CR^7R^{7a})_m$-$S(=O)_qN(R^{8a})_2$, -$(CR^7R^{7a})_m$-$C(=O)O$-$(CR^7R^{7a})_m$-$OC(=O)O$-R^8, -$(CR^7R^{7a})_m$-$C(=O)O$-$(CR^7R^{7a})_m$-$OC(=O)$-R^8, -$(CR^7R^{7a})_m$-$C(=O)O$-$(CR^7R^{7a})_m$-$C(=O)O$-R^8, -$(CR^7R^{7a})_m$-$OC(=O)$-R^8 or -$(CR^7R^{7a})_m$-$C(=O)N(R^8R^{8a})$; each R^{7a} and R^7 is independently H, methyl, ethyl, trifluoromethyl, -$(CH_2)_m$-OH, or -$(CH^2)_m$-$C(=O)O$-R^8; each R^8 and R^{8a} is independently H, methyl, ethyl, propyl, isopropyl, aminomethyl, methoxy, C_{1-4} alkyl-$S(=O)_2$-, phenyl, pyridyl, thiazolyl, furanyl, imidazolyl, isoxazolyl, oxazolyl, pyrrolyl, pyrimidinyl, pyridazinyl, diazolyl, triazolyl, tetrazolyl, thienyl, pyrazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyrazinyl, pyranyl, triazinyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropyl-$S(=O)_2$-, cyclobutyl-$S(=O)_2$-, cyclopentyl-$S(=O)_2$-, cyclohexyl-$S(=O)_2$-, naphthyl-$S(=O)_2$-, phenyl-$S(=O)_2$-, -$(CH_2)_m$-OH, -$(CH_2)_m$-$C(=O)O$-$(CH_2)_m$-H, or -$(CH_2)_m$-$OC(=O)$-$(CH_2)_m$-H; R^{3b} is methoxy or ethoxy; and R^{3a} is H, methyl, ethyl, isopropyl, or propyl.

[0020] According to some embodiments of the present invention, in the method one disclosed herein, the reaction in step (A) is performed at a temperature from 25 °C to 154 °C. In some other embodiments, the reaction in step (A) is performed at a temperature from 60 °C to 100 °C.

[0021] According to some embodiments of the present invention, in the method one disclosed herein, the one-pot reaction in step (A) is performed at a temperature, in some embodiments, the reaction temperature is from 25 °C to 154 °C. In other embodiments, the reaction temperature is from 30 °C to 154 °C. In still other embodiments, the reaction temperature is from 60 °C to 100 °C. In yet other embodiments, the reaction temperature is 25 °C, 30 °C, 40 °C, 56 °C, 60 °C, 64 °C, 65 °C, 77 °C, 78 °C, 80 °C, 82 °C, 100 °C, 110 °C, 120 °C, 130 °C, 140 °C or 154 °C.

[0022] According to some embodiments of the present invention, in the method one disclosed herein, the step (A) further comprises a step of cooling the resulting compound of Formula (Va) of step (A) to obtain a solid compound of Formula (Va) at a cooling temperature from −40 °C to 40 °C. In some other embodiments,

the cooling temperature is from 25 °C to 40 °C. In some embodiments, the cooling is performed for a period of from 0 hour to 24 hours. In some other embodiments, the cooling is performed for from 1 minute to 24 hours. In still other embodiments, the cooling is performed for from 1 hour to 8 hours.

[0023] According to some embodiments of the present invention, in the method one disclosed herein, the cooling in step (A) is carried out at a temperature, in some embodiments, the cooling temperature is from −50 °C to 60 °C. In other embodiments, the cooling temperature is from −40°C to 40 °C. In other embodiments, the cooling temperature is from −30 °C to 40 °C. In other embodiments, the cooling temperature is from −20 °C to 40 °C. In other embodiments, the cooling temperature is from −10 °C to 40 °C. In still other embodiments, the cooling temperature is from 0°C to 40 °C. In yet other embodiments, the cooling temperature is from 25 °C to 40 °C. In yet other embodiments, the cooling temperature is −50 °C, −40 °C, −30 °C, −20 °C, −15 °C, −10 °C, −5°C, 0 °C, 5°C, 10 °C, 15°C, 20 °C, 25 °C, 30 °C, 35 °C, 40 °C, 50 °C or 60 °C.

[0024] According to some embodiments of the present invention, in the method one disclosed herein, the cooling temperature in step (A) is kept for a period of time, in some embodiments, the period of time is from 0 hour to 30 hours. In other embodiments, the period of time is from 0 hour to 24 hours. In other embodiments, the period of time is from 1 minute to 24 hours. In other embodiments, the period of time is from 1 hour to 12 hours. In other embodiments, the period of time is from 1 hour to 10 hours. In other embodiments, the period of time is from 1 hour to 8 hours. In still other embodiments, the period of time is from 1 hour to 6 hours. In yet other embodiments, the period of time is 0 hour, 1 minute, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 10 hours, 12 hours, 14 hours, 16 hours, 18 hours, 20 hours, 22 hours, 24 hours or 30 hours.

[0025] According to some embodiments of the present invention, in the method one disclosed herein, the amidine compound of Formula (II) reacts with the aldehyde compound of Formula (III) and the compound of Formula (IVa) in a first organic solvent. In some embodiments, the first organic solvent is applied in an amount of 0 equivalent to 80 equivalents per 1 equivalent by weight of the amidine compound of Formula (II) or a salt thereof. In some other embodiments, the first organic solvent is applied in an amount of 1 equivalent to 20 equivalents per 1 equivalent by weight of the amidine compound of Formula (II), or a salt thereof.

[0026] According to some embodiments of the present invention, in the method one disclosed herein, the first organic solvent in step (A) is applied in an amount, in some embodiments, the amount is 0 equivalent to 80 equivalents per 1 equivalent by weight of an amidine compound of Formula (II), or Formula (II-1), or a salt thereof. In other embodiments, the amount is 1 equivalent to 80 equivalents per 1 equivalent by weight of an amidine compound of Formula (II), or Formula (II-1), or a salt thereof. In other embodiments, the amount is 1 equivalent to 20 equivalents per 1 equivalent by weight of an amidine compound of Formula (II), or Formula (II-1), or a salt thereof. In other embodiments, the amount is 2 equivalents to 20 equivalents per 1 equivalent by weight of an amidine compound of Formula (II), or Formula (II-1), or a salt thereof. In other embodiments, the amount is 1 equivalent to 10 equivalents per 1 equivalent by weight of an amidine compound of Formula (II), or Formula (II-1), or a salt thereof. In still other embodiments, the amount is 3 equivalents to 10 equivalents per 1 equivalent by weight of an amidine compound of Formula (II), or Formula (II-1), or a salt thereof. In yet other embodiments, the amount is 0, 1, 2, 2.5, 3, 4, 4.5, 5, 6, 7, 8, 9, 10, 12, 15, 16, 18, 20, 30, 40, 50, 60, 70 or

80 equivalents per 1 equivalent by weight of an amidine compound of Formula (II), or Formula (II-1), or a salt thereof.

[0027] According to some embodiments of the present invention, in the method one disclosed herein, the step (A) further comprises a step of purifying the solid compound of Formula (Va). In some embodiments, the solid compound of Formula (Va) is purified by at least one of the following methods: (1) trituration; (2) recrystallization; (3) washing.

[0028] According to some embodiments of the present invention, the purification is carried out in a second organic solvent. In some embodiments, the second organic solvent is applied in an amount of 2 equivalent to 20 equivalents per 1 equivalent by weight of the amidine compound of Formula (II), or a salt thereof.

[0029] According to some embodiments of the present invention, in the method one disclosed herein, the trituration is carried out at a temperature from -20 °C to 50 °C. In some embodiments, the trituration is carried out at a temperature from 0 °C to 40 °C.

[0030] According to some embodiments of the present invention, in the method one disclosed herein, the recrystallization comprises a crystallization process at a temperature from −30 °C to 40 °C. In some embodiments, the crystallization process is carried out at a temperature from 0 °C to 40 °C. In some embodiments, the recrystallization comprises a crystallization process of from 1 hour to 20 hours. In some other embodiments, the recrystallization comprises a crystallization process of from 1 hour to 10 hours.

[0031] According to some embodiments of the present invention, in the method one disclosed herein, the washing is performed at a temperature from 0°C to 30 °C.

[0032] According to some embodiments of the present invention, in the method one disclosed herein, the compound of Formula (Va), Formula (Va-1), or Formula (Va-2) obtained in step (A) is further purified before step (B). In some embodiments, the compound is further purified by triturating with a second organic solvent . In some embodiments, the trituration is carried out at a temperature from −20 °C to 50 °C. In other embodiments, the trituration temperature is from 0 °C to 40 °C. In other embodiments, the trituration temperature is from 5 °C to 40 °C. In still other embodiments, the trituration temperature is from 25 °C to 40 °C. In yet other embodiments, the trituration temperature is −20 °C, −10 °C, 0 °C, 5 °C, 10 °C, 25 °C, 30 °C, 35 °C, 40 °C or 50 °C.

[0033] According to some embodiments of the present invention, in the method one disclosed herein, the compound of Formula (Va), Formula (Va-1), or Formula (Va-2) obtained in step (A) is further purified before step (B). In some embodiments, the compound is further purified by recrystalizing from a second organic solvent. In some embodiments, the recrystallization has a crystallization process at a temperature from −30 °C to 50 °C. In other embodiments, the crystallization temperature is from −30 °C to 40 °C. In other embodiments, the crystallization temperature is from −10 °C to 40 °C. In other embodiments, the crystallization temperature is from −10 °C to 30 °C. In other embodiments, the crystallization temperature is from 0 °C to 40 °C. In other embodiments, the crystallization temperature is from 0 °C to 30 °C. In other embodiments, the crystallization temperature is −30 °C, −20 °C, −10 °C, 0 °C, 5 °C, 10 °C, 15 °C, 20 °C, 25 °C, 30 °C, 35 °C, 40 °C or 50 °C. In some embodiments, the recrystallization has a crystallization process taking a period of time from 1 hour to

20 hours. In other embodiments, the period of time is from 2 hours to 18 hours. In still other embodiments, the period of time is from 1 hour to 10 hours. In yet other embodiments, the period of time is 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 12 hours, 14 hours, 16 hours, 18 hours or 20 hours.

[0034] According to some embodiments of the present invention, in the method one disclosed herein, the compound of Formula (Va), Formula (Va-1), or Formula (Va-2) obtained in step (A) is further purified before step (B). In some embodiments, the compound is further purified by washing with a second organic solvent . In some embodiments, the washing is performed at a temperature from 5 °C to 40 °C. In other embodiments, the washing temperature is from 0 °C to 30 °C. In still other embodiments, the washing temperature is −20 °C, −10 °C, 0 °C, 10 °C, 20 °C, 25 °C, 30 °C, 35 °C, 40 °C or 50 °C.

[0035] According to some embodiments of the present invention, in the method one disclosed herein, the second organic solvent used in the further purification before step (B) is applied in an amount, in some embodiments, the amount is about 0 equivalent to 20 equivalents per 1 equivalent by weight of an amidine compound of Formula (II), or Formula (II-1), or a salt thereof. In other embodiments, the amount is about 1 equivalent to 20 equivalents per 1 equivalent by weight of an amidine compound of Formula (II), or Formula (II-1), or a salt thereof. In other embodiments, the amount is about 2 equivalents to 20 equivalents per 1 equivalent by weight of an amidine compound of Formula (II), or Formula (II-1), or a salt thereof. In other embodiments, the amount is about 2 equivalents to 15 equivalents per 1 equivalent by weight of an amidine compound of Formula (II), or Formula (II-1), or a salt thereof. In still other embodiments, the amount is about 2 equivalents to 10 equivalents per 1 equivalent by weight of an amidine compound of Formula (II), or Formula (II-1), or a salt thereof. In yet other embodiments, the amount is about 0, 1, 2, 3, 3.5, 4, 4.5, 5, 6, 7, 7.5, 8, 9, 10, 12, 13, 15, 16, 18, 20, 30, 40, 50, 60, 70 or 80 equivalents per 1 equivalent by weight of an amidine compound of Formula (II), or Formula (II-1), or a salt thereof.

[0036] According to some embodiments of the present invention, in the method one disclosed herein, in some embodiments, each of the first organic solvent and the second organic solvent is independently a C_{1-4} alcohol, a C_{1-4} alcohol-water, acetone, diethyl ether, isopropyl ether, petroleum ether, tetrahydrofuran, acetonitrile, cyclopentane, cyclohexane, *n*-hexane, a C_{1-4} haloalkane, ethyl acetate, trifluoroethanol, 2-methoxyethanol, 1,2-dimethoxyethane, 2-methoxyethyl ether, *N,N*-dimethyl formamide, *N*-methylpyrolidone, or a combination thereof. In other embodiments, each of the first organic solvent and the second organic solvent is independently methanol, ethanol, *n*-propanol, *i*-propanol, *n*-butanol, *tert*-butanol, an ethanol-water mixture at a volume ratio of from 10:90 to 90:10, an ethanol-water mixture at a volume ratio of 50:50, acetone, tetrahydrofuran, *N*-methylpyrolidone, trifluoroethanol, 2-methoxyethanol, 1,2-dimethoxyethane, 2-methoxyethyl ether, ethyl acetate, glycol, *N,N*-dimethyl formamide, or a combination thereof.

[0037] According to some embodiments of the present invention, in the method one disclosed herein, the halogenating in step (B) is carried out in a third organic solvent, in some embodiments, the third organic solvent is one or more C_{1-4} alcohols, one or more C_{1-4} haloalkanes, acetonitrile, isopropyl ether, petroleum ether,

toluene, xylene, tetrahydrofuran, ethyl acetate, acetone, or a combination thereof. In other embodiments, the third organic solvent is dichloromethane, chloroform, tetrachloromethane, acetonitrile, isopropyl ether, petroleum ether, tetrahydrofuran, methanol, ethanol, propanol, *i*-propanol, *n*-butanol, *tert*-butanol, ethyl acetate, acetone, or a combination thereof.

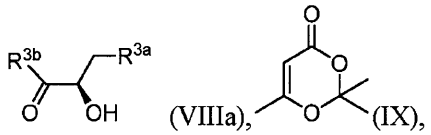
According to some embodiments of the present invention, the method one disclosed herein, in some embodiments, the halogenating reaction in step (B) is carried out in the presence of a halogenating agent, and wherein the halogenating agent is *N*-bromosuccinimide, *N*-chlorosuccinimide, *N*-iodosuccinimide, 1,3-dibromo-5,5-dimethylhydantoin, or 1,3-dichloro-5,5-dimethylhydantoin, or a combination thereof.

[0038] According to some embodiments of the present invention, the method one disclosed herein, in some embodiments, the base used in step (C) is formed by reacting lithium, sodium, or potassium or a combination thereof with a C_{1-4} alcohol.

[0039] According to some embodiments of the present invention, the method one disclosed herein, in some embodiments, the C_{1-4} alcohol for forming the base used in step (C) by reacting with lithium, sodium, or potassium, or a combination thereof is methanol, ethanol, propanol, *i*-propanol, *n*-butanol, *i*-butanol, or *tert*-butanol.

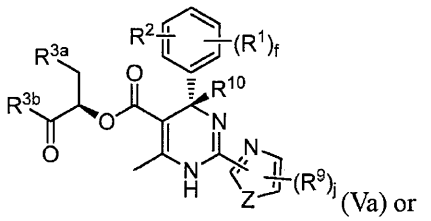
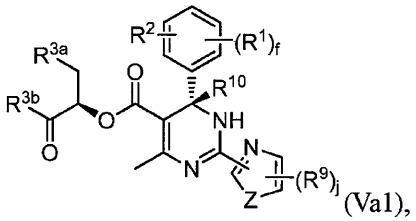
[0040] According to some embodiments of the present invention, the method one disclosed herein, each of the lithium, sodium and potassium or a combination thereof for forming a base used in step (C) by reacting with a C_{1-4} alcohol is independently applied in an amount, in some embodiments, the amount is 0.1 equivalent to 10 equivalents per 1 equivalent by mole of a compound of Formula (VIIa), Formula (VIIa-1), or Formula (VIIa-2). In other embodiments, the amount is 2 equivalents to 6 equivalents per 1 equivalent by mole of a compound of Formula (VIIa), Formula (VIIa-1), or Formula (VIIa-2). In still other embodiments, the amount is 2.5 equivalents to 6 equivalents per 1 equivalent by mole of a compound of Formula (VIIa), Formula (VIIa-1), or Formula (VIIa-2). In yet other embodiments, the amount is 0.1, 0.5, 1, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9 or 10 equivalents per 1 equivalent by mole of a compound of Formula (VIIa), Formula (VIIa-1), or Formula (VIIa-2).

[0041] According to some embodiments of the present invention, the method one disclosed herein, in some embodiments, the compound of Formula (IVa) in step (A) is prepared by a process comprising reacting a compound of Formula (VIIIa) with a compound of Formula (IX),



wherein R^{3a} and R^{3b} are as defined herein.

[0042] In one aspect, provided herein is an intermediate comprising a dihydropyrimidine compound having Formula (Va), or a tautomer thereof having Formula (Va1), or a salt thereof, or a combination thereof,


(Va) or

(Va1),

wherein each R^1 and R^2 is independently F, Cl, or Br;

R^{3b} is methoxy or ethoxy;

R^{3a} is H or C_{1-3} alkyl;

each R^9 is independently H, halo, C_{1-4} alkyl, C_{1-4} alkylthio, C_{1-4} haloalkyl, C_{3-6} cycloalkyl, $-(CR^7R^{7a})_m-C(=O)-N(R^8R^{8a})$, or $-(CR^7R^{7a})_m-C(=O)O-R^8$;

each R^{7a} and R^7 is independently H, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, $-(CH_2)_m-OH$, or $-(CH_2)_m-C(=O)O-R^8$; or R^{7a} and R^7, together with the carbon atom to which they are attached, form a C_{3-6} cycloalkyl group, C_{2-9} heterocyclyl goup, or -(C=O)-;

each R^8 and R^{8a} is independently H, C_{1-4} alkyl, amino-C_{1-4}-alkyl, C_{1-4} alkoxy, C_{1-6} alkyl-$S(=O)_q$-, C_{6-10} aryl, C_{1-9} heteroaryl, C_{3-6} cycloalkyl, C_{2-9} heterocyclyl, C_{6-10} aryl-C_{1-6}-alkyl, C_{1-9} heteroaryl-C_{1-6}-alkyl, C_{3-6} cycloalkyl-C_{1-4}-alkyl, C_{2-9} heterocyclyl-C_{1-6}-alkyl, C_{2-9} heterocyclyl-$S(=O)_q$-, C_{1-9} heteroaryl-$S(=O)_q$-, C_{3-6} cycloalkyl-$S(=O)_q$-, C_{6-10} aryl-$S(=O)_q$-, $-(CH_2)_m-OH$, $-(CH_2)_m-C(=O)O-(CH_2)_m-H$, or $-(CH_2)_m-OC(=O)-(CH_2)_m-H$;

each m is independently 0, 1, 2, 3, or 4;

R^{10} is H or deuterium;

f is 1, 2, 3, or 4;

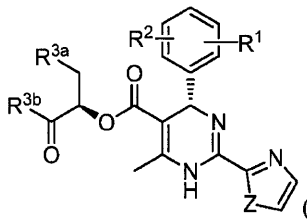
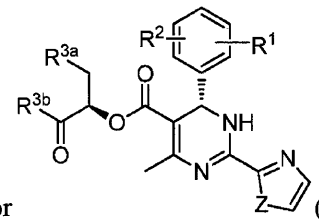
j is 0, 1, or 2;

Z is -O-, -S-, $-S(=O)_t$, or $-N(R^4)$-;

t is 0, 1, or 2; and

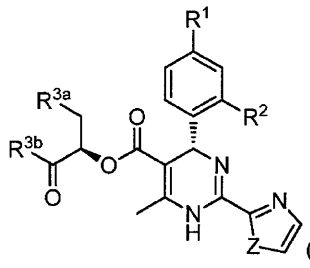
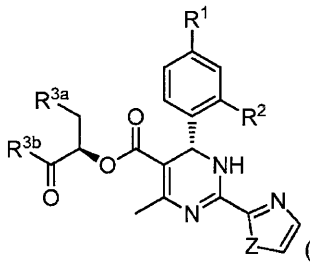
R^4 is H or C_{1-4} alkyl;

[0043] In some embodiments, provided herein is the intermediate having Formula (Va-1), or a tautomer thereof having Formula (Va1-1), or a salt thereof, or a combination thereof,


(Va-1) or

(Va1-1),

wherein R^{3a}, R^{3b}, R^1, R^2 and Z are as defined herein.

[0044] In some embodiments, provided herein is the intermediate having Formula (Va-2), or a tautomer thereof having Formula (Va1-2), or a salt thereof, or a combination thereof,


(Va-2) or

(Va1-2),

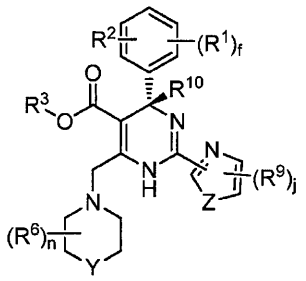
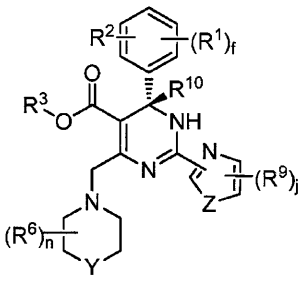
wherein R^1 is F or Cl; and R^2 is Cl or Br;

Z is -O-, -S-, or -N(CH_3)-;

R^{3b} is methoxy or ethoxy; and

R^{3a} is H, methyl, ethyl, isopropyl, or propyl.

[0045] In other aspect, provided herein is a process for preparing a dihydropyrimidine compound having Formula (I), or a tautomer thereof having Formula (Ia), or a combination thereof, (such as the method two depicted in scheme 2),


(I) or

(Ia),

wherein each R^1 and R^2 is independently F, Cl, or Br;

R^3 is C_{1-4} alkyl;

Z is -O-, -S-, -S(=O)$_t$-, or -N(R^4)-;

Y is -O-, -S-, -S(=O)$_t$-, -(CH_2)q-, or -N(R^5)-;

each t and q is independently 0, 1, or 2;

each of R^4 and R^5 is independently H, or C_{1-4} alkyl;

each R^6 is independently H, deuterium, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, amino, C_{1-4} alkylamino, C_{1-4} alkoxy, nitro, triazolyl, tetrazyl,-(CR^7R^{7a})$_m$-OH, -(CR^7R^{7a})$_m$-C(=O)O-R^8, -(CR^7R^{7a})$_t$-N(R^{8a})$_2$, -S(=O)$_q$OR^{8a}, -(CR^7R^{7a})$_m$-S(=O)$_q$N(R^{8a})$_2$, -(CR^7R^{7a})$_m$-C(=O)O-(CR^7R^{7a})$_m$-OC(=O)O-R^8, -(CR^7R^{7a})$_m$-C(=O)O-(CR^7R^{7a})$_m$-OC(=O)-R^8, -(CR^7R^{7a})$_m$-C(=O)O-(CR^7R^{7a})$_m$-C(=O)O-R^8, -(CR^7R^{7a})$_m$-OC(=O)-R^8, or -(CR^7R^{7a})$_m$-C(=O)N(R^8R^{8a});

each R^{7a} and R^7 is independently H, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, -(CH_2)$_m$-OH, or -(CH_2)$_m$-C(=O)O-R^8; or R^{7a} and R^7, together with the carbon atom to which they are attached, form a C_{3-6} cycloalkyl group, C_{2-9} heterocyclyl goup, or -(C=O)-;

each R^8 and R^{8a} is independently H, C_{1-4} alkyl, amino-C_{1-4}-alkyl, C_{1-4} alkoxy, C_{1-6} alkyl-S(=O)$_q$-, C_{6-10} aryl, C_{1-9} heteroaryl, C_{3-6} cycloalkyl, C_{2-9} heterocyclyl, C_{6-10} aryl-C_{1-6}-alkyl, C_{1-9} heteroaryl-C_{1-6}-alkyl, C_{3-6} cycloalkyl-C_{1-4}-alkyl, C_{2-9} heterocyclyl-C_{1-6}-alkyl, C_{2-9} heterocyclyl-S(=O)$_q$-, C_{1-9} heteroaryl-S(=O)$_q$-, C_{3-6}

cycloalkyl-S(=O)$_q$-, C_{6-10} aryl-S(=O)$_q$-, -(CH$_2$)$_m$-OH, -(CH$_2$)$_m$-C(=O)O-(CH$_2$)$_m$-H, or -(CH$_2$)$_m$-OC(=O)-(CH$_2$)$_m$-H;

each R^9 is independently H, halo, C_{1-4} alkyl, C_{1-4} alkylthio, C_{1-4} haloalkyl, C_{3-6} cycloalkyl, -(CR^{7}R^{7a})$_m$-C(=O)-N(R^{8}R^{8a}), or -(CR^{7}R^{7a})$_m$-C(=O)O-R^8;

R^{10} is H or deuterium;

n is 0, 1, 2, 3, 4, or 5;

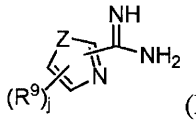
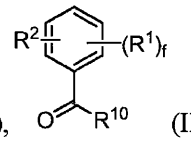
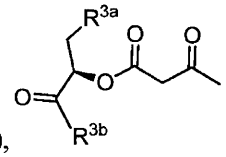
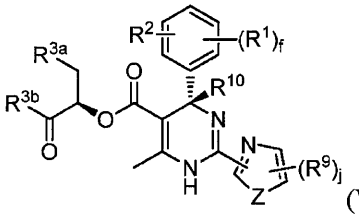
each m is independently 0, 1, 2, 3, or 4;

f is 1, 2, 3, or 4; and

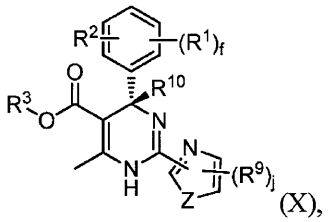
j is 0, 1, or 2;

wherein the process comprises the steps of:

step (1): reacting an amidine compound of Formula (II), or a salt thereof with an aldehyde compound of Formula (III) and a compound of Formula (IVa) to obtain a compound (Va) (according to some embodiments of present invention, the reaction of the step (A) may be, but not limited to an one-pot reaction),


(II),

(III),

(IVa),

(Va),

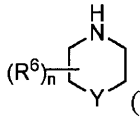
step (2): forming a compound of Formula (X) from a compound of Formula (Va) by means of a transesterification, and the transesterification may be carried out in the presence of a base,


(X),

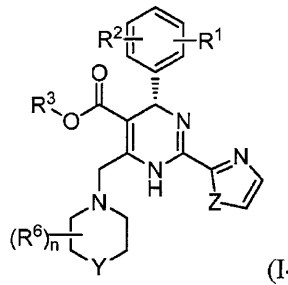
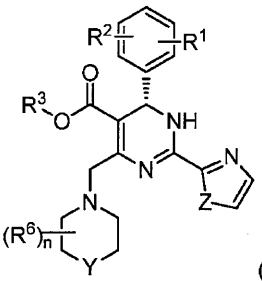
wherein R^{3b} is methoxy or ethoxy; and

R^{3a} is H or C_{1-3} alkyl;

step (3): halogenating the compound of Formula (X) to form a halide; and then reacting the halide with a compound of Formula (VI), or a salt thereof to obtain a compound of Formula (I) or Formula (Ia).


(VI)

[0046] In other embodiments, the dihydropyrimidine compound having Formula (I-1), or a tautomer thereof having Formula (Ia-1),


(I-1) or

(Ia-1),

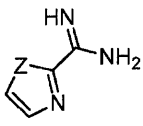
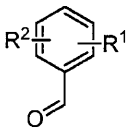
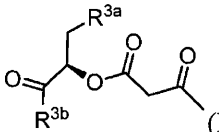
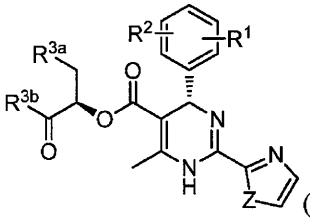
wherein each R^6 is independently H, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, amino, C_{1-4} alkylamino, C_{1-4} alkoxy, nitro, triazolyl, tetrazyl, $-(CR^7R^{7a})_m-OH$, $-(CR^7R^{7a})_m-C(=O)O-R^8$, $-(CR^7R^{7a})_t-N(R^{8a})_2$, $-S(=O)_qOR^{8a}$, $-(CR^7R^{7a})_m-S(=O)_qN(R^{8a})_2$, $-(CR^7R^{7a})_m-C(=O)O-(CR^7R^{7a})_m-OC(=O)O-R^8$, $-(CR^7R^{7a})_m-C(=O)O-(CR^7R^{7a})_m-OC(=O)-R^8$, $-(CR^7R^{7a})_m-C(=O)O-(CR^7R^{7a})_m-C(=O)O-R^8$, $-(CR^7R^{7a})_m-OC(=O)-R^8$, or $-(CR^7R^{7a})_m-C(=O)N(R^8R^{8a})$;

each R^{7a} and R^7 is independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, $-(CH_2)_m-OH$, or $-(CH_2)_m-C(=O)O-R^8$; and

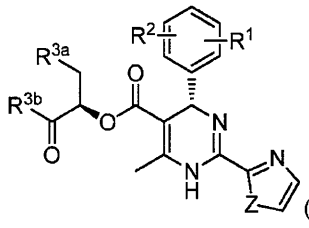
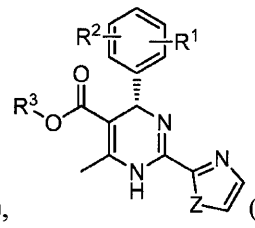
each R^1, R^2, R^3, Z, n, Y, m, q, R^{8a}, t and R^8 is as defined herein;

[0047] According to some embodiments of the present invention, the method two for preparing the optically pure dihydropyrimidine compound having Formula (I-1), or a tautomer thereof having Formula (Ia-1) comprises the steps of:

step (1): reacting an amidine compound of Formula (II-1), or a salt thereof with an aldehyde compound of Formula (III-1) and the compound of Formula (IVa) to obtain a compound (Va-1) (according to some embodiments of present invention, the reaction of the step (A) may be an one-pot reaction).

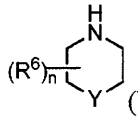

(II-1),

(III-1),

(IVa),

(Va-1),

step (2): forming a compound of Formula (X-1) from a compound of Formula (Va-1) by means of a transesterification, wherein the transesterification may be carried out in the presence of a base,

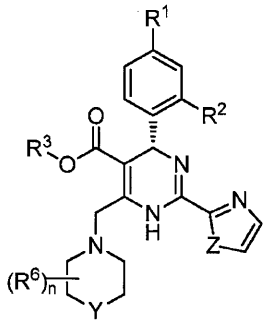
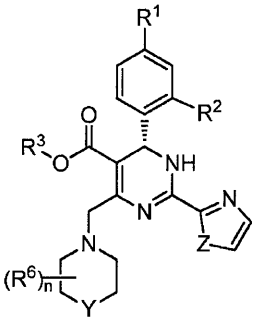

(Va-1),

(X-1),

wherein R^{3a} and R^{3b} are as defined herein;

step (3): halogenating the compound of Formula (X-1) to form a halide; and then reacting the intermediate with a compound of Formula (VI), or a salt thereof to obtain a compound of Formula (I-1) or Formula (Ia-1).


(VI)

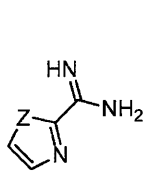
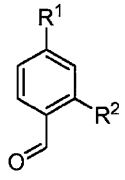
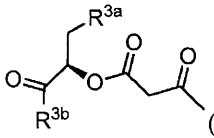
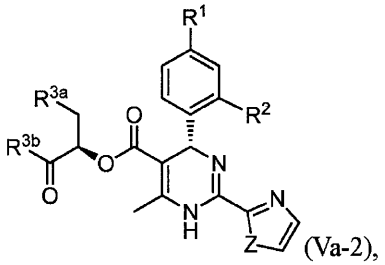
[0048] In other embodiments, the dihydropyrimidine compound having Formula (I-2), or a tautomer thereof having Formula (Ia-2),


(I-2) or

(Ia-2),

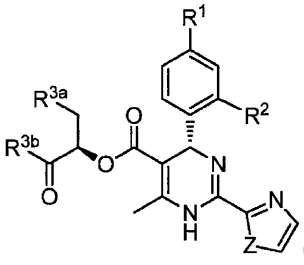
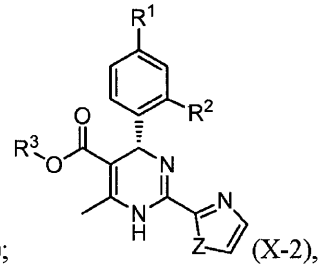
wherein R^1 is F or Cl; and R^2 is Cl or Br; R^3, Z, n, Y and R^6 are as defined herein;

[0049] According to some embodiments of the present invention, the method two for preparing the dihydropyrimidine compound having Formula (I-2), or a tautomer thereof having Formula (Ia-2) comprises the steps of:

step (1): reacting an amidine compound of Formula (II-1), or a salt thereof with an aldehyde compound of Formula (III-2) and the compound of Formula (IVa) to obtain a compound (Va-2) (according to some embodiments of the present invention, the reaction of the step (A) may be an one-pot reaction),

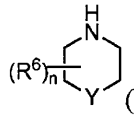

(II-1),

(III-2),

(IVa),

(Va-2),

step (2): forming a compound of Formula (X-2) from a compound of Formula (Va-2) by means of a transesterification, wherein the transesterification may be carried out in the presence of a base,


(Va-2);

(X-2),

wherein R^{3a} and R^{3b} are as defined herein;

step (3): halogenating the compound of Formula (X-2) to form a halide; and then reacting the halide with a compound of Formula (VI), or a salt thereof to obtain a compound of Formula (I-2) or Formula (Ia-2).


(VI)

[0050] According to some embodiments of the present invention, in the method two disclosed herein, in

some embodiments, the R^3 is methyl, ethyl, propyl, isopropyl, *tert*-butyl, or butyl; Z is -O-, -S-, or $-N(CH_3)-$; Y is -O-, -S-, $-S(=O)_2$, or $-(CH_2)_q-$; each R^6 is independently H, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, amino, C_{1-4} alkylamino, C_{1-4} alkoxy, nitro, triazolyl, tetrazyl,$-(CR^7R^{7a})_m-OH$, $-S(=O)_qOR^{8a}$, $-(CR^7R^{7a})_m-S(=O)_qN(R^{8a})_2$, $-(CR^7R^{7a})_t-N(R^{8a})_2$, $-(CR^7R^{7a})_m-C(=O)O-R^8$, $-(CR^7R^{7a})_m-C(=O)O-(CR^7R^{7a})_m-OC(=O)O-R^8$, $-(CR^7R^{7a})_m-C(=O)O-(CR^7R^{7a})_m-OC(=O)-R^8$, $-(CR^7R^{7a})_m-C(=O)O-(CR^7R^{7a})_m-C(=O)O-R^8$, $-(CR^7R^{7a})_m-OC(=O)-R^8$ or $-(CR^7R^{7a})_m-C(=O)N(R^8R^{8a})$; each R^{7a} and R^7 is independently H, methyl, ethyl, trifluoromethyl, $-(CH_2)_m-OH$, or $-(CH^2)_m-C(=O)O-R^8$; each R^8 and R^{8a} is independently H, methyl, ethyl, propyl, isopropyl, aminomethyl, methoxy, C_{1-4} alkyl-$S(=O)_2-$, phenyl, pyridyl, thiazolyl, furanyl, imidazolyl, isoxazolyl, oxazolyl, pyrrolyl, pyrimidinyl, pyridazinyl, diazolyl, triazolyl, tetrazolyl, thienyl, pyrazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyrazinyl, pyranyl, triazinyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropyl-$S(=O)_2-$, cyclobutyl-$S(=O)_2-$, cyclopentyl-$S(=O)_2-$, cyclohexyl-$S(=O)_2-$, naphthyl-$S(=O)_2-$, phenyl-$S(=O)_2-$, $-(CH_2)_m-OH$, $-(CH_2)_m-C(=O)O-(CH_2)_m-H$, or $-(CH_2)_m-OC(=O)-(CH_2)_m-H$; R^{3b} is methoxy or ethoxy; and R^{3a} is H, methyl, ethyl, isopropyl, or propyl.

According to some embodiments of the present invention, in the method two disclosed herein, the reaction in step (1) is performed at a temperature from 25 °C to 154 °C. In some other embodiments, the reaction in step (1) is performed at a temperature from 60 °C to 100 °C.

According to some embodiments of the present invention, in the method two disclosed herein, the step (1) further comprises the step of cooling the resulting compound (Va) of step (1) to obtain a solid compound (Va) at a cooling temperature from −40 °C to 40 °C. In other embodiments, the cooling temperature is from 25 °C to 40 °C. In some embodiments, the cooling is performed for a period of from 0 hour to 24 hours. In some other embodiments, the cooling is performed for from 1 minute to 24 hours. In still other embodiments, the cooling is performed for from 1 hour to 8 hours.

[0051] According to some embodiments of the present invention, in the method two disclosed herein, the amidine compound of Formula (II) reacts with the aldehyde compound of Formula (III) and the compound of Formula (IVa) in a first organic solvent. In some embodiments, the first organic solvent is applied in an amount of 0 equivalent to 80 equivalents per 1 equivalent by weight of the amidine compound of Formula (II), or a salt thereof. In some other embodiments, the first organic solvent is applied in an amount of 1 equivalent to 20 equivalents per 1 equivalent by weight of the amidine compound of Formula (II), or a salt thereof.

[0052] According to some embodiments of the present invention, in the method two disclosed herein, step (1) further comprises the step of purifying the solid compound (Va). In some embodiments, the solid compound of Formula (Va) is purified by at least one of the following methods: (1) trituration; (2) recrystallization; (3) washing.

[0053] According to some embodiments of the present invention, the purification is carried out in a second organic solvent. In some embodiments, the second organic solvent is applied in an amount of 2 equivalent to 20 equivalents per 1 equivalent by weight of the amidine compound of Formula (II), or a salt thereof.

[0054] According to some embodiments of the present invention, in the method two disclosed herein, the trituration is carried out at a temperature from −20 °C to 50 °C. In some embodiments, the trituration is carried out at a temperature from 0 °C to 40 °C.

[0055] According to some embodiments of the present invention, in the method two disclosed herein, the recrystallization comprises a crystallization process at a temperature from −30 °C to 40 °C. In some embodiments, the crystallization process is carried out at a temperature from 0 °C to 40 °C. In some embodiments, the recrystallization comprises a crystallization process of from 1 hour to 20 hours. In some other embodiments, the recrystallization comprises a crystallization process of from 1 hour to 10 hours.

[0056] According to some embodiments of the present invention, in the method two disclosed herein, the washing is performed at a temperature from 0°C to 30 °C.

[0057] According to some embodiments of the present invention, in the method two disclosed herein, in some embodiments, each of the first organic solvent and the second organic solvent is independently a C_{1-4} alcohol, a C_{1-4} alcohol-water, acetone, diethyl ether, isopropyl ether, petroleum ether, tetrahydrofuran, acetonitrile, cyclopentane, cyclohexane, *n*-hexane, C_{1-4} haloalkanes solvent, ethyl acetate, trifluoroethanol, 2-methoxyethanol, 1,2-dimethoxyethane, 2-methoxyethyl ether, *N,N*-dimethyl formamide, *N*-methylpyrolidone, or a combination thereof. In some other embodiments, each of the first organic solvent and the second organic solvent is independently methanol, ethanol, *n*-propanol, *i*-propanol, *n*-butanol, *tert*-butanol, an ethanol-water mixture at a volume ratio from 10:90 to 90:10, an ethanol-water mixture at a volume ratio from 50:50, acetone, tetrahydrofuran, *N*-methylpyrolidone, trifluoroethanol, 2-methoxyethanol, 1,2-dimethoxyethane, 2-methoxyethyl ether, ethyl acetate, glycol, *N,N*-dimethyl formamide, or a combination thereof.

[0058] According to some embodiments of the present invention, in the method two disclosed herein, in some embodiments, the base used in step (2) is formed by reacting lithium, sodium, or potassium or a combination thereof with a C_{1-4} alcohol.

[0059] According to some embodiments of the present invention, in the method two disclosed herein, in some embodiments, the C_{1-4} alcohol for forming the base used in step (2) by reacting with lithium, sodium, or potassium, or a combination thereof is methanol, ethanol, propanol, *i*-propanol, *n*-butanol, *i*-butanol, or *tert*-butanol.

[0060] According to some embodiments of the present invention, in the method two disclosed herein, each of the lithium, sodium and potassium, or a combination threreof for forming the base used in step (2) by reacting with a C_{1-4} alcohol is independently applied in an amount, in some embodiments, the amount is 0.5 equivalent to 10 equivalents per 1 equivalent by mole of a compound of Formula (Va), Formula (Va-1), or Formula (Va-2). In other embodiments, the amount is 2 equivalents to 8 equivalents per 1 equivalent by mole of a compound of Formula (Va), Formula (Va-1), or Formula (Va-2). In still other embodiments, the amount is 2.5 equivalents to 8 equivalents per 1 equivalent by mole of a compound of Formula (Va), Formula (Va-1), or Formula (Va-2). In yet other embodiments, the amount is 0.5, 1, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9 or 10 equivalents per 1 equivalent by mole of a compound of Formula (Va), Formula (Va-1), or Formula (Va-2).

[0061] According to some embodiments of the present invention, in the method two disclosed herein, the halogenating reaction in step (3) is carried out in a forth organic solvent, in some embodiments, the forth organic solvent is one or more C_{1-4} alcohols, one or more C_{1-4} haloalkanes, ethyl acetate, acetonitrile, isopropyl

ether, petroleum ether, toluene, xylene, tetrahydrofuran, acetone, or a combination thereof. In other embodiments, the forth organic solvent is dichloromethane, chloroform, tetrachloromethane, acetonitrile, isopropyl ether, petroleum ether, tetrahydrofuran, methanol, ethanol, propanol, *i*-propanol, *n*-butanol, *tert*-butanol, ethyl acetate, acetone, or a combination thereof.

[0062] According to some embodiments of the present invention, in the method two disclosed herein, in some embodiments, the halogenating reaction in step (2) is carried out in the presence of a halogenating agent, and wherein the halogenating agent is *N*-bromosuccinimide, *N*-chlorosuccinimide, *N*-iodosuccinimide, 1,3-dibromo-5,5-dimethylhydantoin, or 1,3-dichloro-5,5-dimethylhydantoin, or a combination thereof.

DEFINITIONS AND GENERAL TERMINOLOGY

[0063] The term "alkyl" or "alk-" or "alkyl group" as used interchangeably in the context of the present invention, such as in alkyl, aminoalkyl, alkyamino, alkylthio or alkoxy, relfers to a saturated linear or branched-chain monovalent hydrocarbon radical of 1 to 10 carbon atoms. Wherein, the alkyl group may be optionally substituted with one or more substituents disclosed herein. In some embodiments, the alkyl group contains 1-10 carbon atoms. In other embodiments, the alkyl group contains 1-6 carbon atoms. In other embodiments, the alkyl group contains 1-4 carbon atoms. In still other embodiments, the alkyl group contains 1-3 carbon atoms.

[0064] Some non-limiting examples of the alkyl group include, methyl (Me, $-CH_3$), ethyl (Et, $-CH_2CH_3$), *n*-propyl (*n*-Pr, $-CH_2CH_2CH_3$), isopropyl (*i*-Pr, $-CH(CH_3)_2$), *n*-butyl (*n*-Bu, $-CH_2CH_2CH_2CH_3$), isobutyl (*i*-Bu, $-CH_2CH(CH_3)_2$), *sec*-butyl (*s*-Bu, $-CH(CH_3)CH_2CH_3$), *tert*-butyl (*t*-Bu, $-C(CH_3)_3$), *n*-pentyl ($-CH_2CH_2CH_2CH_2CH_3$), 2-pentyl ($-CH(CH_3)CH_2CH_2CH_3$), 3-pentyl ($-CH(CH_2CH_3)_2$), 2-methyl-2-butyl ($-C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl ($-CH(CH_3)CH(CH_3)_2$), 3-methyl-l-butyl ($-CH_2CH_2CH(CH_3)_2$), 2-methyl-l-butyl ($-CH_2CH(CH_3)CH_2CH_3$), *n*-hexyl ($-CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl ($-CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl ($-CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl ($-C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl ($-CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl ($-CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl ($-C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl ($-CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl ($-C(CH_3)_2CH(CH_3)_2$), 3,3-dimethyl-2-butyl ($-CH(CH_3)C(CH_3)_3$, *n*-heptyl and *n*-octyl, *etc.*

[0065] The term "aminoalkyl" refers to a C_{1-10} linear or branched-chain alkyl group substituted with one or more amino groups. In some embodiments, the aminoalkyl group refers to a C_{1-6} aminoalkyl group, wherein the alkyl group is as defined herein. Some non-limiting examples of the aminoalkyl group include aminomethyl, 2-aminoethyl, 2-aminoisopropyl, aminopropyl, aminobutyl and aminohexyl, *etc.*

[0066] The term "alkoxy" refers to an alkyl group attached to the rest part of the molecule through an oxygen atom, wherein the alkyl group is as defined herein. Unless otherwise specified, the alkoxy group contains 1-10 carbon atoms. In some embodiments, the alkoxy group contains 1-6 carbon atoms. In other embodiments, the alkoxy group contains 1-4 carbon atoms. In still other embodiments, the alkoxy group contains 1-3 carbon atoms. Some non-limiting examples of the alkoxy group include methoxy (MeO, $-OCH_3$),

ethoxy (EtO, $-OCH_2CH_3$), propoxy (*n*-PrO, *n*-propoxy, $-OCH_2CH_2CH_3$), isopropoxy (*i*-PrO, *i*-propoxy, $-OCH(CH_3)_2$), *n*-butoxy (*n*-BuO, $-OCH_2CH_2CH_2CH_3$), 1-methyl-propoxy (*s*-BuO, *s*-butoxy, $-OCH(CH_3)CH_2CH_3$), 2-methyl-l-propoxy (*i*-BuO, *i*-butoxy, $-OCH_2CH(CH_3)_2$), *tert*-butoxy (*t*-BuO, *t*-butoxy, $-OC(CH_3)_3$), *n*-pentoxy ($-OCH_2CH_2CH_2CH_2CH_3$), 2-pentoxy ($-OCH(CH_3)CH_2CH_2CH_3$), 3-pentoxy ($-OCH(CH_2CH_3)_2$), 2-methyl-2-butoxy ($-OC(CH_3)_2CH_2CH_3$), 3-methyl-2-butoxy ($-OCH(CH_3)CH(CH_3)_2$), 3-methyl-l-butoxy ($-OCH_2CH_2CH(CH_3)_2$), 2-methyl-l-butoxy ($-OCH_2CH(CH_3)CH_2CH_3$) and *n*-hexyloxy ($-OCH_2CH_2CH_2CH_2CH_2CH_3$), *etc.*

[0067] The terms "haloalkyl", "haloalkenyl" and "haloalkoxy" respectively refer to alkyl, alkenyl or alkoxy, as the case may be, substituted with one or more halogen atoms. Wherein the alkyl, alkenyl and alkoxy are as defined herein. Some non-limiting examples of these groups include $-CF_3$, $-CH_2Cl$, $-CH_2CF_3$, $-CH_2CH_2CF_3$, $-OCF_3$, $-OCHF_2$, $-OCHCl_2$, $-OCH_2CHF_2$, $-OCH_2CHCl_2$ and $-OCH(CH_3)CHF_2$, *etc.*

[0068] The term "alkylamino" refers to "*N*-alkylamino" and "*N,N*-dialkylamino" wherein amino groups are independently substituted with one alkyl radical or two alkyl radicals, respectively. Wherein the amino group and the alkyl group are as defined herein. In some embidiments, the alkylamino radical is "lower alkylamino" radical having one or two C_{1-6} alkyl groups attached to a nitrogen atom. In other embodiments, the alkylamino radical refers to C_{1-4} lower alkylamino group. In still other embodiments, the alkylamino radical refers to C_{1-3} lower alkylamino group. Some non-limiting examples of suitable alkylamino radical include mono or dialkylamino. Some examples include, but are not limited to, methylamino, ethylamino, isopropylamino, propylamino, *tert*-butylamino, *n*-butylamino, 1-methylpropylamino, *n*-pentylamino, *n*-hexylamino, *N,N*-dimethylamino and *N,N*-diethylamino, *etc.*

[0069] The term "alkylthio" refers to a radical containing a linear or branched-alkyl radical of one to ten carbon atoms, attached to a divalent sulfur atom. Wherein the alkyl group is as defined herein. Some non-limiting examples of the alkylthio group include methylthio (CH_3S-) and ethylthio, *etc.*

[0070] The term "cycloalkyl" refers to a monovalent or multivalent saturated ring having 3 to 12 carbon atoms as a monocyclic, bicyclic, or tricyclic ring system. Wherein, the cycloalkyl group may be optionally substituted with one or more substituents disclosed herein. In some embodiments, the cycloalkyl contains 3 to 12 carbon atoms. In still other embodiments, the cycloalkyl contains 3 to 8 carbon atoms. In yet other embodiments, the cycloalkyl contains 3 to 6 carbon atoms. Some examples include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cyclohendecyl and cyclododecyl, *etc.*

[0071] The term "cycloalkylalkyl" refers to an alkyl radical substituted with one or more cycloalkyl radicals, wherein the cycloalkyl and alkyl are as defined herein. Some non-limiting examples of the cycloalkylalkyl group include cyclopropylmethyl, cyclopropylethyl, cyclopropylpropyl, cyclobutylmethyl, cyclobutylethyl, cyclobutylpropyl, cyclopentylmethyl, cyclopentylethyl, cyclopentylpropyl, cyclohexylmethyl, cyclohexylethyl and cyclohexylpropyl, *etc.*

[0072] The term "cycloalkyloxy" or "cycloalkoxy" refers to a cycloalkyl group, attached to the rest part of

the molecule through an oxygen atom. Wherein the cycloalkyl group is as defined herein. Some non-limiting examples of the cycloalkyloxy group include cyclopropoxy, cyclopentyloxy and cyclohexyloxy, *etc.*

[0073] The term "cycloalkylamino" refers to an amino group is substituted with one or two cycloalkyl radicals. Some non-limiting examples of such radical include cyclopropylamino, cyclobutylamino, cyclopentylamino and cyclohexylamino, *etc.* In some embodiments, the cycloalkyl of cycloalkylamino group may be optionally substituted with one or more substituents disclosed herein.

[0074] The term "heterocyclyl" refers to a saturated or unsaturation, nonaromatic, monocyclic, bicyclic or tricyclic ring system in which at least one ring member is selected from nitrogen, sulfur and oxygen. Wherein, the heterocyclyl group may be optionally substituted with one or more substituents disclosed herein. Unless otherwise specified, the heterocyclyl group may be carbon or nitrogen linked, and a $-CH_2-$ group can be optionally replaced by a -C(=O)- group. In which, the sulfur can be optionally oxygenized to *S*-oxide and the nitrogen can be optionally oxygenized to *N*-oxide. In some embodiments, the heterocyclyl group may be a C_{2-10} heterocyclyl group, which refers to a heterocyclyl group containing 2 to 10 carbon atoms and at least one heteroatom selected from nitrogen, sulfur and oxygen. In other embodiments, the heterocyclyl group may be a C_{2-9} heterocyclyl group, which refers to a heterocyclyl group containing 2 to 9 carbon atoms and at least one heteroatom selected from nitrogen, sulfur and oxygen. In still other embodiments, the heterocyclyl group may be a C_{2-7} heterocyclyl group, which refers to an heterocyclyl group containing 2 to 7 carbon atoms and at least one heteroatom selected from nitrogen, sulfur and oxygen. In yet other embodiments, the heterocyclyl group may be a C_{2-5} heterocyclyl group, which refers to a heterocyclyl group containing 2 to 5 carbon atoms and at least one heteroatom selected from nitrogen, sulfur and oxygen. Some non-limiting examples of the heterocyclyl group include oxiranyl, thietanyl, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, oxazolidinyl, tetrahydrofuranyl, dihydrothienyl, dihydropyranyl, piperidinyl, morpholinyl, tetrahydropyrimidinyl, oxazinanyl, thiomorpholinyl and piperazinyl, *etc.* A $-CH_2-$ group of the heterocyclyl group may be substituted with -C(=O), some non-limiting examples of such group include 2-oxopyrrolidinyl, 2-piperidinonyl, 3-morpholinonyl, 3-thiomorpholinonyl and oxotetrahydropyrimidinyl, *etc.*

[0075] The term "heterocyclylalkyl" refers to a heterocyclyl group attached to the rest of the molecule through an alkyl group, wherein the heterocyclyl and alkyl are as defined herein. Some non-limiting examples of such group included pyrrolidinylmethyl, piperidinylmethyl, piperidinylethyl, morpholinylmethyl and morpholinylethyl, *etc.*

[0076] The term "halogen" refers to fluorine(F), chlorine(Cl), bromine(Br) or iodine(I).

[0077] The term "aryl" refers to monocyclic, bicyclic and tricyclic carbocyclic ring systems having a total of six to fourteen ring members, or six to twelve ring members, or six to ten ring members, wherein at least one ring in the system is aromatic, wherein each ring in the system contains 3 to 7 ring members and that has a single point or multipoint of attachment to the rest of the molecule. Wherein the aryl may be optionally substituted with the substituent disclosed herein. The term "aryl" and "aromatic ring" can be used interchangeably herein. Some non-limiting examples of the aryl group include phenyl, 2,3-dihydro-1*H*-indenyl,

naphthalenyl and anthracenyl, *etc.*

[0078] The term "arylalkyl" or "aralkyl" refers to an aryl group attached to the rest of the molecule through an alkyl group, wherein the aryl and alkyl are as defined herein. Some non-limiting examples of such group include benzyl, phenylethyl and naphthalenylmethyl, *etc.*

[0079] The term "arylamino" refers to an amino group substituted with one or two aryl groups. Some non-limiting examples of such group included *N*-phenylamino. In some embodiments, the aryl group of the arylamino may be further substituted.

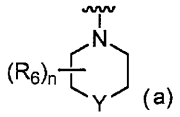
[0080] The term "heteroaryl" refers to monocyclic, bicyclic and tricyclic carbocyclic ring systems having a total of five to twelve ring members, or five to ten ring members, or five to six ring members, wherein at least one ring in the system is aromatic, and in which at least one ring member is selected from nitrogen, sulfur and oxygen, and wherein each ring in the system contains 3 to 7 ring members and that has a single point or multipoint of attachment to the rest of the molecule. The term "hetreroaryl" and "heteroaromatic ring" or "heteroaromatic compound" can be used interchangeably herein. In other embodiments, the heteroaryl group may be a C_{1-9} heteroaryl group, which refers to a heteroaryl group containing 1 to 9 carbon atoms and at least one heteroatom selected from nitrogen, sulfur and oxygen. In other embodiments, the heteroaryl group may be a C_{1-7} heteroaryl group, which refers to a heteroaryl group containing 1 to 7 carbon atoms and at least one heteroatom selected from nitrogen, sulfur and oxygen. In still other embodiments, the heteroaryl group may be a C_{1-6} heteroaryl group, which refers to a heteroaryl group containing 1 to 6 carbon atoms and at least one heteroatom selected from nitrogen, sulfur and oxygen. In other embodiments, the heteroaryl group may be a C_{1-5} heteroaryl group, which refers to a heteroaryl group containing 1 to 5 carbon atoms and at least one heteroatom selected from nitrogen, sulfur and oxygen. In still other embodiments, the heteroaryl group may be a C_{1-4} heteroaryl group, which refers to a heteroaryl group containing 1 to 4 carbon atoms and at least one heteroatom selected from nitrogen, sulfur and oxygen. In yet other embodiments, the heteroaryl group may be a C_{1-3} heteroaryl group, which refers to a heteroaryl group containing 1 to 3 carbon atoms and at least one heteroatom selected from nitrogen, sulfur and oxygen. Some non-limiting examples of such group include furanyl, imidazolyl, isoxazolyl, oxazolyl, pyrrolyl, pyrazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, thienyl, diazolyl, triazolyl, tetrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyranyl and triazinyl, *etc*, and also include the following bicycle ring, but atre not limited to: benzimidazolyl, benzofuranyl, benzothiophenyl, indolyl, oxoindolyl, indolinyl, imidazopyridyl, pyrazopryridyl, pyrazopyrimidinyl, quinolyl, isoquinolyl and quinazolinyl, *etc.* The heteroaryl group may be optionally substituted with one or more substituents disclosed herein.

[0081] The term "heteroarylalkyl" refers to an heteroaryl group attached to the rest of the molecule through a alkyl group, wherein the heteroaryl and alkyl are as defined herein. The "heteroarylalkyl" group may be optionally substituted with one or more substituents disclosed herein. Some non-limiting examples of such group included pyridylmethyl, pyrrolylethyl and quinolylmethyl, *etc.*

[0082] The term "comprise" is an open expression, it means comprising the contents disclosed herein, but

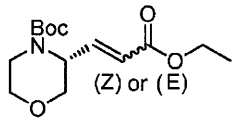
don't exclude other contents.

[0083] Furthermore, unless otherwise stated, the phrase "each...is independently" is used interchangeably with the phrase "each (of)...and...is independently". It should be understood broadly that the specific options expressed by the same symbol are independently of each other in different radicals; or the specific options expressed by the same symbol are independently of each other in same radicals. Such as Formula (a), multiple n are independently of each other, multiple R^6 are independently of each other,



(a)

[0084] As described herein, a system containing a group formed by connecting a double bond with a wave bond indicates that it is (Z) or (E) configuration, or a combination thereof.



(b)

[0085] The solvent used for the reaction of the invention is not particularly restricted, any solvent is contained in the invention so long as it can dissolve the raw materials to a certain extent and doesn't inhibit the reaction. Additionally, many similar modifications in the art, substitutions to same object, or solvent, solvent composition and the solvent composition with different proportions which are equivalent to those described in the invention, all are deemed to be included in the present invention. Wherein the solvent could be alcohols, alcohol-water mixtures, ethers, halohydrocarbons, esters, ketones, aromatic hydrocarbons, alkanes, acetonitrile, trifluoroethanol, *N,N*-dimethyl formamide (DMF), *N*-methylpyrolidone (NMP), or a combination thereof. Such as methanol, ethanol, *n*-propanol, *i*-propanol, *n*-butanol, *i*-butanol, a ethanol-water mixture at a volume ratio of 50:50, trifluoroethanol, *tert*-butanol, petroleum ether, *n*-pentane, *n*-hexane, *n*-heptane, cyclohexane, isopropyl ether, DMF, tetrahydrofuran, ethyl ether, dioxane, methyl tertiary butyl ether (MTBE), 1,2-dimethoxylethane, NMP, 2-methoxyethanol, 1,2-dimethoxyethane, diethylene glycol dimethyl ether, triethylene glycol dimethyl ether, dichloromethane, 1,2-dichloroethane, chloroform, tetrachloromethane, ethyl acetate, isopropyl acetate, acetone, butanone, benzene, toluene, xylene or a combination thereof.

[0086] The amount of water in the solvent is not particularly restricted. So long as the solvent containing a certain amount of water can be used in the reaction disclosed herein, which is deemed to be included in the present invention. The amount of water in the solvent is approximately less than 0.05%, less than 0.1%, less than 0.2%, less than 0.5%, less than 5%, less than 10%, less than 25%, less than 30%, or 0%.

[0087] The solvent used for the recrystallization of the invention is not particularly restricted, any solvent is contained in the invention so long as it can dissolve the crude product and the crystal product can precipitate out under certain conditions. Additionally, many similar modifications in the art, substitutions to same object, or solvent, solvent composition and the solvent composition with different proportions which are equivalent to those described in the invention, all are deemed to be included in the present invention. Wherein the solvent

could be alcohols, alcohol-water mixtures, ethers, alkanes, halohydrocarbons, esters, ketones, aromatic hydrocarbons, acetonitrile, *N*,*N*-dimethyl formamide (DMF), *N*-methylpyrolidone (NMP), or a combination thereof. Such as methanol, ethanol, *n*-propanol, *i*-propanol, *n*-butanol, *i*-butanol, *tert*-butanol, trifluoroethanol, a ethanol-water mixture at a volume ratio of 50:50, petroleum ether, *n*-pentane, *n*-hexane, *n*-heptane, cyclohexane, DMF, tetrahydrofuran, ethyl ether, isopropyl ether, dioxane, methyl tertiary butyl ether (MTBE), 1,2-dimethoxylethane, NMP, 2-methoxyethanol, 1,2-dimethoxyethane, diethylene glycol dimethyl ether, triethylene glycol dimethyl ether, dichloromethane, 1,2-dichloroethane, chloroform, tetrachloromethane, ethyl acetate, isopropyl acetate, acetone, butanone, benzene, toluene, xylene or a combination thereof.

[0088] Any temperature is included in the present invention so long as it is applicable for the one-pot reaction. Additionally, many similar modifications in the art, substitutions to same object, or temperature and temperature scope which are equivalent to those described in the invention, all are deemed to be included in the present invention. In some embodiments, the one-pot reaction temperature is from approximately room temperature (usually 25 °C) to 154 °C. The reaction is carried out at a low temperature at the beginning or at the earlier stage, after rising of the temperature, the reaction is carried out at a higher temperature, which may be from approximately 25 °C to solvent boiling point, from approximately 30 °C to solvent boiling point, from approximately 25 °C to 154 °C, or from approximately 30 °C to 154 °C.

[0089] Any temperature is included in the present invention so long as it is applicable for the cooling after one-pot reaction. . Additionally, many similar modifications in the art, substitutions to same object, or temperature and temperature scope which are equivalent to those described in the invention, all are deemed to be included in the present invention. In some embodiments, the cooling temperature is approximately from −80 °C to 60 °C. After the one-pot reaction is complete, the reaction mixture cooling is carried out at a higher temperature, may be from solvent boiling point to 60 °C, from solvent boiling point to 40 °C, from solvent boiling point to 30 °C, from solvent boiling point to 25 °C, from solvent boiling point to 0 °C, from solvent boiling point to −10 °C, from solvent boiling point to −15 °C, from solvent boiling point to −20 °C, from solvent boiling point to −40 °C, from solvent boiling point to −50 °C, or solvent boiling point to −80 °C, and may be from approximately 60 °C to −20 °C, from approximately 50 °C to −20 °C, from approximately 40 °C to 10 °C, from approximately 30 °C to 10 °C, or from approximately room temperature (usually 25 °C) to 10 °C. The reaction mixture cooling at the later stage is carried out at a lower temperature, may be from approximately −80 °C to approximately 10 °C, from approximately −60 °C to approximately 10 °C, from approximately −40 °C to approximately 10 °C, from approximately −20 °C to approximately 10 °C, or from approximately −10 °C to approximately 10 °C, from approximately 0 °C to approximately 10 °C.

[0090] Any temperature is included in the present invention so long as it can applicable for the crystallization process of recrystallization. Additionally, many similar modifications in the art, substitutions to same object, or temperature and temperature scope which are equivalent to those described in the invention, all are deemed to be included in the present invention. In some embodiments, the crystallization temperature is approximately from −80 °C to 60 °C. After all the crude product is dissolved completely, the crystallization is

at a higher temperature, may be from solvent boiling point to 60 °C, from solvent boiling point to 50 °C, from solvent boiling point to 40 °C, from solvent boiling point to 30 °C, from solvent boiling point to 25 °C, from solvent boiling point to 0 °C, from solvent boiling point to −10 °C, from solvent boiling point to −15 °C, from solvent boiling point to −20 °C, from solvent boiling point to −30 °C, from solvent boiling point to −40 °C, from solvent boiling point to −50 °C, or solvent boiling point to −80 °C, and may be from approximately 60 °C to −20 °C, from approximately 50 °C to −20 °C, from approximately 40 °C to 10 °C, from approximately 30 °C to 10 °C, or from approximately room temperature (usually 25 °C) to 10 °C. The crystallization at the later stage is at a lower temperature, may be from approximately −80 °C to approximately 10 °C, from approximately −60 °C to approximately 10 °C, from approximately −40 °C to approximately 10 °C, from approximately −20 °C to approximately 10 °C, from approximately −10 °C to approximately 10 °C, or from approximately 0 °C to approximately 10 °C.

[0091] Any halogenating agent is included in the present invention so long as it is applicable for the halogenating reaction. For example, *N*-bromosuccinimide (NBS), *N*-chlorosuccinimide (NCS), *N*-iodosuccinimide (NIS), 1,3-dibromo-5,5-dimethylhydantoin, 1,3-dichloro-5,5-dimethylhydantoin, iodomethane, *etc*, or a combination thereof.

[0092] The base used in the present invention may be an organic base or inorganic base. The organic base may be triethylamine, trimethylamine, N,N-diisopropylethylamine, N-methylmorpholine, N-methylpiperidine or a combination thereof; and can also be a base formed by reacting an organic solvent with an alkali metal. The alkali metal comprises lithium, sodium and potassium, or a combination thereof. The organic solvent can be one or more alcohols, or a combination thereof. The alcohols include, but are not limited to, methanol, ethanol, propanol, *i*-propanol, *n*-butanol, *i*-butanol, *tert*-butanol and a combination thereof. The inorganic bases include, but are not limited to, alkali metal hydroxide, alkaline earth metal hydroxide, alkali metal alkoxide, alkaline earth metal alkoxide, alkali metal carbonate, alkaline earth metal carbonate and ammonia. In some embodiments, the inorganic base is ammonia, sodium hydroxide, calcium hydroxide, magnesium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, lithium carbonate, sodium *tert*-butoxide, sodium isopropoxide or potassium *tert*-butoxide.

[0093] After the reaction proceeds to a certain extent in the present invention, such as the raw material is consumed more than 20%, more than 30%, more than 40%, more than 50%, more than 70%, more than 80%, more than 90%, more than 95%, or completely by monitoring, the reaction mixture is worked up, such as cooled, collected, drawn, filtered, separated, purified or a combination thereof. The reaction can be monitored by conventional method such as thin-layer chromatography (TLC), high performance liquid chromatography (HPLC), gas chromatography (GC), and the like. The reaction mixture can be worked up by conventional method, for example, the crude product can be collected by concentrating the reaction mixture through vacuum evaporation or conventional distillation and which is used directly in the next operation; or the crude product can be obtained by filtration of the reaction mixture and which is used directly in the next operation; or the crude product can be get by pouring the supernatant liquid of the reaction mixture after standing for a while and

which is used directly in the next operation. And the reaction mixture can be purified by suitable methods such as extraction, distillation, crystallization, column chromatography, washing, trituration with suitable organic solvents or a combination thereof.

[0094] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric(or conformeric)) forms of the structure; for example, the R and S configurations for each asymmetric center, (Z) and (E) double bond isomers, and (Z) and (E) conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, or geometric (or conformeric) mixtures of the present compounds are within the scope disclosed herein.

[0095] Stereochemical definitions and conventions used herein generally follow Parker *et al.*, *McGraw-Hill Dictionary of Chemical Terms* (1984) McGraw-Hill Book Company, New York and Eliel *et al.*, *Stereochemistry of Organic* Compounds, John Wiley & Sons, Inc., New York, 1994. The compounds disclosed herein may contain asymmetric or chiral centers, and therefore exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds disclosed herein, including, but not limited to, diastereomers, enantiomers and atropisomers, as well as mixtures thereof such as racemic mixtures, form part of the present invention. Many organic compounds exist in optically active forms, *i.e.*, they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L, or R and S, are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or l meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer is referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The term "racemic mixture" or "racemate" refers to an equimolar mixture of two enantiomeric species, devoid of optical activity.

[0096] The term "tautomer" or "tautomeric form" refers to structural isomers of different energies which are interconvertible via a low energy barrier. If tautomerism could happen (such as in a solvent), the chemical balance between tautomers can be reached. For example, proton tautomers (also known as prototropic tautomers) include interconversions via migration of a proton, such as keto-enol and imine-enamine isomerizations. Valence tautomers include interconversions by reorganization of some of the bonding electrons. The specific example of keto-enol tautomerisms is hexane-2,4-dione and 4-hydroxyhex-3-en-2-one tautomerism. Another example of tautomerisms is phenol-keto tautomerism. The specific example of phenol-keto tautomerisms is pyridin-4-ol and pyridin-4(3*H*)-one tautomerism. Unless otherwise stated, all tautomers of the present compounds are within the scope disclosed herein.

GENERAL SYNTHETIC PROCEDURES

[0097] In the present invention, if the chemical name of the compound doesn't match the corresponding

structure, the compound is characterized by the corresponding structure.

[0098] Generally, the compounds of Formula (I), Formula (Ia), Formula (I-1), Formula (Ia-1), Formula (I-2) or Formula (Ia-2) disclosed herein may be prepared by methods described herein, wherein the substituents are as defined in Formula (I), Formula (Ia), Formula (I-1), Formula (Ia-1), Formula (I-2) or Formula (Ia-2), except where further noted. The following examples are presented to further exemplify the invention.

[0099] Persons skilled in the art will recognize that the chemical reactions described may be readily adapted to prepare a number of other compounds disclosed herein, and alternative methods for preparing the compounds disclosed herein are deemed to be within the scope disclosed herein. For example, the synthesis of non-exemplified compounds according to the invention may be successfully performed by modifications apparent to those skilled in the art, *e.g.*, by appropriately protecting interfering groups, by utilizing other suitable reagents known in the art other than those described, and/or by making routine modifications of reaction conditions. Alternatively, other reactions disclosed herein or known in the art will be recognized as having applicability for preparing other compounds disclosed herein.

[00100] In the examples described below, unless otherwise indicated all temperatures are set forth in degrees Celsius (°C). Reagents were purchased from commercial suppliers such as Aldrich Chemical Company, Arco Chemical Company and Alfa Chemical Company, and were used without further purification unless otherwise indicated. Common solvents were purchased from commercial suppliers such as Shantou XiLong Chemical Factory, Guangdong Guanghua Reagent Chemical Factory Co. Ltd., Guangzhou Reagent Chemical Factory, Tianjin YuYu Fine Chemical Ltd., Qingdao Tenglong Reagent Chemical Ltd., and Qingdao Ocean Chemical Factory.

[00101] Column chromatography was conducted using a silica gel column. Silica gel (200 – 300 mesh) was purchased from Qingdao Ocean Chemical Factory. 1H NMR spectra were recorded by a Bruker Avance 400 MHz spectrometer or Bruker Avance III HD 600 spectrometer, using $CDCl_3$, DMSO-d_6, CD_3OD or acetone-d_6 (reported in ppm) as solvent, and using TMS (0 ppm) or chloroform (7.25 ppm) as the reference standard. When peak multiplicities are reported, the following abbreviations are used: s (singlet), d (doublet), t (triplet), m (multiplet), br (broadened), dd (doublet of doublets), dt (doublet of triplets), ddd (doublet of doublet of doublets), ddt (doublet of doublet of triplets), dddd (doublet of doublet of doublet of doublets), td (triplet of doublets), brs (broadened singlet). Coupling constants, when given, are reported in Hertz (Hz).

[00102] Low-resolution mass spectral (MS) data were also determined on an Agilent 6320 series LC-MS spectrometer equipped with G1312A binary pumps, a G1316A TCC (Temperature Control of Column, maintained at 30 °C), a G1329A autosampler and a G1315B DAD detector were used in the analysis. An ESI source was used on the LC-MS spectrometer.

[00103] Low-resolution mass spectral (MS) data were also determined on an Agilent 6120 series LC-MS spectrometer equipped with G1312A binary pumps, a G1316A TCC (Temperature Control of Column, maintained at 30 °C), a G1329A autosampler and a G1315B DAD detector were used in the analysis. An ESI source was used on the LC-MS spectrometer.

[00104] Both LC-MS spectrometers were equipped with an Agilent Zorbax SB-C18, 2.1 x 30 mm, 5 μm column. Injection volume was decided by the sample concentration. The flow rate was 0.6 mL/min. The HPLC peaks were recorded by UV-Vis wavelength at 210 nm and 254 nm. The mobile phase was 0.1% formic acid in acetonitrile (phase A) and 0.1% formic acid in ultrapure water (phase B). The gradient condition is shown in Table 1:

Table 1: The gradient condition of the mobile phase in Low-resolution mass spectrum analysis

Time (min)	A (CH_3CN, 0.1% HCOOH)	B (H_2O, 0.1% HCOOH)
0 - 3	5 - 100	95 - 0
3 - 6	100	0
6 - 6.1	100 - 5	0 - 95
6.1 - 8	5	95

[00105] Purities of compounds were assessed by Agilent 1100 Series high performance liquid chromatography (HPLC) with UV detection at 210 nm and 254 nm (Zorbax SB-C18, 2.1 × 30 mm, 4 micorn, 10 min, 0.6 mL/min flow rate, 5 to 95 % (0.1 % formic acid in CH_3CN) in (0.1 % formic acid in H_2O). Column was operated at 40 °C.

[00106] The following abbreviations are used throughout the specification:

$CDCl_3$ chloroform-*d*

DMF-d_6 *N,N*-dimethylformamide-d_6

DMSO-d_6 dimethyl sulfoxide-d_6

Acetone-d_6 acetone-d_6

D_2O water-d_2

EA, EtOAc ethyl acetate

DMF *N,N*-dimethylformamide

THF tetrahydrofuran

NMP *N*-methylprrolidone

MeCN, CH_3CN acetonitrile

DCM, CH_2Cl_2 dichloromethane

$CHCl_3$ chloroform

CCl_4 tetrachloromethane

PE petroleum ether

CH_3OH, MeOH methanol

g gram

c concentration

mol mole

mmol millimole

h hour, hours

min minute, minutes

mL milliliter

v/v. v:v the ratio of volume

DMSO dimethyl sulfoxide

NBS *N*-bromosuccinimide

NCS *N*-chlorosuccinimide

NIS *N*-iodosuccinimide

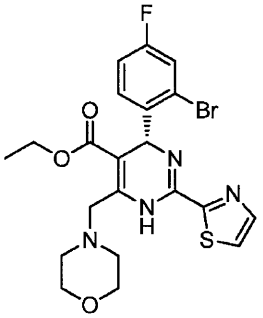
EXAMPLES

[00107] The preparation methods of optically pure dihydropyrimidine compounds disclosed in the examples of the present invention. Skilled in the art can learn from this article to properly improve the process parameters to implement the preparation method. Of particular note is that all similar substitutions and modifications to the skilled person are obvious, and they are deemed to be included in the present invention. The methods disclosed herein were described in the preferred examples. Related person can clearly realize and apply the techniques disclosed herein by making some changes, appropriate alterations or combinations to the methods without departing from spirit, principles and scope of the present disclosure.

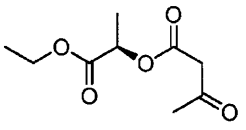
[00108] In order to further understand the invention, it is detailed below through examples.

Example

Example 1: the preparation of (*R*)-ethyl 4-(2-bromo-4-fluorophenyl)-6-(morpholinomethyl)-2-(thiazol-2-yl)-1,4 -dihydropyrimidine-5- carboxylate



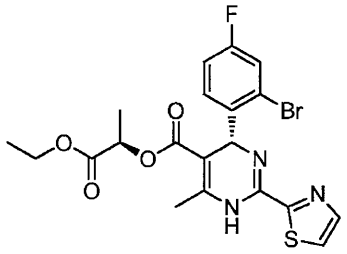
Step 1) (*R*)-1-ethoxy-1-oxopropan-2-yl 3-oxobutanoate



[00109] A flask was charged with (*D*)-ethyl 2-hydroxypropanoate (11.8 g, 10 mmol) and 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (14.2 g, 10 mmol) in turn, and then equipped with distillation apparatus or water segregator. The mixture was stirred at 120 °C for 4 hours. After the reaction, the mixture was cooled and concentrated to obtain the title compound as puce liquid (12.9 g, 64%).

MS (ESI, pos.ion) *m/z*: 203.1 $[M+H]^+$;

Step 2) (*R*)-(*R*)-1-ethoxy-1-oxopropan-2-yl 4-(2-bromo-4-fluorophenyl)-6-methyl-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate



Method one:

[00110] To a flask were added 2-thiazolecarboxamidine hydrochloride (16.4 g, 0.1 mol), 2-bromo-4-fluorobenzaldehyde (20.3 g, 0.1 mol), (*R*)-1-ethoxy-1-oxopropan-2-yl 3-oxobutanoate (20.2 g, 0.1 mol), anhydrous sodium acetate (8.2 g, 0.1 mol) and ethanol (74 g) in turn. The mixture was stirred at 78 °C for 16 hours. After the reaction, the mixture was cooled to 30 °C, kept at 30 °C and stirred for 6 hours. The resulting mixture was filtered. The filter cake was washed with water (330 mL) and dried *in vacuo* at 60 °C for 8 hours to obtain the crude product. To the crude product was added *n*-propanol (74 g). The mixture was heated until dissolved completely, cooled to 25 °C, and then kept at 25 °C, stirred and crystallized for 5 hours. The resulting mixture was filtered. The filter cake was dried *in vacuo* at 60 °C for 8 hours to obtain the product as a yellow solid (13.4 g, 27%).

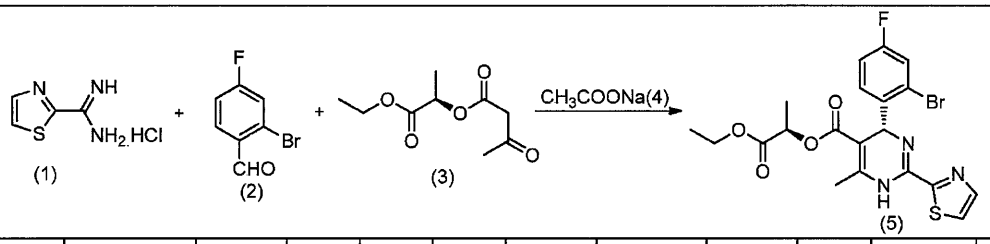
$[\alpha]_D^{25} = -122.46$ (c = 0.3054 g/100 mL, MeOH);

MS (ESI, pos.ion) *m/z*: 497.7 $[M+H]^+$;

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.02 (s,1H), 7.97 (d,1H), 7.89 (d,1H), 7.54 (dd,1H), 7.36 (dd,1H), 7.23 (td,1H), 6.00 (s,1H), 4.82 (q,1H), 4.14-4.01 (m,2H), 2.47 (s,3H), 1.22 (d,3H), 1.13 (t,3H).

[00111] The compound 5 can be prepared under the reaction conditions shown in table 2 by using method one described in step 2 of Example 1.

Table 2: The reaction conditions



No.	(1):(2):(3):(4) (mol); the amount of compound (1) is 16.4 g	Reaction solvent	The mass ratio of reaction solvent to compound (1)	Reaction temperature (°C)	Reaction time(h)	Cooling temperature (°C)	Cooling time(h)	Recrystallization solvent	The mass ratio of recrystallization solvent to compound (1)	Crystallization temperature (°C)	Crystallization time(h)	Quality; yield(%) of product
1	1:1:2:1	—	—	78	12	40	6	ethanol	20	0	3	8.8 g;

												17.8
2	1:1:1:1	ethanol	1	78	12	40	8	ethanol	15	10	6	9.6 g; 19.4
3	1:1:1:1	ethanol	4.5	25	72	25	—	ethanol	4.5	5	2	7.5 g; 15.2
4	1:1:1:1	ethanol	4.5	78	12	25	6	ethanol	3	25	1	12.9 g; 26.1
5	1:1:1:1	ethanol	20	60	24	-20	12	ethanol	4.5	25	6	10.1 g; 20.3
6	1:1:1:1	ethanol	80	78	12	-30	24	ethanol	5	25	4	7.5 g; 15.1
7	1:1:1:1	DMF	4.5	154	1	-30	6	*n*-propanol	4	10	4	5.9 g; 11.9
8	1:1:1:1	*n*-butanol	5	100	5	0	6	*n*-butanol	4	25	6	11.2 g; 22.5
9	1:1:1:1	*n*-propanol	4.5	80	12	25	6	*n*-propanol	3.5	40	10	12.4 g; 25.1
10	1:1:1:1	*i*-propanol	4.5	82	12	25	1	*i*-propanol	5	25	4	9.6 g; 19.3
11	1:1:1:1	*t*-butanol	4.5	82	12	30	12	*i*-propanol	4.5	25	6	10.6 g; 21.4
12	1:1:1:1	2-methoxyethanol	4.5	78	12	-10	12	*i*-propanol	5	25	4	10.1 g; 20.3
13	1:1:1:1	1,2-dimethoxyethane	4.5	78	12	-10	12	*n*-propanol	5	25	4	5.9 g; 11.8
14	1:1:1:1	ethyl acetate	3	77	12	-10	12	*i*-propanol	4.5	25	4	7.6 g; 15.4
15	1:1:1:1	acetone	3	56	12	-20	12	*i*-propanol	5	25	4	4.2 g; 8.5
16	1:1:1:1	methanol	3	64	12	0	6	*n*-propanol	5	25	4	7.8 g; 15.8
17	1:1:1:1	2-methoxyethyl ether	5	78	6	-20	12	*n*-propanol	5	25	6	4.8 g; 9.7
18	1:1:1:1	ethanol	10	78	12	-20	12	ethanol	4.5	30	6	11.6 g; 23.3
19	1:1:1:1	ethyl acetate	3	77	12	-10	12	ethyl acetate	2	-10	4	5.7 g; 11.4
20	1:1:1:1	ethanol	2	78	12	40	8	ethanol	15	10	6	9.9 g; 19.9
21	1:1:1:1	ethanol	1	78	12	40	8	ethanol	10	10	6	10.3g; 20.7

Method two:

[00112] To a flask were added 2-thiazolecarboxamidine hydrochloride (16.4 g, 0.1 mol), 2-bromo-4-fluorobenzaldehyde (20.3 g, 0.1 mol), (*R*)-1-ethoxy-1-oxopropan-2-yl 3-oxobutanoate (20.2 g, 0.1 mol), anhydrous sodium acetate (8.2 g, 0.1 mol) and ethanol (74 g) in turn. The mixture was stirred at 78 °C for 16 hours. After the reaction, the reaction mixture was cooled to 30 °C, kept at 30 °C and stirred for 6 hours. The mixture was filtered. The filtrate was washed with ethanol (50 g) and water (330 mL) in turn, and then dried *in vacuo* at 60 °C for 8 hours to obtain the product as a yellow solid (14.4 g, 29%).

$[\alpha]_D^{25}$ = −122.46 (c = 0.3054 g/100 mL, MeOH);

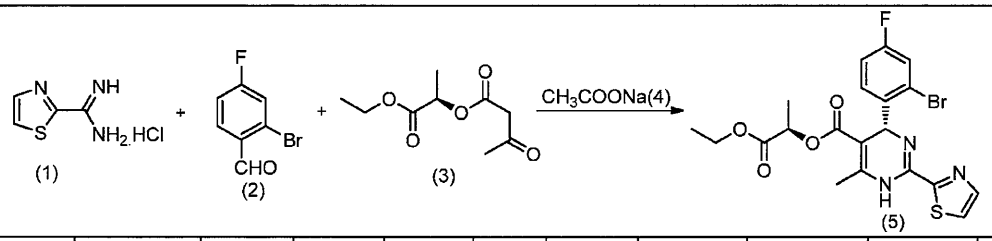
MS (ESI, pos.ion) *m/z*: 497.7 $[M+H]^+$;

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.02 (s,1H), 7.97 (d,1H), 7.89 (d,1H), 7.54 (dd,1H), 7.36 (dd,1H),

7.23 (td,1H), 6.00 (s,1H), 4.82 (q,1H), 4.14-4.01 (m,2H), 2.47 (s,3H), 1.22 (d,3H), 1.13 (t,3H).

[00113] The compound 5 can be prepared under the reaction conditions shown in table 3 by using method two described in step 2 of Example 1.

Table 3: The reaction conditions



No.	(1):(2):(3):(4) (mol); the amount of compound (1) is 16.4 g	Reaction solvent	The mass ratio of reaction solvent to compound (1)	Reaction temperature (°C)	Reaction time(h)	Cooling temperature (°C)	Cooling time(h)	Washing solvent	The mass ratio of washing solvent to compound (1)	Washing temperature(°C)	Quality; yield(%) of product
1	1:1:2:1	—	—	78	12	40	6	ethanol	15	25	9.5 g; 19.2
2	1:1:1:1	ethanol	1	78	12	40	6	ethanol	10	25	10.3 g; 20.8
3	1:1:1:1	ethanol	4.5	25	72	25	—	ethanol	3	25	8.5 g; 17.1
4	1:1:1:1	ethanol	4.5	78	12	25	6	ethanol	3.5	25	13.7 g; 27.6
5	1:1:1:1	ethanol	20	60	24	-10	6	ethanol	4.5	25	11.1 g; 22.4
6	1:1:1:1	ethanol	80	78	12	-30	12	ethanol	5	25	8.4 g; 16.9
7	1:1:1:1	ethanol	8	78	12	25	6	—	—	—	13.1 g; 26.5
8	1:1:1:1	DMF	4.5	154	1	-30	6	ethanol	4	25	6.6 g; 13.3
9	1:1:1:1	*n*-butanol	5	100	5	0	6	*n*-butanol	2	25	12.3 g; 24.7
10	1:1:1:1	*n*-propanol	4.5	80	12	25	6	*n*-propanol	3	25	14.2 g; 28.6
11	1:1:1:1	*i*-propanol	4.5	82	12	25	1	*i*-propanol	3	25	10.7 g; 21.5
12	1:1:1:1	*t*-butanol	4.5	82	12	30	12	*t*-butanol	3	30	11.7 g; 23.6
13	1:1:1:1	2-methoxyethanol	4.5	78	12	-10	12	2-methoxyethanol	1	0	10.9 g; 21.9
14	1:1:1:1	1,2-dimethoxyethane	4.5	78	12	-10	12	*n*-propanol	3	25	6.6 g; 13.4
15	1:1:1:1	ethyl acetate	3	77	12	-10	12	*i*-propanol	3.5	25	8.33 g; 16.8
16	1:1:1:1	acetone	3	56	12	-20	12	*i*-propanol	3	25	5.3 g; 10.6
17	1:1:1:1	methanol	3	64	12	0	6	*n*-propanol	2	25	8.8 g; 17.7
18	1:1:1:1	2-methoxy	5	78	6	-20	12	*n*-propan	2	25	5.6 g;

		ethyl ether						ol			11.3
19	1:1:1:1	*n*-propanol	4.5	80	12	25	6	*i*-propanol	20	0	10.4 g; 20.9

Method three:

[00114] To a flask were added 2-thiazolecarboxamidine hydrochloride (16.4 g, 0.1 mol), 2-bromo-4-fluorobenzaldehyde (20.3 g, 0.1 mol), (*R*)-1-ethoxy-1-oxopropan-2-yl 3-oxobutanoate (20.2 g, 0.1 mol), anhydrous sodium acetate (8.2 g, 0.1 mol) and ethanol (74 g) in turn. The mixture was stirred at 78 °C for 16 hours. After the reaction, the mixture was cooled to 30 °C, kept at 30 °C and stirred for 6 hours. The resulting mixture was filtered. The filter cake was washed with water (330 mL) and dried *in vacuo* at 60 °C for 8 hours to obtain the crude product. The crude product was triturated with *n*-propanol (50 g) at 30 °C for 5 hours and filtered. The filter cake was washed with *n*-propanol (12.8 g) and dried *in vacuo* at 60 °C for 8 hours to obtain the product as a yellow solid (13.9 g, 28%).

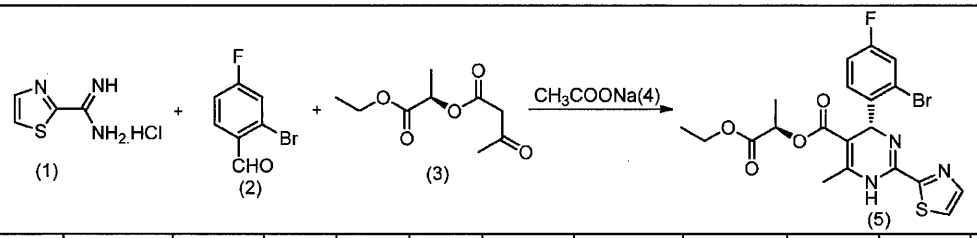
$[\alpha]_D^{25} = -122.46$ (c = 0.3054 g/100 mL, MeOH);

MS (ESI, pos.ion) *m/z*: 497.7 $[M+H]^+$;

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.02 (s,1H), 7.97 (d,1H), 7.89 (d,1H), 7.54 (dd,1H), 7.36 (dd,1H), 7.23 (td,1H), 6.00 (s,1H), 4.82 (q,1H), 4.14-4.01 (m,2H), 2.47 (s,3H), 1.22 (d,3H), 1.13 (t,3H).

[00115] The compound 5 can be prepared under the reaction conditions shown in table 4 by using method three described in step 2 of Example 1.

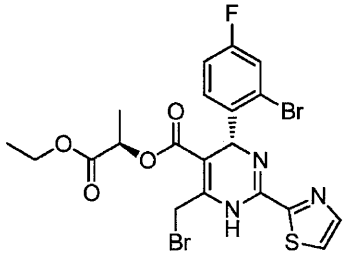
Table 4: The reaction conditions



No.	(1):(2):(3):(4) (mol); the amount of compound (1) is 16.4 g	Reaction solvent	The mass ratio of reaction solvent to compound (1)	Reaction temperature (°C)	Reaction time(h)	Cooling temperature (°C)	Cooling time(h)	Trituration solvent	The mass ratio of trituration solvent to compound (1)	Trituration temperature (°C)	Trituration time(h)	Quality; yield(%) of product
1	1:1:2:1	—	—	78	12	40	6	ethanol	13	25	10	9.2 g; 18.6
2	1:1:1:1	ethanol	1	78	12	40	6	ethanol	9	25	5	10 g; 20.2
3	1:1:1:1	ethanol	4.5	25	72	25	—	ethanol	3	25	4	8.2 g; 16.5
4	1:1:1:1	ethanol	4.5	78	12	25	6	ethanol	6	5	2	13.3 g; 26.8
5	1:1:1:1	ethanol	20	60	24	-20	12	ethanol	4	25	1	10.7 g; 21.5
6	1:1:1:1	ethanol	80	78	12	-30	24	ethanol	4	25	5	7.9 g; 15.9

7	1:1:1:1	DMF	4.5	154	1	-30	6	*n*-propanol	3.5	25	6	6.3 g; 12.7
8	1:1:1:1	*n*-butanol	5	100	5	0	6	*n*-butanol	3.5	25	4	11.6 g; 23.4
9	1:1:1:1	*n*-propanol	4.5	80	12	25	6	*n*-propanol	3	40	8	13.7 g; 27.7
10	1:1:1:1	*i*-propanol	4.5	82	12	25	1	*i*-propanol	4	25	3	10.1 g; 20.4
11	1:1:1:1	*t*-butanol	4.5	82	12	30	12	*i*-propanol	4	30	5	11.2 g; 22.5
12	1:1:1:1	2-methoxyethanol	4.5	78	12	-10	12	*i*-propanol	4	25	5	10.5 g; 21.1
13	1:1:1:1	1,2-dimethoxyethane	4.5	78	12	-10	12	*n*-propanol	3.5	25	3	6.3 g; 12.7
14	1:1:1:1	ethyl acetate	3	77	12	-10	12	*i*-propanol	4	25	4	8 g; 16.2
15	1:1:1:1	acetone	3	56	12	-20	12	*i*-propanol	4	25	6	4.7 g; 9.4
16	1:1:1:1	methanol	3	64	12	0	6	*n*-propanol	3.5	25	3	8.2 g; 16.5
17	1:1:1:1	2-methoxyethyl ether	5	78	6	-20	12	*n*-propanol	3.5	25	3	5.3 g; 10.6
18	1:1:1:1	ethanol	1	78	12	40	6	ethanol	10	25	5	9.4 g; 18.8
19	1:1:1:1	*i*-propanol	4.5	82	12	25	1	*i*-propanol	20	5	3	8.9 g; 17.9
20	1:1:1:1	ethyl acetate	3	77	12	-10	12	ethyl acetate	2	-10	12	6.7 g; 13.5
21	1:1:2:1	—	—	78	12	40	6	ethanol	15	25	10	9.0 g; 18.1

Step 3) (*R*)-(*R*)-1-ethoxy-1-oxopropan-2-yl 4-(2-bromo-4-fluorophenyl)-6-bromomethyl-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate



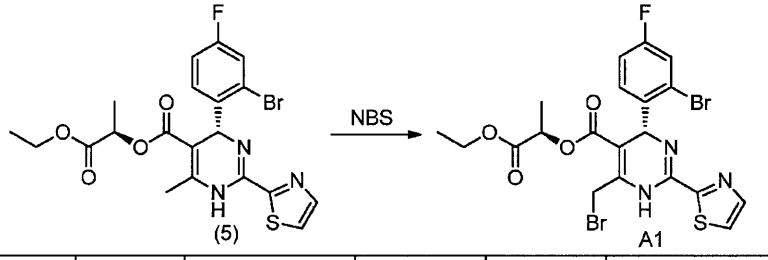
[00116] To a flask were added (*R*)-(*R*)-1-ethoxy-1-oxopropan-2-yl 4-(2-bromo-4-fluorophenyl)-6-methyl-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (49.6 g, 0.1 mol) and tetrachloromethane (1000 g). The mixture was heated at 76 °C, NBS was added (19.6 g, 0.11 mol), and then the reaction mixture was stirred for 30 min. After the reaction, the reaction mixture was cooled and concentrated. To the residue was added ethanol (250 g). The resulting mixture was cooled to 0 °C, kept at 0 °C and stirred. After the solid precipitated out completely, the mixture was filtered. The filter cake was washed with ethanol (50 g) and dried *in vacuo* at 60 °C for 6 hours to obtain the product as a yellow solid (37.4 g, 65%).

MS (ESI, pos.ion) *m/z*: 575.8 $[M+H]^+$;

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.03 (d,1H), 7.98 (br,1H), 7.58 (dd,2H), 7.43 (dd,1H), 7.27(td,1H), 6.01 (s,1H), 4.94 (q,1H), 4.85 (br,2H), 4.14-4.02 (m,2H), 1.28 (d,3H), 1.16 (t,3H).

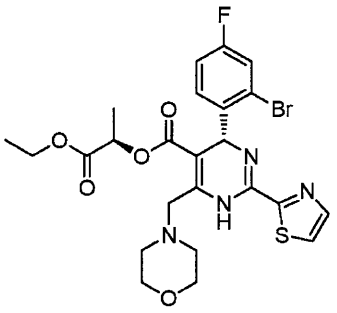
[00117] The compound A1 can be prepared under the reaction conditions shown in table 5 according to the procedure described in step 3 of Example 1

Table 5: The reaction conditions



No.	Compound (5):NBS(mol) the amount of compound (5) is 49.6 g	Reaction solvent	The mass ratio of reaction solvent to compound (5)	Reaction temperature (°C)	The solvent added to the residue	The mass ratio of the additional solvent to compound (5)	Quality; yield(%) of product
1	1:1.1,	DCM	30	39	*i*-propanol	7	41.4 g;72
2	1:1.05,	DCM	10	39	ethanol	5	38 g;66
3	1:1.15,	$CHCl_3$	20	61	*n*-propanol	6	42 g;73
4	1:1.1,	CCl_4	20	76	ethanol	5	43.1 g;75

Step 4) (*R*)-(*R*)-1-ethoxy-1-oxopropan-2-yl 4-(2-bromo-4-fluorophenyl)-6-(morpholinomethyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate



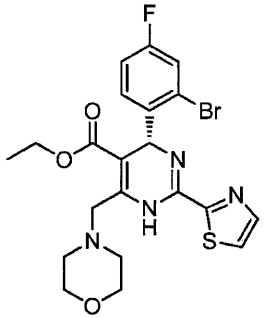
[00118] To a flask were added (*R*)-(*R*)-1-ethoxy-1-oxopropan-2-yl 4-(2-bromo-4-fluorophenyl)-6-(bromomethyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (57.5 g, 0.1 mol), i-propanol (287 g) and morpholine (34.8 g, 0.4 mol). The mixture was stirred at 55 °C for 4 hours. After the reaction, the mixture was cooled to 0 °C, kept at this temperature and stirred. After the solid precipitated out completely, the mixture was filtered. The filter cake was washed with *i*-propanol (58 g) followed by water (575 g), and then dried *in vacuo* at 60 °C for 8 hours to obtain the product as a yellowish solid (40.1 g, 69%).

MS (ESI, pos.ion) *m/z*: 581.2 $[M+H]^+$;

^{1}H NMR (600 MHz, DMSO-d_6): δ 9.98 (s,1H), 8.03 (d,1H), 7.96 (d,1H), 7.56 (d,1H), 7.42 (dd,1H), 7.23 (td,1H), 6.05 (s,1H), 4.84 (q,1H), 4.14-4.05 (m,2H), 3.92 (dd,2H), 3.67 (br,4H), 2.55 (br,4H), 1.23 (d,3H), 1.16 (t,3H).

Step 5) (*R*)-ethyl 4-(2-bromo-4-fluorophenyl)-6-(morpholinomethyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine

-5-carboxylate

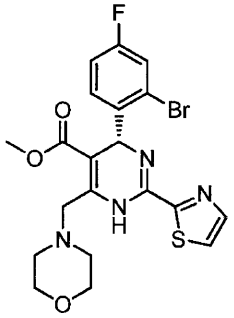


[00119] To a flask were added anhydrous ethanol (435 g) and lithium (1.74 g, 0.25 mol) in turn. The mixture was stirred at 43 °C until the lithium was consumed entirely, and then a solution of (*R*)-(*R*)-1-ethoxy-1-oxopropan-2-yl 4-(2-bromo-4-fluorophenyl)-6-(morphplinomethyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (58.1 g, 0.1 mol) in ethanol (435 g) was added. The reaction mixture was stirred at 78 °C for 1.5 hours. After the reaction, the reaction mixture was cooled and concentrated. To the residue was added ethyl acetate (580 g). The mixture was washed with water (250 g × 2). The combined organic layers were concentrated to obtain the product as a yellow solid (39.7 g, 78%).

MS (ESI, pos.ion) *m/z*: 509.1 $[M+H]^+$;

^{1}H NMR (600 MHz, DMSO-d_6): δ 9.69 (s,1H), 8.02 (d,1H), 7.93 (d,1H), 7.57 (dd,1H), 7.40 (dd,1H), 7.22 (td,1H), 6.05 (s,1H), 3.96 (q,2H), 3.93 (dd,2H), 3.68 (br,4H), 2.56 (br,4H), 1.05 (t,3H).

Example 2: the preparation of (*R*)-methyl 4-(2-bromo-4-fluorophenyl)-6-(morpholinomethyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine -5- carboxylate

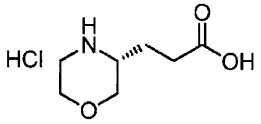


[00120] To a flask were added anhydrous methanol (870 g) and lithium (1.74 g, 0.25 mol) in turn. The mixture was stirred at 43 °C until the lithium was consumed entirely, and then (*R*)-(*R*)-1-ethoxy-1-oxopropan-2-yl 4-(2-bromo-4-fluorophenyl)-6-(morpholinomethyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (58.1 g, 0.1 mol) was added. The reaction mixture was allowed to warm up to 60 °C and stirred for 1.5 hours. After the reaction, the reaction mixture was cooled and concentrated. To the residue was added ethyl acetate (580 g). The mixture was washed with water (250 g × 2). The combined organic layers were concentrated to obtain the product as yellow thick oil (36.1 g, 73%).

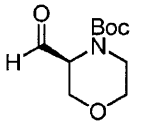
MS (ESI, pos.ion) *m/z*: 494.7 $[M+H]^+$;

^{1}H NMR (600 MHz, DMSO-d_6): δ 9.71 (s,1H), 8.02 (d,1H), 7.94 (d,1H), 7.55 (dd,1H), 7.37 (dd,1H), 7.20 (td,1H), 6.02 (s,1H), 3.91 (dd,2H), 3.67 (br,4H), 3.52 (s,3H), 2.55 (br,4H).

Example 3: the preparation of (*R*)-3-(morpholin-3-yl)propanoic acid hydrochloride

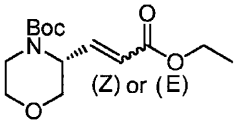


Step 1) (*S*)-*tert*-butyl 3-formylmorpholine-4-carboxylate



[00121] To a flask were added (*R*)-*tert*-butyl 3-(hydroxymethyl)morpholine-4-carboxylate (1.47 g, 6.77 mmol) and DCM (30 mL) in turn, and then Dess-Martin periodinane (3.44 g, 8.12 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 1 hour. After the reaction, the mixture was quenched with saturated aqueous sodium bicarbonate (30 mL) and separated. The organic layer was washed with saturated aqueous sodium bicarbonate (30 mL × 3) and saturated aqueous sodium chloride (30 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was used directly at next operation.

Step 2) (*R*)-*tert*-butyl 3-(3-ethoxy-3-oxoprop-1-en-1-yl)morpholine-4-carboxylate

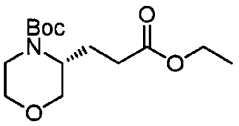


[00122] To a flask were added (*S*)-*tert*-butyl 3-formylmorpholine-4-carboxylate (1.46 g, 6.77 mmol), DCM (40 mL) and ethyl (triphenylphosphoranylidene)acetate (2.36 g, 6.77 mmol) in turn. The mixture was stirred at 25 °C for 12 hours. After the reaction, the mixture was filtered. The filtrate was concentrated. The residue was purified by silica gel chromatography eluted with PE/EtOAc (V/V) = 10/1 to give the product as a colorless oil (1.05 g, 54%).

MS (ESI, pos.ion) *m/z*: 186.1 $[M+H-100]^+$;

^1H NMR (400 MHz, $CDCl_3$): δ 6.69 (dd,1H), 5.89 (dd,1H), 4.56 (s,1H), 4.20-4.12 (m,2H), 3.94-3.82 (m,2H), 3.77-3.65 (m,2H), 353-3.43 (m,1H), 3.27-3.10 (m,1H), 1.41 (s,9H), 1.29-1.23 (m,3H).

Step 3) (*R*)-*tert*-butyl 3-(3-ethoxy-3-oxopropyl)morpholine-4-carboxylate

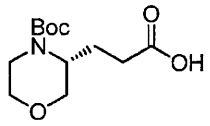


[00123] To a flask were added (*R*)-*tert*-butyl 3-(3-ethoxy-3-oxoprop-1-en-1-yl)morpholine-4-carboxylate (1.05 g, 3.68 mmol), anhydrous ethanol (20 mL) and Pd-C (10%, 0.2 g) in turn. The mixture was stirred at 30 °C under hydrogen atmosphere overnight and filtered. The filtrate was concentrated to give the product as colorless oil (0.96 g, 91%).

MS (ESI, pos.ion) *m/z*: 188.1 $[M+H-100]^+$;

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.12 (q,2H), 3.98 (s,1H), 3.84-3.69 (m,3H), 3.56 (dd,1H), 3.42 (td,1H), 3.12 (t,1H), 2.37-2.27 (m,2H), 2.25-2.15 (m,1H), 1.92-1.83 (m,1H), 1.45 (s,9H), 1.25 (t,3H).

Step 4) (*R*)-3-(4-(*tert*-butoxycarbonyl)morpholin-3-yl)propanoic acid

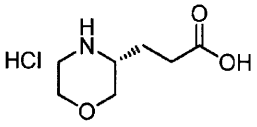


[00124] To a flask were added (*R*)-*tert*-butyl 3-(3-ethoxy-3-oxopropyl)morpholine-4-carboxylate (0.96 g, 3.34 mmol), anhydrous ethanol (10 mL) and a solution of lithium hydroxide hydrate (1.4 g, 33.4 mmol) in water (10 mL) in turn. The mixture was stirred at 25 °C for 30 min. After the reaction, to the reaction mixture was added ethyl acetate (150 mL) and water (50 mL). The resulting mixture was adjusted to pH 5-6 with concentrated hydrochloric acid at 0 °C. After the mixture was partitioned. The organic layer was washed with saturated aqueous sodium chloride (100 mL), dried over anhydrous sodium sulfate and concentrated to give the product as colorless oil (0.85 g, 98%).

MS (ESI, pos.ion) *m/z*: 160.1 $[M+H-100]^+$;

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (br,1H), 4.03 (brs,1H), 3.88-3.72 (m,3H), 3.58 (dd,1H), 3.44 (td,1H), 3.13 (t,1H), 2.43-2.29 (m,2H), 2.27-2.20 (m,1H), 1.94-1.83 (m,1H), 1.46 (s,9H).

Step 5) (*R*)-3-(morpholin-3-yl)propanoic acid hydrochloride



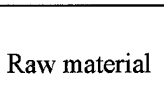
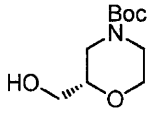
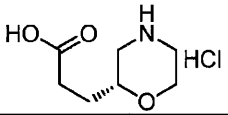
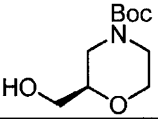
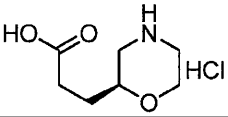
[00125] To a flask were added (*R*)-3-(4-(*tert*-butoxycarbonyl)morpholin-3-yl)propanoic acid (0.9 g, 3.47 mmol) and a solution of hydrogen chloride in ethyl acetate (4 mol/L, 15 mL) in turn. The mixture was stirred at 25 °C for 4 hours. After the reaction, the mixture was filtered to give the product as a white solid (0.53 g, 78%).

MS (ESI, pos.ion) *m/z*: 160.1 $[M+H]^+$;

^{1}H NMR (400 MHz, D_2O): δ 4.04-3.96 (m,2H), 3.75-3.68 (m,1H), 3.52 (dd,1H), 3.40-3.35 (m,1H), 3.34-3.29 (m,1H), 3.22-3.15 (m,1H), 2.47 (t,2H), 1.83 (ddd,2H).

[00126] The compound VI hydrochloride can be prepared under the reaction conditions shown in table 6 according to the procedure described in Example 3.

Table 6: The reaction conditions for preparation of the compound (VI) hydrochloride

Raw material	The amount of raw material	 hydrochloride	Product character	Quality; yield(%) of product
	50 g		white solid	23 g;51
	50 g		white solid	21.2 g;47

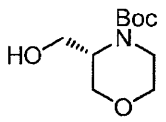
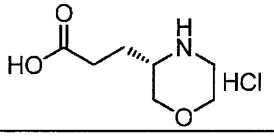
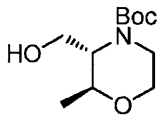
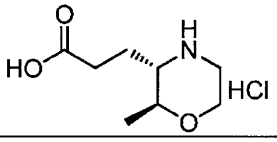
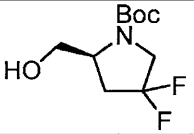
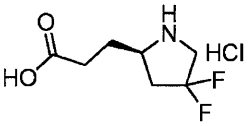
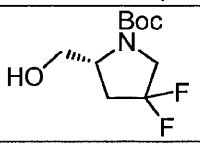
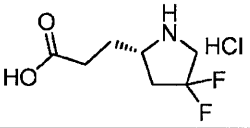
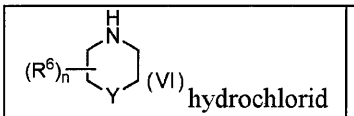
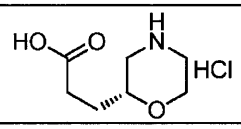
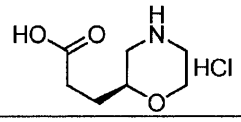
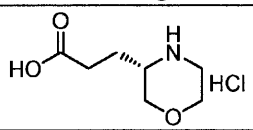
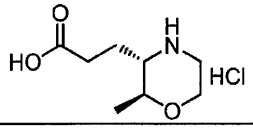
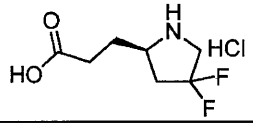
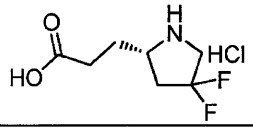
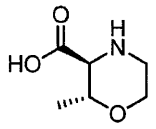
	50 g		white solid	18.5 g;41
	50 g		white solid	17.8 g;39
	50 g		gray solid	16.4 g;36
	50 g		gray solid	17.3 g;38

Table 6-1: The NMR and MS datum of the compound (VI) hydrochloride

 hydrochlorid e	NMR	MS
	^{1}H NMR (400 MHz, D_2O): δ 4.03 (dd,1H), 3.78-3.67 (m,2H), 3.25 (t,2H), 3.08 (td,1H), 2.85 (dd,1H), 2.27-2.23 (m,2H), 1.73-1.67 (m,2H).	MS (ESI, neg.ion) *m/z*: 158.2[M−H]$^-$
	^{1}H NMR (400 MHz, D_2O): δ 4.10-4.02 (m,1H), 3.80-3.74 (m,2H), 3.32-3.25 (m,2H), 3.10 (td,1H), 2.89 (t,1H), 2.47-2.43 (m,2H), 1.88- 1.70 (m,2H).	MS (ESI, pos.ion) *m/z*: 160.1 [M+H]$^+$;
	^{1}H NMR (400 MHz, D_2O): δ 4.07-3.98 (m,2H), 3.78-3.71 (m,1H), 3.55 (dd,1H), 3.43-3.38 (m,1H), 3.35 (dt,1H), 3.24-3.17 (m,1H), 2.50 (t,2H), 1.89-1.83 (m,2H).	MS (ESI, pos.ion) *m/z*: 160.3 [M+H]$^+$;
	^{1}H NMR (600 MHz, D_2O): δ 4.05 (dd,1H), 3.84-3.79 (m,1H), 3.74-3.70 (m,1H), 3.34 (d,1H), 3.21 (td,1H), 3.10 (td,1H), 2.55 (t,2H), 2.06-2.03 (m,1H), 1.82-1.76 (m,1H), 1.26 (d, 3H).	MS (ESI, pos.ion) *m/z*: 174.3 [M+H]$^+$;
	^{1}H NMR (600 MHz, DMSO-d_6): δ 10.21 (br, 1H), 3.80-3.73 (m, 2H), 3.66-3.59 (m, 1H), 2.74-2.67 (m, 1H), 2.43-2.40 (m, 2H), 2.33-2.23 (m, 1H), 2.05-1.95 (m, 2H).	MS (ESI, pos.ion) *m/z*: 180.2 [M+H]$^+$;
	^{1}H NMR (600 MHz, D_2O): δ 4.00-3.94 (m, 1H), 3.82 (dd, 1H), 3.72 (dd, 1H), 2.83-2.76 (m, 1H), 2.57-2.47 (m, 2H), 2.39-2.32 (m, 1H), 2.16-2.03 (m, 2H).	MS (ESI, pos.ion) *m/z*: 180.2 [M+H]$^+$;

Example 4: the preparation of (2*R*,3*S*)-2-methylmorpholine-3-carboxylic acid)

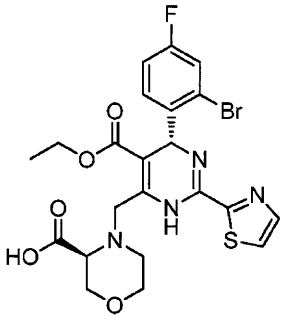


[00127] The title compound ((2*R*,3*S*)-2-methylmorpholine-3-carboxylic acid) was prepared according to the procedure described in example 34 of patent WO2014029193.

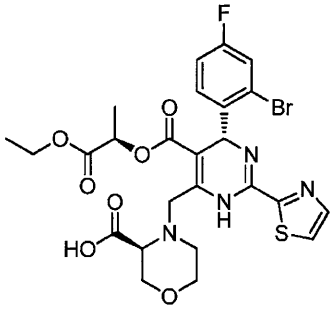
MS (ESI, pos.ion) *m/z*: 146.2 [M+H]$^+$;

^{1}H NMR (600 MHz, D_2O): δ 4.01-3.98 (m,1H), 3.82-3.77 (m,1H), 3.76-3.72 (m,1H), 3.37 (d,1H), 3.27-3.24 (m,1H), 3.19-3.14 (m,1H), 1.26 (d,3H).

Example 5: the preparation of (*S*)-4-(((*R*)-6-(2-bromo-4-fluorophenyl)-5-(ethoxycarbonyl)-2-(thiazol-2-yl)-3,6-dihydropyrimidin-4-yl)methyl)morpholine-3-carboxylic acid



Step 1) (*S*)-4-(((*R*)-6-(2-bromo-4-fluorophenyl)-5-((((*R*)-1-ethoxy-1-oxopropan-2-yl)oxy)carbonyl)-2-(thiazol-2-yl)-3,6-dihydropyrimidin-4-yl)methyl)morpholine-3-carboxylic acid



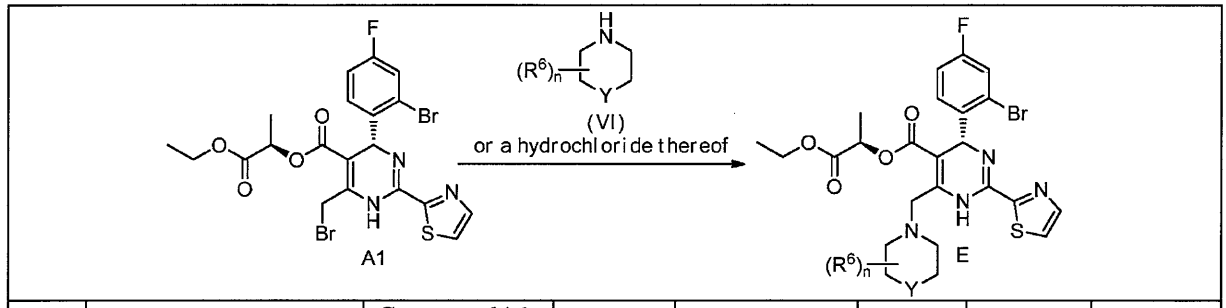
[00128] To a flask were added (*R*)-(*R*)-1-ethoxy-1-oxopropan-2-yl 4-(2-bromo-4-fluorophenyl)-6-(bromomethyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (57.5 g, 0.1 mol), ethanol (840 g), (*S*)-morpholine-3-carboxylic acid (13.1 g, 0.1 mol) and potassium carbonate (27.6 g, 0.2 mol) in turn. The mixture was stirred at 30 °C under nitrogen atmosphere for 12 hours. After the reaction, the mixture was filtered. The filtrate was concentrated. To the residue was added water (840 g), the resulting mixture was extracted with ethyl acetate (840 mL). The organic layer was discarded. To the aqueous layer was added ethyl acetate (900 mL), and the mixture was adjusted to pH 3-6 with concentrated hydrochloric acid. The organic layer was dried over anhydrous sodium sulfate and concentrated to give the product as a yellow solid (46.3 g, 74%).

MS (ESI, pos.ion) *m/z*: 624.5 $[M+H]^+$;

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.03 (d,1H), 7.94 (d,1H), 7.56 (dd,1H), 7.42 (dd,1H), 7.22 (td,1H), 6.06 (s,1H), 4.84 (q,1H), 4.23-4.13 (m,1H), 4.12-4.03 (m,3H), 3.98-3.88 (m,1H), 3.85 (dd,1H), 3.73-3.65 (m,2H), 3.58-3.51 (m,1H), 3.10-3.04 (m,1H), 2.42-2.38 (m,1H), 1.24 (d,3H), 1.13 (t,3H).

[00129] The compound E can be prepared under the reaction conditions shown in table 7 according to the procedure described in step 1 of Example 5.

Table 7: The reaction conditions for preparation of compound E



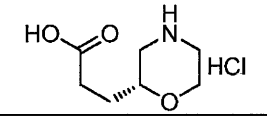
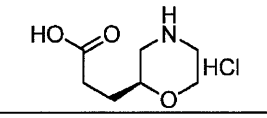
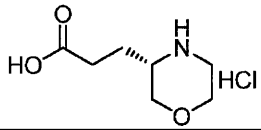
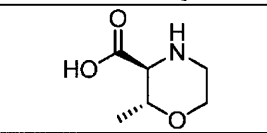
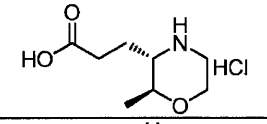
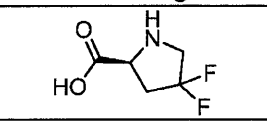
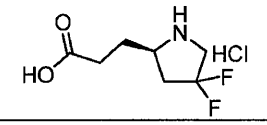
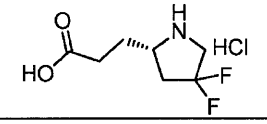
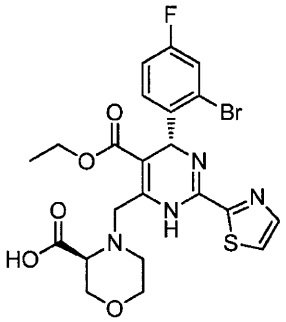
No.	$(R^6)_n$ (VI) or a hydrochloride thereof	CompoundA1: compound(VI) (mol) the amount of compound A1 is 5.75 g	Reaction solvent	Reaction temperature(°C)	Reaction time(h)	Product character	Quality; yield(%) of product
E1		1:1	ethanol	30	12	yellow solid	4.58 g; 70
E2		1:1	ethanol	30	12	yellow solid	4.32 g; 66
E3		1:1	ethanol	30	12	yellow solid	3.2 g; 49
E4		1:1	ethanol	30	12	yellow solid	5.11 g; 80
E5		1:1	ethanol	30	12	yellow solid	3.41g; 51
E6		1:1	ethanol	30	12	yellow solid	4.58 g; 71
E7		1:1	ethanol	30	12	yellow solid	3.5 g; 52
E8		1:1	ethanol	30	12	yellow solid	3.3 g; 49

Table 7-1: The NMR and MS datum of compound E

No.	^{1}H NMR	MS
E1	^{1}H NMR (600 MHz, DMSO-d_6): δ 12.02 (br,1H), 9.74 (s,1H), 8.02 (d,1H), 7.95 (d,1H), 7.56 (dd,1H), 7.40 (dd,1H), 7.22 (td,1H), 6.06 (s,1H), 4.85 (q,1H), 4.12-4.05 (m,2H), 3.92-3.85 (m,3H), 3.59-3.55 (m,1H), 3.52-3.48 (m,1H), 2.79 (t,2H), 2.35-2.23 (m,3H), 2.02 (t,1H), 1.65-1.61 (m,2H), 1.24 (d,3H), 1.14 (t,3H).	MS (ESI, pos.ion) *m/z*: 652.5 $[M+H]^+$;
E2	^{1}H NMR (600 MHz, DMSO-d_6): δ 12.06 (br,1H), 9.76 (s,1H), 8.04 (d,1H), 7.96 (d,1H), 7.56 (dd,1H), 7.40 (dd,1H), 7.23 (td,1H), 6.04 (s,1H), 4.86 (q,1H), 4.14-4.06 (m,2H), 3.94-3.86 (m,3H), 3.58-3.53 (m,1H), 3.51-3.48 (m,1H), 2.77 (t,2H), 2.35-2.22 (m,3H), 2.01 (t,1H), 1.65-1.62 (m,2H), 1.25 (d,3H), 1.12 (t,3H).	MS (ESI, pos.ion) *m/z*: 652.5 $[M+H]^+$;

E3	^{1}H NMR (600 MHz, DMSO-d_6): δ 12.16 (s,1H), 9.91 (s,1H), 8.03 (d,1H), 7.94 (d,1H), 7.55 (dd,1H), 7.40 (dd,1H), 7.22 (td,1H), 6.05 (s,1H), 4.85 (q,1H), 4.18 (d,1H), 4.13-4.01 (m,2H), 3.86 (d,1H), 3.80 (d,1H), 3.73-3.71 (m,1H), 3.62-3.55 (m,1H), 3.36-3.33 (m,1H), 2.94-2.73 (m,1H), 2.56-2.53 (m,1H), 2.39-2.31 (m,1H), 2.28-2.22 (m,1H), 1.88-1.82 (m,1H), 1.66-1.58 (m,1H), 1.25 (d,3H), 1.13 (t,3H).	MS (ESI, pos.ion) *m/z*: 653.2 $[M+H]^+$;
E4	^{1}H NMR (600 MHz, DMSO-d_6): δ 12.98 (br,1H), 9.90 (s,1H), 8.04 (d,1H), 7.94 (d,1H), 7.56 (dd,1H), 7.43 (dd,1H), 7.21 (td,1H), 6.04 (s,1H), 4.86 (q,1H), 4.14-4.03 (m,3H), 3.93-3.85 (m,1H), 3.74-3.67 (m,2H), 3.65-3.60 (m,1H), 3.01 (d,1H), 2.92 (d,1H), 2.49-2.44 (m,1H), 1.23 (d,3H), 1.21 (d,3H), 1.13 (t,3H).	MS (ESI, pos.ion) *m/z*: 639.1 $[M+H]^+$;
E5	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.10 (s,1H), 9.75 (s,1H), 8.04 (d,1H), 7.96 (d,1H), 7.56 (dd,1H), 7.40 (dd,1H), 7.20 (td,1H), 6.05 (s,1H), 4.87 (q,1H), 4.15 (d,1H), 4.11-4.02 (m,2H), 3.85 (d,1H), 3.76-3.71 (m,1H), 3.60-3.55 (m,1H), 3.53-3.46 (m,1H), 2.66 (d,1H),2.46-2.41 (m,1H), 2.37-2.32 (m,3H), 2.07-1.87 (m,1H), 1.79-1.72 (m,1H), 1.24 (d,3H), 1.20 (d,3H), 1.14 (t,3H).	MS (ESI, pos.ion) *m/z*: 668.6 $[M+H]^+$;
E6	^{1}H NMR (600 MHz, DMSO-d_6): δ 13.05 (br,1H), 9.79 (s,1H), 7.98 (d,1H), 7.92 (d,1H), 7.57 (dd,1H), 7.43 (dd,1H), 7.23 (td,1H), 6.04 (s,1H), 4.85 (q,1H), 4.31 (d,1H), 4.13-4.05 (m,3H), 3.92 (t,1H), 3.55-3.49 (m,1H), 3.18-3.12 (m,1H), 2.82-2.72 (m,1H), 2.48-2.43 (m,1H), 1.24 (d,3H), 1.16 (t,3H).	MS (ESI, pos.ion) *m/z*: 644.5 $[M+H]^+$;
E7	^{1}H NMR (600 MHz, DMSO-d_6): δ 9.56 (s, 1H), 8.04 (d, 1H), 7.96(d, 1H), 7.57 (d, 1H), 7.43 (dd, 1H), 7.24(td,1H), 6.04 (s, 1H), 4.86 (q, 1H), 4.12-4.03 (m, 4H), 3.51-3.44 (m, 1H), 3.08-2.94 (m, 2H), 2.48-2.44 (m, 1H), 2.37-2.19 (m, 2H), 2.13-2.01 (m, 1H), 1.98-1.91(m, 1H), 1.58-1.52 (m, 1H), 1.24 (d, 3H), 1.16 (t, 3H).	MS (ESI, pos.ion) *m/z*: 673.1 $[M+H]^+$;
E8	^{1}H NMR (600 MHz, DMSO-d_6): δ 9.52 (br,1H), 9.79 (s,1H), 8.02 (d,1H), 7.94 (d,1H), 7.56 (dd,1H), 7.40 (dd,1H), 7.23 (td,1H), 6.03 (s,1H), 4.87 (q,1H), 4.14 (d,1H), 3.47-3.42 (m,3H), 3.02 (t,1H), 2.60-2.52 (m,1H), 2.41-2.21 (m,1H), 2.12-1.98 (m,1H), 1.61-1.59 (m,1H), 1.24 (d,3H), 1.14 (t,3H).	MS (ESI, pos.ion) *m/z*: 672.7 $[M+H]^+$;

Step 2) (*S*)-4-(((*R*)-6-(2-bromo-4-fluorophenyl)-5-(ethoxycarbonyl)-2-(thiazol-2-yl)-3,6-dihydropyrimidin-4-yl)methyl)morpholine-3-carboxylic acid



[00130] To a flask were added anhydrous ethanol (940 g) and lithium (2.43 g, 0.35 mol) in turn. The mixture was stirred at 43 °C until the lithium was consumed entirely, and then (*S*)-4-(((*R*)-6-(2-bromo-4-fluorophenyl)-5-((((*R*)-1-ethoxy-1-oxopropan-2-yl)oxy)carbonyl)-2-(thiazol-2-yl)-3,6-dihydropyrimidin-4-yl)methyl)morpholine-3-carboxylic acid (62.5 g, 0.1 mol) was added. The reaction mixture was allowed to warm up to 78 °C and stirred for 12 hours. After the reaction, the mixture was cooled and concentrated. To the residue was added water (1200 g), the resulting mixture was extracted with ethyl acetate (1000 mL). The organic layer was discarded. To the aqueous layer was added ethyl acetate (1280 mL), the mixture was adjusted to pH 3-6 with concentrated hydrochloric acid. The organic layer was dried over

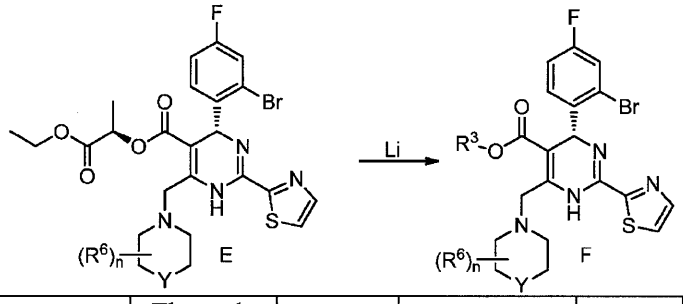
anhydrous sodium sulfate and concentrated to give the product as a yellow solid (37.1 g, 67%).

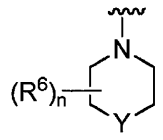
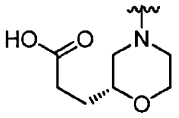
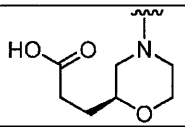
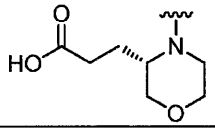
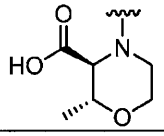
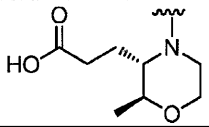
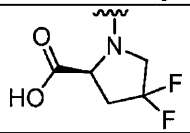
MS (ESI, pos.ion) *m/z*: 553.2 $[M+H]^+$;

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.85 (br,1H), 9.80 (s,1H), 8.00 (d,1H), 7.91 (d,1H), 7.54 (dd,1H), 7.39 (dd,1H), 7.19 (td,1H), 6.01 (s,1H), 4.25 (d,1H), 4.02 (d,1H), 3.97-3.91 (m,3H), 3.81 (dd,1H), 3.72-3.69 (m,1H), 3.66-3.63 (m,1H), 3.61-3.58 (m,1H), 3.10-3.03 (m,1H), 2.42-2.35 (m,1H), 1.04 (t,3H).

[00131] The compound F can be prepared under the reaction conditions shown in table 8 according to the procedure described in step 2 of Example 5.

Table 8: The reaction conditions for preparation of compound F



No.	R^3		The mole ratio of Lithium to compound E; the amount of compound E	Reaction solvent	Reaction temperature(°C)	Reaction time(h)	Product character	Quality; yield(%) of product
F1	ethyl		6; 6.4 g	ethanol	78	2	yellow solid	3.78 g; 65
F2	ethyl		5; 6.4 g	ethanol	78	2	yellow solid	3.66 g; 63
F3	ethyl		5; 6.4 g	ethanol	78	2	yellow solid	3.02 g; 52
F4	ethyl		5; 6.26 g	ethanol	78	12	yellow solid	3.97 g; 70
F5	ethyl		5; 6.54 g	ethanol	78	2	yellow solid	2.86 g; 48
F6	ethyl		5; 6.3 g	ethanol	78	12	yellow solid	3.5 g; 61

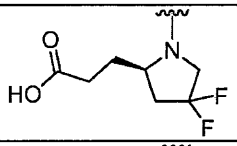
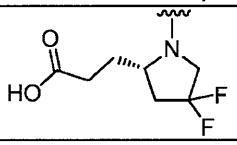
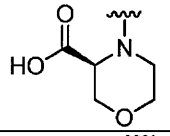
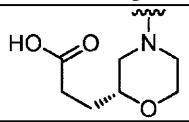
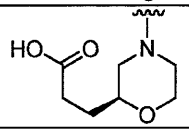
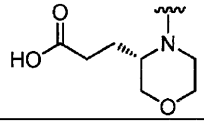
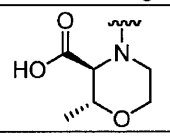
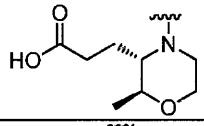
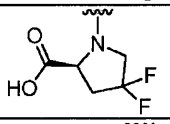
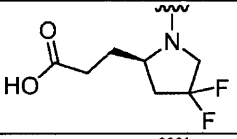
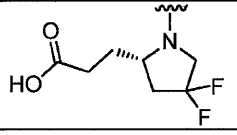
F7	ethyl		5; 6.6 g	ethanol	78	2	yellow solid	3.13 g; 52
F8	ethyl		5; 6.6 g	ethanol	78	2	yellow solid	3 g; 50
F9	methyl		2; 6.1 g	methanol	64	18	yellow solid	3.61 g; 67
F10	methyl		5; 6.4 g	methanol	64	6	yellow solid	3.52 g; 62
F11	methyl		5; 6.4 g	methanol	64	4	yellow solid	3.4 g; 60
F12	methyl		5; 6.4 g	methanol	64	8	yellow solid	2.72 g; 48
F13	methyl		5; 6.26 g	methanol	64	18	yellow solid	3.87 g; 70
F14	methyl		5; 6.54 g	methanol	64	5	yellow solid	2.73 g; 47
F15	methyl		5; 6.3 g	methanol	64	12	yellow solid	3.75 g; 67
F16	methyl		5; 6.87 g	methanol	64	6	yellow solid	2.88 g; 49
F17	methyl		5; 6.87 g	methanol	64	6	yellow solid	2.82 g; 48

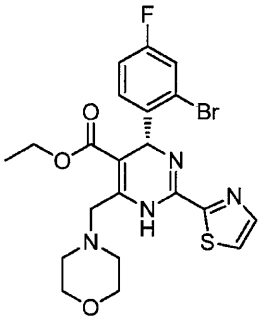
Table 8-1: The NMR and MS datum of compound F

No.	^{1}H NMR	MS
F1	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.06 (s,1H), 9.65 (s,1H), 8.02 (d,1H), 7.94 (d,1H), 7.57 (dd,1H), 7.39 (dd,1H), 7.22 (td,1H), 6.03 (s,1H), 3.96 (q,2H), 3.89-3.85 (m,3H), 3.61-3.47 (m,2H), 2.81-2.75 (m,2H), 2.38-2.21 (m,3H), 2.04-2.02 (m,1H), 1.65-1.60 (m,2H), 1.06 (t,3H).	MS (ESI, pos.ion) *m/z*: 581.2 $[M+H]^+$;
F2	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.06 (s,1H), 9.66 (s,1H), 8.02 (d,1H), 7.95 (d,1H), 7.56 (dd,1H), 7.41 (dd,1H), 7.20 (td,1H), 6.03 (s,1H), 3.97 (q,2H), 3.93-3.83 (m,3H), 3.57-3.46 (m,2H), 2.88 (d,1H), 2.63 (d,1H), 2.37-2.22 (m,3H), 2.13-2.08 (m,1H), 1.75-1.65 (m,2H), 1.06 (t,3H).	MS (ESI, pos.ion) *m/z*: 580.9 $[M+H]^+$;
F3	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.14 (br,1H), 9.82 (s,1H), 8.02 (d,1H), 7.92 (d,1H), 7.54 (dd,1H), 7.40 (dd,1H), 7.22 (td,1H), 6.03 (s,1H), 4.18 (d,1H), 3.96 (q,2H), 3.91 (d,1H), 3.82-3.79 (m,1H), 3.74-3.71 (m,1H), 3.61-3.57 (m,1H), 3.37-3.32 (m,1H), 2.78-2.75 (m,1H), 2.57-2.53	MS (ESI, pos.ion) *m/z*: 580.9 [M+H]+;

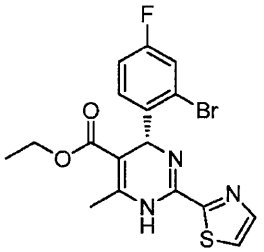
	(m,1H), 2.49-2.47 (m,1H), 2.38-2.32 (m,2H), 1.89-1.84 (m,1H), 1.68-1.58 (m,1H), 1.06 (t,3H).	
F4	^{1}H NMR (400 MHz, DMSO-d_6): δ 13.02 (s,1H), 9.78 (s,1H), 8.03 (d,1H), 7.93 (d,1H), 7.56 (dd,1H), 7.39 (dd,1H), 7.22 (td,1H), 6.00 (s,1H), 4.10 (d,1H), 3.95 (q,2H), 3.90-3.87 (m,1H), 3.76-3.60 (m,3H), 3.46-3.42 (m,1H), 2.98 (d,1H), 2.93 (d,1H), 1.21 (d,3H), 1.05 (t,3H).	MS (ESI, pos.ion) *m/z*: 567.1 $[M+H]^+$;
F5	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.11 (s,1H), 9.74 (s,1H), 8.02 (d,1H), 7.95 (d,1H), 7.56 (dd,1H), 7.39 (dd,1H), 7.19 (td,1H), 6.04 (s,1H), 4.16 (d,1H), 4.00-3.93 (m,2H), 3.86 (d,1H), 3.77-3.72 (m,1H), 3.59-3.53 (m,1H), 3.51-3.45 (m,1H), 2.66 (d,1H), 2.46-2.40 (m,1H), 2.37-2.30 (m,3H), 2.03 -1.91 (m,1H), 1.80-1.73 (m,1H), 1.20 (d,3H), 1.06 (t,3H).	MS (ESI, pos.ion) *m/z*:594.6 $[M+H]^+$
F6	^{1}H NMR (600 MHz, DMSO-d_6): δ 9.98 (br,1H), 8.03 (d,1H), 8.00 (d,1H), 7.61 (dd,1H), 7.48 (dd,1H), 7.28 (td,1H), 6.02 (s,1H), 4.35 (d,1H), 4.13 (d,1H), 4.01-3.94 (m,3H), 3.61-3.51 (m,1H), 3.25-3.19 (m,1H), 3.10-3.04 (m,1H), 2.86-2.68 (m,1H), 1.20 (t,3H).	MS (ESI, pos.ion) *m/z*: 573.0 $[M+H]^+$;
F7	^{1}H NMR (600 MHz, DMSO-d_6): δ 12.08 (s,1H), 9.51 (s,1H), 8.01 (d,1H), 7.93 (d,1H), 7.57 (dd,1H), 7.41 (dd,1H), 7.24 (td,1H), 6.01 (s,1H), 4.12 (dd,2H), 3.97 (q,2H), 3.61-3.52 (m,1H), 3.04-2.96 (m,2H), 2.58-2.56 (m,1H), 2.35-2.20 (m,2H), 2.12-1.98 (m,1H), 1.93-1.90 (m,1H), 1.56-1.48 (m,1H), 1.06 (t,3H).	MS (ESI, pos.ion) *m/z*: 601.1 $[M+H]^+$;
F8	^{1}H NMR (400 MHz, $CDCl_3$): δ 12.19 (br,1H), 9.46 (s,1H), 7.86 (d,1H), 7.50 (d,1H), 7.37-7.33 (m,2H), 7.00 (td,1H), 6.19 (s,1H), 4.52 (d,1H), 4.14-4.03 (m,2H), 3.65 (d,1H), 3.31-3.23 (m,2H), 3.02-2.91 (m,1H), 2.57-2.25 (m,5H), 1.79-1.74 (m,1H), 1.16 (t,3H).	MS (ESI, pos.ion) *m/z*: 601.2 $[M+H]^+$;
F9	^{1}H NMR (600 MHz, DMSO-d_6): δ 12.88 (br,1H), 10.07 (br,1H), 8.02 (d,1H), 7.93 (d,1H), 7.56 (dd,1H), 7.39 (dd,1H), 7.23 (td,1H), 6.01 (s,1H), 4.25 (d,1H), 4.04 (d,1H), 3.99 (dd,1H), 3.84 (dd,1H), 3.73-3.70 (m,1H), 3.69-3.65 (m,1H), 3.62-3.58 (m,1H), 3.51 (s,3H), 3.10-3.07 (m,1H), 2.41-2.39 (m,1H).	MS (ESI, pos.ion) *m/z*: 539.1 $[M+H]^+$;
F10	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.03 (s,1H), 9.69 (s,1H), 8.01 (d,1H), 7.93 (d,1H), 7.56 (dd,1H), 7.38 (dd,1H), 7.23 (td,1H), 6.01 (s,1H), 3.93-3.83 (m,3H), 3.60-3.53 (m,2H), 3.52 (s,3H), 2.77 (dd,2H), 2.38-2.25 (m,3H), 2.05-1.99 (m,1H), 1.65-1.59 (m,2H).	MS (ESI, pos.ion) *m/z*: 567.2 $[M+H]^+$;
F11	^{1}H NMR (600 MHz, DMSO-d_6): δ 12.06 (s,1H), 9.70 (s,1H), 8.03 (d,1H), 7.94 (d,1H), 7.57 (dd,1H), 7.39 (dd,1H), 7.23 (td,1H), 6.02 (s,1H), 3.95 (d,1H), 3.86-3.80 (m,2H), 3.56-3.54 (m,1H), 3.53 (s,3H), 3.52-3.49 (m,1H), 2.88 (d,1H), 2.62 (d,1H), 2.37-2.21 (m,3H), 2.15-2.08 (m,1H), 1.72-1.64 (m,2H).	MS (ESI, pos.ion) *m/z*: 567.2 $[M+H]^+$;
F12	^{1}H NMR (400 MHz, DMSO-*d*6): δ 9.87 (s,1H), 8.03 (d,1H), 7.94 (d,1H), 7.56 (dd,1H), 7.38 (dd,1H), 7.23 (td,1H), 6.01 (s,1H), 4.18 (d,1H), 3.91 (d,1H), 3.83-3.79 (m,1H), 3.75-3.70 (m,1H), 3.61-3.56 (m,1H), 3.53 (s,3H), 3.47-3.40 (m,1H), 3.04-2.86 (m,1H), 2.77-2.75 (m,1H), 2.58-2.54 (m,1H), 2.37-2.22 (m,2H), 1.88-1.84 (m,1H), 1.65-1.58 (m,1H).	MS (ESI, pos.ion) *m/z*: 567.2 $[M+H]^+$;
F13	^{1}H NMR (400 MHz, DMSO-d_6): δ 13.02 (s,1H), 9.83 (s,1H), 8.02 (d,1H), 7.94 (d,1H), 7.56 (dd,1H), 7.38 (dd,1H), 7.22 (td,1H), 5.99 (s,1H), 4.05 (d,1H), 3.90-3.85 (m,1H), 3.75-3.60 (m,3H), 3.52 (s,3H), 3.47-3.42 (m,1H), 3.00 (d,1H), 2.92 (d,1H), 1.21 (d,3H).	MS (ESI, pos.ion) *m/z*: 553.0 $[M+H]^+$;
F14	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.10 (s,1H), 9.75 (s,1H), 8.01 (d,1H), 7.96 (d,1H), 7.54 (dd,1H), 7.40 (dd,1H), 7.20 (td,1H), 6.02 (s,1H), 4.18 (d,1H), 3.88 (d,1H), 3.78-3.73 (m,1H), 3.60-3.54 (m,1H), 3.52 (s,3H), 3.50-3.45 (m,1H), 2.68 (d,1H), 2.47-2.41 (m,1H), 2.36-2.30 (m,3H), 2.04 -1.92 (m,1H), 1.81-1.73 (m,1H), 1.21 (d,3H).	MS (ESI, pos.ion) *m/z*: 581.2 $[M+H]^+$;
F15	^{1}H NMR (600 MHz, DMSO-d_6): δ 9.71 (br,1H), 7.98 (d,1H), 7.91 (d,1H), 7.56 (dd,1H), 7.40 (dd,1H), 7.23 (td,1H), 5.99 (s,1H), 4.33 (d,1H), 4.09 (d,1H), 3.93-3.88 (m,1H), 3.52 (s,3H), 3.49-3.45 (m,1H), 3.22-3.08 (m,2H), 2.82-2.74 (m,1H).	MS (ESI, pos.ion) *m/z*: 558.6 $[M+H]^+$;
F16	^{1}H NMR (400 MHz, DMSO-d_6): δ 11.03 (s,1H), 9.57 (s,1H), 7.99 (d,1H), 7.92 (d,1H), 7.55 (dd,1H), 7.39 (dd,1H), 7.23 (td,1H), 6.00 (s,1H), 4.14 (dd,2H), 3.62-3.54 (m,1H),3.53 (s,3H), 3.05-2.96 (m,2H), 2.57-2.56	MS (ESI, pos.ion) *m/z*: 587.2 $[M+H]^+$;

	(m,1H), 2.36-2.20 (m,2H), 2.13-1.98 (m,1H), 1.95-1.90 (m,1H), 1.56-1.46 (m,1H).	
F17	^{1}H NMR (400 MHz, $CDCl_3$): δ 12.15 (br,1H), 9.47 (s,1H), 7.85 (d,1H), 7.51 (d,1H), 7.38-7.33 (m,2H), 7.01 (td,1H), 6.17 (s,1H), 4.50 (d,1H), 3.66 (d,1H), 3.55 (s,3H), 3.33-3.23 (m,2H), 3.04-2.92 (m,1H), 2.58-2.25 (m,5H), 1.78-1.74 (m,1H).	MS (ESI, pos.ion) *m/z*: 587.2 $[M+H]^+$;

Example 6: the preparation of (*R*)-ethyl 4-(2-bromo-4-fluorophenyl)-6-(morpholinomethyl)-2-(thiazol-2-yl)-1,4 -dihydropyrimidine-5- carboxylate



Step 1) (*R*)-ethyl 4-(2-bromo-4-fluorophenyl)-6-methyl-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate



[00132] To a flask were added anhydrous ethanol (500 g) and lithium (2.43 g, 0.35 mol) in turn. The mixture was stirred at 43 °C until the lithium was consumed entirely, and then (*R*)-(*R*)-1-ethoxy-1-oxopropan-2-yl 4-(2-bromo-4-fluorophenyl)-6-methyl-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (49.6 g, 0.1 mol) was added. The reaction mixture was stirred at 78 °C for 6 hours. After the reaction, the reaction mixture was cooled to 10 °C, kept at 10 °C and stirred for 8 hours. The mixture was filtered. The filter cake was washed with anhydrous ethanol (50 g) and water (500 g) in turn, and then dried *in vacuo* at 60 °C for 8 hours to obtain the product as a yellowish solid (31.8 g, 75%).

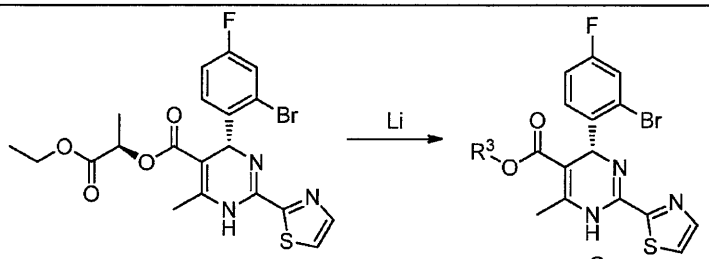
$[a]_D^{25}$ = −80.71 (c = 0.3023 g/100 mL, MeOH);

MS (ESI, pos.ion) *m/z*: 424.0 $[M+H]^+$;

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.88 (s,1H), 7.97 (d,1H), 7.89 (d,1H), 7.54 (dd,1H), 7.35 (dd,1H), 7.23 (td,1H), 5.96 (s,1H), 3.93 (q,2H), 2.46 (s,3H), 1.03 (t,3H).

[00133] The compound G can be prepared under the reaction conditions shown in table 9 according to the procedure described in step 1 of Example 6.

Table 9: The reaction conditions for preparation of compound G

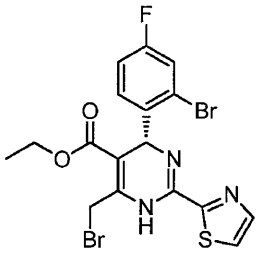


No.	R^3	The mole ratio of Lithium to compound (5); the amount of compound (5) is 49.6 g	Reaction solvent	The mass ratio of reaction solvent to compound (5)	Reaction temperature (°C)	Reaction time(h)	Product character	Quality; yield(%) of product
G1	ethyl	2.5	ethanol	10	78	12	yellow solid	19.5 g;46
G1	ethyl	3	ethanol	6	78	8	yellow solid	31.8 g;75
G1	ethyl	4	ethanol	10	78	4	yellow solid	29.7 g;70
G1	ethyl	5	ethanol	20	78	24	yellow solid	24.2 g;57
G1	ethyl	6	ethanol	30	78	12	yellow solid	20.4 g;48
G1	ethyl	8	ethanol	20	78	12	yellow solid	25.4 g;60
G2	methyl	3	methanol	3	64	20	yellow solid	25.4 g;62
G2	methyl	3	methanol	4	64	6	yellow solid	18.5 g;45
G2	methyl	4	methanol	6	64	8	yellow solid	15.6 g;38

Table 9-1: The NMR, MS and specific rotation datum of the compound G

No.	^{1}H NMR	MS	specific rotation
G1	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.88 (s,1H), 7.97 (d,1H), 7.89 (d,1H), 7.54 (dd,1H), 7.35 (dd,1H), 7.23 (td,1H), 5.96 (s,1H), 3.93 (q,2H), 2.46 (s,3H), 1.03 (t,3H).	MS (ESI, pos.ion) *m/z*: 424.0 $[M+H]^+$;	$[a]_D^{25}$ = -80.71 (c = 0.3023 g/100 mL, MeOH);
G2	^{1}H NMR (400 MHz, DMSO-d_6): δ 7.79 (d,1H), 7.67 (d,1H), 7.42 (dd,2H), 7.36 (dd,1H), 7.15 (td,1H), 5.85 (s,1H), 3.40 (s,3H), 2.33 (s,3H).	MS (ESI, pos.ion) *m/z*: 410.0 $[M+H]^+$;	$[a]_D^{25}$ = -86.04 (c = 0.3022 g/100 mL, MeOH);

Step 2) (*R*)-ethyl 4-(2-bromo-4-fluorophenyl)-6-bromomethyl-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate



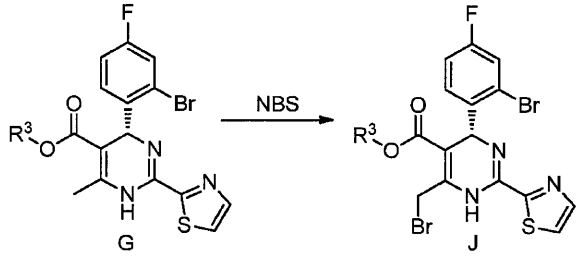
[00134] To a flask were added (*R*)-ethyl 4-(2-bromo-4-fluorophenyl)-6-methyl-2-(thiazol-2-yl) -1,4-dihydropyrimidine-5-carboxylate (42.4 g, 0.1 mol) and CCl_4 (800 mL), followed by NBS (19.6 g, 0.11 mol) at 70 °C. The mixture was stirred for 30 min. After the reaction, the mixture was cooled and filtered. The filtrate was concentrated to obtain the product as a yellow solid (34.2 g, 68%).

MS (ESI, pos.ion) *m/z*: 503.9 $[M+H]^+$;

^1H NMR (600 MHz, DMSO-d_6): δ 10.23 (s,1H), 8.01 (d,1H), 7.98 (d,1H), 7.62 (dd,1H), 7.42 (dd,1H), 7.29 (td,1H), 6.01 (s,1H), 4.79 (br,2H), 4.01 (q,2H), 1.08 (t,3H).

[00135] The compound J can be prepared under the reaction conditions shown in table 10 according to the procedure described in step 2 of Example 6.

Table 10: The reaction conditions for preparation of compound J

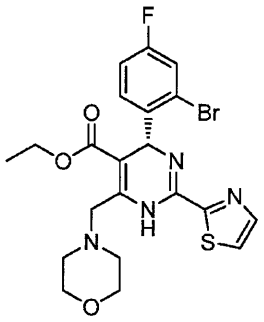


No.	R^3	The mole ratio of NBS to compound G; the amount of compound G	Reaction solvent	The mass ratio of reaction solvent to compound G	Reaction temperature (°C)	Product character	Quality; yield(%) of product
J1	ethyl	1.0;42.4 g	DCM	10	39	yellow solid	35.2 g;70
J1	ethyl	1.0;42.4 g	$CHCl_3$	20	61	yellow solid	36.3 g;72
J1	ethyl	1.1;42.4 g	CCl_4	30	76	yellow solid	44.3 g;88
J2	methyl	1.0;41 g	DCM	10	39	yellow solid	29.9 g;73
J2	methyl	1.1;41 g	$CHCl_3$	20	61	yellow solid	30.8 g;75
J2	methyl	1.1;41 g	CCl_4	30	76	yellow solid	34.9 g;85

Table 10-1: The NMR and MS datum of compound J

No.	^1H NMR	MS
J1	^1H NMR (600 MHz, DMSO-d_6): δ 10.23 (s,1H), 8.01 (d,1H), 7.98 (d,1H), 7.62 (dd,1H), 7.42 (dd,1H), 7.29 (td,1H), 6.01 (s,1H), 4.79 (br,2H), 4.01 (q,2H), 1.08 (t,3H).	MS (ESI, pos.ion) *m/z*: 503.9 $[M+H]^+$;
J2	^1H NMR (400 MHz, $CDCl_3$): δ 8.87 (d,1H), 7.54 (d,1H), 7.40 (dd,1H), 7.35 (dd,1H), 7.03 (td,1H), 6.11 (s,1H), 4.97 (d,1H), 4.64 (d,1H), 3.69 (s,3H).	MS (ESI, pos.ion) *m/z*: 489.9 $[M+H]^+$;

Step 3) (*R*)-ethyl 4-(2-bromo-4-fluorophenyl)-6-(morpholinomethyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine -5-carboxylate



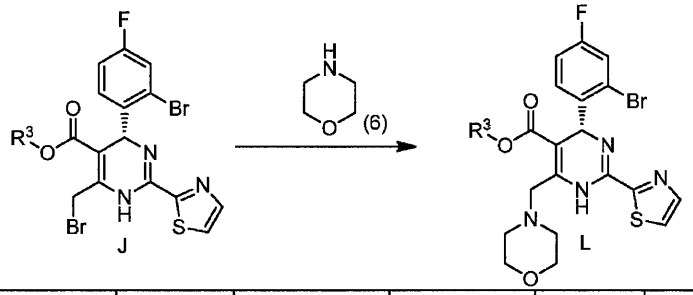
[00136] To a flask were added (R)-ethyl 4-(2-bromo-4-fluorophenyl)-6-(bromomethyl)-2-(thiazol-2-yl)-1,4 -dihydropyrimidine-5-carboxylate (50.3 g, 0.1 mol), anhydrous ethanol (302 g) and morpholine (34.8 g, 0.4 mol). The mixture was stirred at 25 °C under nitrogen atmosphere for 6 hours. After the reaction, the mixture was concentrated. To the residue was added ethyl acetate (500 g), the resulting mixture was washed with water (250 mL × 2). The organic layer was concentrated to give the product as tawny oil (37.7 g, 74%)

MS (ESI, pos.ion) *m/z*: 509.1 $[M+H]^+$;

^{1}H NMR (600 MHz, DMSO-d_6): δ 9.69 (s,1H), 8.02 (d,1H), 7.93 (d,1H), 7.57 (dd,1H), 7.40 (dd,1H), 7.22 (td,1H), 6.05 (s,1H), 3.96 (q,4H), 3.93(dd,2H), 3.68 (br,4H), 2.56 (br,4H), 1.05 (t,3H).

[00137] The compound L can be prepared under the reaction conditions shown in table 11 according to the procedure described in step 3 of Example 6.

Table 11: The reaction conditions for preparation of compound L



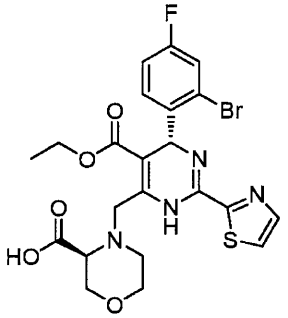
No.	R^3	The mole ratio of compound (6) to compound (J); the amount of compound (J)	Reaction solvent	The mass ratio of reaction solvent to compound (J)	Reaction temperature (°C)	Reaction time(h)	Product character	Quality; yield(%) of product
L1	ethyl	2;50.3g	ethanol	20	25	2	tawny oil	38.2 g;75
L1	ethyl	3;50.3g	acetone	10	40	10	tawny oil	40.8 g;80
L1	ethyl	4;50.3g	methanol	10	30	6	tawny oil	38.7 g;76
L1	ethyl	5;50.3g	ethyl acetate	20	50	24	tawny oil	35.7 g;70
L1	ethyl	6;50.3g	DCM	8	39	6	tawny oil	36.2 g;71
L1	ethyl	3;50.3g	DMF	4	60	1	tawny oil	36.7 g;72
L1	ethyl	4;50.3g	THF	6	50	8	tawny oil	38.2 g;75
L2	methyl	2;48.9g	ethanol	20	25	2	tawny oil	36.2 g;73
L2	methyl	3;48.9g	acetone	10	40	10	tawny oil	37.6 g;76
L2	methyl	4;48.9g	methanol	10	30	6	tawny oil	39.6 g;80
L2	methyl	5;48.9g	ethyl acetate	20	50	24	tawny oil	38.6 g;78
L2	methyl	6;48.9g	DCM	8	39	6	tawny oil	35.2 g;71
L2	methyl	3;48.9g	DMF	4	60	1	tawny oil	36.2 g;73

L2	methyl	4;48.9g	THF	6	50	8	tawny oil	35.7 g;72

Table 11-1: The NMR and MS datum of compound L

No.	^{1}H NMR	MS
L1	^{1}H NMR (600 MHz, DMSO-d_6): δ 9.69 (s,1H), 8.02 (d,1H), 7.93 (d,1H), 7.57 (dd,1H), 7.40 (dd,1H), 7.22 (td,1H), 6.05 (s,1H), 3.96 (q,4H), 3.93 (dd,2H), 3.68 (br,4H), 2.56 (br,4H), 1.05 (t,3H).	MS (ESI, pos.ion) *m/z*: 509.1 $[M+H]^+$;
L2	^{1}H NMR (600 MHz, DMSO-d_6): δ 9.71 (s,1H), 8.02 (d,1H), 7.94 (d,1H), 7.55 (dd,1H), 7.37 (dd,1H), 7.20 (td,1H), 6.02 (s,1H), 3.91 (dd,2H), 3.67 (br,4H), 3.52 (s,3H), 2.55 (br,4H).	MS (ESI, pos.ion) *m/z*: 494.7 $[M+H]^+$;

Example 7: the preparation of (*S*)-4-(((*R*)-6-(2-bromo-4-fluorophenyl)-5-(ethoxycarbonyl)-2-(thiazol-2-yl)-3,6-dihydropyrimidin-4-yl)methyl)morpholine-3-carboxylic acid



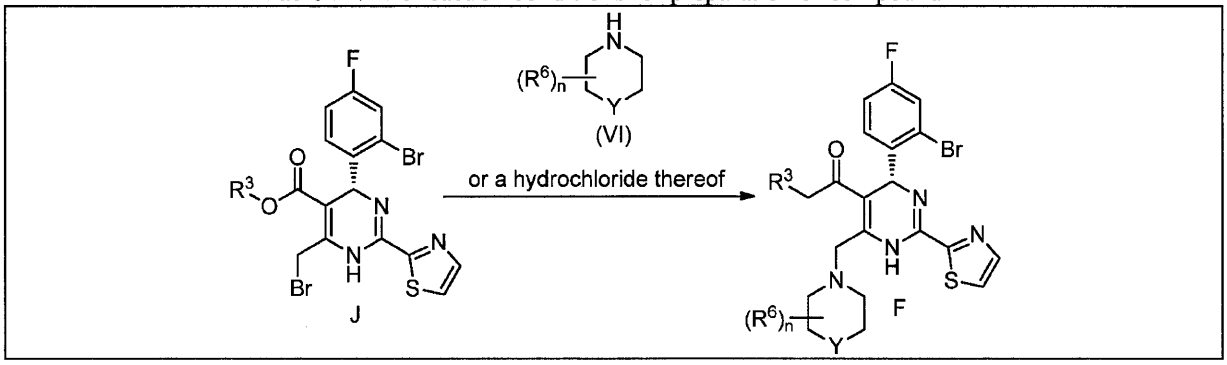
[00138] To a flask were added (*R*)-ethyl 4-(2-bromo-4-fluorophenyl)-6-(bromomethyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (5.03 g, 10 mmol), (*S*)-morpholine-3-carboxylic acid (1.31 g, 10 mmol), potassium carbonate (2.76 g, 20 mmol) and ethanol (100 mL). The mixture was stirred at 30 °C under nitrogen atmosphere for 12 hours. After the reaction, the mixture was filtered. The filtrate was concentrated. To the residue was added water (100 mL), the resulting mixture was extracted with ethyl acetate (100 mL). The organic layer was discarded. To the aqueous layer was added ethyl acetate (100 mL), the mixture was adjusted to pH 3-6 with concentrated hydrochloric acid. The organic layer was dried over anhydrous sodium sulfate and concentrated to give the product as a yellow solid (4.4 g, 80%).

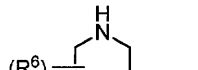
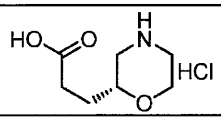
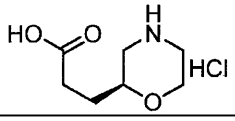
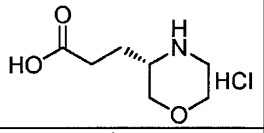
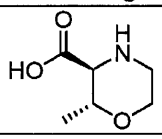
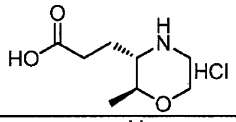
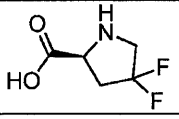
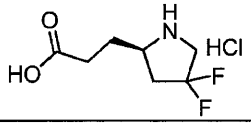
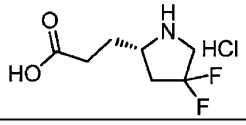
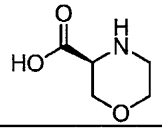
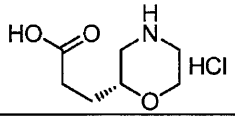
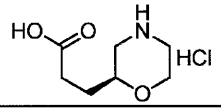
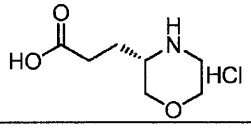
MS (ESI, pos.ion) *m/z*: 553.2 $[M+H]^+$;

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.85 (br,1H), 9.80 (s,1H), 8.00 (d,1H), 7.91 (d,1H), 7.54 (dd,1H), 7.39 (dd,1H), 7.19 (td,1H), 6.01 (s,1H), 4.25 (d,1H), 4.02 (d,1H), 3.97-3.91 (m,3H), 3.81 (dd,1H), 3.72-3.69 (m,1H), 3.66-3.63 (m,1H), 3.61-3.58 (m,1H), 3.10-3.03 (m,1H), 2.42-2.35 (m,1H), 1.04 (t,3H).

[00139] The compound F can be prepared under the reaction conditions shown in table 12 according to the procedure described in Example 7.

Table 12: The reaction conditions for preparation of compound F



No.	R^3	 or a hydrochloride thereof	The mole ratio of compound (J) to compound (VI); the amount of compound (J)	Reaction solvent	The mass ratio of reaction solvent to compound (J)	Reaction temperature (°C)	Reaction time(h)	Product character	Quality; yield(%) of product
F1	ethyl		1; 5.03 g	ethanol	8	30	4	yellow solid	4.07 g; 70
F2	ethyl		1; 5.03 g	ethanol	4	30	8	yellow solid	4.12 g; 71
F3	ethyl		1; 5.03 g	ethanol	20	30	24	yellow solid	2.61 g; 45
F4	ethyl		1; 5.03 g	ethanol	30	30	6	yellow solid	4.54 g; 80
F5	ethyl		1; 5.03 g	ethanol	15	30	24	yellow solid	3.04 g; 51
F6	ethyl		1; 5.03 g	ethanol	20	30	6	yellow solid	4.47 g; 78
F7	ethyl		1; 5.03 g	ethanol	25	30	12	yellow solid	3.91 g; 65
F8	ethyl		1; 5.03 g	ethanol	14	30	12	yellow solid	4.09 g; 68
F9	methyl		1; 4.89 g	ethanol	8	30	4	yellow solid	3.83 g; 71
F10	methyl		1; 4.89 g	ethanol	4	30	8	yellow solid	3.85 g; 68
F11	methyl		1; 4.89 g	ethanol	10	30	12	yellow solid	3.74 g; 66
F12	methyl		1; 4.89 g	ethanol	30	30	6	yellow solid	2.50 g; 44

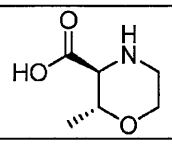
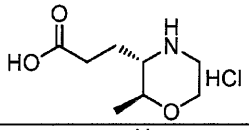
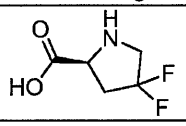
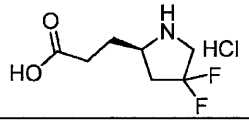
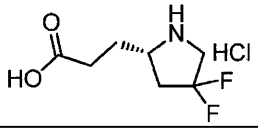
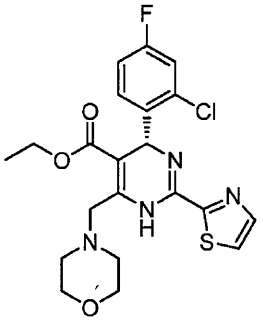
F13	methyl		1; 4.89 g	ethanol	8	30	12	yellow solid	4.32g; 78
F14	methyl		1; 4.89 g	ethanol	20	30	6	yellow solid	2.79 g; 48
F15	methyl		1; 4.89 g	ethanol	25	30	12	yellow solid	4.14 g; 74
F16	methyl		1; 4.89 g	ethanol	14	30	12	yellow solid	3.64 g; 62
F17	methyl		1; 4.89 g	ethanol	15	30	24	yellow solid	3.7 g; 63

Table 12-1: The NMR and MS datum of compound L

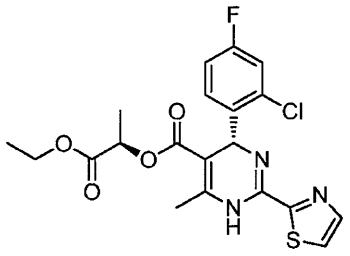
No.	^{1}H NMR	MS
F1	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.06 (s,1H), 9.65 (s,1H), 8.02 (d,1H), 7.94 (d,1H), 7.57 (dd,1H), 7.39 (dd,1H), 7.22 (td,1H), 6.03 (s,1H), 3.96 (q,2H), 3.89-3.85 (m,3H), 3.61-3.47 (m,2H), 2.81-2.75 (m,2H), 2.38-2.21 (m,3H), 2.04-2.02 (m,1H), 1.65-1.60 (m,2H), 1.06 (t,3H).	MS (ESI, pos.ion) *m/z*: 581.2 $[M+H]^+$;
F2	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.06 (s,1H), 9.66 (s,1H), 8.02 (d,1H), 7.95 (d,1H), 7.56 (dd,1H), 7.41 (dd,1H), 7.20 (td,1H), 6.03 (s,1H), 3.97 (q,2H), 3.93-3.83 (m,3H), 3.57-3.46 (m,2H), 2.88 (d,1H), 2.63 (d,1H), 2.37-2.22 (m,3H),2.13-2.08 (m,1H), 1.75-1.65 (m,2H), 1.06 (t,3H).	MS (ESI, pos.ion) *m/z*: 580.9 $[M+H]^+$;
F3	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.14 (br,1H), 9.82 (s,1H), 8.02 (d,1H), 7.92 (d,1H), 7.54(dd,1H), 7.40 (dd,1H), 7.22 (td,1H), 6.03 (s,1H), 4.18 (d,1H), 3.96 (q,2H), 3.91 (d,1H), 3.82-3.79 (m,1H), 3.74-3.71 (m,1H), 3.61-3.57 (m,1H), 3.37-3.32 (m,1H), 2.78-2.75 (m,1H), 2.57-2.53 (m,1H), 2.49-2.47 (m,1H), 2.38-2.32 (m,2H), 1.89-1.84 (m,1H), 1.68-1.58 (m,1H), 1.06 (t,3H).	MS (ESI, pos.ion) *m/z*: 580.9 [M+H]+;
F4	^{1}H NMR (400 MHz, DMSO-d_6): δ 13.02 (s,1H), 9.78 (s,1H), 8.03 (d,1H), 7.93 (d,1H), 7.56 (dd,1H), 7.39 (dd,1H), 7.22 (td,1H), 6.00 (s,1H), 4.10 (d,1H), 3.95 (q,2H), 3.90-3.87 (m,1H), 3.76-3.60 (m,3H), 3.46-3.42 (m,1H), 2.98 (d,1H), 2.93 (d,1H), 1.21 (d,3H), 1.05 (t,3H).	MS (ESI, pos.ion) *m/z*: 567.1 $[M+H]^+$;
F5	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.11 (s,1H), 9.74 (s,1H), 8.02 (d,1H), 7.95 (d,1H), 7.56 (dd,1H), 7.39 (dd,1H), 7.19 (td,1H), 6.04 (s,1H), 4.16 (d,1H), 4.00-3.93 (m,2H), 3.86 (d,1H), 3.77-3.72 (m,1H), 3.59-3.53 (m,1H), 3.51-3.45 (m,1H), 2.66 (d,1H), 2.46-2.40 (m,1H), 2.37-2.30 (m,3H), 2.03 -1.91 (m,1H), 1.80-1.73 (m,1H), 1.20 (d,3H), 1.06 (t,3H).	MS (ESI, pos.ion) *m/z*: 594.6 $[M+H]^+$;
F6	^{1}H NMR (600 MHz, DMSO-d_6): δ 9.98 (br,1H), 8.03 (d,1H), 8.00 (d,1H), 7.61 (dd,1H), 7.48 (dd,1H), 7.28 (td,1H), 6.02 (s,1H), 4.35 (d,1H), 4.13 (d,1H), 4.01-3.94 (m,3H), 3.61-3.51 (m,1H), 3.25-3.19 (m,1H), 3.10-3.04 (m,1H), 2.86-2.68 (m,1H), 1.20 (t,3H).	MS (ESI, pos.ion) *m/z*: 573.0 $[M+H]^+$;
F7	^{1}H NMR (600 MHz, DMSO-d_6): δ 12.08 (s,1H), 9.51 (s,1H), 8.01 (d,1H), 7.93 (d,1H), 7.57 (dd,1H), 7.41 (dd,1H), 7.24 (td,1H), 6.01 (s,1H), 4.12 (dd,2H), 3.97 (q,2H), 3.61-3.52 (m,1H), 3.04-2.96 (m,2H), 2.58-2.56 (m,1H), 2.35-2.20 (m,2H), 2.12-1.98 (m,1H), 1.93-1.90 (m,1H), 1.56-1.48 (m,1H), 1.06 (t,3H).	MS (ESI, pos.ion) *m/z*: 601.1 $[M+H]^+$;
F8	^{1}H NMR (400 MHz, $CDCl_3$): δ 12.19 (br,1H), 9.46 (s,1H), 7.86 (d,1H), 7.50 (d,1H), 7.37-7.33 (m,2H), 7.00 (td,1H), 6.19 (s,1H), 4.52 (d,1H), 4.14-4.03 (m,2H), 3.65 (d,1H), 3.31-3.23 (m,2H), 3.02-2.91 (m,1H), 2.57-2.25 (m,5H), 1.79-1.74 (m,1H), 1.16 (t,3H).	MS (ESI, pos.ion) *m/z*: 601.2 $[M+H]^+$;

F9	^{1}H NMR (600 MHz, DMSO-d_6): δ 12.88 (br,1H), 10.07 (br,1H), 8.02 (d,1H), 7.93 (d,1H), 7.56 (dd,1H), 7.39 (dd,1H), 7.23 (td,1H), 6.01 (s,1H), 4.25 (d,1H), 4.04 (d,1H), 3.99 (dd,1H), 3.84 (dd,1H), 3.73-3.70 (m,1H), 3.69-3.65 (m,1H), 3.62-3.58 (m,1H), 3.51 (s,3H), 3.10-3.07 (m,1H), 2.41-2.39 (m,1H).	MS (ESI, pos.ion) *m/z*: 539.1 $[M+H]^+$;
F10	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.03 (s,1H), 9.69 (s,1H), 8.01 (d,1H), 7.93 (d,1H), 7.56 (dd,1H), 7.38 (dd,1H), 7.23 (td,1H), 6.01 (s,1H), 3.93-3.83 (m,3H), 3.60-3.53 (m,2H), 3.52 (s,3H), 2.77 (dd,2H), 2.38-2.25 (m,3H), 2.05-1.99 (m,1H), 1.65-1.59 (m,2H).	MS (ESI, pos.ion) *m/z*: 567.2 $[M+H]^+$;
F11	^{1}H NMR (600 MHz, DMSO-d_6): δ 12.06 (s,1H), 9.70 (s,1H), 8.03 (d,1H), 7.94 (d,1H), 7.57 (dd,1H), 7.39 (dd,1H), 7.23 (td,1H), 6.02 (s,1H), 3.95 (d,1H), 3.86-3.80 (m,2H), 3.56-3.54 (m,1H), 3.53 (s,3H), 3.52-3.49 (m,1H), 2.88 (d,1H), 2.62 (d,1H), 2.37-2.21 (m,3H), 2.15-2.08 (m,1H), 1.72-1.64 (m,2H).	MS (ESI, pos.ion) *m/z*: 567.2 $[M+H]^+$;
F12	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.87 (s,1H), 8.03 (d,1H), 7.94 (d,1H), 7.56 (dd,1H), 7.38 (dd,1H), 7.23 (td,1H), 6.01 (s,1H), 4.18 (d,1H), 3.91 (d,1H), 3.83-3.79 (m,1H), 3.75-3.70 (m,1H), 3.61-3.56 (m,1H), 3.53 (s,3H), 3.47-3.40 (m,1H), 3.04-2.86 (m,1H), 2.77-2.75 (m,1H), 2.58-2.54 (m,1H), 2.37-2.22 (m,2H), 1.88-1.84 (m,1H), 1.65-1.58 (m,1H).	MS (ESI, pos.ion) *m/z*: 567.2 $[M+H]^+$;
F13	^{1}H NMR (400 MHz, DMSO-d_6): δ 13.02 (s,1H), 9.83 (s,1H), 8.02 (d,1H), 7.94 (d,1H), 7.56 (dd,1H), 7.38 (dd,1H), 7.22 (td,1H), 5.99 (s,1H), 4.05 (d,1H), 3.90-3.85 (m,1H), 3.75-3.60 (m,3H), 3.52 (s,3H), 3.47-3.42 (m,1H), 3.00 (d,1H), 2.92 (d,1H), 1.21 (d,3H).	MS (ESI, pos.ion) *m/z*: 553.0 $[M+H]^+$;
F14	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.10 (s,1H), 9.75 (s,1H), 8.01 (d,1H), 7.96 (d,1H), 7.54 (dd,1H), 7.40 (dd,1H), 7.20 (td,1H), 6.02 (s,1H), 4.18 (d,1H), 3.88 (d,1H), 3.78-3.73 (m,1H), 3.60-3.54 (m,1H), 3.52 (s,3H), 3.50-3.45 (m,1H), 2.68 (d,1H), 2.47-2.41 (m,1H), 2.36-2.30 (m,3H), 2.04 -1.92 (m,1H), 1.81-1.73 (m,1H), 1.21 (d,3H).	MS (ESI, pos.ion) *m/z*: 581.2 $[M+H]^+$;
F15	^{1}H NMR (600 MHz, DMSO-d_6): δ 9.71 (br,1H), 7.98 (d,1H), 7.91 (d,1H), 7.56 (dd,1H), 7.40 (dd,1H), 7.23 (td,1H), 5.99 (s,1H), 4.33 (d,1H), 4.09 (d,1H), 3.93-3.88 (m,1H), 3.52 (s,3H), 3.49-3.45 (m,1H), 3.22-3.08 (m,2H), 2.82-2.74 (m,1H).	MS (ESI, pos.ion) *m/z*: 558.6 $[M+H]^+$;
F16	^{1}H NMR (400 MHz, DMSO-d_6): δ 11.03 (s,1H), 9.57 (s,1H), 7.99 (d,1H), 7.92 (d,1H), 7.55 (dd,1H), 7.39 (dd,1H), 7.23 (td,1H), 6.00 (s,1H), 4.14 (dd,2H), 3.62-3.54 (m,1H), 3.53 (s,3H), 3.05-2.96 (m,2H), 2.57-2.56 (m,1H), 2.36-2.20 (m,2H), 2.13-1.98 (m,1H), 1.95-1.90 (m,1H), 1.56-1.46 (m,1H).	MS (ESI, pos.ion) *m/z*: 587.2 $[M+H]^+$;
F17	^{1}H NMR (400 MHz, $CDCl_3$): δ 12.15 (br,1H), 9.47 (s,1H), 7.85 (d,1H), 7.51 (d, 1H), 7.38-7.33 (m,2H), 7.01 (td,1H), 6.17 (s,1H), 4.50 (d,1H), 3.66 (d,1H), 3.55 (s,3H), 3.33-3.23 (m,2H), 3.04-2.92 (m,1H), 2.58-2.25 (m,5H), 1.78-1.74 (m,1H).	MS (ESI, pos.ion) *m/z*: 587.2 $[M+H]^+$;

Example 8: the preparation of (*R*)-ethyl 4-(2-chloro-4-fluorophenyl)-6-(morpholinomethyl)-2-(thiazol-2-yl)-1,4 -dihydropyrimidine-5-carboxylate



Step 1) (*R*)-(*R*)-1-ethoxy-1-oxopropan-2-yl 4-(2-chloro-4-fluorophenyl)-6-methyl-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate



Method one:

[00140] To a flask were added 2-thiazolecarboxamidine hydrochloride (16.4 g, 0.1 mol), 2-chloro-4-fluorobenzaldehyde (15.9 g, 0.1 mol), (*R*)-1-ethoxy-1-oxopropan-2-yl 3-oxobutanoate (20.2 g, 0.1 mol), anhydrous sodium acetate (8.2 g, 0.1 mol) and ethanol (74 g) in turn. The mixture was stirred at 78 °C for 16 hours. After the reaction, the mixture was cooled to 30 °C, kept at 30 °C and stirred for 6 hours. The resulting mixture was filtered. The filter cake was washed with water (330 mL) and dried *in vacuo* at 60 °C for 8 hours to obtain the crude product. To the crude product was added *n*-propanol (50 g). The mixture was heated until dissolved completely, cooled to 30 °C, and then kept at 30 °C, stirred and crystallized for 8 hours. The resulting mixture was filtered. The filter cake was dried *in vacuo* at 60 °C for 8 hours to obtain the product as a yellow solid (10.4 g, 23%).

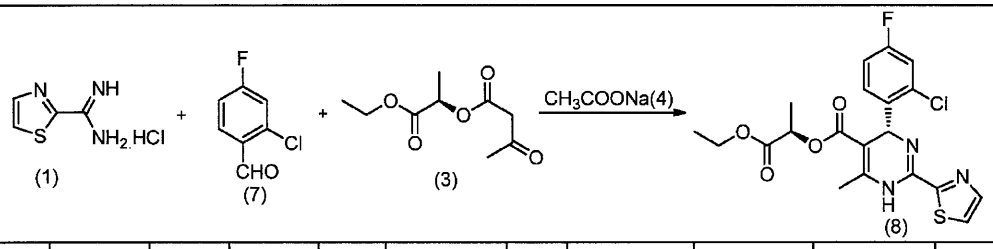
$[a]_D^{25}$ = –91.47 (c = 0.3083 g/100 mL, MeOH);

MS (ESI, pos.ion) *m/z*: 452.2 $[M+H]^+$;

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.05 (s,1H), 7.98 (d,1H), 7.91 (d,1H), 7.42-7.37 (m,2H), 7.20 (td,1H), 6.03 (s,1H), 4.84 (q,1H), 4.12-4.04 (m,2H), 2.47 (s,3H), 1.22 (d,3H), 1.14 (t,3H).

[00141] The compound 8 can be prepared under the reaction conditions shown in table 13 by using method one described in step 1 of Example 8.

Table 13: The reaction conditions



No.	(1):(7):(3):(4):(mol); the amount of compound (1) is 16.4 g	Reaction solvent	The mass ratio of reaction solvent to compound (1)	Reaction temperature (°C)	Reaction time(h)	Cooling temperature(°C)	Cooling time(h)	Recrystallization solvent	The mass ratio of recrystallization solvent to compound (1)	Crystallization temperature(°C)	Crystallization time(h)	Quality; yield(%) of product
1	1:1:2:1	—	—	78	12	40	6	ethanol	20	0	3	7.9 g; 17.5

2	1:1:1:1	ethanol	1	78	12	40	6	ethanol	15	25	10	8.5 g; 18.8
3	1:1:1:1	ethanol	4.5	25	72	25	—	ethanol	4	5	8	9.1 g; 20.2
4	1:1:1:1	ethanol	5	78	12	25	6	ethanol	3	15	5	10.2 g; 22.5
5	1:1:1:1	ethanol	20	60	24	-20	12	ethanol	3	25	6	8.9 g; 19.6
6	1:1:1:1	ethanol	80	78	12	-40	24	ethanol	5	25	4	7.6 g; 16.9
7	1:1:1:1	*n*-butanol	4.5	100	5	25	6	*n*-butanol	4	25	6	10.4 g; 23.1
8	1:1:1:1	*n*-propanol	4.5	80	12	25	6	*n*-propanol	3	25	6	11.8 g; 26.2
9	1:1:1:1	*i*-propanol	4.5	82	12	25	2	*i*-propanol	3	30	6	11.4 g; 25.3
10	1:1:1:1	*t*-butanol	4.5	82	12	30	12	*t*-butanol	4	25	6	11 g; 24.4
11	1:1:1:1	2-methoxyethanol	4.5	78	12	-10	12	*i*-propanol	3.5	25	4	9 g; 20
12	1:1:1:1	1,2-dimethoxyethane	4.5	78	12	-15	12	*i*-propanol	3.5	25	6	8.6 g; 19.1

Method two

[00142] To a flask were added 2-thiazolecarboxamidine hydrochloride (16.4 g, 0.1 mol), 2-chloro-4-fluorobenzaldehyde (15.9 g, 0.1 mol), (*R*)-1-ethoxy-1-oxopropan-2-yl 3-oxobutanoate (20.2 g, 0.1 mol), anhydrous sodium acetate (8.2 g, 0.1 mol) and ethanol (74 g) in turn. The mixture was stirred at 78 °C for 16 hours. After the reaction, the reaction mixture was cooled to 30 °C, kept at 30 °C and stirred for 6 hours. The mixture was filtered. The filtrate was washed with ethanol (16.4 g) and water (330 mL) in turn, and then dried *in vacuo* at 60 °C for 8 hours to obtain the product as a yellow solid (12.2 g, 27%).

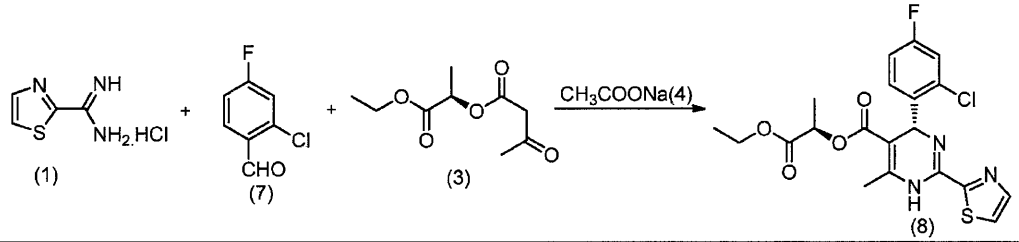
$[a]_D^{25}$ = –91.47 (c = 0.3083 g/100 mL, MeOH);

MS (ESI, pos.ion) *m/z*: 452.2 $[M+H]^+$;

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.05 (s,1H), 7.98 (d,1H), 7.91 (d,1H), 7.42-7.37 (m,2H), 7.20 (td,1H), 6.03 (s,1H), 4.84 (q,1H), 4.12-4.04 (m,2H), 2.47 (s,3H), 1.22 (d,3H), 1.14 (t,3H).

[00143] The compound 8 can be prepared under the reaction conditions shown in table 14 by using method two described in step 1 of Example 8.

Table 14: The reaction conditions



No.	(1):(7):(3):(4):(mol);	Reaction solvent	The mass ratio of	Reaction tempera	Reaction time(h)	Cooling temperature(°C)	Cooling time(h)	Washing solvent	The mass ratio of	Washing temperature(°C)	Quality; yield(%) of product

	the amount of compound (1) is 16.4 g		reaction solvent to compound (1)	ture					washing solvent to compound (1)		
1	1:1:2:1	—	—	78	12	40	6	ethanol	10	25	8.8 g; 19.4
2	1:1:1:1	ethanol	1	78	12	40	6	ethanol	7.5	25	9.3 g; 20.5
3	1:1:1:1	ethanol	4.5	25	72	25	—	ethanol	2	25	10 g; 22.2
4	1:1:1:1	ethanol	5	78	12	25	6	ethanol	3	25	11.1 g; 24.6
5	1:1:1:1	*n*-propanol	6	80	12	25	6	—	—	—	13.1 g; 28.9
6	1:1:1:1	ethanol	20	60	24	-20	6	ethanol	3	25	9.6 g; 21.3
7	1:1:1:1	ethanol	80	78	12	-30	24	ethanol	5	25	9.3 g; 18.8
8	1:1:1:1	*n*-butanol	4.5	100	5	25	6	*n*-butanol	3	25	11.4 g; 25.2
9	1:1:1:1	*n*-propanol	4.5	80	12	25	6	*n*-propanol	2	25	12.8 g; 28.4
10	1:1:1:1	*i*-propanol	4.5	82	12	25	2	*i*-propanol	2	30	12.6 g; 27.8
11	1:1:1:1	*t*-butanol	4.5	82	12	30	12	*t*-butanol	3	25	12 g; 26.5
12	1:1:1:1	2-methoxyethanol	4.5	78	12	-10	12	2-methoxyethanol	1	0	9.9 g; 21.8
13	1:1:1:1	1,2-dimethoxyethane	4.5	78	12	-15	12	*i*-propanol	2	25	9.6 g; 21.3

Method three:

[00144] To a flask were added 2-thiazolecarboxamidine hydrochloride (16.4 g, 0.1 mol), 2-chloro-4-fluorobenzaldehyde (15.9 g, 0.1 mol), (*R*)-1-ethoxy-1-oxopropan-2-yl 3-oxobutanoate (20.2 g, 0.1 mol), anhydrous sodium acetate (8.2 g, 0.1 mol) and ethanol (74 g) in turn. The mixture was stirred at 78 °C for 16 hours. After the reaction, the mixture was cooled to 30 °C, kept at 30 °C and stirred for 6 hours. The resulting mixture was filtered. The filter cake was washed with water (330 mL) and dried *in vacuo* at 60 °C for 8 hours to obtain the crude product. The crude product was triturated with *n*-propanol (50 g) at 30 °C for 5 hours and filtered. The filter cake was dried *in vacuo* at 60 °C for 8 hours to obtain the product as a yellow solid (11.3 g, 25%).

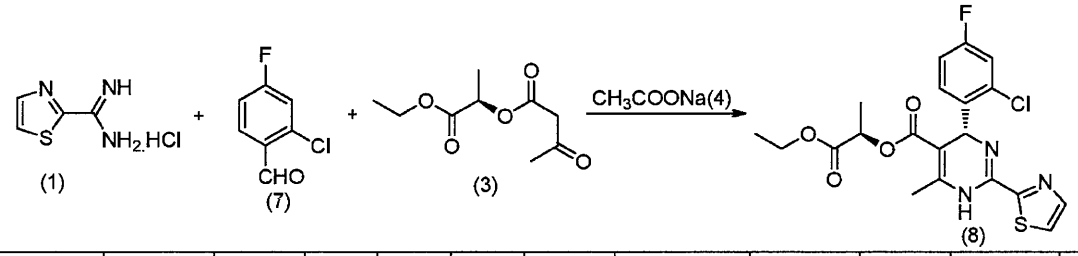
$[a]_D^{25}$ = –91.47 (c = 0.3083 g/100 mL, MeOH);

MS (ESI, pos.ion) *m/z*: 452.2 $[M+H]^+$;

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.05 (s,1H), 7.98 (d,1H), 7.91 (d,1H), 7.42-7.37 (m,2H), 7.20 (td,1H), 6.03 (s,1H), 4.84 (q,1H), 4.12-4.04 (m,2H), 2.47 (s,3H), 1.22 (d,3H), 1.14 (t,3H).

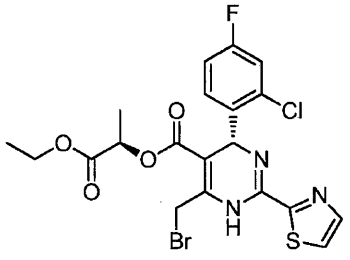
[00145] The compound 8 can be prepared under the reaction conditions shown in table 15 by using method three described in step 1 of Example 8.

Table 15: The reaction conditions



No.	(1):(7):(3):(4) (mol); the amount of compound (1) is 16.4 g	Reaction solvent	The mass ratio of reaction solvent to compound (1)	Reaction temperature (°C)	Reaction time(h)	Cooling temperature (°C)	Cooling time(h)	Trituration solvent	The mass ratio of trituration solvent to compound (1)	Trituration temperature (°C)	Trituration time(h)	Quality; yield(%) of product
1	1:1:2:1	—	—	78	12	40	6	ethanol	8	25	10	8.4 g; 18.6
2	1:1:1:1	ethanol	1	78	12	40	6	ethanol	7	25	5	8.8 g; 19.5
3	1:1:1:1	ethanol	4.5	25	72	25	—	ethanol	3	25	3	9.6 g; 21.3
4	1:1:1:1	ethanol	5	78	12	25	6	ethanol	4	5	1	10.5 g;23.2
5	1:1:1:1	ethanol	20	60	24	-20	12	ethanol	3	25	4	9.3 g; 20.6
6	1:1:1:1	ethanol	80	78	12	-40	24	ethanol	5	25	2	8.1 g; 17.8
7	1:1:1:1	*n*-butanol	4.5	100	5	25	6	*n*-butanol	4	25	3	10.9 g; 24.1
8	1:1:1:1	*n*-propanol	4.5	80	12	25	6	*n*-propanol	3	25	4	12.4 g; 27.5
9	1:1:1:1	*i*-propanol	4.5	82	12	25	2	*i*-propanol	3	30	2	12.1 g; 26.7
10	1:1:1:1	*t*-butanol	4.5	82	12	30	12	*t*-butanol	4	25	4	11.4 g; 25.3
11	1:1:1:1	2-methoxyethanol	4.5	78	12	-10	12	*i*-propanol	3	25	3	9.4 g; 20.9
12	1:1:1:1	1,2-dimethoxyethane	4.5	78	12	-15	12	*i*-propanol	3	25	2	9.2 g; 20.4

Step 2) (*R*)-(*R*)-1-ethoxy-1-oxopropan-2-yl 4-(2-chloro-4-fluorophenyl)-6-bromomethyl-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate



[00146] To a flask were added (*R*)-(*R*)-1-ethoxy-1-oxopropan-2-yl 4-(2-chloro-4-fluorophenyl)-6-methyl-

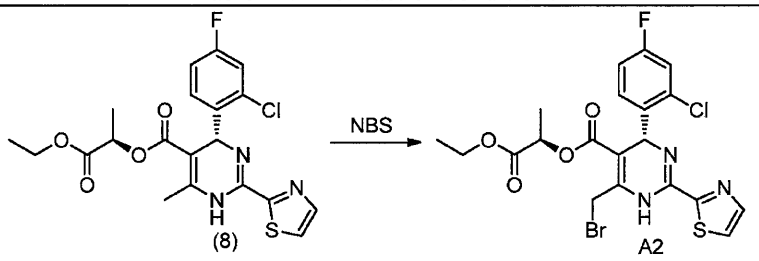
2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (45.2 g, 0.1 mol) and tetrachloromethane (900 g). The mixture was heated at 76 °C, NBS was added (19.6 g, 0.11 mol), and then the reaction mixture was stirred for 30 min. After the reaction, the reaction mixture was cooled and concentrated. To the residue was added ethanol (226 g). The resulting mixture was cooled to 0 °C, kept at 0 °C and stirred. After the solid precipitated out completely, the mixture was filtered. The filter cake was washed with ethanol (45 g) and dried *in vacuo* at 60 °C for 6 hours to obtain the product as a yellow solid (31.3 g, 59%).

MS (ESI, pos.ion) *m/z*: 531.6 $[M+H]^+$;

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.37 (s,1H), 8.03 (d,1H), 8.00 (d,1H), 7.47-7.42 (m,2H), 7.23 (td,1H), 6.01 (s,1H), 4.94 (q,1H), 4.87-4.78 (m,2H), 4.16-4.04 (m,2H), 1.27 (d,3H), 1.15 (t,3H).

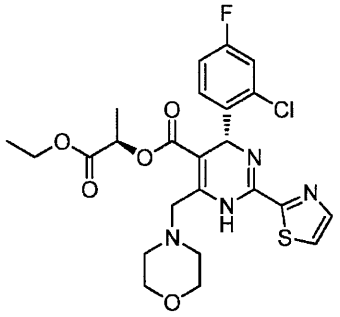
[00147] The compound A2 can be prepared under the reaction conditions shown in table 16 according to the procedure described in step 2 of Example 8.

Table 16: The reaction conditions



No.	Compound (8):NBS(mol) the amount of compound (8) is 45.2 g	Reaction solvent	The mass ratio of reaction solvent to compound (8)	Reaction temperature (°C)	The solvent added to the residue	The mass ratio of the additional solvent to compound (8)	Quality; yield(%) of product
1	1:1.1,	DCM	30	39	*i*-propanol	7	33.5 g; 63%
2	1:1.05,	DCM	10	39	ethanol	5	31.9 g; 60%
3	1:1.15,	$CHCl_3$	20	61	*n*-propanol	6	34.5 g; 65%
4	1:1.1,	CCl_4	20	76	ethanol	5	36.1 g; 68%

Step 3) (*R*)-(*R*)-1-ethoxy-1-oxopropan-2-yl 4-(2-chloro-4-fluorophenyl)-6-morpholinomethyl-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate



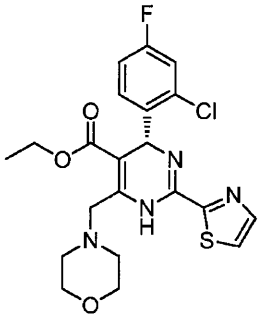
[00148] To a flask were added (*R*)-(*R*)-1-ethoxy-1-oxopropan-2-yl 4-(2-chloro-4-fluorophenyl)-6-(bromomethyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (53.1 g, 0.1 mol), i-propanol (287 g) and

morpholine (34.8 g, 0.4 mol). The mixture was stirred at 55 °C for 4 hours. After the reaction, the mixture was cooled to 0 °C, kept at this temperature and stirred. After the solid precipitated out completely, the mixture was filtered. The filter cake was washed with *i*-propanol (53 g) followed by water (530 g), and then dried *in vacuo* at 60 °C for 8 hours to obtain the product as a yellowish solid (34.4 g, 64%).

MS (ESI, pos.ion) *m/z*: 537.2 $[M+H]^+$;

^1H NMR (600 MHz, DMSO-d_6): δ 9.77 (s,1H), 8.04 (d,1H), 7.95 (d,1H), 7.44-7.41 (m,2H), 7.18 (td,1H), 6.09 (s,1H), 4.86 (q,1H), 4.12-4.04 (m,2H), 3.90 (dd,2H), 3.68 (t,4H), 2.56 (br,4H), 1.25 (d,3H), 1.14 (t,3H).

Step 4) (*R*)-ethyl 4-(2-chloro-4-fluorophenyl)-6-(morpholinomethyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine -5-carboxylate

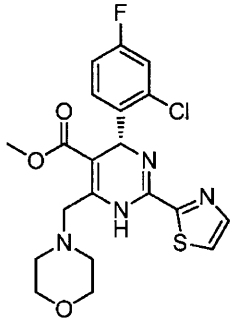


[00149] To a flask were added anhydrous ethanol (403 g) and lithium (1.74 g, 0.25 mol) in turn. The mixture was stirred at 43 °C until the lithium was consumed entirely, and then a solution of (*R*)-(*R*)-1-ethoxy-1-oxopropan-2-yl 4-(2-chloro-4-fluorophenyl)-6-(morphplinomethyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (53.7 g, 0.1 mol) in ethanol (403 g) was added. The reaction mixture was stirred at 78 °C for 1.5 hours. After the reaction, the reaction mixture was cooled and concentrated. To the residue was added ethyl acetate (540 g). The mixture was washed with water (250 g × 2). The organic layer was concentrated to obtain the product as yellow thick oil (34.9 g, 75%).

MS (ESI, pos.ion) *m/z*: 465.2 $[M+H]^+$;

^1H NMR (400 MHz, DMSO-d_6): δ 9.65 (s,1H), 8.00 (d,1H), 7.91 (d,1H),7.40-7.37 (m,2H), 7.15 (td,1H), 6.03 (s,1H), 3.94 (q,2H), 3.88 (dd,2H), 3.65 (br,4H), 2.56 (br,4H), 1.05 (t,3H).

Example 9: the preparation of (*R*)-methyl 4-(2-chloro-4-fluorophenyl)-6-(morpholinomethyl)-2-(thiazol-2-yl)-1,4 -dihydropyrimidine-5-carboxylate



[00150] To a flask were added anhydrous methanol (806 g) and lithium (1.74 g, 0.25 mol) in turn. The mixture was stirred at 43 °C until the lithium was consumed entirely, and then

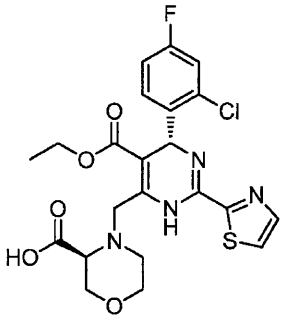
(*R*)-(*R*)-1-ethoxy-1-oxopropan-2-yl

4-(2-chloro-4-fluorophenyl)-6-(morpholinomethyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (53.7 g, 0.1 mol) was added. The reaction mixture was allowed to warm up to 60 °C and stirred for 1.5 hours. After the reaction, the reaction mixture was cooled and concentrated. To the residue was added ethyl acetate (540 g). The mixture was washed with water (250 g × 2). The organic layer was concentrated to obtain the product as yellow thick oil (32.9 g, 73%).

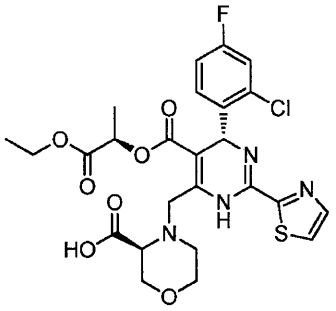
MS (ESI, pos.ion) *m/z*: 450.8 $[M+H]^+$;

^1H NMR (600 MHz, DMSO-d_6): δ 9.72 (s,1H), 8.03 (d,1H), 7.94 (d,1H), 7.43-7.38 (m,2H), 7.17 (td,1H), 6.05 (s,1H),3.93 (dd,2H), 3.68 (br,4H),3.53 (s,3H), 2.56 (br,4H).

Example 10: the preparation of (*S*)-4-(((*R*)-6-(2-chloro-4-fluorophenyl)-5-(ethoxycarbonyl)-2-(thiazol-2-yl) -3,6-dihydropyrimidin-4-yl)methyl)morpholine-3-carboxylic acid



Step 1) (*S*)-4-(((*R*)-6-(2-chloro-4-fluorophenyl)-5-((((*R*)-1-ethoxy-1-oxopropan-2-yl)oxy)carbonyl)-2-(thiazol-2-yl)- 3,6-dihydropyrimidin-4-yl)methyl)morpholine-3-carboxylic acid



[00151] To a flask were added (*R*)-(*R*)-1-ethoxy-1-oxopropan-2-yl 4-(2-chloro-4-fluorophenyl)-6-(bromomethyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (53.1 g, 0.1 mol), ethanol (800 g), (*S*)-morpholine-3-carboxylic acid (13.1 g, 0.1 mol) and potassium carbonate (27.6 g, 0.2 mol) in turn. The mixture was stirred at 30 °C for 12 hours. After the reaction, the mixture was filtered. The filtrate was concentrated. To the residue was added water (840 g), the resulting mixture was extracted with ethyl acetate (840 mL), the organic layer was discarded. To the aqueous layer was added ethyl acetate (900 mL), the mixture was adjusted to pH 3-6 with concentrated hydrochloric acid. The organic layer was dried over anhydrous sodium sulfate and concentrated to give the product as a yellow solid (41.8 g, 72%).

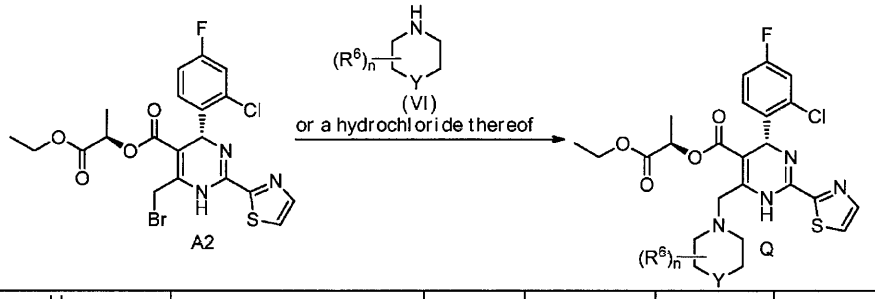
MS (ESI, pos.ion) *m/z*: 581.1 $[M+H]^+$;

^1H NMR (400MHz, DMSO-d_6): δ 8.01 (d,1H), 7.96 (d,1H), 7.43-7.39 (m,2H), 7.18 (td,1H), 6.04 (s,1H),

4.86 (q,1H), 4.25-4.14 (m,1H), 4.11-4.02 (m,3H), 3.99-3.87 (m,1H), 3.84 (dd,1H), 3.74-3.65 (m,2H), 3.57-3.51 (m,1H), 3.11-3.04 (m,1H), 2.43-2.38 (m,1H), 1.22 (d,3H), 1.14 (t,3H).

[00152] The compound Q can be prepared under the reaction conditions shown in table 17 according to the procedure described in step 1 of Example 10.

Table 17: The reaction conditions for preparation of compound Q



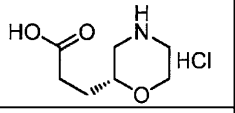
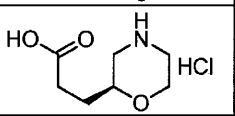
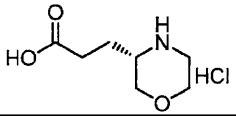
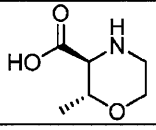
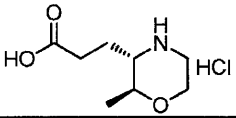
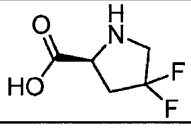
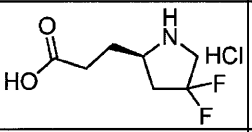
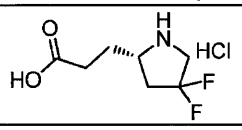
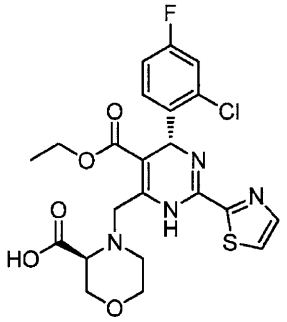
No.	(R6)n Y (VI) or a hydrochloride thereof	compound A2: compound(VI)(mol); the amount of compound A2 is 5.31 g	Reaction solvent	Reaction temperature (°C)	Reaction time(h)	Product character	Quality; yield(%) of product
Q1		1:1	ethanol	30	12	yellow solid	4.14 g; 68
Q2		1:1	ethanol	30	12	yellow solid	4.08 g; 67
Q3		1:1	ethanol	30	12	yellow solid	2.68 g; 44
Q4		1:1	ethanol	30	12	yellow solid	4.22 g; 71
Q5		1:1	ethanol	30	12	yellow solid	2.68 g; 43
Q6		1:1	ethanol	30	12	yellow solid	4.09 g; 68
Q7		1:1	ethanol	30	12	yellow solid	3.4 g; 54
Q8		1:1	ethanol	30	12	yellow solid	3.2 g; 51

Table 17-1: The NMR and MS datum of compound Q

No.	^{1}H NMR	MS
Q1	^{1}H NMR (600 MHz, DMSO-d_6): δ 12.03 (br,1H), 9.76 (s,1H), 8.02 (d,1H), 7.95 (d,1H), 7.44-7.39 (m,2H), 7.20 (td,1H), 6.05 (s,1H), 4.86 (q,1H), 4.13-4.05 (m,2H), 3.93-3.85 (m,3H), 3.59-3.56 (m,1H), 3.53-3.48	MS (ESI, pos.ion) *m/z*: 609.1 $[M+H]^+$;

	(m,1H), 2.78 (t,2H), 2.36-2.23 (m,3H), 2.01 (t,1H), 1.65-1.62 (m,2H), 1.24 (d,3H), 1.13 (t,3H).	
Q2	^{1}H NMR (600 MHz, DMSO-d_6): δ 12.06 (br,1H), 9.72 (s,1H), 8.04 (d,1H), 7.96 (d,1H), 7.43-7.39 (m,2H), 7.19 (td,1H), 6.04 (s,1H), 4.84 (q,1H), 4.14-4.06 (m,2H), 3.94-3.86 (m,3H), 3.58-3.55 (m,1H), 3.52-3.48 (m,1H), 2.77 (t,2H), 2.37-2.23 (m,3H), 2.02 (t,1H), 1.66-1.62 (m,2H), 1.24 (d,3H), 1.14 (t,3H).	MS (ESI, pos.ion) *m/z*: 608.7 $[M+H]^+$;
Q3	^{1}H NMR (600 MHz, DMSO-d_6): δ 9.78 (s,1H), 8.04 (d,1H), 7.96 (d,1H), 7.44-7.40 (m,2H), 7.20 (td,1H), 6.03 (s,1H), 4.84 (q,1H), 4.16 (d,1H), 4.12-4.02 (m,2H), 3.86 (d,1H), 3.81 (d,1H), 3.74-3.72 (m,1H), 3.62-3.54 (m,1H), 3.35-3.33 (m,1H), 2.93-2.73 (m,1H), 2.57-2.54 (m,1H), 2.39-2.32 (m,1H), 2.29-2.23 (m,1H), 1.89-1.82 (m,1H), 1.67-1.58 (m,1H), 1.25 (d,3H), 1.12 (t,3H).	MS (ESI, pos.ion) *m/z*: 609.2 $[M+H]^+$;
Q4	^{1}H NMR (600 MHz, DMSO-d_6): δ 9.91 (s,1H), 8.04 (d,1H), 7.94 (d,1H), 7.44-7.41 (m,2H), 7.18 (td,1H), 6.06 (s,1H), 4.85 (q,1H), 4.13-4.04 (m,3H), 3.92-3.86 (m,1H), 3.73-3.68 (m,2H), 3.64-3.61 (m,1H), 3.00 (d,1H), 2.91 (d,1H), 2.49-2.45 (m,1H), 1.24 (d,3H), 1.22 (d,3H), 1.14 (t,3H).	MS (ESI, pos.ion) *m/z*: 595.2 $[M+H]^+$;
Q5	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.12 (s,1H), 9.76 (s,1H), 8.03 (d,1H), 7.96 (d,1H), 7.40-7.36 (m,2H), 7.18 (td,2H), 6.05 (s,1H), 4.86 (q,1H), 4.15 (d,1H), 4.10-4.01 (m,2H), 3.84 (d,1H), 3.76-3.72 (m,1H), 3.61-3.56 (m,1H), 3.55-3.46 (m,1H), 2.68 (d,1H),2.46-2.41 (m,1H), 2.38-2.32 (m,3H), 2.08-1.87 (m,1H), 1.79-1.71 (m,1H), 1.24 (d,3H), 1.21 (d,3H), 1.16 (t,3H).	MS (ESI, pos.ion) *m/z*: 623.2 $[M+H]^+$;
Q6	^{1}H NMR (600 MHz, DMSO-d_6): δ 9.78 (s,1H), 7.98 (d,1H), 7.92 (d,1H), 7.46-7.41 (m,2H), 7.21-7.18 (m,1H), 6.06 (s,1H), 4.87-4.77 (m,1H), 4.33 (dd,1H), 4.11-4.04 (m,3H), 3.94-3.91 (m,1H), 3.52-3.50 (m,1H), 3.17-3.11 (m,1H), 2.80-2.73 (m,1H), 2.47-2.42 (m,1H), 1.24 (d,3H), 1.14 (t,3H).	MS (ESI, pos.ion) *m/z*: 601.2 $[M+H]^+$;
Q7	^{1}H NMR (600 MHz, DMSO-d_6): δ 12.06 (s,1H), 9.58 (s,1H), 8.01 (d,1H), 7.94 (d,1H), 7.46-7.41 (m,2H), 7.20 (td,1H), 6.08 (s,1H), 4.87 (q,1H), 4.17-4.05 (m,4H), 3.58-3.52 (m,1H), 3.03-2.93 (m,2H), 2.63-2.53 (m,1H), 2.36-2.19 (m,2H), 2.12-2.01 (m,1H), 1.95-1.88 (m,1H), 1.59-1.52 (m,1H), 1.25 (d,3H), 1.14 (t,3H).	MS (ESI, pos.ion) *m/z*: 629.2 $[M+H]^+$;
Q8	^{1}H NMR (600 MHz, DMSO-d_6): δ 12.15 (s,1H), 9.55 (s,1H), 8.01 (d,1H), 7.95 (d,1H), 7.47 (dd,1H), 7.43 (dd,1H), 7.19 (td,1H), 6.09 (s,1H), 4.86 (q,1H), 4.17-4.05 (m,4H), 3.48-3.43 (m,1H), 3.01-2.91 (m,2H), 2.59-2.52 (m,1H), 2.40-2.23 (m,2H), 2.14-1.97 (m,2H), 1.63-1.60 (m,1H), 1.26 (d,3H), 1.14 (t,3H).	MS (ESI, pos.ion) *m/z*: 629.2 $[M+H]^+$;

Step 2) (*S*)-4-(((*R*)-6-(2-chloro-4-fluorophenyl)-5-(ethoxycarbonyl)-2-(thiazol-2-yl)-3,6-dihydropyrimidin-4-yl)methyl)morpholine-3-carboxylic acid



[00153] To a flask were added anhydrous ethanol (870 g) and lithium (2.43 g, 0.35 mol) in turn. The mixture was stirred at 43 °C until the lithium was consumed entirely, and then (*S*)-4-(((*R*)-6-(2-chloro-4-fluorophenyl)-5-((((*R*)-1-ethoxy-1-oxopropan-2-yl)oxy)carbonyl)-2-(thiazol-2-yl)-3,6-dihydropyrimidin-4-yl)methyl)morpholine-3-carboxylic acid (58.1 g, 0.1 mol) was added. The reaction

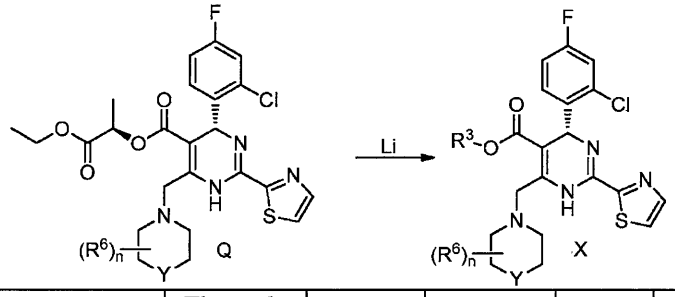
mixture was allowed to warm up to 78 °C and stirred for 12 hours. After the reaction, the mixture was cooled and concentrated. To the residue was added water (1100 g), the resulting mixture was extracted with ethyl acetate (1000 mL). The organic layer was discarded. To the aqueous layer was added ethyl acetate (1280 mL), the mixture was adjusted to pH 3-6 with concentrated hydrochloric acid. The organic layer was dried over anhydrous sodium sulfate and concentrated to give the product as a yellow solid (33.1 g, 65%).

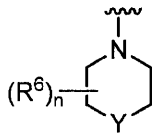
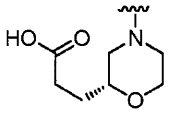
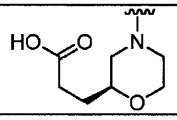
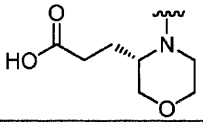
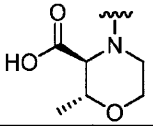
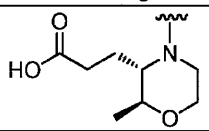
MS (ESI, pos.ion) *m/z*: 509.2 $[M+H]^+$;

^{1}H NMR (400 MHz, DMSO-d_6): δ 13.00 (br,1H), 9.95 (s,1H), 8.02 (d,1H), 7.93 (d,1H), 7.46-7.38 (m,2H), 7.17 (td,1H), 6.05 (s,1H), 4.20 (d,1H), 4.05-4.02 (m,1H), 3.97-3.91 (m,3H), 3.81 (dd,1H), 3.72-3.63 (m,2H), 3.58-3.53 (m,1H), 3.08-3.05 (m,1H), 2.42-2.38 (m,1H), 1.06 (t,3H).

[00154] The compound X can be prepared under the reaction conditions shown in table 18 according to the procedure described in step 2 of Example 10.

Table 18: The reaction conditions for preparation of compound X



No.	R^3		The mole ratio of Lithium to compound Q; the amount of compound Q	Reaction solvent	Reaction temperature (°C)	Reaction time(h)	Product character	Quality; yield(%) of product
X1	ethyl		5;6.4 g	ethanol	78	2	yellow solid	3.38 g;63
X2	ethyl		5;6.4 g	ethanol	78	2	yellow solid	3.33 g;62
X3	ethyl		5;6.4 g	ethanol	78	2	yellow solid	2.63 g;49
X4	ethyl		5;6.26 g	ethanol	78	12	yellow solid	3.77 g;72
X5	ethyl		5;6.54 g	ethanol	78	2	yellow solid	2.48 g;45

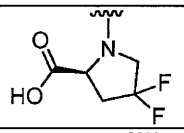
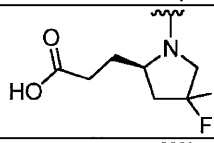
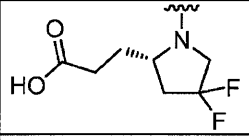
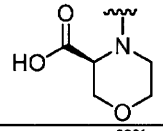
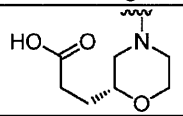
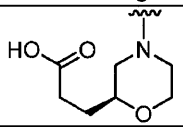
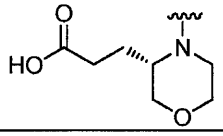
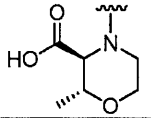
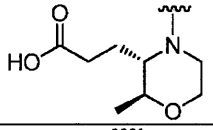
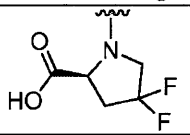
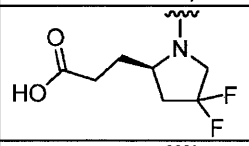
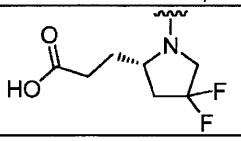
X6	ethyl		5;6.3 g	ethanol	78	12	yellow solid	3.07 g;58
X7	ethyl		5;6.6 g	ethanol	78	2	yellow solid	2.73 g;49
X8	ethyl		5;6.6 g	ethanol	78	2	yellow solid	2.9 g;52
X9	methyl		5;6.1 g	methanol	64	18	yellow solid	3.47 g;70
X10	methyl		5;6.4 g	methanol	64	6	yellow solid	3.14 g;60
X11	methyl		5;6.4 g	methanol	64	4	yellow solid	3.09 g;59
X12	methyl		5;6.4 g	methanol	64	8	yellow solid	2.41 g;46
X13	methyl		5;6.26 g	methanol	64	18	yellow solid	3.51 g;69
X14	methyl		5;6.54 g	methanol	64	5	yellow solid	2.31 g;43
X15	methyl		5;6.3g	methanol	64	12	yellow solid	2.83 g;55
X16	methyl		5;6.87 g	methanol	64	6	yellow solid	2.55 g;47
X17	methyl		5;6.87 g	methanol	64	6	yellow solid	2.66 g;49

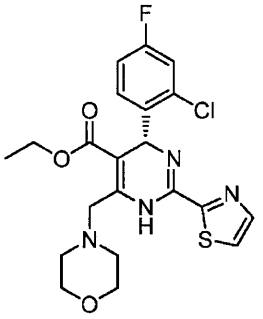
Table 18-1: The NMR and MS datum of compound X

No.	^{1}H NMR	MS
X1	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.65 (s,1H), 8.02 (d,1H), 7.94 (d,1H), 7.44-7.38 (m,2H), 7.18 (td,1H), 6.05 (s,1H), 3.96 (q,2H), 3.89-3.85 (m,3H), 3.59-3.46 (m,2H), 2.80-2.74 (m,2H), 2.36-2.21 (m,3H), 2.03-1.98 (m,1H), 1.64-1.59 (m,2H), 1.06 (t,3H).	MS (ESI, pos.ion) *m/z*: 537.3 $[M+H]^+$;
X2	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.07 (s,1H), 9.65 (s,1H), 8.02 (d,1H), 7.94 (d,1H), 7.44-7.40 (m,2H), 7.19 (td,1H), 6.06 (s,1H), 3.97 (q,2H), 3.92-3.82 (m,3H), 3.58-3.46 (m,2H), 2.88 (d,1H), 2.63 (d,1H), 2.37-2.22	MS (ESI, pos.ion) *m/z*: 536.9 $[M+H]^+$;

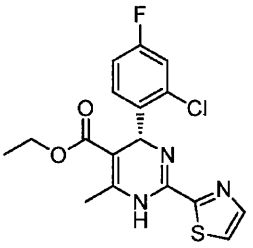
	(m,3H),2.08-1.99 (m,1H), 1.72-1.65 (m,2H), 1.05 (t,3H).	
X3	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.13 (br,1H), 9.81 (s,1H), 8.02 (d,1H), 7.94 (d,1H), 7.44-7.38 (m,2H), 7.18 (td,1H), 6.02 (s,1H), 4.20 (d,1H), 3.98 (q,2H), 3.92 (d,1H), 3.83-3.78 (m,1H), 3.75-3.72 (m,1H), 3.62-3.58 (m,1H), 3.37-3.33 (m,1H), 2.79-2.75 (m,1H), 2.58-2.53 (m,1H), 2.49-2.46 (m,1H), 2.39-2.32 (m,2H), 1.89-1.83 (m,1H), 1.66-1.58 (m,1H), 1.06 (t,3H).	MS (ESI, pos.ion) *m/z*: 537.2 $[M+H]^+$;
X4	^{1}H NMR (600 MHz, DMSO-d_6): δ 13.00 (s,1H), 9.78 (s,1H), 8.03 (d,1H), 7.93 (d,1H), 7.43-7.30 (m,2H), 7.18 (td,1H), 6.03 (s,1H), 4.06 (d,1H), 3.95 (q,2H), 3.90 (d,1H), 3.74-3.69 (m,2H), 3.65-3.60 (m,1H), 2.98 (d,1H), 2.89 (d,1H), 2.49-2.45 (m,1H), 1.21 (d,3H), 1.04 (t,3H).	MS (ESI, pos.ion) *m/z*: 523.2 $[M+H]^+$;
X5	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.12 (s,1H), 9.75 (s,1H), 8.02 (d,1H), 7.95 (d,1H), 7.42-7.36 (m,2H), 7.15 (td,1H), 6.06 (s,1H), 4.15 (d,1H), 4.02-3.91 (m,2H), 3.86 (d,1H), 3.75-3.73 (m, 1H), 3.59-3.54 (m,1H), 3.51-3.45 (m,1H), 2.66 (d,1H), 2.46-2.40 (m,1H), 2.37-2.30 (m,3H), 2.03 -1.92 (m,1H), 1.80-1.74 (m,1H), 1.20 (d,3H), 1.06 (t,3H).	MS (ESI, pos.ion) *m/z*: 551.2 $[M+H]^+$;
X6	^{1}H NMR (600 MHz, DMSO-d_6): δ 13.01 (br,1H), 9.66 (s,1H), 7.98 (d,1H), 7.91 (d,1H), 7.45-7.41 (m,2H), 7.19 (td,1H), 6.04 (s,1H), 4.33 (d,1H), 4.08 (d,1H), 4.05-4.02 (m,1H), 3.97 (q,2H), 3.92-3.89 (m,1H), 3.53-3.48 (m,1H), 3.19-3.12 (m,1H), 2.82-2.72 (m,1H), 1.05 (t, 3H).	MS (ESI, pos.ion) *m/z*: 529.1 $[M+H]^+$;
X7	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.08 (s,1H), 9.52 (s,1H), 7.99 (d,1H), 7.92 (d,1H), 7.44-7.40 (m,2H), 7.19 (td,1H), 6.03 (s,1H), 4.13 (dd,2H), 3.97 (q,2H), 3.60-3.52 (m,1H), 3.06-2.96 (m,2H), 2.59-2.56 (m,1H), 2.36-2.20 (m,2H), 2.13-1.99 (m,1H), 1.93-1.88 (m,1H), 1.57-1.44 (m,1H), 1.05 (t,3H).	MS (ESI, pos.ion) *m/z*: 556.9 $[M+H]^+$;
X8	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.16 (br,1H), 9.45 (s,1H), 8.00 (d,1H), 7.94 (d,1H), 7.47-7.41 (m,2H), 7.18 (td,1H), 6.06 (s,1H), 4.12 (dd,2H), 4.00-3.93 (m,2H), 3.46-3.38 (m,1H), 3.01-2.85 (m,2H), 2.60-2.53 (m,1H), 2.40-2.23 (m,2H), 2.15-1.99 (m,2H), 1.66-1.56 (m,1H), 1.05 (t,3H).	MS (ESI, pos.ion) *m/z*: 557.2 $[M+H]^+$;
X9	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.52 (br,1H), 9.86 (s,1H), 8.03 (d,1H), 7.94 (d,1H), 7.43-7.38 (m,2H), 7.16 (td,1H), 6.04 (s,1H), 4.24 (d,1H), 4.06-3.97 (m,2H), 3.84 (dd,1H), 3.73-3.66 (m,2H), 3.64-3.59 (m,1H), 3.51 (s,3H), 3.10-3.06 (m,1H), 2.43-2.39 (m,1H).	MS (ESI, pos.ion) *m/z*: 494.9 $[M+H]^+$;
X10	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.12 (s,1H), 9.71 (s,1H), 8.03 (d,1H), 7.96 (d,1H), 7.44-7.38 (m,2H), 7.18 (td,1H), 6.02 (s,1H), 3.94-3.82 (m,3H), 3.62-3.54 (m,2H), 3.53 (s,3H), 2.78 (dd,2H), 2.38-2.26 (m,3H), 2.06-1.99 (m,1H), 1.66-1.59 (m,2H).	MS (ESI, pos.ion) *m/z*: 522.9 $[M+H]^+$;
X11	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.09 (br,1H), 9.70 (s,1H), 8.03 (d,1H), 7.94 (d,1H), 7.44-7.38 (m,2H), 7.18 (td,1H), 6.04 (s,1H), 3.95 (d,1H), 3.86-3.81 (m,2H), 3.57-3.54 (m,1H), 3.52 (s,3H), 3.50-3.47 (m,1H), 2.87 (d,1H), 2.62 (d,1H), 2.35-2.19 (m,3H), 2.14-2.08 (m,1H), 1.73–1.61 (m,2H).	MS (ESI, pos.ion) *m/z*: 523.2 $[M+H]^+$;
X12	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.87 (s,1H), 8.03 (d,1H), 7.94 (d,1H), 7.44-7.40 (m,2H), 7.16 (td,1H), 6.02 (s,1H), 4.20 (d,1H), 3.93 (d,1H), 3.84-3.79 (m,1H), 3.75-3.71 (m,1H), 3.62-3.56 (m,1H), 3.52 (s,3H), 3.48-3.41 (m,1H), 3.05-2.87 (m,1H), 2.78-2.75 (m,1H), 2.58-2.56 (m,1H), 2.38-2.23 (m,2H), 1.87-1.84 (m,1H), 1.66-1.58 (m,1H).	MS (ESI, pos.ion) *m/z*: 523.1 $[M+H]^+$;
X13	^{1}H NMR (600 MHz, DMSO-d_6): δ 13.01 (s,1H), 9.83 (s,1H), 8.02 (d,1H), 7.93 (d,1H), 7.42-7.38 (m,2H), 7.17 (td,1H), 6.02 (s,1H), 4.07 (d,1H), 3.89 (d,1H), 3.76-3.62 (m,3H), 3.51 (s,3H), 3.47-3.43 (m,1H), 2.98 (d,1H), 2.89 (d,1H), 1.20 (d,3H).	MS (ESI, pos.ion) *m/z*: 508.7 $[M+H]^+$;
X14	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.11 (s,1H), 9.76 (s,1H), 8.02 (d,1H), 7.96 (d,1H), 7.44-7.40 (m,2H), 7.16 (td,1H), 6.01 (s,1H), 4.16 (d,1H), 3.88 (d,1H), 3.78-3.74 (m,1H), 3.60-3.55 (m,1H), 3.53 (s,3H), 3.50-3.46 (m,1H), 2.68 (d,1H), 2.48-2.42 (m,1H); 2.36-2.31 (m,3H), 2.04-1.93 (m,1H), 1.82-1.73 (m,1H), 1.21 (d,3H).	MS (ESI, pos.ion) *m/z*: 537.1 $[M+H]^+$;
X15	^{1}H NMR (600 MHz, DMSO-d_6): δ 9.70 (br,1H), 8.01 (d,1H), 7.92 (d,1H),	MS (ESI, pos.ion) *m/z*:

	7.44-7.38 (m,2H), 7.18 (td,1H), 6.01 (s,1H), 4.31 (d,1H), 4.09 (d,1H), 3.94-3.89 (m,1H), 3.53 (s,3H), 3.48-3.44 (m,1H), 3.23-3.07 (m,2H), 2.84-2.75 (m,1H).	515.1 $[M+H]^+$;
X16	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.07 (br,1H), 9.55 (s,1H), 7.99 (d,1H), 7.92 (d,1H), 7.43-7.39 (m,2H), 7.18 (td,1H), 6.03 (s,1H), 4.15 (d,1H), 4.09 (d,1H), 3.56-3.54 (m,1H), 3.53 (s,3H), 3.05-2.95 (m,2H), 2.48-2.46 (m,1H), 2.36-2.17 (m,2H), 2.15-2.02 (m,1H), 1.97-1.85 (m,1H), 1.59-1.50 (m,1H).	MS (ESI, pos.ion) *m/z*: 543.0 $[M+H]^+$;
X17	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.06 (br,1H), 9.56 (s,1H), 8.01 (d,1H), 7.94 (d,1H), 7.44-7.40 (m,2H), 7.16 (td,1H), 6.05 (s,1H), 4.13 (d,1H), 4.09 (d,1H), 3.57-3.54 (m,1H), 3.52 (s,3H), 3.06-2.96 (m,2H), 2.47-2.45 (m,1H), 2.37-2.17 (m,2H), 2.16-2.02 (m,1H), 1.98-1.85 (m,1H), 1.60-1.51 (m,1H).	MS (ESI, pos.ion) *m/z*: 543.0 $[M+H]^+$;

Example 11: the preparation of (*R*)-ethyl 4-(2-chloro-4-fluorophenyl)-6-(morpholinomethyl)-2-(thiazol-2-yl)-1,4 -dihydropyrimidine-5-carboxylate



Step 1) (*R*)-ethyl 4-(2-chloro-4-fluorophenyl)-6-methyl-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate



[00155] To a flask were added anhydrous ethanol (360 g) and lithium (2.43 g, 0.35 mol) in turn. The mixture was stirred at 43 °C until the lithium was consumed entirely, and then (*R*)-(*R*)-1-ethoxy-1-oxopropan-2-yl 4-(2-chloro-4-fluorophenyl)-6-methyl-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (45.2 g, 0.1 mol) was added. The reaction mixture was stirred at 78 °C for 6 hours. After the reaction, the reaction mixture was cooled to 10 °C, kept at 10 °C and stirred for 8 hours. The mixture was filtered. The filtrate was washed with anhydrous ethanol (45 g) and water (500 g) in turn, and then dried *in vacuo* at 60 °C for 8 hours to obtain the product as a yellow solid (23.6 g, 62%).

$[a]_D^{25} = -59.6$ (c = 0.3020 g/100 mL, MeOH);

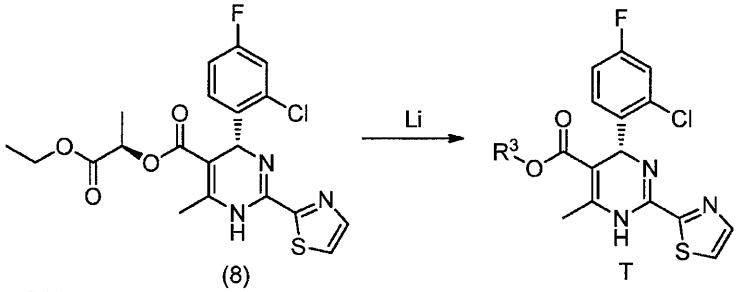
MS (ESI, pos.ion) *m/z*: 380.2 $[M+H]^+$;

^{1}H NMR (600 MHz, DMSO-d_6): δ 9.92 (s,1H), 7.97 (d,1H), 7.90 (d,1H), 7.41 (dd,1H), 7.37 (dd,1H), 7.19 (td,1H), 6.00 (s,1H), 3.93 (q,2H), 2.46 (s,3H), 1.03 (t,3H).

[00156] The compound T can be prepared under the reaction conditions shown in table 19 according to the

procedure described in step 1 of Example 11.

Table 19: The reaction conditions for preparation of compound T

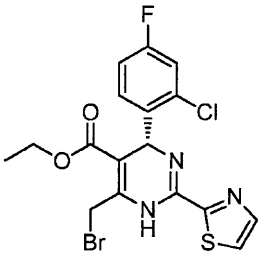


No.	R^3	The mole ratio of Lithium to compound (8); the amount of compound (8) is 49.6 g	Reaction solvent	The mass ratio of reaction solvent to compound (8)	Reaction temperature (°C)	Reaction time(h)	Product character	Quality; yield(%) of product
T1	ethyl	2.5	ethanol	10	78	12	yellow solid	15.2 g;40
T1	ethyl	3	ethanol	6	78	8	yellow solid	26.6 g;70
T1	ethyl	4	ethanol	10	78	4	yellow solid	22 g;58
T1	ethyl	5	ethanol	20	78	24	yellow solid	17.1 g;45
T1	ethyl	6	ethanol	30	78	12	yellow solid	14.1 g;37
T1	ethyl	8	ethanol	20	78	12	yellow solid	17.9 g;47
T2	methyl	3	methanol	3	64	20	yellow solid	20.9 g;57
T2	methyl	3	methanol	4	64	6	yellow solid	17.9 g;49
T2	methyl	4	methanol	6	64	8	yellow solid	11.7 g;32

Table 19-1: The NMR, MS and specific rotation datum of the compound T

No.	^{1}H NMR	MS	specific rotation
T1	^{1}H NMR (600 MHz, DMSO-d_6): δ 9.92 (s,1H), 7.97 (d,1H), 7.90 (d,1H), 7.41 (dd,1H), 7.37 (dd,1H), 7.19 (td,1H), 6.00 (s,1H), 3.93 (q,2H), 2.46 (s,3H), 1.03 (t,3H).	MS (ESI, pos.ion) *m/z*: 380.2 $[M+H]^+$;	[α]$_D^{20}$ = -59.6 (c = 0.3020 g/100 mL, MeOH);
T2	^{1}H NMR (400 MHz, DMSO-d_6): δ 7.81 (d,1H), 7.68 (d,1H), 7.36 (dd,1H), 7.29 (dd,1H), 7.11 (td,1H), 5.90 (s,1H), 3.41 (s,3H), 2.34 (s,3H).	MS (ESI, pos.ion) *m/z*: 366.1 $[M+H]^+$;	[α]$_D^{20}$ = -81.49 (c = 0.5031 g/100 mL, MeOH);

Step 2) (*R*)-ethyl 4-(2-chloro-4-fluorophenyl)-6-bromomethyl-2-(thiazol-2-yl)-1,4-dihydropyrimidine -5-carboxylate



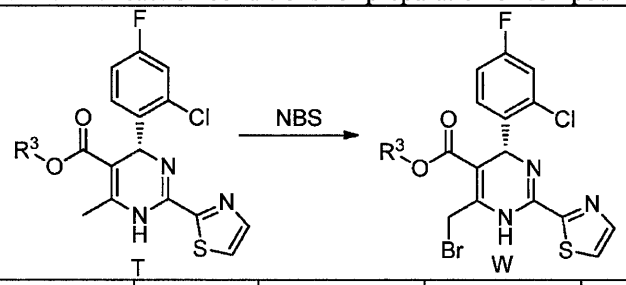
[00157] To a dry flask were added (*R*)-ethyl 4-(2-chloro-4-fluorophenyl)-6-methyl-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (38 g, 0.1 mol) and CCl_4 (760 g), followed by NBS (19.6 g, 0.11 mol) at 70 °C. The mixture was stirred for 30 min and cooled, and then filtered. The filtrate was concentrated to obtain a yellow solid (37.6 g, 82%).

MS (ESI, pos.ion) *m/z*: 457.9 $[M+H]^+$;

^1H NMR (400 MHz, DMSO-d_6): δ 9.67 (s,1H), 8.01 (d,1H), 7.97 (br,1H), 7.44-7.41 (m,2H), 7.22 (td,1H), 5.99 (s,1H), 4.83(br,2H), 4.02 (q,2H), 1.07 (t,3H).

[00158] The compound W can be prepared under the reaction conditions shown in table 20 according to the procedure described in step 2 of Example 11.

Table 20: The reaction conditions for preparation of compound W

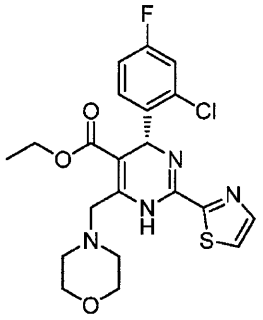


No.	R^3	The mole ratio of NBS to compound T; the amount of compound T	Reaction solvent	The mass ratio of reaction solvent to compound (W)	Reaction temperature (°C)	Product character	Quality; yield(%) of product
W1	ethyl	1.0;38 g	DCM	10	39	yellow solid	37.2 g;81
W1	ethyl	1.0;38 g	$CHCl_3$	20	61	yellow solid	35.8 g;78
W1	ethyl	1.1;38 g	CCl_4	30	76	yellow solid	38.6 g;84
W2	methyl	1.0;36.6 g	DCM	10	39	yellow solid	32 g;72
W2	methyl	1.1;36.6 g	$CHCl_3$	20	61	yellow solid	32.5 g;73
W2	methyl	1.1;36.6 g	CCl_4	30	76	yellow solid	36.5 g;82

Table 20-1: The NMR and MS datum of compound W

No.	^1H NMR	MS
W1	^1H NMR (400 MHz, DMSO-d_6): δ 9.62 (s,1H), 8.01 (d,1H), 7.92 (d,1H), 7.44-7.38 (m,2H), 7.18 (td,1H), 6.04 (s,1H), 4.94 (d,1H), 4.62 (d,1H), 4.15 (q,2H), 1.12 (t,3H).	MS (ESI, pos.ion) *m/z*: 457.9 $[M+H]^+$;
W2	^1H NMR (600 MHz, DMSO-d_6): δ 8.02 (d,1H), 7.96 (br,1H), 7.46-7.40 (m,2H), 7.22 (td,1H), 5.98 (s,1H), 4.83 (br,2H), 3.57 (s,3H).	MS (ESI, pos.ion) *m/z*: 445.6 $[M+H]^+$;

Step 3) (*R*)-ethyl 4-(2-chloro-4-fluorophenyl)-6-(morpholinomethyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine -5-carboxylate



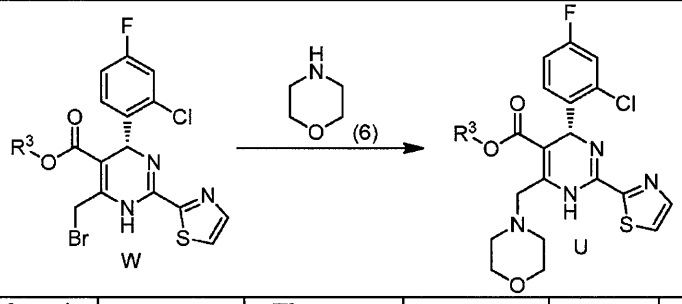
[00159] To a flask were added (*R*)-ethyl 4-(2-chloro-4-fluorophenyl)-6-(bromomethyl)-2-(thiazol-2-yl)-1,4 -dihydropyrimidine-5-carboxylate (45.9 g, 0.1 mol), anhydrous ethanol (275 g) and morpholine (34.8 g, 0.4 mol). The mixture was stirred at 25 °C under nitrogen atmosphere for 6 hours. After the reaction, the mixture was concentrated. To the residue was added ethyl acetate (500 g), the resulting mixture was washed with water (250 mL × 2). The organic layer was concentrated to give the product as tawny oil (35.8 g, 77%)

MS (ESI, pos.ion) *m/z*: 465.2 $[M+H]^+$;

^1H NMR (400 MHz, DMSO-d_6): δ 9.65 (s,1H), 8.00 (d,1H), 7.91 (d,1H),7.40-7.37 (m,2H), 7.15 (td,1H), 6.03 (s,1H), 3.94 (q,2H), 3.88 (dd,2H), 3.65 (br,4H), 2.56 (br,4H), 1.05 (t,3H).

[00160] The compound U can be prepared under the reaction conditions shown in table 21 according to the procedure described in step 3 of Example 11.

Table 21: The reaction conditions for preparation of compound U

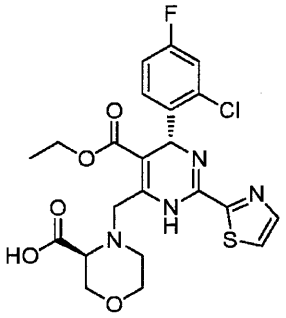


No.	R^3	The mole ratio of compound (6) to compound W; the amount of compound W	Reaction solvent	The mass ratio of reaction solvent to compound (J)	Reaction temperature (°C)	Reaction time(h)	Product character	Quality; yield(%) of product
U1	ethyl	2;45.9 g	ethanol	20	25	2	tawny oil	34 g;73
U1	ethyl	3;45.9 g	acetone	10	40	10	tawny oil	36.3 g;78
U1	ethyl	4;45.9 g	methanol	10	30	6	tawny oil	33.5 g;72
U1	ethyl	5;45.9 g	ethyl acetate	20	50	24	tawny oil	34.4 g;74
U1	ethyl	6;45.9 g	DCM	8	39	6	tawny oil	33 g;71
U1	ethyl	3;45.9 g	DMF	4	60	1	tawny oil	31.6 g;68
U1	ethyl	4;45.9 g	THF	6	50	8	tawny oil	33.5 g;72
U2	methyl	2;44.5 g	ethanol	20	25	2	tawny oil	33.8 g;75
U2	methyl	3;44.5 g	acetone	10	40	10	tawny oil	32.4 g;72
U2	methyl	4;44.5 g	methanol	10	30	6	tawny oil	34.6 g;77
U2	methyl	5;44.5 g	ethyl acetate	20	50	24	tawny oil	33.3 g;74
U2	methyl	6;44.5 g	DCM	8	39	6	tawny oil	30.2 g;67
U2	methyl	3;44.5 g	DMF	4	60	1	tawny oil	32 g;71
U2	methyl	4;44.5 g	THF	6	50	8	tawny oil	30.6 g;68

Table 21-1: The NMR and MS datum of compound U

No.	^{1}H NMR	MS
U1	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.65 (s,1H), 8.00 (d,1H), 7.91 (d,1H), 7.40-7.37 (m,2H), 7.15 (td,1H), 6.03 (s,1H), 3.94 (q,2H), 3.88 (dd,2H), 3.65 (br,4H), 2.56 (br,4H), 1.05 (t,3H).	MS (ESI, pos.ion) *m/z*: 465.2 $[M+H]^+$;
U2	^{1}H NMR (600 MHz, DMSO-d_6): δ 9.72 (s,1H), 8.03 (d,1H), 7.94 (d,1H),7.43-7.38 (m,2H), 7.17 (td,1H), 6.05 (s,1H), 3.93 (dd,2H), 3.68 (br,4H), 3.53 (s,3H), 2.56 (br,4H).	MS (ESI, pos.ion) *m/z*: 450.8 $[M+H]^+$;

Example 12: the preparation of (*S*)-4-(((*R*)-6-(2-chloro-4-fluorophenyl)-5-(ethoxycarbonyl)-2-(thiazol-2-yl)-3,6-dihydropyrimidin-4-yl)methyl)morpholine-3-carboxylic acid



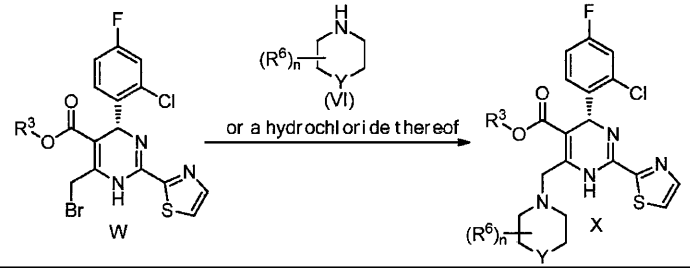
[00161] To a flask were added (*R*)-ethyl 4-(2-chloro-4-fluorophenyl)-6-(bromomethyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (4.59 g, 10 mmol), (*S*)-morpholine-3-carboxylic acid (1.31 g, 10 mmol), potassium carbonate (2.76g, 20 mmol) and ethanol (90 mL). The mixture was stirred at 30 °C under nitrogen atmosphere for 12 hours. After the reaction, the mixture was filtered. The filtrate was concentrated. To the residue was added water (100 mL), the resulting mixture was extracted with ethyl acetate (100 mL). The organic layer was discarded. To the aqueous layer was added ethyl acetate (100 mL), and the mixture was adjusted to pH 3-6 with concentrated hydrochloric acid. The organic layer was dried over anhydrous sodium sulfate and concentrated to give the product as a yellow solid (3.96 g, 78%).

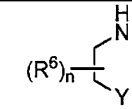
MS (ESI, pos.ion) *m/z*: 509.2 $[M+H]^+$;

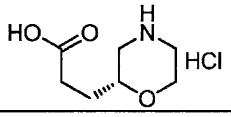
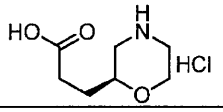
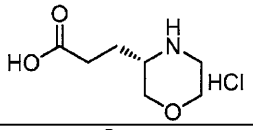
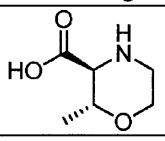
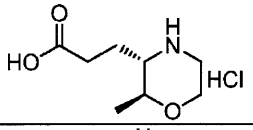
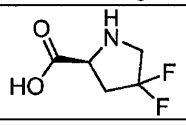
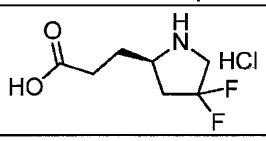
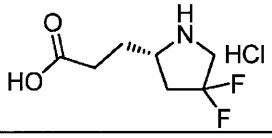
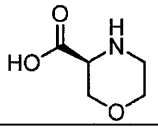
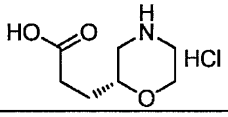
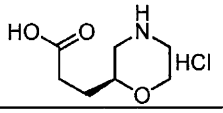
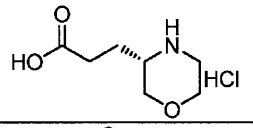
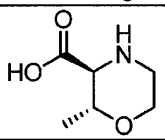
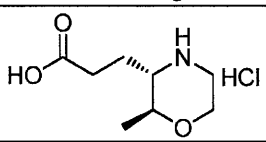
^{1}H NMR (400 MHz, DMSO-d_6): δ 13.00 (br,1H), 9.95 (s,1H), 8.02 (d,1H), 7.93 (d,1H), 7.46-7.38 (m,2H), 7.17 (td,1H), 6.05 (s,1H), 4.20 (d,1H), 4.05-4.02 (m,1H), 3.97-3.91 (m,3H), 3.81 (dd,1H), 3.72-3.63 (m,2H), 3.58-3.53 (m,1H), 3.08-3.05 (m,1H), 2.42-2.38 (m,1H), 1.06 (t,3H).

[00162] The compound X can be prepared under the reaction conditions shown in table 22 according to the procedure described Example 12.

Table 22: The reaction conditions for preparation of compound X



No.	R^3	 or a hydrochloride thereof	The mole ratio of compound W to compound	Reaction solvent	The mass ratio of reaction solvent to compound	Reaction temperature (°C)	Reaction time(h)	Product character	Quality; yield(%) of product

			(VI); the amount of compound W		(W)				
X1	ethyl		1;4.59 g	ethanol	20	30	4	yellow solid	3.65 g; 68
X2	ethyl		1;4.59 g	ethanol	15	30	6	yellow solid	3.6 g; 67
X3	ethyl		1;4.59 g	ethanol	10	30	12	yellow solid	2.31 g; 43
X4	ethyl		1;4.59 g	ethanol	4	30	24	yellow solid	4.1 g;78
X5	ethyl		1;4.59 g	ethanol	12	30	16	yellow solid	2.76 g; 50
X6	ethyl		1;4.59 g	ethanol	20	30	24	yellow solid	3.97 g; 75
X7	ethyl		1;4.59 g	ethanol	10	30	12	yellow solid	3.45 g; 62
X8	ethyl		1;4.59 g	ethanol	15	30	18	yellow solid	3.4 g; 61
X9	methyl		1;4.45 g	ethanol	6	30	24	yellow solid	3.47 g; 70
X10	methyl		1;4.45 g	ethanol	10	30	12	yellow solid	3.45 g; 66
X11	methyl		1;4.45 g	ethanol	20	30	16	yellow solid	3.29 g;63
X12	methyl		1;4.45 g	ethanol	15	30	20	yellow solid	2.2 g; 42
X13	methyl		1;4.45 g	ethanol	30	30	2	yellow solid	3.82 g; 75
X14	methyl		1;4.45 g	ethanol	8	30	10	yellow solid	2.47 g; 46

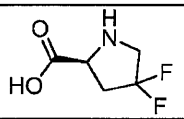
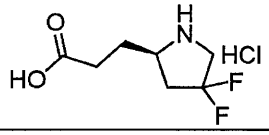
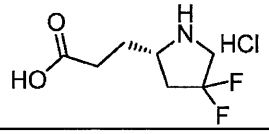
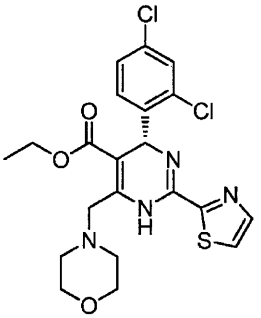
X15	methyl		1;4.45 g	ethanol	15	30	16	yellow solid	3.71 g; 72
X16	methyl		1;4.45 g	ethanol	10	30	8	yellow solid	3.2 g; 59
X17	methyl		1;4.45 g	ethanol	20	30	8	yellow solid	3.15 g; 58

Table 22-1: The NMR and MS datum of compound X

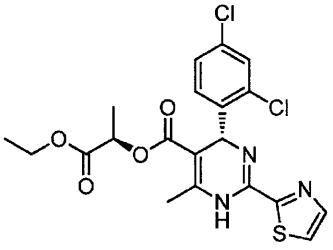
No.	^{1}H NMR	MS
X1	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.65 (s,1H), 8.02 (d,1H), 7.94 (d,1H), 7.44-7.38 (m,2H), 7.18 (td,1H), 6.05 (s,1H), 3.96 (q,2H), 3.89-3.85 (m,3H), 3.59-3.46 (m,2H), 2.80-2.74 (m,2H), 2.36-2.21 (m,3H), 2.03-1.98 (m,1H), 1.64-1.59 (m,2H), 1.06 (t,3H).	MS (ESI, pos.ion) *m/z*: 537.3 $[M+H]^+$;
X2	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.07 (s,1H), 9.65 (s,1H), 8.02 (d,1H), 7.94 (d,1H), 7.44-7.40 (m,2H), 7.19 (td,1H), 6.06 (s,1H), 3.97 (q,2H), 3.92-3.82 (m,3H), 3.58-3.46 (m,2H), 2.88 (d,1H), 2.63 (d,1H), 2.37-2.22 (m,3H),2.08-1.99 (m,1H), 1.72-1.65 (m,2H), 1.05 (t,3H).	MS (ESI, pos.ion) *m/z*: 536.9 $[M+H]^+$;
X3	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.13 (br,1H), 9.81 (s,1H), 8.02 (d,1H), 7.94 (d,1H), 7.44-7.38 (m,2H), 7.18 (td,1H), 6.02 (s,1H), 4.20 (d,1H), 3.98 (q,2H), 3.92 (d,1H), 3.83-3.78 (m,1H), 3.75-3.72 (m,1H), 3.62-3.58 (m,1H), 3.37-3.33 (m,1H), 2.79-2.75 (m,1H), 2.58-2.53 (m,1H), 2.49-2.46 (m,1H), 2.39-2.32 (m,2H), 1.89-1.83 (m,1H), 1.66-1.58 (m,1H), 1.06 (t,3H).	MS (ESI, pos.ion) *m/z*: 537.2 $[M+H]^+$;
X4	^{1}H NMR (600 MHz, DMSO-d_6): δ 13.00 (s,1H), 9.78 (s,1H), 8.03 (d,1H), 7.93 (d,1H), 7.43-7.30 (m,2H), 7.18 (td,1H), 6.03 (s,1H), 4.06 (d,1H), 3.95 (q,2H), 3.90 (d,1H), 3.74-3.69 (m,2H), 3.65-3.60 (m,1H), 2.98 (d,1H), 2.89 (d,1H), 2.49-2.45 (m,1H), 1.21 (d,3H), 1.04 (t,3H).	MS (ESI, pos.ion) *m/z*: 523.2 $[M+H]^+$;
X5	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.12 (s,1H), 9.75 (s,1H), 8.02 (d,1H), 7.95 (d,1H), 7.42-7.36 (m,2H), 7.15 (td,1H), 6.06 (s,1H), 4.15 (d,1H), 4.02-3.91 (m,2H), 3.86 (d,1H), 3.75-3.73 (m,1H), 3.59-3.54 (m,1H), 3.51-3.45 (m,1H), 2.66 (d,1H), 2.46-2.40 (m,1H), 2.37-2.30 (m,3H), 2.03 -1.92 (m,1H), 1.80-1.74 (m,1H), 1.20 (d,3H), 1.06 (t,3H).	MS (ESI, pos.ion) *m/z*: 551.2 $[M+H]^+$;
X6	^{1}H NMR (600 MHz, DMSO-d_6): δ 13.01 (br,1H), 9.66 (s,1H), 7.98 (d,1H), 7.91 (d,1H), 7.45-7.41 (m,2H), 7.19 (td,1H), 6.04 (s,1H), 4.33 (d,1H), 4.08 (d,1H), 4.05-4.02 (m,1H), 3.97 (q,2H), 3.92-3.89 (m,1H), 3.53-3.48 (m,1H), 3.19-3.12 (m,1H), 2.82-2.72 (m,1H), 1.05 (t,3H).	MS (ESI, pos.ion) *m/z*: 529.1 $[M+H]^+$;
X7	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.08 (s,1H), 9.52 (s,1H), 7.99 (d,1H), 7.92 (d,1H), 7.44-7.40 (m,2H), 7.19 (td,1H), 6.03 (s,1H), 4.13 (dd,2H), 3.97 (q,2H), 3.60-3.52 (m,1H), 3.06-2.96 (m,2H), 2.59-2.56 (m,1H), 2.36-2.20 (m,2H), 2.13-1.99 (m,1H), 1.93-1.88 (m,1H), 1.57-1.44 (m,1H), 1.05 (t,3H).	MS (ESI, pos.ion) *m/z*: 556.9 $[M+H]^+$;
X8	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.16 (br,1H), 9.45 (s,1H), 8.00 (d,1H), 7.94 (d,1H), 7.47-7.41 (m,2H), 7.18 (td,1H), 6.06 (s,1H), 4.12 (dd,2H), 4.00-3.93 (m,2H), 3.46-3.38 (m,1H), 3.01-2.85 (m,2H), 2.60-2.53 (m,1H), 2.40-2.23 (m,2H), 2.15-1.99 (m,2H), 1.66-1.56 (m,1H), 1.05 (t,3H).	MS (ESI, pos.ion) *m/z*: 557.2 $[M+H]^+$;
X9	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.52 (br,1H), 9.86 (s,1H), 8.03 (d,1H), 7.94 (d,1H), 7.43-7.38 (m,2H), 7.16 (td,1H), 6.04 (s,1H), 4.24 (d,1H), 4.06-3.97 (m,2H), 3.84 (dd,1H), 3.73-3.66 (m,2H), 3.64-3.59 (m,1H), 3.51 (s,3H), 3.10-3.06 (m,1H), 2.43-2.39 (m,1H).	MS (ESI, pos.ion) *m/z*: 494.9 $[M+H]^+$;
X10	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.12 (s,1H), 9.71 (s,1H), 8.03 (d,1H), 7.96 (d,1H), 7.44-7.38 (m,2H), 7.18 (td,1H), 6.02 (s,1H), 3.94-3.82 (m,3H), 3.62-3.54 (m,2H), 3.53 (s,3H), 2.78 (dd,2H), 2.38-2.26 (m,3H), 2.06-1.99 (m,1H), 1.66-1.59 (m,2H).	MS (ESI, pos.ion) *m/z*: 522.9 $[M+H]^+$;
X11	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.09 (br,1H), 9.70 (s,1H), 8.03 (d,1H), 7.94 (d,1H), 7.44-7.38 (m,2H), 7.18 (td,1H), 6.04 (s,1H), 3.95 (d,1H), 3.86-3.81	MS (ESI, pos.ion) *m/z*: 523.2

	(m,2H), 3.57-3.54 (m,1H), 3.52 (s,3H), 3.50-3.47 (m,1H), 2.87 (d,1H), 2.62 (d,1H), 2.35-2.19 (m,3H), 2.14-2.08 (m,1H), 1.73–1.61 (m,2H).	$[M+H]^+$;
X12	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.87 (s,1H), 8.03 (d,1H), 7.94 (d,1H), 7.44-7.40 (m,2H), 7.16 (td,1H), 6.02 (s,1H), 4.20 (d,1H), 3.93 (d,1H), 3.84-3.79 (m,1H), 3.75-3.71 (m,1H), 3.62-3.56 (m,1H), 3.52 (s,3H), 3.48-3.41 (m,1H), 3.05-2.87 (m,1H), 2.78-2.75 (m,1H), 2.58-2.56 (m,1H), 2.38-2.23 (m,2H), 1.87-1.84 (m,1H), 1.66-1.58 (m,1H).	MS (ESI, pos.ion) *m/z*: 523.1 $[M+H]^+$;
X13	^{1}H NMR (600 MHz, DMSO-d_6): δ 13.01 (s,1H), 9.83 (s,1H), 8.02 (d,1H), 7.93 (d,1H), 7.42-7.38 (m,2H), 7.17 (td,1H), 6.02 (s,1H), 4.07 (d,1H), 3.89 (d,1H), 3.76-3.62 (m,3H), 3.51 (s,3H), 3.47-3.43 (m,1H), 2.98 (d,1H), 2.89 (d,1H), 1.20 (d,3H).	MS (ESI, pos.ion) *m/z*: 508.7 $[M+H]^+$;
X14	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.11 (s,1H), 9.76 (s,1H), 8.02 (d,1H), 7.96 (d,1H), 7.44-7.40 (m,2H), 7.16 (td,1H), 6.01 (s,1H), 4.16 (d,1H), 3.88 (d,1H), 3.78-3.74 (m,1H), 3.60-3.55 (m,1H), 3.53 (s,3H), 3.50-3.46 (m,1H), 2.68 (d,1H), 2.48-2.42 (m,1H), 2.36-2.31 (m,3H), 2.04 -1.93 (m,1H), 1.82-1.73 (m,1H), 1.21 (d,3H).	MS (ESI, pos.ion) *m/z*: 537.1 $[M+H]^+$;
X15	^{1}H NMR (600 MHz, DMSO-d_6): δ 9.70 (br,1H), 8.01 (d,1H), 7.92 (d,1H), 7.44-7.38 (m,2H), 7.18 (td,1H), 6.01 (s,1H), 4.31 (d,1H), 4.09 (d,1H), 3.94-3.89 (m,1H), 3.53 (s,3H), 3.48-3.44 (m,1H), 3.23-3.07 (m,2H), 2.84-2.75 (m,1H).	MS (ESI, pos.ion) *m/z*: 515.1 $[M+H]^+$;
X16	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.07 (br,1H), 9.55 (s,1H), 7.99 (d,1H), 7.92 (d,1H), 7.43-7.39 (m,2H), 7.18 (td,1H), 6.03 (s,1H), 4.15 (d,1H), 4.09 (d,1H), 3.56-3.54 (m,1H), 3.53 (s,3H), 3.05-2.95 (m,2H), 2.48-2.46 (m,1H), 2.36-2.17 (m,2H), 2.15-2.02 (m,1H), 1.97-1.85 (m,1H), 1.59-1.50 (m,1H).	MS (ESI, pos.ion) *m/z*: 543.0 $[M+H]^+$;
X17	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.06 (br,1H), 9.56 (s,1H), 8.01 (d,1H), 7.94 (d,1H), 7.44-7.40 (m,2H), 7.16 (td,1H), 6.05 (s,1H), 4.13 (d,1H), 4.09 (d,1H), 3.57-3.54 (m,1H), 3.52 (s,3H), 3.06-2.96 (m,2H), 2.47-2.45 (m,1H), 2.37-2.17 (m,2H), 2.16-2.02 (m,1H), 1.98-1.85 (m,1H), 1.60-1.51 (m,1H).	MS (ESI, pos.ion) *m/z*: 543.0 $[M+H]^+$;

Example 13: the preparation of (*R*)-ethyl 4-(2,4-dichlorophenyl)-6-(morpholinomethyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate



Step 1) (*R*)-(*R*)-1-ethoxy-1-oxopropan-2-yl 4-(2,4-dichlorophenyl)-6-methyl-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate



Method one:

[00163] To a flask were added 2-thiazolecarboxamidine hydrochloride (16.4 g, 0.1 mol), 2,4-dichlorobenzaldehyde (17.5 g, 0.1 mol), (*R*)-1-ethoxy-1-oxopropan-2-yl 3-oxobutanoate (20.2 g, 0.1 mol),

anhydrous sodium acetate (8.2 g, 0.1 mol) and ethanol (107 g) in turn. The mixture was stirred at 78 °C for 16 hours. After the reaction, the mixture was cooled to 30 °C, kept at 30 °C and stirred for 6 hours. The resulting mixture was filtered. The filter cake was washed with water (330 mL) and dried *in vacuo* at 60 °C for 8 hours to obtain the crude product. To the crude product was added *n*-propanol (82 g). The mixture was heated until dissolved completely, cooled to 30 °C, and then kept at 30 °C, stirred and crystallized for 5 hours. The resulting mixture was filtered. The filter cake was dried *in vacuo* at 60 °C for 8 hours to obtain the product as a yellow solid (12.1 g, 25.9%).

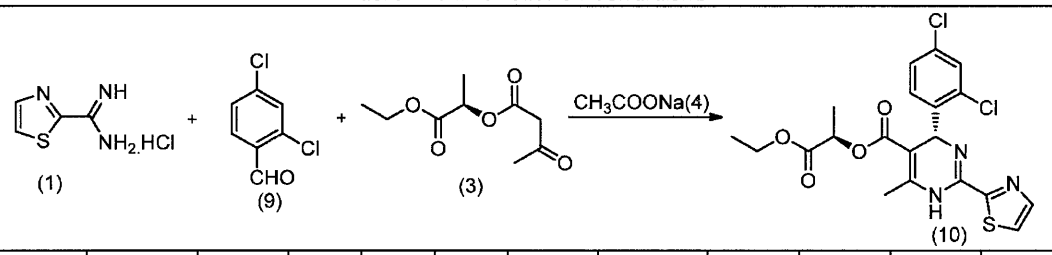
$[\alpha]_D^{25}$ = −74.42 (c = 0.3037 g/100 mL, MeOH);

MS (ESI, pos.ion) *m/z*: 467.7 $[M+H]^+$;

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.07 (s,1H), 7.98 (d,1H), 7.91 (d,1H), 7.59 (d,1H), 7.41 (dd,1H), 7.36 (d, H), 6.03 (s,1H), 4.83 (q,1H), 4.12-4.03 (m,2H), 2.47 (s,3H), 1.22 (d,3H), 1.13 (t,3H).

[00164] The compound 10 can be prepared under the reaction conditions shown in table 23 by using method one described in step 1 of Example 13.

Table 23: The reaction conditions



No.	(1):(9):(3):(4) (mol); the amount of compound (1) is 16.4 g	Reaction solvent	The mass ratio of reaction solvent to compound (1)	Reaction temperature (°C)	Reaction time(h)	Cooling temperature (°C)	Cooling time(h)	Recrystallization solvent	The mass ratio of recrystallization solvent to compound (1)	Crystallization temperature(°C)	Crystallization time(h)	Quality; yield(%) of product
1	1:1:2:1	—	—	78	12	40	6	ethanol	20	5	6	9.8 g;20.9
2	1:1:1:1	ethanol	1	78	12	40	6	ethanol	15	15	8	10.6 g;22.6
3	1:1:1:1	ethanol	4.5	25	72	25	—	ethanol	5	0	6	9.3 g;19.8
4	1:1:1:1	ethanol	20	60	24	-10	12	ethanol	6	25	4	11.1 g;23.7
5	1:1:1:1	ethanol	80	78	12	-40	24	ethanol	6	25	6	10.7 g;22.8
6	1:1:1:1	DMF	4.5	154	1	-20	6	*i*-propanol	6	20	4	7.3 g;15.7
7	1:1:1:1	*n*-butanol	4.5	100	2	-5	10	*n*-butanol	4.5	25	4	9.1 g;19.4
8	1:1:1:1	*n*-propanol	4.5	80	12	30	6	*n*-propanol	4	40	10	12.8 g;27.4
9	1:1:1:1	*i*-propanol	4.5	82	12	25	1	*i*-propanol	5	25	1	13.2 g;28.3
10	1:1:1:1	*t*-butanol	5	82	12	30	6	*t*-butanol	5	25	6	13.3 g;28.5

Method two

[00165] To a flask were added 2-thiazolecarboxamidine hydrochloride (16.4 g, 0.1 mol), 2,4-dichlorobenzaldehyde (17.5 g, 0.1 mol), (*R*)-1-ethoxy-1-oxopropan-2-yl 3-oxobutanoate (20.2 g, 0.1 mol),

anhydrous sodium acetate (8.2 g, 0.1 mol) and ethanol (107 g) in turn. The mixture was stirred at 78 °C for 16 hours. After the reaction, the reaction mixture was cooled to 30 °C, kept at 30 °C and stirred for 3 hours. The mixture was filtered. The filtrate was washed with ethanol (50 g) and water (330 mL) in turn, and then dried *in vacuo* at 60 °C for 8 hours to obtain the product as a yellow solid (14.4 g, 30.8%).

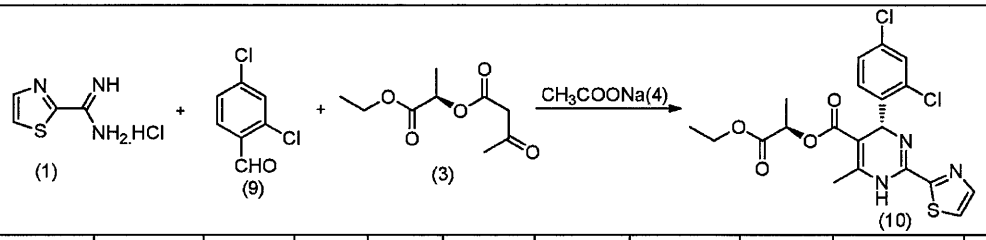
$[a]_D^{25}$ = −74.42 (c = 0.3037 g/100 mL, MeOH);

MS (ESI, pos.ion) *m/z*: 467.7 $[M+H]^+$;

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.07 (s,1H), 7.98 (d,1H), 7.91 (d,1H), 7.59 (d,1H), 7.41 (dd,1H), 7.36 (d,1H), 6.03 (s,1H), 4.83 (q,1H), 4.12-4.03 (m,2H), 2.47 (s,3H), 1.22 (d,3H), 1.13 (t,3H).

[00166] The compound 10 can be prepared under the reaction conditions shown in table 24 by using method two described in step 1 of Example 13.

Table 24: The reaction conditions



No.	(1):(9):(3):(4):(mol); the amount of compound (1) is 16.4 g	Reaction solvent	The mass ratio of reaction solvent to compound (1)	Reaction temperature (°C)	Reaction time(h)	Cooling temperature(°C)	Cooling time(h)	Washing solvent	The mass ratio of washing solvent to compound (1)	Washing temperature (°C)	Quality; yield(%) of product
1	1:1:2:1	—	—	78	12	40	6	ethanol	10	25	10.9 g; 23.3
2	1:1:1:1	ethanol	1	78	12	40	6	ethanol	8	25	11.6 g; 24.7
3	1:1:1:1	ethanol	5	25	72	25	—	ethanol	1	25	10.2 g; 21.8
4	1:1:1:1	ethanol	9	78	12	25	4	—	—	—	12.4 g; 26.6
5	1:1:1:1	ethanol	20	60	24	-10	6	ethanol	3.5	25	11.7 g; 24.9
6	1:1:1:1	ethanol	80	78	12	-30	24	ethanol	5	25	11.6 g; 24.7
7	1:1:1:1	DMF	4.5	154	1	-20	6	*i*-propanol	3	0	7.9 g; 16.9
8	1:1:1:1	*n*-butanol	4.5	100	2	-5	7	*n*-butanol	3.5	25	10 g; 21.4
9	1:1:1:1	*n*-propanol	4.5	80	12	30	6	*n*-propanol	3	25	13.9 g; 29.6
10	1:1:1:1	*i*-propanol	4.5	82	12	25	1	*i*-propanol	2	30	14.3 g; 30.5
11	1:1:1:1	*t*-butanol	5	82	12	30	6	*t*-butanol	3.5	25	13.9 g; 29.8

Method three:

[00167] To a flask were added 2-thiazolecarboxamidine hydrochloride (16.4 g, 0.1 mol), 2,4-dichlorobenzaldehyde (17.5 g, 0.1 mol), (*R*)-1-ethoxy-1-oxopropan-2-yl 3-oxobutanoate (20.2 g, 0.1 mol), anhydrous sodium acetate (8.2 g, 0.1 mol) and ethanol (107 g) in turn. The mixture was stirred at 78 °C for 16 hours. After the reaction, the mixture was cooled to 30 °C, kept at 30 °C and stirred for 3 hours. The resulting mixture was filtered. The filter cake was washed with water (330 mL) and dried *in vacuo* at 60 °C for 8 hours to obtain the crude product. The crude product was triturated with *i*-propanol (82 g) at 30 °C for 5 hours and filtered. The filter cake was dried *in vacuo* at 60 °C for 8 hours to obtain the product as a yellow solid (12.9 g, 27.5%).

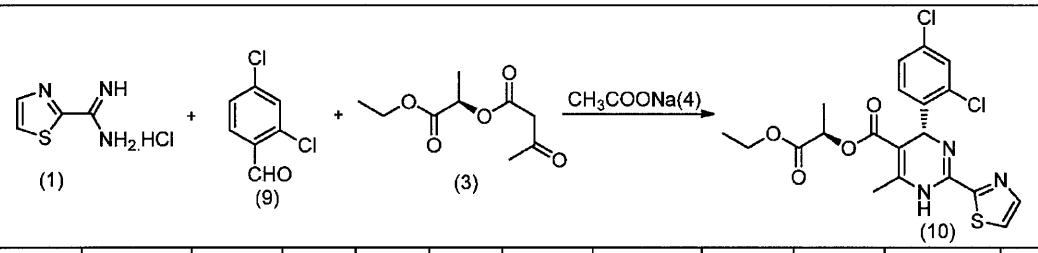
$[a]_D^{25}$ = -74.42 (c = 0.3037 g/100 mL, MeOH);

MS (ESI, pos.ion) *m/z*: 467.7 $[M+H]^+$;

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.07 (s,1H), 7.98 (d,1H), 7.91 (d,1H), 7.59 (d,1H), 7.41 (dd,1H), 7.36 (d,1H), 6.03 (s,1H), 4.83 (q,1H), 4.12-4.03 (m,2H), 2.47 (s,3H), 1.22 (d,3H), 1.13 (t,3H).

[00168] The compound 10 can be prepared under the reaction conditions shown in table 25 by using method three described in step 1 of Example 13.

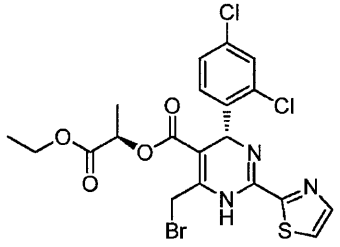
Table 25: The reaction conditions



No.	(1):(9):(3):(4) (mol); the amount of compound (1) is 16.4 g	Reaction solvent	The mass ratio of reaction solvent to compound (1)	Reaction temperature (°C)	Reaction time(h)	Cooling temperature (°C)	Cooling time(h)	Trituration solvent	The mass ratio of trituration solvent to compound (1)	Trituration temperature (°C)	Trituration time(h)	Quality; yield(%) of product
1	1:1:2:1	—	—	78	12	40	6	ethanol	12	25	10	10.5 g; 22.4
2	1:1:1:1	ethanol	1	78	12	40	6	ethanol	8	25	4	11 g; 23.5
3	1:1:1:1	ethanol	5	25	72	25	—	ethanol	3	40	3	9.8 g; 20.9
4	1:1:1:1	ethanol	20	60	24	-10	12	ethanol	5	25	2	11.4 g; 24.3
5	1:1:1:1	ethanol	80	78	12	-40	24	ethanol	4	25	3	10.7 g; 22.9
6	1:1:1:1	DMF	4.5	154	1	-20	6	*i*-propanol	4.5	25	2	7.6 g; 16.3
7	1:1:1:1	*n*-butanol	4.5	100	2	-5	10	*n*-butanol	4	25	3	9.6 g; 20.6
8	1:1:1:1	*n*-propanol	4.5	80	12	30	6	*n*-propanol	5	0	2	13.3 g; 28.5

9	1:1:1:1	*i*-propanol	4.5	82	12	25	1	*i*-propanol	6	5	4	13.7 g; 29.2
10	1:1:1:1	*t*-butanol	5	82	12	30	6	*t*-butanol	4	25	4	13.6 g; 29.1

Step 2) (*R*)-(*R*)-1-ethoxy-1-oxopropan-2-yl 4-(2,4-dichlorophenyl)-6-bromomethyl-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate



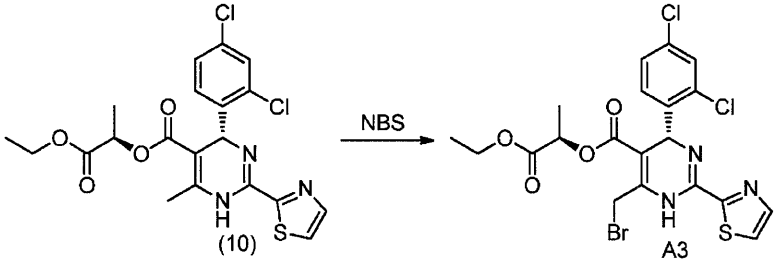
[00169] To a flask were added (*R*)-(*R*)-1-ethoxy-1-oxopropan-2-yl 4-(2,4-dichlorophenyl)-6-methyl-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (46.8 g, 0.1 mol) and tetrachloromethane (936 g). The mixture was heated at 76 °C, NBS was added (19.6 g, 0.11 mol), and then the reaction mixture was stirred for 30 min. After the reaction, the reaction mixture was cooled and concentrated. To the residue was added ethanol (234 g). The resulting mixture was cooled to 0 °C, kept at 0 °C and stirred. After solid was precipitated out completely, the mixture was filtered. The filter cake was washed with ethanol (47 g) and dried *in vacuo* at 60 °C for 6 hours to obtain the product as a yellow solid (30.1 g, 55%).

MS (ESI, pos.ion) *m/z*: 548.0 $[M+H]^+$;

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.81 (s,1H), 8.01 (d,1H), 7.96 (d,1H), 7.59 (br,2H), 7.39 (br,2H), 6.01 (s,1H), 4.96 (q,1H), 4.88-4.79 (m,2H), 4.14-4.03 (m,2H), 1.26 (d,3H), 1.12 (t,3H).

[00170] The compound A3 can be prepared under the reaction conditions shown in table 26 according to the procedure described in step 2 of Example 13

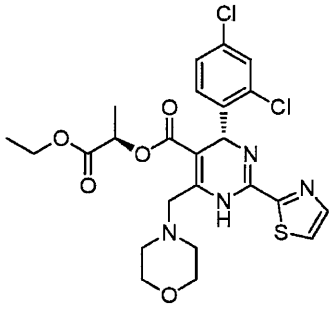
Table 26: The reaction conditions



No.	Compound (10)/NBS(mol) the amount of compound (10) is 46.8 g	Reaction solvent	The mass ratio of reaction solvent to compound (10)	Reaction temperature (°C)	The solvent added to the residue	The mass ratio of the additional solvent to compound (10)	Quality; yield(%) of product
1	1/1.1	DCM	30	39	*i*-propanol	7	28.9 g;53
2	1/1.05	DCM	10	39	ethanol	5	31.2 g;57
3	1/1.15	$CHCl_3$	20	61	*n*-propanol	6	30.6 g;56
4	1/1.1	CCl_4	20	76	ethanol	5	32.3 g;59

Step 3) (*R*)-(*R*)-1-ethoxy-1-oxopropan-2-yl 4-(2,4-dichlorophenyl)-6-(morpholinomethyl)-2-(thiazol-2-yl)-1,4-

dihydropyrimidine-5-carboxylate

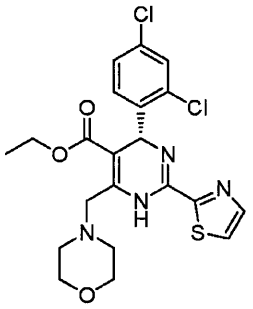


[00171] To a flask were added (*R*)-(*R*)-1-ethoxy-1-oxopropan-2-yl 4-(2,4-dichlorophenyl)-6-(bromomethyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (54.7 g, 0.1 mol), *i*-propanol (273 g) and morpholine (34.8 g, 0.4 mol). The mixture was stirred at 55 °C for 4 hours. After the reaction, the mixture was cooled to 0 °C, kept at this temperature and stirred. After the solid precipitated out completely, the mixture was filtered. The filter cake was washed with *i*-propanol (55 g) followed by water (550 g), and then dried *in vacuo* at 60 °C for 8 hours to obtain the product as a yellowish solid (33.7 g, 61%).

MS (ESI, pos.ion) *m/z*: 553.1 $[M+H]^+$;

^{1}H NMR (600 MHz, DMSO-d_6): δ 9.87 (s,1H), 8.01 (d,1H), 7.96 (d,1H), 7.59 (br,1H), 7.38 (br,2H), 6.05 (s,1H), 4.86 (q,1H), 4.14-4.06 (m,2H), 3.92 (dd,2H), 3.67 (br,4H), 2.56 (br,4H), 1.24 (d,3H), 1.13 (t,3H).

Step 4) (*R*)-ethyl 4-(2,4-dichlorophenyl)-6-(morpholinomethyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine -5-carboxylate



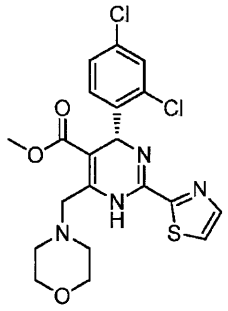
[00172] To a flask were added anhydrous ethanol (415 g) and lithium (1.74 g, 0.25 mol) in turn. The mixture was stirred at 43 °C until the lithium was consumed entirely, and then a solution of (*R*)-(*R*)-1-ethoxy-1-oxopropan-2-yl 4-(2,4-dichlorophenyl)-6-(morphplinomethyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (55.3 g, 0.1 mol) in ethanol (415 g) was added. The reaction mixture was stirred at 78 °C for 1.5 hours. After the reaction, the reaction mixture was cooled and concentrated. To the residue was added ethyl acetate (540 g). The mixture was washed with water (250 g × 2). The organic layer was concentrated to obtain the product as yellow thick oil (34.6 g, 72%).

MS (ESI, pos.ion) *m/z*: 480.7 $[M+H]^+$;

^{1}H NMR (600 MHz, DMSO-d_6): δ 9.69 (s,1H), 8.03 (d,1H), 7.94 (d,1H), 7.60 (s,1H), 7.39 (s,2H), 6.06 (s,1H), 3.97 (q,2H), 3.92 (dd,2H), 3.67 (br,4H), 2.56 (br,4H), 1.06 (t,3H).

Example 14: the preparation of (*R*)-methyl 4-(2,4-dichlorophenyl)-6-(morpholinomethyl)-2-(thiazol-2-yl)-1,4

-dihydropyrimidine-5-carboxylate

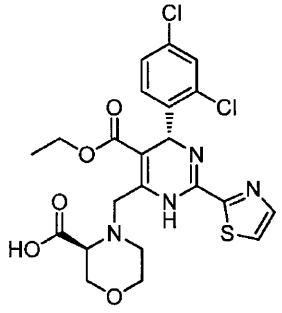


[00173] To a flask were added anhydrous methanol (830 g) and lithium (1.74 g, 0.25 mol) in turn. The mixture was stirred at 43 °C until the lithium was consumed entirely, and then (*R*)-(*R*)-1-ethoxy-1-oxopropan-2-yl 4-(2,4-dichlorophenyl)-6-(morphplinomethyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (55.3 g, 0.1 mol) was added. The reaction mixture was stirred at 60 °C for 1.5 hours. After the reaction, the reaction mixture was cooled and concentrated. To the residue was added ethyl acetate (550 g). The mixture was washed with water (250 g × 2). The combined organic layers were concentrated to obtain the product as yellow thick oil (32.2 g, 69%).

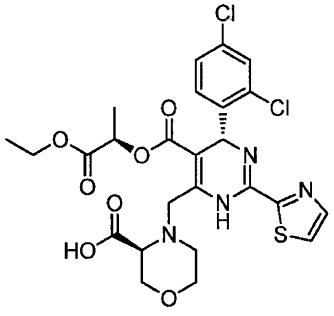
MS (ESI, pos.ion) *m/z*: 467.1 $[M+H]^+$;

^1H NMR (400 MHz, $CDCl_3$): δ 9.73 (s,1H), 7.87 (d,1H), 7.47 (d,1H), 7.42 (d,1H), 7.24 (d,1H), 7.18 (dd,1H), 6.21 (s,1H), 4.02 (d,1H), 3.89 (d,1H), 3.85 (t,4H), 3.62 (s,3H), 2.65 (t,4H).

Example 15: the preparation of (*S*)-4-(((*R*)-6-(2,4-dichlorophenyl)-5-(ethoxycarbonyl)-2-(thiazol-2-yl)-3,6-dihydropyrimidin-4-yl)methyl)morpholine-3-carboxylic acid



Step 1) (*S*)-4-(((*R*)-6-(2,4-dichlorophenyl)-5-((((*R*)-1-ethoxy-1-oxopropan-2-yl)oxy)carbonyl)-2-(thiazol-2-yl)-3,6-dihydropyrimidin-4-yl)methyl)morpholine-3-carboxylic acid



[00174] To a flask were added (*R*)-(*R*)-1-ethoxy-1-oxopropan-2-yl 4-(2,4-dichlorophenyl)-6-(bromomethyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (54.7 g, 0.1 mol), ethanol (820 g),

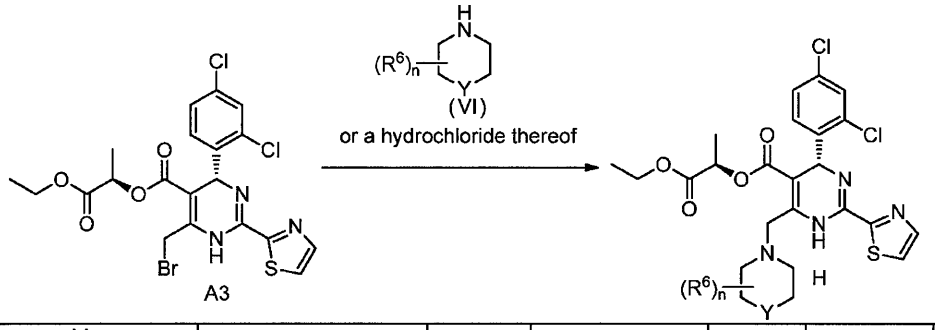
(*S*)-morpholine-3-carboxylic acid (13.1 g, 0.1 mol) and potassium carbonate (27.6 g, 0.2 mol) in turn. The mixture was stirred at 30 °C for 12 hours. After the reaction, the mixture was filtered. The filtrate was concentrated. To the residue was added water (820 g), the resulting mixture was extracted with ethyl acetate (820 mL). The organic layer was discarded. To the aqueous layer was added ethyl acetate (900 mL), the mixture was adjusted to pH 3-6 with concentrated hydrochloric acid. The organic layer was dried over anhydrous sodium sulfate and concentrated to give the product as a yellow solid (43.6 g, 73%).

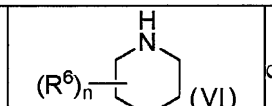
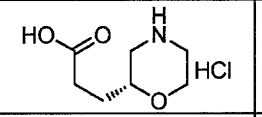
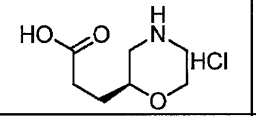
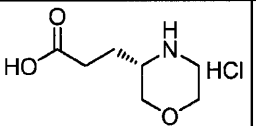
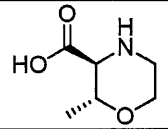
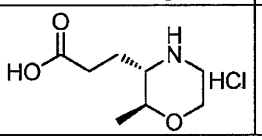
MS (ESI, pos.ion) *m/z*: 596.6 $[M+H]^+$;

^1H NMR (400MHz, DMSO-d_6): δ 12.87 (br,1H), 9.93 (s,1H), 8.04 (d,1H), 7.96 (d,1H), 7.60 (d,1H), 7.43-7.37 (m,2H), 6.09 (s,1H), 4.85 (q,1H), 4.22 (d,1H), 4.13-3.99 (m,4H), 3.85 (dd,1H), 3.74-3.61 (m,3H), 3.12-3.04 (m,1H), 2.43-2.38 (m,1H), 1.24 (d,3H), 1.13 (t,3H).

[00175] The compound H can be prepared under the reaction conditions shown in table 27 according to the procedure described in step 1 of Example 15.

Table 27: The reaction conditions for preparation of compound H



No.	 or a hydrochloride thereof	compound A3: compound(VI)(mol); the amount of compound A3 is 5.47 g	Reaction solvent	Reaction temperature(°C)	Reaction time(h)	Product character	Quality; yield(%) of product
H1		1:1	ethanol	30	12	yellow solid	4.44 g; 71
H2		1:1	ethanol	30	12	yellow solid	4.32 g; 69
H3		1:1	ethanol	30	12	yellow solid	2.63 g; 42
H4		1:1	ethanol	30	12	yellow solid	4.52 g; 74
H5		1:1	ethanol	30	12	yellow solid	2.56 g; 40

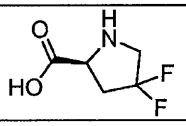
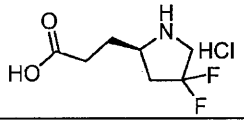
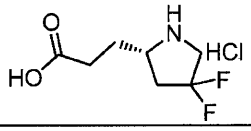
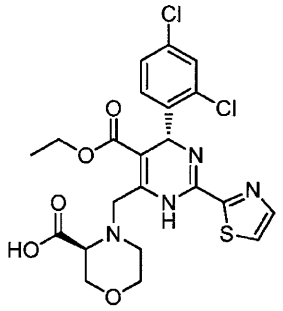
H6		1:1	ethanol	30	12	yellow solid	4.89 g; 63
H7		1:1	ethanol	30	12	yellow solid	3.23 g; 50
H8		1:1	ethanol	30	12	yellow solid	3.04 g; 47

Table 27-1: The NMR and MS datum of compound H

No.	^{1}H NMR	MS
H1	^{1}H NMR (600 MHz, DMSO-d_6): δ 12.08 (br,1H), 9.75 (s,1H), 8.04 (d,1H), 7.96 (d,1H), 7.62 (br,1H), 7.41 (br,2H), 6.07 (s,1H), 4.86 (q,1H), 4.15-4.06 (m,2H), 3.98-3.86 (m,3H), 3.58-3.47 (m,2H), 2.85-2.75 (m,2H), 2.35-2.25 (m,3H), 2.02 (br,1H), 1.67-1.62 (m,2H), 1.25 (d,3H), 1.09 (t,3H).	MS (ESI, pos.ion) *m/z*: 624.6 $[M+H]^+$;
H2	^{1}H NMR (600 MHz, DMSO-d_6): δ 9.83 (s,1H), 8.03 (d,1H), 7.94 (d,1H), 7.60 (br,1H), 7.39 (br,2H), 6.03 (s,1H), 4.87 (q,1H), 4.16-4.06 (m,2H), 3.97-3.86 (m,3H), 3.59-3.57 (m,1H), 3.54-3.48 (m,1H), 2.79 (t,2H), 2.37-2.24 (m,3H), 2.01 (t,1H), 1.68-1.63 (m,2H), 1.22 (d,3H), 1.12 (t,3H).	MS (ESI, pos.ion) *m/z*: 624.6 $[M+H]^+$;
H3	^{1}H NMR (600 MHz, DMSO-d_6): δ 9.79 (s,1H), 8.02 (d,1H), 7.96 (d,1H), 7.58 (br,1H), 7.39 (br,2H), 6.05 (s,1H), 4.86 (q,1H), 4.17 (d,1H), 4.13-4.03 (m,2H), 3.87 (d,1H), 3.82 (d,1H), 3.76-3.72 (m,1H), 3.62-3.56 (m,1H), 3.37-3.33 (m,1H), 2.94-2.73 (m,1H), 2.58-2.54 (m,1H), 2.38-2.31 (m,1H), 2.29-2.21 (m,1H), 1.89-1.84 (m,1H), 1.68-1.59 (m,1H), 1.24 (d,3H), 1.14 (t,3H).	MS (ESI, pos.ion) *m/z*: 625.1 $[M+H]^+$;
H4	^{1}H NMR (600 MHz, DMSO-d_6): δ 9.81 (s,1H), 8.03 (d,1H), 7.94 (d,1H), 7.59 (br,1H), 7.40 (br,2H), 6.04 (s,1H), 4.85 (q,1H), 4.12-4.03 (m,3H), 3.93-3.86 (m,1H), 3.74-3.68 (m,2H), 3.65-3.61 (m,1H), 2.99 (d,1H), 2.92 (d,1H), 2.48-2.44 (m,1H), 1.24 (d,3H), 1.21 (d,3H), 1.12 (t,3H).	MS (ESI, pos.ion) *m/z*: 611.1 $[M+H]^+$;
H5	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.14 (s,1H), 9.87 (s,1H), 8.04 (d,1H), 7.96 (d,1H), 7.61 (br,1H), 7.38 (br,2H), 6.09 (s,1H), 4.87 (q,1H), 4.16 (d,1H), 4.12-4.02 (m,2H), 3.83 (d,1H), 3.77-3.74 (m,1H), 3.60-3.55 (m,1H), 3.50-3.46 (m,1H), 2.69 (d,1H),2.45-2.41 (m,1H), 2.36-2.31(m,3H), 2.08-1.88 (m,1H), 1.79-1.72 (m,1H), 1.25 (d,3H), 1.20 (d,3H), 1.14 (t,3H).	MS (ESI, pos.ion) *m/z*: 639.2 $[M+H]^+$;
H6	^{1}H NMR (600 MHz, DMSO-d_6): δ 9.69 (s,1H), 7.98 (d,1H), 7.94 (d,1H), 7.59 (br,1H), 7.40 (br,2H), 6.04 (s,1H), 4.86-4.81 (m,1H), 4.31 (d,1H), 4.10-4.03 (m,3H), 3.93-3.90 (m,1H), 3.52-3.49 (m,1H), 3.18-3.13 (m,1H), 2.81-2.75 (m,1H), 2.48-2.43 (m,1H), 1.23 (d,3H), 1.12 (t,3H).	MS (ESI, pos.ion) *m/z*: 617.1 $[M+H]^+$;
H7	^{1}H NMR (600 MHz, DMSO-d_6): δ 12.05 (s,1H), 9.58 (s,1H), 8.04 (d,1H), 7.96 (d,1H), 7.60 (br,1H), 7.39 (br,2H), 6.07 (s,1H), 4.86 (q,1H), 4.15-4.04 (m,4H), 3.56-3.51 (m,1H), 3.05-2.94 (m,2H), 2.63-2.54 (m,1H), 2.37-2.21 (m,2H), 2.13-2.01 (m,1H), 1.96-1.89 (m,1H), 1.58-1.52 (m,1H), 1.24 (d,3H), 1.12 (t,3H).	MS (ESI, pos.ion) *m/z*: 645.1 $[M+H]^+$;
H8	^{1}H NMR (600 MHz, DMSO-d_6): δ 12.14 (s,1H), 9.51 (s,1H), 8.01 (d,1H), 7.95 (d,1H), 7.59 (br,1H), 7.40 (br,2H), 6.09 (s,1H), 4.87 (q,1H), 4.16-4.05 (m,4H), 3.51-3.47 (m,1H), 3.03-2.92 (m,2H), 2.61-2.58 (m,1H), 2.41-2.23 (m,2H), 2.14-1.99 (m,2H), 1.61-1.54 (m,1H), 1.26 (d,3H), 1.16 (t,3H).	MS (ESI, pos.ion) *m/z*: 645.1 $[M+H]^+$;

Step 2) (*S*)-4-(((*R*)-6-(2,4-dichlorophenyl)-5-(ethoxycarbonyl)-2-(thiazol-2-yl)-3,6-dihydropyrimidin-4-yl)methyl)morpholine-3-carboxylic acid



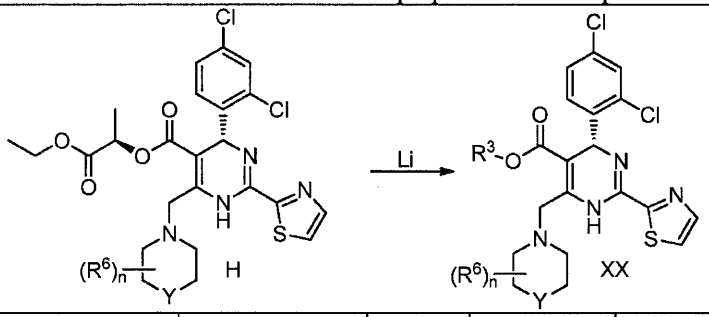
[00176] To a flask were added anhydrous ethanol (870 g) and lithium (2.43 g, 0.35 mol) in turn. The mixture was stirred at 43 °C until the lithium was consumed entirely, and then (*S*)-4-(((*R*)-6-(2,4-dichlorohenyl)-5-((((*R*)-1-ethoxy-1-oxopropan-2-yl)oxy)carbonyl)-2-(thiazol-2-yl)-3,6-dihydropyrimidin-4-yl)methyl)morpholine-3-carboxylic acid (59.7 g, 0.1 mol) was added. The reaction mixture was allowed to warm up to 78 °C and stirred for 12 hours. After the reaction, the mixture was cooled and concentrated. To the residue was added water (1200 g), the resulting mixture was extracted with ethyl acetate (1200 mL) The organic layer was discarded. To the aqueous layer was added ethyl acetate (1280 mL), and the mixture was adjusted to pH 3-6 with concentrated hydrochloric acid. The organic layer was dried over anhydrous sodium sulfate and concentrated to give the product as a yellow solid (35.7 g, 68%).

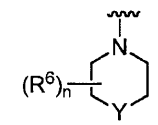
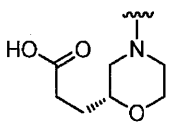
MS (ESI, pos.ion) *m/z*: 524.7 $[M+H]^+$;

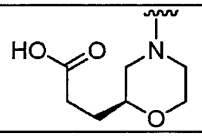
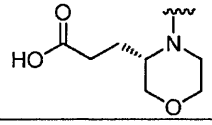
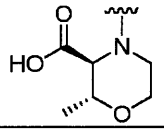
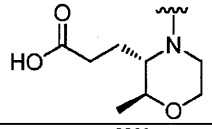
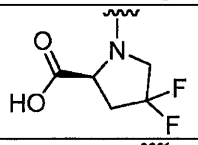
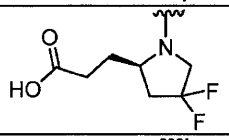
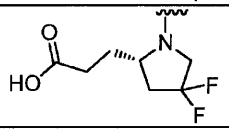
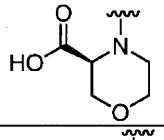
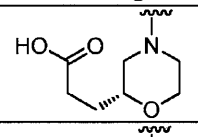
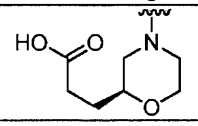
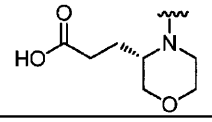
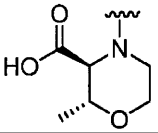
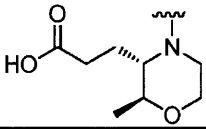
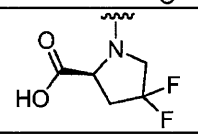
^{1}H NMR (400 MHz, DMSO-d_6): δ 12.86 (br,1H), 9.84 (s,1H), 8.03 (d,1H), 7.94 (d,1H), 7.60 (br,1H), 7.42-7.36 (m,2H), 6.05 (s,1H), 4.25 (d,1H), 4.09-3.91 (m,4H), 3.83 (dd,1H), 3.75-3.58 (m,3H), 3.12-3.03 (m,1H), 2.43-2.36 (m,1H), 1.06 (t,3H).

[00177] The compound XX can be prepared under the reaction conditions shown in table 28 according to the procedure described in step 2 of Example 15.

Table 28: The reaction conditions for preparation of compound XX



No.	R^3		The mole ratio of Lithium to compound Q; the amount of compound Q	Reaction solvent	Reaction temperature (°C)	Reaction time(h)	Product character	Quality; yield(%) of product
XX1	ethyl		5;6.25 g	ethanol	78	2	yellow solid	3.33 g; 60

XX2	ethyl		5;6.25 g	ethanol	78	2	yellow solid	3.21 g; 58
XX3	ethyl		5;6.25 g	ethanol	78	2	yellow solid	2.38 g; 43
XX4	ethyl		5;6.11 g	ethanol	78	12	yellow solid	3.61 g; 67
XX5	ethyl		5;6.39 g	ethanol	78	2	yellow solid	2.38 g; 42
XX6	ethyl		5;6.17 g	ethanol	78	12	yellow solid	2.83 g; 52
XX7	ethyl		5;6.46 g	ethanol	78	2	yellow solid	2.58 g; 45
XX8	ethyl		5;6.46 g	ethanol	78	2	yellow solid	2.87 g; 50
XX9	methyl		5;5.97 g	methanol	64	18	yellow solid	3.53 g; 69
XX10	methyl		5;6.25 g	methanol	64	6	yellow solid	3.13 g; 58
XX11	methyl		5;6.25 g	methanol	64	4	yellow solid	3.02 g; 56
XX12	methyl		5;6.25 g	methanol	64	8	yellow solid	2.21 g; 41
XX13	methyl		5;6.11 g	methanol	64	18	yellow solid	3.36 g; 64
XX14	methyl		5;6.39 g	methanol	64	5	yellow solid	2.21 g; 40
XX15	methyl		5;6.17 g	methanol	64	12	yellow solid	2.6 g; 49

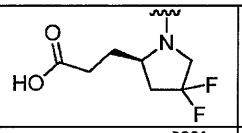
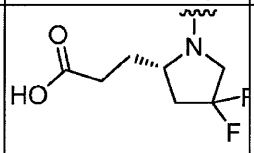
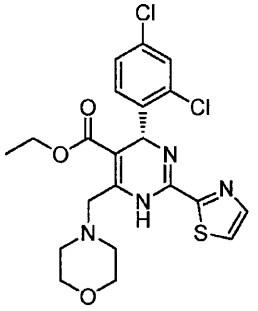
XX16	methyl		5;6.87 g	methanol	64	6	yellow solid	2.57 g; 46
XX17	methyl		5;6.46 g	methanol	64	6	yellow solid	2.63 g; 47

Table 28-1: The NMR and MS datum of compound XX

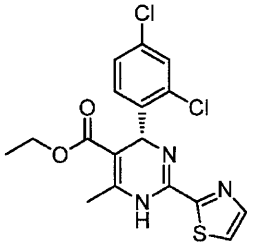
No.	^{1}H NMR	MS
XX1	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.04 (s,1H), 9.66 (s,1H), 8.02 (d,1H), 7.95 (d,1H), 7.61 (br,1H), 7.38 (br,2H), 6.05 (s,1H), 3.96 (q,2H), 3.89-3.86 (m,3H), 3.61-3.46 (m,2H), 2.77 (t,2H), 2.36-2.23 (m,3H), 2.02 (t,1H), 1.63 (dd,2H), 1.05 (t,3H).	MS (ESI, pos.ion) *m/z*: 553.2 $[M+H]^+$;
XX2	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.08 (s,1H), 9.66 (s,1H), 8.03 (d,1H), 7.95 (d,1H), 7.61 (br,1H), 7.40 (br,2H), 6.06 (s,1H), 3.98-3.93 (m,H), 3.86-3.82 (m,2H), 3.58-3.48 (m,2H), 2.87 (d,1H), 2.63 (d,1H), 2.36-2.23 (m,3H), 2.10 (t,1H), 1.72-1.63 (m,2H), 1.06 (t,3H).	MS (ESI, pos.ion) *m/z*: 552.9 $[M+H]^+$;
XX3	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.84 (s,1H), 8.03 (d,1H), 7.95 (d,1H), 7.60 (br,1H), 7.40 (br,2H), 6.05 (s,1H), 4.18 (d,1H), 3.97 (q,2H), 3.90 (d,1H), 3.82-3.80 (m,1H), 3.74-3.72 (m,1H), 3.61-3.55 (m,1H), 3.37-3.35 (m,1H), 2.78-2.76 (m,1H), 2.56-2.54 (m,1H), 2.49-2.46 (m,1H), 2.35-2.20 (m,2H), 1.88-1.83 (m,1H), 1.64-1.54 (m,1H), 1.07 (t,3H).	MS (ESI, pos.ion) *m/z*: 552.9 $[M+H]^+$;
XX4	^{1}H NMR (400 MHz, DMSO-d_6): δ 13.12 (s,1H), 9.79 (s,1H), 8.02 (d,1H), 7.94 (d,1H), 7.60 (br,1H), 7.39 (br,2H), 6.03 (s,1H), 4.06 (d,1H), 3.96 (q,2H), 3.90-3.87 (m,1H), 3.74-3.59 (m,3H), 3.47-3.43 (m,1H), 2.98 (d,1H), 2.90 (d,1H), 1.20 (d,3H), 1.04 (t,3H).	MS (ESI, pos.ion) *m/z*: 539.2 $[M+H]^+$;
XX5	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.09 (s,1H), 9.76 (s,1H), 8.03 (d,1H), 7.96 (d,1H), 7.59 (br,1H), 7.38 (br,2H), 6.06 (s,1H), 4.15 (d,1H), 4.02-3.93 (m,2H), 3.87 (d,1H), 3.78-3.73 (m,1H), 3.60-3.54 (m,1H), 3.51-3.46 (m,1H), 2.67 (d,1H), 2.45-2.41 (m,1H), 2.38-2.30 (m,3H), 2.04-1.92 (m,1H), 1.81-1.73 (m,1H), 1.21 (d,3H), 1.08 (t,3H).	MS (ESI, pos.ion) *m/z*: 567.1 $[M+H]^+$;
XX6	^{1}H NMR (600 MHz, DMSO-d_6): δ 12.90 (s,1H), 9.67 (s,1H), 7.98 (d,1H), 7.92 (d,1H), 7.60 (br,1H), 7.42 (br,2H), 6.03 (s,1H), 4.33 (d,1H), 4.08 (d,1H), 3.96 (q,2H), 3.92-3.89 (m,1H), 3.53-3.48 (m,1H), 3.19-3.13 (m,1H), 2.79-2.73 (m,1H), 2.47-2.45 (m,1H), 1.06 (t,3H).	MS (ESI, pos.ion) *m/z*: 545.1 $[M+H]^+$;
XX7	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.05 (s,1H), 9.52 (s,1H), 8.00 (d,1H), 7.94 (d,1H), 7.60 (br,1H), 7.41 (br,2H), 6.04 (s,1H), 4.14 (dd,2H), 3.97 (q,2H), 3.57-3.49 (m,1H), 3.07-2.97 (m,2H), 2.58-2.54 (m,1H), 2.34-2.21 (m,2H), 2.18-2.03 (m,1H), 1.95-1.91 (m,1H), 1.60-1.49 (m,1H), 1.06 (t,3H).	MS (ESI, pos.ion) *m/z*: 573.3 $[M+H]^+$;
XX8	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.17 (s,1H), 9.47 (s,1H), 8.00 (d,1H), 7.94 (d,1H), 7.60 (br,1H), 7.45-7.37 (m,2H), 6.06 (s,1H), 4.15 (dd,2H), 3.96 (q,2H), 3.47-3.39 (m,1H), 3.01-2.86 (m,2H), 2.59-2.53 (m,1H), 2.38-2.25 (m,2H), 2.15-2.01 (m,2H), 1.65-1.55 (m,1H), 1.05 (t,3H).	MS (ESI, pos.ion) *m/z*: 573.2 $[M+H]^+$;
XX9	^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (s,1H), 7.87 (d,1H), 7.50 (d,1H), 7.42 (d,1H), 7.28 (br,1H), 7.20 (dd,1H), 6.20 (s,1H), 4.23-4.15 (m,2H), 4.13-4.05 (m,2H), 3.90-3.80 (m,2H), 3.61 (s,3H), 3.59-3.57 (m,1H), 3.27-3.23 (m,1H), 2.62-2.54 (m,1H).	MS (ESI, pos.ion) *m/z*: 511.1 $[M+H]^+$;
XX10	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.03 (s,1H), 9.70 (s,1H), 8.01 (d,1H), 7.94 (d,1H), 7.59 (br,1H), 7.37 (br,2H), 6.04 (s,1H), 3.89-3.86 (m,3H), 3.63-3.57 (m,1H), 3.52 (s,3H), 3.49-3.47 (m,1H), 2.76 (t,2H), 2.39-2.24 (m,3H), 2.04 (t,1H), 1.63 (dd,2H).	MS (ESI, pos.ion) *m/z*: 538.8 $[M+H]^+$;
XX11	^{1}H NMR (600 MHz, DMSO-d_6): δ 12.06 (s,1H), 9.70 (s,1H), 8.03 (d,1H), 7.94 (d,1H), 7.59 (br,1H), 7.40 (br,2H), 6.03 (s,1H), 3.96 (d,1H), 3.85-3.80 (m,2H), 3.57-3.55 (m,1H), 3.52 (s,3H), 3.51-3.48 (m,1H), 2.88 (d,1H), 2.61 (d,1H), 2.38-2.21 (m,3H), 2.16-2.09 (m,1H), 1.72-1.65	MS (ESI, pos.ion) *m/z*: 539.1 $[M+H]^+$;

	(m,2H).	
XX12	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.17 (s,1H), 9.89 (s,1H), 8.04 (d,1H), 7.95 (d,1H), 7.60 (br,1H), 7.42-7.37 (m,2H), 6.04 (s,1H), 4.18 (d,1H), 3.90 (d,1H), 3.84-3.80 (m,1H), 3.76-3.72 (m,1H), 3.61-3.56 (m,1H),3.53 (s,3H), 3.46-3.42 (m,1H), 3.30-3.26 (m,1H), 2.80-2.75 (m,1H), 2.56-2.53 (m,1H), 2.37-2.22 (m,2H), 1.93-1.83 (m,1H), 1.62-1.58 (m,1H).	MS (ESI, pos.ion) *m/z*: 538.9 $[M+H]^+$;
XX13	^{1}H NMR (600 MHz, DMSO-d_6): δ 13.00 (s,1H), 9.83 (s,1H), 8.03 (d,1H), 7.94 (d,1H), 7.60 (br,1H), 7.39-7.36 (m,2H), 6.02 (s,1H), 4.05 (d,1H), 3.90-3.86 (m,1H), 3.74 (d,1H), 3.70-3.68 (m,1H), 3.65-3.60 (m,1H), 3.51 (s,3H), 3.42-3.36 (m,1H), 2.99 (d,1H), 2.89 (d,1H), 1.20 (d,3H).	MS (ESI, pos.ion) *m/z*: 524.7 $[M+H]^+$;
XX14	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.09 (s,1H), 9.76 (s,1H), 8.03 (d,1H), 7.94 (d,1H), 7.59 (br,1H), 7.39 (br,1H), 6.03 (s,1H), 4.17 (d,1H), 3.89 (d,1H), 3.78-3.74 (m,1H), 3.61-3.55 (m,1H), 3.53 (s,3H), 3.50-3.46 (m,1H), 2.67 (d,1H), 2.48-2.42 (m,1H), 2.37-2.31 (m,3H), 2.03-1.93 (m,1H), 1.82-1.73 (m,1H), 1.21 (d,3H).	MS (ESI, pos.ion) *m/z*: 553.1 $[M+H]^+$;
XX15	^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (s,1H), 7.88 (d,1H), 7.57 (d,1H), 7.45 (br,1H), 7.28 (br,2H), 6.15 (s,1H), 4.67 (d,1H),3.98-3.93 (m,1H), 3.76 (d,1H), 3.64 (s,3H), 3.60-3.55 (m,1H), 3.34-3.24 (m,1H), 2.86-2.76 (m,1H), 2.68-2.54 (m,1H).	MS (ESI, pos.ion) *m/z*: 531.1 $[M+H]^+$;
XX16	^{1}H NMR (400 MHz, DMSO-d_6): δ 11.07 (br,1H), 9.56 (s,1H), 7.99 (d,1H), 7.92 (d,1H), 7.60 (br,1H), 7.39 (br,2H), 6.02 (s,1H), 4.14 (dd,2H), 3.52 (s,3H),3.08-2.94 (m,3H), 2.55-2.53 (m,1H), 2.30-2.19 (m,2H), 2.12-1.99 (m,1H), 1.95-1.84 (m,1H), 1.60-1.46 (m,1H).	MS (ESI, pos.ion) *m/z*: 559.0 $[M+H]^+$;
XX17	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.15 (s,1H), 9.52 (s,1H), 8.00 (d,1H), 7.94 (d,1H), 7.60 (s,1H), 7.41 (br,2H), 6.05 (s,1H), 4.13 (dd,2H), 3.52 (s,3H), 3.47-3.39 (m,1H),3.01-2.87 (m,2H), 2.59-2.53 (m,1H), 2.37-2.25 (m,2H), 2.15-2.02 (m,2H), 1.64-1.55 (m,1H).	MS (ESI, pos.ion) *m/z*: 558.6 $[M+H]^+$;

Example 16: the preparation of (*R*)-ethyl 4-(2,4-dichlorophenyl)-6-(morpholinomethyl)-2-(thiazol-2-yl)-1,4 -dihydropyrimidine-5-carboxylate



Step 1) (*R*)-ethyl 4-(2,4-dichlorophenyl)-6-methyl-2-(thiazol-2-yl)-1,4-dihydropyrimidine -5-carboxylate



[00178] To a flask were added anhydrous ethanol (374 g) and lithium (2.43 g, 0.35 mol) in turn. The mixture was stirred at 43 °C until the lithium was consumed entirely, and then (*R*)-(*R*)-1-ethoxy-1-oxopropan-2-yl 4-(2,4-dichlorophenyl)-6-methyl-2-(thiazol-2-yl)- 1,4-dihydropyrimidine-5-carboxylate (46.8 g, 0.1 mol) was added. The reaction mixture was stirred at 78 °C for 6 hours. After the reaction, the reaction mixture was

cooled to 10 °C, kept at 10 °C and stirred for 8 hours. The mixture was filtered. The filter cake was washed with anhydrous ethanol (47 g) and water (500 g) in turn, and then dried *in vacuo* at 60 °C for 8 hours to obtain the product as a yellow solid (28.1 g, 71%).

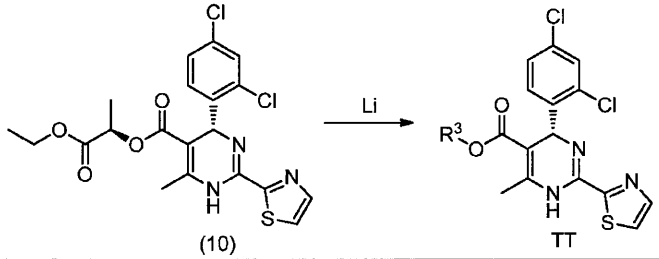
$[\alpha]_D^{25}$ = −39.07 (c = 0.3032 g/100 mL, MeOH);

MS (ESI, pos.ion) *m/z*: 396.1 $[M+H]^+$;

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.93 (s,1H), 7.97 (d,1H), 7.90 (d,1H), 7.58 (d,1H), 7.41 (dd,1H), 7.35 (d,1H), 6.00 (s,1H), 3.93 (q,2H), 2.46 (s,3H), 1.03 (t,3H).

[00179] The compound TT can be prepared under the reaction conditions shown in table 29 according to the procedure described in step 1 of Example 16.

Table 29: The reaction conditions for preparation of compound TT



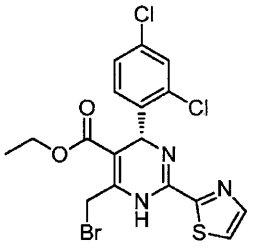
No.	R^3	The mole ratio of Lithium to compound (10); the amount of compound (10) is 46.8 g	Reaction solvent	The mass ratio of reaction solvent to compound (10)	Reaction temperature (°C)	Reaction time(h)	Product character	Quality; yield(%) of product
TT1	ethyl	2.5	ethanol	10	78	12	yellow solid	17 g;43
TT1	ethyl	3	ethanol	6	78	8	yellow solid	28.5 g;72
TT1	ethyl	4	ethanol	10	78	4	yellow solid	21.4 g;54
TT1	ethyl	5	ethanol	20	78	24	yellow solid	18.6 g;47
TT1	ethyl	6	ethanol	30	78	12	yellow solid	15.4 g;39
TT1	ethyl	8	ethanol	20	78	12	yellow solid	17.9 g;45
TT2	methyl	3	methanol	3	64	20	yellow solid	22.9 g;60%
TT2	methyl	3	methanol	4	64	6	yellow solid	17.6 g;46

TT2	methyl	4	methanol	6	64	8	yellow solid	12.9 g;34

Table 29-1: The NMR, MS and specific rotation datum of the compound TT

No.	^{1}H NMR	MS	specific rotation
TT1	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.93 (s,1H), 7.97 (d,1H), 7.90 (d,1H), 7.58 (d,1H), 7.41 (dd,1H), 7.35 (d,1H), 6.00 (s,1H), 3.93 (q,2H), 2.46 (s,3H), 1.03 (t,3H).	MS (ESI, pos.ion) *m/z*: 396.1 $[M+H]^+$;	$[\alpha]_D^{25}$ = −39.07 (c = 0.3032 g/100 mL, MeOH);
TT2	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.99 (s,1H), 7.98 (d,1H), 7.90 (d,1H), 7.59 (d,1H), 7.40 (dd,1H), 7.33 (d,1H), 5.98 (s,1H), 3.49 (s,3H), 2.47 (s,3H).	MS (ESI, pos.ion) *m/z*: 382.1 $[M+H]^+$	$[\alpha]_D^{25}$ = −46.08 (c = 0.3038 g/100 mL, MeOH);

Step 2) (*R*)-ethyl 4-(2,4-dichlorophenyl)-6-(bromomethyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine -5-carboxylate



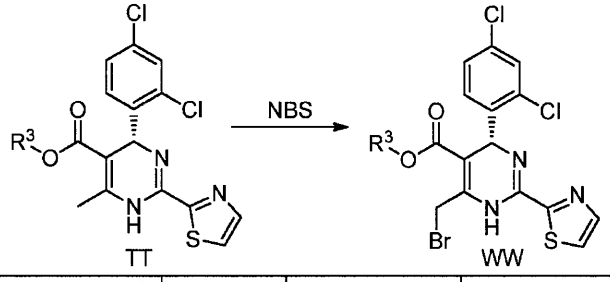
[00180] To a flask were added (*R*)-ethyl 4-(2,4-chlorophenyl)-6-methyl-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (39.6 g, 0.1 mol) and CCl_4 (800 mL), followed by NBS (19.6 g, 0.11 mol) at 70 °C. The mixture was stirred for 30 min. After the reaction, the mixture was cooled and filtered. The filtrate was concentrated to obtain the product as a yellow solid (37.1 g, 78%).

MS (ESI, pos.ion) *m/z*: 475.6 $[M+H]^+$;

^{1}H NMR (600 MHz, DMSO-d_6): δ 8.03 (d,1H), 7.98 (d,1H), 7.66-7.62 (m,1H), 7.47-7.35 (m,2H), 5.99 (s,1H), 4.82 (br,2H), 4.02 (q,2H), 1.09 (t,3H).

[00181] The compound WW can be prepared under the reaction conditions shown in table 30 according to the procedure described in step 2 of Example 16.

Table 30: The reaction conditions for preparation of compound WW



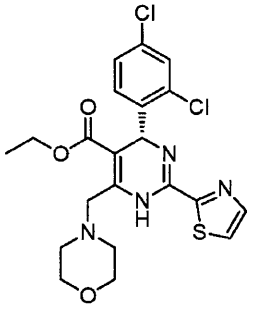
No.	R^3	The mole ratio of NBS to	Reaction solvent	The mass ratio of	Reaction temperature	Product character	Quality; yield(%) of

		compound TT; the amount of compound TT		reaction solvent to compound (TT)	(°C)		product
WW1	ethyl	1.0;39.6 g	DCM	10	39	yellow solid	35.2 g;72
WW1	ethyl	1.0;39.6 g	$CHCl_3$	20	61	yellow solid	36.3 g;75
WW1	ethyl	1.1;39.6 g	CCl_4	30	76	yellow solid	44.3 g;80
WW2	methyl	1.0;38.2 g	DCM	10	39	yellow solid	29.9 g;70
WW2	methyl	1.1;38.2 g	$CHCl_3$	20	61	yellow solid	30.8 g;72
WW2	methyl	1.1;38.2 g	CCl_4	30	76	yellow solid	34.9 g;79

Table 30-1: The NMR and MS datum of compound WW

No.	^{1}H NMR	MS
WW1	^{1}H NMR (600 MHz, DMSO-d_6): δ 8.03 (d,1H), 7.98 (d,1H), 7.66-7.62 (m,1H), 7.47-7.35 (m,2H), 5.99 (s,1H), 4.82 (br,2H), 4.02 (q,2H), 1.09 (t,3H).	MS (ESI, pos.ion) *m/z*: 475.6 $[M+H]^+$;
WW2	^{1}H NMR (600 MHz, DMSO-d_6): δ 9.91 (s,1H), 8.01 (d,1H), 7.96 (d,1H), 7.62 (br,1H), 7.40 (br,2H), 6.01 (s,1H), 4.86 (br,2H), 3.56 (s,3H).	MS (ESI, pos.ion) *m/z*: 459.9 $[M+H]^+$;

Step 3) (*R*)-ethyl 4-(2,4-dichlorophenyl)-6-(morpholinomethyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine -5-carboxylate



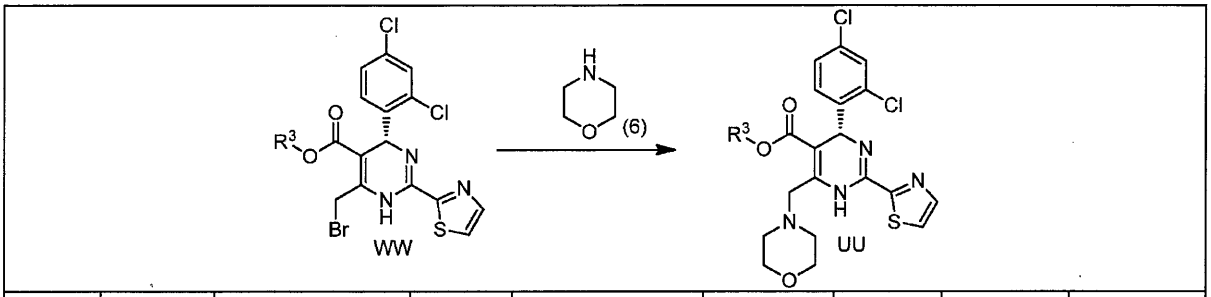
[00182] To a flask were added (*R*)-ethyl 4-(2,4-dichlorophenyl)-6-(bromomethyl)-2-(thiazol-2-yl)-1,4 -dihydropyrimidine-5-carboxylate (47.5 g, 0.1 mol), anhydrous ethanol (285 g) and morpholine (34.8 g, 0.4 mol). The mixture was stirred at 25 °C for 6 hours. After the reaction, the mixture was concentrated. To the residue was added ethyl acetate (475 g), the resulting mixture was washed with water (250 mL × 2). The organic layer was concentrated to give the product as tawny oil (37.5 g, 78%)

MS (ESI, pos.ion) *m/z*: 480.7 $[M+H]^+$;

^{1}H NMR (600 MHz, DMSO-d_6): δ 9.69 (s,1H), 8.03 (d,1H), 7.94 (d,1H), 7.60 (s,1H), 7.39 (s,2H), 6.06 (s,1H), 3.97 (q,2H), 3.92 (dd,2H), 3.67 (br,4H), 2.56 (br,4H), 1.06 (t,3H).

[00183] The compound UU can be prepared under the reaction conditions shown in table 31 according to the procedure described in step 3 of Example 16.

Table 31: The reaction conditions for preparation of compound UU

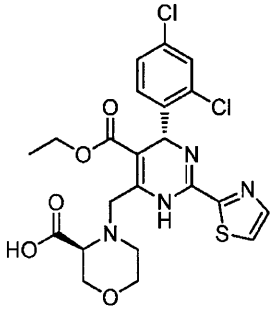


No.	R^3	The mole ratio of compound (6) to compound WW; the amount of compound WW	Reaction solvent	The mass ratio of reaction solvent to compound (WW)	Reaction temperature (°C)	Reaction time(h)	Product character	Quality; yield(%) of product
UU1	ethyl	2;47.5 g	ethanol	20	25	2	tawny oil	36.6 g;76
UU1	ethyl	3;47.5 g	acetone	10	40	10	tawny oil	35.1 g;73
UU1	ethyl	4;47.5 g	methanol	10	30	6	tawny oil	34.6 g;72
UU1	ethyl	5;47.5 g	ethyl acetate	20	50	24	tawny oil	34.2 g;71
UU1	ethyl	6;47.5g	DCM	8	39	6	tawny oil	31.7 g;66
UU1	ethyl	3;47.5 g	DMF	4	60	1	tawny oil	33.2 g;69
UU1	ethyl	4;47.5 g	THF	6	50	8	tawny oil	34.6 g;72
UU2	methyl	2;46.1 g	ethanol	20	25	2	tawny oil	33.2 g;71
UU2	methyl	3;46.1 g	acetone	10	40	10	tawny oil	36.9 g;79
UU2	methyl	4;46.1 g	methanol	10	30	6	tawny oil	36 g;77
UU2	methyl	5;46.1 g	ethyl acetate	20	50	24	tawny oil	34.1 g;73
UU2	methyl	6;46.1 g	DCM	8	39	6	tawny oil	31.3 g;67
UU2	methyl	3;46.1 g	DMF	4	60	1	tawny oil	33.2 g;71
UU2	methyl	4;46.1 g	THF	6	50	8	tawny oil	31.8 g;68

Table 31-1: The NMR and MS datum of compound UU

No.	^{1}H NMR	MS
UU1	^{1}H NMR (600 MHz, DMSO-d_6): δ 9.69 (s,1H), 8.03 (d,1H), 7.94 (d,1H), 7.60 (s,1H), 7.39 (s,2H), 6.06 (s,1H), 3.97 (q,2H), 3.92 (dd,2H), 3.67 (br,4H), 2.56 (br,4H), 1.06 (t,3H).	MS (ESI, pos.ion) *m/z*: 480.7 $[M+H]^+$;
UU2	^{1}H NMR (400 MHz, $CDCl_3$): δ 9.73 (s,1H), 7.87 (d,1H), 7.47 (d,1H), 7.42 (d,1H), 7.24 (d,1H), 7.18 (dd,1H), 6.21 (s,1H), 4.02 (d,1H), 3.89 (d,1H), 3.85 (t,4H), 3.62 (s,3H), 2.65 (t,4H).	MS (ESI, pos.ion) *m/z*: 467.1 $[M+H]^+$;

Example 17: the preparation of (*S*)-4-(((*R*)-6-(2,4-dichlorophenyl)-5-(ethoxycarbonyl)-2-(thiazol-2-yl)-3,6-dihydropyrimidin-4-yl)methyl)morpholine-3-carboxylic acid



[00184] To a flask were added (*R*)-ethyl 4-(2,4-dichlorophenyl)-6-(bromomethyl)-2-(thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate (4.75 g, 10 mmol), (*S*)-morpholine-3-carboxylic acid (1.31 g, 10 mmol), potassium carbonate (2.76g, 20 mmol) and ethanol (95 mL). The mixture was stirred at 30 °C for 12 hours.

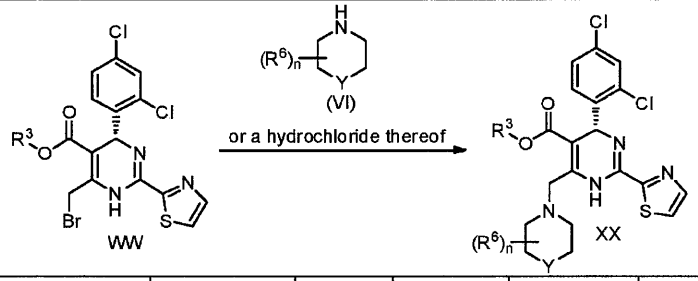
After the reaction, the mixture was filtered. The filtrate was concentrated. To the residue was added water (100 mL), the resulting mixture was extracted with ethyl acetate (100 mL). The organic layer was discarded. To the aqueous layer was added ethyl acetate (100 mL), the mixture was adjusted to pH 3-6 with concentrated hydrochloric acid. The organic layer was dried over anhydrous sodium sulfate and concentrated to give the product as a yellow solid (4.1 g, 78%).

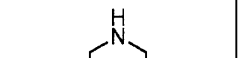
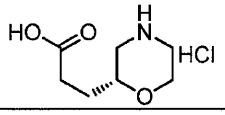
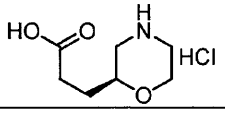
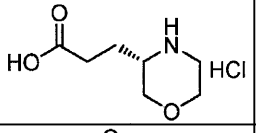
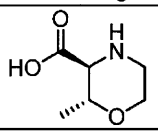
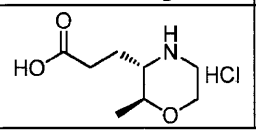
MS (ESI, pos.ion) *m/z*: 524.7 $[M+H]^+$;

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.86 (br,1H), 9.84 (s,1H), 8.03 (d,1H), 7.94 (d,1H), 7.60 (br,1H), 7.42-7.36 (m,2H), 6.05 (s,1H), 4.25 (d,1H), 4.09-3.91 (m,4H), 3.83 (dd,1H), 3.75-3.58 (m,3H), 3.12-3.03 (m,1H), 2.43-2.36 (m,1H), 1.06 (t,3H).

[00185] The compound XX can be prepared under the reaction conditions shown in table 32 according to the procedure described in Example 17.

Table 32: The reaction conditions for preparation of compound XX



No.	R^3	 or a hydrochloride thereof	The mole ratio of compound WW to compound (VI); the amount of compound WW	Reaction solvent	The mass ratio of reaction solvent to compound WW	Reaction temperature (°C)	Reaction time(h)	Product character	Quality; yield(%) of product
XX1	ethyl		1;4.75 g	ethanol	8	30	4	yellow solid	3.76 g;68
XX2	ethyl		1;4.75 g	ethanol	4	30	8	yellow solid	3.65 g;66
XX3	ethyl		1;4.75 g	ethanol	20	30	24	yellow solid	2.38 g;43
XX4	ethyl		1;4.75 g	ethanol	30	30	6	yellow solid	4.2 g;78
XX5	ethyl		1;4.75 g	ethanol	15	30	24	yellow solid	3.12 g;55

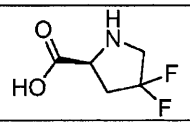
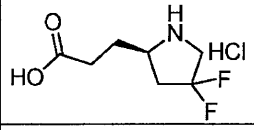
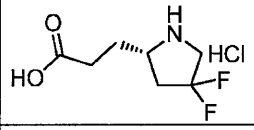
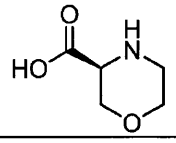
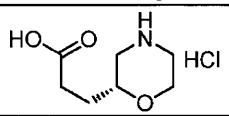
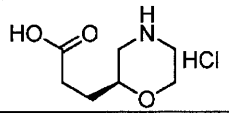
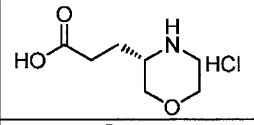
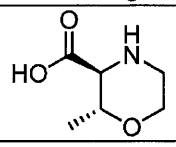
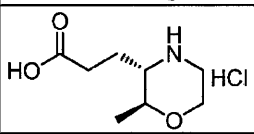
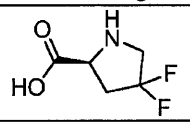
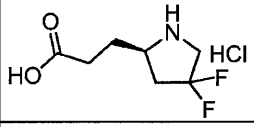
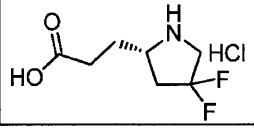
XX6	ethyl		1;4.75 g	ethanol	20	30	6	yellow solid	3.98 g;73
XX7	ethyl		1;4.75 g	ethanol	25	30	12	yellow solid	3.55 g;62
XX8	ethyl		1;4.75 g	ethanol	14	30	12	yellow solid	3.67 g;64
XX9	methyl		1;4.61 g	ethanol	8	30	4	yellow solid	3.73 g;73
XX10	methyl		1;4.61 g	ethanol	4	30	8	yellow solid	3.4 g;63
XX11	methyl		1;4.61 g	ethanol	10	30	12	yellow solid	3.34 g;62
XX12	methyl		1;4.61 g	ethanol	30	30	6	yellow solid	2.2 g;41
XX13	methyl		1;4.61 g	ethanol	8	30	12	yellow solid	3.83 g;73
XX14	methyl		1;4.61 g	ethanol	20	30	6	yellow solid	2.49 g;45
XX15	methyl		1;4.61 g	ethanol	25	30	12	yellow solid	3.77 g;71
XX16	methyl		1;4.61 g	ethanol	14	30	12	yellow solid	3.3 g;59
XX17	methyl		1;4.61 g	ethanol	15	30	24	yellow solid	3.63 g;65

Table 32-1: The NMR and MS datum of compound XX

No.	^{1}H NMR	MS
XX1	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.04 (s,1H), 9.66 (s,1H), 8.02 (d,1H), 7.95 (d,1H), 7.61 (br,1H), 7.38 (br,2H), 6.05 (s,1H), 3.96 (q,2H), 3.89-3.86 (m,3H), 3.61-3.46 (m,2H), 2.77 (t,2H), 2.36-2.23 (m,3H), 2.02 (t,1H), 1.63 (dd,2H), 1.05 (t,3H).	MS (ESI, pos.ion) *m/z*: 553.2 $[M+H]^+$;
XX2	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.08 (s,1H), 9.66 (s,1H), 8.03 (d,1H), 7.95 (d,1H), 7.61 (br,1H), 7.40 (br,2H), 6.06 (s,1H), 3.98-3.93 (m,3H), 3.86-3.82 (m,2H), 3.58-3.48 (m,2H), 2.87 (d,1H), 2.63 (d,1H), 2.36-2.23 (m,3H), 2.10 (t,1H), 1.72-1.63 (m,2H), 1.06 (t,3H).	MS (ESI, pos.ion) *m/z*: 552.9 $[M+H]^+$;
XX3	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.84 (s,1H), 8.03 (d,1H), 7.95	MS (ESI, pos.ion)

	(d,1H), 7.60 (br,1H), 7.40 (br,2H), 6.05 (s,1H), 4.18 (d,1H), 3.97 (q,2H), 3.90 (d,1H), 3.82-3.80 (m,1H), 3.74-3.72 (m,1H), 3.61-3.55 (m,1H), 3.37-3.35 (m,1H), 2.78-2.76 (m,1H), 2.56-2.54 (m,1H), 2.49-2.46 (m,1H), 2.35-2.20 (m,2H), 1.88-1.83 (m,1H), 1.64-1.54 (m,1H), 1.07 (t,3H).	*m/z*: 552.9 $[M+H]^+$;
XX4	^{1}H NMR (400 MHz, DMSO-d_6): δ 13.12 (s,1H), 9.79 (s,1H), 8.02 (d,1H), 7.94 (d,1H), 7.60 (br,1H), 7.39 (br,2H), 6.03 (s,1H), 4.06 (d,1H), 3.96 (q,2H), 3.90-3.87 (m,1H), 3.74-3.59 (m,3H), 3.47-3.43 (m,1H), 2.98 (d,1H), 2.90 (d,1H), 1.20 (d,3H), 1.04 (t,3H).	MS (ESI, pos.ion) *m/z*: 539.2 $[M+H]^+$;
XX5	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.09 (s,1H), 9.76 (s,1H), 8.03 (d,1H), 7.96 (d,1H), 7.59 (br,1H), 7.38 (br,2H), 6.06 (s,1H), 4.15 (d,1H), 4.02-3.93 (m,2H), 3.87 (d,1H), 3.78-3.73 (m,1H), 3.60-3.54 (m,1H), 3.51-3.46 (m,1H), 2.67 (d,1H), 2.45-2.41 (m,1H), 2.38-2.30 (m,3H), 2.04 -1.92 (m,1H), 1.81-1.73 (m,1H), 1.21 (d,3H), 1.08 (t,3H).	MS (ESI, pos.ion) *m/z*: 567.1 $[M+H]^+$;
XX6	^{1}H NMR (600 MHz, DMSO-d_6): δ 12.90 (s,1H), 9.67 (s,1H), 7.98 (d,1H), 7.92 (d,1H), 7.60 (br,1H), 7.42 (br,2H), 6.03 (s,1H), 4.33 (d,1H), 4.08 (d,1H), 3.96 (q,2H), 3.92-3.89 (m,1H), 3.53-3.48 (m,1H), 3.19-3.13 (m,1H), 2.79-2.73 (m,1H), 2.47-2.45 (m,1H), 1.06 (t,3H).	MS (ESI, pos.ion) *m/z*: 545.1 $[M+H]^+$;
XX7	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.05 (s,1H), 9.52 (s,1H), 8.00 (d,1H), 7.94 (d,1H), 7.60 (br,1H), 7.41 (br,2H), 6.04 (s,1H), 4.14 (dd,2H), 3.97 (q,2H), 3.57-3.49 (m,1H), 3.07-2.97 (m,2H), 2.58-2.54 (m,1H), 2.34-2.21 (m,2H), 2.18-2.03 (m,1H), 1.95-1.91 (m,1H), 1.60-1.49 (m,1H), 1.06 (t,3H).	MS (ESI, pos.ion) *m/z*: 573.3 $[M+H]^+$;
XX8	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.17 (s,1H), 9.47 (s,1H), 8.00 (d,1H), 7.94 (d,1H), 7.60 (br,1H), 7.45-7.37 (m,2H), 6.06 (s,1H), 4.15 (dd,2H), 3.96 (q,2H), 3.47-3.39 (m,1H), 3.01-2.86 (m,2H), 2.59-2.53 (m,1H), 2.38-2.25 (m,2H), 2.15-2.01 (m,2H), 1.65-1.55 (m,1H), 1.05 (t,3H).	MS (ESI, pos.ion) *m/z*: 573.2 $[M+H]^+$;
XX9	^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (s,1H), 7.87 (d,1H), 7.50 (d,1H), 7.42 (d,1H), 7.28 (br,1H), 7.20 (dd,1H), 6.20 (s,1H), 4.23-4.15 (m,2H), 4.13-4.05 (m,2H), 3.90-3.80 (m,2H), 3.61 (s,3H), 3.59-3.57 (m,1H), 3.27-3.23 (m,1H), 2.62-2.54 (m,1H).	MS (ESI, pos.ion) *m/z*: 511.1 $[M+H]^+$;
XX10	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.03 (s,1H), 9.70 (s,1H), 8.01 (d,1H), 7.94 (d,1H), 7.59 (br,1H), 7.37 (br,2H), 6.04 (s,1H), 3.89-3.86 (m,3H), 3.63-3.57 (m,1H), 3.52 (s,3H), 3.49-3.47 (m,1H), 2.76 (t,2H), 2.39-2.24 (m,3H), 2.04 (t,1H), 1.63 (dd,2H).	MS (ESI, pos.ion) *m/z*: 538.8 $[M+H]^+$;
XX11	^{1}H NMR (600 MHz, DMSO-d_6): δ 12.06 (s,1H), 9.70 (s,1H), 8.03 (d,1H), 7.94 (d,1H), 7.59 (br,1H), 7.40 (br,2H), 6.03 (s,1H), 3.96 (d,1H), 3.85-3.80 (m,2H), 3.57-3.55 (m,1H), 3.52 (s,3H), 3.51-3.48 (m,1H), 2.88 (d,1H), 2.61 (d,1H), 2.38-2.21 (m,3H), 2.16-2.09 (m,1H), 1.72-1.65 (m,2H).	MS (ESI, pos.ion) *m/z*: 539.1 $[M+H]^+$;
XX12	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.17 (s,1H), 9.89 (s,1H), 8.04 (d,1H), 7.95 (d,1H), 7.60 (br,1H), 7.42-7.37 (m,2H), 6.04 (s,1H), 4.18 (d,1H), 3.90 (d,1H), 3.84-3.80 (m,1H), 3.76-3.72 (m,1H), 3.61-3.56 (m,1H),3.53 (s,3H), 3.46-3.42 (m,1H), 3.30-3.26 (m,1H), 2.80-2.75 (m,1H), 2.56-2.53 (m,1H), 2.37-2.22 (m,2H), 1.93-1.83 (m,1H), 1.62-1.58 (m,1H).	MS (ESI, pos.ion) *m/z*: 538.9 $[M+H]^+$;
XX13	^{1}H NMR (600 MHz, DMSO-d_6): δ 13.00 (s,1H), 9.83 (s,1H), 8.03 (d,1H), 7.94 (d,1H), 7.60 (br,1H), 7.39-7.36 (m,2H), 6.02 (s,1H), 4.05 (d,1H), 3.90-3.86 (m,1H), 3.74 (d,1H), 3.70-3.68 (m,1H), 3.65-3.60 (m,1H), 3.51 (s,3H), 3.42-3.36 (m,1H), 2.99 (d,1H), 2.89 (d,1H), 1.20 (d,3H).	MS (ESI, pos.ion) *m/z*: 524.7 $[M+H]^+$;
XX14	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.09 (s,1H), 9.76 (s,1H), 8.03 (d,1H), 7.94 (d,1H), 7.59 (br,1H), 7.39 (br,1H), 6.03 (s,1H), 4.17 (d,1H), 3.89 (d,1H), 3.78-3.74 (m,1H), 3.61-3.55 (m,1H), 3.53 (s,3H), 3.50-3.46 (m,1H), 2.67 (d,1H), 2.48-2.42 (m,1H), 2.37-2.31 (m,3H), 2.03 -1.93 (m,1H), 1.82-1.73 (m,1H), 1.21 (d,3H).	MS (ESI, pos.ion) *m/z*: 553.1 $[M+H]^+$;
XX15	^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (s,1H), 7.88 (d,1H), 7.57 (d,1H), 7.45 (br,1H), 7.28 (br,2H), 6.15 (s,1H), 4.67 (d,1H),3.98-3.93 (m,1H),	MS (ESI, pos.ion) *m/z*: 531.1

	3.76 (d,1H), 3.64 (s,3H), 3.60-3.55 (m,1H), 3.34-3.24 (m,1H), 2.86-2.76 (m,1H), 2.68-2.54 (m,1H).	$[M+H]^+$;
XX16	^{1}H NMR (400 MHz, DMSO-d_6): δ 11.07 (br,1H), 9.56 (s,1H), 7.99 (d,1H), 7.92 (d,1H), 7.60 (br,1H), 7.39 (br,2H), 6.02 (s,1H), 4.14 (dd,2H), 3.52 (s,3H),3.08-2.94 (m,3H), 2.55-2.53 (m,1H), 2.30-2.19 (m,2H), 2.12-1.99 (m,1H), 1.95-1.84 (m,1H), 1.60-1.46 (m,1H).	MS (ESI, pos.ion) *m/z*: 559.0 $[M+H]^+$;
XX17	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.15 (s,1H), 9.52 (s,1H), 8.00 (d,1H), 7.94 (d,1H), 7.60 (s,1H), 7.41 (br,2H), 6.05 (s,1H), 4.13 (dd,2H), 3.52 (s,3H), 3.47-3.39 (m,1H),3.01-2.87 (m,2H), 2.59-2.53 (m,1H), 2.37-2.25 (m,2H), 2.15-2.02 (m,2H), 1.64-1.55 (m,1H).	MS (ESI, pos.ion) *m/z*: 558.6 $[M+H]^+$;

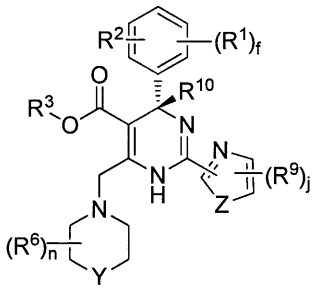
In the specification, Unless specified or limited otherwise, terms such as "first" and "second" are used herein for purposes of description and are not intended to indicate or imply relative importance or significance.

Reference throughout this specification to "an embodiment," "some embodiments," "one embodiment", "another example," "an example," "a specific examples," or "some examples," means that a particular feature, structure, material, or characteristic described in connection with the embodiment or example is included in at least one embodiment or example of the present disclosure. Thus, the appearances of the phrases such as "in some embodiments," "in one embodiment", "in an embodiment", "in another example, "in an example," "in a specific examples," or "in some examples," in various places throughout this specification are not necessarily referring to the same embodiment or example of the present disclosure. Furthermore, the particular features, structures, materials, or characteristics may be combined in any suitable manner in one or more embodiments or examples.

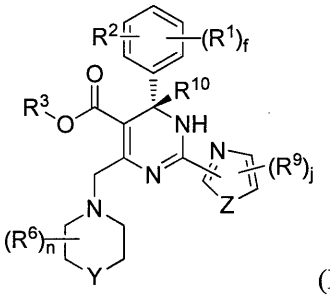
Although explanatory embodiments have been shown and described, it would be appreciated by those skilled in the art that the above embodiments cannot be construed to limit the present disclosure, and changes, alternatives, and modifications can be made in the embodiments without departing from spirit, principles and scope of the present disclosure.

WHAT IS CLAIMED IS:

1. A process for preparing a dihydropyrimidine compound having Formula (I), or a tautomer thereof having Formula (Ia),



(I) or



(Ia),

wherein each R^1 and R^2 is independently F, Cl, or Br;

R^3 is C_{1-4} alkyl;

Z is -O-, -S-, $-S(=O)_t-$, or $-N(R^4)-$;

Y is -O-, -S-, $-S(=O)_t-$, $-(CH_2)_q-$, or $-N(R^5)-$;

each t and q is independently 0, 1, or 2;

each of R^4 and R^5 is independently H or C_{1-4} alkyl;

each R^6 is independently H, deuterium, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, amino, C_{1-4} alkylamino, C_{1-4} alkoxy, nitro, triazolyl, tetrazyl, $-(CR^7R^{7a})_m-OH$, $-S(=O)_qOR^{8a}$, $-(CR^7R^{7a})_m-S(=O)_qN(R^{8a})_2$, $-(CR^7R^{7a})_t-N(R^{8a})_2$, $-(CR^7R^{7a})_m-C(=O)O-R^8$, $-(CR^7R^{7a})_m-C(=O)O-(CR^7R^{7a})_m-OC(=O)O-R^8$, $-(CR^7R^{7a})_m-C(=O)O-(CR^7R^{7a})_m-OC(=O)-R^8$, $-(CR^7R^{7a})_m-C(=O)O-(CR^7R^{7a})_m-C(=O)O-R^8$, $-(CR^7R^{7a})_m-OC(=O)-R^8$, or $-(CR^7R^{7a})_m-C(=O)-N(R^8R^{8a})$;

each R^{7a} and R^7 is independently H, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, $-(CH_2)_m-OH$, or $-(CH_2)_m-C(=O)O-R^8$; or R^{7a} and R^7, together with the carbon atom to which they are attached, form a C_{3-6} cycloalkyl group, C_{2-9} heterocyclyl goup, or -(C=O)-;

each R^8 and R^{8a} is independently H, C_{1-4} alkyl, amino-C_{1-4}-alkyl, C_{1-4} alkoxy, C_{1-6} alkyl-$S(=O)_q-$, C_{6-10} aryl, C_{1-9} heteroaryl, C_{3-6} cycloalkyl, C_{2-9} heterocyclyl, C_{6-10} aryl-C_{1-6}-alkyl, C_{1-9} heteroaryl-C_{1-6}-alkyl, C_{3-6} cycloalkyl-C_{1-4}-alkyl, C_{2-9} heterocyclyl-C_{1-6}-alkyl, C_{2-9} heterocyclyl-$S(=O)_q-$, C_{1-9} heteroaryl-$S(=O)_q-$, C_{3-6} cycloalkyl-$S(=O)_q-$, C_{6-10} aryl-$S(=O)_q-$, $-(CH_2)_m-OH$, $-(CH_2)_m-C(=O)O-(CH_2)_m-H$, or $-(CH_2)_m-OC(=O)-(CH_2)_m-H$;

each R^9 is independently H, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkylthio, C_{3-6} cycloalkyl, $-(CR^7R^{7a})_m-C(=O)-N(R^8R^{8a})$, or $-(CR^7R^{7a})_m-C(=O)O-R^8$;

R^{10} is H or deuterium;

n is 0, 1, 2, 3, 4, or 5;

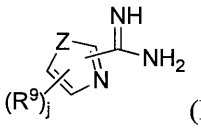
each m is independently 0, 1, 2, 3, or 4;

f is 1, 2, 3, or 4; and

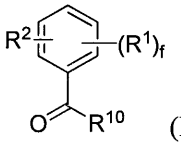
j is 0, 1, or 2;

wherein the process comprises the steps of:

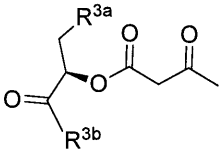
step (A): reacting an amidine compound of Formula (II), or a salt thereof


(II),

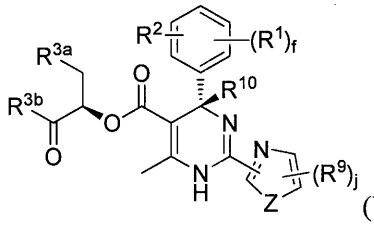
with an aldehyde compound of Formula (III)


(III),

and a compound of Formula (IVa)


(IVa),

to obtain a compound of Formula (Va),

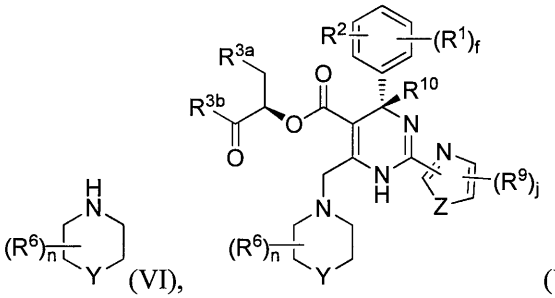

(Va),

wherein R^{3b} is methoxy or ethoxy; and

R^{3a} is H or C_{1-3} alkyl;

step (B): halogenating the compound of Formula (Va) to form a halide; and then reacting the halide with a compound of Formula (VI), or a salt thereof to obtain a compound of Formula

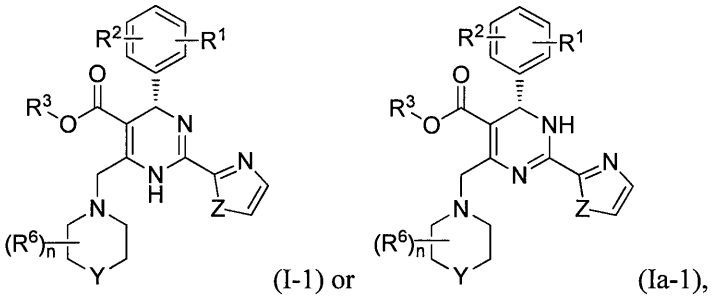
(VIIa),



(VI), (VIIa); and

step (C): forming the compound of Formula (I) or Formula (Ia) from the compound of Formula (VIIa) by means of a transesterification.

2. The process of claim 1, wherein the dihydropyrimidine compound has Formula (I-1), or a tautomer thereof having Formula (Ia-1),

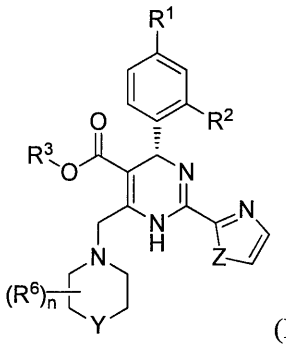
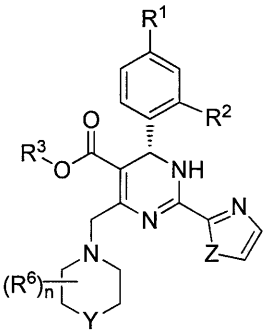


(I-1) or (Ia-1),

wherein, each R^6 is independently H, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, amino, C_{1-4} alkylamino, C_{1-4} alkoxy, nitro, triazolyl, tetrazyl, $-(CR^7R^{7a})_m-OH$, $-S(=O)_qOR^{8a}$, $-(CR^7R^{7a})_m-S(=O)_qN(R^{8a})_2$, $-(CR^7R^{7a})_t-N(R^{8a})_2$, $-(CR^7R^{7a})_m-C(=O)O-R^8$, $-(CR^7R^{7a})_m-C(=O)O-(CR^7R^{7a})_m-OC(=O)O-R^8$, $-(CR^7R^{7a})_m-C(=O)O-(CR^7R^{7a})_m-OC(=O)-R^8$, $-(CR^7R^{7a})_m-C(=O)O-(CR^7R^{7a})_m-C(=O)O-R^8$, $-(CR^7R^{7a})_m-OC(=O)-R^8$, or $-(CR^7R^{7a})_m-C(=O)-N(R^8R^{8a})$; and

each R^{7a} and R^7 is independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, $-(CH_2)_m-OH$, or $-(CH_2)_m-C(=O)O-R^8$.

3. The process of claim 2, wherein the dihydropyrimidine compound has Formula (I-2), or a tautomer thereof having Formula (Ia-2),


(I-2) or

(Ia-2),

wherein R^1 is F or Cl; and R^2 is Cl or Br.

4. The process of claim 1, 2, or 3, wherein

R^3 is methyl, ethyl, propyl, isopropyl, *tert*-butyl, or butyl;

Z is -O-, -S-, or $-N(CH_3)-$;

Y is -O-, -S-, $-S(=O)_2-$, or $-(CH_2)_q-$;

each R^6 is independently H, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, amino, C_{1-4} alkylamino, C_{1-4} alkoxy, nitro, triazolyl, tetrazyl, $-(CR^7R^{7a})_m-OH$, $-(CR^7R^{7a})_m-C(=O)O-R^8$, $-(CR^7R^{7a})_t-N(R^{8a})_2$, $-S(=O)_qOR^{8a}$, $-(CR^7R^{7a})_m-S(=O)_qN(R^{8a})_2$, $-(CR^7R^{7a})_m-C(=O)O-(CR^7R^{7a})_m-OC(=O)O-R^8$, $-(CR^7R^{7a})_m-C(=O)O-(CR^7R^{7a})_m-OC(=O)-R^8$, $-(CR^7R^{7a})_m-C(=O)O-(CR^7R^{7a})_m-C(=O)O-R^8$, $-(CR^7R^{7a})_m-OC(=O)-R^8$, or $-(CR^7R^{7a})_m-C(=O)N(R^8R^{8a})$;

each R^{7a} and R^7 is independently H, methyl, ethyl, trifluoromethyl, $-(CH_2)_m-OH$, or $-(CH_2)_m-C(=O)O-R^8$;

each R^8 and R^{8a} is independently H, methyl, ethyl, propyl, isopropyl, aminomethyl, methoxy, C_{1-4} alkyl-$S(=O)_2-$, phenyl, pyridyl, thiazolyl, furanyl, imidazolyl, isoxazolyl, oxazolyl, pyrrolyl, pyrimidinyl, pyridazinyl, diazolyl, triazolyl, tetrazolyl, thienyl, pyrazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyrazinyl, pyranyl, triazinyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropyl-$S(=O)_2-$, cyclobutyl-$S(=O)_2-$, cyclopentyl-$S(=O)_2-$, cyclohexyl-$S(=O)_2-$, naphthyl-$S(=O)_2-$, phenyl-$S(=O)_2-$, $-(CH_2)_m-OH$, $-(CH_2)_m-C(=O)O-(CH_2)_m-H$, or $-(CH_2)_m-OC(=O)-(CH_2)_m-H$;

R^{3b} is methoxy or ethoxy; and

R^{3a} is H, methyl, ethyl, isopropyl, or propyl.

5. The process of claim 1, 2, or 3, wherein the reaction in step (A) is performed at a temperature from 25 °C to 154°C or from 60 °C to 100°C.

6. The process of claim 1, 2, or 3, wherein the step (A) further comprises a step of cooling the resulting compound of Formula (Va) of step (A) to obtain a solid compound of Formula (Va) at a cooling temperature from −40 °C to 40 °C or from 25 °C to 40°C.

7. The process of claim 6, wherein the cooling is performed for a period of from 0 hour to 24 hours, or from 1 minute to 24 hours, or from 1 hour to 8 hours.

8. The process of claim 1, 2, or 3, wherein the amidine compound of Formula (II) reacts with the aldehyde compound of Formula (III) and the compound of Formula (IVa) in a first organic solvent, and the first organic solvent is applied in an amount of 0 equivalent to 80 equivalents, or 1 equivalent to 20 equivalents per 1 equivalent by weight of the amidine compound of Formula (II), or a salt thereof.

9. The process of claim 1, 2, or 3, wherein step (A) further comprises a step of purifying the solid compound of Formula (Va), wherein the solid compound of Formula (Va) is purified by at least one of the following methods:

(1) trituration, wherein the trituration is carried out at a temperature from −20 °C to 50 °C or from 0 °C to 40 °C;

(2) recrystallization, wherein the recrystallization comprises a crystallization process at a temperature from −30 °C to 40 °C or from 0 °C to 40°C, and wherein the recrystallization comprises a crystallization process of from 1 hour to 20 hours or from 1 hour to 10 hours; or

(3) washing, wherein the washing is performed at a temperature from 0°C to 30 °C.

10. The process of claim 9, wherein the purification is carried out in a second organic solvent, wherein the second organic solvent is applied in an amount of 2 equivalent to 20 equivalents per 1 equivalent by weight of the amidine compound of Formula (II), or a salt thereof.

11. The process of claim 8 or 10, wherein each of the first organic solvent and the second organic solvent is independently a C_{1-4} alcohol, a C_{1-4} alcohol-water mixture, acetone, diethyl ether, isopropyl ether, petroleum ether, tetrahydrofuran, acetonitrile, cyclopentane, cyclohexane, *n*-hexane, a C_{1-4} haloalkane solvent, ethyl acetate, trifluoroethanol, 2-methoxyethanol, 1,2-dimethoxyethane, 2-methoxyethyl ether, *N*,*N*-dimethyl formamide, *N*-methylpyrolidone, or a combination thereof, or wherein each of the first organic solvent and the second organic solvent is independently methanol, ethanol, *n*-propanol, *i*-propanol, *n*-butanol, *tert*-butanol, an ethanol-water mixture at a volume ratio of from 10:90 to 90:10, acetone, tetrahydrofuran, *N*-methylpyrolidone,

trifluoroethanol, 2-methoxyethanol, 1,2-dimethoxyethane, 2-methoxyethyl ether, ethyl acetate, glycol, *N*,*N*-dimethyl formamide, or a combination thereof.

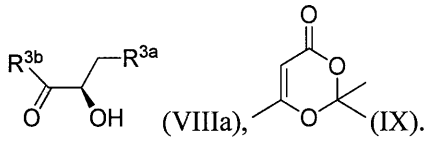
12. The process of claim 1, 2, or 3, wherein the halogenating reaction in step (B) is carried out in a third organic solvent, and wherein the third organic solvent is one or more C_{1-4} alcohols, one or more C_{1-4} haloalkanes, acetonitrile, isopropyl ether, petroleum ether, toluene, xylene, tetrahydrofuran, ethyl acetate, acetone, or a combination thereof, or wherein the third organic solvent is dichloromethane, chloroform, tetrachloromethane, acetonitrile, isopropyl ether, petroleum ether, tetrahydrofuran, methanol, ethanol, propanol, *i*-propanol, *n*-butanol, *tert*-butanol, ethyl acetate, acetone, or a combination thereof.

13. The process of claim 1, 2, or 3, wherein the halogenating reaction in step (B) is carried out in the presence of a halogenating agent, and wherein the halogenating agent is *N*-bromosuccinimide, *N*-chlorosuccinimide, *N*-iodosuccinimide, 1,3-dibromo-5,5-dimethylhydantoin, or 1,3-dichloro-5,5-dimethylhydantoin, or a combination thereof.

14. The process of claim 1, 2, or 3, wherein the transesterification in step (C) is performed in the present of a base, and wherein the base is formed by reacting lithium, sodium, or potassium or a combination thereof with a C_{1-4} alcohol.

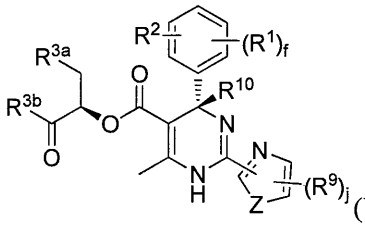
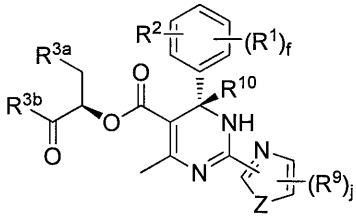
15. The process of claim 14, wherein the C_{1-4} alcohol is methanol, ethanol, propanol, *i*-propanol, *n*-butanol, *i*-butanol, or *tert*-butanol, and wherein the lithium, sodium or potassium or a combination thereof is applied in an amount of 2 equivalents to 6 equivalents per 1 equivalent by mole of the compound of Formula (VIIa).

16. The process of claim 1, wherein the compound of Formula (IVa) in step (A) is prepared by a process comprising reacting a compound of Formula (VIIIa) with a compound of Formula (IX),



(VIIIa), (IX).

17. A compound having Formula (Va), or a tautomer thereof having Formula (Va1), or a salt thereof, or a combination thereof,


(Va) or

(Va1),

wherein each R^1 and R^2 is independently F, Cl, or Br;

R^{3b} is methoxy or ethoxy;

R^{3a} is H or C_{1-3} alkyl;

each R^9 is independently H, halo, C_{1-4} alkyl, C_{1-4} alkylthio, C_{1-4} haloalkyl, C_{3-6} cycloalkyl, $-(CR^7R^{7a})_m-C(=O)-N(R^8R^{8a})$, or $-(CR^7R^{7a})_m-C(=O)O-R^8$;

each R^{7a} and R^7 is independently H, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, $-(CH_2)_m-OH$, or $-(CH_2)_m-C(=O)O-R^8$; or R^{7a} and R^7, together with the carbon atom to which they are attached, form a C_{3-6} cycloalkyl group, C_{2-9} heterocyclyl goup, or -(C=O)-;

each R^8 and R^{8a} is independently H, C_{1-4} alkyl, amino-C_{1-4}-alkyl, C_{1-4} alkoxy, C_{1-6} alkyl-$S(=O)_q$-, C_{6-10} aryl, C_{1-9} heteroaryl, C_{3-6} cycloalkyl, C_{2-9} heterocyclyl, C_{6-10} aryl-C_{1-6}-alkyl, C_{1-9} heteroaryl-C_{1-6}-alkyl, C_{3-6} cycloalkyl-C_{1-4}-alkyl, C_{2-9} heterocyclyl-C_{1-6}-alkyl, C_{2-9} heterocyclyl-$S(=O)_q$-, C_{1-9} heteroaryl-$S(=O)_q$-, C_{3-6} cycloalkyl-$S(=O)_q$-, C_{6-10} aryl-$S(=O)_q$-, $-(CH_2)_m-OH$, $-(CH_2)_m-C(=O)O-(CH_2)_m-H$, or $-(CH_2)_m-OC(=O)-(CH_2)_m-H$;

each m is independently 0, 1, 2, 3, or 4;

R^{10} is H or deuterium;

f is 1, 2, 3, or 4;

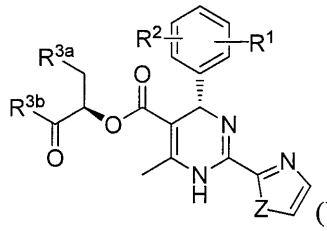
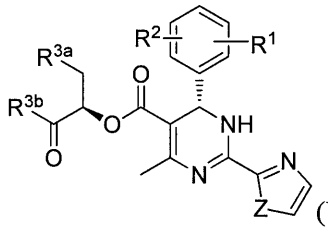
j is 0, 1, or 2;

Z is -O-, -S-, $-S(=O)_t$, or $-N(R^4)$-;

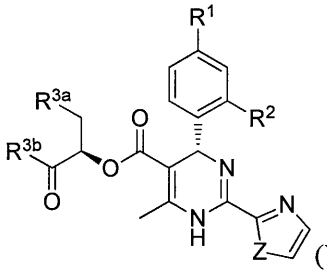
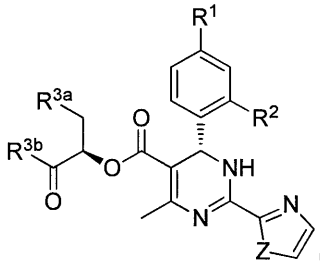
t is 0, 1, or 2; and

R^4 is H or C_{1-4} alkyl.

18. The compound of claim 17 having Formula (Va-1), or a tautomer thereof having Formula (Va1-1), or a salt thereof, or a combination thereof,


(Va-1) or

(Va1-1).

19. The compound of claim 17 or 18 having Formula (Va-2), or a tautomer thereof having Formula (Va1-2), or a salt thereof, or a combination thereof,


(Va-2) or

(Va1-2),

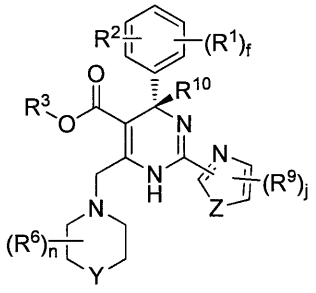
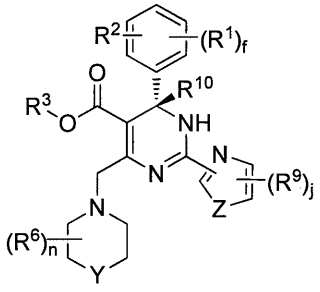
wherein R^1 is F or Cl; and R^2 is Cl or Br;

Z is -O-, -S-, or -N(CH_3)-;

R^{3b} is methoxy or ethoxy; and

R^{3a} is H, methyl, ethyl, isopropyl, or propyl.

20. A process for preparing a dihydropyrimidine compound having Formula (I), or a tautomer thereof having Formula (Ia),


(I) or

(Ia),

wherein each R^1 and R^2 is independently F, Cl, or Br;

R^3 is C_{1-4} alkyl;

Z is -O-, -S-, -S(=O)$_t$-, or -N(R^4)-;

Y is -O-, -S-, -S(=O)$_t$-, -(CH_2)q-, or -N(R^5)-;

each t and q is independently 0, 1, or 2;

each of R^4 and R^5 is independently H or C_{1-4} alkyl;

each R^6 is independently H, deuterium, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, amino, C_{1-4}

alkylamino, C_{1-4} alkoxy, nitro, triazolyl, tetrazyl, $-(CR^7R^{7a})_m-OH$, $-(CR^7R^{7a})_m-C(=O)O-R^8$, $-(CR^7R^{7a})_t-N(R^{8a})_2$, $-S(=O)_qOR^{8a}$, $-(CR^7R^{7a})_m-S(=O)_qN(R^{8a})_2$, $-(CR^7R^{7a})_m-C(=O)O-(CR^7R^{7a})_m-OC(=O)O-R^8$, $-(CR^7R^{7a})_m-C(=O)O-(CR^7R^{7a})_m-OC(=O)-R^8$, $-(CR^7R^{7a})_m-C(=O)O-(CR^7R^{7a})_m-C(=O)O-R^8$, $-(CR^7R^{7a})_m-OC(=O)-R^8$, or $-(CR^7R^{7a})_m-C(=O)N(R^8R^{8a})$;

each R^{7a} and R^7 is independently H, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, $-(CH_2)_m-OH$, or $-(CH_2)_m-C(=O)O-R^8$; or R^{7a} and R^7, together with the carbon atom to which they are attached, form a C_{3-6} cycloalkyl group, C_{2-9} heterocyclyl goup, or -(C=O)-;

each R^8 and R^{8a} is independently H, C_{1-4} alkyl, amino-C_{1-4}-alkyl, C_{1-4} alkoxy, C_{1-6} alkyl-$S(=O)_q$-, C_{6-10} aryl, C_{1-9} heteroaryl, C_{3-6} cycloalkyl, C_{2-9} heterocyclyl, C_{6-10} aryl-C_{1-6}-alkyl, C_{1-9} heteroaryl-C_{1-6}-alkyl, C_{3-6} cycloalkyl-C_{1-4}-alkyl, C_{2-9} heterocyclyl-C_{1-6}-alkyl, C_{2-9} heterocyclyl-$S(=O)_q$-, C_{1-9} heteroaryl-$S(=O)_q$-, C_{3-6} cycloalkyl-$S(=O)_q$-, C_{6-10} aryl-$S(=O)_q$-, $-(CH_2)_m-OH$, $-(CH_2)_m-C(=O)O-(CH_2)_m-H$, or $-(CH_2)_m-OC(=O)-(CH_2)_m-H$;

each R^9 is independently H, halo, C_{1-4} alkyl, C_{1-4} alkylthio, C_{1-4} haloalkyl, C_{3-6} cycloalkyl, $-(CR^7R^{7a})_m-C(=O)-N(R^8R^{8a})$, or $-(CR^7R^{7a})_m-C(=O)O-R^8$;

R^{10} is H or deuterium;

n is 0, 1, 2, 3, 4, or 5;

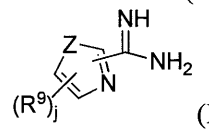
each m is independently 0, 1, 2, 3, or 4;

f is 1, 2, 3, or 4; and

j is 0, 1, or 2;

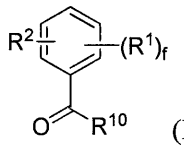
wherein the process comprises the steps of:

step (1): reacting an amidine compound of Formula (II), or a salt thereof



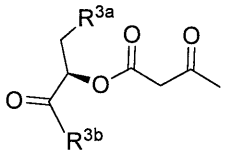
(II),

with an aldehyde compound of Formula (III)



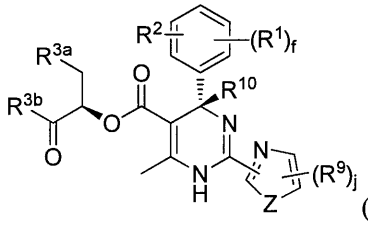
(III),

and a compound of Formula (IVa)



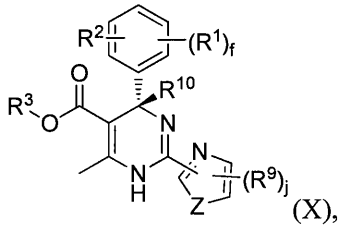
(IVa),

to obtain a compound (Va),



(Va);

step (2): forming a compound of Formula (X) from a compound of Formula (Va) by means of a transesterification,

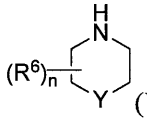


(X),

wherein R^{3b} is methoxy or ethoxy; and

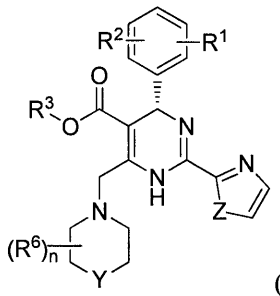
R^{3a} is H or C_{1-3} alkyl; and

step (3): halogenating the compound of Formula (X) to form a halide; and then reacting the halide with a compound of Formula (VI), or a salt thereof to obtain a compound of Formula (I) or Formula (Ia),

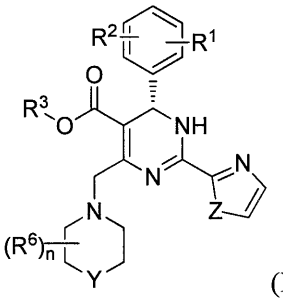


(VI).

21. The process of claim 20, wherein the dihydropyrimidine compound has Formula (I-1), or a tautomer thereof having Formula (Ia-1),



(I-1) or



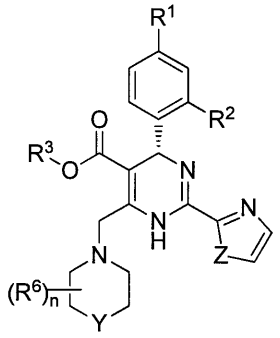
(Ia-1),

wherein, each R^6 is independently H, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, amino, C_{1-4} alkylamino,

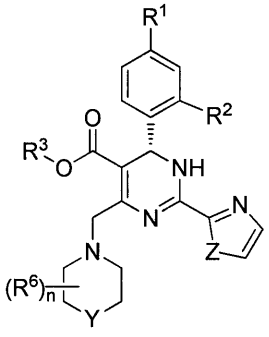
C_{1-4} alkoxy, nitro, triazolyl, tetrazyl, $-(CR^7R^{7a})_m-OH$, $-(CR^7R^{7a})_m-C(=O)O-R^8$, $-(CR^7R^{7a})_t-N(R^{8a})_2$, $-S(=O)_qOR^{8a}$, $-(CR^7R^{7a})_m-S(=O)_qN(R^{8a})_2$, $-(CR^7R^{7a})_m-C(=O)O-(CR^7R^{7a})_m-OC(=O)O-R^8$, $-(CR^7R^{7a})_m-C(=O)O-(CR^7R^{7a})_m-OC(=O)-R^8$, $-(CR^7R^{7a})_m-C(=O)O-(CR^7R^{7a})_m-C(=O)O-R^8$, $-(CR^7R^{7a})_m-OC(=O)-R^8$, or $-(CR^7R^{7a})_m-C(=O)N(R^8R^{8a})$; and

each R^{7a} and R^7 is independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, $-(CH_2)_m-OH$, or $-(CH_2)_m-C(=O)O-R^8$.

22. The process of claim 21, wherein the dihydropyrimidine compound has Formula (I-2), or a tautomer thereof having Formula (Ia-2),



(I-2) or



(Ia-2),

wherein R^1 is F or Cl; and R^2 is Cl or Br.

23. The process of claim 20, 21, or 22, wherein

R^3 is methyl, ethyl, propyl, isopropyl, *tert*-butyl, or butyl;

Z is -O-, -S-, or $-N(CH_3)-$;

Y is -O-, -S-, $-S(=O)_2-$, or-$(CH_2)_q-$;

each R^6 is independently H, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, amino, C_{1-4} alkylamino, C_{1-4} alkoxy, nitro, triazolyl, tetrazyl, $-(CR^7R^{7a})_m-OH$, $-S(=O)_qOR^{8a}$, $-(CR^7R^{7a})_m-S(=O)_qN(R^{8a})_2$, $-(CR^7R^{7a})_t-N(R^{8a})_2$, $-(CR^7R^{7a})_m-C(=O)O-R^8$, $-(CR^7R^{7a})_m-C(=O)O-(CR^7R^{7a})_m-OC(=O)O-R^8$, $-(CR^7R^{7a})_m-C(=O)O-(CR^7R^{7a})_m-OC(=O)-R^8$, $-(CR^7R^{7a})_m-C(=O)O-(CR^7R^{7a})_m-C(=O)O-R^8$, $-(CR^7R^{7a})_m-OC(=O)-R^8$, or $-(CR^7R^{7a})_m-C(=O)-N(R^8R^{8a})$;

each R^{7a} and R^7 is independently H, methyl, ethyl, trifluoromethyl, $-(CH_2)_m-OH$, or $-(CH_2)_m-C(=O)O-R^8$;

each R^8 and R^{8a} is independently H, methyl, ethyl, propyl, isopropyl, aminomethyl, methoxy, C_{1-4} alkyl-$S(=O)_2-$, phenyl, pyridyl, thiazolyl, furanyl, imidazolyl, isoxazolyl, oxazolyl, pyrrolyl, pyrimidinyl, pyridazinyl, diazolyl, triazolyl, tetrazolyl, thienyl, pyrazolyl, isothiazolyl, oxadiazolyl,

thiadiazolyl, pyrazinyl, pyranyl, triazinyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropyl-$S(=O)_2$-, cyclobutyl-$S(=O)_2$-, cyclopentyl-$S(=O)_2$-, cyclohexyl-$S(=O)_2$-, naphthyl-$S(=O)_2$-, phenyl-$S(=O)_2$-, $-(CH_2)_m$-OH, $-(CH_2)_m$-C(=O)O-$(CH_2)_m$-H, or $-(CH_2)_m$-OC(=O)-$(CH_2)_m$-H;

R^{3b} is methoxy or ethoxy; and

R^{3a} is H, methyl, ethyl, isopropyl, or propyl.

24. The process of claim 20, 21, or 22, wherein the transesterification in step (2) is performed in the present of a base, wherein the base is formed by reacting lithium, sodium, or potassium or a combination thereof with a C_{1-4} alcohol, wherein the C_{1-4} alcohol is methanol, ethanol, propanol, *i*-propanol, *n*-butanol, *i*-butanol, or *tert*-butanol, and wherein the lithium, sodium, potassium or a combination thereof is applied in an amount of 2 equivalents to 8 equivalents per 1 equivalent by mole of the compound of Formula (Va).

25. The process of claim 20, 21, or 22, wherein the halogenating reaction in step (3) is carried out in a fourth organic solvent, and wherein the organic solvent is one or more C_{1-4} alcohols, one or more C_{1-4} haloalkanes, ethyl acetate, acetonitrile, isopropyl ether, petroleum ether, toluene, xylene, tetrahydrofuran, acetone, or a combination thereof, or the fourth organic solvent is methanol, ethanol, propanol, *i*-propanol, *n*-butanol, *tert*-butanol, dichloromethane, chloroform, tetrachloromethane, ethyl acetate, acetonitrile, isopropyl ether, petroleum ether, tetrahydrofuran, acetone, or a combination thereof.

26. The process of claim 20, 21, or 22, wherein the halogenating reaction in step (3) is carried out in the presence of a halogenating agent, and wherein the halogenating agent is *N*-bromosuccinimide, *N*-chlorosuccinimide, *N*-iodosuccinimide, 1,3-dibromo-5,5-dimethylhydantoin, 1,3-dichloro-5,5-dimethylhydantoin, or a combination thereof.