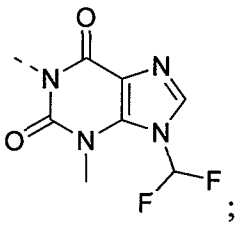
specifically replaced with  ;

[9] L_{11} is selected from absence, or C(R)(R');

[10] each of R, R' is independently selected from H, a halogen, OH, NH_2, CN, or, an optionally substituted 1- to 6- membered alkyl or heteroalkyl;

[11] optionally, R, R' can form a 3- to 6- membered cycloalkyl, heterocyoalkyl by cyclization;

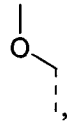
[12] A represents absence, or is selected from cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, each of which is optionally substituted;

[13] L_{12} is selected from an optionally substituted 1- to 6- membered alkyl or heteroalkyl;

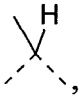
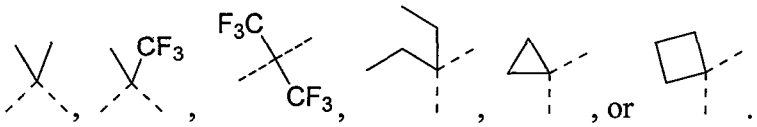
[14] R_1 is selected from an optionally substituted 1- to 6- membered alkyl or heteroalkyl;

[15] "hetero" represents N, O, S, C(=O), S(=O), or $S(=O)_2$, the number of the heteroatom on each group is selected from 1, 2, 3 or 4.

[16] In some embodiments of the present invention, the substituents in the R, R', A, L_{12} and R_1 are independently selected from the halogen, OH, NH_2, CN, or, the optionally substituted 1- to 6- membered alkyl or heteroalkyl, the number of the substituent on each group is independently selected from 1, 2 or 3.

[17] In some embodiments of the present invention, the substituents in the R, R', A, L_{12} and R_1 are independently selected from the halogen, CF_3, CN, OH, Me, Et, *n*-propyl, isopropyl, cyclopropyl,  , or  .

[18] In some embodiments of the present invention, the R and R' are independently selected from H, Me, CF_3, or Et.

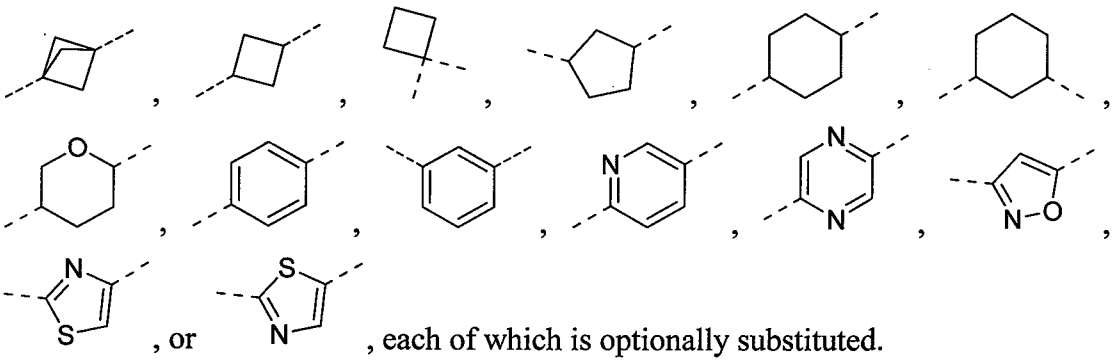
[19] In some embodiments of the present invention, the L_{11} is selected from  ,  .

[20] In some embodiments of the present invention, the A is selected from the 3- to 12-membered alkyl or cycloalkyl, or the 5- to 12-membered aryl or heteroaryl, each of which

is optionally substituted.

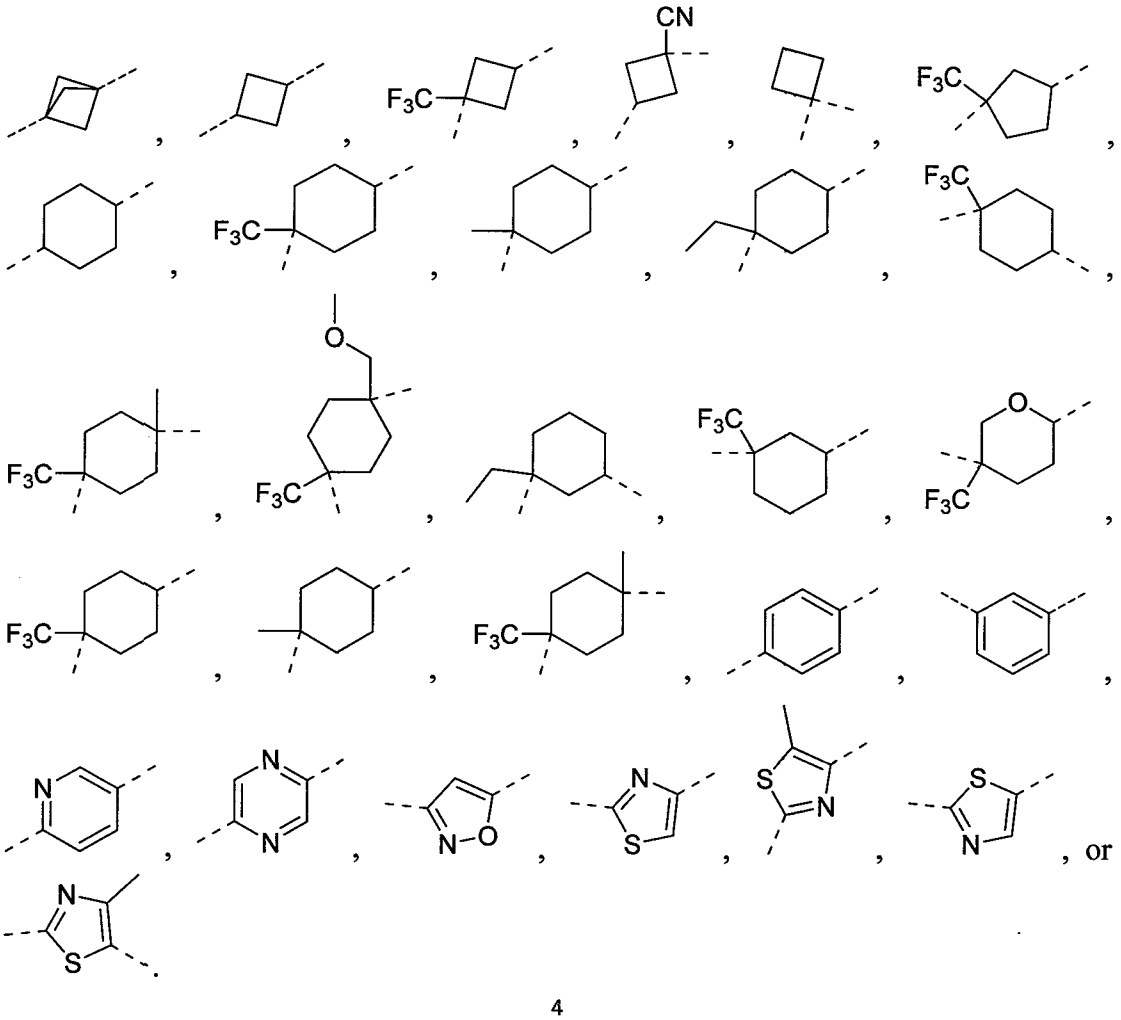
[21] In some embodiments of the present invention, the A is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, epoxypentyl, phenyl, pyridyl, pyrazinyl, oxazolyl, isoxazolyl, thiazolyl, or bicyclo[1.1.1]pentane, or a bicyclic group, a spiro group or a fused cyclic group consisting of any two of the above groups, each of which is optionally substituted.

[22] In some embodiments of the present invention, the A is selected from  ,



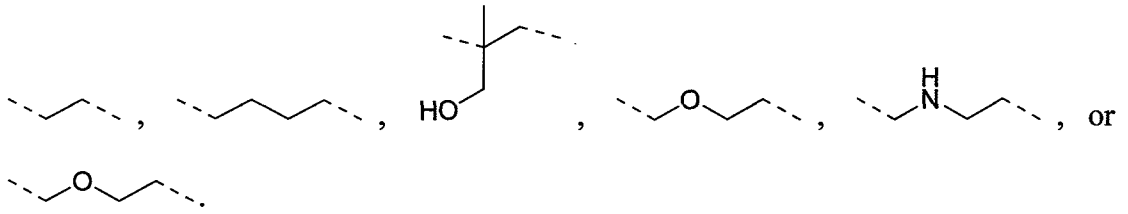
, or , each of which is optionally substituted.

[23] In some embodiments of the present invention, the A is selected from  ,

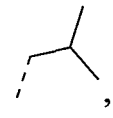


, or .

[24] In some embodiments of the present invention, the L_{12} is selected from methylene,

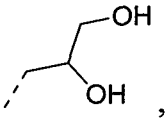


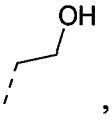
[25] In some embodiments of the present invention, the R_1 is selected from Me, CHF_2, CF_3, Et, CH_2CF_3, isopropyl,



, cyclopropyl,

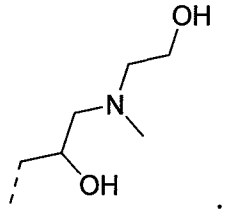






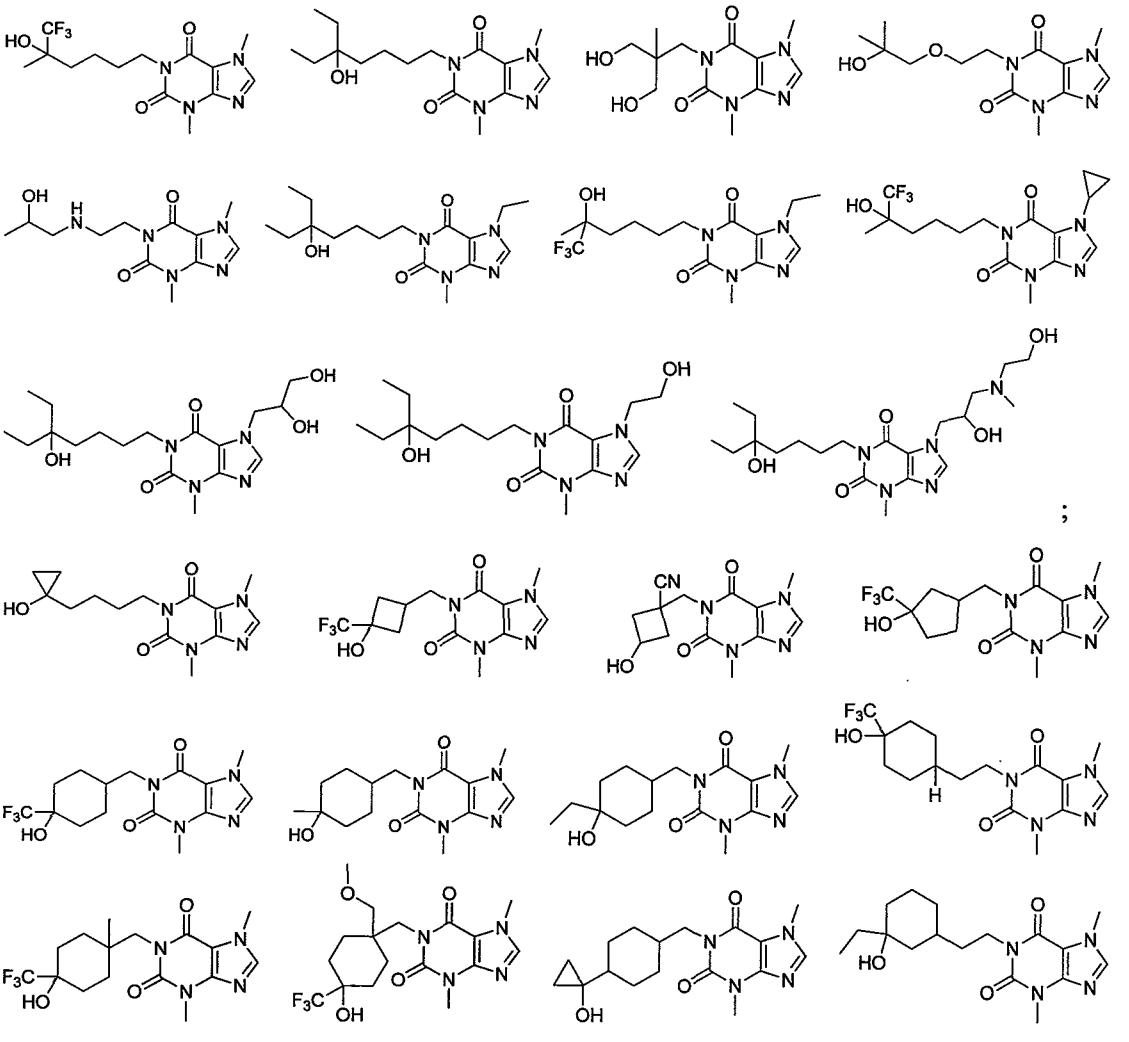
,

or



.

[26] The present invention is selected from the group consisting of:



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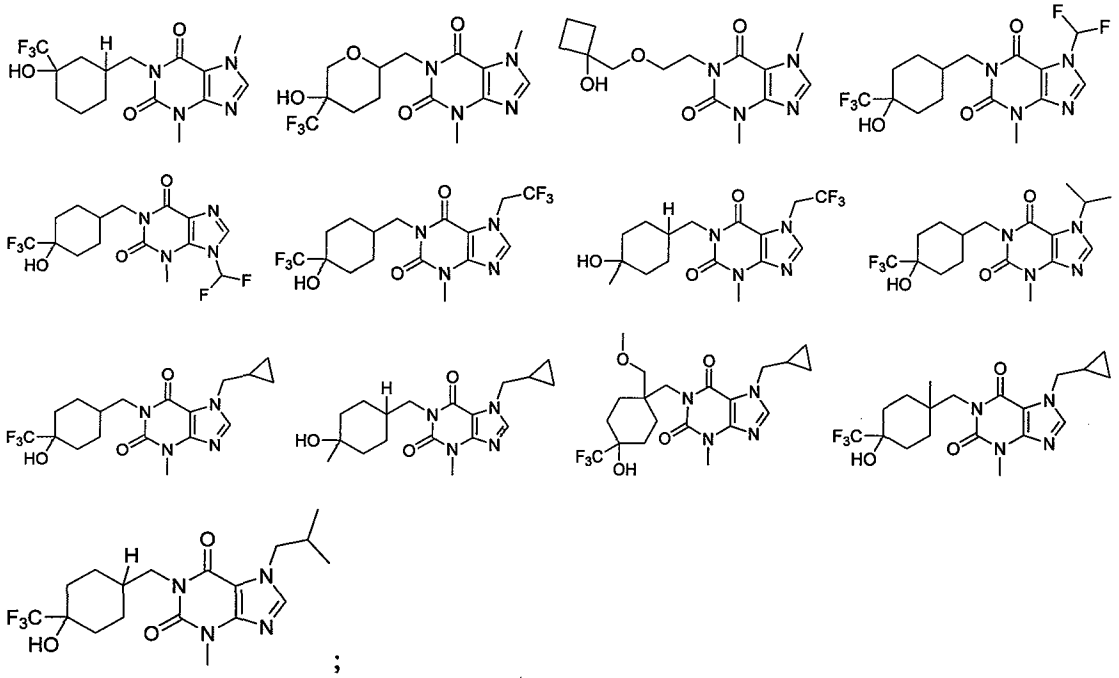

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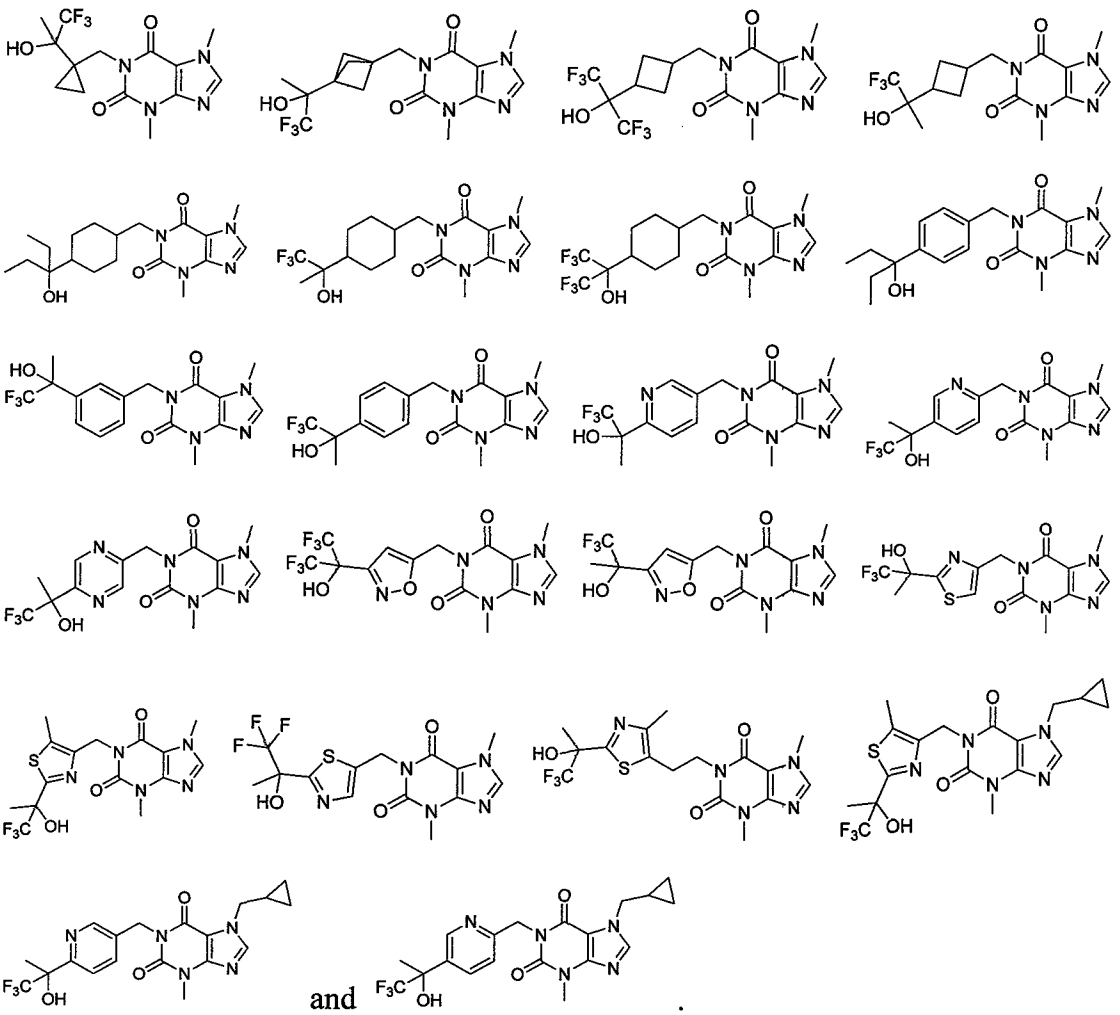
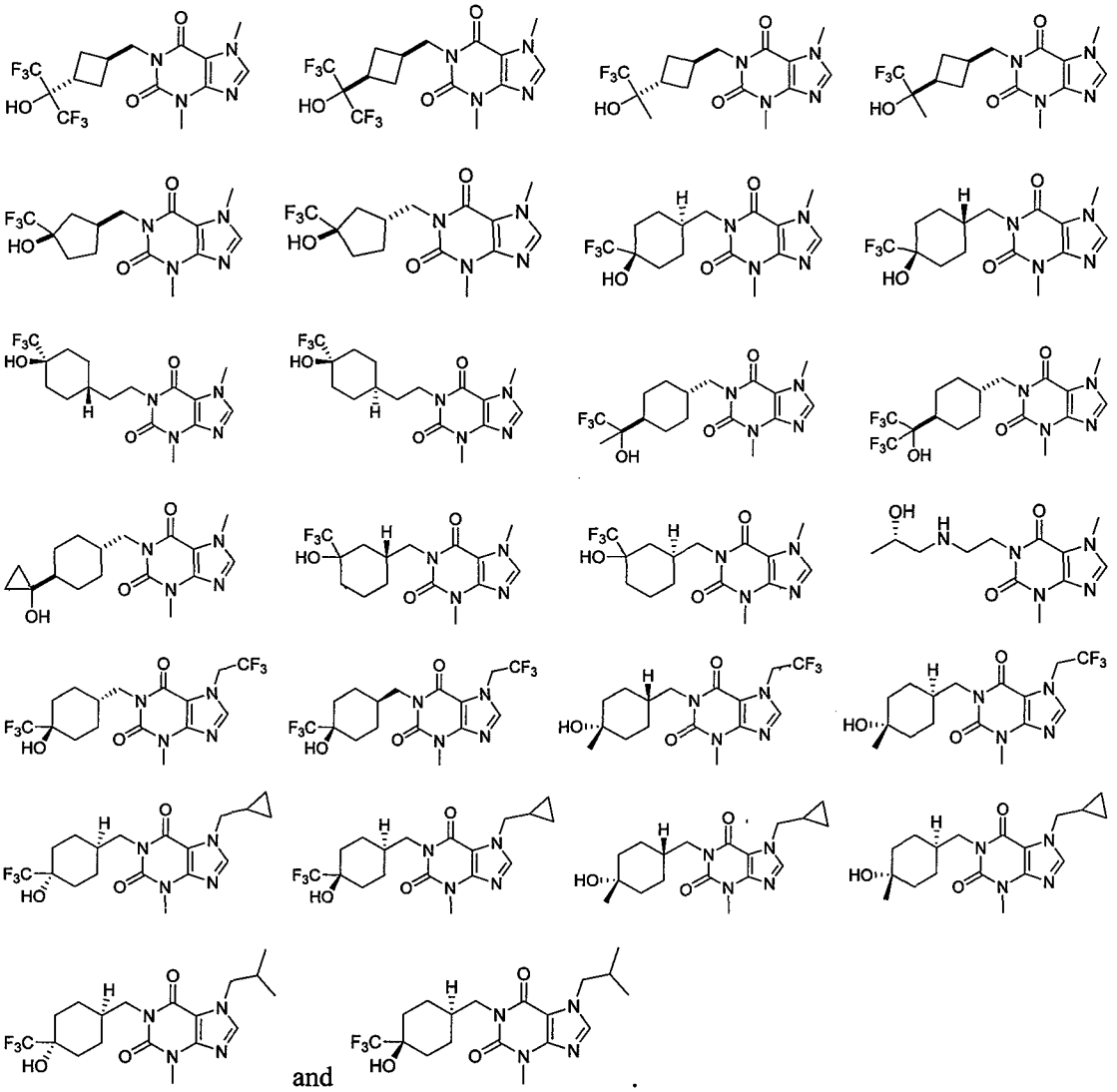


and

[27] Further, the present invention is selected from the group consisting of:



and

[28] The present invention also provides an application of the compound, the tautomer thereof or the pharmaceutically acceptable salt thereof in manufacturing a PDE2 inhibitor and a TNF-α inhibitor.

Relevant Definitions

[29] Unless otherwise specified, the following terms and phrases used herein are intended to have the following meanings. A particular term or phrase should not be considered uncertain or unclear in the absence of a specific definition while should be understood according to the ordinary meaning. When a trade name appears herein, it refers to the corresponding commodity or its active ingredient.

[30] Herein, the term "pharmaceutically acceptable" is aimed at those compounds, materials, compositions and/or dosage forms, which are within the scope of reliable medical judgment and applicable for use in contact with human and animal tissue but without too much toxicity, irritation, allergic reactions or other problems or complications, also meet the reasonable benefit/risk ratio.

[82]Methyl-3-oxocyclobutanecarboxylate (25.0 g, 195 mmol), ethylene glycol (35.0 g, 564 mmol) and *p*-toluenesulfonic acid (3.50 g, 20.0 mmol) were dissolved in toluene (250 mL), after equipped with a water separator, the reaction mixture was heated to reflux overnight. The reaction solution was cooled to 25°C and washed successively with water (300 mL × 2), saturated sodium bicarbonate aqueous solution (500 mL × 2). The organic phase was dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated under reduced pressure to deliver methyl 5,8-dioxaspiro[3.4]octane-2-carboxylate (22.5 g, yellow liquid), yield: 90%.

Step 3

5,8-Dioxaspiro[3.4]octan-2-ylmethanol

[83]Under the nitrogen gas atmosphere, lithium aluminum hydride (5.20 g, 136 mmol) was slowly dissolved in tetrahydrofuran (240 mL) at 0°C, and then methyl 5,8-dioxaspiro[3.4]octane-2-carboxylate (19.5 g, 113 mmol) dissolved in tetrahydrofuran (60 mL) was added dropwise. The reaction was slowly warmed to 25°C and stirred for 3.5 hours. The reaction solution was cooled to 0°C and water (5.20 g, 289 mmol), 15% sodium hydroxide (5.20 g, 19.5 mmol) and water (15.6 g, 867 mmol) were slowly added successively. The reaction mixture was filtered and the filter cake was washed with tetrahydrofuran (10 mL × 3) and the filtrate was concentrated under reduced pressure and purified by silica gel column chromatography (1:1 petroleum ether / ethyl acetate, Rf = 0.4) to deliver the product 5,8-dioxaspiro[3.4]octan-2-ylmethanol (10.0 g, yellow liquid), yield: 62%. ^{1}H-NMR: (400 MHz, $CDCl_3$) δ 3.90-3.87 (m, 4H), 3.67 (d, J = 6.4 Hz, 2H), 2.45-2.40 (m, 2H), 2.38-2.26 (m, 1H), 2.13-2.08 (m, 2H).

Step 4

5,8-Dioxaspiro[3.4]octan-2-ylmethyl methanesulfonate

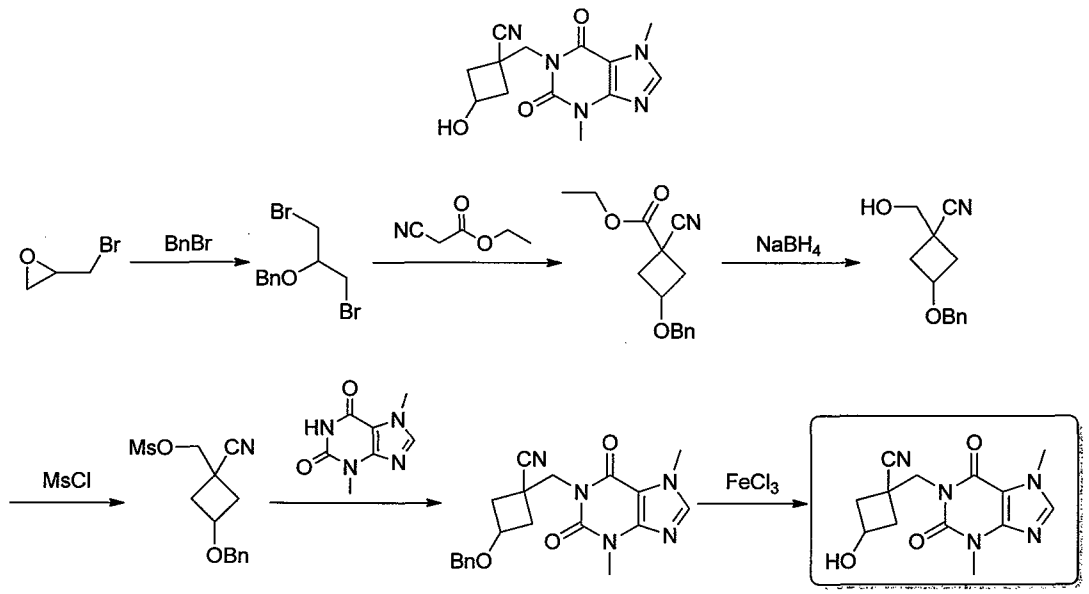
[84]5,8-Dioxaspiro[3.4]octan-2-ylmethanol (500 mg, 53.1 mmol) and triethylamine (896 mg, 6.90 mmol) were dissolved in dichloromethane (23 mL), methanesulfonyl chloride (1.40 g, 12.6 mmol) was slowly added at 0°C. The reaction solution was warmed to 25°C and stirred overnight. The reaction was quenched by the addition of water (50 mL) and extracted with ethyl acetate (50 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to deliver the product 5,8-dioxaspiro[3,4]octan-2-ylmethyl methanesulfonate (2.30 g, yellow liquid).

[85]MS-ESI calcd. for $[M+H]^+$ 223, found 223.

Step 5

1-(5,8-Dioxaspiro[3.4]octan-2-ylmethyl)-3,7-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione

[86]5,8-Dioxaspiro[3,4]octan-2-ylmethyl methanesulfonate (1.00 g, 4.50 mmol), 3,7-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (810 mg, 4.50 mmol), potassium carbonate (1.20 g, 13.5 mmol) and potassium iodide (75.0 mg, 0.45 mmol) were dissolved in *N*,*N*-



Step 1

(((1,3-Dibromopropan-2-yl)oxy)methyl)benzene

[89] 2-(Bromomethyl)oxirane (8.40 g, 61.3 mmol) was added to a solution of cuprous chloride (6.87 g, 51.1 mmol) in benzyl bromide (8.74 g, 51.1 mmol) at room temperature. The reaction was stirred at 150°C for 11 hours. The reaction solution was cooled to room temperature, water (100 mL) was slowly added and the reaction mixture was extracted with ethyl acetate (100 mL × 3). The organic phases were combined and dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure, the resulting product was purified by silica gel column chromatography (petroleum ether, Rf = 0.6) to deliver the product (((1,3-dibromopropan-2-yl)oxy) methyl)benzene (8.60 g, yellow oil), yield: 44%. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.39-7.31 (m, 5H), 4.67 (s, 2H), 3.82-3.78 (m, 1H), 3.58 (d, J = 5.2 Hz, 4H).

Step 2

Ethyl 3-(benzyloxy)-1-cyanocyclobutane carboxylate

[90] Ethyl cyanoacetate (2.76 g, 24.3 mmol) was added slowly at room temperature to a solution of (((1,3-dibromopropan-2-yl)oxy)methyl)benzene (7.00 g, 18.2 mmol) and potassium carbonate (10.0 g, 72.7 mmol) in *N*, *N*-dimethylformamide (35 mL). The reaction was stirred at 90°C for 4 hours. The reaction mixture was cooled to room temperature, filtered, and the solid was washed with ethyl acetate (20 mL). The resulting organic phase was washed with saturated ammonium chloride aqueous solution (20 mL x 3). The organic phase was dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure, the resulting product was purified by silica gel column chromatography (30:1 petroleum ether / ethyl acetate, Rf = 0.4) to give the product ethyl 3-(benzyloxy)-1-cyanocyclobutane carboxylate (3.80 g, colorless oil), yield: 81%. ^{1}H NMR: (400 MHz, Methanol-d_4) δ

7.40-7.28 (m, 5H), 4.48-4.44 (m, 2H), 4.37-4.31 (m, 1H), 4.30-4.24 (m, 2H), 2.97 -2.80 (m, 2H), 2.73-2.65 (m, 2H), 1.37-1.30 (m, 3H).

Step 3

3-(Benzyloxy)-1-(hydroxymethyl)cyclobutanecarbonitrile

[91]Sodium borohydride (1.39 g, 36.6 mmol) was dissolved in tetrahydrofuran and water (20 mL:2 mL), and a solution of ethyl 3-(benzyloxy)-1-cyanocyclobutane carboxylate (3.80 g, 14.6 mmol) in tetrahydrofuran (22 mL) was slowly added dropwise at 0°C over 20 minutes. The reaction was stirred at room temperature for 2 hours. The mixture was diluted with ethyl acetate (50 mL), washed with water (30 mL) and saturated brine (30 mL) seperately, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give the crude product 3-(benzyloxy)-1-(hydroxymethyl)cyclobutanecarbonitrile (3.70 g, colorless oil). ^{1}H NMR: (400 MHz, DMSO-*d*$_6$) δ 7.38-7.25 (m, 5H), 5.57-5.52 (m, 1H), 4.39-4.36 (m, 2H), 4.13-4.04 (m, 1H), 3.57-3.51 (m, 2H), 2.58-2.51 (m, 1H), 2.49-2.45 (m, 1H), 2.31-2.09 (m, 2H).

Step 4

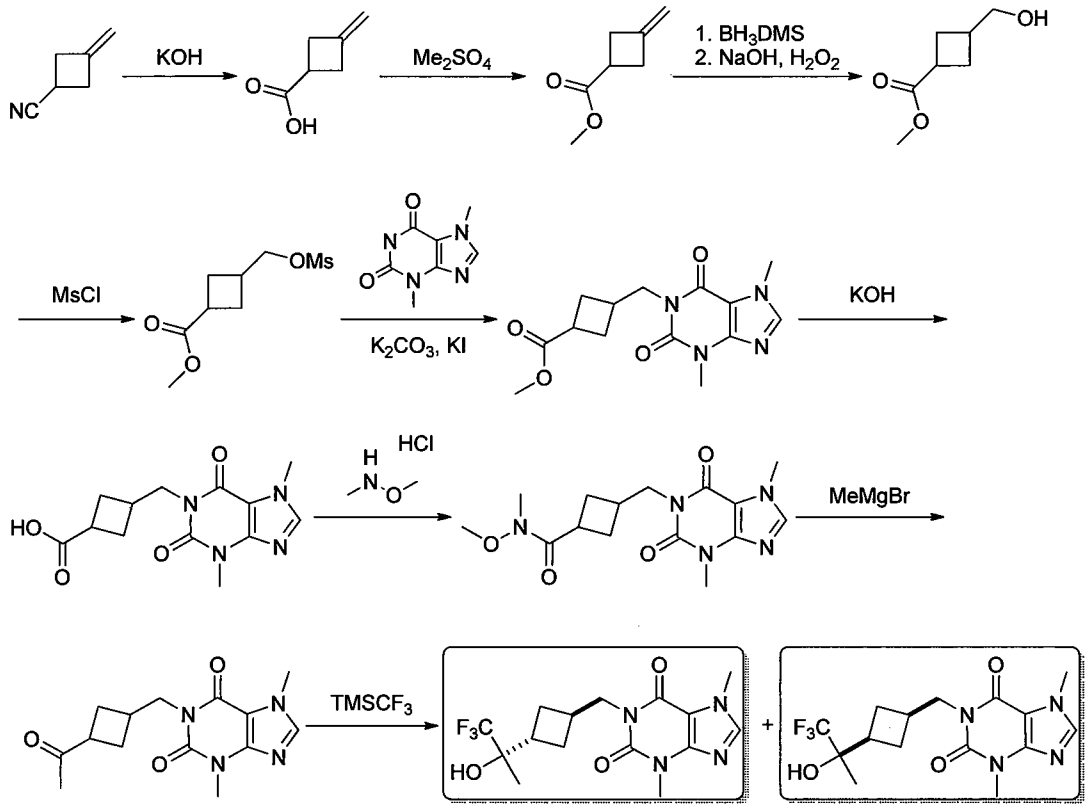
(3-(Benzyloxy)-1-cyanocyclobutyl)methyl methanesulfonate

[92]3-(Benzyloxy)-1-(hydroxymethyl)cyclobutanecarbonitrile (3.70 g, 15.3 mmol) and triethylamine (3.10 g, 30.6 mmol) were dissolved in dichloromethane (35 mL), methanesulfonyl chloride (3.29 g, 28.7 mmol) was slowly added at 0°C. The reaction was stirred at room temperature for 4 hours, saturated ammonium chloride aqueous solution (30 mL) was added and the reaction mixture was extracted with ethyl acetate (50 mL × 2), the organic phase was dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to deliver the crude product (3-(benzyloxy)-1-cyanocyclobutyl)methyl methanesulfonate (4.56 g, dark brown oil). ^{1}H NMR: (400 MHz, Methanol-*d*$_4$) δ 7.36-7.26 (m, 5H), 4.47-4.45 (m, 2H), 4.44-4.38 (m, 2H), 3.21-3.18 (m, 1H), 3.17 -3.14 (m, 3H), 2.81-2.60 (m, 2H), 2.53-2.26 (m, 2H).

Step 5

3-(Benzyloxy)-1-((3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)methyl)cyclobutanecarbonitrile

[93](3-(Benzyloxy)-1-cyanocyclobutyl)methyl methanesulfonate (4.50 g, 15.2 mmol), 3,7-dimethyl-1*H*-purine-2,6-(3*H*,7*H*)-dione (2.75 g, 15.2 mmol) and potassium iodide (1.26 g, 7.62 mmol) were dissolved in *N*,*N*-dimethylformamide (100 mL), potassium carbonate (6.32 g, 45.7 mmol) was added, the reaction mixture was heated to 120°C and refluxed for 4 hours. The reaction mixture was cooled to room temperature, filtered, the filtrate was concentrated under reduced pressure, water (50 mL) was added and the reaction mixture was extracted with ethyl acetate (50 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give the crude product 3-(benzyloxy)-1-



Step 1

3-Methylene cyclobutanecarboxylic acid

[106] 3-Methylene cyclobutyronitrile (10.0 g, 107 mmol) and potassium hydroxide (18.1 g, 322 mmol) were dissolved in ethanol (100 mL) and water (50 mL), after reacted at 100°C for 2 hours, 1 N hydrochloric acid (120 mL) was added. The resulting mixture was extracted with dichloromethane (30 mL × 3), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to deliver 3-methylene cyclobutanecarboxylic acid (11.0 g, yellow oil), yield: 91%. ^{1}H NMR: (400 MHz, Methanol-d_4) δ 4.83-4.76 (m, 2H), 3.15-2.96 (m, 1H), 2.95-2.92 (m, 4H).

Step 2

Methyl-3-methylene cyclobutanecarboxylate

[107] 3-Methylene cyclobutanecarboxylic acid (11.0 g, 98.1 mmol) and potassium carbonate (27.1 g, 196 mmol) were dissolved in acetone (100 mL), dimethyl sulfate (14.8 g, 117 mmol) was added at 25°C. After reacting at 70°C for 12 hours, the reaction was quenched by the addition of water (20 mL), extracted with dichloromethane (30 mL × 3), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to deliver methyl-3-methylene cyclobutanecarboxylate (12.0 g, yellow oil), yield: 97%. ^{1}H NMR: (400 MHz, Methanol-d_4) δ 4.83-4.79 (m, 2H), 3.96 (s, 2H), 3.68 (s, 3H), 3.17-3.15 (m, 1H), 2.95-2.92 (m, 2H).

Step 3

Methyl 3-(hydroxymethyl) cyclobutane carboxylate

[108] Methyl-3-methylene cyclobutanecarboxylate (2.00 g, 15.8 mmol) was dissolved in tetrahydrofuran (30 mL), borane dimethyl sulfide (3.61 g, 47.5 mmol) was added dropwise at -10°C and then reacted at -10°C for 3 hours, 3 N sodium hydroxide aqueous solution (10 mL) and hydrogen peroxide (5 mL) were added and the reaction was continued for 1 hour, the reaction solution was quenched by the addition of saturated sodium thiosulfate aqueous solution (30 mL), extracted with dichloromethane (10 mL × 3), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to deliver methyl 3-(hydroxymethyl) cyclobutane carboxylate (2.00 g, yellow oil), yield: 87%. ^{1}H NMR: (400 MHz, Methanol-d_4) δ 3.70 (s, 3H), 3.58 (d, J = 6.8 Hz, 1H), 3.49 (d, J = 6.8 Hz, 1H), 3.10-3.05 (m, 1H), 2.32-2.26 (m, 3H), 2.03-1.98 (m, 2H).

Step 4

Methyl 3-(((methylsulfonyl)oxy)methyl)cyclobutane carboxylate

[109] Methyl 3-(hydroxymethyl) cyclobutane carboxylate (1.00 g, 6.94 mmol) and triethylamine (2.11 g, 20.8 mmol) were dissolved in dichloromethane (20 mL), methanesulfonyl chloride (1.59 g, 13.9 mmol) was added at 0°C. The reaction solution was slowly warmed to room temperature and stirred for 2 hours. The reaction was quenched by the addition of sodium bicarbonate aqueous solution (50 mL). The resulting mixture was extracted with dichloromethane (10 mL × 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to deliver methyl 3-(((methylsulfonyl)oxy)methyl)cyclobutane carboxylate (1.40 g, yellow oil), yield: 91%. ^{1}H NMR: (400 MHz, Methanol-d_4) δ 4.28 (d, J = 6.8 Hz, 1H), 4.19 (d, J = 6.8 Hz, 1H), 3.70 (s, 3H), 3.20-3.08 (m, 4H), 2.40-2.34 (m, 3H), 2.13-2.09 (m, 2H). MS-ESI calcd. for $[M+H]^+$ 223, found 223.

Step 5

Methyl 3-[(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)methyl]cyclobutanecarboxylate

[110] Ethyl 3-(((methylsulfonyl)oxy)methyl)cyclobutane carboxylate (1.40 g, 6.30 mmol), 3,7-dimethyl-1*H*-purine-2,6-(3*H*,7*H*)-dione (1.13 g, 6.30 mmol), potassium iodide (209 mg, 1.26 mmol) and potassium carbonate (2.61 g, 18.90 mmol) were dissolved in *N*,*N*-dimethylformamide (100 mL). The reaction solution was heated to 120°C and stirred for 3 hours. Then the reaction mixture was cooled to room temperature, filtered, into which water (100 mL) was added, extracted with dichloromethane (10 mL × 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to deliver methyl 3-[(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)methyl]cyclobutanecarboxylate (1.50 g, yellow solid), yield: 78%. ^{1}H NMR: (400 MHz, Methanol-d_4) δ 7.51 (s, 1H), 4.18-4.10 (m, 2H), 3.99 (s, 3H), 3.67 (s, 3H),

3.55 (s, 3H) 3.26-2.65 (m, 2H), 2.29-2.13 (m, 4H). MS-ESI calcd. for $[M+H]^+$ 307, found 307.

Step 6

3-[(3,7-Dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)methyl]cyclobutanecarboxylic acid

[111] Methyl 3-[(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)methyl]cyclobutanecarboxylate (1.00 g, 3.26 mmol) and potassium hydroxide (548 mg, 9.78 mmol) were dissolved in methanol (10 mL) and water (5 mL). The reaction solution was heated to 90°C and stirred for 3 hours. The resulting mixture was cooled to room temperature, neutralized by the addition of 1 N hydrochloric acid (20 mL) and filtered, extracted with dichloromethane (10 mL × 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to deliver 3-[(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)methyl] cyclobutanecarboxylic acid (800.00 mg, yellow solid), yield: 84%. MS-ESI calcd. for $[M+H]^+$ 293, found 293.

Step 7

3-[(3,7-Dimethyl-2,6-dioxo-purin-1-yl)methyl]-*N*-methoxy-*N*-methyl cyclobutanecarboxamide

[112] 3-[(3,7-Dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)methyl] cyclobutanecarboxylic acid (300 mg, 1.03 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (200 mg, 2.05 mmol), 1-ethyl-(3-dimethylaminopropyl)carbodiimide hydrochloride (394 mg, 2.06 mmol), 1-hydroxybenzotriazole (27.8 mg, 0.206 mmol) and triethylamine (312 mg, 3.09 mmol) were dissolved in dichloromethane (10 mL). The reaction mixture was stirred at 25°C for 12 hours. The reaction mixture was concentrated under reduced pressure, the residue was isolated and purified by preparative TLC plate (ethyl acetate, the value of Rf = 0.3) to deliver 3-[(3,7-dimethyl-2,6-dioxo-purin-1-yl)methyl]-*N*-methoxy-*N*-methylcyclobutanecarboxamide (200 mg, yellow solid), yield: 58%. MS-ESI calcd. for $[M+H]^+$ 336, found 336.

Step 8

1-[(3-Acetylcyclobutyl)methyl]-3,7-dimethylpurine-2,6-dione

[113] 3-[(3,7-Dimethyl-2,6-dioxo-purin-1-yl)methyl]-*N*-methoxy-*N*-methylcyclobutanecarboxamide (300 mg, 0.894 mmol) was dissolved in tetrahydrofuran (10 mL). Methylmagnesium bromide (3 M ether solution, 1.49 mL, 4.47 mmol) was added dropwise at 0°C and stirred for 3 hours. The reaction solution was quenched by the addition of saturated ammonium chloride aqueous solution (20 mL) and extracted with dichloromethane (10 mL × 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, filtered, the filtrate was concentrated under reduced pressure, the residue was isolated and purified by preparative TLC plate (ethyl acetate, the value of Rf = 0.5) to deliver 1-[(3-acetylcyclobutyl)methyl]-3,7-dimethylpurine-2,6-dione (200 mg, yellow solid), yield:

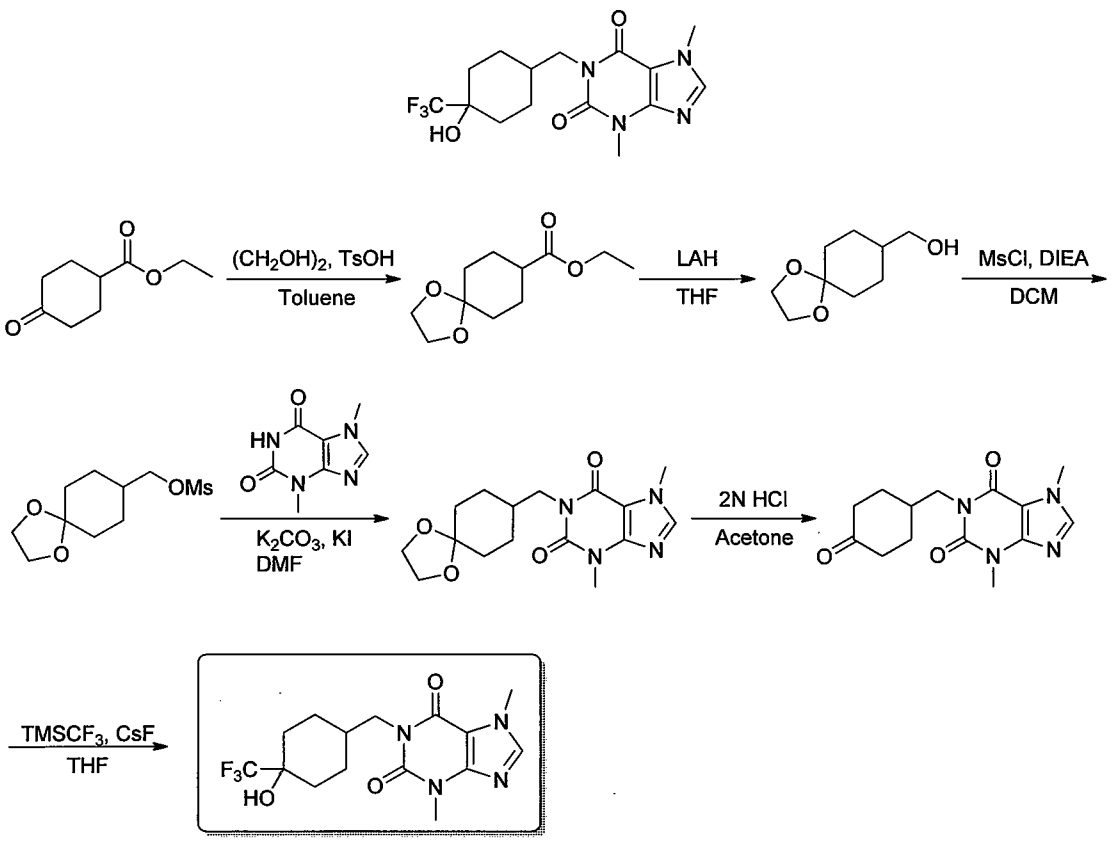
concentrated under reduced pressure and purified by preparative high performance liquid chromatography to give two isomeric products.

[123] Product 1 (isomer 1, the first peak) (40.0 mg, white solid), yield: 32%. ^{1}H NMR: (400 MHz, Methanol-d_4) δ 7.68 (s, 1H), 4.13-4.08 (m, 2H), 4.05 (s, 3H), 3.61 (s, 3H), 2.80-2.78 (m, 1H), 2.40-2.24 (m, 1H), 2.04-2.03 (m, 1H), 2.01-1.87 (m, 2H), 1.84-1.76 (m, 1H), 1.62-1.60 (m, 1H). MS-ESI calcd. for $[M+H]^+$ 347, found 347.

[124] Product 2 (isomer 2, the second peak) (20.0 mg, white solid), yield: 16%. ^{1}H NMR: (400 MHz, Methanol-d_4) δ 7.62 (s, 1H), 4.22-4.18 (m, 1H), 4.05-4.04 (m, 1H), 4.00 (s, 3H), 3.63 (s, 3H), 2.65-2.63 (m, 1H), 2.09-2.01 (m, 4H), 1.70-1.68 (m, 1H), 1.67-1.65 (m, 1H). MS-ESI calcd. for $[M+H]^+$ 347, found 347.

Embodiment 11

1-((4-Hydroxy-4-(trifluoromethyl)cyclohexyl)methyl)-3,7-dimethyl-1*H*-purine-2,6(3*H*, 7*H*)-dione



Step 1

Ethyl 1,4-dioxaspiro[4.5]decane-8-carboxylate

[125] Ethyl 4-oxocyclohexanecarboxylate (30.0 g, 176 mmol), ethylene glycol (22.0 g, 353 mmol) and *p*-toluenesulfonic acid (304 mg, 1.70 mmol) were dissolved in toluene (315 mL), after equipped with a water separator, the reaction mixture was heated to reflux overnight. The reaction mixture was cooled to 25°C and washed

successively with water (300 mL × 2), saturated sodium bicarbonate aqueous solution (500 mL × 2), the organic phase was dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated under reduced pressure, purified by silica gel column chromatography (1:1 petroleum ether / ethyl acetate, Rf = 0.3) to deliver the product ethyl 1,4-dioxaspiro[4.5]decane-8-carboxylate (37.2 g, yellow liquid), yield: 99%. MS-ESI calcd. for $[M+H]^+$ 215, found 215.

Step 2

1,4-Dioxaspiro[4.5]decan-8-ylmethanol

[126] Under the nitrogen gas atmosphere, lithium aluminum hydride (2.30 g, 61.0 mmol) was slowly added into tetrahydrofuran (60 mL) at 0°C, a solution of ethyl 1,4-dioxaspiro[4.5]decane-8-carboxylate (10.0 g, 42.0 mmol) in tetrahydrofuran (40 mL) was added dropwise. The reaction was slowly warmed to 25°C and stirred for 3.5 hours. The reaction solution was cooled to 0°C and water (2.3 g, 127 mmol), 15% sodium hydroxide (2.3 g, 8.60 mmol) and water (6.9 g, 383 mmol) were slowly added successively. The resulting mixture was filtered and the filter cake was washed with tetrahydrofuran (50 mL × 3), the organic phases were combined, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to deliver the product 1,4-dioxaspiro[4.5]decan-8-ylmethanol (6.22 g, yellow liquid), yield: 89%. MS-ESI calcd. for $[M+H]^+$ 173, found 173.

Step 3

1,4-Dioxaspiro[4.5]decan-8-ylmethyl methanesulfonate

[127] 1,4-Dioxaspiro[4.5]decan-8-ylmethanol (2.00 g, 12.0 mmol) and diisopropylethylamine (3.10 g, 24.0 mmol) were dissolved in dichloromethane (40 mL), methanesulfonyl chloride (3.90 g, 30.0 mmol) was slowly added at 0°C. The reaction solution was warmed to 25°C and stirred overnight. The reaction was quenched by the addition of a saturated ammonium chloride aqueous solution (100 mL) and extracted with ethyl acetate (200 mL× 3). The organic phases were combined, dried over anhydrous magnesium sulfate and filtered, the filtrate was concentrated under reduced pressure and purified by silica gel column chromatography (3:1 petroleum ether / ethyl acetate, Rf = 0.4) to deliver the product 1,4-dioxaspiro[4.5]decan-8-ylmethyl methanesulfonate (1.80 g, yellow liquid), yield: 60%. MS-ESI calcd. for $[M+H]^+$ 251, found 251.

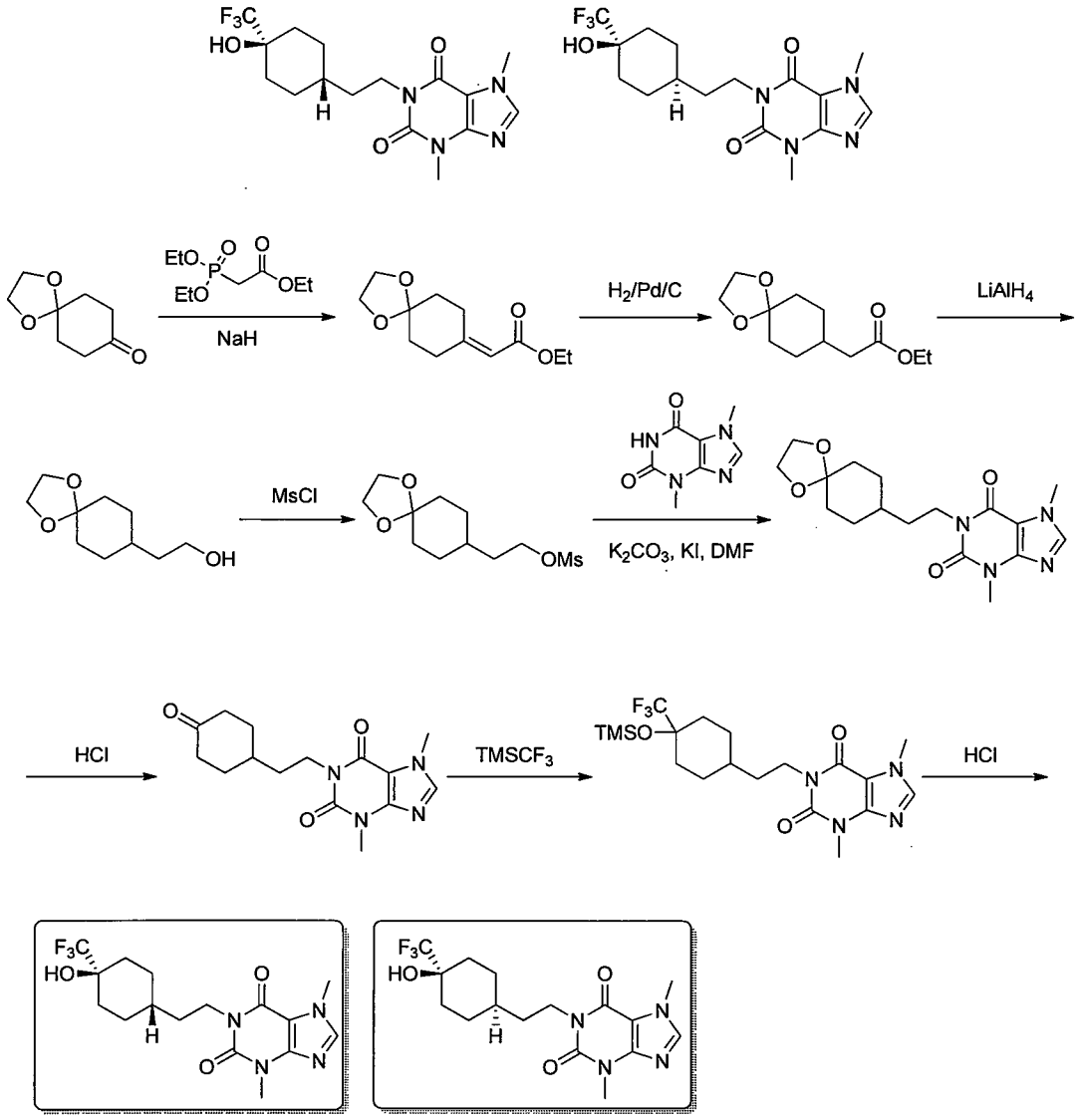
Step 4

1-(1,4-Dioxaspiro[4.5]decan-8-ylmethyl)-3,7-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione

[128] 1,4-Dioxaspiro[4.5]decan-8-ylmethyl methanesulfonate (1.50 g, 6.00 mmol), 3,7-dimethyl-1*H*-purine-2,6-(3*H*,7*H*)-dione(1.00 g, 6.00 mmol), potassium carbonate (2.50 g, 18.0 mmol), potassium iodide (100 mg, 0.600 mmol) were dissolved in *N*,*N*-dimethylformamide (20 mL), the reaction solution was heated to 130°C and stirred for

which was adjusted to 7. Then the resulting mixture was extracted with ethyl acetate, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and purified by preparative high performance liquid chromatography to deliver the product 1-((4-ethyl-4-hydroxycyclohexyl)methyl)-3,7-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (42.0 mg, white solid), yield: 77%. ^{1}H NMR: (400 MHz, Methanol-d_4) δ 7.86 (s, 1H), 3.97 (s, 3H), 3.88 (d, J = 7.6 Hz, 2H), 3.54-3.50 (m, 3H), 1.93-1.80 (m, 1H), 1.76-1.72 (m, 2H), 1.66-1.51 (m, 3H), 1.38-1.28 (m, 3H), 1.27-1.13 (m, 2H), 0.89 (t, J = 7.2 Hz, 3H). MS-ESI calcd. for $[M+H-H_2O]^+$ 303, found 303.

Embodiment 15



Step 1

Ethyl 2-(1,4-dioxaspiro[4.5]decan-8-ylidene) acetate

[140] Triethyl phosphonoacetate (12.2 g, 54.4 mmol) was dissolved in tetrahydrofuran (100 mL), sodium hydride (1.92 g, 48.0 mmol) was added in portions at 0°C, the reaction was stirred under the nitrogen gas atmosphere for 30 minutes. A

solution of 1,4-cyclohexanedione monoethylene acetal (5.00 g, 32.0 mmol) dissolved in tetrahydrofuran (15 mL) was added dropwise to the reaction solution at 0°C, and the reaction was stirred at 25°C for 3 hours. The reaction was quenched by the addition of water (25 mL) and extracted with dichloromethane (20 mL × 3). The organic phases were combined, washed with saturated brine (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure, the residue was purified by silica gel column chromatography (5:1 petroleum ether / ethyl acetate, Rf = 0.3) to deliver ethyl 2-(1,4-dioxaspiro[4.5]decan-8-ylidene)acetate (6.30 g, colorless oil), yield: 93%. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.67 (s, 1H), 4.15 (q, J = 7.2 Hz, 2H), 3.98 (s, 4H), 3.00 (t, J = 6.4 Hz, 2H), 2.38 (t, J = 6.4 Hz, 2H), 1.84-1.68 (m, 4H), 1.28 (t, J = 7.2 Hz, 3H). MS-ESI calcd. for $[M+H]^+$ 227, found 227.

Step 2

Ethyl 2-(1,4-dioxaspiro[4.5]decan-8-yl)acetate

[141] Eethyl 2-(1,4-dioxaspiro[4.5]decan-8-ylidene)acetate (3.80 g, 17.9 mmol) was dissolved in methanol (50 mL), dry palladium on carbon (palladium 10%, water 1%, 400 mg) was added, the reaction was reacted under hydrogen gas atomsphere (50 psi) for 18 hours at room temperature. The reaction solution was filtered and the filtrate was concentrated under reduced pressure to deliver ethyl 2-(1,4-dioxaspiro[4.5]decan-8-yl)acetate (3.50 g, colorless oil), yield: 91%.

[142] ^{1}H-NMR: (400 MHz, $CDCl_3$) δ 4.12 (q, J = 7.2 Hz, 2H), 3.93 (s, 4H), 2.22 (d, J = 7.2 Hz, 2H), 1.90-1.64 (m, 5H), 1.63-1.48 (m, 2H), 1.40-1.16 (m, 5H). MS-ESI calcd. for $[M+H]^+$ 229, found 229.

Step 3

2-(1,4-Dioxaspiro[4.5]decan-8-yl)ethanol

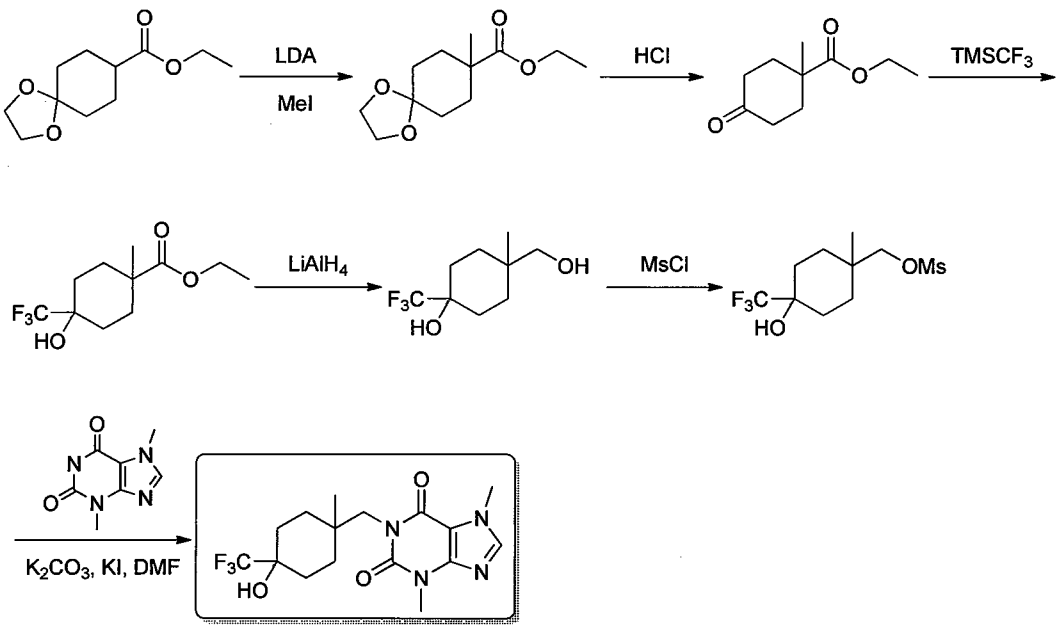
[143] Ethyl 2-(1,4-dioxaspiro[4.5]decan-8-yl)acetate (1.00 g, 4.38 mmol) was dissolved in tetrahydrofuran (20 mL), lithium aluminum hydride (216 mg, 5.69 mmol) was added in portions at 0°C and stirred for 18 hours under the nitrogen gas atmosphere. The reaction solution was cooled to 0°C, water (0.2 mL), 15% sodium hydroxide aqueous solution (0.2 mL) and water (0.6 mL) were slowly added successively. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to deliver the product 2-(1,4-dioxaspiro[4.5]decan-8-yl)ethanol (780 mg, yellow oil), yield: 96%.

[144] ^{1}H NMR: (400 MHz, $CDCl_3$) δ 3.94 (s, 4H), 3.69 (t, J = 6.4 Hz, 2H), 1.79-1.65 (m, 4H), 1.59-1.38 (m, 5H), 1.34-1.17 (m, 2H). MS-ESI calcd. for $[M+H]^+$ 187, found 187.

Step 4

2-(1,4-Dioxaspiro[4.5]decan-8-yl)ethyl methanesulfonate

[145] 2-(1,4-Dioxaspiro[4.5]decan-8-yl)ethanol (400 mg, 2.15 mmol) and



Step 1

Ethyl-8-methyl-1,4-dioxaspiro[4.5]decane-8-carboxylate

[155] Ethyl 1,4-dioxaspiro[4.5]decane-8-carboxylic acid ethyl ester (5.00 g, 23.3 mmol) was dissolved in anhydrous tetrahydrofuran (100 mL), under the nitrogen gas atmosphere, a solution of lithium diisopropylamide (2 M tetrahydrofuran solution, 14.0 mL, 28.0 mmol) was slowly added dropwise at -78°C, the reaction solution was stirred at -78°C for 1 hour. Iodomethane (6.62 g, 46.7 mmol) was slowly added and the reaction mixture was stirred for a further 1 hour. The reaction was quenched by the addition of water (100 mL). The reaction mixture was extracted with ethyl acetate (100 mL × 3) and the organic phases were combined, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure, the residue was purified by silica gel column chromatography (10:1 petroleum ether / ethyl acetate, Rf = 0.4) to deliver ethyl-8-methyl-1,4-dioxaspiro[4.5]decane-8-carboxylate (5.00 g, yellow oil), yield: 94%. ^{1}H NMR: (400 MHz, Methanol-d_4) δ 4.16-4.10 (m, 2H), 3.93-3.86 (m, 4H), 2.13-2.06 (m, 2H), 1.61-1.48 (m, 6H), 1.25-1.22 (m, 3H), 1.15 (s, 3H).

Step 2

Ethyl-1-methyl-4-oxocyclohexanecarboxylate

[156] Ethyl-8-methyl-1,4-dioxaspiro[4.5]decane-8-carboxylate (5.00 g, 21.9 mmol) was dissolved in tetrahydrofuran (50 mL), and 1 N hydrochloric acid aqueous solution (20 mL) was added dropwise at 0°C, and then stirred at 20°C for 1 hour. The mixture was cooled to 0°C and the reaction was quenched by the addition of a sodium bicarbonate aqueous solution (50 mL). The mixture was extracted with ethyl acetate (100 mL × 3). The organic phase was washed with saturated brine (100 mL × 3), dried over anhydrous sodium sulfate and concentrated under reduced pressure.

The residue was purified by silica gel column chromatography (10:1 petroleum ether / ethyl acetate, Rf = 0.4) to deliver ethyl-1-methyl-4-oxocyclohexanecarboxylate (3.00 g, colorless oil), yield 74%. ^{1}H NMR: (400 MHz, Methanol-d_4) δ 4.26-4.11 (m, 2H), 2.46-2.29 (m, 5H), 1.74-1.55 (m, 3H), 1.33-1.26 (m, 6H).

Step 3

Ethyl 4-hydroxy-1-methyl-4-(trifluoromethyl) cyclohexanecarboxylate

[157] Ethyl-1-methyl-4-oxocyclohexanecarboxylate (3.00 g, 16.3 mmol), cesium fluoride (247 mg, 1.63 mmol) was dissolved in tetrahydrofuran (50 mL) and then trifluoromethyltrimethylsilane (4.63 g, 35.3 mmol) was added at 0°C. Under the nitrogen gas atmosphere, the reaction solution was reacted at 20°C for 6 hours. Then 4 N hydrochloric acid aqueous solution (4 mL) was added. Under the nitrogen gas atmosphere, the mixture was reacted at room temperature for 6 hours. The reaction was quenched with saturated sodium bicarbonate aqueous solution (30 mL) and extracted with ethyl acetate (100 mL × 3), the organic phase was dried over anhydrous sodium sulfate and filtered, the filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (10:1 petroleum ether / ethyl acetate, Rf = 0.3) to deliver ethyl 4-hydroxy-1-methyl-4-(trifluoromethyl)cyclohexanecarboxylate (3.00 g, colorless oil), yield: 73%. ^{1}H NMR: (400 MHz, Methanol-d_4) δ 4.20-4.12 (m, 2H), 2.03-1.31 (m, 8H), 1.29-1.23 (m, 6H).

Step 4

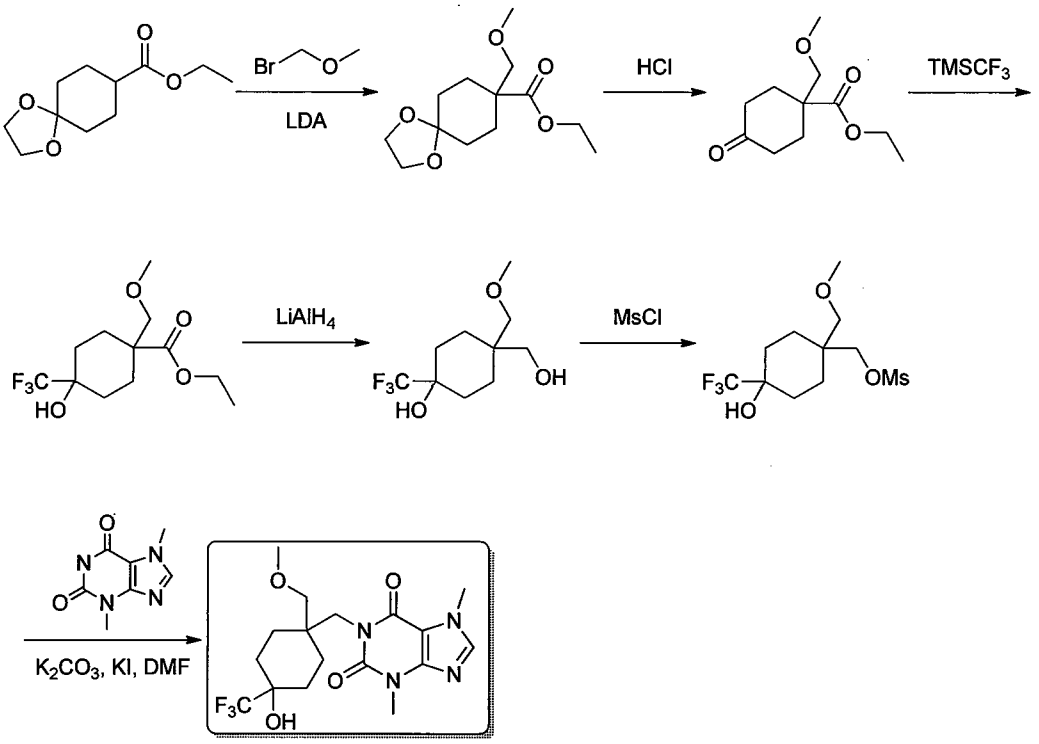
4-(Hydroxymethyl)-4-methyl-1-(trifluoromethyl)cyclohexanol

[158] Ethyl-4-hydroxy-1-methyl-4-(trifluoromethyl)cyclohexanecarboxylate (3.00 g, 11.8 mmol) was dissolved in anhydrous tetrahydrofuran (50 mL), lithium aluminium hydride (896 mg, 23.6 mmol) was added at 0°C. The reaction solution was warmed to 25°C and stirred for 1 hour. The reaction was quenched by the addition of water (20 mL), extracted with ethyl acetate (50 mL × 3), dried over anhydrous sodium sulfate, filtered, the filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (3:1 petroleum ether / ethyl acetate, Rf = 0.2) to deliver 4-(hydroxymethyl)-4-methyl-1-(trifluoromethyl)cyclohexanol (2.00 g, colorless oil), yield: 80%. ^{1}H NMR: (400 MHz, Methanol-d_4) δ 3.25 (s, 2H), 1.76-1.64 (m, 6H), 1.29-1.26 (m, 2H), 0.93-0.91 (m, 3H).

Step 5

(4-Hydroxy-1-methyl-4-(trifluoromethyl)cyclohexyl)methyl methanesulfonate

[159] 4-(Hydroxymethyl)-4-methyl-1-(trifluoromethyl)cyclohexanol (2.00 g, 9.42 mmol) was dissolved in dichloromethane (30 mL), triethylamine (953 mg, 9.42 mmol) and methanesulfonyl chloride (1.08 g, 9.42 mmol) were added at 0°C. The reaction solution was reacted at 0°C for 2 hours. The reaction was quenched by the addition of a saturated sodium bicarbonate aqueous solution (10 mL), extracted with



Step 1

Ethyl 8-(methoxymethyl)-1,4-dioxaspiro[4.5]decane-8-carboxylate

[161] Ethyl 1,4-dioxaspiro[4.5]decane-8-carboxylate (5.00 g, 23.3 mmol) was dissolved in anhydrous tetrahydrofuran (100 mL), under the nitrogen gas atmosphere, a solution of lithium diisopropylamide (2 M *n*-hexane solution, 14.0 mL, 28.0 mmol) was slowly added dropwise at -78°C, and the reaction was stirred at -78°C for 1 hour. Methoxybromomethane (5.83 g, 46.7 mmol) was slowly added and the reaction mixture was stirred for a further 1 hour. The reaction was quenched by the addition of water (100 mL). The reaction mixture was extracted with ethyl acetate (100 mL × 3) and the organic phases were combined, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure, the residue was purified by silica gel column chromatography (10:1 petroleum ether / ethyl acetate, Rf = 0.3) to deliver ethyl 8-(methoxymethyl)-1,4-dioxaspiro[4.5]decane-8-carboxylate (5.00 g, yellow oil), yield: 83%. ^{1}H NMR: (400 MHz, Methanol-d_4) δ 4.18 (q, J = 6.8 Hz, 2H), 3.94 (s, 4H), 3.55 (s, 2H), 3.33 (s, 3H), 2.14-2.12 (m, 2H), 1.65-1.57 (m, 6H), 1.26 (t, J = 6.8 Hz, 3H).

Step 2

Ethyl 1-(methoxymethyl)-4-oxocyclohexanecarboxylate

[162] Ethyl 8-(methoxymethyl)-1,4-dioxaspiro[4.5]decane-8-carboxylate (5.00 g, 19.4 mmol) was dissolved in tetrahydrofuran (50 mL), 1 N dilute hydrochloric acid (10 mL) was added dropwise at 0°C and stirred at 20°C for 1 hour. The mixture was cooled to 0°C and quenched by the addition of a sodium bicarbonate aqueous solution (50 mL). The mixture was extracted with ethyl acetate (100 mL ×

3). The organic phase was washed with saturated brine (100 mL × 3), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10:1 petroleum ether / ethyl acetate, Rf = 0.4) to deliver ethyl 1-(methoxymethyl)-4-oxocyclohexanecarboxylate (3.00 g, white oil), yield: 73%. ^{1}H NMR: (400 MHz, Methanol-d_4) δ 4.25 (q, J = 6.8 Hz, 2H), 3.52 (s, 2H), 3.34 (s, 3H), 2.52-2.30 (m, 6H), 1.82-1.78 (m, 2H), 1.30 (t, J = 6.8 Hz, 3H).

Step 3

Ethyl 4-hydroxy-1-(methoxymethyl)-4-(trifluoromethyl)cyclohexanecarboxylate

[163] Ethyl 1-(methoxymethyl)-4-oxocyclohexanecarboxylate (3.00 g, 14.0 mmol), cesium fluoride (243 mg, 1.40 mmol) was dissolved in tetrahydrofuran (50 mL) and then trifluoromethyltrimethylsilane (3.98 g, 28.0 mmol) was added at 0°C. Under the nitrogen gas atmosphere, the reaction solution was reacted at 20°C for 6 hours. Then 4 N dilute hydrochloric acid (7 mL) was added. Under the nitrogen gas atmosphere, the mixture was reacted at room temperature for 6 hours. The reaction was quenched with saturated sodium bicarbonate aqueous solution (30 mL) and extracted with ethyl acetate (100 mL × 3), the organic phase was dried over anhydrous sodium sulfate and filtered, the filtrate was concentrated under reduced pressure and purified by silica gel column chromatography (10:1 petroleum ether / ethyl acetate, Rf = 0.4) to deliver ethyl 4-hydroxy-1-(methoxymethyl)-4-(trifluoromethyl) cyclohexanecarboxylate (1.7 g, colorless oil), yield: 43%. ^{1}H NMR: (400 MHz, Methanol-d_4) 4.18-4.09 (m, 2H), 3.61 (s, 2H), 3.33 (s, 3H), 1.84-1.71 (m, 8H), 1.28-1.25 (m, 3H).

Step 4

4-(Hydroxymethyl)-4-(methoxymethyl)-1-(trifluoromethyl)cyclohexanol

[164] Ethyl 4-hydroxy-1-(methoxymethyl)-4-(trifluoromethyl)cyclohexane carboxylate (1.50 g, 5.28 mmol) was dissolved in anhydrous tetrahydrofuran (50 mL), lithium aluminum hydride (220 mg, 5.81 mmol) was added at 0°C. The reaction solution was heated to 25°C and stirred for 1 hour. The reaction was quenched by the addition of water (20 mL), extracted with ethyl acetate (50 mL × 3), dried over anhydrous sodium sulfate, filtered, the filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (1:1 petroleum ether / ethyl acetate, Rf = 0.2) to deliver 4-(hydroxymethyl)-4-(methoxymethyl)- 1-(trifluoromethyl) cyclohexanol (1.20 g, colorless oil), yield: 84%. ^{1}H NMR: (400 MHz, Methanol-d_4) δ 3.33-3.32 (m, 7H), 1.67-1.63 (m, 4H), 1.52-1.48 (m, 4H).

Step 5

(4-Hydroxy-1-methyl-4-(trifluoromethyl)cyclohexyl)methyl methanesulfonate

[165] 4-(Hydroxymethyl)-4-(methoxymethyl)-1-(trifluoromethyl)cyclohexanol (1.20 g, 4.95 mmol) was dissolved in dichloromethane (20 mL), triethylamine (851 mg,

Step 1

Methyl 4-(hydroxymethyl)cyclohexane carboxylate

[167] 4-(Methoxycarbonyl)cyclohexanecarboxylic acid (1.20 g, 6.45 mmol) was dissolved in anhydrous tetrahydrofuran (20 mL), under the nitrogen gas atmosphere borane dimethyl sulfide (10 M, 1.0 mL, 10.3 mmol) was slowly added dropwise at 0°C, the reaction solution was stirred at 0°C for 0.5 hour, slowly warmed to 25°C and then stirred for a further 1 hour. The reaction was quenched by the addition of water (40 mL) and the reaction solution was extracted with ethyl acetate. The organic phases were combined, washed successively with water and saturated sodium chloride aqueous solution, dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated under reduced pressure to deliver methyl 4-(hydroxymethyl)cyclohexanecarboxylate (1.00 g, white solid), yield: 91%. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 3.67 (s, 3H), 3.48-3.46 (m, 2H), 2.26-2.25 (m, 1H), 2.05-2.01 (m, 2H), 1.89-1.85 (m, 2H), 1.47-1.43 (m, 2H), 1.31 (s, 1H), 1.01-0.98 (m, 2H). MS-ESI calcd. for $[M+H]^+$ 173, found 173.

Step 2

Methyl 4-(((methylsulfonyl)oxy)methyl)cyclohexanecarboxylate

[168] Methyl 4-(hydroxymethyl)cyclohexanecarboxylate (900 mg, 5.20 mmol) and triethylamine (1.58 g, 15.6 mmol) were dissolved in anhydrous dichloromethane (5 mL), under the nitrogen gas atmosphere, methanesulfonyl chloride (720 mg, 6.30 mmol) was added at 0°C. The reaction solution was warmed to 25°C and stirred for 2 hours. The reaction was quenched by the addition of water (60 mL) and the reaction solution was extracted with ethyl acetate. The organic phases were combined, washed successively with water and saturated sodium chloride aqueous solution, dried over anhydrous magnesium sulfate, filtered, and the filtrate was concentrated under reduced pressure, the residue was purified by preparative TLC plate (3:1 petroleum ether / ethyl acetate, Rf = 0.5) to deliver methyl 4-(((methylsulfonyl)oxy)methyl)cyclohexanecarboxylate (1.00 g, white solid), yield: 91%. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 3.67 (s, 3H), 3.48-3.46 (m, 2H), 3.01 (s, 3H), 2.26-2.25 (m, 1H), 2.05-2.01 (m, 2H), 1.89-1.85 (m, 2H), 1.47-1.43 (m, 2H), 1.31 (s, 1H), 1.01-0.98 (m, 2H). MS-ESI calcd. for $[M+H]^+$ 251, found 251.

Step 3

Methyl 4-((3,7-Dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)methyl)cyclohexanecarboxylate

[169] Methyl 4-(((methylsulfonyl)oxy)methyl)cyclohexanecarboxylate (350 mg, 2.32 mmol) was dissolved in 5 mL anhydrous *N*,*N*-dimethylformamide, under the nitrogen gas atmosphere, potassium carbonate (640 mg, 4.64 mmol), potassium iodide (38.0 mg, 0.230 mmol) and 2,6-hydroxy-3,7-dimethylpurine (501 mg, 2.80 mmol) were added at 25°C. The reaction solution was stirred at 130°C for 3 hours. 40 mL water was added into the reaction solution, which was extracted with ethyl acetate, the organic

phases were combined, washed successively with water and saturated sodium chloride aqueous solution, dried over anhydrous magnesium sulfate, filtered, and the filtrate was concentrated under reduced pressure, the residue was purified by preparative TLC plate to deliver the product Methyl 4-((3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)methyl)cyclohexanecarboxylate (400 mg, white solid), yield: 52%. MS-ESI calcd. for $[M+H]^+$ 335, found 335.

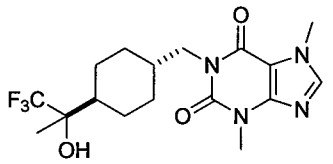
Step 4

1-((4-(3-Hydroxypentan-3-yl)-cyclohexyl)methyl)-3,7-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione

[170] Methyl 4-((3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)methyl)cyclohexanecarboxylate (100 mg, 0.30 mmol) was dissolved in 5 mL anhydrous tetrahydrofuran, under the nitrogen gas atmosphere, ethyl magnesium bromide solution (3 M solution in ether, 1 mL, 3.00 mmol) was slowly added dropwise at -65°C and the reaction was stirred at -65 C for 2 hours. The reaction solution was added with water (40 mL) and extracted with ethyl acetate, the organic phases were combined, washed with saturated sodium chloride aqueous solution (50 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated under reduced pressure, the residue was purified by preparative high performance liquid chromatography to deliver the product 1-((4-(3-hdroxypentan-3-yl)-cyclohexyl)methyl)-3,7-dimethyl-1H-purine-2,6(3*H*,7*H*)-dione (20.0 mg, white solid), yield: 19%. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.52 (s, 1H), 4.00 (s, 3H), 3.90-3.88 (m, 2H), 3.59 (s, 3H), 1.80-1.74 (m, 6H)-1.45 (m, 4H), 1.11-1.10 (m, 4H), 0.86-0.82 (m, 6H). MS ESI calcd. for $[M+H]^+$ 363, found 363.

Embodiment 19

3,7-Dimethyl-1-[[*trans*-4-(2,2,2-trifluoro-1-hydroxy-1-methyl-ethyl)cyclohexyl]methyl]purine-2,6-dione



yellow oil), yield: 99%. ^{1}H NMR: (400 MHz, Methanol-d_4) δ 4.10-4.03 (m, 2H), 3.65 (s, 3H), 3.07 (s, 3H), 2.42-2.31 (m, 1H), 2.10-2.03 (m 2H), 1.90-1.82 (m, 2H), 1.75-1.66 (m, 1H), 1.48-1.42 (m, 2H), 1.21-1.10 (m, 2H). MS-ESI calcd. for $[M+H]^+$ 251, found 251.

Step 3

trans-Methyl 4-((3,7-dimethyl-2,6-dioxo-purin-1-yl)methyl)cyclohexanecarboxylate

[173] *trans*-Methyl 4-(((methylsulfonyl)oxy)methyl)cyclohexanecarboxylate (1.00 g, 4.00 mmol), 3,7-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (719 mg, 4.00 mmol), potassium iodide (66.0 mg, 0.397 mmol) and potassium carbonate (1.10 g, 7.96 mmol) were dissolved in *N,N*-dimethylformamide (10 mL). The reaction solution was heated to 120°C and stirred for 3 hours. The reaction mixture was cooled to room temperature, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate, Rf = 0.1) to deliver *trans*-methyl 4-((3,7-dimethyl-2,6-dioxo-purin-1-yl)methyl)cyclohexanecarboxylate (800 mg, yellow solid), yield: 60%. ^{1}H NMR: (400 MHz, Methanol-d_4) δ 7.88 (s, 1H), 3.98 (s, 3H), 3.90-3.82 (m, 2H), 3.72 (s, 3H), 3.51 (s, 3H) 2.33-2.25 (m, 1H), 2.03-1.98 (m, 2H), 1.80-1.74 (m, 3H), 1.42-1.36 (m, 2H), 1.21-1.10 (m, 2H). MS-ESI calcd. for$[M+H]^+$ 335, found 335.

Step 4

1-(*trans*-4-Acetylcyclohexylmethyl)-3,7-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione

[174] *trans*-Methyl 4-((3,7-dimethyl-2,6-dioxo-purin-1-yl)methyl)cyclohexanecarboxylic acid (300 mg, 0.897 mmol) and *O,N*-dimethylhydroxylamine hydrochloride (114 mg, 1.17 mmol) were dissolved in tetrahydrofuran (25 mL), methylmagnesium bromide (3 M ether solution, 1.50 mL, 4.50 mmol) was added at 0°C. The reaction solution was warmed to room temperature slowly and stirred for 12 hours. The reaction was quenched by the addition of saturated ammonium chloride aqueous solution (10 mL). The resulting mixture was extracted with ethyl acetate (10 mL × 3). The organic phases were combined, washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC plate (ethyl acetate, Rf = 0.4) to deliver 1-(*trans*-4-acetylcyclohexylmethyl)-3,7-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (80.0 mg, yellow oil), yield: 29%. ^{1}H NMR: (400 MHz, Methanol-d_4) δ 7.88 (s, 1H), 3.98 (s, 3H), 3.92-3.84 (m, 2H), 3.55 (s, 3H), 2.42-2.33 (m, 1H), 2.15 (s, 3H), 1.98-1.88 (m, 2H), 1.85-1.75 (m, 3H), 1.32-1.10 (m, 4H). MS-ESI calcd. for $[M+H]^+$ 319, found 319.

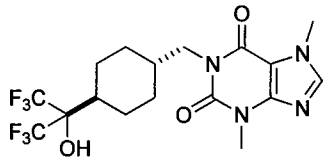
Step 5

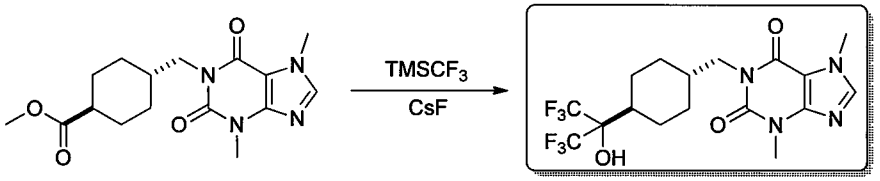
3,7-Dimethyl-1-[[*trans*-4-(2,2,2-trifluoro-1-hydroxy-1-methyl-ethyl)cyclohexyl]methyl]-1*H*-purine-2,6(3*H*,7*H*)-dione

[175] 1-(*trans*-4-Acetylcyclohexylmethyl)-3,7-dimethyl-3,7-dihydro-purine-2,6-dione (80.0 mg, 0.251 mmol), cesium fluoride (11.5 mg, 0.753 mmol) were dissolved in tetrahydrofuran (10 mL), trimethyl-trifluoromethyl-silane (71.6 mg, 0.502 mmol) was added at room temperature and stirred for 12 hours. 1 N hydrochloric acid (10 mL) was added into the reaction solution, which was then stirred at room temperature for 1 hour, the reaction was quenched by the addition of saturated sodium bicarbonate aqueous solution (50 mL). The resulting mixture was extracted with ethyl acetate (10 mL × 3). The organic phases were combined, washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure. And the residue was purified by preparative high performance liquid chromatography to deliver 3,7-dimethyl-1-[[*trans*-4-(2,2,2-trifluoro-1-hydroxy-1-methyl-ethyl)cyclohexyl]methyl]-1*H*-purine-2,6(3*H*,7*H*)-dione (35.0 mg, yellow solid), yield: 70%. ^{1}H NMR: (400 MHz, Methanol-d_4) δ 7.88 (s, 1H), 3.98 (s, 3H), 3.88 (d, J = 6.8 Hz, 2H), 3.53 (s, 3H), 1.96-1.67 (m, 6H), 1.22 (s, 3H), 1.15-1.06 (m, 4H). MS-ESI calcd. for $[M+H]^+$ 389, found 389.

Embodiment 20

3,7-Dimethyl-1-[*trans*-4-(2,2,2-trifluoro-1-hydroxy-1-trifluoromethyl-ethyl)cyclohexylmethyl]-3,7-dihydro-purine-2,6-dione





Step 1

3,7-Dimethyl-1-[*trans*-4-(2,2,2-trifluoro-1-hydroxy-1-trifluoromethyl-ethyl)cyclohexylmethyl]-3,7-dihydro-purine-2,6-dione

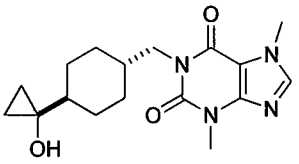
[176] *trans*-Methyl 4-((3,7-dimethyl-2,6-dioxo-purin-1-yl)methyl)cyclohexane carboxylate (200 mg, 0.598 mmol), cesium fluoride (45.4 mg, 0.299 mmol) were dissolved in tetrahydrofuran (10 mL), trimethyl-trifluoromethyl-silane (340 mg, 2.39 mmol) was added at room temperature and stirred for 12 hours. 1 N hydrochloric acid (10 mL) was added into the reaction soluton, which was then stirred at room temperature for 1 hour, the reaction was quenched by the addition of saturated sodium bicarbonate aqueous solution (50 mL). The resulting mixture was extracted with ethyl acetate (10 mL × 3). The organic phases were combined, washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure. And the residue was purified by preparative high

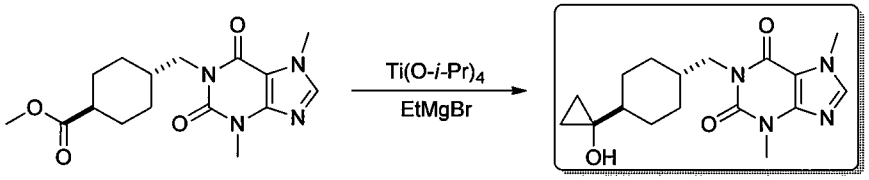
performance liquid chromatography to deliver 3,7-dimethyl-1-[trans-4-(2,2,2-trifluoro-1-hydroxy-1-trifluoromethyl-ethyl)cyclohexylmethyl]-3,7-dihydro-purine-2,6-dione (35.0 mg, yellow solid), yield: 41%.

[177] ^{1}H NMR: (400 MHz, Methanol-d_4) δ 7.88 (s, 1H), 3.98 (s, 3H), 3.88 (d, J = 6.8 Hz, 2H), 3.53 (s, 3H), 2.08-1.79 (m, 6H), 1.30-1.24 (m, 2H), 1.11-1.08 (m, 2H). MS-ESI calcd. for $[M+H]^+$ 443, found 443.

Embodiment 21

1-[[*trans*-4-(1-hydroxycyclopropyl)cyclohexyl]methyl]-3,7-dimethylpurine-2,6-dione





Step 1

1-[[*trans*-4-(1-Hydroxycyclopropyl)cyclohexyl]methyl]-3,7-dimethylpurine-2,6-dione

[178] *trans*-Methyl 4-[(3,7-dimethyl-2,6-dioxo-purin-1-yl)methyl]cyclohexane carboxylate (200 mg, 0.598 mmol), tetraisopropyl titanate (340 mg, 1.20 mmol) was dissolved in tetrahydrofuran (10 mL), ethylmagnesium bromide (3 M ether solution, 0.39 mL, 1.17 mmol) was added at room temperature and stirred for 12 hours. The reaction was quenched by the addition of saturated ammonium chloride aqueous solution (50 mL). The resulting mixture was extracted with ethyl acetate (10 mL × 3). The organic phases were combined, washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by preparative high performance liquid chromatography to deliver 1-[[*trans*-4-(1-hydroxycyclopropyl)cyclohexyl)methyl)-3,7-dimethylpurine-2,6-dione (70.0 mg, yellow solid), yield: 35%.

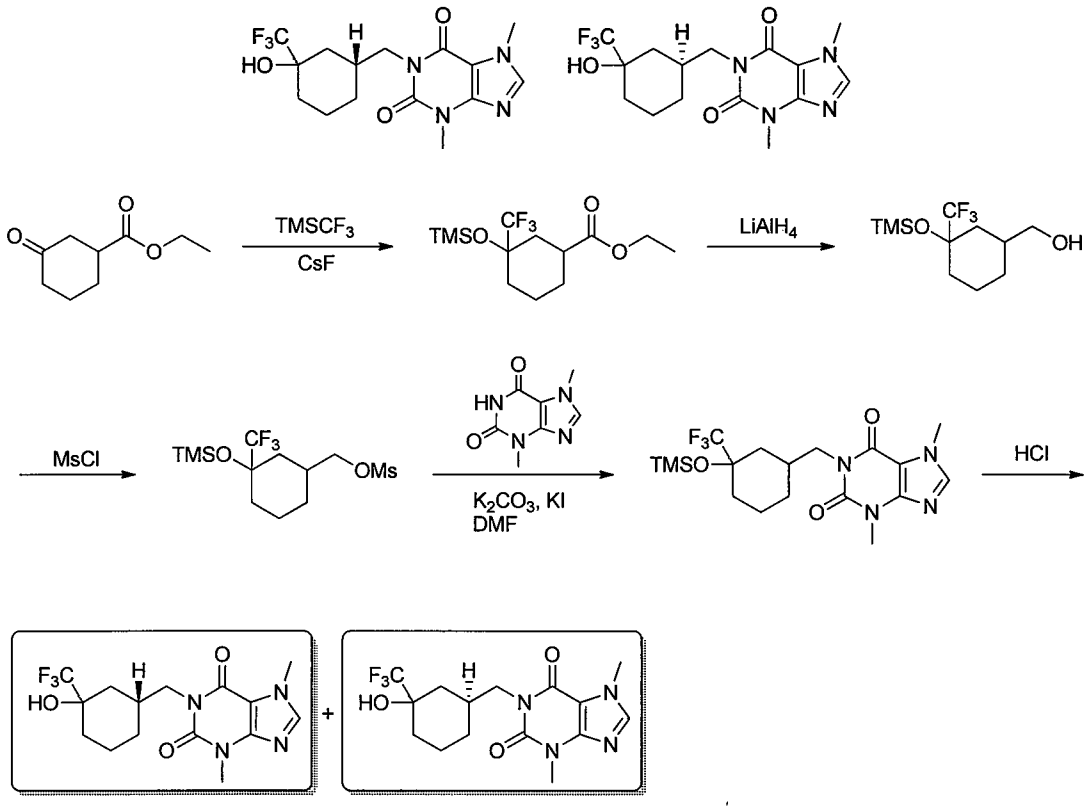
[179] ^{1}H NMR: (400 MHz, Methanol-d_4) δ 7.87 (s, 1H), 3.98 (s, 3H), 3.88 (d, J = 6.8 Hz, 2H), 3.53 (s, 3H), 1.79-1.71 (m, 5H), 1.29-1.07 (m, 5H), 0.60-0.57 (m, 2H), 0.42-0.39 (m, 2H). MS-ESI calcd. for $[M+H]^+$ 333, found 333.

Embodiment 22

1-(2-(3-Ethyl-3-hydroxycyclohexyl)ethyl)-3,7-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione

3.94 (m, 5H), 3.52 (s, 3H), 1.88-1.84 (m, 1H), 1.80-1.40 (m, 10H), 1.26-1.16 (m, 1H), 1.02-0.95 (m, 1H), 0.91 (t, J = 7.2 Hz, 3H). MS-ESI calcd. for $[M+H-18]^+$ 317, found 317.

Embodiment 23



Step 1

Ethyl 3-trifluoromethyl-3-trimethylsilyloxy-cyclohexanecarboxylate

[182] Ethyl-3-oxocyclohexanecarboxylate (1.00 g, 5.88 mmol), cesium fluoride (446 mg, 2.94 mmol) were dissolved in tetrahydrofuran (30 mL), trimethyl-trifluoromethyl-silane (1.67 g, 11.7 mmol) was added at room temperature and stirred for 12 hours. The reaction was quenched by the addition of water (20 mL). The resulting mixture extracted with ethyl acetate (20 mL × 3). The organic phases were combined, washed with saturated brine (60 mL), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to deliver ethyl 3-trifluoromethyl-3-trimethylsiloxy-cyclohexanecarboxylate (1.40 g, yellow oil), yield: 76%. MS-ESI calcd. for $[M+H]^+$ 313, found 313.

Step 2

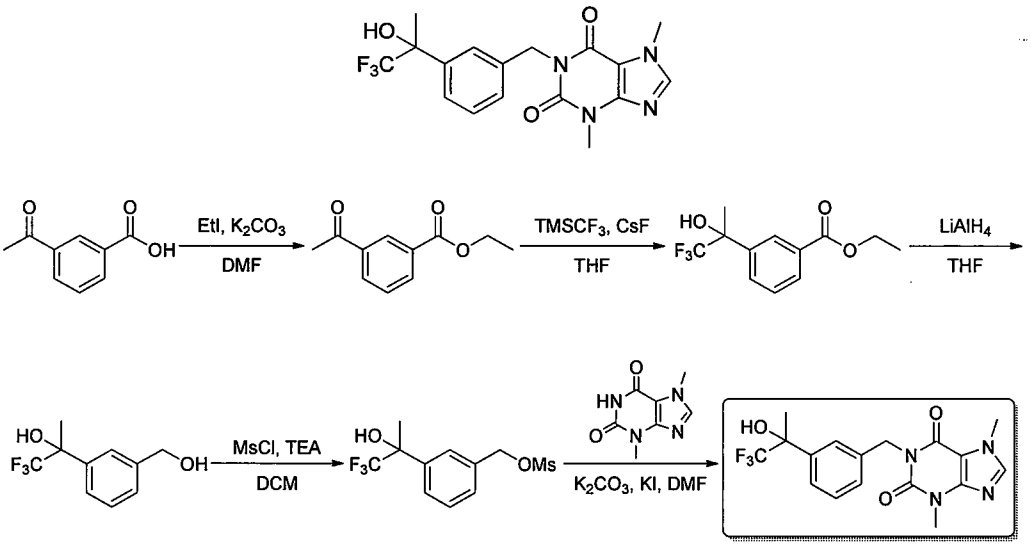
(3-Ttrifluoromethyl-3-trimethylsilanyloxycyclohexyl) methanol

[183] Ethyl 3-trifluoromethyl-3-trimethylsilyloxy-cyclohexanecarboxylate (1.00 g, 3.20 mmol) was dissolved in tetrahydrofuran (10 mL), and lithium tetrahydropyran (243 mg, 6.40 mmol) was added at 0°C for 1 hour. The reaction was quenched by the

= 0.3) to deliver 1-(4-(3-hydroxypentan-3-yl)benzyl)-3,7-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (190 mg, white solid), yield: 87%. ^{1}H NMR: (400 MHz, Methanol-d_4) δ 7.85 (s, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 5.25 (s, 2H), 3.96 (s, 3H), 3.52 (s, 3H), 1.82-1.72 (m, 4H), 0.69 (t, J = 7.2 Hz, 6H). MS-ESI calcd. for $[M+H]^+$ 357, found 357.

Embodiment 26

3,7-dimethyl-1-(3-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzyl)-1*H*-purine-2,6-(3*H*,7*H*)-dione



Step 1

Ethyl 3-acetylbenzoate

[197] 3-Acetylbenzoic acid (500 mg, 3.05 mmol) was dissolved in *N*,*N*-dimethylformamide (20 mL), ethyl iodide (475 mg, 3.05 mmol) and potassium carbonate (632 mg, 4.57 mmol) were added at room temperature, after stirring at room temperature for 2 hours, the reaction solution was concentrated and diluted with ethyl acetate (30 mL), the organic phase was washed with water (20 mL × 2), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure, the residue was isolated and purified by silica gel column chromatography (5:1 petroleum ether / ethyl acetate, Rf = 0.5) to deliver ethyl 3-acetylbenzoate (530 mg, white solid), yield: 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.24 (d, J = 7.6 Hz, 1H), 8.15 (d, J = 7.6 Hz, 1H), 7.56 (t, J = 7.6 Hz, 1H), 4.41 (q, J = 7.2 Hz, 2H), 2.66 (s, 3H), 1.42 (t, J = 7.2 Hz, 3H). MS-ESI calcd. for $[M+H]^+$ 193, found 193.

Step 2

Ethyl 3-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzoate

[198] Ethyl 3-acetylbenzoate (500 mg, 2.60 mmol) was dissolved in tetrahydrofuran (20 mL), trifluoromethyltrimethylsilane (370 mg, 2.60 mmol) and cesium fluoride (79.0 mg, 0.520 mmol) were added at room temperature. The reaction solution was stirred

at room temperature for 12 hours, diluted with ethyl acetate (30 mL), the organic phase was washed with water (20 mL × 2), dried with anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure, the residue was isolated and purified by silica gel column chromatography (2:1 petroleum ether / ethyl acetate, Rf = 0.5) to deliver ethyl 3-(1,1,1-trifluoro-2-hydroxypropan-2-yl) benzoate (600 mg, yellow solid), yield: 88%. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 8.05 (d, J = 7.6 Hz, 1H), 7.80 (d, J = 7.6 Hz, 1H), 7.48 (t, J = 7.6 Hz, 1H), 4.39 (q, J = 7.2 Hz, 2H), 1.82 (s, 3H), 1.40 (t, J = 7.2 Hz, 3H). MS-ESI calcd. for $[M+H]^+$ 263, found 263.

Step 3

1,1,1-Trifluoro-2-(3-hydroxymethyl)phenyl)propan-2-ol

[199] Ethyl 3-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzoate (500 mg, 1.91 mmol) was dissolved in tetrahydrofuran (20 mL), and lithium aluminum hydride (108 mg, 2.87 mmol) was added to the reaction solution at 0°C, the mixture was stirred at room temperature for 2 hours, water (0.1 mL), 15% sodium hydroxide (0.1 mL) and water (0.3 mL) were added separately to the reaction solution and stirred for 20 minutes. The reaction solution was diluted with ethyl acetate (30 mL) and the organic phase was washed with water (20 mL × 2), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to deliver 1,1,1-trifluoro-2-(3-hydroxymethyl)phenyl)propan-2-ol (400 mg, yellow solid), yield: 95%.

[200] ^{1}H-NMR: (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 8.05 (d, J = 7.6 Hz, 1H), 7.41-7.37 (m, 2H), 4.73 (s, 2H), 1.80). MS-ESI calcd. for $[M+H]^+$ 221, found 221.

Step 4

3-(1,1,1-Trifluoro-2-hydroxypropan-2-yl)benzyl methanesulfonate

[201] 1,1,1-Trifluoro-2-(3-hydroxymethyl)phenyl)propan-2-ol (400 mg, 1.82 mmol) and triethylamine (275 mg, 2.72 mmol) were dissolved in dichloromethane (20 mL), methanesulfonyl chloride (250 mg, 2.18 mmol) was added to the reaction solution at 0°C, stirred for 2 hours. The reaction solution was diluted by dichloromethane (30 mL), and the organic phase was washed with water (20 mL × 2), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to deliver 3-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzyl methanesulfonate (500 mg, yellow oil), yield: 92%.

[202] MS-ESI calcd. for $[M+H]^+$ 299, found 299.

Step 5

3,7-Dimethyl-1-(3-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzyl)-1*H*-purine-2,6-(3*H*, 7*H*)-dione

[203] 3-(1,1,1-Trifluoro-2-hydroxypropan-2-yl)benzyl methanesulfonate (100 mg, 0.335 mmol) and 3,7-dimethyl-1*H*-purine-2,6-(3*H*, 7*H*)-dione (60.0 mg, 0.335 mmol)

1-(5-Methylpyrazin-2-yl)ethanone

[218] *N*-methoxy-*N*,5-dimethylpyrazine-2-carboxamide (1.50 g, 8.28 mmol) was dissolved in tetrahydrofuran (30 mL), methylmagnesium bromide (3 M ether solution, 13.3 mL, 39.9 mmol) was added at 0°C, followed by stirring at 25°C for 1 hour. The mixture was cooled to 0°C and the reaction was quenched by the addition of water (10 mL). The mixture was extracted with ethyl acetate (30 mL × 3), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (20:1 petroleum ether / ethyl acetate, Rf = 0.2) to deliver 1-(5-methylpyrazin-2-yl)ethanone (700 mg, yellow oil), yield: 62%. MS-ESI calcd. for $[M+H]^+$ 137, found 137.

Step 3

1-(5-(Bromomethyl)pyrazin-2-yl)ethanone

[219] 1-(5-Methylpyrazin-2-yl)ethanone (700 mg, 5.14 mmol) was dissolved in carbon tetrachloride (20 mL), and then azobisisobutyronitrile (169 mg, 1.03 mmol) and N-bromosuccinimide (1.14 g, 6.43 mmol) were added. The reaction solution was reacted at 100°C under the nitrogen gas atmosphere for 5 hours. The reaction mixture was directly filtered and concentrated under reduced pressure, the residue was purified by silica gel column chromatography (20:1 petroleum ether / ethyl acetate, Rf = 0.5) to deliver 1-(5-(bromomethyl)pyrazine-2-yl)ethanone (300 mg, yellow oil), yield: 27%. MS-ESI calcd. for $[M+H]^+$ 215 and 217, found 215 and 217.

Step 4

1-((5-Acetylpyrazin-2-yl)methyl)-3,7-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione

[220] 1-(5-(bromomethyl)pyrazin-2-yl)ethanone (300 mg, 1.40 mmol), 3,7-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (251 mg, 1.40 mmol), potassium iodide (23.2 mg, 0.140 mmol) and potassium carbonate (578 mg, 4.19 mmol) were dissolved in anhydrous *N*,*N*-dimethylformamide (20 mL). The reaction solution was heated to 120°C and reacted for 3 hours. The reaction solution was cooled to 20°C, filtered, and the filtrate was concentrated under reduced pressure, the residue was purified by silica gel column chromatography (ethyl acetate, Rf = 0.3) to deliver 1-((5-acetylpyrazin-2-yl)methyl)-3,7-dimethyl-1*H*-purine-2,6(3*H*, 7*H*)-dione (300 mg, yellow solid), yield: 68%. MS ESI calcd. for $[M+H]^+$ 315, found 315.

Step 5

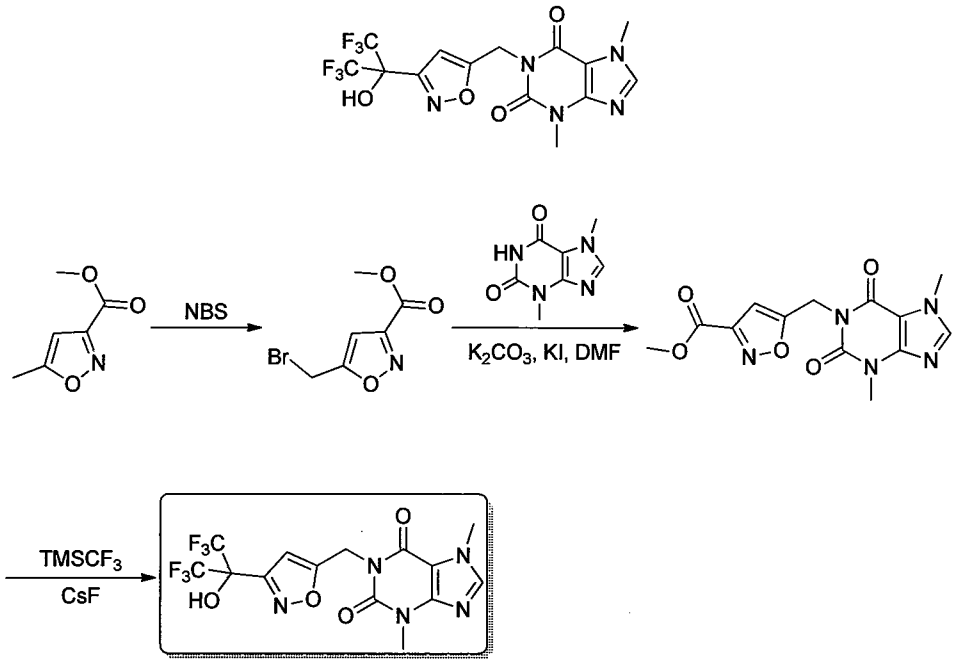
3,7-Dimethyl-1-((5-(1,1,1-trifluoro-2-hydroxypropan-2-yl)pyrazin-2-yl)-1*H*-purine-2,6(3*H*, 7*H*)-dione

[221] 1-((5-Acetylpyrazin-2-yl)methyl)-3,7-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (300 mg, 0.954 mmol), cesium fluoride (14.5 mg, 0.0954 mmol) were dissolved in anhydrous tetrahydrofuran (10 mL). Then trimethylsilyl trifluoromethyl (407 mg, 2.86 mmol) was added. Under the nitrogen gas atmosphere, the reaction solution was reacted at 25°C for 2 hours. Then hydrochloric acid (4 N, 4 mL) was added. Under

the nitrogen gas atmosphere, the mixture was reacted at room temperature for 1 hour. The reaction was quenched by the addition of saturated sodium bicarbonate aqueous solution (10 mL), the resulting mixture was extracted with ethyl acetate (10 × 3 mL), the organic phase was dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure, the residue was purified by silica gel column chromatography (1:1 petroleum ether / ethyl acetate, Rf = 0.3) to deliver 3,7-dimethyl-1-((5-(1,1,1-trifluoro-2-hydroxypropan-2-yl)pyrazin-2-yl)-1*H*-purine-2,6(3*H*, 7*H*)-dione (100 mg, white solid), yield: 40%. ^{1}H NMR: (400 MHz, Methanol-d_4) δ 8.85 (s, 1H), 8.65 (s, 1H), 7.92 (s, 1H), 5.40 (s, 2H), 3.99 (s, 3H), 3.56 (s, 3H), 1.78 (s, 3H). MS ESI calcd. for $[M+H]^+$ 385, found 385.

Embodiment 31

1-((3-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)isoxazol-5-yl)-3,7-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione



Step 1

Methyl 5-(bromomethyl)isoxazole-3-carboxylate

[222] Methyl 5-methylisoxazole-3-carboxylic acid ethyl ester (5.00 g, 35.4 mmol), *N*-bromosuccinimide (6.31 g, 35.4 mmol), benzoyl peroxide (858 mg, 3.54 mmol) were dissolved in carbon tetrachloride (20 mL), which was then reacted at 80°C for 12 hours. The reaction was quenched by the addition of saturated sodium thiosulfate aqueous solution (30 mL). The mixture was extracted with dichloromethane (20 mL × 3), dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure, the residue was purified by silica gel column chromatography (3:1 petroleum ether / ethyl acetate, Rf = 0.5) to deliver methyl 5-(bromomethyl)isoxazole-3-carboxylic acid ethyl ester (2.00 g, yellow oil), yield: 26%. ^{1}H NMR: (400 MHz,

Methanol-d_4) δ 6.88 (s, 1H), 4.73 (s, 2H), 3.97 (s, 3H). MS-ESI calcd. for $[M+H]^+$ 220, 222, found 220, 222.

Step 2

Methyl 5-((3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)methyl)carboxylate

[223] Ethyl 5-(bromomethyl) isoxazole-3-carboxylate (2.00 g, 9.09 mmol), 3,7-dimethyl-1*H*-purine-2,6-(3*H*,7*H*)-dione (1.64 g, 9.09 mmol), potassium iodide (151 mg, 0.909 mmol) and potassium carbonate (2.51 g, 18.2 mmol) were dissolved in *N*,*N*-dimethylformamide (50 mL). The reaction solution was heated to 120°C and stirred for 3 hours. Then the reaction mixture was cooled to room temperature, filtered, and the filtrate was concentrated under reduced pressure, the residue was isolated and purified by silica gel column chromatography (ethyl acetate, Rf = 0.4) to deliver methyl 5-((3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)methyl) carboxylate (1.70 g, yellow solid), yield: 59%. ^{1}H NMR: (400 MHz, Methanol-d_4) δ 8.06 (s, 1H), 6.82 (s, 1H), 5.22 (s, 2H), 3.87 (s, 3H), 3.83 (s, 3H), 3.45 (s, 3H). MS-ESI calcd. for $[M+H]^+$ 320, found 320.

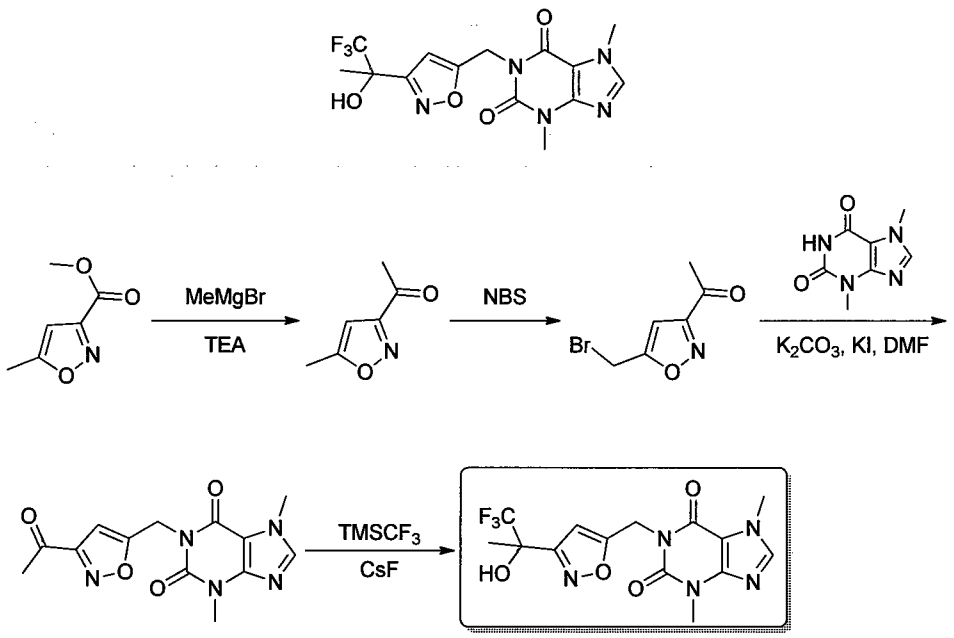
Step 3

1-((3-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)isoxazol-5-yl)-3,7-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione

[224] Methyl 5-((3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)methyl) carboxylate (200 mg, 0.626 mmol), cesium fluoride (95.0 mg, 0.626 mmol) were dissolved in tetrahydrofuran (10 mL), trimethyl trifluoromethylsilane (445 mg, 3.13 mmol) was added at room temperature and the resulting mixture was stirred for 12 hours. 1 N hydrochloric acid (10 mL) was added and the resulting mixture was stirred at room temperature for 1 hour. The reaction was quenched by the addition of saturated sodium bicarbonate aqueous solution (50 mL). The mixture was extracted with ethyl acetate (10 mL × 3). The organic phases were combined, washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by preparative high performance liquid chromatography to deliver 1-((3-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)isoxazol-5-yl)-3,7-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (10.0 mg, yellow solid), yield: 4%. ^{1}H NMR: (400 MHz, Methanol-d_4) δ 7.95 (s, 1H), 6.52 (s, 1H), 5.37 (s, 2H), 4.00 (s, 3H), 3.57 (s, 3H). MS-ESI calcd. for $[M+H]^+$ 428, found 428.

Embodiment 32

3,7-Dimethyl-1-((3-(1,1,1-trifluoro-2-hydroxypropan-2-yl)isoxazol-5-yl)-1*H*-purine-2,6-(3*H*,7*H*)-dione



Step 1

1-(5-Methylisoxazol-3-yl)ethanone

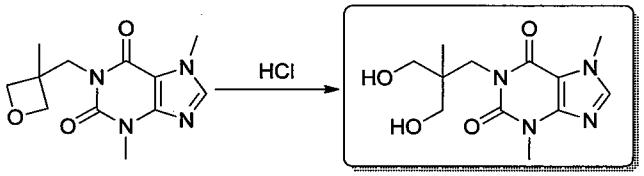
[225] Methyl 5-methylisoxazole-3-carboxylate (5.00 g, 35.4 mmol) and triethylamine (21.5 g, 213 mmol) were dissolved in tetrahydrofuran (80 mL), methylmagnesium bromide (3 M ether solution, 35 mL, 105 mmol) was added at 0°C, the resulting mixture was reacted for 3 hours. The reaction was quenched by the addition of saturated ammonium chloride aqueous solution (30 mL). The mixture was extracted with ethyl acetate (30 mL × 3), dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure, the residue was purified by silica gel column chromatography (3:1 petroleum ether / ethyl acetate, Rf = 0.7) to deliver 1-(5-methylisoxazol-3-yl)ethanone (1.00 g, yellow oil), yield: 23%. ^{1}H NMR: (400 MHz, Methanol-d_4) δ 6.39 (s, 1H), 2.58 (s, 3H), 2.49 (s, 3H). MS-ESI calcd. for $[M+H]^+$ 126, found 126.

Step 2

1-(5-(Bromomethyl)isoxazol-3-yl)ethanone

[226] 1-(5-Methylisoxazol-3-yl)ethanone (100 mg, 0.799 mmol), *N*-bromosuccinimide (142 mg, 0.799 mmol), benzoyl peroxide (19.3 mg, 0.0800 mmol) were dissolved in carbon tetrachloride (10 mL), which was then reacted at 90°C for 12 hours. The reaction was quenched by the addition of saturated sodium thiosulfate solution (30 mL). The mixture was extracted with dichloromethane (10 mL x 3), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to deliver 1-(5-(bromomethyl)isoxazol-3-yl)ethanone (150 mg, yellow oil), yield: 93%. MS-ESI calcd/ for $[M+H]^+$ 204 and 206, found 204 and 206.

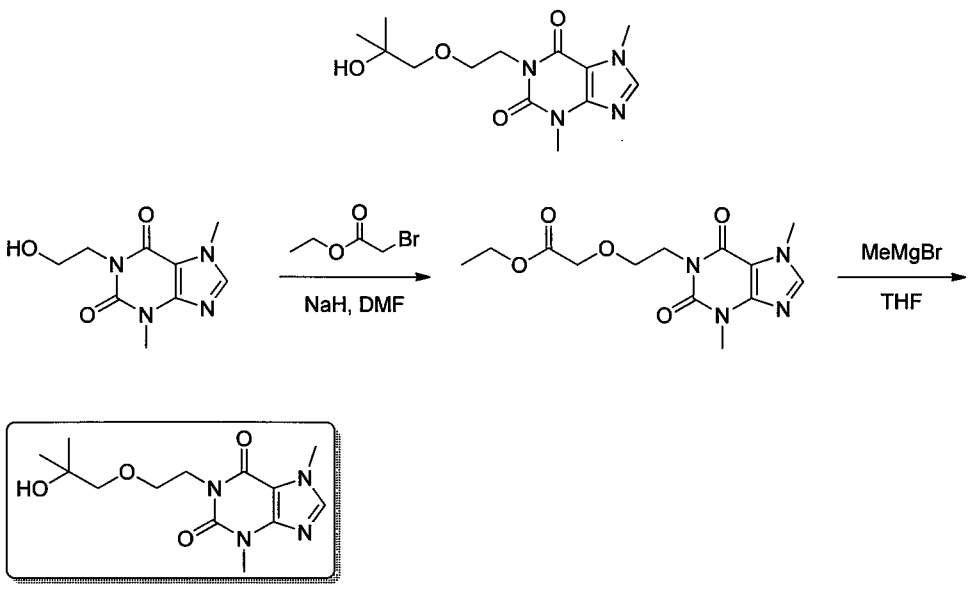
Step 3



[243] 3,7-Dimethyl-1-((3-methyloxetan-3-yl)methyl)1*H*-purine-2,6(3*H*,7*H*)-dione (20.0 mg, 0.0757 mmol) was dissolved in 0.16% hydrochloric acid (0.5 mL) and the reaction was stirred at room temperature for 6 hours, the pH value of which was adjusted to 7 with saturated sodium bicarbonate aqueous solution and the residue was purified by high performance liquid chromatography to deliver 1-(3-hydroxy-2-(hydroxymethyl)-2-methylpropyl)-3,7-dimethyl-1*H*-purine-2,6-(3*H*,7*H*)-dione (12.0 mg, white solid), yield: 56%. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.58 (s, 1H), 4.25-3.94 (m, 7H), 3.62 (s, 3H), 3.35-3.26 (m, 2H), 3.25-3.14 (m, 2H), 1.01 (s, 3H). MS-ESI calcd. for $[M+H]^+$ 283, found 283.

Embodiment 38

1-(2-(2-Hydroxy-2-methylcyclopropyl)ethyl)-3,7-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione



Step 1

Ethyl 2-(2-(3,7-Dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)ethoxy)acetate

[244] 1-(2-Hydroxyethyl)-3,7-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (100 mg, 0.446 mmol) was added to a solution of sodium hydride (21.0 mg, 0.890 mmol) in *N*,*N*-dimethylformamide (10 mL) at room temperature, the reaction solution was stirred at 25°C for 1 hour. Ethyl 2-bromoacetate (149 mg, 0.890 mmol) was added then. The reaction solution was stirred for a further 16 hours. The insoluble substance was removed by filtration, and the filtrate was concentrated under reduced pressure, the residue was isolated and purified by preparative high performance liquid

chromatography to deliver ethyl 2-(2-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)ethoxy)acetate (60.0 mg, white solid), yield: 43%.

[245] MS-ESI calcd. for $[M+H]^+$ 311, found 311.

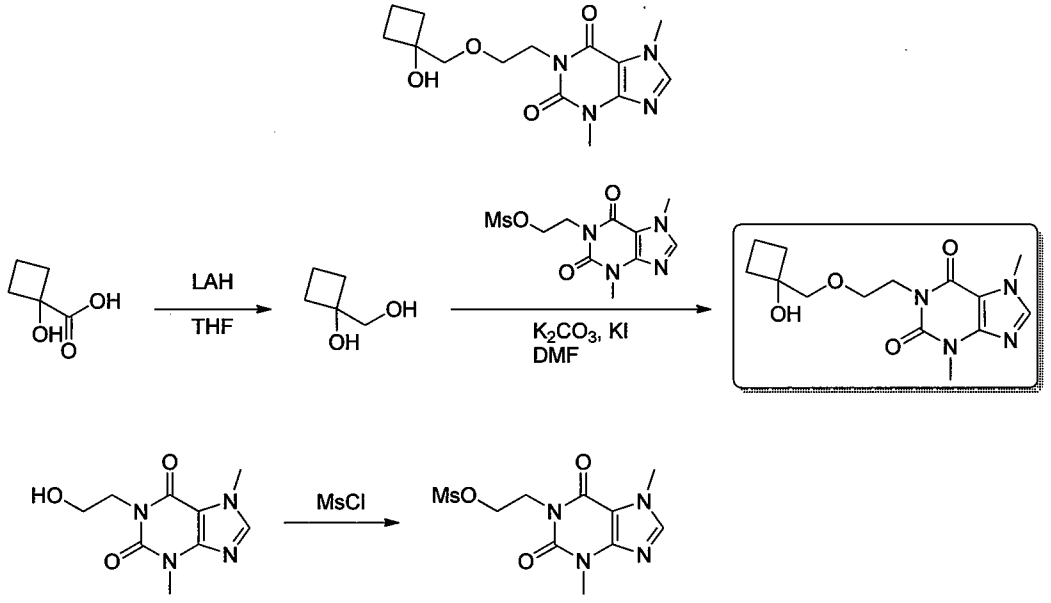
Step 2

1-(2-(2-Hydroxy-2-methylcyclopropyl)ethyl)-3,7-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione

[246] Methyl magnesium bromide solution (3 M tetrahydrofuran solution, 0.43 mL, 1.29 mmol) was slowly added dropwise to a solution of ethyl 2-(2-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)ethoxy)acetate in tetrahydrofuran (5 mL) at -78°C. The reaction solution was stirred at -78°C for 2 hours. The reaction was quenched by the addition of saturated ammonium chloride aqueous solution (20 mL). The mixture was extracted with ethyl acetate (20 mL × 3). The organic phases were combined and concentrated under reduced pressure, the residue was isolated and purified by preparative high performance liquid chromatography to deliver 1-(2-(2-hydroxy-2-methylcyclopropyl)ethyl)-3,7-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (40.0 mg, colorless oil), yield: 42%. ^{1}H NMR: (400 MHz, Methanol-d_4) δ 7.88 (s, 1H), 4.23 (t, J = 5.8 Hz, 2H), 3.98 (s, 3H), 3.72 (t, J = 5.8 Hz, 2H), 3.53 (s, 3H), 3.32 (s, 2H), 1.13 (s, 6H). MS-ESI calcd. for $[M+H]^+$ 296, found 296.

Embodiment 39

1-(2-((1-Hydroxycyclobutyl)methoxy)ethyl)-3,7-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione



Step 1

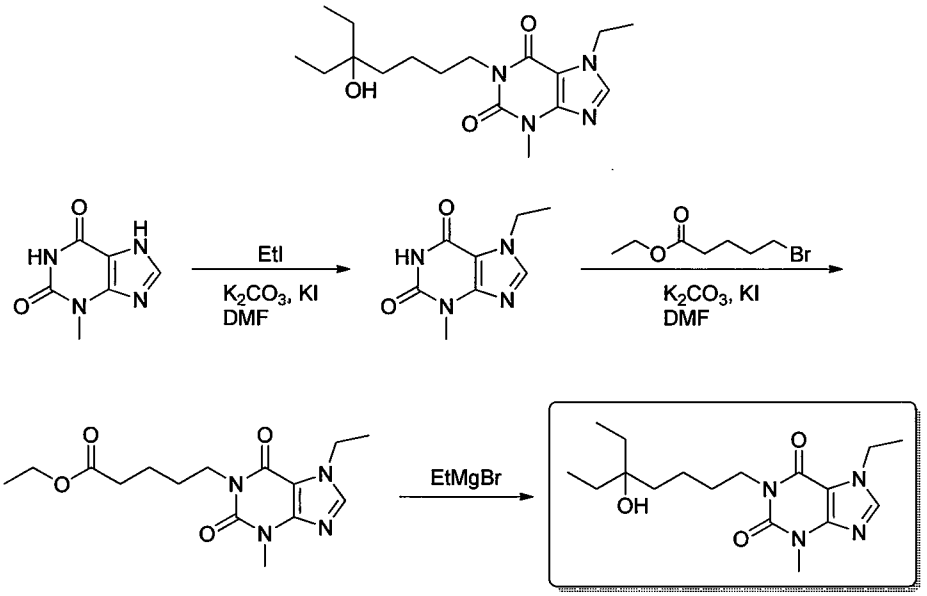
1-(Hydroxymethyl)cyclobutanol

[247] A solution of 1-hydroxycyclobutanoic acid (1.16 g, 10.0 mmol) in

(trifluoromethyl)cyclohexyl)methyl)-3-methyl-1*H*-purine-2,6(3*H*,7*H*)-dione (12 mg, white solid), yield: 10%. ^{1}H NMR: (400 MHz, Methanol-d_4) δ 8.49 (s, 1H), 7.93-7.89 (m, 1H), 4.07 (d, J = 7.2 Hz, 2H), 3.59 (s, 3H), 2.20-2.19 (m, 1H), 2.05-1.99 (m, 2H), 1.88-1.85 (m, 2H), 1.61-1.58 (m, 2H), 1.51-1.48 (m, 2H). MS-ESI calcd. for $[M+H]^+$ 397, found 397.

Embodiment 42

7-Ethyl-1-(5-ethyl-5-hydroxyheptyl)-3-methyl-1*H*-purine-2,6(3*H*,7*H*)-dione



Step 1

7-Ethyl-3-methyl-1*H*-purine-2,6(3*H*,7*H*)-dione

[258] 3-Methyl-1*H*-purine-2,6(3*H*,7*H*)-dione (500 mg, 3.00 mmol), potassium carbonate (414 mg, 3.00 mmol) and potassium iodide (4.0 mg, 0.300 mmol) were dissolved in *N*,*N*-dimethylformamide (15 mL). The reaction solution was heated to 80°C for half an hour. Ethyl iodide (470 mg, 4.50 mmol) was added. The reaction was continued for 5 hours. The reaction was quenched by pouring the reaction solution into sodium hydroxide aqueous solution (50 mL) and extracted with ethyl acetate (20 mL × 3). The pH value of the aqueous phase was adjusted to 7 with 1 N dilute hydrochloric acid (10 mL), then the mixture was filtered, the filter cake was dried to deliver 7-ethyl-3-methyl-1*H*-purine-2,6(3*H*,7*H*)-dione (500 mg, pale yellow solid), yield: 86%. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 8.05 (s, 1H), 4.25-4.19 (m, 2H), 3.34 (s, 3H), 1.37 (t, J = 7.2 Hz, 3H). MS-ESI calcd. for $[M+H]^+$ 195, found 195.

Step 2

Ethyl 5-(7-ethyl-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)valate

[259] 7-Ethyl-3-methyl-1*H*-purine-2,6(3*H*,7*H*)-dione (0.300 g, 1.55 mmol), ethyl bromovalerate (480 mg, 2.32 mmol), potassium carbonate (430 mg, 3.10 mmol) and

potassium iodide (26.0 mg, 0.155 mmol) were dissolved in *N*,*N*-dimethylformamide (4 mL). The reaction solution was heated to 110°C for 2 hours. The reaction was quenched by pouring the reaction solution into water (20 mL) and the mixture was extracted with ethyl acetate (20 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to deliver ethyl 5-(7-ethyl-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)valate (320 mg, yellow solid), yield: 62%. MS-ESI calcd. for $[M+H]^+$ 323, found 323.

Step 3

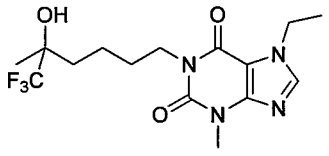
7-Ethyl-1-(5-ethyl-5-hydroxyheptyl)-3-methyl-1*H*-purine-2,6(3*H*,7*H*)-dione

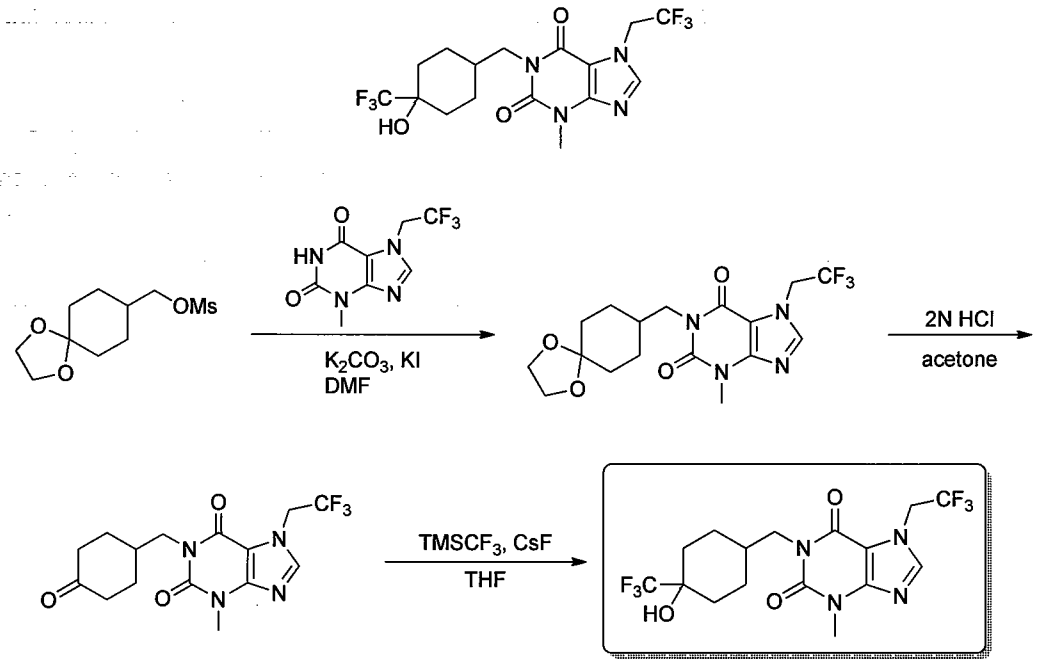
[260] Ethyl 5-(7-ethyl-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl) valate (0.100 g, 0.310 mmol) was dissolved in anhydrous tetrahydrofuran (10 mL) and ethyl magnesium bromide (3 M tetrahydrofuran solution, 0.62 mL, 1.86 mmol) was slowly added dropwise at -78°C. The reaction solution was reacted at -78°C for 0.5 hour and slowly warmed to 0°C and reacted for 0.5 hour. After the reaction was complete, the reaction solution was poured into water (20 mL) and extracted with ethyl acetate (30 mL × 3). The organic phase was dried over anhydrous sodium sulfate, filtered, concentrated under reduced pressure and the residue was purified by silica gel column chromatography to deliver 7-ethyl-1-(5-ethyl-5-hydroxyheptyl)-3-methyl-1*H*-purine-2,6(3*H*,7*H*)-dione (30.0 mg, colorless oil), yield: 30%.

[261] ^{1}H NMR: (400 MHz, $CDCl_3$): δ 7.56 (s, 1H), 4.37-4.32 (m, 2H), 4.05 (t, J = 7.2 Hz, 2H), 3.60 (s, 3H), 1.68-1.37 (m, 13H), 0.86 (t, J = 7.2 Hz, 6H). MS-ESI calcd. for $[M+H]^+$ 337, found 337.

Embodiment 43

7-Ethyl-3-methyl-1-(6,6,6-trifluoro-5-hydroxy-5-methylhexyl)-1*H*-purine-2,6(3*H*,7*H*)-dione





Step 1

1-(1,4-Dioxaspiro[4.5]decan-8-ylmethyl)-3-methyl-7-(2,2,2-trifluoroethyl)-1*H*-purine-2,6(3*H*,7*H*)-dione

[264] 1,4-Dioxaspiro[4.5]decan-8-ylmethyl methanesulfonate (200 mg, 0.800 mmol), 3-methyl-7-(2,2,2-trifluoroethyl)-1*H*-purine-2,6(3*H*,7*H*)-dione (200 g, 0.800 mmol) and potassium carbonate (334 mg, 2.42 mmol), potassium iodide (14.0 mg, 0.0800 mmol) were dissolved in *N*,*N*-dimethylformamide (3 mL), the reaction solution was heated to 130°C and stirred for 3.5 hours. The reaction solution was directly filtered and the filtrate was concentrated under reduced pressure to obtain a crude product 1-(1,4-dioxaspiro[4.5]decan-8-ylmethyl)-3-methyl-7-(2,2,2-trifluoroethyl)-1*H*-purine-2,6(3*H*,7*H*)-dione. MS-ESI calcd. for $[M+H]^+$ 403, found 403.

Step 2

3-Methyl-1-((4-oxocyclohexyl)methyl)-7-(2,2,2-trifluoroethyl)-1*H*-purine-2,6(3*H*,7*H*)-dione

[265] 1-(1,4-Dioxaspiro[4.5]decan-8-ylmethyl)-3-methyl-7-(2,2,2-trifluoroethyl)-1*H*-purine-2,6(3*H*,7*H*)-dione (2.50 g, 6.00 mmol) was dissolved in acetone (18 mL) and hydrochloric acid aqueous solution (4 N, 2.5 mL) was added. The reaction was stirred at 30°C overnight, water (50 mL) was added and the resulting mixture was extracted with ethyl acetate (20 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure and purified by silica gel column chromatography (1:3 petroleum ether / ethyl acetate, Rf = 0.3) to deliver the product 3-methyl-1-((4-oxocyclohexyl)methyl)-7-(2,2,2-trifluoroethyl)-1*H*-purine-2,6(3*H*,7*H*)-dione (220 mg, white solid), yield: 11%. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.68 (s, 1H), 5.08-4.99 (m, 2H), 4.00 (d, J = 7.0 Hz, 2H), 3.61 (s, 3H), 2.46-2.24 (m,

[277] Under the nitrogen gas atmosphere, 7-cyclopropyl-3-methyl-1*H*-purine-2,6(3*H*,7*H*)-dione (100 mg, 0.480 mmol), 6-chlorohexan-2-one (97.0 mg, 0.730 mmol) and potassium carbonate (132 mg, 0.960 mmol) were dissolved in *N*, *N*-dimethylformamide (5 mL). The reaction solution was heated to 120°C for 3 hours. After cooling to room temperature, the mixture was diluted with water (20 mL) and ethyl acetate (10 mL), extracted with ethyl acetate (30 mL × 2), the organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to deliver the crude product 7-cyclopropyl-3-methyl-1-(5-oxohexane)-1*H*-purine-2,6(3*H*,7*H*)-dione, which was used directly for the next step. MS-ESI calcd. for $[M+H]^+$ 305, found 305.

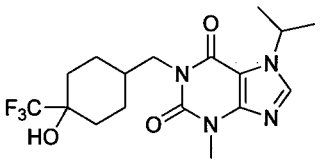
Step 5

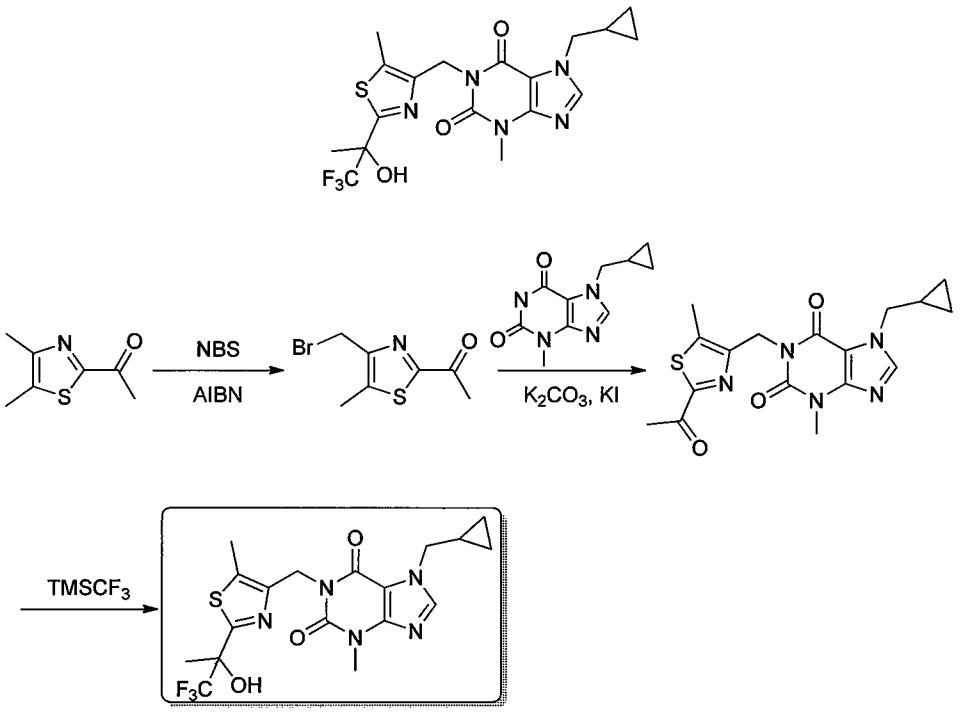
7-Cyclopropyl-3-methyl-1-(6,6,6-trifluoro-5-hydroxy-5-methylhexyl)-1*H*-purine-2,6(3*H*,7*H*)-dione

[278] Under the nitrogen gas atmosphere, 7-cyclopropyl-3-methyl-1-(5-oxohexane)-1*H*-purine-2,6(3*H*,7*H*)-dione (200 mg, 0.660 mmol) was dissolved in anhydrous tetrahydrofuran (3 mL), trifluoromethyltrimethylsilane (0.2 mL, 0.990 mmol) and cesium fluoride (20.0 mg, 0.130 mmol) were then added successively. The resulting reaction solution was reacted at 30°C for 2 hours. The reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (30 mL × 2), the organic phase was dried over anhydrous sodium sulfate and filtered, the filtrate was concentrated under reduced pressure and the residue was purified by preparative TLC plate (1:2 petroleum ether / ethyl ester, Rf = 0.3) to deliver 7-cyclopropyl-3-methyl-1-(6,6,6-trifluoro-5-hydroxy-5-methylhexyl)-1*H*-purine-2,6(3*H*,7*H*)-dione (150 mg, white solid), yield: 61%. ^{1}H-NMR: (400 MHz, $CDCl_3$) δ 7.55 (s, 1H), 4.13-4.02 (m, 2H), 3.63-3.61 (m, 1H), 3.55 (s, 3H), 2.96 (s, 1H), 1.90-1.68 (m, 2H), 1.67-1.64 (m, 2H), 1.47-1.45 (m, 2H), 1.28 (s, 3H), 1.18-1.16 (m, 2H), 1.06-1.04 (m, 2H). MS-ESI calcd. for $[M+H]^+$ 375, found 375.

Embodiment 48

7-(Cyclopropylmethyl)-1-((4-hydroxy-4-(trifluoromethyl)cyclohexyl)methyl)-3-methyl-1*H*-purine-2,6(3*H*,7*H*)-dione





Step 1

1-(4-(Bromomethyl)-5-methylthiazol-2-yl)ethanone

[293] 1-(4,5-Dimethylpyridin-2-yl)ethanone (200 mg, 1.29 mmol), *N*-bromosuccinimide (229 mg, 1.29 mmol), azobisisobutyronitrile (21.2 mg, 0.129 mmol) were dissolved in carbon tetrachloride (20 mL), which was reacted at 80°C for 12 hours. The reaction was quenched by the addition of saturated sodium thiosulfate aqueous solution (30 mL). The reaction mixture was extracted with dichloromethane (10 mL × 3), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to deliver 1-(4-(bromomethyl)-5-methylthiazol-2-yl)ethanone (200 mg, yellow oil), yield: 46%. MS-ESI calcd. for $[M+H]^+$ 234, 236, found 234, 236.

Step 2

1-((2-Acetyl-5-methylthiazol-4-yl)methyl)-7-(cyclopropylmethyl)-3-methyl-1*H*-purine-2,6-(3*H*,7*H*)-dione

[294] 1-(4-(Bromomethyl)-5-methylthiazol-2-yl)ethanone (200 mg, 0.598 mmol), 7-(cyclopropylmethyl)-3-methyl-1*H*-purine-2,6-(3*H*,7*H*)-dione (132 mg, 0.598 mmol), potassium iodide (19.8 mg, 0.119 mmol) and potassium carbonate (248 mg, 1.79 mmol) were dissolved in *N*,*N*-dimethylformamide (10 mL). The reaction solution was heated to 120°C and stirred for 3 hours. The reaction mixture was cooled to room temperature, filtered and the filtrate was concentrated under reduced pressure, the residue was isolated and purified by preparative TLC plate (1:1 petroleum ether / ethyl acetate, Rf value = 0.4) to deliver 1-((2-acetyl-5-methylthiazol-4-yl)methyl)-7-(cyclopropylmethyl)-3-methyl-1*H*-purine-2,6-(3*H*,7*H*)-dione (100 mg, yellow solid),

1-[5-(Bromomethyl)-2-pyridyl]ethanone

[296] 1-(5-Methyl-2-pyridyl)ethanone (500 mg, 3.70 mmol), *N*-bromosuccinimide (658 mg, 3.70 mmol), azobisisobutyronitrile (182 mg, 1.11 mmol) were dissolved in carbon tetrachloride (20 mL), which was reacted at 90°C for 12 hours. The reaction was quenched by the addition of saturated sodium thiosulfate aqueous solution (30 mL). Then the reaction mixture was extracted with dichloromethane (10 mL × 3), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to deliver 1-[5-(bromomethyl)-2-pyridyl]ethanone (125 mg, yellow oil), yield: 16%. MS-ESI calcd. for $[M+H]^+$ 214 and 216, found 214 and 216.

Step 2

1-[(6-Acetyl-3-pyridyl)methyl]-7-(cyclopropylmethyl)-3-methyl-1*H*-purine-2,6-(3*H*,7*H*)-dione

[297] 1-[5-(Bromomethyl)-2-pyridyl]ethanone (100 mg, 0.467 mmol), 7-(cyclopropylmethyl)-3-methyl-1*H*-purine-2,6-dione (103 mg, 0.467 mmol), potassium iodide (15.5 mg, 0.0934 mmol) and potassium carbonate (193 mg, 1.40 mmol) were dissolved in *N,N*-dimethylformamide (10 mL). The reaction solution was heated to 120°C and stirred for 3 hours. Then the reaction mixture was cooled to room temperature, filtered and the filtrate was concentrated under reduced pressure, the residue was isolated and purified by preparative TLC plate (ethyl acetate, Rf = 0.4) to deliver 1-[(6-acetyl-3-pyridyl)methyl-7-(cyclopropylmethyl)-3-methyl-1*H*-purine-2,6-(3*H*,7*H*)-dione (50.0 mg, yellow solid), yield: 30%. MS-ESI calcd. for $[M+H]^+$ 354, found 354.

Step 3

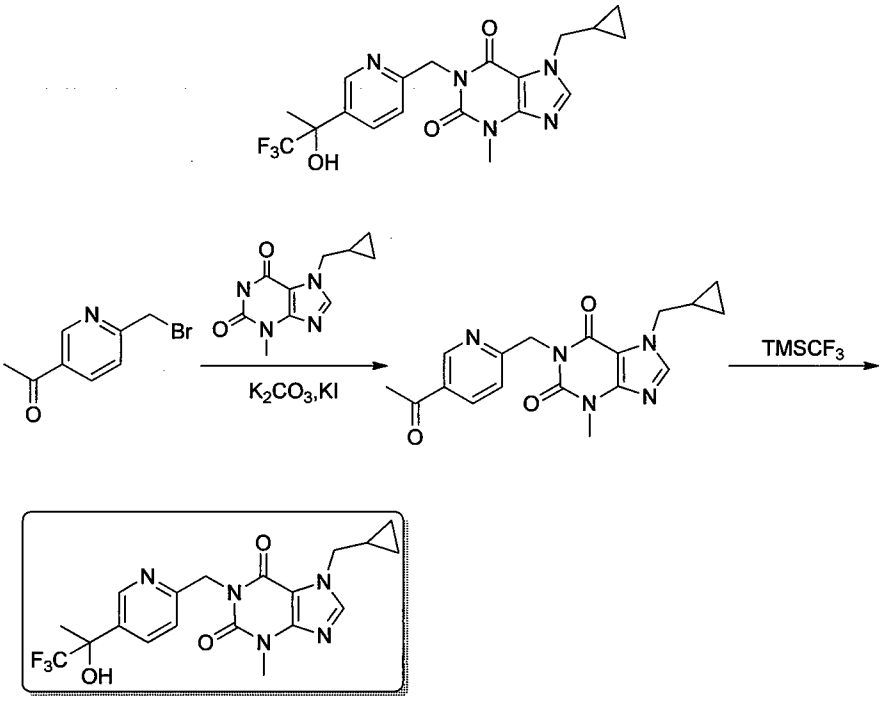
7-(Cyclopropylmethyl)-3-methyl-1-((6-(1,1,1-trifluoro-2-hydroxypropan-2-yl)pyridin-3-yl)methyl)-1*H*-purine-2,6-(3*H*,7*H*)-dione

[298] 1-[(6-Acetyl-3-pyridyl)methyl]-7-(cyclopropylmethyl)-3-methyl-1*H*-purine-2,6-(3*H*,7*H*)-dione (100 mg, 0.283 mmol), cesium fluoride (43.0 mg, 0.283 mmol) were dissolved in tetrahydrofuran (10 mL), trimethyl-trifluoromethyl-silane (60.4 mg, 0.424 mmol) was added at room temperature and stirred for 12 hours. The reaction was quenched by the addition of water (20 mL). Then the reaction mixture was extracted with ethyl acetate (10 mL × 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by preparative high performance liquid chromatography to deliver 7-(cyclopropylmethyl)-3-methyl-1-((6-(1,1,1-trifluoro-2-hydroxypropan-2-yl)pyridin-3-yl)methyl)-1*H*-purine-2,6-(3*H*,7*H*)-dione (40.0 mg, yellow solid), yield: 32%. ^{1}H NMR: (400 MHz, Methanol-d_4) δ 9.00 (s, 1H), 8.80-8.72 (m, 1H), 8.46 (s, 1H), 8.35-8.29 (m, 1H), 5.43 (s, 2H), 4.28 (d, J = 7.6 Hz, 2H), 3.58 (s, 3H), 1.95 (s, 3H), 1.50-1.46 (m, 1H), 0.68-0.64 (m, 2H), 0.53-0.51 (m, 2H). MS-ESI calcd. for $[M+H]^+$ 424, found 424.

Embodiment 56

7-(Cyclopropylmethyl)-3-methyl-1-((5-methyl-2-(1,1,1-trifluoro-2-hydroxypropan-2-

yl)thiazol-4-yl)methyl)-1*H*-purine-2,6-(3*H*,7*H*)-dione



Step 1

1-[(5-Acetyl-2-pyridyl)methyl]-7-(cyclopropylmethyl)-3-methyl-1*H*-purine-2,6-(3*H*,7*H*)-dione

[299] 1-[6-(Bromomethyl)-3-pyridyl]ethanone (100 mg, 0.467 mmol), 7-(cyclopropylmethyl)-3-methyl-1*H*-purine-2,6-(3*H*,7*H*)-dione (103 mg, 0.467 mmol), potassium iodide (15.5 mg, 0.0934 mmol) and potassium carbonate (193 mg, 1.40 mmol) were dissolved in *N*,*N*-dimethylformamide (10 mL). The reaction solution was heated to 120°C and stirred for 3 hours. The reaction mixture was cooled to room temperature, filtered, and the filtrate was concentrated under reduced pressure and purified by preparative TLC plate (ethyl acetate, Rf = 0.5) to deliver 1-((5-acetyl-2-pyridyl)methyl)-7-(cyclopropylmethyl)-3-methyl-1*H*-purine-2,6-(3*H*,7*H*)-dione (50.0 mg, yellow solid), yield: 30%. MS-ESI calcd. for $[M+H]^+$ 354, found 354.

Step 2

7-(Cyclopropylmethyl)-3-methyl-1-((5-methyl-2-(1,1,1-trifluoro-2-hydroxypropan-2-yl)thiazol-4-yl)methyl)-1*H*-purine-2,6-(3*H*,7*H*)-dione

[300] 1-[(5-Acetyl-2-pyridyl)methyl]-7-(cyclopropylmethyl)-3-methyl-1*H*-purine-2,6-(3*H*,7*H*)-dione (100 mg, 0.283 mmol), cesium fluoride (43.0 mg, 0.283 mmol) were dissolved in tetrahydrofuran (10 mL), trimethyl-trifluoromethyl-silane (60.4 mg, 0.424 mmol) was added at room temperature and stirred for 12 hours. The reaction was quenched by the addition of water (20 mL). The reaction mixture was extracted with ethyl acetate (10 mL × 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure. And the residue was purified by preparative high

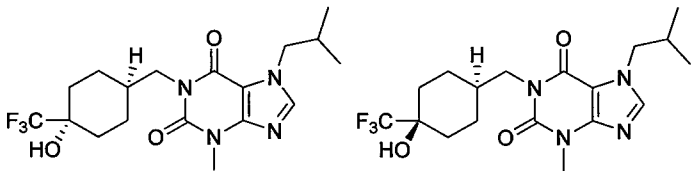
was dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure, the resulting product was purified by silica gel column chromatography (1:2 petroleum ether / ethyl acetate, Rf = 0.3) to deliver the product 7-isobutyl-3-methyl-1-((4-oxocyclohexyl)methyl)-1*H*-purine-2,6(3*H*,7*H*)-dione (150 mg, white solid), yield: 13%. ^{1}H NMR: (400 MHz, Methanol-d_4) δ 7.94 (s, 1H), 4.14 (d, J = 7.6 Hz, 2H), 3.99 (d, J = 7.6 Hz, 2H), 3.55 (s, 3H), 2.29-2.38 (m, 5H), 2.20-2.13 (m, 1H), 2.03-1.98 (m, 2H), 1.53-1.47 (m, 2H), 0.92 (d, J = 6.4 Hz, 6H). MS-ESI calcd. for $[M+H]^+$ 333, found 333.

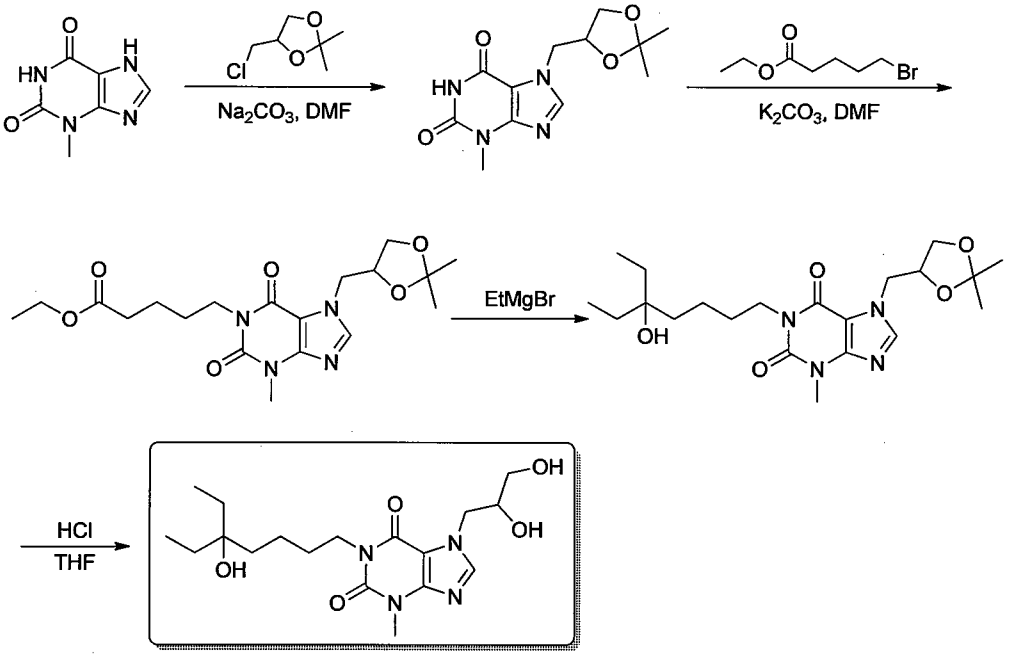
Step 3

1-((4-Hydroxy-4-(trifluoromethyl)cyclohexyl)methyl)-7-isobutyl-3-methyl-1*H*-purine-2,6(3*H*,7*H*)-dione

[303] 7-Isobutyl-3-methyl-1-((4-oxocyclohexyl)methyl)-1*H*-purine-2,6(3*H*,7*H*)-dione (150 mg, 0.450 mmol) and cesium fluoride (8.0 mg, 0.0450 mmol) were dissolved in tetrahydrofuran (3 mL), under the nitrogen gas atmosphere, trifluoromethyltrimethylsilane (950 mg, 0.640 mmol) was added. The reaction was stirred at 30°C for 16 hours. 4 N hydrochloric acid aqueous solution (3 mL) was added, and after stirring at 25°C for half an hour, the pH value of the reaction mixture was added to 7 by the addition of saturated sodium bicarbonate aqueous solution (15 mL), water (50 mL) was added, and extracted with ethyl acetate (50 mL × 3), the organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure to deliver the crude product, which was purified by preparative high performance liquid chromatography to deliver the product 1-((4-hydroxy-4-(trifluoromethyl)cyclohexyl)methyl)-7-isobutyl-3-methyl-1*H*-purine-2,6(3*H*,7*H*)-dione (86.0 mg, white solid), yield: 48%. ^{1}H NMR: (400 MHz, Methanol-d_4) δ 7.93 (s, 1H), 4.15-4.04 (m, 2H), 3.89 (d, J = 7.6 Hz, 1H), 3.54 (s, 3H), 2.20-1.98 (m, 3H), 1.86-1.79 (m, 2H), 1.61-1.42 (m, 5H), 0.92 (d, J = 6.4 Hz, 6H). MS-ESI calcd. for $[M+H]^+$ 403, found 403.

Embodiment 58





Step 1

7-((2,2-Dimethyl-1,3-dioxolan-4-yl)methyl)-3-methyl-1*H*-purine-2,6(3*H*,7*H*)-dione

[307] 3-Methyl-1*H*-purine-2,6(3*H*,7*H*)-dione (200 mg, 1.20 mmol), sodium carbonate (128 mg, 1.20 mmol), 4-(chloromethyl)-2,2-dimethyl-1,3-dioxolane (217 mg, 1.44 mmol) and potassium iodide (20.0 mg, 0.120 mmol) were dissolved in *N*,*N*-dimethylformamide (10 mL). The reaction solution was heated to 110°C and reacted for 36 hours. The reaction was quenched by the addition of water (10 mL), then the reaction mixture was extracted with ethyl acetate (10 mL × 3) and the organic phase was washed with saturated brine (5 mL), dried over anhydrous sodium sulfate, concentrated under reduced pressure and purified by preparative TLC plate (ethyl acetate, Rf = 0.5) to deliver 7-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-3-methyl-1*H*-purine-2,6(3*H*,7*H*)-dione (169 mg, yellow solid), yield: 50%. MS-ESI calcd. for $[M+H]^+$ 281, found 281.

Step 2

Ethyl 5-(7-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purinan-1-yl) valate

[308] 7-((2,2-Dimethyl-1,3-dioxolan-4-yl)methyl)-3-methyl-1*H*-purine-2,6(3*H*,7*H*)-dione (169 mg, 0.604 mmol), ethyl bromovalerate (178 mg, 0.906 mmol), potassium carbonate (167 mg, 1.21 mmol) and potassium iodide (20.0 mg, 0.0600 mmol) were dissolved in *N*,*N*-dimethylformamide (10 mL). The reaction solution was heated to 130°C, reacted for 3 hours, then the reaction mixture was filtered and concentrated, the residue was isolated and purified by preparative TLC plate (ethyl acetate, Rf = 0.4) to deliver ethyl 5-(7-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purinan-1-yl)valate (124 mg, yellow solid), yield: 50%. MS-ESI calcd. for $[M+H]^+$ 409, found 409.

Step 3

7-((2,2-Dimethyl-1,3-dioxolan-4-yl)methyl)-1-(5-ethyl-5-hydroxyheptyl)-3-methyl-1*H*-purine-2,6(3*H*,7*H*)-dione

[309] Ethyl 5-(7-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purinan-1-yl)valate (30.0 mg, 0.0750 mmol) was dissolved in anhydrous tetrahydrofuran (1 mL), ethylmagnesium bromide (3 M tetrahydrofuran solution, 0.15 mL, 0.450 mmol) was slowly added dropwise at -65°C. The reaction was reacted at -65°C for 0.5 hour and then reacted at 0°C for 0.5 hour. The reaction was quenched by pouring the reaction solution into water (5 mL), which was then extracted with ethyl acetate (5 mL × 3), dried over anhydrous sodium sulfate, filtered, concentrated under reduced pressure and purified by preparative TLC plate (ethyl acetate, Rf = 0.5) to deliver 7-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-1- (5-ethyl-5-hydroxyheptyl)-3-methyl-1*H*-purine-2,6(3*H*,7*H*)-dione (20.0 mg, yellow oil), yield: 63%. MS-ESI calcd. for $[M+H]^+$ 423, found 423.

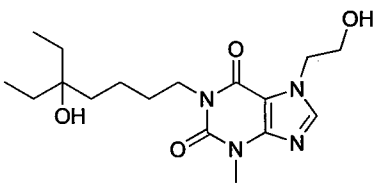
Step 4

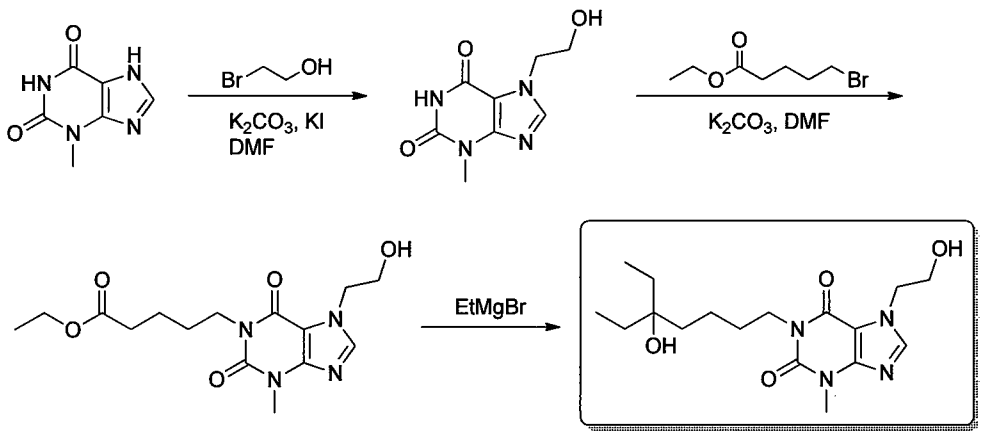
7-(2,3-Dihydroxypropyl)-1-(5-ethyl-5-hydroxyheptyl)-3-methyl-1*H*-purine-2,6(3*H*,7*H*)-dione

[310] 7-((2,2-Dimethyl-1,3-dioxolan-4-yl)methyl)-1-(5-ethyl-5-hydroxyheptyl)-3-methyl-1*H*-purine-2,6(3*H*,7*H*)-dione (20.0 mg, 0.0470 mmol) was dissolved in anhydrous tetrahydrofuran (1 mL) and dilute hydrochloric acid (0.3 mL), reacted at 25°C for 36 hours. After the reaction was complete, the reaction mixture was concentrated under reduced pressure and purified by preparative TLC plate (8:1 ethyl acetate / methanol, Rf = 0.3) to deliver 7-(2,3-dihydroxypropyl)-1-(5-ethyl-5-hydroxyheptyl)-3-methyl-1*H*-purine-2,6(3*H*,7*H*)-dione (5.0 mg, white solid), yield: 28%. ^{1}H NMR: (400 MHz, Methanol-d_4) δ 7.90 (s, 1H), 4.57-4.53 (m, 1H), 4.26-4.22 (m, 1H), 4.03-3.96 (m, 3H), 3.58-3.55 (m, 2H), 3.54 (s, 3H), 1.66-1.61 (m, 2H), 1.48-1.44 (m, 6H), 1.34-1.29 (m, 2H), 0.85 (t, J = 8.0 Hz, 6H). MS-ESI calcd. for $[M+H]^+$ 383, found 383.

Embodiment 60

1-(5-Ethyl-5-hydroxyheptyl)-7-(2-hydroxyethyl)-3-methyl-1*H*-purine-2,6(3*H*,7*H*)-dione





Step 1

7-(2-Hydroxyethyl)-3-methyl-1*H*-purine-2,6(3*H*,7*H*)-dione

[311] 3-Methyl-1*H*-purine-2,6(3*H*,7*H*)-dione (1.00 g, 6.00 mmol), potassium carbonate (830 mg, 6.00 mmol) were dissolved in *N*,*N*-dimethylformamide (10 mL). The reaction solution was heated to 80°C for 0.5 hour and 2-bromoethanol (900 mg, 7.20 mmol) was added. The reaction solution was heated to 130°C and reacted overnight. The reaction solution was concentrated to deliver the crude 7-(2-hydroxyethyl)-3-methyl-1*H*-purine-2,6(3*H*,7*H*)-dione, which was used directly for the next step.

Step 2

Ethyl 5-(7-(2-hydroxyethyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)valate

[312] 7-(2-Hydroxyethyl)-3-methyl-1*H*-purine-2,6(3*H*,7*H*)-dione (1.05 g, 5.00 mmol), ethyl 5-bromovalerate (1.25 g, 6.00 mmol) and potassium carbonate (1.66 g, 12.0 mmol) were dissolved in *N*,*N*-dimethylformamide (3 mL). The reaction solution was heated to 130°C for 3 hours. The reaction was quenched by pouring the reaction solution into water (20 mL) and the mixture was then extracted with ethyl acetate (20 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, concentrated under reduced pressure, the residue was isolated and purified by preparative TLC plate to deliver ethyl 5-(7-(2-hydroxyethyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)valate (700 mg, yellow oil), yield: 35%. MS-ESI calcd. for $[M+H]^+$ 339, found 339.

Step 3

1-(5-Ethyl-5-hydroxyheptyl)-7-(2-hydroxyethyl)-3-methyl-1*H*-purine-2,6(3*H*,7*H*)-dione

[313] Ethyl 5-(7-(2-hydroxyethyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)valate (700 mg, 2.07 mmol) was dissolved in anhydrous tetrahydrofuran (7 mL), ethylmagnesium bromide (3 M tetrahydrofuran solution, 7 mL,

[314] 2-(Methylamino)ethanol (135 mg, 1.80 mmol) was dissolved in *N*,*N*-dimethylformamide (5 mL), 2-(bromomethyl)oxirane (206 mg, 1.51 mmol) was added and reacted at room temperature for 1.5 hours. After the reaction was complete, the reaction solution was directly used for the next reaction step.

Step 2

7-(2-Hydroxy-3-((2-hydroxyethyl)(methyl)amino)propyl)-3-methyl-1*H*-purine-2,6(3*H*,7*H*)-dione

[315] 3-Methyl-1*H*-purine-2,6(3*H*,7*H*)-dione (100 mg, 0.602 mmol), sodium carbonate (64.0 mg, 0.602 mmol) and potassium iodide (10.0 mg, 0.0600 mmol) were added to a solution of 1-bromo-3-((2-hydroxyethyl)(methyl)amino)propan-2-ol. The reaction solution was heated to 80°C and reacted for 10 hours. After the reaction was complete, the reaction mixture was filtered and concentrated under reduced pressure to give the crude product 7-(2-hydroxy-3-((2-hydroxyethyl)(methyl)amino)propyl)-3-methyl-1*H*-purine-2,6(3*H*,7*H*)-dione, which was used directly for the next step. MS-ESI calcd. for $[M+H]^+$ 298, found 298.

Step 3

Ethyl 5-(7-(2-Hydroxy-3-((2-hydroxyethyl)(methyl)amino)propyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purinan-1-yl) valate

[316] 7-(2-Hydroxy-3-((2-hydroxyethyl)(methyl)amino)propyl)-3-methyl-1*H*-purine-2,6(3*H*,7*H*)-dione (170 mg, 0.572 mmol), ethyl bromovalerate (169 mg, 0.858 mmol), potassium carbonate (158 mg, 1.14 mmol) and potassium iodide (10.0 mg, 0.0570 mmol) were dissolved in *N*,*N*-dimethylformamide (5 mL). The reaction solution was heated to 130°C and reacted for 3 hours. The reaction solution was quenched by pouring into water (5 mL), extracted with ethyl acetate (10 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered and concentrated, isolated and purified by preparative TLC plate (8:1 dichloromethane / methanol, Rf = 0.4) to deliver ethyl 5-(7-(2-hydroxy-3-((2-hydroxyethyl)(methyl)amino)propyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purinan-1-yl) valate (118 mg, yellow oil), yield: 49%. MS-ESI calcd. for $[M+H]^+$ 426, found 426.

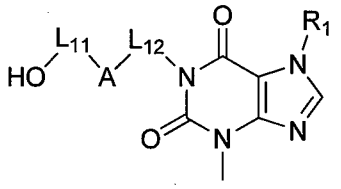
Step 4

1-(5-Ethyl-5-hydroxyheptolol)-7-(2-hydroxy-3-((2-hydroxyethyl)(methyl)amino)propyl)-3-methyl-1*H*-2,6(3*H*,7*H*)-dione

[317] Ethyl 5-(7-(2-hydroxy-3-((2-hydroxyethyl)(methyl)amino)propyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purinan-1-yl)valate (100 mg, 0.235 mmol) was dissolved in anhydrous tetrahydrofuran (4 mL) and ethyl magnesium bromide (3 M tetrahydrofuran solution, 0.47 mL, 1.41 mmol) was slowly added dropwise at -65°C. The reaction was reacted at -65°C for 0.5 hour and then reacted at 0°C for 0.5 hour. After the reaction was complete, the reaction solution was quenched

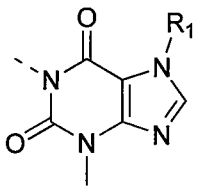
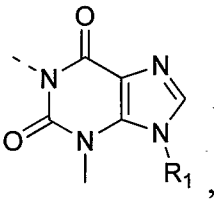
What is claimed is:

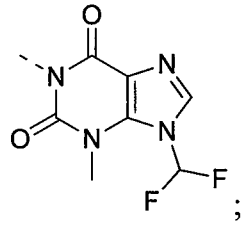
1. A compound having a structure of formula (**I**), a tautomer thereof or a pharmaceutically acceptable salt thereof,



(**I**)

wherein,

the structural unit  can be replaced with  ,

specifically replaced with  ;

L_{11} is selected from absence, or C(R)(R');

each of R and R' is independently selected from H, a halogen, OH, NH_2, CN, or, an optionally substituted 1- to 6- membered alkyl or heteroalkyl;

optionally, R, R' can form a 3- to 6- membered cycloalkyl, heterocyoalkyl by cyclization;

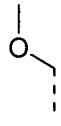
A represents absence or is selected from cycloalkyl, heterocycloalkyl, aryl or heteroaryl, each of which is optionally substituted;

L_{12} is selected from an optionally substituted 1- to 6- membered alkyl or heteroalkyl;

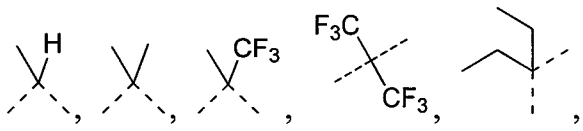
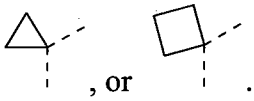
R_1 is selected from an optionally substituted 1- to 6- membered alkyl or heteroalkyl;

"hetero" represents N, O, S, C(=O), S(=O), or $S(=O)_2$, the number of the heteroatom on each group is selected from 1, 2, 3 or 4.

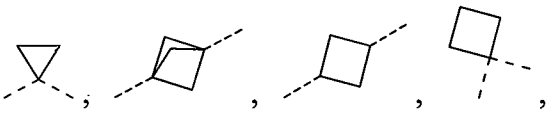
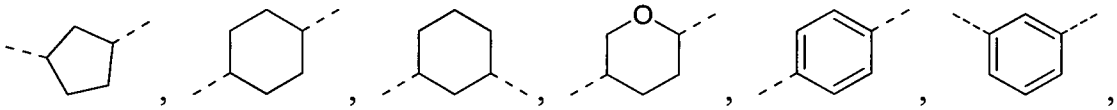
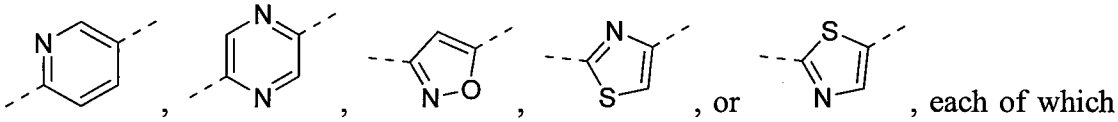
2. The compound according to claim 1, wherein the substituents in the R, R', A, L_{12} and R_1 are independently selected from the halogen, OH, NH_2, CN, or, the optionally substituted 1- to 6- membered alkyl and heteroalkyl, the number of the substituent on each group is independently selected from 1, 2 or 3, specifically, the substituents in the

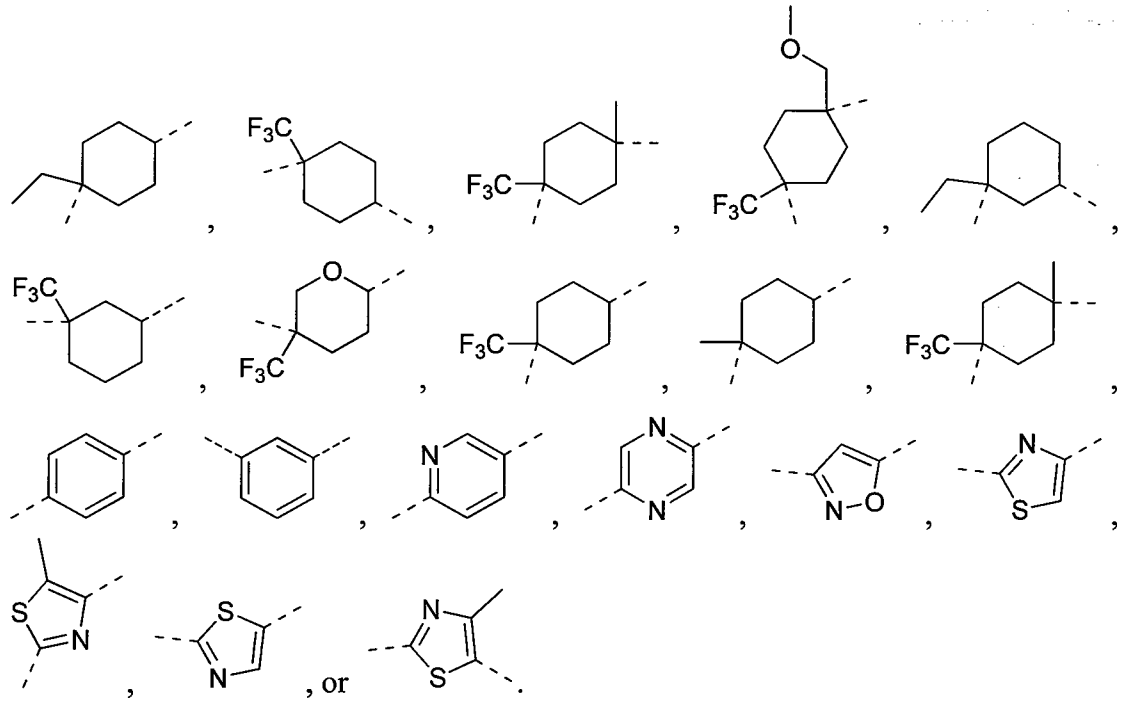
R, R', A, L_{12} and R_1 are independently selected from the halogen, CF_3, CN, OH, Me, Et, *n*-propyl, isopropyl, cyclopropyl,  , or  .

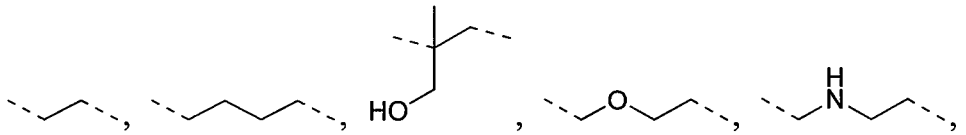
3. The compound according to claim 1 or 2, wherein the R and R' are independently selected from H, Me, CF_3, or Et;

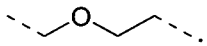
specifically, the L_{11} is selected from  ,  , or .

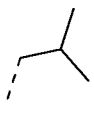
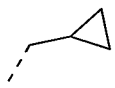
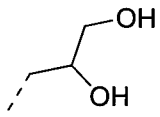
4. The compound according to claim 1 or 2, wherein the A is selected from the 3- to 12-membered cycloalkyl or cycloalkyl, or the 5- to 12-membered aryl or heteroaryl, each of which is optionally substituted;

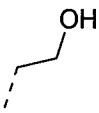
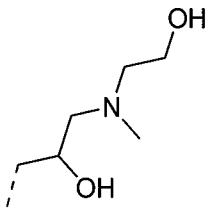
specifically, the A is selected from the A is selected from  ,  ,  ,



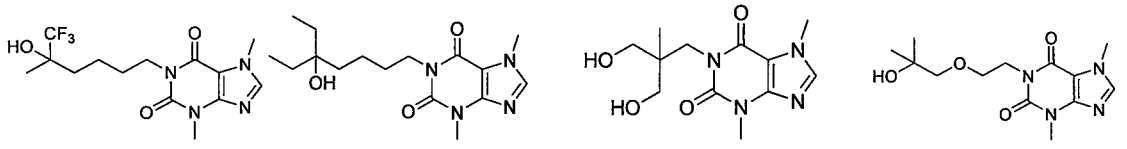
5. The compound according to claim 1 or 2, wherein the L_{12} is selected from methylene, 

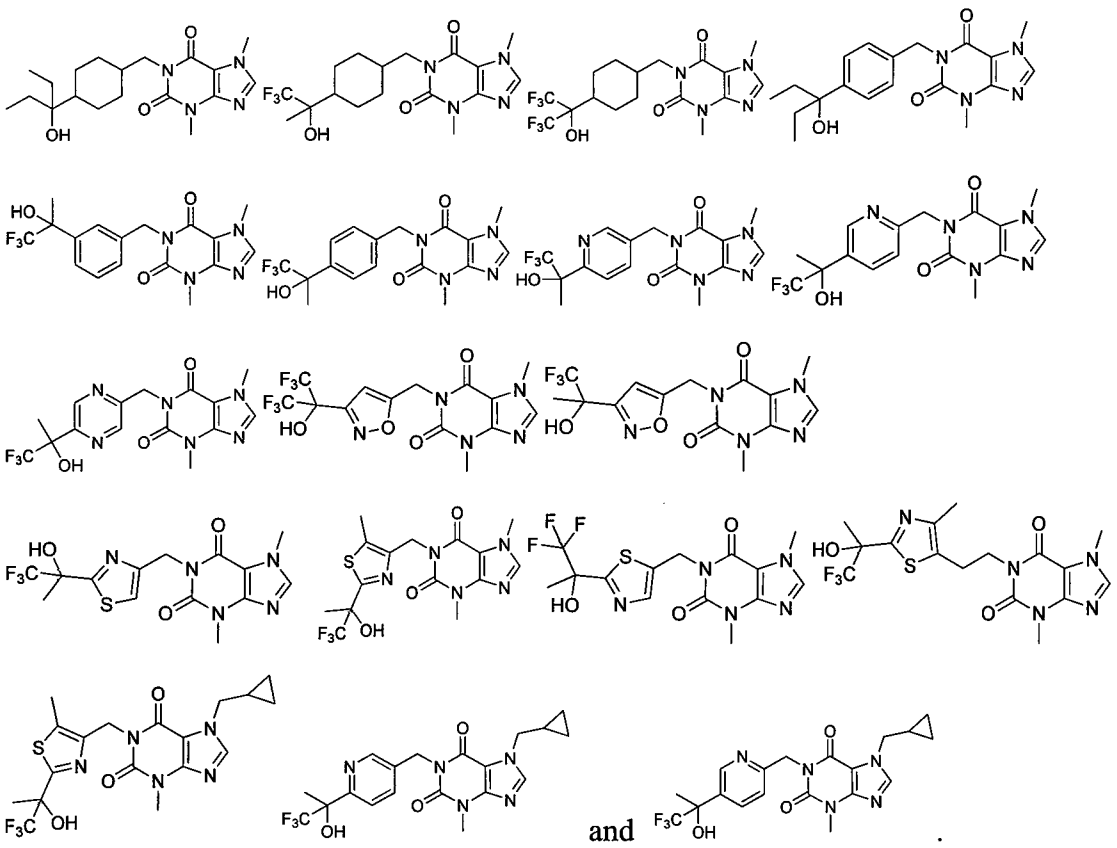
or 

6. The compound according to claim 1 or 2, wherein the R_1 is selected from Me, CHF_2, CF_3, Et, CH_2CF_3, isopropyl,  , cyclopropyl,  ,  ,

 , or  .

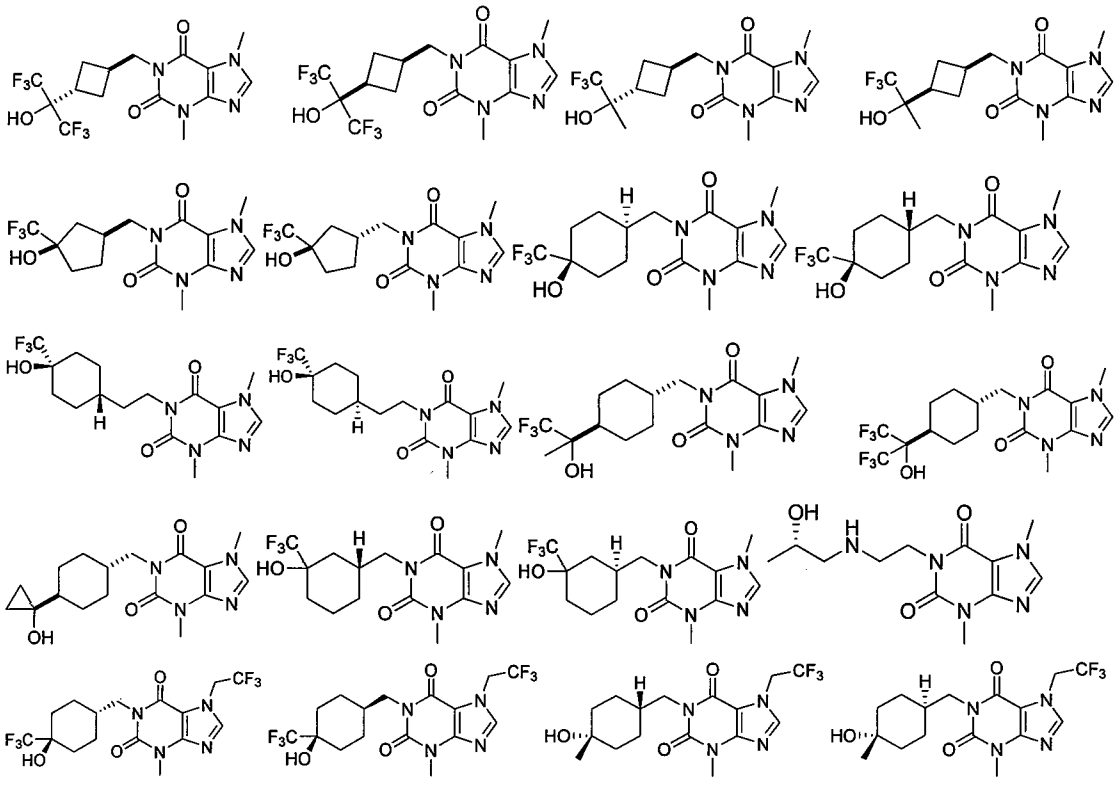
7. A compound selected from the group consisting of:

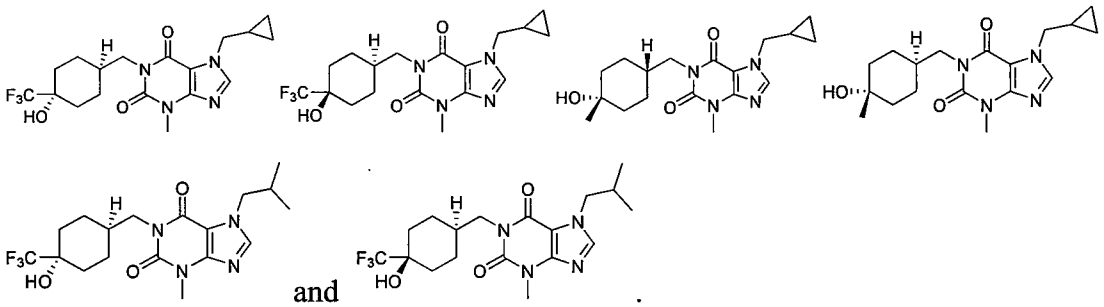




and

8. A compound selected from the group consisting of:





and

9. An application of the compound, the tautomer thereof or the pharmaceutically acceptable salt thereof according to any claims of 1 to 8 in manufacturing a PDE2 inhibitor and a TNF-α inhibitor.