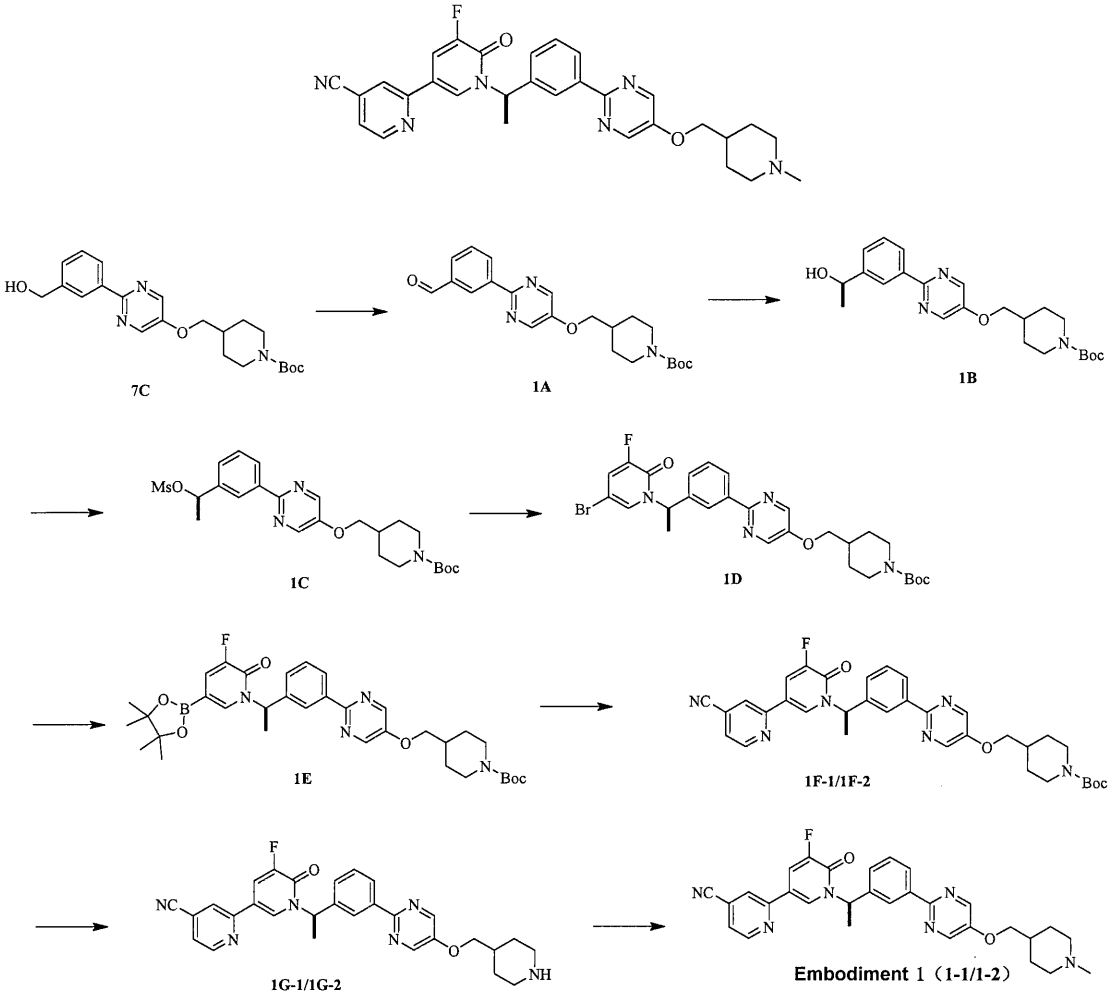


[0059] Step A:

[0060] The solution of intermediate 7C (synthetic method see embodiment 7) (20.4 g, 50.88 mmol) and manganese dioxide (44.23 g, 508.7 mmol) in DCM (300 mL) was stirred at room temperature for 16 hours. After the reaction was complete, the mixture was filtered and concentrated to give the intermediate 1A (18.4 g) which was used directly for the next step. LCMS (ESI) m/z: 398(M+1).

[0061] Step B:

[0062] Methylmagnesium bromide (3 M, 38.58 mL) was added into a solution of intermediate 1A (23.0 g, 57.87 mmol) in THF (200 mL) at 0°C. The solution was stirred at room temperature for 1 hour. After the reaction was complete, the mixture was quenched by saturated sodium chloride solution (300 mL), extracted by ethyl acetate (200 mL*2), dried over anhydrous sodium sulfate, filtered and concentrated to give intermediate 1B (22.76 g, yield 95.11%). LCMS (ESI) m/z: 414(M+1). HNMR (400MHz, CHLOROFORM-d) δ =8.46 (s, H), 8.38-8.33 (m,1H), 8.26 (td, J=1.9,6.9 Hz, 1H), 7.53 - 7.44 (m, 2H), 5.02 (q, J=6.4 Hz, 1H), 4.31 - 4.12 (m, 2H), 3.95 (d, J=6.4 Hz, 2H), 2.78 (br t, J=12.1 Hz, 2H), 2.13 (br s, 1H), 2.08 - 1.96 (m, 1H), 1.86 (br d, J=12.9 Hz, 2H), 1.58 (d, J=6.5 Hz, 3H), 1.49 (s, 9H), 1.39 - 1.29 (m, 2H).

[0063] Step C:

[0064] Diisopropylethylamine (21.34 g, 165.12 mmol) and methanesulfonyl chloride (9.12 g, 79.62 mmol) were added into a solution of intermediate 1B (22.7 g, 55.04 mmol) in DCM (300 mL) at 0°C. The reaction solution was stirred at room temperature for 1h. After the reaction was complete as monitored by TLC, the mixture was washed with saturated ammonium chloride solution (200 mL) twice, dried over anhydrous sodium sulfate, filtered and concentrated to give the intermediate 1C (30 g, crude product) which was used directly for the next step.

[0065] Step D:

[0066] Potassium carbonate (10.68 g, 77.30 mmol), potassium iodide (641.58 mg, 3.86 mmol) and 5-bromo-3-fluoro-1*H*-pyridin-2-one (11.13 g, 57.97 mmol) were added into a solution of intermediate 1C (19 g, 3.86 mmol) in DMF (100 mL) at room temperature. The reaction solution was stirred at 90°C for 3 hours. After the reaction was complete, ethyl acetate (300 mL) was added into the solution and the solution was washed with brine (300mL) three times. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give the intermediate 1D (5.8 g, yield 25.54%). HNMR (400MHz, CHLOROFORM-d) δ = 8.47 (s, 2H), 8.41 - 8.32 (m, 2H), 7.55 - 7.47 (m, 1H), 7.39 (d, J=7.7 Hz, 1H), 7.15 (dd, J=2.4, 8.4 Hz, 1H), 7.11 - 7.07 (m, 1H), 6.52 (q, J=7.0 Hz, 1H), 4.31 - 4.12 (m, 2H), 4.01 - 3.93 (m, 2H), 2.87 - 2.72 (m, 2H), 2.09 - 1.98 (m, 1H), 1.89 - 1.80 (m, 5H), 1.49 (s, 9H), 1.39 - 1.30 (m, 2H).

[0067] Step E:

[0068] Under nitrogen atmosphere, intermediate 1D (2.0 g, 3.4 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (1.04 g, 4.09 mmol), acetate potassium (668.21 mg, 6.81 mmol) and $Pd(dppf)Cl_2$ (498.20 mg, 680.87 μmol) were dissolved in dioxane (30 mL) at room temperature. The reaction solution was stirred at 90°C for 2 hours. After the reaction was complete, a solution (30 mL) of intermediate 1E in dioxane was obtained and used directly for the next step.

[0069] Step F (1F-1, 1F-2):

[0070] Under nitrogen atmosphere, a solution (30 mL) of intermediate 1E (1.92 g, 3.03 mmol) in dioxane, sodium carbonate (642.30 mg, 6.06 mmol), 2-bromo-5-cyanopyridine (665.42 mg, 3.64 mmol) and $Pd(dppf)Cl_2$ (443.43 mg, 606.0 μmol) were dissolved in dioxane (40 mL) and water (6 mL) at room temperature. The reaction was stirred at 90°C for 3 hours. After the reaction was complete, the mixture was filtered and water (100 mL) was added into the filtrate and extracted with ethyl acetate (60 mL*3). The organic phase was dried over anhydrous sodium sulfate and then filtered and concentrated. The crude product was purified by preparative plate, and the intermediate 1F-1 (t=2.819, 490 mg, 26.04% yield) and intermediate 1F-2 (t=3.933, 480 mg, 25.95% yield) were isolated by SFC (column type: AS (250 mm*30 mm,10 um); mobile phase: [B： 0.1% NH_3H_2O EtOH]; B%: 55%-55%, 10 min; 200 minmin).

[0071] LCMS (ESI) m/z: 611 (M+1).

[0072] HNMR （intermediate 1F-1） (400MHz, METHANOL-d4) δ = 8.73 (dd, J=0.9, 5.0 Hz, 1H), 8.55 (s, 2H), 8.39 (s, 1H), 8.34 - 8.26 (m, 2H), 8.17 - 8.08 (m, 2H), 7.58 - 7.49 (m, 3H), 6.50 (q, J=7.2 Hz, 1H), 4.15 (br d, J=13.3 Hz, 2H), 4.06 (d, J=6.3 Hz, 2H), 2.84 (br s, 2H), 2.14 - 2.01 (m, 1H), 1.97 (d, J=7.3 Hz, 3H), 1.87 (br d, J=11.9 Hz, 2H), 1.48 (s, 9H), 1.35 - 1.28 (m, 2H).

[0073] HNMR （intermediate 1F-2）(400MHz, METHANOL-d4) δ = 8.73 (dd, J=0.8, 5.0 Hz, 1H), 8.55 (s, 2H), 8.39 (s, 1H), 8.34 - 8.26 (m, 2H), 8.16 - 8.09 (m, 2H), 7.61 - 7.49 (m, 3H), 6.50 (q, J=7.2 Hz, 1H), 4.15 (br d, J=13.2 Hz, 2H), 4.06 (d, J=6.3 Hz, 2H), 2.84 (br s, 2H), 2.12 - 2.01 (m, 1H), 1.99 - 1.95 (m, 3H), 1.87 (br d, J=10.9 Hz, 2H), 1.48 (s, 9H), 1.35 - 1.29 (m, 2H).

[0074] Step G (1G-1, 1G-2)

[0075] Trifluoroacetic acid (3 mL) was added into a solution of intermediate 1F-1 (490 mg, 786.01 μmol) in DCM (10 mL) at 0°C. The reaction solution was stirred at room temperature for 1 hour. After the reaction was complete, the mixture was evaporated to dryness to give intermediate 1G-1 (502 mg, crude product) which was directly used for the next step. Intermediate 1G-2 (491 mg, crude product) was obtained with the same method as intermediate 1G-1.

[0076] Step H:

[0077] Formalin (326.27 mg, 4.02 mmol, 37% purity) and sodium triacetoxyborohydride (511.03 mg, 2.41 mmol) were added into a solution of intermediate 1G-1 (502.00 mg, 803.74 mmol) in DCM (10 mL) at 0°C. The reaction solution was stirred at room temperature for 2 hours. After the reaction was complete, the mixture was quenched with water (50 mL) and DCM (30 mL*2). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated. The crude product obtained was purified by preparative HPLC to give the embodiment 1-1 (150 mg, 35.41% yield).

[0078] Embodiment 1-2 (100.6 mg, 23.91% yield) was obtained with the same method as embodiment 1-1, started from intermediate 1G-2.

[0079] Embodiment 1-1:

[0080] LCMS (ESI) m/z: 525 (M+1).

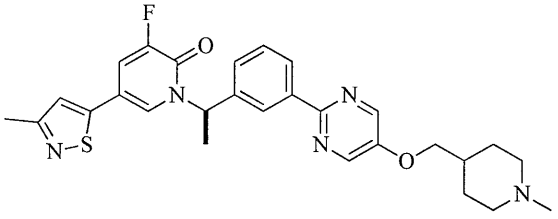
[0081] HNMR (400MHz, METHANOL-d4) δ = 8.73 (d, J=4.9 Hz, 1H), 8.56 (s, 2H), 8.49 (s, 1H), 8.39 (s, 1H), 8.34 - 8.26 (m, 2H), 8.18 - 8.09 (m, 2H), 7.61 - 7.49 (m, 3H), 6.50 (q, J=7.2 Hz, 1H), 4.13 (d, J=5.8 Hz, 2H), 3.53 (br d, J=12.4 Hz, 2H), 3.03 (br t, J=12.4 Hz, 2H), 2.87 (s, 3H), 2.27 - 2.08 (m, 3H), 1.97 (d, J=7.2 Hz, 3H), 1.81 - 1.63 (m, 2H).

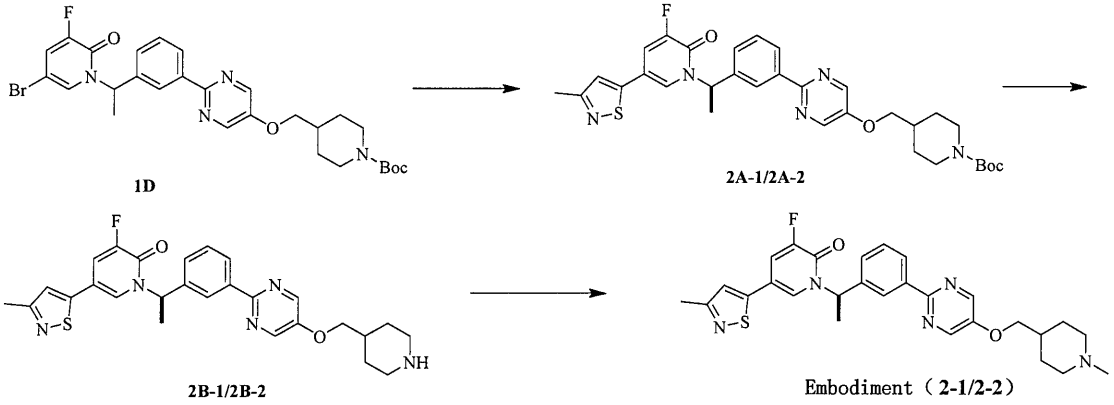
[0082] Embodiment 1-2：

[0083] LCMS (ESI) m/z: 525 (M+1).

[0084] HNMR (400MHz, METHANOL-d4) δ = 8.72 (dd, J=0.8, 5.0 Hz, 1H), 8.61 - 8.46 (m, 3H), 8.38 (s, 1H), 8.33 - 8.25 (m, 2H), 8.16 - 8.08 (m, 2H), 7.58 - 7.47 (m, 3H), 6.49 (q, J=7.1 Hz, 1H), 4.12 (d, J=5.9 Hz, 2H), 3.50 (br d, J=12.2 Hz, 2H), 3.05 - 2.93 (m, 2H), 2.83 (s, 3H), 2.22 - 2.06 (m, 3H), 1.96 (d, J=7.2 Hz, 3H), 1.80 - 1.62 (m, 2H).

Embodiment 2（2-1 and 2-2）





[0085] Step A:

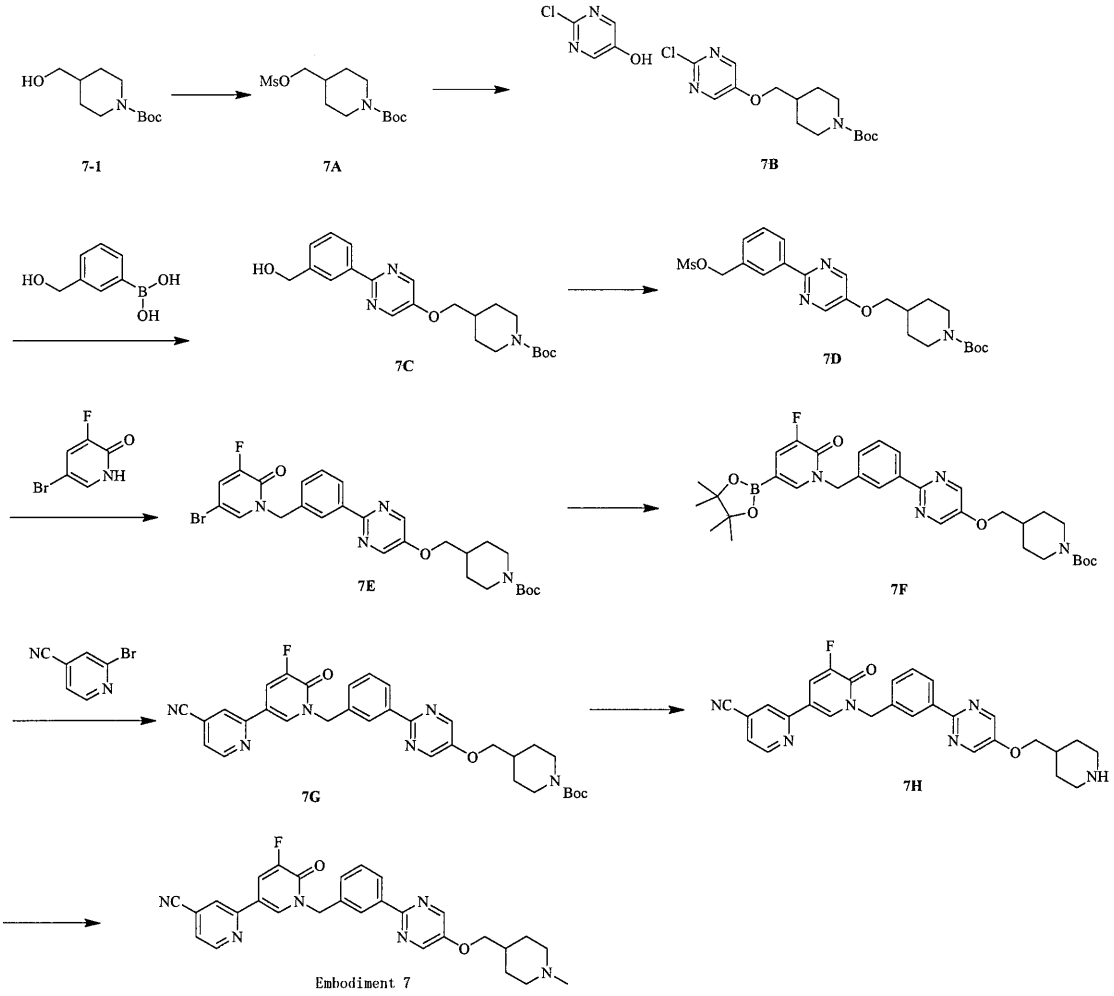
[0086] Under nitrogen atmosphere, intermediate 1D (1.0 g*2, 1.70 mmol), 3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)isothiazole (1.15 g, 5.10 mmol), potassium phosphate (1 M, 3.4 mL) and 1,1-(tert-butylphosphino)ferrocene palladium dichloride (110.80 mg, 170.00 μmol) were dissolved in THF (10 mL) at room temperature. The reaction solution was stirred at 70°C for 16 hours. The reaction solution was then filtered and water (50 mL) was added into. The mixture was extracted by ethyl acetate (30 mL*3). The organic phase was then dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was then purified by preparative HPLC. The intermediate 2A-1 (t=2.529, 560 mg, 24.28% yield) and intermediate 2A-2 (t=3.494, 500 mg, 27.19% yield) were isolated by SFC (column type: AS (250 mm*30 mm,10 um); mobile phase: [B： 0.1% NH_3H_2O EtOH]; B%: 35%-35%, 7.2 min; 200 minmin).

[0087] LCMS (ESI) m/z: 605 (M+1)

[0088] HNMR （intermediate 2A-1）(400MHz, METHANOL-d4) δ = 8.61 - 8.50 (m, 2H), 8.41 - 8.26 (m, 2H), 7.76 (d, J=2.1 Hz, 1H), 7.70 (dd, J=2.1, 10.0 Hz, 1H), 7.57 - 7.50 (m, 2H), 7.29 (s, 1H), 6.45 (q, J=7.1 Hz, 1H), 4.16 (br d, J=13.3 Hz, 2H), 4.07 (d, J=6.1 Hz, 2H), 2.85 (br s, 2H), 2.45 (s, 3H), 2.08 (br s, 1H), 1.96 - 1.84 (m, 5H), 1.48 (s, 9H), 1.37 - 1.29 (m, 2H).

[0089] HNMR （intermediate 2A-2） (400MHz, METHANOL-d4) δ = 8.59 - 8.53 (m, 2H), 8.41 - 8.27 (m, 2H), 7.76 (s, 1H), 7.73 - 7.66 (m, 1H), 7.58 - 7.49 (m, 2H), 7.28 (d, J=2.8 Hz, 1H), 6.45 (q, J=6.9 Hz, 1H), 4.16 (br d, J=13.6 Hz, 2H), 4.06 (dd, J=3.9, 6.1 Hz, 2H), 2.94 - 2.78 (m, 2H), 2.44 (d, J=2.1 Hz, 3H), 2.07 (td, J=3.7, 9.6 Hz, 1H), 1.96 - 1.84 (m, 5H), 1.48 (s, 9H), 1.36 - 1.27 (m, 2H).

[0090] Step B: intermediate 2B-1 and intermediate 2B-2 were prepared according to the preparation method of intermediate 1G-1.



[0138] Step A:

[0139] Under nitrogen atmosphere, methane disulfonyl chloride (45.15 g, 394.15 mmol) was added dropwise into a solution of tert-butyl-4-(hydroxymethyl)piperidine-1-carbomate (68.00 g, 315.85 mmol) and diisopropylethylamine (81.64 g, 631.71 mmol) in dichloromethane (800 mL) while stirring. After the dropwise addition was complete, the reaction solution was stirred at 25°C for 2 hours. Thin layer chromatography was used to ensure the reaction was complete. The reaction solution was washed with saturated ammonium chloride solution (500 mL*2) and brine (300 mL *2) and dried over anhydrous sodium sulfate, filtered and concentrated to give intermediate 7A (red oily liquid, 95.00 g, 100% yield) which was used directly for the next step without further purification.

[0140] Step B

[0141] Under nitrogen atmosphere, potassium carbonate (74.12 g, 536.28 mmol) was added into a solution of intermediate 7A (94.40 g, 321.77 mmol) and 2-chloropyrimidin-5-ol (35.00 g, 268.14 mmol) in DMF (1.00 L). The reaction solution was left at 80°C for 16 hours, and thin layer chromatography was used to detect the completion of the reaction. Then the reaction solution was cooled to room temperature and concentrated, then water (500 mL) was added into the residue and extracted with ethyl acetate (300 mL*3). The organic phase was washed with brine (400 mL*2) and dried over anhydrous sodium sulfate, then filtered and concentrated. Then the residue was purified

by column chromatography to give the intermediate 7B (pale yellow solid, 84.00 g, 95.05% yield). LCMS (ESI) m/z: 327.7 (M+1). 1HNMR (400 MHz, DMSO-d6) δ ppm 1.08 - 1.25 (m, 2 H) 1.40 (s, 9 H) 1.69 - 1.78 (m, 2 H) 1.88 - 2.03 (m, 1 H) 2.58 - 2.88 (m, 2 H) 3.89 - 4.05 (m, 4 H) 8.50 - 8.57 (m, 2 H)

[0142] Step C:

[0143] Under nitrogen atmosphere, a mixed solution of intermediate 7B (84.00 g, 254.85 mmol), [3-(hydroxymethyl)phenyl]boronic acid (42.60 g, 280.34 mmol), $Pd(PPh_3)_2Cl_2$ (17.89 g, 25.49 mmol) and potassium carbonate (70.45 g, 509.71 mmol) in 1.4-dioxane (1.00 L) and water (200.00 mL) was stirred at 80°C for 16 hours. Then the reaction solution was cooled to room temperature then filtered, followed by extraction with dichloromethane (500 mL*3), then the organic layers were combined together, washed with brine (500 mL *2) and dried over anhydrous sodium sulfate, then filtered and concentrated. The residue was recrystallized with methanol to give intermediate 7C (white solid, 77.60 g, 76.22% yield). LCMS (ESI) m/z: 400.1 (M+1). 1HNMR (400 MHz, DMSO-d6) δ ppm 1.14 - 1.31 (m, 2 H) 1.45 (s, 9 H) 1.75 - 1.87 (m, 2 H) 1.95 - 2.10 (m, 1 H) 2.66 - 2.93 (m, 2 H) 3.94 - 4.22 (m, 4 H) 4.63 (d, J=5.62 Hz, 2 H) 5.34 (t, J=5.81 Hz, 1 H) 7.41 - 7.54 (m, 2 H) 8.21 (d, J=7.46 Hz, 1 H) 8.35 (s, 1 H) 8.68 (s, 2 H)

[0144] Step D:

[0145] Under nitrogen atmosphere, methane disulfonyl chloride (3.44 g, 30.04 mmol) was added dropwise into a solution of intermediate 7C (10.00 g, 25.03 mmol) and diisopropylethylamine (6.47 g, 50.06 mmol) in dichloromethane (100.00 mL) while stirring. After the addition was complete, the reaction solution was stirred at 25°C for 2 hours. The thin layer chromatography was used to detect the completion of the reaction. The reaction solution was washed with saturated ammonium chloride solution (500 mL*2) and brine (300 mL*2), dried over anhydrous sodium chloride, filtered and concentrated to give intermediate 7D (gray solid, 14.00 g, 100% yield) which was used directly for the next step without further purification. LCMS (ESI) m/z: 478.1 (M+1).

[0146] Step E:

[0147] Under nitrogen atmosphere, potassium carbonate (6.95 g, 50.26 mmol) was added into a solution of intermediate 7D (12.00 g, 25.13 mmol) and 5-bromo-3-fluoro-1-H-pyridin-2-one (5.79 g, 30.16 mmol) in DMF (100.00 mL) at 25°C. The reaction solution was left at 90°C for 3 hours, then the reaction was complete as monitored by thin layer chromatography. Then the reaction solution was cooled to room temperature and concentrated. The residue was washed by water (100 mL), extracted with ethyl acetate (100 mL *3) and then the organic phase was washed by brine (200 mL*2) and dried over anhydrous sodium sulfate, then filtered and concentrated. The residue was purified by column chromatography to give intermediate 7E (yellow solid, 9.60 g 66.62% yield). LCMS (ESI) m/z: 574.9 (M+1). 1HNMR (400 MHz, DMSO-d6) δ ppm 1.09 - 1.27 (m, 2 H) 1.41 (s, 9 H) 1.77 (br d, J=11.13 Hz, 2 H) 1.90 - 2.10 (m, 1 H) 2.62 - 2.91 (m, 2 H) 3.87 - 4.14 (m, 4 H) 5.16 - 5.30 (m, 2 H) 7.39 - 7.52 (m, 2 H) 7.76 (dd, J=9.66, 2.45 Hz, 1 H) 8.14 - 8.19 (m, 1 H) 8.24 (d, J=7.58 Hz, 1 H) 8.28 (s, 1 H) 8.65 (s, 2 H)

[0148] Step F:

[0149] Under nitrogen atmosphere, a mixed solution of intermediate 7F (200.00 mg, 348.77

mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-1,3,2-dioxaborolane (92.99 mg, 366.21 mmol), $Pd(dppf)Cl_2$ (25.52 mg, 34.88 μmol) and potassium acetate (102.68 mg ,1.05 mmol) in 1,4-dioxane (10.00 mL) was stirred at 70°C for 2 hours to give a solution of intermediate 7F in dioxane, which was used directly for the next step without further purification.

[0150] Step G:

[0151] Under nitrogen atmosphere, a mixed solution of intermediate 7F in dioxane solution (210.00 mg, 338.43 μmol), 2-bromopyridin-4-carbonitrile (185.81 mg, 1.02 mmol), $Pd(dppf)Cl_2$-CH_2Cl_2 (55.28 mg, 67.69 μmol) and potassium carbonate (93.55 mg, 676.86 μmol) in 1,4-dioxane (10.00 mL) and water (2.00 mL) was stirred at 80°C for 3 hours. The reaction solution was then cooled to room temperature, filtered and concentrated. The residue was dissolved by adding water (50 mL) and extracted with ethyl acetate (30 mL *3). Then organic phases were combined, washed with brine (30 ml *2), dried over anhydrous sodium sulfate, followed by filtration and concentration. The residue was purified by preparative thin layer chromatography to give intermediate 7G (yellow solid, 50.00 mg, 24.76% yield). LCMS (ESI) m/z: 619.2 (M+23).

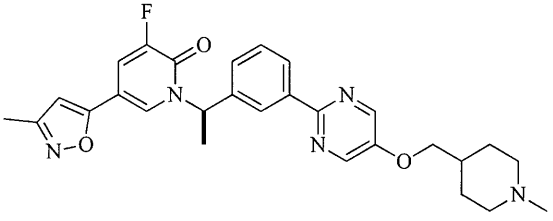
[0152] Step H:

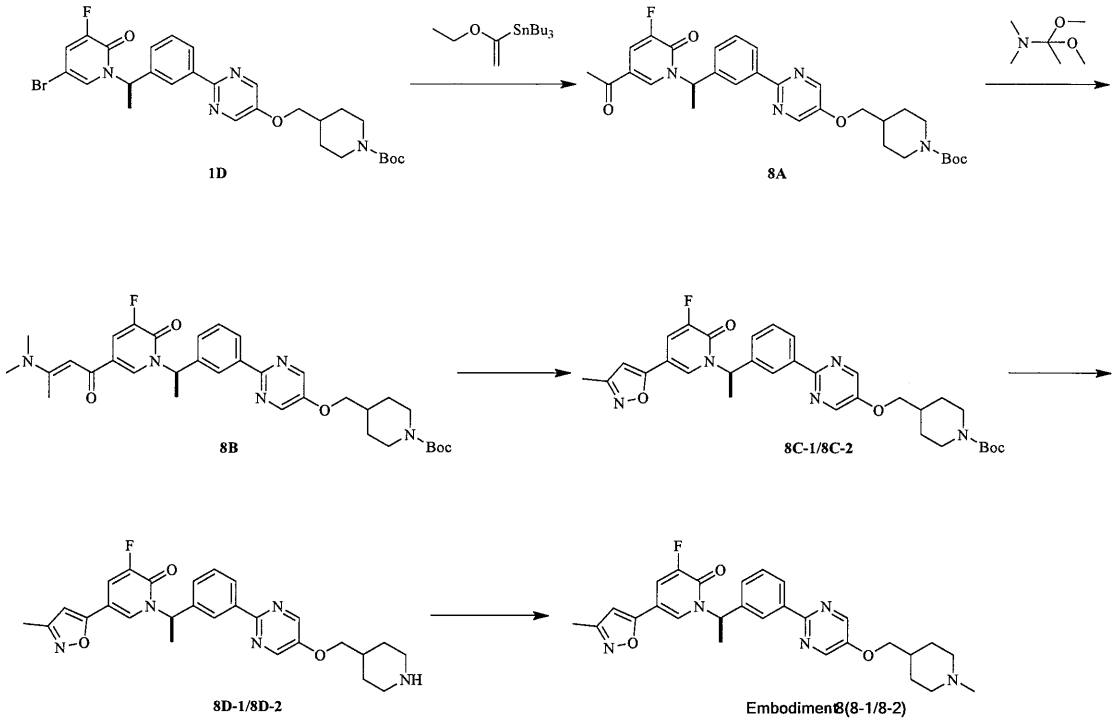
[0153] Under nitrogen atmosphere, trifluoroacetic acid (4.62 g, 40.52 mmol, 3.00 mL) was added into a solution of intermediate 7G (50.00 mg, 83.80 μmol) in dichloromethane (10.00 mL) at 0°C. The reaction solution was stirred at 25°C for 1 hour, then concentrated to obtain intermediate 7H (brownish black oily liquid, 60.00 mg, 100% yield, trifluoroacetate), which was used for the next step directly without further purification. LCMS (ESI) m/z: 497.2 (M+1).

[0154] Step I:

[0155] Under nitrogen atmosphere, formaldehyde (40.87 mg, 503.50 μmol, 37.50 μL, 37% aqueous solution) and sodium triacetoxyborohydride (64.03 mg, 302.10 μmol) were added into a solution of intermediate 7H (50.00 mg, 100.70 μmol) in dichloromethane (5.00 mL) at 0°C. The reaction solution was left at 25°C for 16 hours, then concentrated. The residue was purified by preparative HPLC to obtain embodiment 7 (21.70 mg, 38.48% yield, formate). LCMS (ESI) m/z: 511.1 (M+1). 1HNMR(400 MHz, DMSO-d6) δ ppm 1.27 - 1.43 (m, 2 H) 1.77 (br d, J=9.78 Hz, 3 H) 1.99 (br t, J=11.43 Hz, 2 H) 2.22 (s, 3 H) 2.85 (br d, J=11.37 Hz, 2 H) 4.05 (d, J=5.99 Hz, 2 H) 5.39 (s, 2 H) 7.50 (d, J=5.01 Hz, 2 H) 7.75 (dd, J=5.01, 1.22 Hz, 1 H) 8.18 - 8.26 (m, 2 H) 8.28 (s, 1 H) 8.33 (s, 1 H) 8.40 (s, 1 H) 8.64 (s, 2 H) 8.78 (d, J=1.34 Hz, 1 H) 8.82 (d, J=5.01 Hz, 1 H)

Embodiment 8（8-1 and 8-2）





[0156] Step A:

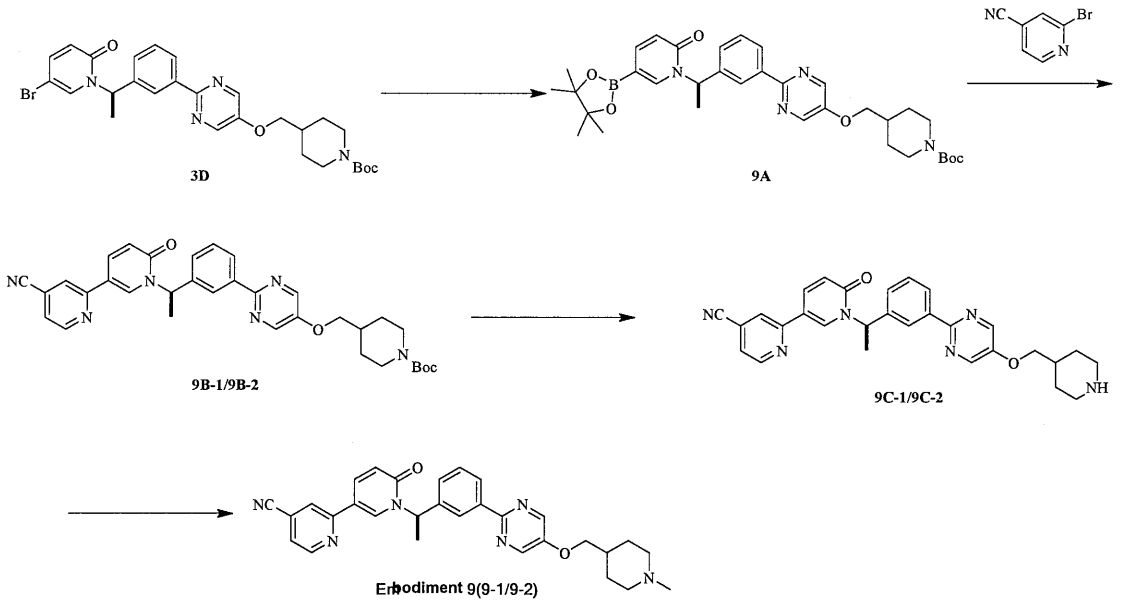
[0157] Under nitrogen atmosphere, a solution of intermediate 1D (1.50 g, 2.55 μmol), tributyl(1-ethoxyethylene)tin (1.14 g, 3.16 mmol, 1.07 mL) and $Pd(dppf)Cl_2$ (358.43 mg, 510.66 μmol) in toluene (10.00 mL) was stirred at 100°C for 3 hours. Hydrochloric acid (10.21 mL, 1 N aqueous solution) was added into the reaction solution after the solution was cooled to room temperature and then the solution was stirred at 25°C for 1 hour, filtered and concentrated. The residue was purified by column chromatography to give intermediate 8A (yellow oily liquid, 1.13 g, 80.48% yield). LCMS (ESI) m/z: 573.1 (M+23). 1HNMR (400 MHz, CHLOROFORM-d) δ ppm 1.50 (s, 9 H) 1.89 (d, J=7.03 Hz, 6 H) 1.98 - 2.10 (m, 2 H) 2.31 (s, 3 H) 2.72 - 2.86 (m, 2 H) 3.98 (d, J=6.27 Hz, 2 H) 4.12 - 4.31 (m, 2 H) 6.54 (q, J=7.28 Hz, 1 H) 7.42 (br d, J=7.65 Hz, 1 H) 7.61 (dd, J=9.66, 2.26 Hz, 1 H) 7.65 - 7.74 (m, 1 H) 7.84 (d, J=1.38 Hz, 1 H) 8.38 (d, J=7.78 Hz, 1 H) 8.42 (s, 1 H) 8.47 (s, 2 H)

[0158] Step B:

[0159] Under nitrogen atmosphere, a solution of intermediate 8A (1.13 g, 2.05 mmol) in 1,1-dimethoxy-N,N-dimethyl-ethane (5.00 mL) was stirred at 120°C for 3 hours. Then the reaction solution was cooled to room temperature and concentrated to dryness to obtain the intermediate 8B (brownish black oily liquid, 1.27 g, 100% yield), which was used directly for next step without further purification. LCMS (ESI) m/z: 620.1 (M+1).

[0160] Step C:

[0161] Under nitrogen atmosphere, hydroxylamine (213.61 mg, 3.08 mmol, hydrochloride salt) was added into a solution of intermediate 8B (1.27 g, 2.05 mmol) in ethanol (20.00 mL). The mixture was left at 80°C for 16 hours, then concentrated. The residue was purified by preparative HPLC, the racemates were separated by preparative SFC (column : AS（250 mm*30 mm,10 um）;



[0173] Step A:

[0174] Under nitrogen atmosphere, a mixture of intermediate 3D (1.00 g, 1.76 mmol), 4,4,5,5-tetramethyl-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-1,3,2-dioxaborolane (469.28 mg, 1.85 mmol), Pd(dppf)Cl_2 (128.78 mg, 176.00 μmol) and potassium acetate (518.17 mg, 5.28 mmol) in 1,4-dioxane (15.00 mL) was stirred at 80°C for 2 hours, then intermediate 9A in dioxane was obtained and was used directly for the next step without further treatment.

[0175] Step B:

[0176] Under nitrogen atmosphere, a mixture of intermediate 9A (1.09 g, 1.77 mmol) in dioxane, 2-bromopyridine-4-carbonitrile (485.89 mg, 2.66 mmol), Pd(dppf)Cl_2·CH_2Cl_2 (289.09 mg, 354.00 μmol) and potassium carbonate (489.26 mg, 3.54 mmol) in 1,4-dioxane (20.00 mL) and water (4.00 mL) in solution was stirred at 80°C for 3 hours. Then the reaction solution was cooled to room temperature, filtered and concentrated. The residue was purified by preparative thin layer chromatography, the racemates was separated by preparative SFC (column: AS（250 mm*30 mm,10 um）; phase mobile: [0.1% NH_3-H_2O EtOH]; B%: 55%-55%, 8.2 min; 100 minmin) to intermediate 9B-1 (yellow oily liquid, 200.00 mg, 100% ee value, 19.06% yield, Rt=2.973 min) and intermediate 9B-2 (yellow oily liquid, 200.00 mg, 100% ee value, 19.06% yield, Rt=3.605min). LCMS (ESI) m/z: 593.1 (M+1).

[0177] Step C

[0178] Intermediate 9C-1, 9C-2 was prepared according to the preparation method of 1G.

[0179] Step D:

[0180] Embodiment 9-1, 9-2 was prepared according to the preparation method of embodiment 1.

[0181] Embodiment 9-1:

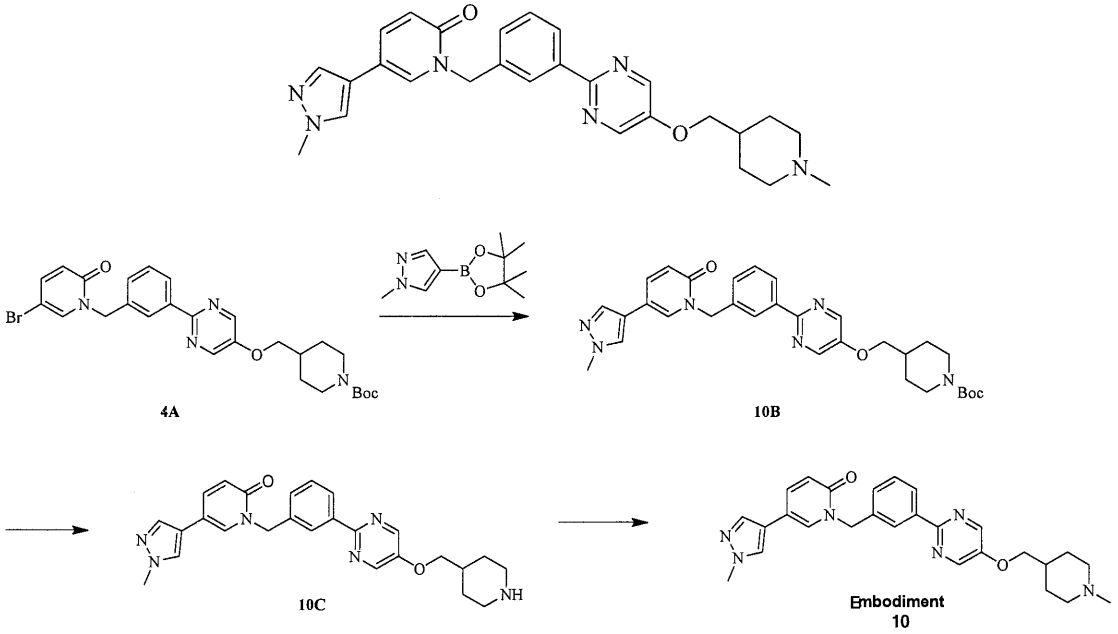
[0182] LCMS (ESI) m/z: 507.1 (M+1). 1HNMR (400 MHz, DMSO-d6) δ ppm 1.29 - 1.45 (m,

2 H) 1.80 (br d, J=10.54 Hz, 3 H) 1.88 (d, J=7.28 Hz, 3 H) 2.14 (br t, J=11.17 Hz, 2 H) 2.30 (s, 3 H) 2.94 (br d, J=11.29 Hz, 2 H) 4.05 (d, J=6.02 Hz, 2 H) 6.32 (d, J=7.15 Hz, 1 H) 6.62 (d, J=9.66 Hz, 1 H) 7.46 - 7.55 (m, 2 H) 7.69 (dd, J=5.02, 1.25 Hz, 1 H) 8.19 - 8.26 (m, 3 H) 8.27 (s, 1 H) 8.43 (t, J=1.07 Hz, 1 H) 8.49 (d, J=2.38 Hz, 1 H) 8.64 (s, 2 H) 8.77 (dd, J=5.02, 0.88 Hz, 1 H)

[0183] Embodiment 9-2

[0184] LCMS (ESI) m/z: 507.1 (M+1). 1HNMR (400 MHz, DMSO-d6) δ ppm 1.27 - 1.46 (m, 2 H) 1.81 (br d, J=10.54 Hz, 3 H) 1.89 (d, J=7.28 Hz, 3 H) 2.17 (br t, J=11.17 Hz, 2 H) 2.31 (s, 3 H) 2.96 (br d, J=11.29 Hz, 2 H) 4.09 (d, J=6.02 Hz, 2 H) 6.35 (d, J=7.15 Hz, 1 H) 6.65 (d, J=9.66 Hz, 1 H) 7.42 - 7.57 (m, 2 H) 7.66 (dd, J=5.02, 1.25 Hz, 1 H) 8.21 - 8.27 (m, 3 H) 8.29 (s, 1 H) 8.45 (t, J=1.07 Hz, 1 H) 8.51 (d, J=2.38 Hz, 1 H) 8.67 (s, 2 H) 8.79 (dd, J=5.02, 0.88 Hz, 1 H)

Embodiment 10



[0185] Step A:

[0186] Under nitrogen atmosphere, a mixture of intermediate 4A (200.00 mg, 346.53 μmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)pyrazole (108.15 mg, 519.80 μmol), $Pd(dppf)Cl_2$ (25.36 mg, 34.65 μmol) and sodium carbonate (110.19 mg, 1.04 mmol) in 1,4-dioxane (10.00 mL) was stirred at 80°C for 2 hours, then the reaction solution was cooled to room temperature, filtered and concentrated. The residue was dissolved by adding water (60 mL) and then extracted with ethyl acetate (50 mL*3). Then organic phases were combined and washed with brine (80 mL *2), and dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by preparative thin layer chromatography to give intermediate 10B (yellow oily liquid, 200.00 mg, 95.45% yield). LCMS (ESI) m/z: 557.3 (M+1).

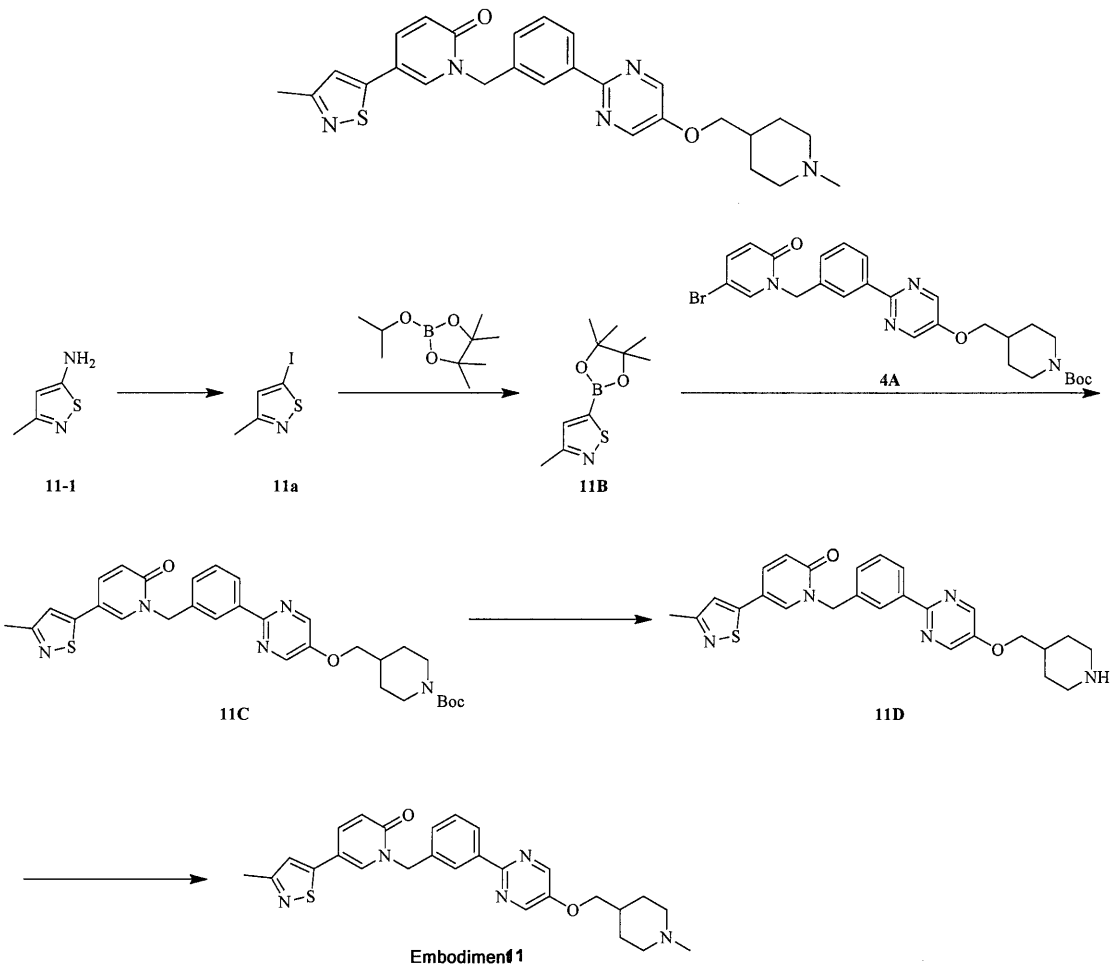
[0187] Step B:

[0188] Intermediate 10C was prepared according to the preparation method of intermediate 1G.

[0189] Step C:

[0190] Embodiment 10 was prepared according to the preparation method of embodiment 1. LCMS (ESI) m/z: 471.2 (M+1). 1HNMR (400 MHz, METHANOL-d4): 1.63 - 1.80 (m, 2 H) 2.09 - 2.25 (m, 3 H) 2.88 (s, 3 H) 3.05 (t, J=12.17 Hz, 2 H) 3.55 (d, J=12.67 Hz, 2 H) 3.91 (s, 3 H) 4.12 (d, J=5.90 Hz, 2 H) 5.34 (s, 2 H) 6.67 (d, J=9.41 Hz, 1 H) 7.42 - 7.51 (m, 2 H) 7.75 (s, 1 H) 7.81 (dd, J=9.35, 2.57 Hz, 1 H) 7.88 (s, 1 H) 8.05 (d, J=2.38 Hz, 1 H) 8.25 - 8.29 (m, 1 H) 8.33 (s, 1 H) 8.47 (s, 1 H) 8.55 (s, 2 H).

Embodiment 11



[0191] Step A:

[0192] Under nitrogen atmosphere, a solution of sodium nitrite (2.52 g, 36.54 mmol) in water (50 mL) was added dropwise into a mixed solution of 3-methyisothiazol-5-amine (5.00 g, 33.19 mmol, hydrochloride salt) in water (14.00 mL) and sulfuric acid (10.00 mL, 98% purity) at 0°C. The reaction solution was stirred at 0°C for 1 hour, then a solution of potassium iodide (6.06 g, 36.51 mmol) in water (35 mL) was added and the solution was left at 80°C for 1 hour for reaction. The reaction solution was cooled to room temperature, diluted with water (100 mL) and extracted with dichloromethane (50 mL*2). Then the organic phases were combined and washed with brine (25 mL*2), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography to give intermediate 11A (yellow solid, 4.00 g, 53.55% yield). LCMS (ESI) m/z: 225.9 (M+1). 1HNMR (400 MHz, CHLOROFORM-d) δ ppm 2.39 - 2.48 (m, 3 H)

7.04 - 7.13 (m, 1 H).

[0193] Step B:

[0194] Under nitrogen atmosphere, isopropylamagnesium chloride-lithium chloride complex (3.66 mL, 1.3 M tetrahydrofuran solution) was added dropwise into a solution of intermediate 11A (1.00 g, 4.44 mmol) and 2-isopropoxy-4,4,5,5-1,3,2-dioxaborolane (850 mg, 4.57 mmol) in tetrahydrofuran (5.00 mL) at -25°C. The reaction solution was stirred at -25°C for 0.5 hour. After the reaction, the solution was quenched by dripping into a solution of acetic acid (0.24 mL) in tetrahydrofuran (0.67 mL), then petroleum ether (48 mL) and tert-butyl methyl ether (24 mL) were added into the reaction solution. After filtration, tert-butyl methyl ether (32 mL) was added into filtrate, then the filtrate was again filtered and concentrated to give intermediate 11B (yellow oily liquid, 512 mg, 51.22% yield)which was used for the next step directly without further purification. 1HNMR (400 MHz, CHLOROFORM-d) δ ppm 1.28 (s, 12 H) 2.46 - 2.48 (m, 3 H) 7.31 (s, 1 H).

[0195] Step C:

[0196] Under nitrogen atmosphere, a mixture of intermediate 11B (283.69 mg, 1.26 mmol), intermediate 4A (500.00 mg, 900.15 μmol), 1,1-di(tert-butylphosphino)ferrocene palladium chloride (58.67 mg, 90.02 μmol) and potassium phosphate trihydrate (479.44 mg, 1.80 mmol) in tetrahydrofuran (5.00 mL) and water (1.00 mL) was stirred at 65°C for 12 hours. Then the reaction solution was cooled to room temperature, filtered and concentrated. After the residue was dissolved in water (50 mL) and extracted with ethyl acetate (100 mL*2), the organic phases were combined and washed with brine (50 mL*2), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by preparative thin layer chromatography to give intermediate 11C (yellow solid, 266.00 mg, 51.51% yield). LCMS (ESI) m/z: 574.2 (M+1). 1HNMR (400 MHz, CHLOROFORM-d) δ ppm 1.27 - 1.34 (m, 6 H) 1.60 - 1.64 (m, 10 H) 1.60 - 1.65 (m, 10 H) 1.83 - 1.91 (m, 2 H) 1.95 (s, 1 H) 2.46 - 2.52 (m, 3 H) 3.95 - 4.01 (m, 2 H) 5.28 - 5.31 (m, 2 H) 6.71 - 6.77 (m, 1 H) 6.94 - 6.97 (m, 1 H) 7.39 - 7.56 (m, 3 H) 7.63 - 7.68 (m, 1 H) 8.37 (s, 2 H) 8.47 (s, 2 H).

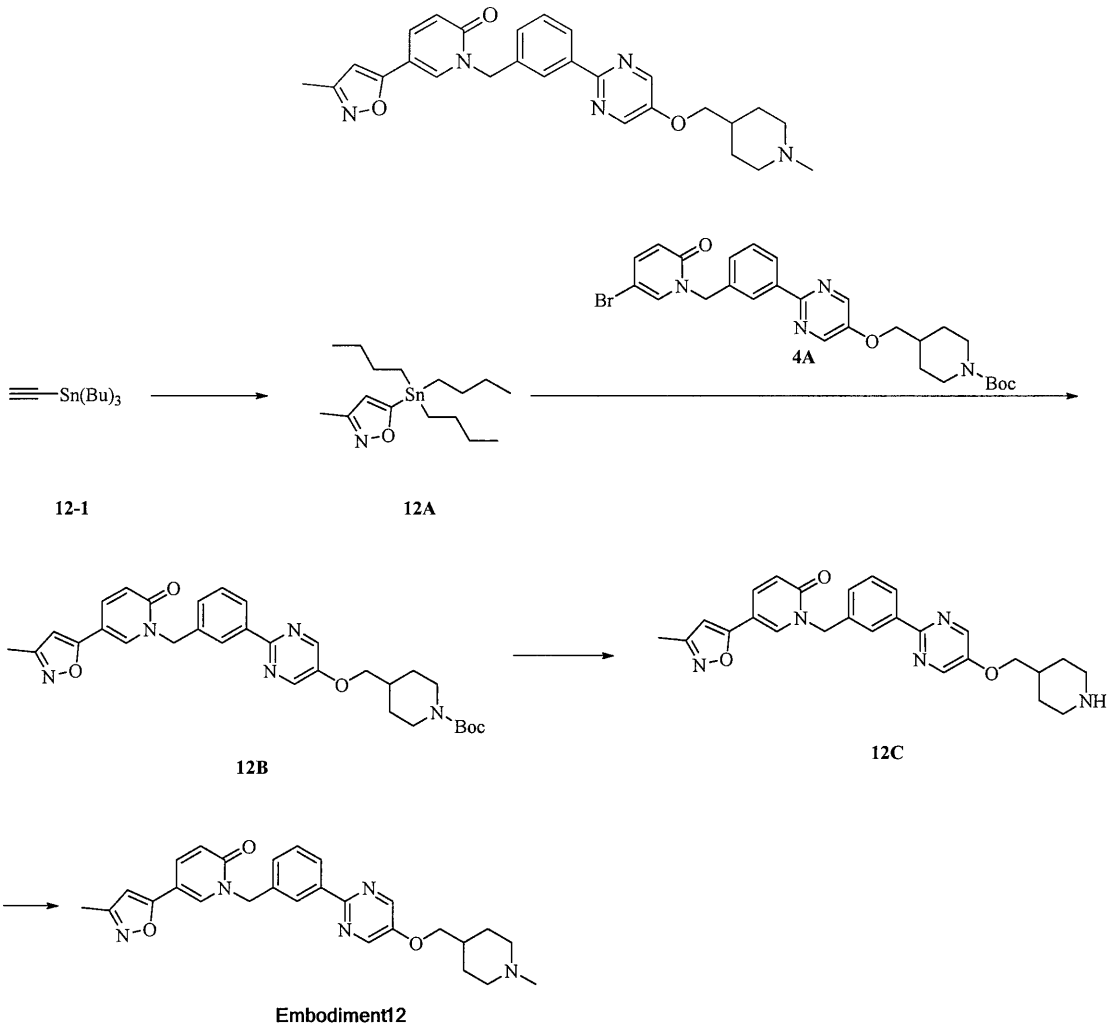
[0197] Step D:

[0198] Intermediate 11D was prepared according to the preparation method of intermediate 1F. LCMS (ESI) m/z: 474.2 (M+1).

[0199] Step E:

[0200] Embodiment 11 was prepared according to the preparation method of embodiment 1. LCMS (ESI) m/z: 488.2 (M+1). 1HNMR (400 MHz, DMSO-d6) δ ppm 1.37 (br d, J=10.54 Hz, 2 H) 1.79 (br d, J=10.04 Hz, 3 H) 2.11 (br s, 2 H) 2.26 - 2.31 (m, 3 H) 2.40 - 2.44 (m, 3 H) 2.89 - 2.97 (m, 2 H) 4.01 - 4.09 (m, 2 H) 5.25 (s, 2 H) 6.57 (d, J=9.41 Hz, 1 H) 7.45 (d, J=11.80 Hz, 3 H) 7.79 (dd, J=9.41, 2.64 Hz, 1 H) 8.20 - 8.26 (m, 2 H) 8.29 (s, 1 H) 8.53 - 8.56 (m, 1 H) 8.62 - 8.66 (m, 2 H).

Embodiment 12



[0201] Step A:

[0202] Triethylamine (32.08 mg, 317.00 μmol, 43.94 μL) was added into a solution of phenyl isocyanate (830.74 mg, 6.97 mmol) in nitroethane (261.77 mg, 3.49 mmol, 249.30 μL) and the reaction solution was stirred at 50°C for 30 minutes, then a solution of tributyl(ethynyl)stannane (1.00 g, 3.17 mmol) in toluene (8.00 mL) was added into the reaction solution, followed by stirring at 50°C for 5 hours. Thin layer chromatography was used to detect the completion of the reaction. Then water (100 mL) was added into the solution, which then was extracted with ethyl acetate (100 mL). The organic phase was then washed with brine (50 mL) and dried over anhydrous sodium sulfate, filtered and concentrated with a rotary evaporator. The residue was purified by column chromatography to give intermediate 12A (yellow oily liquid, 700.00 mg, 42.13% yield). LCMS (ESI) m/z: 373.14 (M+1). 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 0.82 - 0.85 (m, 9 H) 0.97 - 1.11 (m, 6 H) 1.20 - 1.34 (m, 12 H) 1.49 - 1.52 (m, 3 H) 7.18 - 7.20 (m, 1 H).

[0203] Step B:

[0204] Intermediate 12A (200 mg, 348.77 μmol) and $Pd(PPh_3)_2Cl_2$ (25.27 mg, 36.01 μmol) were added into a solution of intermediate 4A (200.00 mg, 360.06 μmol) in dioxane (4.00 mL) at 20°C, then heated to 100°C and stirred for 12 hours under nitrogen atmosphere. Thin layer

each of them 75 nL.

[0220] 3) The mixture of 7.5μL antibody (1/375 nM) and kinase (10 nM) was added to the compound plate, followed by addition of 7.5 μL Tracer (60 nM). Final concentration: cMET: 5 nM, Tracer 236: 30 nM, Eu-Anti-His AB (MAb Anti 6HIS-K): 1/750 nM.

[0221] 4) After 60 mins of incubation at 4°C, Envision readings were performed with a multi-labelled microplate reader (data analysis of 665 nm/615 mm signal values with Prism 5; Ex excitation light: Laser mirror 446, Em excitation light; 615 and 665 nM.

[0222] Experimental result: See Table 1.

[0223] Conclusion: the compounds of the present invention have a relatively strong inhibitory effect on the c-MET enzyme.

Table 1

Test compound	c-MET IC_{50} (nM)	Test compound	c-MET IC_{50} (nM)
Embodiment 1-2	1.09	Embodiment 7	15.50
Embodiment 2-2	9.33	Embodiment 8-2	3.79
Embodiment 4	6.16	Embodiment 10	69.50
Embodiment 5	2.90	Embodiment 11	5.00
Embodiment 6	4.37		

Assay 2: Inhibitory effect assay on proliferation

[0224] Reagents and consumables:

[0225] 1) Cell culture: DMEM cell medium, fetal bovine serum, DPBS

[0226] 2) Cell line: MHCC97-H

[0227] 3) Detection reagent: live cell detection kit CellTiter-Glo

[0228] 4) Other major consumables and reagents: compound dilution plate, intermediate plate, test plate, DMSO

[0229] Experimental principle:

[0230] The amount of ATP directly reflects the number of cells and the state of the cells, thus the number of living cells could be directly detected by quantitatively measuring ATP. The live cell assay kit contains luciferase and its substrate. With the presence of ATP, a stable optical signal would be emitted by the luciferase catalyzed substrate. Thus the amount of ATP in the cell could be determined by detecting the intensity of the signal. The light signal was proportional to the amount of ATP in the cell, while the ATP was positively correlated with the number of living cells, so that the proliferation in the cell could be detected. The assay plate used was analyzed by Envision from PE Corporation.

[0231] Experimental method:

[0232] 1. Preparation of the cell plates

[0233] MHCC97-H cells were seeded separately into 384-well plates, each of the well contains 500 cells. The cell plates were placed and incubated in a carbon dioxide incubator overnight.

[0234] 2. Preparation of the compound.

[0235] Echo was used for 4-time dilution and 9 concentration was prepared, ready for double duplicate wells assay.

[0236] 3. Compound treatment of cells

[0237] The compounds were transferred to cell plates at a starting concentration of 10μM. The cell plates were incubated in a carbon dioxide incubator for 3 days.

[0238] 4. Detection

[0239] The Promegaer-Glo reagent was added into the cell plates and the plate was incubated at room temperature for 10 mins to stabilize the luminescence signal. PerkinElmer Envision multi-label analyzer was used for readings.

[0240] Experimental results: See Table 2:

[0241] Conclusion: the compounds of the present invention exhibit good inhibitory activity against MHCC97H cells.

Table 2

Test compound	MHCC97H cell IC_{50} (nM)	Test compound	MHCC97H cell IC_{50} (nM)
Embodiment 1	8.80	Embodiment 7	22.30
Embodiment 2-2	13.80	Embodiment 9-2	22.10
Embodiment 3-2	19.0	Embodiment 10	166.00
Embodiment 4	72.90	Embodiment 11	93.80
Embodiment 5	58.80	Embodiment 12	51.40
Embodiment 6	32.90		

Assay 3: pharmacodynamics assay of MHCC97H liver cancer cell subcutaneous xanograft tumor model

[0242] Cell culture:

[0243] MHCC97H cells were cultured in a single layer in-vitro. The culturing condition was RPMI1640 medium supplemented with 10% heat-inactivated fetal bovine serum, 1% penicillin-streptomycin double antibody under 37°C, 5% carbon dioxide. Digestion and passage treatment