mm; Phenomenex Gemini C18, 5 m, 150×30 mm; Boston Symmetrix C18, 5m, 150×30 mm; or Phenomenex Synergi C18, 4 m, 150×30 mm. Low gradient acetonitrile/water is used to elute the compound when the velocity is about 25 mL/min, wherein the water contains 0.05% HCl, 0.25% HCOOH or 0.5% $NH_3•H_2O$, and the total operational time is 8 -15 min.

The following abbreviations are used herein: n-BuLi: n-butyllithium; THF: tetrahydrofuran; SEM: 2-(trimethylsilyl)ethoxyl methyl; DIPEA: diisopropyl ethyl amine; IPA: isopropanol; TFA: trifluoroacetic acid; DMF: N,N-dimethylformamide; *n*-BuOH: n-butanol; Et_3SiH: triethylsilane.

Advantageous effect

The compounds according to the invention have high binding activity to Toll-like receptor 7 and low binding activity to Toll-like receptor 8, showing better selectivity, activity and safety as well as lower side effect, and can be used to effectively treat and prevent viral infection, particularly hepatitis B or hepatitis C viral infection.

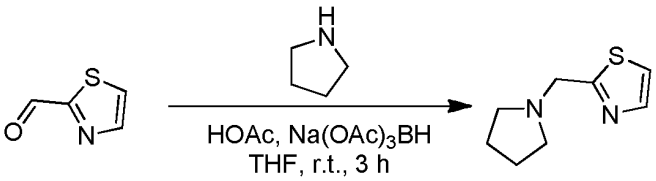
Examples

The following Examples are provided for a person skilled in the art to clearly illustrate and practice the invention. They are illustrative and exemplary only and should not be understood as a limitation to the scope. Unless stated otherwise, the ratios (including percentages) or parts are based on weight.

Example 1:

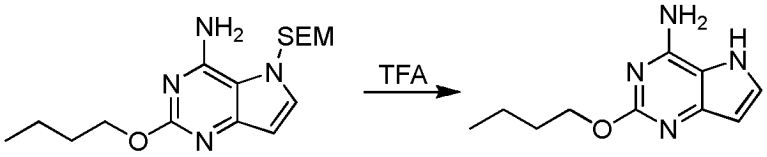
2-butoxy-7-((2-(pyrrolidin-1-ylmethyl)thiazol-5-yl)methyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine (I)

Step 1: 2-(pyrrolidin-1-ylmethyl)thiazole



To a 500 mL reaction bottle were added thiazol-2-formaldehyde (25.00 g, 220.90 mmol) and tetrahydrofuran (300.0 mL), which was stirred for 5 min and then glacial acetic acid (39.80 g, 662.90 mmol) was added. The system was cooled to 0-10°C with stirring and pyrrolidine (13.80 g, 194.40 mmol) was added dropwise. The temperature was kept below 10°C during addition. After addition, sodium triacetoxyborohydride (56.20 g, 265.10 mmol) was added in portions. The reaction was performed at 10-20°C for 12 hr and was monitored with TLC until the starting materials totally disappeared. After completion of the reaction, to the reaction liquid was added aqueous saturated sodium bicarbonate slowly to pH of 9-10 and the reaction liquid was extracted with 150 mL of ethyl acetate three times. The organic phases were combined, dried over anhydrous sodium sulfate and concentrated under reduce pressure. The residue was purified with column chromatography (mobile phase gradient: ethyl acetate/petroleum ether: 3/1/-1/1) to give 15.00 g of title compound as yellow oil, yield: 40.3%.

Step 6: 2-butoxy-5H-pyrrolo[3,2-d]pyrimidin-4-amine

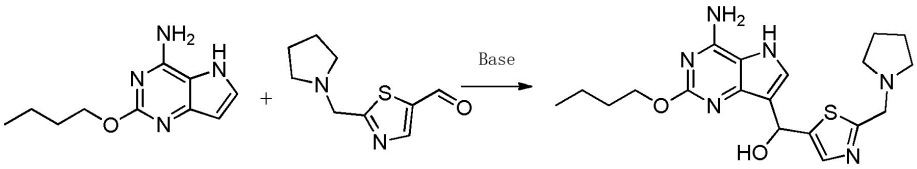


2-butoxy-5-((2-(trimethylsilyl)ethoxyl)methyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine (1.10 kg, 3.27 mol) was dissolved in TFA (5.50 L) and the reaction liquid was stirred for 16 hours at 25°C. Completion of the reaction was monitored with HPLC and TFA was distilled off under reduced pressure. The residue was dissolved in methanol (1.2 L) and ice water (1.2 L) and pH of the system was adjusted to 12 with concentrated aqueous ammonia with uniform stirring and then stirred for 2 hours. Precipitate continued to appear in the solution. After filtration, the filter cake as white solid was slurried with 15% aqueous ammonia (1.2 L×3) and ethyl acetate (4L) to give the title compound as white solid (550.00 g, 2.67 mol, 81.7%).

^{1}H NMR (400 MHz, METHANOL-d_4) δ 7.37 (d, *J*=2.89 Hz, 1 H), 6.29 (d, *J*=3.01 Hz, 1 H), 4.27 (t, *J*=6.53 Hz, 2 H), 1.75 (d, *J*=7.91 Hz, 2 H), 1.44 - 1.61 (m, 2 H), 1.00 (t, *J*=7.40 Hz, 3 H).

Step 7:

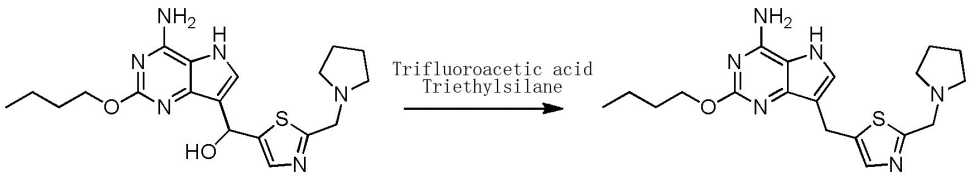
(4-amino-2-butoxy-5H-pyrrolo[3,2-d]pyrimidin-7-yl)-[2-(pyrrolidin-1-ylmethyl)thiazol-5-yl]methanol



To a 500 mL three neck flask were added 2-butoxy-5H-pyrrolo[3,2-d]pyrimidin-4-amine (10.00 g, 48.49 mmol), potassium carbonate (7.37 g, 53.34 mmol), water (100 mL) and isopropanol (100 mL), to which was added 2-(pyrrolidin-1-ylmethyl)thiazol-5-formaldehyde (14.27 g, 72.74 mmol) with stirring. The reaction was performed at 25°C for 16 hr and 2-(pyrrolidin-1-ylmethyl)thiazol-5-formaldehyde was monitored with LCMS for completion of the reaction. The reaction liquid was added with 100 mL of water for dilution and extracted with 100 mL of dichloromethane three times. The combined organic phases were dried over anhydrous sodium sulfate, filtered off solid and concentrated under reduced pressure to give residue, which was purified with column chromatography (mobile phase gradient: dichloromethane /methanol/aqueous ammonia/: 30/1/0.1 to 10/1/0.1) to give the title compound as brown solid (5.20 g, 12.92 mmol, yield: 26.6%). MS (ESI) m/z: 403.3 [M+H$^+$].

Step 8:

2-butoxy-7-((2-(pyrrolidin-1-ylmethyl)thiazol-5-yl)methyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine



To a 100 mL eggplant flask were charged (4-amino-2-butoxy-5H-pyrrolo[3,2-d]pyrimidin-7-yl)-[2-(pyrrolidin-1-ylmethyl)thiazol-5-yl]methanol (5.10 g, 12.60 mmol), triethylsilane (10.00 mL) and trifluoroacetic acid (40.00 mL) and the reaction mixture was stirred at 20°C for 12 hours. The raw materials were monitored with LCMS for completion of the reaction. The solvent was removed by concentration under reduced pressure. To the system was added 100 mL of ethyl acetate and then saturated sodium carbonate solution was added to adjust the solution to pH=9-10. Extraction was performed with 50 mL of ethyl acetate three times. The organic phases were combined, dried over anhydrous sodium sulfate, filtered off solid and concentrated under reduced pressure to give residue, which was separated with prep. High Performance Liquid Chromatography to give 4.2 g of 2-butoxy-7-((2-(pyrrolidin-1-ylmethyl)thiazol-5-yl)methyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine as light yellow oil (diformate of the title compound).

^{1}HNMR (400 MHz, Methanol-d_4) δ 8.30 (s, 2H), 7.61 (s, 1H), 7.41 (s, 1H), 4.51 (s, 2H), 4.44 (q, *J*=6.6 Hz, 2H), 4.24 (s, 2H), 3.33 – 3.28 (m, 4H), 2.02 (s, 4H), 1.83 – 1.73 (m, 2H), 1.56 – 1.46 (m, 2H), 0.99 (t, *J*=7.2 Hz, 3H).

Experimental Example 1: Toll-like receptor 7 and Toll-like receptor 8 *in vitro* receptor binding activity

Reagents:

HEK-blue hTLR7 cell and HEK-blue hTLR8 cell (available from InvivoGen)

DMEM medium

heat inactivated fetal bovine serum

Anti Mycoplasma reagent Normocin™

bleomycin

blasticidin

The GS-9620 and R848 used have the following structures. GS-9620 can be prepared according the process disclosed in US20100143301; R848 is purchased from ABGENT (Catalog: IMG-2208, 0.5 mg).