Synthesis of 5-(4-Morpholino-7, 8-dihydro-5*H*-thiopyrano[4,3-*d*]pyrimidin-2-yl)pyridin-2-amine

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Abstract. A novel thiopyrano[4,3-*d*]pyrimidine derivative compound **1** was synthesized with methyl dimethyl 3,3'-thiodipropionate as starting material through five steps, including cyclization, chlorination, substitution with morpholine and coupling with 5-bromopyridin-2-amine through Suzuki reaction. And its structure was confirmed by ^{1}H NMR and MS. The total yield of the five steps was 18.6% (calculated from methyl dimethyl 3,3'-thiodipropionate).Compound **1** is an important intermediate in the design and synthesis of thiopyrano[4,3-d]pyrimidine derivatives small molecule inhibitors.Therefore, the synthesis of Compound **1** has an important significance in the the study of anticancer drugs.

Introduction

Cancer is a major public health problem in the world, which caused by the disorders of cell proliferation mechanism. According to the World Health Organization (WHO) statistics, an estimated 14.1 million new cancer cases and 8.2 million cancer-related deaths occurred in 2012, compared with 12.7 million and 7.6 million in 2008, respectively [1,2].Therefore, developing an efficiently and safety method to treatment the malignancies has become a hot pot in nowadays. Because of orientation, location, less dosage, efficacy, little toxicity advantages, molecular targeted therapy attracted more and more attention.

In recent years, there were many small molecule anticancer drugs had been reported [3-11]. Among them, many molecules contained the thiopyrano[4,3-*d*]pyrimidine scaffold (Fig.1). Therefore, design and synthesis of thiopyrano[4,3-*d*]pyrimidine derivative as small molecule inhibitors played a great role in the study of anticancer drugs.

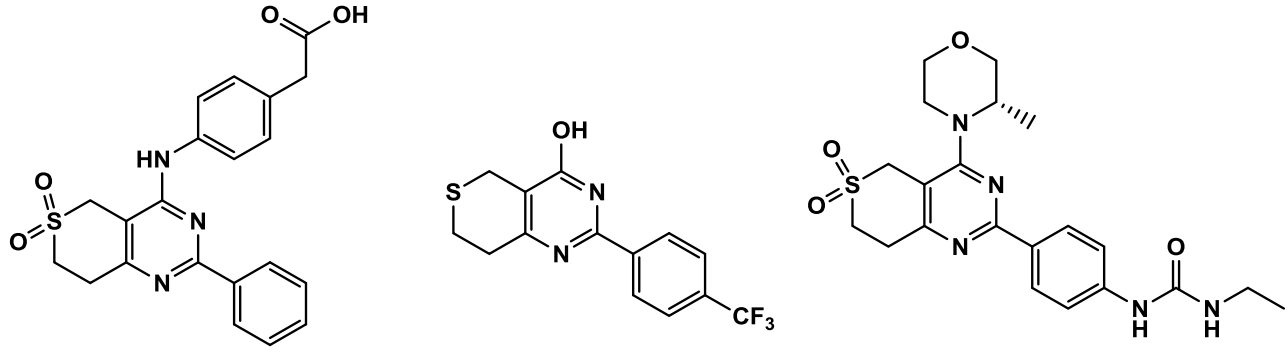


Figure. 1 Some thiopyrano[4,3-*d*]pyrimidine small molecule inhibitors

Herein we synthesized a novel thiopyrano[4,3-*d*]pyrimidine derivative compound **1** which is an important intermediate in the design and synthesis of thiopyrano[4,3-d]pyrimidine derivatives small

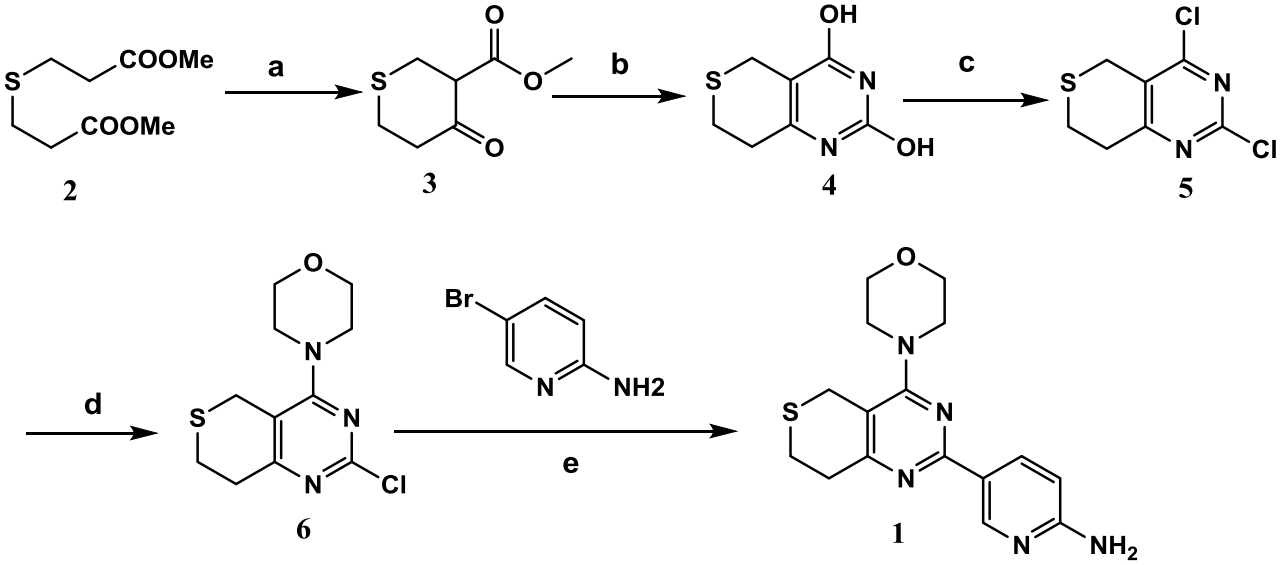
molecule inhibitors. Compound **1** was synthesized from methyl dimethyl 3,3'-thiodipropionate through five steps. First, methyl dimethyl 3,3'-thiodipropionate **2** with NaH through intramolecular condensation to get methyl 4-oxotetrahydro-2*H*-thiopyran-3-carboxylate **3**.Compound **3** was treated with urea and NaOEt in EtOH from rt. to 70 °C to give compound **4** as a white solid. Then **4** was chlorinated with $POCl_3$ at 105°C to yield compound **5**.Substitution reaction of **5** with morpholine at room temperature to afford **6** and then through the Suzuki reaction furnish target compound **1**.

Materials and methods

All melting points were obtained on a Büchi Melting Point B-540 apparatus (Büchi Labortechnik,Flawil, Switzerland) and were uncorrected. The IR spectra were recorded by means of the KBr pellet technique on a Bruker FTS 135 spectrometer. NMR spectra were performed using Bruker 400 MHz spectrometers (Bruker Bioscience, Billerica, MA, USA) with TMS as an internal standard. Mass spectra (MS) were taken in ESI mode on Agilent 1100 LC–MS (Agilent, Palo Alto, CA, USA).Elemental analysis was determined on a Carlo-Erba 1106 Elemental analysis instrument (Carlo Erba,Milan, Italy). All the materials were obtained from commercial suppliers and used without purification, unless otherwise specified. Yields were not optimized. TLC analysis was carried out on silica gel plates GF254 (Qindao Haiyang Chemical,China).

Synthesis of compounds

The structures and the synthetic route were shown in Scheme 1.



Scheme. 1 The synthetic route of compound **1**

Reagents and conditions: (a) NaH, THF, rt, 3 h; (b) 3 equiv urea, C_2H_5ONa, EtOH, reflux, 24 h; (c) $POCl_3$, reflux, 3 h; (d) 2.4 equiv morpholine, MeOH, rt, 1.5 h; (e) i: bis(pinacolato)diboron, KAc, $Pd(PPh_3)Cl_2$, 1,2-dimethoxyethane, reflux, 2 h; ii: H_2O, Na_2CO_3, $Pd(PPh_3)Cl_2$, reflux, 6 h.

Methyl 4-oxotetrahydro-2*H*-thiopyran-3-carboxylate (3). To the mixture of NaH (60%, 8.19g, 0.205mol) and anhydrous THF (100 mL), a solution of dimethyl 3,3'-thiodipropionate (31.8 g, 0.154 mol) in anhydrous THF (40 mL) was added via a dropping funnel over 1 h (the dropping funnel was rinsed with 15 mL of THF) at room temperature under N_2. After stirring for 2 h at r.t, the reaction was complete by TLC analysis (20%EtOAc in petroleum ether). The mixture was transferred to a beake， dilute hydrochloric acid was added slowly with stirring maintaining the temperature below 20 ℃; the final pH was 6–7. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2

(3×50mL). The combined organic layers were washed with brine(3×50mL), then dried over Na_2SO_4, the filtrate was concentrated under reduced pressure to afford **3** as a yellow viscous oil (26.8g, 99.8%) and was used for next step without further purification. ESI-MS m/z: $[M + H]^+$ 175.2

7,8-dihydro-5*H*-thiopyrano[4,3-*d*]pyrimidine-2,4-diol (4). Finely cut sodium metal (16.2g, 0.704mol) was added into 300mL anhydrous ethanol at ice bath with stirring. After the sodium metal was completely consumed, urea (32.7g, 0.545mol) and methyl 4-oxotetrahydro-2*H*-thiopyran-3-carboxylate (31.3g, 0.180mol) was added to the solution. The mixture was heated and refluxed for 24 h, and the reaction was monitored by TLC. The reaction mixture was concentrated under reduced pressure and the residue was poured onto ice water , then adjusted the pH to 6-7 with acetic acid under ice bath , filtration, the filter cake was washed with ice-water, dried to obtain a white solid (13.6g, 41.2%). m.p. >300 ℃. ESI-MS *m/z*: $[M - H]^-$ 183.2, ^1H NMR (400 MHz, DMSO) δ 11.10 (s, 1H), 10.75 (s, 1H), 3.39 (s, 2H), 2.80 (t, *J* = 5.8 Hz, 2H), 2.57 (t, *J* = 5.6 Hz, 2H).

2,4-dichloro-7,8-dihydro-5*H*-thiopyrano[4,3-*d*]pyrimidine (5). A mixture of 7,8-dihydro-5H-thiopyrano[4,3-*d*]pyrimidine-2,4(3H,5H)-dione (3.03g, 0.016 mol), phosphorous oxychloride (20mL) was heated at reflux for 3 h and the reaction was monitored by TLC. The reaction mixture was slowly added to ice/water with vigorous stirring yielding a precipitate. The mixture was then filtered to yield 2, 4-dichloro-7, 8-dihydro-5*H*-thiopyrano[4,3-*d*]pyrimidine as a yellow solid (3.12g, 85.7%). m.p. 87.1-87.9 ℃. ^1H NMR (400 MHz, CDCl3) δ 3.81 (s, 2H), 3.23 (t, *J* = 5.9 Hz, 2H), 2.96 (t, *J* = 6.0 Hz, 2H).

4-(2-chloro-7,8-dihydro-5H-thiopyrano[4,3-d]pyrimidin-4-yl)morpholine (6). To the mixture of 2,4-dichloro-7,8-dihydro-5*H*-thiopyrano[4,3-*d*]pyrimidine (7.40 g, 0.033 mol) and MeOH (150 mL), morpholine (7 mL, 0.08 mol) was added drop-wise at room temperature. The reaction mixture then was stirred at room temperature for 1.5 h. After completion of reaction as indicated by TLC, the mixture was then filtered, washed with water and MeOH, to yield the title compound as a white solid (6.84 g, 75.3%). m.p. 161.1-162.4 ℃. ESI-MS *m/z*: $[M + H]^+$ 272.1. ^1H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 2H), 3.23 (t, J = 5.9 Hz, 2H), 2.96 (t, J = 6.0 Hz, 2H).

5-(4-morpholino-7,8-dihydro-5*H*-thiopyrano[4,3-*d*]pyrimidin-2-yl)pyridin-2-amine(1). The mixture of 5-bromopyridin-2-amine (5.0 g, 28.9 mmol), bis(pinacolato)diboron(11.0 g, 43.3 mmol), potassium acetate (8.7 g, 88.8 mmol), $Pd(PPh_3)Cl_2$(0.5g, 0.7mmol) and 1,2-dimethoxyethane (250 mL) was refluxed for 2 h under nitrogen atmosphere, and then cooled to room temperature. To the resulted mixture were added **6** (5.9 g, 21.7 mmol), Na_2CO_3 (4.7 g, 44.3 mmol), $Pd(PPh_3)Cl_2$ (0.5 mg, 0.7 mmol) and water (60 mL).The reaction mixture was refluxed under nitrogen atmosphere for 6 h. The volatiles were removed in vacuum and the residue was added into water, stirred and filtered. The cake further decolourized with activated carbon, get compound **1** as pale-yellow solid (5.0g, 70%). m.p. >300 ℃. ESI-MS *m/z*: $[M + H]^+$ 330.2. ^1H NMR (400 MHz, DMSO) δ 8.88 (d, *J* = 1.6 Hz, 1H), 8.22 (dd, *J* = 8.7, 2.1 Hz, 1H), 6.50 (d, *J* = 8.7 Hz, 1H), 6.42 (s, 2H), 3.80 – 3.71 (m, 4H), 3.68 (s, 2H), 3.34 (s, 4H), 3.00 (dd, *J* = 12.1, 4.9 Hz, 4H).

Conclusions

In conclusion, one novel thiopyrano[4,3-*d*]pyrimidine derivative compound **1** was synthesized from methyl dimethyl 3,3'-thiodipropionate through cyclization, chlorination, substitution with morpholine and coupling with 5-bromopyridin-2-amine through Suzuki reaction. The compound **1**, an important intermediate of PI3K inhibitors, played an important role in the further design and synthesis of thiopyrano[4,3-d]pyrimidine derivatives anticancer drugs.

Acknowledgments

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