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Short Note

1,3-Bis(5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidin-4-yl)imidazolidine-4,5-dione

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Abstract: A thieno[2,3-*d*]pyrimidine derivative 3 bearing a 4,5-imidazolidinedione moiety, 1,3-bis(5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidin-4-yl)imidazolidine-4,5-dione, was efficiently synthesized in 66% yield by the reaction of *N*,*N*′-bis(5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidin-4-yl)methanediamine 2 with oxalyl chloride in the presence of pyridine in refluxing dichloroethane for 10 h. The structure of the new synthesized compounds was fully characterized by 1H, 13C NMR, IR spectroscopy, mass-spectrometry and elemental analysis.

Keywords: thieno[2,3-*d*]pyrimidine; 4,5-imidazolidinedione; oxalyl chloride

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1. Introduction

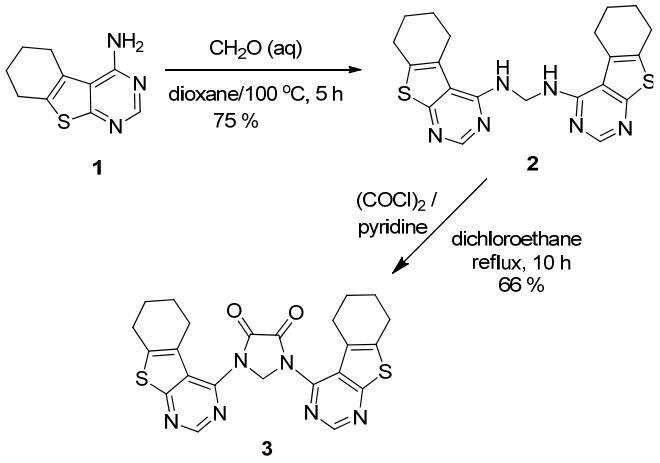
Thienopyrimidine compounds continue to attract considerable interest in medicinal chemistry because of their structural relationship with the purine base and therapeutic potential [1,2]. Among them, thieno[2,3-*d*]pyrimidine derivatives are known to have remarkable biological properties, such as anticancer [3], antibacterial [4], anti-inflammatory [5,6], antiviral [7], and antimalarial activities [8]. Imidazolidinedione derivatives, including hydantoin (2,4-imidazolidinedione) as a useful scaffold, displayed diverse biological and pharmacological activities, such as antimicrobial [9], anticonvulsant [10], antitumor [11] and antiviral activities [12]. Recently, 2,5-imidazolidinedione derivatives were prepared as histone deacetylase 6 (HDAC6) selective inhibitors for various human diseases, including diverse neurodegenerative diseases and cancer [13]. However, there are very few reports on the synthesis of 4,5-imidazolidinedione compounds [14–16]. We report herein the synthesis of a hybrid compound **3**, thieno[2,3-*d*]pyrimidine derivative bearing a 4,5-imidazolidinedione moiety.

2. Results

The synthetic route to the new compound **3** is described in Scheme 1. When thieno[2,3-*d*]pyrimidin-4-amine **1** [17] was allowed to react with aqueous formaldehyde in 1,4-dioxane at 100 °C using a modified method [18], a new compound **2**, *N*,*N*′-bis(5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidin-4-yl)methanediamine, was formed in 75% yield. Subsequent cyclization of **2** with oxalyl chloride in the presence of pyridine in refluxing dichloroethane gave a new cyclic compound **3** in 66% yield.

The ^{1}H NMR spectrum of **2** showed a sharp triplet at δ 5.29 ppm due to methylene protons between two NHs, and a triplet at δ 7.34 ppm for NH protons (J = 4.7 Hz) (Supplementary Materials). It presented a sharp signal at δ 8.38 ppm attributed to a pyrimidine proton in the thieno[2,3-*d*]pyrimidine ring, and showed three multiplets at δ 2.89, 2.74 and 1.80 ppm for cyclohexyl protons. In the ^{13}C NMR spectrum, compound **2** showed a peak at δ 47.5 ppm for the methylene carbon between two NHs, including six peaks for the thienopyrimidine ring at δ 164.9, 156.2, 152.4, 132.3, 126.2 and 115.8 ppm. The IR spectrum revealed a characteristic NH absorption at 3446 cm^{-1}. The mass spectrum showed

m/z = 423 (MH^+) corresponding to the molecular formula, $C_{21}H_{22}N_6S_2$. The structure of **3** was also confirmed by ^1H, ^{13}C NMR, IR spectroscopy, mass spectrometry and elemental analysis (Supplementary Materials). The ^1H NMR spectrum of **3** (NMR solvent: CD_3OD + CD_2Cl_2) exhibited the expected pattern with a sharp singlet at δ 5.38 ppm slightly upfield for the methylene group of a cyclic 4,5-imidazolidinedione moiety. One single peak at δ 8.94 attributed to a pyrimidine proton in the thieno[2,3-*d*]pyrimidine ring, and three multiplets at δ 2.99, 2.88 and 1.95 ppm were shown due to cyclohexyl protons. In the ^{13}C NMR spectrum, compound **3** showed a peak δ 157.8 ppm for the newly formed amide carbon, including six peaks for thienopyrimidine at δ 171.9, 152.2, 148.3, 141.9, 127.8 and 127.3 ppm. The methylene carbon of a cyclic 4,5-imidazolidinedione moiety was shown at 61.1 ppm at a downfield when compared to the methylene carbon of **2**. The IR spectrum revealed a characteristic carbonyl absorption at 1752 cm^{-1} and missing NH absorption. The mass spectrum showed m/z = 476 (M^+) corresponding to the molecular formula, $C_{23}H_{20}N_6O_2S_2$. Elemental analysis also provided satisfactory results. The compound **3** showed low solubility in most common solvents, and a high melting point (mp = 298–299 °C), suggesting high thermal stability.



Scheme 1. Synthesis of the target compound **3**.

In conclusion, a hybrid compound **3**, thieno[2,3-*d*]pyrimidine derivative **3** bearing a 4,5-imidazolidinedione moiety was synthesized efficiently by the reaction of *N*,*N*′-bis(5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidin-4-yl)methanediamine **2** with oxalyl chloride in the presence of pyridine in refluxing dichloroethane. This thieno[2,3-*d*]pyrimidine derivative could be used as a useful component of biologically active molecules for drug development.

3. Materials and Methods

3.1. General Information

All chemicals and reagents were purchased from Sigma-Aldrich (St. Louis, MO, USA) and TCI (Tokyo, Japan). The solvents used were purified using standard techniques. Melting point was determined on Kofler apparatus and was uncorrected. Thin-layer chromatography (TLC) was used to monitor reactions and performed using aluminum sheets precoated with silica gel 60 (HF_{254}, Merck, Waltham, MA, USA), and visualized with UV radiation (Fisher Scientific, Waltham, MA, USA). The ^1H and ^{13}C NMR spectra were recorded in deuterated DMSO or $MeOH/CH_2Cl_2$ with TMS as the standard on a Bruker Avancell FT-NMR. The IR spectrum was recorded on Bruker Invenio FT-IR. The mass spectrum was obtained with Agilent 6890 Mstation instrument.

3.2. Synthesis of N,N′-Bis(5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4-yl)methanediamine (**2**)

A solution of thieno[2,3-*d*]pyrimidin-4-amine **1** (206 mg, 1.0 mmol) and formaldehyde (1.64 g of 37% aqueous solution, 1.5 mmol, 1.5 equiv) in 1,4-dioxane (15 mL) was heated at 100 °C with stirring. After completion of the reaction (5 h, monitored by TLC), the mixture was cooled to room temperature. The white precipitate was filtered, washed with cold 1,4-dioxane and dried. The crude product was recrystallized from chloroform as light-yellow solid of **2** in 75% yield (316 mg). Mp 255 °C–256 °C; TLC R_f = 0.53 (dichloromethane:MeOH = 15:1). ^{1}H NMR (850 MHz, DMSO-d_6) (ppm) δ 8.38 (s, 2H), 7.34 (t, *J* = 4.7 Hz, 2H), 5.29 (t, *J* = 4.7 Hz, 2H), 2.89–2.88 (m, 4H), 2.75–2.73 (m, 4H), 1.82–1.78 (m, 8H). ^{13}C NMR (213 MHz, DMSO-d_6) (ppm) δ 164.9, 156.2, 152.4, 132.3, 126.2, 115.8, 47.5, 25.4, 24.8, 22.0, 21.8. IR (KBr) 3446 (NH), 1671, 1548, 1482 cm^{-1}. MS (FAB) *m*/*z* = 423 (MH$^+$, 76%). Anal. calcd. for $C_{21}H_{22}N_6S_2$, %: C, 59.69; H, 5.25; N, 19.89. Found, %: C, 59.40; H, 5.01; N, 19.99.

3.3. Synthesis of 1,3-Bis(5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4-yl)imidazolidine-4,5-dione (**3**)

Oxalyl chloride (127 mg, 1.0 mmol) was added dropwise with ice-cooling to a solution of *N*,*N*′-bis(5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidin-4-yl)methanediamine 2 (300 mg, 0.7 mmol) in an anhydrous dichloroethane (15 mL) containing pyridine (160 mg, 2.0 mmol) under nitrogen. The reaction mixture was stirred at 0 °C to room temperature for 0.5 h, and kept at reflux for additional time. After completion of the reaction (10 h, monitored by TLC), the mixture was cooled and evaporated to dryness. The residue was dissolved in ethyl acetate (15 mL), washed with water and dried. The crude product was purified by recrystallization from methanol to afford a pale-greenish solid of **3** in 66% yield (220 mg). Mp 298 °C–299 °C; TLC R_f = 0.63 (dichloromethane:MeOH = 17:1). ^{1}H NMR (500 MHz, CD_3OD + CD_2Cl_2) (ppm) δ 8.94 (s, 2H), 5.38 (s, 2H), 3.00–2.97 (m, 4H), 2.88 (m, 4H), 2.00–1.90 (m, 8H). ^{13}C NMR (125 MHz, CD_3OD + CD_2Cl_2) (ppm) δ 171.9, 157.8, 152.2, 148.3, 141.9, 127.8, 127.3, 61.1, 26.7, 25.1, 23.1, 22.9. IR (KBr) 1752 (C=O), 1564, 1439 cm^{-1}. MS (FAB) *m*/*z* = 476 (M$^+$, 36%). Anal. calcd. for $C_{23}H_{20}N_6O_2S_2$, %: C, 59.97; H, 4.23; N, 17.63. Found, %: C, 59.85; H, 4.11; N, 17.81.

Supplementary Materials: The following supporting information can be downloaded online. Figures S1–S8: ^{1}H NMR, ^{13}C NMR, Mass and IR spectra of compounds **2** and **3**.

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