2-Amino-4-arylthiophene-3-carbonitrile and Formamidine Acetate as Key Building Units for the Synthesis of 5-Arylthieno[2,3-d]pyrimidin-4- amines

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Abstract

A novel series of thieno[2,3-\textit{d}]pyrimidine analogues was designed and synthesized \textit{via} three-step reactions. A novel condition has been developed for the preparation of substituted 2-aminothiophenes employing the Knoevenagel condensation followed by the Gewald method and in the last step to form thieno[2,3-\textit{d}]pyrimidines by using formamidine acetate. The structure of these compounds was confirmed by IR, $^1$H-NMR, $^{13}$C-NMR, and CHN analysis.

Introduction

Thieno[2,3-\textit{d}]pyrimidines, bicyclic systems with three heteroatoms, comprise a thiophene ring fused with the pyrimidine moiety [1]. The thieno[2,3-\textit{d}]pyrimidine skeleton an important class of bioactive heterocycles, which has shown broad pharmaceutical and biological activities such as anti-inflammatory (A) [2], antibacterial (B) [3-5], antimicrobial (C) [6], anticancer (D) [7-9], antimalarial (E) [10], anti-leukemic (F) [11], anti-tumor (G) [12,13], antioxidant (H) [14], and antiviral agents (I) (Fig. 1) [15].

Moreover, thieno[2,3-\textit{d}]pyrimidine cores were tested for analgesic activities [16,17], together with ulcerogenic properties [18]. In addition the thieno[2,3-\textit{d}]pyrimidines and their analogues have been reported to have antiproliferative [19], and properties potent antagonist for the human luteinizing hormone-releasing hormone receptor and potent EGFR kinase inhibitors [20,21].

Due to the wide range of applications of these thieno[2,3-\textit{d}]pyrimidine cores in chemistry, several effective routes have been reported for the synthesis of these compounds. Most of the methods starting from thiophene moiety followed by construction of pyrimidine moiety on it (Scheme 1, a-e) [13,23-26], or starting with pyrimidine basis followed by construction of thiophene nucleus on it (Scheme 1, f-j) [6,22,27-29]. Among these two methods, the most commonly employed procedures for the synthesis of thieno[2,3-\textit{d}]pyrimidines involve multi-step synthesis starting from suitably substituted $\alpha$-amino-thiophenes and subsequent formation of the pyrimidine ring.

Motivated by the aforementioned biological and pharmacological importance of the title compounds, and as continuation with our previous work on thienopyrimidines [30], we report herein the synthesis of some new 5-arylthieno[2,3-\textit{d}]pyrimidin-4-amines \textit{7a-i} moiety \textit{via} three-step reactions.

One of the useful strategy for synthesis of thienopyrimidine framework is using Gewald method. The 2-aminothiophene nucleus can be easily prepared by the classical Gewald method. There are two common routes for the Gewald method: the first route, an one-pot procedure in which ketones or aldehydes react with an activated nitrile and elemental sulfur, and the second described route starts from a two-step procedure in which alkene produced by the Knoevenagel condensation is isolated prior to cyclization with sulfur and base Scheme 2 [26]. We demonstrate herein a convenient way to synthesis of thieno[2,3-\textit{d}]pyrimidine derivatives. The convenience of this method is based on two points: first, the reaction can be carried out in all cases in a way that the Gewald products precipitate, and this leads to high-quality products without the need to run time and cost intensive purifications. Second, the class of the new
thieno[2,3-d]pyrimidines was currently described by us to be available in a very convenient way by simply mixing 2-aminoisothiophenes with formamidine acetate.

**Results And Discussion***

The sequence of reactions leading to the formation of the target compounds 7a-i is shown in Scheme 3. In general, for the preparation of compounds 3a-i, we chose acetophenones 1a-i and malononitrile 2 as the starting materials in dry toluene with amount of NH₄OAc, and acetic acid as catalyst. Then, the compounds 3a-i were reacted with sulfur in the presence of NaHCO₃ as catalyst in THF to give the thiophenes 5a-i. The compounds 5a-i were reacted with formamidine acetate 6 to give the final compounds 7a-i.

It should be noted that, to find the optimized conditions, we studied the synthesis of 5-phenylthieno[2,3-d]pyrimidin-4-amine 7a. The reaction of 2-amino-4-phenylthiophene-3-carbonitrile 5a with formamidine acetate 6 was carried out in the various solvents such as EtOH, MeOH, and DMF with ratios of 1:1, 1:2.5, 1:5, and 1:7 at thermal and thermal microwave-assisted conditions. First, various solvents were examined (Table 1, entries 1–3), and DMF was shown to be the preeminent solvent for this reaction. As mentioned in Table 1 (entries 3-6) by this results we observed that the amount of formamidine acetate 6 has important effect on the improved of reaction yield. Then, we examined the influence of different temperatures on this reaction. The product yield at 110 °C for 12 h was 92% and in the reflux conditions during the same time was 92% (Table 1, entries 6 and 7). In addition, increasing the reaction time in DMF at 110 °C did not improve the yield (Table 1, entry 8). Finally, we decided to carry out the reaction in thermal microwave-assisted conditions instead of thermal conditions. The results showed that, the reaction of 2-amino-4-phenylthiophene-3-carbonitrile 5a with formamidine acetate 6 did not improve the performance under microwave-assisted heating conditions in DMF at 110 °C in 5 minutes, and the yield of 7a reached 32% (Table 1, entry 9). In addition, increasing the reaction time under the condition of microwave thermal radiation did not improve the performance (Table 1, entry 10).

Under the optimized reaction conditions, a series of 5-arylthieno[2,3-d]pyrimidin-4-amine derivatives 7a–i were synthesized (Table 2). To explore the scope of this novel transformation, various substituted acetophenones were tested in three-step process under the same reaction conditions, and the results are summarized in Table 2. The nature of the substituted acetophenones resulted in products with different reaction yields. When the acetophenones especially with electron-withdrawing groups were employed, a higher yield was obtained.

All the products structure was characterized by ¹H-NMR, ¹³C-NMR, IR, CHN analysis, and melting points. The IR spectrum of 2-(1-phenylethylidene)malononitrile 3a showed absorption bands at 2226 cm⁻¹ for CN, and 1491 cm⁻¹ for C=C groups. The ¹H-NMR spectrum of the compound 3a consisted of a singlet at δ = 2.61 ppm for the methyl group in the product. The aromatic protons resonated in the region δ = 7.52-7.66 ppm. The IR spectrum of 2-amino-4-phenylthiophene-3-carbonitrile 5a showed bands at 3426, 3303, and
2207 cm\(^{-1}\) corresponding to the NH\(_2\), and CN groups, respectively. The \(^1\)H-NMR spectrum of the compound 5a consisted of a singlet at \(\delta = 6.51\) ppm for the methine proton, and a broad singlet for two hydrogens was observed at \(\delta = 7.20\) ppm for the NH\(_2\) protons. The aromatic protons resonated in the region \(\delta = 7.34-7.52\) ppm. The \(^{13}\)C-NMR spectrum of compound 5a showed 9 distinct signals in agreement with the proposed structure. The IR spectrum of 5-phenylthieno[2,3-\(d\)]pyrimidin-4-amine 7a showed bands at 3447, 3293, and 1638 cm\(^{-1}\) corresponding to the NH\(_2\), and C=N groups, respectively. The \(^1\)H-NMR spectrum of 7a exhibited a broad singlet for the NH\(_2\) protons at \(\delta = 7.47\) ppm. The aromatic protons resonated in the region \(\delta = 7.48-7.54\) ppm, also a singlet for one hydrogen was observed at \(\delta = 6.51\) ppm for the methine proton. The \(^{13}\)C-NMR spectrum of compound 7a showed 10 distinct signals in agreement with the proposed structure. Partial assignments of these resonances for the other products are given in the experimental section. This process was achieved in excellent yields 84-96%.

**Proposed mechanism**

According to the obtained results, the following mechanism can be proposed for the synthesis of 5-arylthieno[2,3-\(d\)]pyrimidin-4-amine 7 from three-step reactions (Scheme 4). Initially, the Knoevenagel condensation between the substituted acetophenone 1, and malononitrile 2 gave the 2-(1-arylethylidene)malononitrile 3. Then, the NaHCO\(_3\) abstracts the proton of the compound 3. Subsequently, the NaHCO\(_3\) abstracts the acidic proton of the 2-(1-arylethylidene)malononitrile 3 and forms the intermediate A. Then, an intermediate A opens the S\(_8\) ring 4 through nucleophilic addition. The intermediate B undergoes ring closure through the intramolecular nucleophilic attack at the nitrile group to provide the intermediate C. Consequently, 4-arylthiophene-2,3-dicarbonitrile 5 is formed by tautomerization in THF at 35 °C. Condensation of formamidine acetate 6 and the compound 5 produces the intermediate D which undergoes the intramolecular addition to the cyano group to give E. Then, 5-arylthieno[2,3-\(d\)]pyrimidin-4-amine 7 is formed by elimination of molecule of NH\(_3\) and intramolecular H-shift.

**Conclusions**

In the current study, based on the modified Gewald method, we have prepared a series 5-arylthieno[2,3-\(d\)]pyrimidin-4-amine bearing various substituted groups in excellent yields. These compounds were prepared conveniently via a three-step sequence consisting of a key step such as Gewald method. This procedure can be employed for a three-step reactions or as part of the preparation of a series of standard compounds. It can be used also as a convenient tool in total synthesis. Notable advantages of the proposed method include readily available substrate, mild reaction conditions, and good to excellent yield.

**Experimental**

**General**
All commercially available reagents and other solvents were purchased from Aldrich or Merck and used without further purification. Melting points were obtained on a Kruss Optronic KSP1N automatic melting point apparatus and are uncorrected. IR spectra were acquired on a Bruker FT-IR Equinox-55 spectrometer. Peaks are reported in wavenumbers (cm\(^{-1}\)). All of the NMR spectra were recorded on a Varian model UNITY Inova 500 MHz (\(^1\)H: 500, \(^13\)C: 125 MHz) NMR spectrometer. Chemical shifts of \(^1\)H and \(^13\)C-NMR are reported in parts per million (ppm) from tetramethylsilane (TMS) as an internal standard in DMSO-d\(_6\) as solvent. Elemental analysis were done by Carlo Erba EA 1108 instrument.

**General procedure for the synthesis of 2-(1-arylethylidene)malononitriles (3a-i).**

A mixture of acetophenone derivatives 1 (5.0 mmol), malononitrile 2 (6.0 mmol), ammonium acetate (6.0 mmol), and acetic acid (0.5 mL) was stirred in dry toluene (25.0 mL) at 105 °C for 24 hours. Using a Dean-Stark trap, the condensed water was removed from the reaction system. The solvent was evaporated, and the resulting solution was cooled to room temperature. The separated solid was collected, and then recrystallized from 95% ethanol to afford 2-(1-arylethylidene)malononitrile 3.

**Physical and spectral data for compounds 3a-i**

**2-(1-Phenylethylidene)malononitrile (3a)**

Yield: 0.823 g (98%); White solid; mp = 94-96 °C. (Lit. mp 94.5-95.5 °C). IR (KBr, \(\nu/\text{cm}^{-1}\)): 1491 (C=C), 2226 (CN). \(^1\)H-NMR (500 MHz, DMSO-d\(_6\)) \(\delta = 2.61\) (s, 3H, CH\(_3\)), 7.52-7.60 (m, 3H, Ar), 7.66 (d, \(J = 7.5\) Hz, 2H, Ar) ppm.

**2-(1-(4-Methoxyphenyl)ethylidene)malononitrile (3b)**

Yield: 0.792 g (80%); White solid; mp 114-115 °C. (Lit. Mp = 79.5-80.5 °C). IR (KBr, \(\nu/\text{cm}^{-1}\)): 1464 (C=C), 2223 (CN).

**2-(1-(p-Tolyl)ethylidene)malononitrile (3c)**

Yield: 0.737 g (81%); White solid; mp 96-98 °C. IR (KBr, \(\nu/\text{cm}^{-1}\)): 1491 (C=C), 2224 (CN).

**2-(4-Chlorophenyl)malononitrile (3d)**

Yield: 0.858 g (85%); White solid; mp 94-96 °C. IR (KBr, \(\nu/\text{cm}^{-1}\)): 1490 (C=C), 2226 (CN).

**2-(2-Methoxyphenyl)malononitrile (3e)**

Yield: 0.723 g (73%); White solid; mp 97-99 °C. IR (KBr, \(\nu/\text{cm}^{-1}\)): 1433 (C=C), 2224 (CN).

**2-(3,4-Dimethoxyphenyl)malononitrile (3f)**

Yield: 0.855 g (75%); White; mp 89-91 °C. IR (KBr, \(\nu/\text{cm}^{-1}\)): 1466 (C=C), 2221 (CN).
2-(2,4-Dimethoxyphenyl)malononitrile (3g)
Yield: 0.889 g (78%); White solid; mp 106-108 °C. IR (KBr, u/cm⁻¹): 1435 (C=C), 2221 (CN).

2-(2,5-Dimethoxyphenyl)malononitrile (3h)
Yield: 0.889 g (78%); White solid; mp 64-66 °C. IR (KBr, u/cm⁻¹): 1491 (C=C), 2226 (CN).

2-(4-Fluorophenyl)malononitrile (3i)
Yield: 0.799 g (86%); White solid; mp 120-122 °C. IR (KBr, u/cm⁻¹): 1509 (C=C), 2230 (CN).

General procedure for the synthesis of 2-amino-4-arylthiophene-3-carbonitriles (5a-i)
2-(1-Arylethylidene)malononitrile 3 (5.0 mmol) and elemental sulfur 4 (6.5 mmol) are suspended in 16 mL THF and warmed to an internal temperature of 35 °C. A solution of sodium bicarbonate (0.8 g in 16 mL H₂O) was added over 1 hour. The mixture is stirred at 35 °C for 35 min before the solution is transferred to a separatory funnel. Then, the organic layers were separated, and the water phase was extracted with ethyl acetate by combining the organic phase. After removal of the solvent, the residue was recrystallized from 95% ethanol to give 2-amino-4-arylthiophene-3-carbonitrile 5.

Physical and spectral data for compounds 5a-i

2-Amino-4-phenylthiophene-3-carbonitrile (5a)
Yield: 0.750 g (75%); Yellow solid; mp 101-103 °C. (Lit. Mp = 102.3-105.1 °C).²⁰ IR (KBr, u/cm⁻¹): 2207 (CN), 3303, 3426 (NH₂).¹H-NMR (500 MHz, DMSO-d₆) δ = 6.51 (s, 1H, CH), 7.20 (bs, 2H, NH₂) 7.34 (t, J = 8.5 Hz, 2H, Ar), 7.41 (t, J = 8.5 Hz, 1H, Ar), 7.52 (d, J = 8.5 Hz, 2H, Ar) ppm.¹³C-NMR (125 MHz, DMSO-d₆) δ = 83.7, 105.5, 117.0, 127.3, 128.2, 129.1, 134.9, 138.9, 166.8 ppm.

2-Amino-4-(4-methoxyphenyl)thiophene-3-carbonitrile (5b)
Yield: 0.816 g (71%); Yellow solid; mp 160-162 °C. (Lit. Mp = 164-166.5 °C).²⁰ IR (KBr, u/cm⁻¹): 2196 (CN), 3329, 3474 (NH₂).¹H-NMR (500 MHz, DMSO-d₆) δ = 3.76 (s, 3H, OCH₃), 6.39 (s, 1H, CH), 6.97 (d, J = 8.7 Hz, 2H, Ar), 7.16 (s, 1H, NH₂), 7.46 (d, J = 8.7 Hz, 2H, Ar) ppm.¹³C-NMR (125 MHz, DMSO-d₆) δ = 55.6, 83.9, 104.1, 114.5, 117.1, 127.5, 128.5, 138.6, 159.4, 166.7 ppm.

2-Amino-4-(p-tolyl)thiophene-3-carbonitrile (5c)
Yield: 0.792 g (74%); Yellow solid; mp 128-130 °C. IR (KBr, u/cm⁻¹): 2205 (CN), 3437, 3331 (NH₂).¹H-NMR (500 MHz, DMSO-d₆) δ = 2.31 (s, 3H, CH₃), 6.44 (s, 1H, CH), 7.16-7.22 (m, 4H, NH₂, Ar), 7.42 (d, J = 8.5 Hz, 2H, Ar) ppm.¹³C-NMR (125 MHz, DMSO-d₆) δ = 21.1, 83.8, 104.8, 117.0, 127.2, 129.6, 132.1, 137.6, 138.9, 166.7 ppm.
2-Amino-4-(4-chlorophenyl)thiophene-3-carbonitrile (5d)

Yield: 0.865 g (79%); Yellow solid; mp 168-169 °C. IR (KBr, u/cm\(^{-1}\)): 2217 (CN), 3204, 3303 (NH\(_2\)). \(^1\)H-NMR (500 MHz, DMSO-d\(_6\)) \(\delta = 6.57\) (s, 1H, CH), 7.26 (s, 2H, NH\(_2\)), 7.48 (d, \(J = 8.4\) Hz, 2H, Ar), 7.54 (d, \(J = 8.4\) Hz, 2H, Ar) ppm. \(^13\)C-NMR (125 MHz, DMSO-d\(_6\)) \(\delta = 83.4, 106.1, 116.8, 129.0, 129.1, 132.9, 133.7, 137.4, 166.9\) ppm.

2-Amino-4-(2-methoxyphenyl)thiophene-3-carbonitrile (5e)

Yield: 0.771 g (67%); Yellow solid; mp 140-142 °C. IR (KBr, \(\nu/cm\)^{-1}): 2210 (CN), 3321, 3383 (NH\(_2\)). \(^1\)H-NMR (500 MHz, DMSO-d\(_6\)) \(\delta = 3.76\) (s, 3H, OCH\(_3\)), 6.33 (s, 1H, CH), 6.96 (t, \(J = 8.5\) Hz, 1H, Ar), 7.05-7.09 (m, 3H, NH\(_2\), Ar), 7.23 (d, \(J = 8.5\) Hz, 1H, Ar), 7.34 (t, \(J = 8.5\) Hz, 1H, Ar) ppm. \(^13\)C-NMR (125 MHz, DMSO-d\(_6\)) \(\delta = 55.7, 86.5, 106.6, 111.9, 116.7, 120.8, 124.2, 129.9, 130.6, 136.5, 156.9, 165.0\) ppm.

2-Amino-4-(3,4-dimethoxyphenyl)thiophene-3-carbonitrile (5f)

Yield: 0.910 g (70%); Yellow solid; mp 140-142 °C. IR (KBr, \(\nu/cm\)^{-1}): 2197 (CN), 3336, 3424 (NH\(_2\)). \(^1\)H-NMR (500 MHz, DMSO-d\(_6\)) \(\delta = 3.77\) (s, 3H, OCH\(_3\)), 3.78 (s, 3H, OCH\(_3\)), 6.45 (s, 1H, CH), 7.00 (s, 1H, Ar), 7.07 (d, \(J = 8.6\) Hz, 1H, Ar), 7.11 (d, \(J = 8.6\) Hz, 1H, Ar), 7.18 (bs, 2H, NH\(_2\)) ppm. \(^13\)C-NMR (125 MHz, DMSO-d\(_6\)) \(\delta = 56.0, 56.0, 83.9, 104.2, 111.4, 112.4, 117.2, 119.6, 127.7, 138.8, 149.1, 166.6\) ppm.

2-Amino-4-(2,4-dimethoxyphenyl)thiophene-3-carbonitrile (5g)

Yield: 0.898 g (69%); Yellow solid; mp 160-162 °C. IR (KBr, \(\nu/cm\)^{-1}): 2210 (CN), 3319, 3406 (NH\(_2\)). \(^1\)H-NMR (500 MHz, DMSO-d\(_6\)) \(\delta = 3.75\) (s, 3H, OCH\(_3\)), 3.78 (s, 3H, OCH\(_3\)), 6.24 (s, 1H, CH), 7.54 (d, \(J = 8.0\) Hz, 1H, Ar), 6.61 (s, 1H, Ar), 6.99 (s, 2H, NH\(_2\)), 7.14 (d, \(J = 8.0\) Hz, 1H, Ar) ppm. \(^13\)C-NMR (125 MHz, DMSO-d\(_6\)) \(\delta = 55.7, 55.8, 86.6, 99.2, 105.4, 105.8, 116.8, 116.9, 131.1, 136.3, 158.0, 161.0, 164.8\) ppm.

2-Amino-4-(2,5-dimethoxyphenyl)thiophene-3-carbonitrile (5h)

Yield: 0.910 g (70%); Yellow solid; mp 157-159 °C. IR (KBr, \(\nu/cm\)^{-1}): 2214 (CN), 3336, 3366 (NH\(_2\)). \(^1\)H-NMR (500 MHz, DMSO-d\(_6\)) \(\delta = 3.70\) (s, 3H, OCH\(_3\)), 3.71 (s, 3H, OCH\(_3\)), 6.37 (s, 1H, CH), 6.82 (d, \(J = 8.1\) Hz, 1H, Ar), 6.90 (d, \(J = 8.1\) Hz, 1H, Ar), 6.99 (s, 1H, Ar), 7.01 (s, 2H, NH\(_2\)) ppm. \(^13\)C-NMR (125 MHz, DMSO-d\(_6\)) \(\delta = 55.9, 56.2, 86.4, 106.9, 113.1, 114.5, 116.3, 116.7, 124.8, 136.2, 151.0, 153.3, 165.0\) ppm.

2-Amino-4-(4-fluorophenyl)thiophene-3-carbonitrile (5i)

Yield: 0.883 g (81%); Yellow solid; mp 157-159 °C. IR (KBr, \(\nu/cm\)^{-1}): 2205 (CN), 3331, 3437 (NH\(_2\)). \(^1\)H-NMR (500 MHz, DMSO-d\(_6\)) \(\delta = 6.51\) (s, 1H, CH), 7.24-7.27 (m, 3H, NH\(_2\), Ar), 7.55-7.57 (m, 2H, Ar) ppm. \(^13\)C-NMR (125 MHz, DMSO-d\(_6\)) \(\delta = 83.7, 105.5, 116.0\) (d, \(^2J_{CF} = 22.5\) Hz, CH), 116.9, 129.4 (d, \(^3J_{CF} = 7.5\) Hz, CH), 129.7 (d, \(^1J_{CF} = 8.75\) Hz, C), 131.4 (d, \(^4J_{CF} = 2.5\) Hz, C), 131.4, 137.7, 166.8 ppm.
General procedure for the synthesis of 5-arylthieno[2,3-d]pyrimidin-4-amines (7a-i).

Compound 5 (1.0 mmol) was dissolving in DMF (3 mL) at 110 °C, formamidine acetate (7.0 mmol) was added carefully over 60 min and the mixture was stirred for 12 hours at 110 °C. After completion, the brown solution was cooled to room temperature, then brine (3 mL) was added to the reaction mixture slowly, then the precipitate was extracted with CHCl₃ (3 × 3.0 mL), dried (MgSO₄), and the solvent evaporated. The precipitated solid was separated by filtration, washed with ether and allowed to be dry to give desired compound 7.

Physical and spectral data for compounds 7a-i

5-Phenylthieno[2,3-d]pyrimidin-4-amine (7a)

Yield: 0.230 g (92%); White solid; mp 152-154 °C. IR (KBr, \(\nu/cm^{-1}\)): 1638 (C=N), 3293, 3447 (NH₂). \(^1\)H-NMR (500 MHz, DMSO-d₆) \(\delta = 7.47\) (bs, 2H, NH₂), 7.48-7.52 (m, 5H, CH, Ar), 7.54 (t, \(J = 8.0\) Hz, 1H, Ar), 8.34 (s, 1H, CH) ppm. \(^13\)C-NMR (125 MHz, DMSO-d₆) \(\delta = 113.4, 121.2, 128.8, 129.3, 129.3, 135.3, 136.2, 154.2, 158.8, 167.6\) ppm. Anal. Calcd for C₁₂H₉N₃S (227.29): C, 63.41; H, 3.99; N, 18.49; Found: C, 63.12; H, 3.94; N, 18.37 %.

5-(4-Methoxyphenyl)thieno[2,3-d]pyrimidin-4-amine (7b)

Yield: 0.249 g (88%); White solid; mp 258-260 °C. IR (KBr, \(\nu/cm^{-1}\)): 1633 (C=N), 3285, 3472 (NH₂). \(^1\)H-NMR (500 MHz, DMSO-d₆) \(\delta = 3.79\) (s, 3H, OCH₃), 5.42 (bs, 2H, NH₂), 7.05 (d, \(J = 7.7\) Hz, 2H, Ar), 7.32-7.38 (m, 3H, Ar), 8.31 (s, 1H, CH) ppm. \(^13\)C-NMR (125 MHz, DMSO-d₆) \(\delta = 55.7, 113.6, 114.7, 120.6, 128.2, 130.6, 135.0, 154.2, 158.8, 159.8, 167.5\) ppm. Anal. Calcd for C₁₃H₁₁N₃OS (257.31): C, 60.68; H, 4.31; N, 16.33; Found: C, 60.91; H, 4.37; N, 16.31 %.

5-(p-Tolyl)thieno[2,3-d]pyrimidin-4-amine (7c)

Yield: 0.239 g (90%); White solid; mp 191-193 °C. IR (KBr, \(\nu/cm^{-1}\)): 3449, 3284 (NH₂), 1637 (C=N). \(^1\)H-NMR (500 MHz, DMSO-d₆) \(\delta = 2.38\) (s, 3H, CH₃), 6.00 (bs, 2H, NH₂, Ar), 7.32 (d, \(J = 8.0\) Hz, 2H, CH, Ar), 7.34 (d, \(J = 8.0\) Hz, 2H, CH, Ar), 7.42 (s, 1H, Ar), 8.33 (s, 1H, CH) ppm. \(^13\)C-NMR (125 MHz, DMSO-d₆) \(\delta = 21.3, 113.6, 120.9, 129.2, 129.9, 133.3, 135.3, 138.4, 154.1, 158.8, 167.5\) ppm. Anal. Calcd for C₁₃H₁₁N₃S (241.31): C, 64.71; H, 4.59; N, 17.41; Found: C, 64.44; H, 4.53; N, 17.23 %.

5-(4-Chlorophenyl)thieno[2,3-d]pyrimidin-4-amine (7d)

Yield: 0.270 g (94%); White solid; mp 196-197 °C. IR (KBr, \(\nu/cm^{-1}\)): 1641 (C=N), 3299, 3376 (NH₂). \(^1\)H-NMR (500 MHz, DMSO-d₆) \(\delta = 6.27\) (bs, 2H, NH₂), 7.47 (s, 1H, CH, Ar), 7.48 (d, \(J = 5.5\) Hz, 2H, Ar), 7.55 (d, \(J = 8.4\) Hz, 2H, Ar), 8.32 (s, 1H, CH) ppm. \(^13\)C-NMR (125 MHz, DMSO-d₆) \(\delta = 83.4, 106.1, 116.8, 129.0, 129.1, 154.2, 158.8, 167.5\) ppm.
132.9, 133.7, 137.4, 166.9 ppm. Anal. Calcd for C_{12}H_{8}ClN_{3}S (261.73): C, 55.07; H, 3.08; N, 16.06; Found: C, 55.29; H, 3.11; N, 15.88 %.

5-(2-Methoxyphenyl)thieno[2,3-d]pyrimidin-4-amine (7e)

Yield: 0.189 g (85%); White solid; mp 229-231 °C. IR (KBr, u/cm⁻¹): 1629 (C=N), 3284, 3467 (NH₂). ¹H-NMR (500 MHz, DMSO-d₆) δ = 3.27 (s, 3H, OCH₃), 5.86 (bs, 2H, NH₂), 7.07 (t, J = 7.4 Hz, 2H, Ar), 7.18 (d, J = 7.4 Hz, 2H, Ar), 7.31 (d, J = 7.4 Hz, 2H, Ar), 7.63 (s, 1H, CH), 7.48 (t, J = 7.2 Hz, 1H, Ar), 8.30 (s, 1H, CH) ppm. ¹³C-NMR (125 MHz, DMSO-d₆) δ = 55.0, 112.2, 114.9, 121.0, 121.3, 124.8, 131.0, 131.4, 131.6, 154.1, 157.1, 159.0, 167.0 ppm. Anal. Calcd for C_{13}H₁₁N₃OS (257.31): C, 60.68; H, 4.31; N, 16.33; Found: C, 60.37; H, 4.25; N, 16.47 %.

5-(3,4-Dimethoxyphenyl)thieno[2,3-d]pyrimidin-4-amine (7f)

Yield: 0.265 g (84%); White solid; mp 226-227 °C. IR (KBr, u/cm⁻¹): 1635 (C=N), 3286, 3450 (NH₂). ¹H-NMR (500 MHz, DMSO-d₆) δ = 3.78 (s, 3H, OCH₃), 3.81 (s, 3H, OCH₃), 5.36 (bs, 2H, NH₂), 6.98 (d, J = 8.1 Hz, 1H, Ar), 7.04 (s, 1H, CH), 7.07 (d, J = 8.1 Hz, 2H, Ar), 7.40 (s, 1H, CH), 8.31 (s, 1H, CH) ppm. ¹³C-NMR (125 MHz, DMSO-d₆) δ = 56.0, 56.1, 112.4, 113.1, 113.6, 120.6, 121.5, 128.4, 135.2, 149.2, 149.4, 154.2, 158.8, 167.4 ppm. Anal. Calcd for C_{14}H_{13}N₃O₂S (287.34): C, 58.52; H, 4.56; N, 14.62; Found: C, 58.74; H, 4.58; N, 14.51 %.

5-(2,4-Dimethoxyphenyl)thieno[2,3-d]pyrimidin-4-amine (7g)

Yield: 0.271 g (86%); White solid; mp 226-227 °C. IR (KBr, u/cm⁻¹): 1633 (C=N), 3285, 3472 (NH₂). ¹H-NMR (500 MHz, DMSO-d₆) δ = 3.71 (s, 3H, OCH₃), 3.83 (s, 3H, OCH₃), 5.83 (bs, 2H, NH₂), 6.64 (d, J = 8.3 Hz, 1H, Ar), 6.72 (s, 1H, CH), 6.21 (d, J = 8.3 Hz, 1H, Ar), 7.27 (s, 1H, CH), 8.29 (s, 1H, CH) ppm. ¹³C-NMR (125 MHz, DMSO-d₆) δ = 55.8, 56.0, 99.5, 105.8, 115.1, 117.3, 121.1, 125.5, 131.3, 132.2, 154.0, 158.2, 159.0, 161.7, 166.8 ppm. Anal. Calcd for C_{14}H_{13}N₃O₂S (287.34): C, 58.52; H, 4.56; N, 14.62; Found: C, 58.80; H, 4.61; N, 14.61 %.

5-(2,5-Dimethoxyphenyl)thieno[2,3-d]pyrimidin-4-amine (7h)

Yield: 0.268 g (85%); White solid; mp 199-201 °C. IR (KBr, u/cm⁻¹): 1633 (C=N), 3289, 3458 (NH₂). ¹H-NMR (500 MHz, DMSO-d₆) δ = 3.66 (s, 3H, OCH₃), 3.75 (s, 3H, OCH₃), 6.01 (bs, 2H, NH₂), 6.90 (s, 1H, Ar), 7.04 (d, J = 8.6 Hz, 1H, Ar), 7.11 (d, J = 8.6 Hz, 1H, Ar), 7.37 (s, 1H, CH), 8.30 (s, 1H, CH) ppm. ¹³C-NMR (125 MHz, DMSO-d₆) δ = 56.0, 56.4, 113.4, 114.9, 115.6, 117.3, 121.1, 125.5, 131.3, 151.0, 153.6, 154.1, 159.0, 166.9 ppm. Anal. Calcd for C_{14}H_{13}N₃O₂S (287.34): C, 58.52; H, 4.56; N, 14.62; Found: C, 58.35; H, 4.51; N, 14.73 %.

5-(4-Fluorophenyl)thieno[2,3-d]pyrimidin-4-amine (7i)
Yield: 0.259 g (96%); White solid; mp 169-170 °C. IR (KBr, \(\text{cm}^{-1}\)) \(\nu\): 1630 (C=N), 3280, 3476 (NH\(_2\)). \(^1\)H-NMR (500 MHz, DMSO-d\(_6\)) \(\delta\) = 6.40 (bs, 2H, NH\(_2\)), 7.33 (m, 2H, Ar), 7.48 (s, 1H, CH), 7.49-7.52 (m, 2H, Ar), 8.36 (s, 1H, CH) ppm. \(^{13}\)C-NMR (125 MHz, DMSO-d\(_6\)) \(\delta\) = 113.4, 116.3, 121.8, 132.2, 134.3, 153.5, 158.4, 161.6, 163.6, 167.2 ppm. Anal. Calcd for C\(_{12}\)H\(_8\)FN\(_3\)S (245.28): C, 58.76; H, 3.29; N, 17.13; Found: C, 58.47; H, 3.26; N, 17.06 %.

### Declarations

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All the three authors contributed to the study conception and design, material preparation, data collection and analysis. The first draft of the manuscript was written by Farzaneh Alizadeh-Bami and then, Hossein Mehrabi read and approved the final manuscript.

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### References


Tables

Tables 1-2 is available in the Supplementary Files section.
Scheme

Scheme 1-4 is available in supplementary section.

Figures

Figure 1

Selected examples of compounds containing thieno[2,3-d]pyrimidine scaffolds

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SUPPORTINGINFORMATION.rar
- Scheme1.png
- Scheme2.png
- Scheme3.png
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