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New synthetic approaches to thieno[3,2-*d*]pyrimidine and thieno[3,4-*b*]pyridine derivatives

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Abstract

In this work, 3-amino-4-cyano-2-thiophenecarboxamides **1a-k** were used as versatile synthons for the preparation of thieno[3,2-*d*]pyrimidine-7-carbonitriles **2a-k** and **4a-d** as well as the unexpectedly prepared thieno[3,4-*b*]pyridine-7-carboxamides **5a-e**. Thus, heating thiophene-2-carboxamides **1a-k** in formic acid afforded thieno[3,2-*d*]pyrimidin-4-ones **2a-k**. Alternatively, the reaction of compounds **1a-i** with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (TMD) in xylene produced the *β*-keto amides **3a-i**. The latter were cyclized to thienopyrimidine-2,4-diones **4a-d** by heating with pyrrolidine in toluene using calcium chloride as a desiccant. While refluxing a mixture of *β*-keto amide derivatives **3a, 3d**, **3e, 3f** or **3 h** and potassium carbonate in ethanol or in ethylene glycol afforded the thieno[3,4-*b*]pyridine derivatives **5a-e**.

Keywords 3-Amino-4-cyanothiophene · Thiophene-2-carboxamide · *β*-Keto amide · Thieno[3, 2-*d*]pyrimidine · Thieno[3, 4-*b*]pyridine

Introduction

Thieno[3,2-*d*]pyrimidines represent an important class of chemical compounds with diverse biological activities (Abdel-Megid et al. 2016; Ibrahim et al. 1996; Litvinov, 2004, 2006). The most common synthetic methods of thieno[3,2-*d*]pyrimidin-4-ones, involved cyclization of 3-amino-thiophene-2-carboxylate derivatives using a one-carbon source reagent such as formic acid, triethyl orthoformate (El-Telbany and Hutchins 1985; Hafez et al. 2017; Kim et al. 2014, 2015; Sasikumar et al. 2009), or dimethylformamide dimethylacetal (DMF-DMA); in addition to a primary amine (Ahmad et al. 2016; Brumfield et al. 2012; Carpenter et al. 2006; Sasikumar et al. 2009; Tavares et al. 2006; Warshakoon et al. 2006; Washburn et al. 2014; Zhang et al. 2007; Zheng et al. 2005). Alternatively, the synthesis of thienopyrimidine-4-one derivatives can be achieved by heating 3-amino-thiophene-2-carboxamides either with triethyl orthoformate (El-Hamed et al. 2001; Sasikumar et al. 2010) or formic acid (Ahmed2008; Hertzog et al. 2006; Ryndina et al. 2002).

On the other hand, literature reported the synthesis of thieno[3,2-*d*]pyrimidine-2,4-dione derivatives via pyrimidine ring closure and were almost exclusively conducted using 2-amino-thiophene-3-carboxylate derivatives as the reaction substrate. (Bakhite 2003; Ibrahim et al. 1996; Litvinov 2004, 2006; Varvounis and Giannopoulos 1996) One of the synthetic strategies that offered a direct route to the key ureido intermediates was based on the reaction of thiophene derivatives with isocyanates. Subsequent base-promoted cyclization of the intermediates yielded the target thienopyrimidines (Fukumi et al. 1989; Meyer et al. 1997, 2001; Press et al. 1991; Romeo et al. 2006; Russell et al. 1988; Shestakov et al. 2014; Sugiyama et al. 1989).

Literature review revealed that limited reports described the synthesis of thieno[3,4-*b*]pyridine derivatives, which may be attributed to the difficulty of synthesis of their starting precursors (Bakhite 2003; Barker 1977; Björk et al. 1994; Klemm et al. 1970; Litvinov et al. 2005). The first synthetic route to thieno[3,4-*b*]pyridine was reported by Klemm et al. in 1970. This method was based upon the cyclization of bis-chloromethylpyridine to the dihydrothienopyridine using sodium sulfide, followed by oxidation of the latter with iodobenzene dichloride to the sulfoxide derivative. Dehydration and subsequent aromatization of the latter with alumina afforded thieno[3,4-*b*]pyridine ring (Klemm et al. 1970).

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Recently, new tetrasubstituted thiophene derivatives have been successively prepared by our team (El-Meligie et al. 2020). The method developed by us was a modification of a previously reported procedure by Thomae et al.(2009). The modification consisted in separation of the enethiolate intermediate, which was further reacted with only one molar equivalent of the α-haloketone. The reaction was conducted in green solvents (ethanol, water, or a mixture of them) using mild bases (K_2CO_3 or TEA). Following this procedure, three series of tetrasubstituted thiophenes were reported in high yields and in pure forms. Among them, 3-amino-4-cyano-2-thiophenecarboxamides **1a-k** were documented for the first time.

In continuation to this work, herein we reported the preparation of thieno[3,2-*d*]pyrimidine-7-carbonitriles **2a–k** and **4a–d** as well as thieno[3,4-*b*]pyridine-7-carboxamides **5a-e** from 3-amino-4-cyano-2-thiophenecarboxamides **1a–k.** Moreover, two new procedures were developed for the synthesis of two series of thieno[3,2-*d*]pyrimidine-2,4-diones **4a-d** and thieno[3,4-*b*]pyridines **5a-e** starting with the β-keto amide derivatives **3.**

Experimental

The melting points were determined using Stuart SMP20 apparatus and are uncorrected. The IR spectra were performed using Shimadzu IR-435 spectrophotometer and the values are represented in cm^{-1}. Bruker AVANCETM III 400 MHz spectrophotometer was used for the acquisition of ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra of the new compounds using DMSO-d_6 as a solvent. Nuclear magnetic resonance spectra were processed on MestreNova 11.0.4 program using residual solvent peak as the internal standard. Chemical shifts and coupling constants are presented in ppm and in Hz, respectively. Both IR and NMR spectra were carried out at Faculty of Pharmacy, Cairo University, Cairo, Egypt. Elemental analyses were carried out at The Regional Center for Mycology and Biotechnology, Al-Azhar University, Cairo, Egypt. The preparation of thiophene-2-carboxamides **1a–k** was performed as previously reported (El-Meligie et al. 2020).

4-Oxo-3-(substituted) phenyl-6-(4-phenylpiperazin-1-yl)-3,4-dihydrothieno[3,2-d]pyrimidine-7-carbonitriles 2a-k

A suspension of thiophene-2-carboxamides **1a–k** (2 mmol) in formic acid (15 mL) was heated under reflux with continuous stirring for 5 h. The reaction mixture was then cooled to room temperature, poured onto ice-water (100 mL), then stirred for 30 min. The precipitated solid was filtered, washed with water (2 × 20 mL), then with ethanol (2x20 mL), oven-dried until a constant weight, and crystallized from the suitable solvent.

4-Oxo-3-phenyl-6-(4-phenylpiperazin-1-yl)-3,4-dihydrothieno[3,2-d]pyrimidine-7-carbonitrile (2a)

Yield: 98%, crystallized from toluene; mp 285–286 °C; IR (cm^{-1}): 2210 (C ≡ N); 1678 (C = O). ^1H NMR (ppm): 3.41 (t, 4H, J = 5.0 Hz, CH_2); 3.91 (t, 4H, J = 5.0 Hz, CH_2); 6.82–7.58 (m, 10H, ArH); 8.45 (s, 1H, = CH). ^{13}C NMR (ppm): 47.2, 49.9 (piperazine Cs); 80.7, 107.1, 115.1, 115.7, 119.4, 127.4, 128.9, 129.0, 129.1, 136.8, 150.0, 150.6, 154.4, 158.1, 167.9 (Ar. Cs, C ≡ N, and C = O). Anal Calcd for $C_{23}H_{19}N_5OS$ (413.49): C, 66.81; H, 4.63; N, 16.94. Found: C, 67.09; H, 4.78; N, 17.19.

3-(4-Methylphenyl)-4-oxo-6-(4-phenylpiperazin-1-yl)- 3,4-dihydrothieno[3,2-d]pyrimidine-7-carbonitrile (2b)

Yield: 95%, crystallized from ethanol–toluene (1:1) mixture; mp 263-264 °C;IR (cm^{-1}): 2214 (C ≡ N); 1678 (C = O). ^1H NMR (ppm): 2.38 (s, 3H, CH_3); 3.39-3.41 (m, 4H, CH_2); 3.88–3.90 (m, 4H, CH_2); 6.82–7.28 (m, 5H, ArH); 7.34 (d, 2H, J = 8.0 Hz, ArH); 7.39 (d, 2H, J = 8.0 Hz, ArH); 8.39 (s, 1H, = CH). ^{13}C NMR (ppm): 20.6 (CH_3); 47.2, 49.9 (piperazine Cs); 80.7, 107.1, 115.1, 115.7, 119.4, 127.1, 128.1, 129.0, 129.5, 134.2, 138.6, 150.0, 154.4, 158.0, 167.8 (Ar. Cs, C ≡ N, and C = O). Anal Calcd for $C_{24}H_{21}N_5OS$ (427.52): C, 67.43; H, 4.95; N, 16.38. Found: C, 67.68; H, 5.03; N, 16.54.

3-(4-Ethylphenyl)-4-oxo-6-(4-phenylpiperazin-1-yl)-3,4-dihydrothieno[3,2-d]pyrimidine-7-carbonitrile (2c)

Yield: 86%, crystallized from ethanol–toluene (1:1) mixture; mp 253–254 °C;IR (cm^{-1}): 2210 (C ≡ N); 1678 (C = O). ^1H NMR (ppm): 1.22 (t, 3H, J = 7.6 Hz, CH_3); 2.68 (q, 2H, J = 7.6 Hz, CH_2); 3.39–3.41 (m, 4H, CH_2); 3.87–3.89 (m, 4H, CH_2); 6.82–7.27 (m, 5H, ArH); 7.37 (d, 2H, J = 8.0 Hz, ArH); 7.42 (d, 2H, J = 8.0 Hz, ArH), 8.40 (s, 1H, = CH). ^{13}C NMR (ppm): 15.5 (CH_3); 27.8 (CH_2); 47.2, 49.9 (piperazine Cs); 80.7, 107.2, 115.1, 115.7, 119.4, 127.2, 128.4, 129.0, 134.4, 144.8, 150.0, 150.7, 154.5, 158.1, 167.9 (Ar. Cs, C ≡ N, and C = O). Anal Calcd for $C_{25}H_{23}N_5OS$ (441.55): C, 68.00; H, 5.25; N, 15.86. Found: C, 67.92; H, 5.41; N, 16.04.

3-(2-Chlorophenyl)-4-oxo-6-(4-phenylpiperazin-1-yl) -3,4-dihydrothieno[3,2-d]pyrimidine-7-carbonitrile (2d)

Yield: 83%, crystallized from toluene; mp 266-267 °C; IR (cm^{-1}): 2210 (C≡N); 1670 (C=O). ^{1}H NMR (ppm): 3.41 (t, 4H, J=5.0 Hz, CH_2); 3.91 (t, 4H, J=5.0 Hz, CH_2); 6.82–7.74 (m, 9H, ArH); 8.44 (s, 1H, =CH). ^{13}C NMR (ppm): 47.2, 50.0 (piperazine Cs); 80.9, 106.8, 115.0, 115.7, 119.4, 128.3, 129.0, 130.0, 130.5, 131.4, 131.4, 134.3, 150.0, 150.7, 153.8, 158.3, 168.0 (Ar. Cs, C≡N, and C=O). Anal Calcd for $C_{23}H_{18}ClN_5OS$ (447.94): C, 61.67; H, 4.05; N, 15.63. Found: C, 61.88; H, 4.23; N, 15.88.

3-(4-Chlorophenyl)-4-oxo-6-(4-phenylpiperazin-1-yl) -3,4-dihydrothieno[3,2-d]pyrimidine-7-carbonitrile (2e)

Yield: 88%, crystallized from toluene; mp 284-285 °C;IR (cm^{-1}): 2210 (C≡N); 1670 (C=O). ^{1}H NMR (ppm): 3.40-3.42 (m, 4H, CH_2); 3.89–3.91 (m, 4H, CH_2); 6.82–7.28 (m, 5H, ArH); 7.57 (d, 2H, J=8.5 Hz, ArH); 7.63 (d, 2H, J=8.5 Hz, ArH); 8.44 (s, 1H, =CH). ^{13}C NMR (ppm): 47.2, 49.9 (piperazine Cs); 80.7, 107.0, 115.7, 119.4, 129.0, 129.1, 129.3, 133.6, 135.6, 150.0, 150.4, 154.2, 158.1, 160.1, 167.8 (Ar. Cs, C≡N, and C=O). Anal Calcd for $C_{23}H_{18}ClN_5OS$ (447.94): C, 61.67; H, 4.05; N, 15.63. Found: C, 61.92; H, 4.18; N, 15.79.

3-(3-Nitrophenyl)-4-oxo-6-(4-phenylpiperazin-1-yl) -3,4-dihydrothieno[3,2-d]pyrimidine-7-carbonitrile (2f)

Yield: 85%, crystallized from acetic acid; mp 277-278 °C;IR (cm^{-1}): 2206 (C≡N); 1678 (C=O); 1527, 1350 (NO_2). ^{1}H NMR (ppm): 3.40–3.42 (m, 4H, CH_2); 3.90–3.92 (m, 4H, CH_2); 6.82–8.53 (m, 10H, 9 ArH and =CH). ^{13}C NMR (ppm): 47.2, 50.0 (piperazine Cs); 80.7, 106.9, 115.1, 115.7, 119.4, 122.9, 123.8, 129.0, 130.5, 134.3, 137.6, 147.8, 150.0, 150.3, 154.2, 158.2, 167.9 (Ar. Cs, C≡N, and C=O). Anal. Calcd for $C_{23}H_{18}N_6O_3S$ (458.49): C, 60.25; H, 3.96; N, 18.33. Found: C, 60.44; H, 4.01; N, 18.49.

3-(2,4-Dichlorophenyl)-4-oxo-6-(4-pheny lpiperazin-1-yl)-3,4-dihydrothieno[3,2-d] pyrimidine-7-carbonitrile (2 g)

Yield: 85%, crystallized from toluene; mp 268–269 °C; IR (cm^{-1}): 2210 (C≡N); 1678 (C=O). ^{1}H NMR (ppm): 3.41 (t, 4H, J=5.0 Hz, CH_2); 3.91 (t, 4H, J=5.0 Hz, CH_2); 6.82–7.95 (m, 8H, ArH); 8.45 (s, 1H, =CH). ^{13}C NMR (ppm): 47.2, 50.0 (piperazine Cs); 80.9, 106.7, 115.0, 115.7, 119.4, 128.5, 129.0, 129.5, 131.8, 132.8, 133.4, 135.2, 150.0, 150.5, 153.6, 158.4, 168.0 (Ar. Cs, C≡N, and C=O). Anal Calcd for $C_{23}H_{17}Cl_2N_5OS$ (482.38): C, 57.27; H, 3.55; N, 14.52. Found: C, 57.43; H, 3.72; N, 14.68.

3-(2-Bromophenyl)-4-oxo-6-(4-phenylpiperazin-1-yl) -3,4-dihydrothieno[3,2-d]pyrimidine-7-carbonitrile (2 h)

Yield: 85%, crystallized from toluene; mp 280–281 °C;IR (cm^{-1}): 2210 (C≡N); 1670 (C=O). ^{1}H NMR (ppm): 3.41 (t, 4H, J=5.0 Hz, CH_2); 3.92 (t, 4H, J=5.0 Hz, CH_2); 6.82–7.89 (m, 9H, ArH); 8.43 (s, 1H, =CH). ^{13}C NMR (ppm): 47.2, 50.0 (piperazine Cs); 80.8, 106.9, 115.0, 115.7, 119.4, 122.0, 128.9, 129.0, 130.6, 131.5, 133.1, 135.9, 150.0, 150.7, 153.7, 158.3, 168.0 (Ar. Cs, C≡N, and C=O). Anal Calcd for $C_{23}H_{18}BrN_5OS$ (492.39): C, 56.10; H, 3.68; N, 14.22. Found: C, 56.42; H, 3.75; N, 14.34.

N-(3-(7-Cyano-4-oxo-6-(4-phenylpiperazin-1-yl) thieno[3,2-d]pyrimidin-3(4H)-yl)phenyl)benzamide (2i)

Yield: 88%, crystallized from ethyl acetate–methanol (1:1); mp 265–266 °C; IR (cm^{-1}): 3302 (NH); 2210 (C≡N); 1662 (C=O). ^{1}H NMR (ppm): 3.39–3.41 (m, 4H, CH_2); 3.89–3.91 (m, 4H, CH_2); 6.81–8.03 (m, 14H, ArH); 8.47 (s, 1H, =CH); 10.52 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR (ppm): 47.3, 49.9 (piperazine Cs); 80.7, 107.1, 115.1, 115.7, 119.0, 119.4, 120.6, 122.5, 127.6, 128.4, 129.0, 129.4, 131.7, 134.5, 136.9, 139.9, 150.0, 150.4, 154.3, 158.1, 165.7, 167.8 (Ar. Cs, C≡N, and C=O). Anal. Calcd for $C_{30}H_{24}N_6O_2S$ (532.62): C, 67.65; H, 4.54; N, 15.78. Found: C, 67.23; H, 4.19; N, 15.42.

N-(3-(7-Cyano-4-oxo-6-(4-phenylpiperazin-1-yl) thieno[3,2-d]pyrimidin-3(4H)-yl)-4-methylphenyl) benzamide (2j)

Yield: 96%, crystallized from ethyl acetate–methanol (1:1); mp 179-180 °C; IR (cm^{-1}): 3479 (NH); 2210 (C≡N); 1678, 1651 (2 C=O). ^{1}H NMR (ppm): 2.06 (s, 3H, CH_3); 3.40–3.42 (m, 4H, CH_2); 3.91–3.93 (m, 4H, CH_2); 6.82–7.97 (m, 13H, ArH); 8.44 (s, 1H, =CH); 10.44 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR (ppm): 16.6 (CH_3); 47.3, 50.0 (piperazine Cs); 80.8, 107.2, 115.1, 115.7, 119.5, 119.8, 121.3, 127.6, 128.4, 129.0, 130.4, 130.8, 131.7, 134.6, 135.8, 138.0, 150.0, 150.7, 154.0, 158.4, 165.5, 168.0 (Ar. Cs, C≡N, and C=O). Anal. Calcd for $C_{31}H_{26}N_6O_2S$ (546.65): C, 68.11; H, 4.79; N, 15.37. Found: C, 67.85; H, 4.53; N, 15.52.

N-(3-(7-cyano-4-oxo-6-(4-phenylpiperazin-1-yl) thieno[3,2-d]pyrimidin-3(4H)-yl)-4-methoxyphenyl) benzamide (2 k)

Yield: 80%, crystallized from ethyl acetate–methanol (1:1); mp 250–251 °C; IR (cm^{-1}): 3317 (NH); 2210 (C≡N); 1662 (C=O). ^{1}H NMR (ppm): 3.39–3.41 (m, 4H, CH_2); 3.78 (s, 3H, OCH_3); 3.90–3.92 (m, 4H, CH_2); 6.81–7.98 (m, 13H, ArH); 8.38 (s, 1H, =CH); 10.37 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR (ppm): 47.3, 50.0 (piperazine Cs); 56.1 (OCH_3); 80.9, 107.2, 112.6, 115.1, 115.7, 119.4, 121.5, 122.8, 124.6, 127.5, 128.4, 129.0, 131.5, 132.3, 134.6, 150.0, 150.6, 151.4, 154.1, 158.2, 165.3, 167.9 (Ar. Cs, C≡N, and C=O). Anal. Calcd for $C_{31}H_{26}N_6O_3S$ (562.65): C, 66.18; H, 4.66; N, 14.94. Found: C, 65.89; H, 4.35; N, 14.56.

4-Cyano-3-(3-oxobutanamido)-N-(substi tuted) phenyl-5-(4-phenylpiperazin-1-yl) thiophene-2-carboxamides 3a-i

A mixture of the appropriate thiophenecarboxamides **1a-i** (7 mmol), and TMD (1.11 g, 1 mL, 7.78 mmol) in xylene (25 mL) was heated under reflux for 15 min in a 50-mL round bottom flask fitted with an air condenser. The reaction mixture was then cooled to room temperature, poured onto ethanol (100 mL), and stirred for 30 min. The solid product was filtered, washed with ethanol (2 × 20 mL), oven-dried until a constant weight, and crystallized from ethanol–acetone (1:1) mixture.

4-Cyano-3-(3-oxobutanamido)-N-phenyl-5-(4-pheny lpiperazin-1-yl)thiophene-2-carboxamide (3a)

Yield: 86%, mp 212–214 °C; IR (cm^{-1}): 3348, 3170 (2 NH); 2210 (C≡N); 1716, 1701, 1693 (3 C=O). ^{1}H NMR (ppm): 2.24 (s, 3H, CH_3); 3.36–3.38 (m, 4H, CH_2); 3.69 (s, 2H, $COCH_2$); 3.72 (t, 4H, J = 5.0 Hz, CH_2); 6.82–7.66 (m, 10H, ArH); 9.34 (s, 1H, NH, D_2O exchangeable); 10.36 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR (ppm): 30.1 (CH_3); 47.4, 49.6 (piperazine Cs); 51.4 ($CO\underline{C}H_2$); 87.0, 114.1, 115.0, 115.8, 119.5, 120.7, 124.0, 128.6, 129.0, 135.5, 138.0, 150.2, 158.3, 164.4, 166.0 (Ar. Cs, C≡N, and 2 amide C=O); 203.3 (C=O). Anal Calcd for $C_{26}H_{25}N_5O_3S$ (487.57): C, 64.05; H, 5.17; N, 14.36. Found: C, 64.32; H, 5.03; N, 14.62.

4-Cyano-N-(4-methylphenyl)-3-(3-oxob utanamido)-5-(4-phenylpiperazin-1-yl) thiophene-2-carboxamide (3b)

Yield: 70%, mp 204–206 °C;IR (cm^{-1}): 3402, 3240 (2 NH); 2202 (C≡N); 1724, 1658, 1651 (3 C=O). ^{1}H NMR (ppm): 2.24 (s, 3H, CH_3); 2.27 (s, 3H, CH_3); 3.33–3.35 (m, 4H, CH_2); 3.69 (s, 2H, $COCH_2$); 3.72 (t, 4H, J = 5.0 Hz, CH_2); 6.82–7.54 (m, 9H, ArH); 9.26 (s, 1H, NH, D_2O exchangeable); 10.34 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR (ppm): 20.4 (CH_3); 30.1 ($\underline{C}H_3CO$); 47.4, 49.5 (piperazine Cs); 51.4 ($CO\underline{C}H_2$); 87.0, 114.4, 115.0, 115.8, 119.5, 120.1, 120.8, 129.0, 133.1, 135.3, 135.5, 150.2, 158.1, 164.4, 166.1 (Ar. Cs, C≡N, and 2 amide C=O); 203.3 (C=O). Anal Calcd for $C_{27}H_{27}N_5O_3S$ (501.60): C, 64.65; H, 5.43; N, 13.96. Found: C, 64.91; H, 5.48; N, 14.17.

4-Cyano-N-(4-ethylphenyl)-3-(3-oxobutanamido)-5 -(4-phenylpiperazin-1-yl)thiophene-2-carboxamide (3c)

Yield: 87%, mp 196–198 °C;IR (cm^{-1}): 3348, 3147 (2 NH); 2210 (C≡N); 1720, 1693, 1627 (3 C=O). ^{1}H NMR (ppm): 1.17 (t, 3H, J = 7.6 Hz, $\underline{C}H_3CH_2$); 2.24 (s, 3H, $\underline{C}H_3CO$); 2.57 (q, 2H, J = 7.6 Hz, $CH_3\underline{C}H_2$); 3.35–3.37 (m, 4H, CH_2); 3.69 (s, 2H, $CO\underline{C}H_2$); 3.72 (t, 4H, J = 5.0 Hz, CH_2); 6.82–7.55 (m, 9H, ArH); 9.27 (s, 1H, NH, D_2O exchangeable); 10.34 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR (ppm): 15.6 ($\underline{C}H_3CH_2$); 27.6 ($CH_3\underline{C}H_2$); 30.1 ($\underline{C}H_3CO$); 47.4, 49.5 (piperazine Cs); 51.4 ($CO\underline{C}H_2$); 87.0, 114.4, 115.0, 115.8, 119.5, 120.9, 127.8, 129.0, 135.3, 135.7, 139.5, 150.2, 158.1, 164.4, 166.1 (Ar. Cs, C≡N, and 2 amide C=O); 203.3 (C=O). Anal Calcd for $C_{28}H_{29}N_5O_3S$ (515.63): C, 65.22; H, 5.67; N, 13.58. Found: C, 65.38; H, 5.81; N, 13.69.

N-(2-Chlorophenyl)-4-cyano-3-(3-oxobutanamido)-5 -(4-phenylpiperazin-1-yl)thiophene-2-carboxamide (3d)

Yield: 79%, mp 176–178 °C; IR (cm^{-1}): 3394, 3217 (2 NH); 2206 (C≡N); 1735, 1666, 1651 (3 C=O). ^{1}H NMR (ppm): 2.22 (s, 3H, CH_3); 3.35–3.37 (m, 4H, CH_2); 3.67 (s, 2H, $COCH_2$); 3.75 (t, 4H, J = 5.0 Hz, CH_2); 6.82–7.91 (m, 9H, ArH); 9.17 (s, 1H, NH, D_2O exchangeable); 10.45 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR (ppm): 30.0 (CH_3); 47.3, 49.5 (piperazine Cs); 51.3 ($CO\underline{C}H_2$); 86.8, 114.4, 114.9, 115.8, 119.5, 125.0, 125.9, 126.4, 127.7, 129.0, 129.4, 134.2, 136.1, 150.2, 158.2, 164.6, 166.6 (Ar. Cs, C≡N, and 2 amide C=O); 202.3 (C=O). Anal Calcd for $C_{26}H_{24}ClN_5O_3S$ (522.02): C, 59.82; H, 4.63; N, 13.42. Found: C, 60.07; H, 4.72; N, 13.60.

N-(4-Chlorophenyl)-4-cyano-3-(3-oxobutanamido)-5 -(4-phenylpiperazin-1-yl)thiophene-2-carboxamide (3e)

Yield: 85%, mp 222–224 °C; IR (cm^{-1}): 3298, 3190 (2 NH); 2214 (C≡N); 1712, 1678, 1639 (3 C=O). ^{1}H NMR (ppm): 2.24 (s, 3H, CH_3); 3.35–3.37 (m, 4H, CH_2); 3.68 (s, 2H, $COCH_2$); 3.71-3.73 (m, 4H, CH_2); 6.82–7.27 (m, 5H, ArH);

7.41 (d, 2H, $J = 8.8$ Hz, ArH); 7.68 (d, 2H, $J = 8.8$, ArH); 9.47 (s, 1H, NH, D_2O exchangeable); 10.35 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR (ppm): 30.0 (CH_3); 47.4, 49.6 (piperazine Cs); 51.4 ($CO\underline{C}H_2$); 87.0, 113.3, 114.9, 115.8, 119.5, 122.2, 127.6, 128.5, 129.0, 135.9, 137.1, 150.2, 158.4, 164.5, 165.9 (Ar. Cs, C ≡ N, and 2 amide C = O); 203.3 (C = O). Anal Calcd for $C_{26}H_{24}ClN_5O_3S$ (522.02): C, 59.82; H, 4.63; N, 13.42. Found: C, 59.96; H, 4.78; N, 13.67.

4-Cyano-N-(3-nitrophenyl)-3-(3-oxobutanamido)-5-(4-phenylpiperazin-1-yl)thiophene-2-carboxamide (3f)

Yield: 90%, mp 216–218 °C; IR (cm^{-1}): 3367, 3259 (2 NH); 2206 (C ≡ N); 1724, 1670, 1643 (3 C = O); 1527, 1354 (NO_2). ^{1}H NMR (ppm): 2.24 (s, 3H, CH_3); 3.36–3.38 (m, 4H, CH_2); 3.69 (s, 2H, $COCH_2$); 3.74 (t, 4H, $J = 5.0$ Hz, CH_2); 6.82–8.65 (m, 9H, ArH); 9.82 (s, 1H, NH, D_2O exchangeable); 10.38 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR (ppm): 30.1 (CH_3); 47.4, 49.6 (piperazine Cs); 51.4 ($CO\underline{C}H_2$); 87.0, 112.1, 114.8, 114.9, 115.8, 118.4, 119.5, 126.6, 129.0, 130.0, 136.8, 139.4, 147.8, 150.2, 158.9, 164.7, 165.8 (Ar. Cs, C ≡ N, and 2 amide C = O); 203.4 (C = O). Anal Calcd for $C_{26}H_{24}N_6O_5S$ (532.57): C, 58.64; H, 4.54; N, 15.78. Found: C, 58.78; H, 4.67; N, 16.04.

4-Cyano-N-(2,4-dichlorophenyl)-3-(3-oxo butanamido)-5-(4-phenylpiperazin-1-yl) thiophene-2-carboxamide (3 g)

Yield: 69%, mp 213-215 °C; IR (cm^{-1}): 3317, 3221 (2 NH); 2210 (C ≡ N); 1728, 1666, 1635 (3 C = O). ^{1}H NMR (ppm): 2.22 (s, 3H, CH_3); 3.35–3.37 (m, 4H, CH_2); 3.67 (s, 2H, $COCH_2$); 3.75 (t, 4H, $J = 5.0$ Hz, CH_2); 6.81–7.91 (m, 8H, ArH); 9.20 (s, 1H, NH, D_2O exchangeable); 10.45 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR (ppm): 30.0 (CH_3); 47.3, 49.5 (piperazine Cs); 51.3 ($CO\underline{C}H_2$); 86.8, 114.9, 115.8, 119.5, 126.2, 127.1, 127.8, 128.7, 128.9, 129.0, 129.6, 133.5, 136.4, 150.1, 158.2, 164.6, 166.6 (Ar. Cs, C ≡ N, and 2 amide C = O); 202.5 (C = O). Anal Calcd for $C_{26}H_{23}Cl_2N_5O_3S$ (556.46): C, 56.12; H, 4.17; N, 12.59. Found: C, 56.40; H, 4.23; N, 12.65.

N-(2-Bromophenyl)-4-cyano-3-(3-oxobutanamido)-5-(4-phenylpiperazin-1-yl)thiophene-2-carboxamide (3 h)

Yield: 73%, mp 182–183 °C; IR (cm^{-1}): 3344, 3232 (2 NH); 2210 (C ≡ N); 1724, 1689, 1658 (3 C = O). ^{1}H NMR (ppm): 2.23 (s, 3H, CH_3), 3.34–3.36 (m, 4H, CH_2); 3.69 (s, 2H, $COCH_2$); 3.75 (t, 4H, $J = 5.0$ Hz, CH_2); 6.82–7.87 (m, 9H, ArH); 9.13 (s, 1H, NH, D_2O exchangeable); 10.44 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR (ppm): 30.1 (CH_3); 47.3, 49.5 (piperazine Cs); 51.4 ($CO\underline{C}H_2$); 86.9, 114.3, 114.9, 115.8, 116.9, 119.5, 125.6, 126.9, 128.2, 129.0, 132.6, 135.6, 136.2, 150.1, 158.2, 164.6, 166.6 (Ar. Cs, C ≡ N, and 2 amide C = O); 202.4 (C = O). Anal Calcd for $C_{26}H_{24}BrN_5O_3S$ (566.47): C, 55.13; H, 4.27; N, 12.36. Found: C, 55.01; H, 4.39; N, 12.19.

N-(3-Benzamidophenyl)-4-cyano-3-(3-oxobutanamido)-5-(4-phenylpiperazin-1-yl) thiophene-2-carboxamide (3i)

Yield: 86%, mp 210–212 °C; IR (cm^{-1}): 3383, 3275, 3248 (3 NH); 2206 (C ≡ N); 1712, 1674, 1643, 1608 (4 C = O). ^{1}H NMR (ppm): 2.25 (s, 3H, CH_3); 3.34–3.36 (m, 4H, CH_2); 3.69 (s, 2H, $COCH_2$); 3.72–3.74 (m, 4H, CH_2); 6.82–8.23 (m, 14H, ArH); 9.42 (s, 1H, NH, D_2O exchangeable); 10.32 (s, 1H, NH, D_2O exchangeable); 10.39 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR (ppm): 30.0 (CH_3); 47.4, 49.6 (piperazine Cs); 51.4 ($CO\underline{C}H_2$); 87.0, 113.2, 114.1, 115.0, 115.8, 116.3, 119.5, 127.6, 128.3, 128.6, 129.0, 131.5, 134.9, 135.5, 135.6, 138.2, 139.4, 150.2, 158.3, 164.4, 165.5, 166.0, (Ar. Cs, C ≡ N, and 3 amide C = O); 203.1 (C = O). Anal Calcd for $C_{33}H_{30}N_6O_4S$ (606.70): C, 65.33; H, 4.98; N, 13.85. Found: C, 64.98; H, 5.02; N, 13.59.

2,4-Dioxo-3-(substituted) phenyl-6-(4-phenylpiperazin-1-yl)-1,2,3,4-tetrahydrothieno[3,2-d] pyrimidine-7-carbonitriles 4a-d

Pyrrolidine (0.14 g, 0.16 mL, 2 mmol) was added to a stirred suspension of freshly dried $CaCl_2$ (5 g), and β-keto amides **3a, c, e,** and **f** (2 mmol) in anhydrous toluene (50 mL). The reaction mixture was then placed in a water bath and the temperature was gradually raised to 45–50 °C over a period of 2 h. Heating was continued for 70 h at 45–50 °C, followed by further heating for 4 h under reflux. The mixture was then filtered, while hot and the obtained residue was oven-dried, re-suspended in water (50 mL), and stirred at room temperature for 30 min. The suspension was filtered, washed with water (2 × 20 mL), oven-dried until a constant weight, and crystallized from acetic acid.

2,4-Dioxo-3-phenyl-6-(4-phenylpiperazin-1-yl)-1,2,3,4-tetrahydrothieno[3,2-d]pyrimidine-7-carbonitrile (4a)

Yield: 80%, mp > 300 °C; IR (cm^{-1}): 3132 (NH); 2214 (C ≡ N); 1708, 1658 (2 C = O). ^{1}H NMR (ppm): 3.38-4.00 (m, 4H, CH_2); 3.83–3.85 (m, 4H, CH_2); 6.82-7.47 (m, 10H,

ArH); 12.15 (s, 1H, NH). ^{13}C NMR (ppm): 47.2, 50.0 (piperazine Cs); 76.2, 94.1, 114.1, 115.7, 119.4, 127.8, 128.6, 129.0, 129.1, 135.9, 150.0, 152.2, 156.8, 157.1, 168.6 (Ar. Cs and CN). Anal Calcd for $C_{23}H_{19}N_5O_2S$ (429.50): C, 64.32; H, 4.46; N, 16.31. Found: C, 64.17; H, 4.39; N, 16.56.

3-(4-Ethylphenyl)-2,4-dioxo-6-(4-phenylpiperazin-1-yl)-1,2,3,4-tetrahydrothieno[3,2-d]pyrimidine-7-carbonitrile (4b)

Yield: 71%, mp > 300 °C; IR (cm^{-1}): 3182 (NH); 2210 (C≡N); 1732, 1654 (2 C=O). ^{1}H NMR (ppm): 1.22 (t, 3H, J = 7.6 Hz, CH_3); 2.65 (q, 2H, J = 7.6 Hz, CH_2); 3.38 (t, 4H, J = 5.0 Hz, CH_2); 3.85 (t, 4H, J = 5.0 Hz, CH_2); 6.82-7.29 (m, 9H, ArH); 12.18 (s, 1H, NH). ^{13}C NMR (ppm): 15.5 (CH_3); 27.8 (CH_2); 47.2, 50.1 (piperazine Cs); 75.4, 94.3, 115.6, 119.4, 119.4, 128.1, 128.8, 129.0, 129.1, 132.8, 132.9, 143.6, 150.0, 156.9, 168.8 (Ar. Cs and CN). Anal Calcd for $C_{25}H_{23}N_5O_2S$ (457.55): C, 65.63; H, 5.07; N, 15.31. Found: C, 65.49; H, 5.21; N, 15.43.

3-(4-Chlorophenyl)-2,4-dioxo-6-(4-phenylpiperazin-1-yl)-1,2,3,4-tetrahydrothieno[3,2-d]pyrimidine-7-carbonitrile (4c)

Yield: 60%, mp > 300 °C; IR (cm^{-1}): 3132 (NH); 2214 (C≡N); 1708, 1658 (2 C=O). ^{1}H NMR (ppm): 3.35–3.37 (m, 4H, CH_2); 3.83 (t, 4H, J = 5.0 Hz, CH_2); 6.81–7.50 (m, 9H, ArH); 12.15 (s, 1H, NH). ^{13}C NMR (ppm): 15.5 (CH_3); 27.8 (CH_2); 47.2, 49.9 (piperazine Cs); 80.7, 107.0, 115.7, 119.4, 129.0, 129.1, 129.3, 133.6, 135.6, 150.0, 150.4, 154.2, 158.1, 160.1, 167.8 (Ar. Cs and CN). Anal Calcd for $C_{23}H_{18}ClN_5O_2S$ (463.94): C, 59.54; H, 3.91; N, 15.10. Found: C, 59.76; H, 4.15; N, 15.37.

3-(3-Nitrophenyl)-2,4-dioxo-6-(4-phenylpiperazin-1-yl)-1,2,3,4-tetrahydrothieno[3,2-d]pyrimidine-7-carbonitrile (4d)

Yield: 69%, mp > 300 °C; IR (cm^{-1}): 3178 (NH); 2210 (C≡N); 1732, 1654 (2 C=O); 1535, 1357 (NO_2). ^{1}H NMR (ppm): 3.39 (t, 4H, J = 5.0 Hz, CH_2); 3.88 (t, 4H, J = 5.0 Hz, CH_2); 6.82-8.30 (m, 9H, ArH); 12.34 (s, 1H, NH). ^{13}C NMR (ppm): 47.2, 50.1 (piperazine Cs); 75.4, 94.1, 113.7, 115.6, 119.4, 123.2, 124.6, 129.0, 130.1, 136.4, 136.6, 146.4, 148.0, 150.0, 151.1, 156.6, 168.9 (Ar. Cs and CN). Anal Calcd for $C_{23}H_{18}N_6O_4S$ (474.50): C, 58.22; H, 3.82; N, 17.71. Found: C, 58.01; H, 3.96; N, 17.88.

3-Acetyl-2-hydroxy-4-imino-N-(substituted)-phenyl-5-(4-phenylpiperazin-1-yl)-1,4-dihydrothieno[3,4-b]pyridine-7-carboxamides 5a-e

Method A (for the synthesis of compounds 5a, b, d, e)

A mixture of the appropriate 3-oxobutanamido thiophenecarboxamides **3a, d, f,** and **h** (3 mmol), and K_2CO_3 (0.83 g, 6 mmol) in ethanol (25 mL) was heated under reflux with continuous stirring for 6 h. The reaction mixture was cooled to room temperature and filtered. The obtained solid product was washed with ethanol (2 × 20 mL), oven-dried until a constant weight, and crystallized from acetic acid.

Method B (for the synthesis of compound 5c)

A solution of K_2CO_3 (0.83 g, 6 mmol) in water (2 mL) was added to a stirred solution of 3-oxobutanamido thiophenecarboxamide **3e** in ethylene glycol (25 mL) maintained at 120 °C. The reaction mixture was then heated for 10 min, cooled to room temperature, and poured onto water (75 mL). The formed solid was filtered, washed with water (2 × 50 mL), oven-dried until a constant weight, and crystallized from acetic acid.

3-Acetyl-2-hydroxy-4-imino-N-phenyl-5-(4-phenylpiperazin-1-yl)-1,4-dihydrothieno[3,4-b]pyridine-7-carboxamide (5a)

Yield: 63%, mp 273–275 °C; IR (cm^{-1}): 3356, 3332, 3317 (3 NH); 1658, 1651 (2 C=O). ^{1}H NMR (ppm): 2.53 (s, 3H, CH_3); 2.90–3.16 (m, 4H, CH_2); 3.45–3.75 (m, 4H, CH_2); 6.82–7.69 (m, 10H, ArH); 8.21 (s, 1H, NH or OH, D_2O exchangeable); 9.92 (s, 1H, NH, D_2O exchangeable); 10.08 (s, 1H, NH, D_2O exchangeable); 10.76 (s, 1H, NH or OH, D_2O exchangeable). ^{13}C NMR (ppm): 32.7 (CH_3); 47.6, 54.6 (piperazine Cs); 97.2, 98.1, 109.7, 115.8, 119.5, 121.1, 121.2, 123.9, 128.6, 129.1, 138.4, 141.8, 150.5, 155.0, 161.6, 162.4 (Ar. Cs and C=O); 199.9 (C=O). Anal Calcd for $C_{26}H_{25}N_5O_3S$ (487.57): C, 64.05; H, 5.17; N, 14.36. Found: C, 64.31; H, 5.28; N, 14.19.

3-Acetyl-N-(2-chlorophenyl)-2-hydroxy-4-imino-5-(4-phenylpiperazin-1-yl)-1,4-dihydrothieno[3,4-b]pyridine-7-carboxamide (5b)

Yield: 65%, mp 284–286 °C; IR (cm^{-1}): 3394, 3348, 3313 (3 NH); 1658, 1651 (2 C=O). ^{1}H NMR (ppm): 2.95–3.05 (m, 4H, CH_2); 3.04 (s, 3H, CH_3); 3.35–3.50 (s, 2H, CH_2); 3.60–3.77 (m, 4H, CH_2); 7.03–8.22 (m, 9H, ArH); 8.26 (s, 1H, NH or OH, D_2O exchangeable); 10.04 (s, 1H, NH, D_2O exchangeable); 10.68 (s, 1H, NH, D_2O exchangeable); 11.32 (s, 1H, NH or OH, D_2O exchangeable). ^{13}C NMR (ppm):

33.7 (CH_3); 49.2, 55.7 (piperazine Cs); 98.5, 100.0, 111.7, 117.2, 121.0, 127.4, 127.5, 128.2, 128.8, 130.0, 130.3, 135.7, 143.4, 151.6, 156.1, 162.4, 162.7, 163.4 (Ar. Cs and C = O); 201.6 (C = O). Anal Calcd for $C_{26}H_{24}ClN_5O_3S$ (522.02): C, 59.82; H, 4.63; N, 13.42. Found: C, 59.67; H, 4.71; N, 13.68.

3-Acetyl-N-(4-chlorophenyl)-2-hydroxy-4-imino-5-(4-phenylpiperazin-1-yl)-1,4-dihydrothieno[3,4-b]pyridine-7-carboxamide (5c)

Yield: 60%, mp 294–296 °C; IR (cm^{-1}): 3371, 3340, 3309 (3 NH); 1651, 1643 (2 C = O). ^{1}H NMR (ppm): 2.52 (s, 3H, CH_3); 2.85–3.25 (m, 4H, CH_2); 3.40–3.85 (m, 4H, CH_2); 6.82-7.73 (m, 9H, ArH); 8.18 (s, 1H, NH or OH, D_2O exchangeable); 10.02 (s, 1H, NH, D_2O exchangeable); 10.04 (s, 1H, NH, D_2O exchangeable); 10.76 (s, 1H, NH or OH, D_2O exchangeable). ^{13}C NMR (ppm): 32.70 (CH_3); 47.5, 54.6 (piperazine Cs); 96.8, 98.0, 109.5, 115.7, 119.4, 122.4, 127.4, 128.4, 129.0, 137.4, 142.0, 150.4, 154.9, 161.6, 162.0, 162.6 (Ar. Cs and C = O); 199.8 (C = O). Anal Calcd for $C_{26}H_{24}ClN_5O_3S$ (522.02): C, 59.82; H, 4.63; N, 13.42. Found: C, 59.70; H, 4.72; N, 13.74.

3-Acetyl-2-hydroxy-4-imino-N-(3-nitrophenyl)-5-(4-phenylpiperazin-1-yl)-1,4-dihydrothieno[3,4-b]pyridine-7-carboxamide (5d)

Yield: 45%, mp 293–295 °C; IR (cm^{-1}): 3402, 3360, 3348 (3 NH); 1658, 1639 (2 C = O); 1531, 1350 (NO_2). ^{1}H NMR (ppm): 2.53 (s, 3H, CH_3); 2.90–3.25 (m, 4H, CH_2); 3.40–3.95 (m, 4H, CH_2); 6.83–8.69 (m, 9H, ArH); 8.17 (s, 1H, NH or OH, D_2O exchangeable); 10.04 (s, 1H, NH, D_2O exchangeable); 10.35 (s, 1H, NH, D_2O exchangeable); 10.77 (s, 1H, NH or OH, D_2O exchangeable). ^{13}C NMR (ppm): 32.7 (CH_3); 47.6, 54.5 (piperazine Cs); 96.5, 98.0, 109.4, 114.4, 115.8, 117.8, 119.5, 126.1, 129.0, 129.6, 139.8, 142.4, 147.6, 150.4, 150.4, 154.8, 161.7, 162.8 (Ar. Cs and C = O); 199.7 (C = O). Anal Calcd for $C_{26}H_{24}N_6O_5S$ (532.57): C, 58.64; H, 4.54; N, 15.78. Found: C, 58.91; H, 4.63; N, 15.96.

3-Acetyl-N-(2-bromophenyl)-2-hydroxy-4-imino-5-(4-phenylpiperazin-1-yl)-1,4-dihydrothieno[3,4-b]pyridine-7-carboxamide (5e)

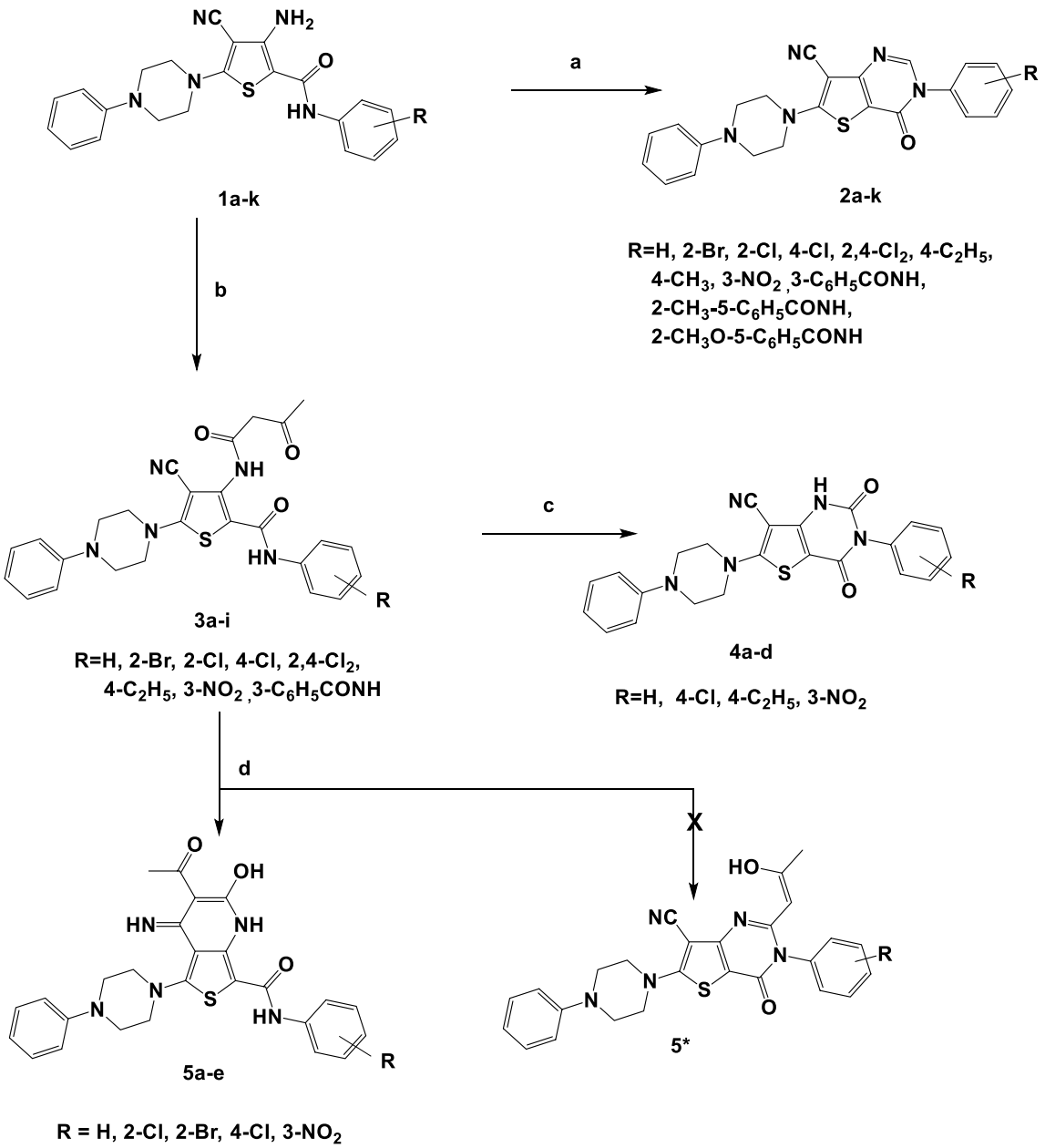
Yield: 64%, mp 287–289 °C; IR (cm^{-1}): 3379, 3348, 3298 (3 NH); 1658, 1651 (2 C = O). ^{1}H NMR (ppm): 2.52 (s, 3H, CH_3); 2.90–3.30 (m, 4H, CH_2); 3.40–3.90 (m, 4H, CH_2); 6.82-7.72 (m, 9H, ArH); 8.21 (s, 1H, NH or OH, D_2O exchangeable); 9.82 (s, 1H, NH, D_2O exchangeable); 9.96 (s, 1H, NH, D_2O exchangeable); 10.76 (s, 1H, NH or OH, D_2O exchangeable). ^{13}C NMR (ppm): 32.7 (CH_3); 47.5, 54.6 (piperazine Cs); 96.6, 98.0, 109.6, 115.8, 119.4, 121.1, 128.1, 128.2, 129.0, 129.2, 132.7, 135.8, 141.8, 150.4, 154.9, 161.7, 162.0, 162.6 (Ar. Cs and C = O); 199.8 (C = O). Anal Calcd for $C_{26}H_{24}BrN_5O_3S$ (566.47): C, 55.13; H, 4.27; N, 12.36. Found: C, 55.37; H, 4.40; N, 12.47.

Results and discussion

In this work, thieno[3,2-*d*]pyrimidin-4-ones **2a–k** were synthesized in excellent yields (80-98%) by heating the respective thiophene-2-carboxamides **1a–k** in formic acid (Scheme 1). The IR spectra of compounds **2a–k** revealed the disappearance of NH_2/NH bands of the precursor thiophene derivatives. Other characteristic bands of compounds **2a-k** were observed at 2214–2206 cm^{-1}, and at 1678–1662 cm^{-1} corresponding to C ≡ N, and C = O groups, respectively. The ^{1}H NMR and ^{13}C NMR spectra offered further confirmation of the structure of compounds **2a–k**. The ^{1}H NMR spectra of compounds **2a–k** showed a characteristic singlet signal at δ 8.38–8.54 ppm corresponding to C(2)-H. Furthermore, no exchangeable protons were detected for compounds **2a–h**, whereas derivatives **2i–k** showed an exchangeable signal at δ 10.37–10.52 ppm corresponding to the CONH proton. Moreover, the ^{13}C NMR spectra of compounds **2a–k** showed the expected number of signals for each derivative.

β-Keto amides comprise an important class of organic reagents that has widespread use in the construction of various heterocyclic rings (Alagesan et al. 2018; El-Meligie et al. 2019). In the synthetic pathway to *β*-keto amides **3a–i**, compounds **1a–i** were reacted with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (TMD) in xylene. It is noteworthy that the commercially available TMD was of 90–95% concentration; therefore, optimization of the amount of the reagent used was necessary. When the reagent was used in a stoichiometric amount to the amine **1a**, TLC analysis of the crude **3a** revealed an incomplete reaction. Optimum ratio of TMD reagent relative to **1a** was found to be 1.11 to 1 molar equivalents. Moreover, as a precautionary measure, an air condenser was used to bar the evolving acetone from returning to the reaction medium, thereby preventing the consumption of the acetyl ketene intermediate **A** in the formation of the side product **B** (Scheme 2).

The structure of compounds **3a–i** was confirmed by spectral analysis. IR spectra of compounds **3a–i** showed two bands at 3402–3147 cm^{-1} corresponding to the NH functions. Moreover, characteristic absorption bands at 2214–2202 cm^{-1} and 1735-1627 cm^{-1} confirmed the presence of C ≡ N and C = O groups, respectively. ^{1}H NMR spectra showed two new singlet signals at δ 2.22–2.25 ppm and at δ 3.67–3.69 ppm corresponding to the CH_3 and CH_2 protons of the *β*-keto acyl moiety, respectively. Moreover, the disappearance of the D_2O-exchangeable singlet signal

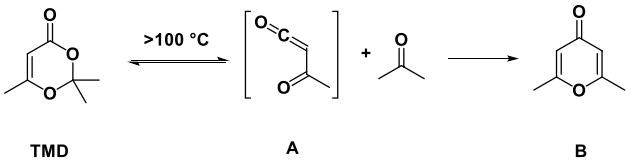


Reaction conditions

a. **Formic acid, reflux, 5 h**
b. **2,2,6-Trimethyl-4*H*-1,3-dioxin-4-one (TMD), xylene, reflux, 15 min**
c. **1) Pyrrolidine, $CaCl_2$, toluene, 50 °C, 70 h; 2) Reflux, 4 h**
d. **K_2CO_3, ethanol, 70 °C, 6 h**
or K_2CO_3, ethylene glycol, 120 °C, 10 min

Scheme 1 Synthesis of fused thiophene derivatives **2-5**

of the NH_2 protons of the parent compounds and the concomitant appearance of a new D_2O-exchangeable signal at δ 10.32–10.45 ppm confirmed the introduction of the *β*-keto acyl moiety at the amino group of the parent precursor. ^{13}C NMR spectra revealed the appearance of two new aliphatic carbon signals at δ 30.0-51.4 ppm, in addition to a signal

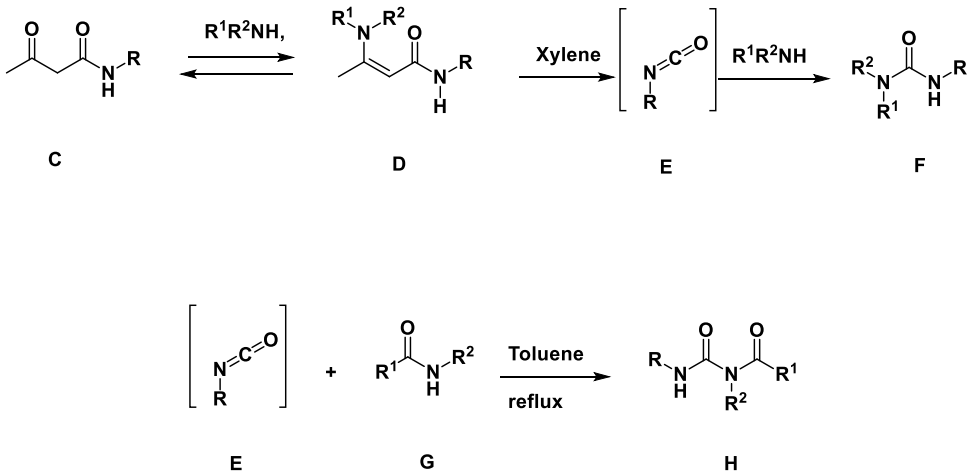


Scheme 2 Potential side product formation in TMD reaction

at δ 202.3–203.4 ppm corresponding to the ketonic C = O carbon.

The prepared *β*-keto amides **3a–i** were used as precursors for the synthesis of thieno[3,2-*d*]pyrimidine-2,4-diones **4a–d** and the infrequently reported thieno[3,4-*b*]pyridines **5a–e**. The reported procedures are of practical and theoretical values, since no previous reports was published describing similar procedures.

Reaction of *β*-keto amides **3a, c, e,** and **f** with pyrrolidine in toluene using $CaCl_2$ as a desiccant afforded the thieno[3,2-*d*]pyrimidine-2,4-diones **4a–d**. The concept of using *β*-keto amide derivatives **3** as substrates for pyrimidine ring closure stemmed from the work published in 2010 by Wei et al. (Wei et al. 2010), who reported the synthesis of asymmetrical urea derivatives **F** via thermally induced fragmentation of enamino amide **D** to the respective isocyanate **E** (Scheme 3); and the earlier observation by Wiley that substituted amides **G** add to isocyanates **E** to form *N*-acyl urea derivatives **H**.(Wiley, 1949a, 1949b).

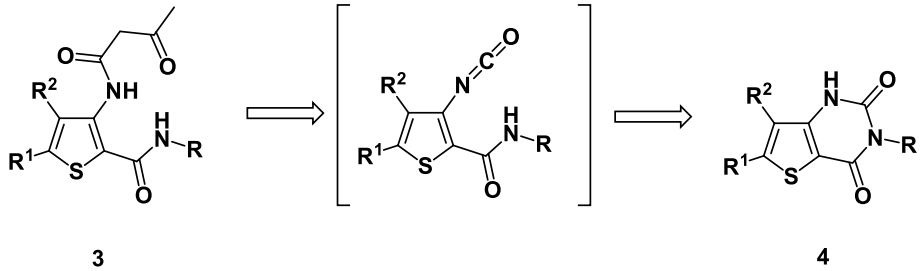


Scheme 3 Synthesis of asymmetrical urea derivatives using *β*-keto amides

Based on the above findings, it stood to reason that subjecting *β*-keto amide derivatives **3** to conditions similar to those reported by Wei et al. (Wei et al. 2010), may potentially generate an isocyanate intermediate which can be subsequently captured by the *ortho* carboxamide group to afford the thieno[3,2-*d*]pyrimidine-2,4-dione derivatives **4** according to Scheme 4.

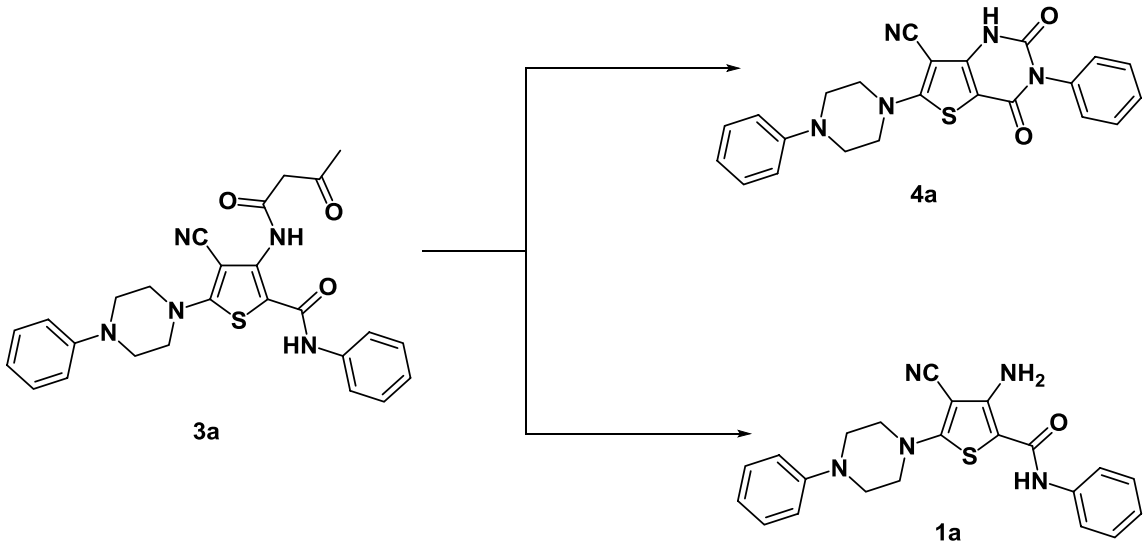
In an initial attempt to prepare compound **4a,** a mixture of **3a** and a slight molar excess of piperidine was heated under reflux for 2 h in accordance with the experimental procedures described by Wei et al.(2010). Unfortunately, the desired product **4a** was not obtained, yet the starting compound **3a** was quantitatively converted to 3-aminothiophene-2-carboxamide **1a**. Promising results, however, were achieved when pyrrolidine was used as the secondary amine, giving rise to the target thienopyrimidine **4a** in 30% yield (Table 1). The observed hydrolysis of *β*-keto amide **3a** could be attributed to the moisture susceptibility of the isocyanate intermediate. Therefore, $CaCl_2$ was added to the reaction medium as a desiccant to prevent the hydrolysis of the isocyanate. Under these conditions, the target thieno[3,2-*d*]pyrimidine-2,4-diones **4a–d** were obtained in moderate to good yields ranging from 60 to 80% (Table 1).

This cyclization reaction may have proceeded according to the mechanism proposed in Scheme 5, whereby the formed enamine was fragmented to isocyanate intermediate that was subsequently captured by the carboxamide group (Pathway A). Another plausible explanation for the



Scheme 4 Potential pyrimidine ring annulation via enamino amide fragmentation

Table 1 Initial attempts of preparation of thienopyrimidine **4a** from the *β*-keto amide **3a**



Reaction conditions	**1a**	**4a**
Piperidine, xylene, reflux, 3 h	Quantitative	–
Pyrrolidine, xylene, reflux, 3 h	62%	30%
i. Pyrrolidine, $CaCl_2$, toluene, 50 °C for 70 h; ii. reflux, 4 h	15%	80%

formation of **4a–d** was nucleophilic 1,2-addition of the carboxamide nitrogen on the enamino amide, followed by proton extraction of the spatially adjacent enamine, and subsequent departure of the 1-(prop-1-en-2-yl)pyrrolidine moiety (Pathway B).

The structure of compounds **4a–d** was confirmed by spectral and elemental analyses. The absorption bands at 3187–3132 cm^{-1}, 2210–2214 cm^{-1}, and 1732–1654 cm^{-1} in the IR spectra of **4a–d** indicated the presence of NH, C≡N, and two C=O groups, respectively. The ^{1}H NMR spectra of these compounds revealed the disappearance of the two CONH signals along with the CH_3COCH_2 protons of the parent **3a, c, e,** and **f**. Moreover, there is no trace of the NH_2 and CONH protons of the parent compounds **1** (that would otherwise have indicated the cleavage of the acetoacetyl group). On the other hand, the spectrum revealed the appearance of a new characteristic singlet signal at δ 12.15-12.34 ppm corresponding to pyrimidine NH proton.

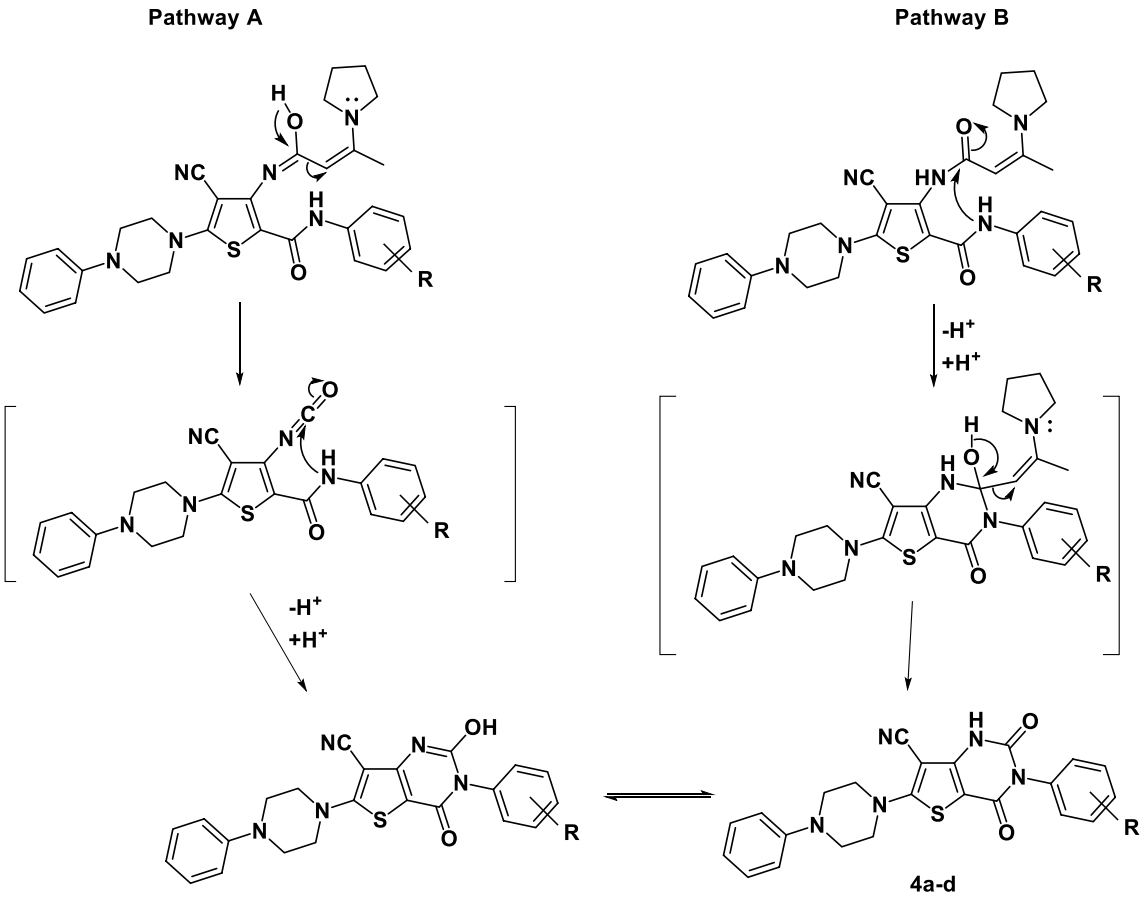
Another new method for the synthesis of thieno[3,4-*b*] pyridine was developed. Thus, heating a mixture of *β*-keto amide derivatives **3a, d**, **f** and **h** and K_2CO_3 in ethanol under reflux conditions afforded the target derivatives **5a**, **b**, **d**, and **e**.

Our initial goal, however, was to assess the applicability of base-promoted pyrimidine ring closure of ortho diamides in compounds **3** to achieve the synthesis of thienopyrimidine derivatives **5*** (Scheme 1). Therefore, a mixture of *β*-keto amide **3a** and NaOH was heated either in ethanol or in dioxane. However, this reaction condition resulted in quantitative hydrolysis of **3a** to its parent thiophene **1a**. Nevertheless, when K_2CO_3 was used, the thienopyridine derivative **5a** was obtained.

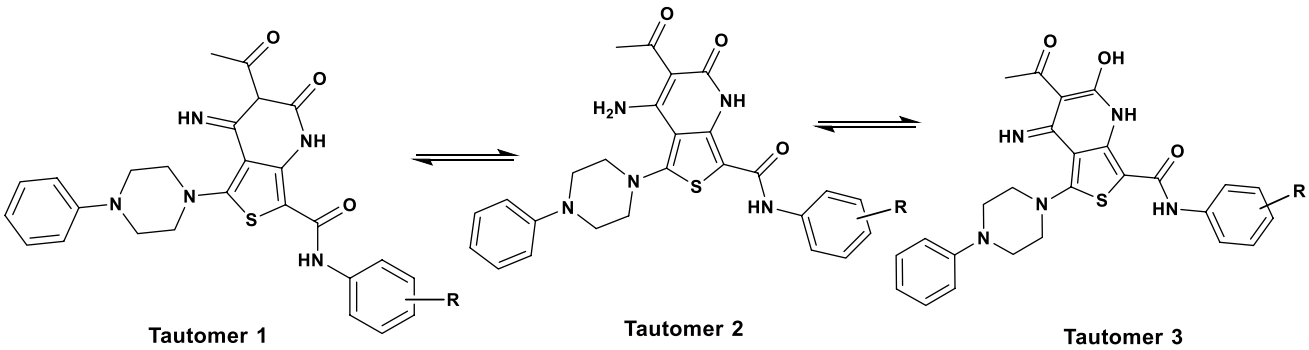
Following the same procedure, thienopyridines **5b, d,** and **e** were synthesized in 45-65% yield. However, the *β*-keto amide **3e** failed to cyclize to the respective thienopyridine under these reaction conditions. When ethanol was replaced by higher boiling point solvent such as ethylene glycol, thienopyridine **5c** was obtained in 60% yield.

The chemical structure of compounds **5a–e** was confirmed using IR, ^{1}H NMR, ^{13}C NMR, and elemental analyses. IR spectra of the compounds revealed the disappearance of the C≡N group of the parent *β*-keto amide derivatives **3a, d, e, f,** and **h.** This ruled out the formation of **5*.** Moreover, their ^{1}H NMR spectra showed four exchangeable proton signals between δ 8.17–11.32 ppm.

Three possible tautomers were suggested for compounds **5a-e** (Scheme 6). The existence of tautomer 1 was excluded due to absence of any aliphatic signal corresponding to 3-CH proton or carbon of pyridine in the NMR spectra. Tautomers 2 (the keto form) and 3 (the enol form) are possible tautomers; however, the ^{1}H NMR spectra of the compounds did not show a signal corresponding to the 2 protons of amino group



Scheme 5 Possible mechanism for the formation of compounds **4a-d**

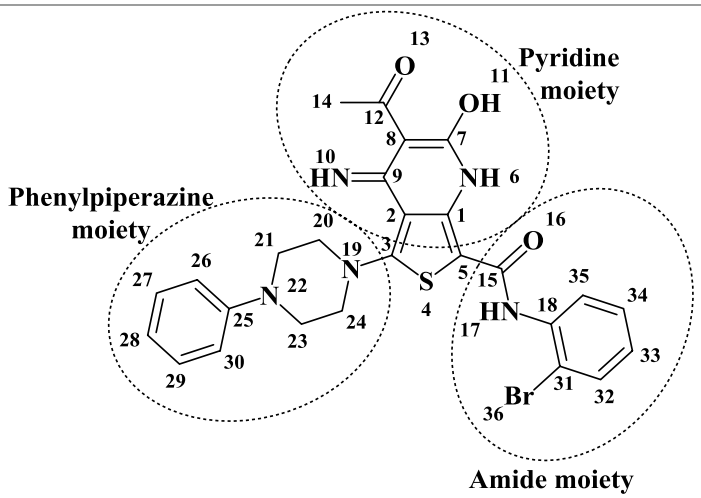


Scheme 6 Possible tautomeric forms of compounds **5a-e**

that are present in tautomer 2. On the other hand, ^{1}H NMR spectra distinctly revealed the existence of four exchangeable signals, each integrated for one proton. Therefore, we assumed that tautomer 3 (the enol form) is more appropriate. The stability of tautomer 3 might be attributed to the intramolecular H-bond between the enolic OH and the adjacent carbonyl.

Heteronuclear H–C 2D spectra were acquired for further confirmation of the proposed structure of thienopyridine **5e**. HSQC spectrum revealed that proton signals at δ 7.24, 7.42, 7.50, and 7.71 ppm showed H–C correlations with the carbon signals appearing at δ 128.2, 128.1, 129.2, and 132.7 ppm, respectively. These protons also showed HMBC correlations with the named carbon signals in addition to two more signals appearing at δ 121.1 and 135.8 ppm. These

Table 2 H-C HSQC and HMBC correlations of **5e**



^{1}H NMR	HSQC	HMBC	carbon number	^{1}H NMR	HSQC	HMBC	carbon number
$H_{2.52}$	$C_{32.7}$	$C_{98.0}$, $C_{199.8}$	14	$H_{7.26}$	$C_{129.0}$	$C_{115.8}$, $C_{129.0}$, $C_{150.4}$	30, 26
$H_{3.00}$	$C_{54.6}$	-	20, 24	$H_{7.42}$	$C_{128.1}$	$C_{132.7}$, $C_{135.8}$	33
$H_{3.15}$	$C_{47.9}$	-	20, 24	$H_{7.50}$	$C_{129.2}$	$C_{121.1}$, $C_{128.2}$	35
$H_{3.46}$	$C_{54.6}$	-	21, 23	$H_{7.71}$	$C_{132.7}$	$C_{121.1}$, $C_{128.1}$, $C_{135.8}$	32
$H_{3.73}$	$C_{47.9}$	-	21, 23	$H_{8.21}$	-	$C_{98.0}$, $C_{109.6}$	6
$H_{6.84}$	$C_{119.4}$	$C_{115.8}$, $C_{129.0}$, $C_{150.4}$	28	$H_{9.82}$	-	$C_{121.1}$, $C_{129.2}$, $C_{161.7}$	17
$H_{7.02}$	$C_{115.8}$	$C_{115.8}$, $C_{119.4}$, $C_{150.4}$	27, 29	$H_{9.96}$	-	$C_{98.0}$, $C_{109.6}$, $C_{199.8}$	10
$H_{7.24}$	$C_{128.2}$	$C_{121.1}$, $C_{135.8}$	34	$H_{10.77}$	-	$C_{98.0}$, $C_{109.6}$	11

observations allowed for assigning the carbon signals at δ 121.1, 135.8, 129.2, 128.2, 128.1, 132.7 ppm to C(31), C(18), C(35), C(34), C(33), and C(32), respectively. Moreover, the singlet proton signal at δ 9.82 ppm which showed no HSQC correlations, exhibited HMBC correlations with both carbon signal at δ 121.1, and 129.2 ppm that were assigned to C(31) and C(35), respectively. In addition, HMBC correlation of this proton with the carbon signal at δ 161.7 ppm, which could be assigned to C(15), allowed for assigning this proton signal to H(17) Table 2).

The newly formed pyridine moiety was also confirmed by the observed HSQC and HMBC correlation patterns: Aliphatic proton signal at δ 2.52 ppm showed an HSQC correlation with carbon signal at δ 32.7 ppm, in addition to an HMBC correlation with carbon signal at δ 199.8 ppm, which confirmed the presence of an acyl group. Moreover, this proton signal showed an additional HMBC correlation with the sp^2 carbon appearing at δ 98.0 ppm, which in turn, did not correlate with any proton in the HSQC spectrum, but showed three additional HMBC correlations with the exchangeable protons at δ 8.21, 9.96, and 10.77 ppm.

Conclusion

In summary, two series of thieno[3,2-*d*]pyrimidines and a series of thieno[3,4-*b*]pyridines were synthesized starting from 3-amino-4-cyano-2-thiophenecarboxamides. Two novel procedures were developed and optimized for the synthesis of thienopyrimidine-2,4-diones **4** and thieno[3,4-*b*] pyridine derivatives **5** using *β*-keto amides **3**. The thieno[3,4-*b*]pyridine ring is infrequently documented in the literature; therefore, the reaction conditions were optimized to provide an appropriate synthetic route and reaction conditions to this ring system.

Compliance with ethical standards

Conflict of interest No conflict of interest.

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