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New convenient synthesis of 2,3-diaminothieno[2,3-*d*]pyrimidin-4(3*H*)-one derivates from substituted alkyl 2-(1*H*-tetrazol-1-yl)thiophene-3-carboxylates

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Abstract

4,5-Disubstituted and 4-substituted alkyl 2-amino-thiophene-3-carboxylates react with triethyl orthoformate and sodium azide in acetic acid to yield new 2-(1*H*-tetrazol-1-yl)-4-R^1-5-R^2-thiophene derivates. It was established that the reaction of these tetrazoles with hydrazine generates the insufficiently studied 2,3-diaminothieno[2,3-*d*]pyrimidin-4(3*H*)-one system. It is significant that the reaction mentioned above is the unique tetrazole ring cleavage under the action of hydrazine.

Keywords: Tetrazole; Thiophene; Thieno[2,3-*d*]pyrimidin-4(3*H*)-one; Heterocyclization

1. Introduction

Tetrazole derivates are well known as compounds with a high level of biological activity.[1–8] The tetrazole ring is a bioisostere of the carboxylic acid group[9–12] and at the same time does not have acidic properties. It was also noticed that toxic properties of a drug can decrease through the introduction of a tetrazole ring into the molecule.[13] Tetrazole derivatives form stable complexes with metals.[14–16] Furthermore, they have been used as ligands for palladium-catalyzed reactions.[17,18]

For tetrazole ring construction the synthetic equivalents of synthons **I** (sodium azide, organic azides) and **II** (cyanides, isocyanides, isocyanates, isothiocyanates, and others) are used most frequently (Fig. 1).

They can be brought into the reaction as individual compounds or generated directly in a reaction medium. The strategies of the synthesis and properties of tetrazole derivates are reported in a recent review.[19]

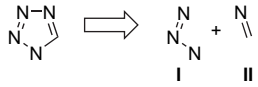

Figure 1.

Another method of a tetrazole ring synthesis is based on the reaction of amines with triethyl orthoformate and sodium azide.[18,20–22] However, only arylamines were studied. In contrast heterocyclic amines have been used only sparingly. For example, in a paper[20] pyridinamines were converted into tetrazolylpyridines.

In this paper we have investigated the possibility of the synthesis of tetrazoles from 4,5-disubstituted and 4-substituted alkyl 2-amino-thiophene-3-carboxylates, using the method mentioned above.

2. Results and discussion

We showed that alkyl 2-amino-thiophene-3-carboxylates **1a–h** actively react with triethyl orthoformate and sodium azide, forming an alkyl 2-(1*H*-tetrazol-1-yl)-4-R^1-5-R^2-thiophene-3-carboxylates **2a–h** in good yields (Scheme 1, Table 1).

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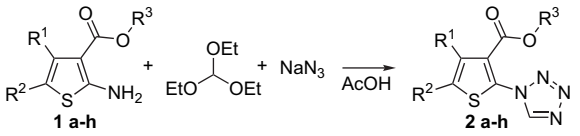
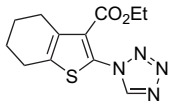
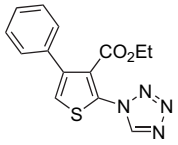
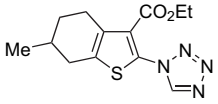
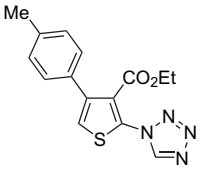
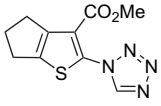
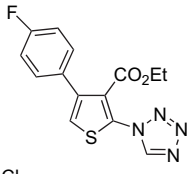
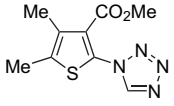
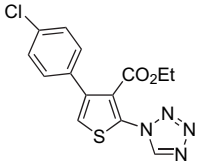


Scheme 1.

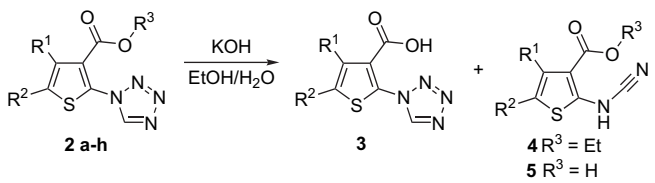
Table 1
Alkyl 2-(1*H*-tetrazol-1-yl)-4-R^1-5-R^2-thiophene-3-carboxylates **2a–h**

Product		Yield (%)	Product		Yield (%)
2a		81	**2e**		83
2b		84	**2f**		79
2c		72	**2g**		70
2d		91	**2h**		87

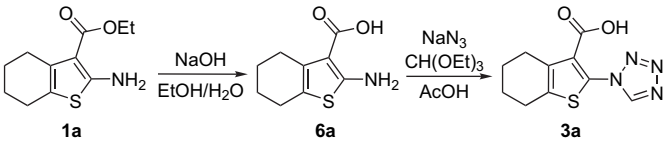
The products **2a–h** are white crystalline compounds. Their structure is confirmed by NMR spectroscopy.

We also studied some properties of the compounds **2a–h**. It was established that in 0.5 M sodium hydroxide solution and EtOH/H_2O (1:1.5) **2a**,**b**, are converted to the corresponding acids **3a**,**b** (Scheme 2). But in the case of compounds **2c–h** decomposition of the tetrazole ring takes place faster than the hydrolysis of the ester group. After 2 h hydrolysis, the mixture of products consisting of initial tetrazole **2** and cyanamide **4** was extracted from the reaction medium. More protracted reflux and introduction of another equivalent of base to the reaction did not drive the formation of individual products to completion. It is significant to note that at higher concentrations of alkali a mixture of products **3**, **4**, **5** was obtained in all cases.

We also tried to prepare acids **3** via another path. By the hydrolysis of ethyl 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate **1a**, amino acid **6** was synthesized and under the same conditions as in case of amino ethers, the tetrazole ring was formed (Scheme 3). That the yield of acid **3a** was 25% proves the advantage of the first path.

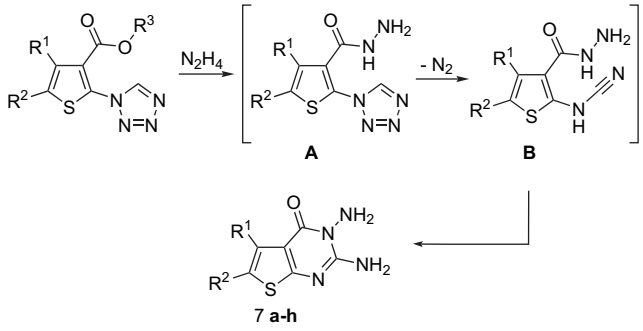


Scheme 2.



Scheme 3.

The experiment shown in Scheme 4 shows that the introduction of a tetrazole ring into the 2-position contributes to hydrazinolyzation of the ester group. Furthermore, under the conditions of the reaction, the tetrazole ring cleaves and loses a molecule of N_2. The ultimate product of the reaction is a thieno[2,3-*d*]pyrimidine, **7a–h** (Scheme 4).



Scheme 4.

It is well known that 2,3-substituted thiophenes often serve as reagents for thieno[2,3-*d*]pyrimidine.[23–26] We established that alkyl 2-(1*H*-tetrazol-1-yl)-4-R^1-5-R^2-thiophene-3-carboxylates can be used as reagents for constructing the thieno-[2,3-*d*]pyrimidine system. At the same time, the insufficiently studied 2,3-diaminothieno[2,3-*d*]pyrimidin-4(3*H*)-ones were prepared.[27] The ability of the tetrazole ring to cleave with the loss of nitrogen is used in this approach. Thus, the cyanamide group formed in intermediate **B** reacts with the hydrazide group, forming a pyrimidine ring. We have to point out that in the explored reaction, the tetrazole ring cleaves under mild conditions (hydrazine solution) unlike other known examples (e.g., NaOH in DMSO[22]).

The mechanism of the reaction (Scheme 4) is confirmed by NMR spectroscopy. In the ^{1}H NMR spectrum of samples selected 10 min after the beginning of reflux, the signal of a cyanamide group proton is visible at 8.11–8.29 ppm and NH_2 of hydrazide at 5.70–5.80 ppm. It is clear that cleavage of the tetrazole ring as well as hydrazinolyzation occurs concurrently and rapidly, while cyclization proceeds during a few hours.

3. Conclusion

For the first time, the hitherto rare 2,3-diaminopyrimidines were easily prepared by the transformation of neighboring ester group and tetrazole ring.

4. Experimental

4.1. General

^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a Varian Mercury 400 instrument (400 MHz for ^{1}H, 125 MHz for ^{13}C). The ^{1}H and ^{13}C chemical shifts are reported in parts per million relative to tetramethylsilane or the deuterated solvent as an internal reference. Mass spectra were run using Agilent 1100 series LC/MSD with an API-ES/APCI ionization mode.

4.2. General procedure for the synthesis of alkyl 2-(1H-tetrazol-1-yl)thiophene-3-carboxylates **2a–h**

A suspension of 50 mmol of the required thiophene **1**, triethyl orthoformate (37.9 mL, 0.23 mol), and sodium azide (3.9 g, 0.06 mol) in glacial acetic acid (40 mL) was stirred and heated at reflux for 2 h. The reaction mixture was cooled to room temperature and 7 mL of concd HCl was added. The solid was filtered off and the filtrate evaporated and the residue was recrystallized from ethanol.

4.2.1. Ethyl 2-(1H-tetrazol-1-yl)-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate **2a**

Yield: 81% as white solid; mp: 88 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.05 (3H, t, J 7.2 Hz, CH_3), 1.86 (4H, m, CH_2), 2.83 (4H, m, CH_2), 4.06 (2H, q, J 7.2 Hz, CH_3CH_2), 9.70 (1H, s, tetrazole); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0, 22.2, 22.6, 24.9, 26.0, 61.2, 127.7, 133.4, 135.5, 137.8, 146.6, 161.1; IR (KBr): 3480, 3408, 3360, 3288, 3248, 3185, 2990, 2920, 1725, 1565, 1460, 1420, 1390, 1320, 1260, 1225, 1180, 1142, 1090, 1020, 960, 880 cm^{-1}; MS (*m*/*z*): 278 (M^+). Anal. Calcd for $C_{12}H_{14}N_4O_2S$: C 51.78, H 5.07, N 20.13; found: C 51.54, H 5.14, N 20.06.

4.2.2. Ethyl 6-methyl-2-(1H-tetrazol-1-yl)-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate **2b**

Yield: 84% as white solid; mp: 86 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.05 (3H, t, J 7.6 Hz, CH_3CH_2), 1.11 (3H, d, J 6.8 Hz, CH_3), 1.38–1.49 (1H, m, cyclohexane), 1.90–2.02 (2H, m, cyclohexane), 2.39–2.45 (1H, m, cyclohexane), 2.68–2.78 (1H, m, cyclohexane), 2.89–3.03 (2H, m, cyclohexane), 4.07 (2H, q, J 7.6 Hz, CH_3CH_2), 9.68 (1H, s, tetrazole); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0, 21.4, 25.7, 28.9, 30.3, 32.7, 61.2, 127.5, 133.5, 135.2, 137.4, 146.6, 161.1; IR (KBr): 3472, 3408, 3360, 3288, 3248, 3176, 2990, 2928, 1716, 1568, 1464, 1420, 1392, 1320, 1256, 1236, 1184, 1144, 1096, 1024, 1016, 956, 780 cm^{-1}; MS (*m*/*z*): 292 (M^+). Anal. Calcd for $C_{13}H_{16}N_4O_2S$: C 53.41, H 5.52, N 19.16; found: C 53.55, H 5.44, N 19.02.

4.2.3. Methyl 2-(1H-tetrazol-1-yl)-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carboxylate **2c**

Yield: 72% as white solid; mp: 183 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.42–2.49 (2H, m, CH_2), 2.97–3.05 (4H, m, CH_2), 3.69 (3H, s, CH_3), 9.70 (1H, s, tetrazole); ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.4, 29.5, 32.9, 52.1, 127.4, 132.2, 133.4, 135.3, 146.4, 162.0; IR (KBr): 3480, 3408, 3360, 3288, 3248, 3185, 2990, 2920, 1720, 1565, 1460, 1420, 1390, 1320, 1256, 1225, 1188, 1142, 1090, 1020, 956, 880 cm^{-1}; MS (*m*/*z*): 250 (M^+). Anal. Calcd for $C_{10}H_{10}N_4O_2S$: C 47.99, H 4.03, N 22.39; found: C 47.75, H 3.96, N 22.46.

4.2.4. Methyl 4,5-dimethyl-2-(1H-tetrazol-1-yl)-3-thiophenecarboxylate **2d**

Yield: 91% as white solid; mp: 86–87 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.32 (3H, s, CH_3), 2.45 (3H, s, CH_3), 3.62 (3H, s, CH_3O), 9.70 (1H, s, tetrazole); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.3, 13.8, 52.5, 128.4, 132.2, 133.5, 135.0, 146.3, 162.0; IR (KBr): 3488, 3360, 3280, 3248, 3176, 2992, 1720, 1564, 1472, 1416, 1288, 1256, 1192, 1168, 1088, 1024, 880, 780 cm^{-1}; MS (*m*/*z*): 238 (M^+). Anal. Calcd for $C_9H_{10}N_4O_2S$: C 45.37, H 4.23, N 23.51; found: C 45.33, H 4.30, N 23.37.

4.2.5. Ethyl 4-phenyl-2-(1H-tetrazol-1-yl)-3-thiophenecarboxylate **2e**

Yield: 83% as white solid; mp: 107 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.86 (3H, t, J 6.8 Hz, CH_3), 3.99 (2H, q, J 6.8 Hz, OCH_2), 7.34–7.51 (5H, m, Ph), 7.85 (1H, s, thiophene), 9.96 (1H, s, tetrazole); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.7, 61.7, 111.8, 115.1, 126.5, 127.5, 129.3, 132.2, 136.7, 141.1, 146.7, 161.6; IR (KBr): 3480, 3408, 3340, 3260, 3185, 2600, 1704, 1672, 1552, 1512, 1488, 1440, 1416, 1288, 1264, 1188, 1080, 1024, 1008, 864, 832, 792, 760 cm^{-1}; MS (*m*/*z*): 300 (M^+). Anal. Calcd for $C_{14}H_{12}N_4O_2S$: C 55.99, H 4.03, N 18.65; found: C 55.63, H 4.01, N 18.72.

4.2.6. Ethyl 4-(4-methylphenyl)-2-(1H-tetrazol-1-yl)-3-thiophenecarboxylate **2f**

Yield: 79% as white solid; mp: 111 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.94 (3H, t, J 6.8 Hz, CH_3CH_2), 2.39 (3H, s, CH_3), 4.02 (2H, q, J 6.8 Hz, OCH_2), 7.20 (2H, d, J 8.0 Hz, C_6H_4), 7.25 (2H, d, J 8.0 Hz, C_6H_4), 7.66 (1H, s, thiophene), 9.80 (1H, s, tetrazole); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.8, 21.2, 61.7, 125.0, 126.1, 128.7, 128.9, 129.4, 132.3, 137.9, 141.5, 146.3, 161.8; IR (KBr): 3648, 3408, 3120, 2992, 2640, 1720, 1552, 1520, 1480, 1448, 1416, 1288, 1260, 1224, 1192, 1088, 1024, 824, 768, 656 cm^{-1}; MS (*m*/*z*): 314 (M^+). Anal. Calcd for $C_{15}H_{14}N_4O_2S$: C 57.31, H 4.49, N 17.82; found: C 57.19, H 4.31, N 17.77.

4.2.7. Ethyl 4-(4-fluorophenyl)-2-(1H-tetrazol-1-yl)-3-thiophenecarboxylate **2g**

Yield: 70% as white solid; mp: 84 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.91 (3H, t, J 7.8 Hz, CH_3), 4.01 (2H, q, J 7.8 Hz, OCH_2), 7.09 (2H, d, J 7.8 Hz, C_6H_4), 7.15 (2H, d, J 8.0 Hz, C_6H_4), 7.72 (1H, s, thiophene), 9.78 (1H, s, tetrazole); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.7, 61,7, 115.5, 115.7, 125.7, 128.6, 131.1, 131.8, 136.3, 140.5, 146.4, 162.5 (d, J_{CF} 241.2 Hz, 4-C C_6H_4); IR (KBr): 3128, 2936, 1712, 1520, 1296, 1256, 1216, 840, 784 cm^{-1}; MS (*m*/*z*): 318 (M^+). Anal. Calcd for $C_{14}H_{11}FN_4O_2S$: C 52.82, H 3.48, N 17.60; found: C 52.87, H 3.57, N 17.55.

*4.2.8. Ethyl 4-(4-chlorophenyl)-2-(1H-tetrazol-1-yl)-3-thiophenecarboxylate **2h***

Yield: 87% as white solid; mp: 131–132 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.94 (3H, t, J 6.8 Hz, CH_3), 4.02 (2H, q, J 6.8 Hz, OCH_2), 7.38 (2H, d, J 8.8 Hz, C_6H_4), 7.42 (2H, d, J 8.8 Hz, C_6H_4), 7.75 (1H, s, thiophene), 9.79 (1H, s, tetrazole); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.7, 61.7, 126.1, 128.4, 128.7, 130.8, 133.3, 134.2, 136.5, 140.3, 146.4, 161.4; IR (KBr): 3464, 3264, 3056, 1684, 1640, 1536, 1504, 1312, 1252, 1216, 1168, 1020, 968, 936, 880, 848, 766, 720, 672, 592, 544 cm^{-1}; MS (*m*/*z*): 335 (M^+). Anal. Calcd for $C_{14}H_{11}ClN_4O_2S$: C 50.23, H 3.31, N 16.74; found: C 50.05, H 3.23, N 16.59.

*4.3. Preparations of 2-(1H-tetrazol-1-yl)-3-thiophenecarboxylic acids **3a** and **3b***

Compound **2a** (0.01 mol) was added to a solution of 0.56 g (0.01 mol) potassium hydroxide in 50 mL ethanol/H_2O (1:1.5) and heated at reflux for 3 h. Then, the reaction mixture was poured into 15 mL of concd HCl. The solid formed was filtered off and recrystallized from ethanol.

*4.3.1. 2-(1H-Tetrazol-1-yl)-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylic acid **3a***

Yield: 71% as white solid; mp: 178 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.74–1.80 (2H, m, CH_2), 1.80–1.88 (2H, m, CH_2), 2.59–2.65 (2H, m, CH_2), 2.75–2.80 (2H, m, CH_2), 10.76 (1H, s, tetrazole), 11.62 (1H, s, COOH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.8, 25.4, 29.5, 32.8, 113.1, 124.7, 130.0, 153.7, 158.1, 164.4; IR (KBr): 3552, 3098, 3010, 2940, 2842, 2312, 1688, 1664, 1576, 1512, 1436, 1368, 1280, 1200, 1088, 984, 880, 792, 656 cm^{-1}; MS (*m*/*z*): 250 (M^+). Anal. Calcd for $C_{10}H_{10}N_4O_2S$: C 47.99, H 4.03, N 22.39; found: C 48.02, H 3.96, N 22.31.

*4.3.2. 6-Methyl-2-(1H-tetrazol-1-yl)-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylic acid **3b***

Yield: 64% as white solid; mp: 185 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.11 (3H, d, J 5.9 Hz, CH_3), 1.38–1.49 (1H, m, cyclohexane), 1.92–2.06 (2H, m, cyclohexane), 2.39–2.45 (1H, m, cyclohexane), 2.70–2.77 (1H, m, cyclohexane), 2.89–3.06 (2H, m, cyclohexane), 10.32 (1H, s, tetrazole); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.0, 26.7, 31.1, 33.3, 34.7, 123.5, 130.5, 135.2, 153.4, 158.4, 164.1; IR (KBr): 3552, 3098, 3020, 2940, 2842, 2300, 1676, 1664, 1576, 1512, 1440, 1368, 1280, 1200, 1096, 1024, 984, 880, 780 cm^{-1}; MS (*m*/*z*): 264 (M^+). Anal. Calcd for $C_{11}H_{12}N_4O_2S$: C 49.99, H 4.58, N 21.20; found: C 50.00, H 4.49, N 21.28.

*4.4. General procedure for the synthesis of 2,3-diamino-5-R^1-6-R^2-thieno[2,3-d]pyrimidin-4(3H)-ones **7a–h***

A suspension of the appropriate alkyl 2-(1*H*-tetrazol-1-yl)-thiophene-3-carboxylates **2a–h** (0.01 mol) in 15 mL hydrazine hydrate was heated at reflux for 7 h, then cooled and diluted with 50 mL water. The solid was filtered and recrystallized from ethanol.

*4.4.1. 2,3-Diamino-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-4(3H)-one **7a***

Yield: 74% as white solid; mp: 281 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.76–1.89 (4H, m, CH_2), 2.62 (2H, t, J 5.9 Hz, CH_2), 2.83 (2H, t, J 5.9 Hz, CH_2), 5.25 (2H, s, CNH_2), 6.86 (2H, s, NNH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.4, 23.8, 24.8, 25.9, 113.2, 125.1, 130.4, 153.6, 158.1, 164.3; IR (KBr): 3472, 3320, 3200, 2928, 2856, 1660, 1632, 1596, 1504, 1456, 1352, 1304, 1248, 1176, 944, 872, 768, 476 cm^{-1}; MS (*m*/*z*): 236 (M^+). Anal. Calcd for $C_{10}H_{12}N_4OS$: C 50.83, H 5.12, N 23.71, S 13.57; found: C 50.92, H 5.06, N 23.85, S 13.69.

*4.4.2. 2,3-Diamino-7-methyl-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-4(3H)-one **7b***

Yield: 79% as white solid; mp: 320 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.09 (3H, d, J 5.9 Hz, CH_3), 1.32–1.44 (1H, m, cyclohexane), 1.82–1.96 (2H, m, cyclohexane), 2.22–2.28 (1H, m, cyclohexane), 2.61–2.69 (2H, m, cyclohexane), 2.97–3.06 (1H, m, cyclohexane), 5.24 (2H, s, CNH_2), 6.86 (2H, s, NNH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.8, 25.4, 29.5, 30.7, 32.8, 113.1, 124.7, 130.0, 153.7, 158.1, 164.4; IR (KBr): 3472, 3296, 3192, 2944, 2864, 1676, 1632, 1608, 1504, 1456, 1352, 1304, 1248, 1176, 1020, 944, 848, 768, 490 cm^{-1}; MS (*m*/*z*): 250 (M^+). Anal. Calcd for $C_{11}H_{14}N_4OS$: C 52.78, H 5.64, N 22.38, S 12.81; found: C 52.44, H 5.59, N 22.34, S 12.90.

*4.4.3. 2,3-Diamino-3,5,6,7-tetrahydro-4H-cyclopenta[4,5]thieno[2,3-d]pyrimidin-4-one **7c***

Yield: 75% as white solid; mp: 313 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.30–2.40 (2H, m, CH_2), 2.80 (2H, t, J 6.8 Hz, CH_2), 2.86 (2H, t, J 6.8 Hz, CH_2), 5.27 (2H, s, CNH_2), 6.86 (2H, s, NNH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.4, 29.5, 32.9, 113.2, 124.9, 130.1, 153.4, 158.1, 164.3; IR (KBr): 3472, 3320, 3200, 2944, 2864, 1676, 1632, 1510, 1504, 1456, 1352, 1304, 1248, 1176, 944, 768 cm^{-1}; MS (*m*/*z*): 222 (M^+). Anal. Calcd for $C_9H_{10}N_4OS$: C 48.63, H 4.53, N 25.21, S 14.43; found: 48.80, H 4.46, N 25.13, S 14.36.

*4.4.4. 2,3-Diamino-5,6-dimethylthieno[2,3-d]pyrimidin-4(3H)-one **7d***

Yield: 85% as white solid; mp: 285 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.26 (3H, s, CH_3), 2.34 (3H, s, CH_3), 5.24 (2H, s, CNH_2), 6.83 (2H, s, NNH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.7, 13.2, 114.2, 122.0, 128.1, 153.8, 158.4, 163.7; IR (KBr): 3472, 3304, 3240, 3152, 2950, 2864, 1680, 1616, 1512, 1460, 1368, 1336, 1252, 1196, 1020, 936, 864, 768 cm^{-1}; MS (*m*/*z*): 210 (M^+). Anal. Calcd for $C_8H_{10}N_4OS$: C 45.70, H 4.79, N 26.65, S 15.25; found: C 45.73, H 4.71, N 26.50, S 15.37.

4.4.5. 2,3-Diamino-5-phenylthieno[2,3-d]pyrimidin-4(3H)-one ***7e***

Yield: 73% as white solid; mp: 227 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.23 (2H, s, CNH_2), 6.79 (1H, s, thiophene), 7.27–7.37 (3H, m, Ph), 7.49 (2H, d, J 6.8 Hz, Ph); ^{13}C NMR (125 MHz, $CDCl_3$): δ 111.8, 115.1, 127.5, 127.9, 129.5, 136.2, 138.7, 154.1, 157.7, 167.0; IR (KBr): 3490, 3390, 3296, 3264, 3010, 2860, 1680, 1636, 1548, 1488, 1332, 1304, 1176, 1096, 960, 872, 760, 576, 486 cm^{-1}; MS (*m*/*z*): 258 (M^+). Anal. Calcd for $C_{12}H_{10}N_4OS$: C 55.80, H 3.90, N 21.69, S 12.41; found: C 55.66, H 4.01, N 21.72, S 12.29.

4.4.6. 2,3-Diamino-5-(4-methylphenyl)thieno[2,3-d]pyrimidin-4(3H)-one ***7f***

Yield: 77% as white solid; mp: 252 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.35 (3H, s, CH_3), 5.29 (2H, br s, CNH_2), 6.67 (1H, s, thiophene), 7.03 (2H, br s, NNH_2), 7.11 (2H, d, J 7.2 Hz, C_6H_4), 7.37 (2H, d, J 7.2 Hz, C_6H_4); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.3, 111.9, 114.3, 128.4, 129.2, 133.7, 137.2, 139.0, 154.4, 158.8, 167.8; IR (KBr): 3496, 3392, 3368, 3272, 3104, 3048, 2888, 1680, 1636, 1616, 1552, 1496, 1320, 1296, 1248, 1184, 956, 880, 486 cm^{-1}; MS (*m*/*z*): 272 (M^+). Anal. Calcd for $C_{13}H_{12}N_4OS$: C 57.34, H 4.44, N 20.57, S 11.77; found: C 57.56, H 4.31, N 20.64, S 11.71.

4.4.7. 2,3-Diamino-5-(4-fluorophenyl)thieno[2,3-d]pyrimidin-4(3H)-one ***7g***

Yield: 69% as white solid; mp: 246 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.28 (2H, s, CNH_2), 6.73 (1H, s, thiophene), 7.02–7.11 (4H, m, NNH_2+C_6H_4), 7.51 (2H, dd, J 5.9, 8.8 Hz, C_6H_4); ^{13}C NMR (125 MHz, $CDCl_3$): δ 111.6, 114.7, 131.4, 131.5, 132.6, 137.4, 154.1, 157.9, 162.0 (d, J_{CF} 242.5 Hz, 4-C C_6H_4), 167.3; IR (KBr): 3460, 3160, 3080, 3000, 1712, 1552, 1504, 1472, 1416, 1296, 1256, 1192, 944, 880, 796 cm^{-1}; MS (*m*/*z*): 276 (M^+). Anal. Calcd for $C_{12}H_9FN_4OS$: C 52.17, H 3.28, N 20.28, S 11.61; found: C 52.08, H 3.22, N 20.41, S 11.68.

4.4.8. 2,3-Diamino-5-(4-chlorophenyl)thieno[2,3-d]pyrimidin-4(3H)-one ***7h***

Yield: 88% as white solid; mp: 270 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.29 (2H, br s, CNH_2), 6.77 (1H, s, thiophene), 7.07 (2H, br s, NNH_2), 7.33 (2H, d, J 7.6 Hz, C_6H_4), 7.50 (2H, d, J 7.6 Hz, C_6H_4); ^{13}C NMR (125 MHz, $CDCl_3$): δ 111.5, 115.0, 127.8, 131.2, 132.3, 135.0, 137.1, 154.1, 157.9, 167.4; IR (KBr): 3416, 3380, 3096, 1672, 1628, 1536, 1496, 1312, 1248, 1216, 1088, 1008, 940, 876, 768, 536, 496 cm^{-1}; MS (*m*/*z*): 293 (M^+). Anal. Calcd for $C_{12}H_9ClN_4OS$: C 49.23, H 3.10, N 19.14, S 10.95; found: C 49.02, H 3.22, N 19.20, S 11.04.

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