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An efficient multicomponent reaction for synthesis of 4-amino-6-aryl-2-alkylthiopyrimidine-5-carbonitrile derivatives

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Abstracts An efficient and facile synthesis of thiosubstituted pyrimidine derivatives (4-amino-6-aryl-2-alkylthiopyrimidine-5-carbonitrile derivatives) by one-pot multicomponent reaction of aromatic aldehydes, malononitrile, and *S*-methylisothiouronium sulfate (or *S*-benzylisothiourea hydrochloride) in ethanolic NaOH is reported. Because of the simple work-up procedure, low cost, and, especially, high product yields, this method is a useful and attractive procedure for synthesis of these thiosubstituted pyrimidine compounds.

Keywords Multicomponent reactions · 4-Amino-6-aryl-2-alkylthilpyrimidine · Heterocyclic compound · Synthesis

Introduction

The pyrimidine nucleus is found in many biologically active natural products and has substantial therapeutic potential [1]. Because of the wide range of biological activity of synthetic pyrimidine-based structures, for example anti-allergic [2], antitumor [3], anti-inflammatory [4], and antiparasitic [5], a several of these compounds have attracted much attention. 5-(4-Fluorophenyl)-2-(2-methanesulfinylbenzylsulfanyl)-4-pyridin-4-yl-pyrimidine, a thiosubstituted pyrimidine derivative (Fig. 1), is the most effective inhibitor of release of tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) from peripheral blood mononuclear cells [6]. Although several methods have been developed for preparation of the pyrimidine

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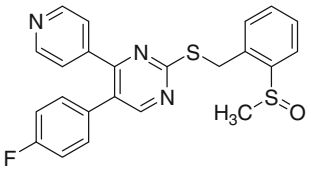


Fig. 1 The inhibitor of release of tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β)

ring [7–12], general and highly selective preparations of the alkylthiol-substituted pyrimidine skeleton have rarely been studied.

Multicomponent reactions (MCRs) have become extremely important synthetic methods because they are efficient and powerful means of construction of organic compounds by one-pot reaction without isolation of intermediates or modification the reaction conditions [13–16]. Herein, we report an efficient process for synthesis of 2-alkylthiol-substituted pyrimidine derivatives by means of a multicomponent reaction.

Results and discussion

First, we wanted to find an efficient method for this synthesis. Reaction of 4-chlorobenzaldehyde, malononitrile, and *S*-methylisolthiouronium sulfate as starting materials, catalyzed by Na_2CO_3, was chosen as the model reaction, and was investigated under different solvent conditions (Table 1). The results showed that when nonpolar solvents, for example toluene, CH_3CN, and CH_2Cl_2, were used reaction did not occur. We also found the reaction was unsuccessful under solvent–free conditions. However, when polar solvents (95 % EtOH and THF) were used, the reaction could be performed smoothly with good yields. Taking into account the toxicity and cost of the solvents, we chose ethanol (95 %) as the preferred solvent for the reaction.

Although the reaction was catalyzed by Na_2CO_3, we wished to discover whether the other catalysts also promoted the reaction, so different catalysts were screened in ethanol (95 %) under reflux conditions. We found that acid catalysts (HCl, H_2SO_4) had no effect on this reaction. In contrast, alkaline catalysts, whether organic or

Table 1 Solvent optimization for synthesis of **4c**

Entry	Solvent	Time (h)	Yield[a] (%)
1	Toluene	6	0
2	CH_3CN	6	0
3	CH_2Cl_2	6	0
4	EtOH	6	56
5	THF	6	45
6	None	6	0

Reagents and conditions: 4-chlorobenzaldehyde (2 mmol), *S*-methylisothiouronium sulfate (2 mmol), malononitrile (3 mmol), Na_2CO_3 (1 mmol), and solvent (10 mL), reflux

[a] Isolated yields

Table 2 Effect of catalyst and temperature on the model reaction

Entry	Catalyst (mmol)	Temperature (°C)	Time (h)	Yield[a] (%)
1	None	60	8	0
2	HCl (1)	60	8	0
3	H_2SO_4 (1)	60	8	0
4	Piperidine (1)	60	6	34
5	Et_3N (1)	60	6	37
6	NaOH (1)	60	6	80
7	NaOH (1)	70	2	81
8	NaOH (1)	80	2	89
9	NaOH (1)	80	4	88
10	NaOH (1)	90	2	87

Reagents and conditions: 4-chlorobenzaldehyde (2 mmol), *S*-methylisothiouronium sulfate (2 mmol), and malononitrile (3 mmol), 95 % ethanol (10 mL)

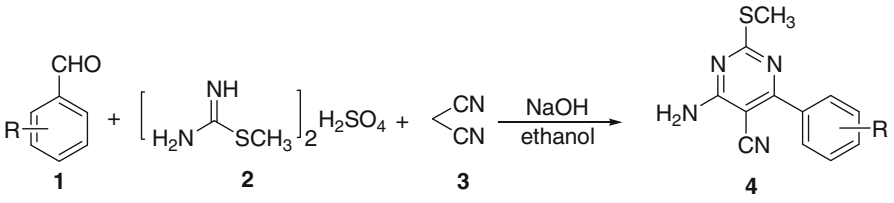
[a] Isolated yields

inorganic alkalis, all promote the reaction with different yields. Study of the results obtained from the reaction revealed that inorganic alkali catalysts were more efficient than organic alkalis. Further research revealed sodium hydroxide was the best catalyst for this synthesis. The results obtained are summarized in Table 2.

Using these optimized conditions, different aromatic aldehydes were reacted with malononitrile, and *S*-methylisothiouronium sulfate and a series of 4-amino-6-aryl-2-methylthiopyrimidine-5-carbonitrile derivatives were obtained with high yields (Scheme 1). The results, summarized in Table 3, revealed that highly sterically hindered aromatic aldehydes, for example 3,4,5-trimethoxybenzaldehyde and 1-naphthaldehyde, reacted well with malononitrile and *S*-methylisothiouronium to give corresponding products.

To extend the range of this synthesis, *S*-benzylisothiouronium chloride was reacted with aromatic aldehydes and malononitrile under the same conditions (Scheme 2). To our delight, we found the reaction proceeded smoothly and different products, 4-amino-6-aryl-2-benzylthiopyrimidine-5-carbonitrile derivatives, were obtained with excellent yields. The results are summarized in Table 4.

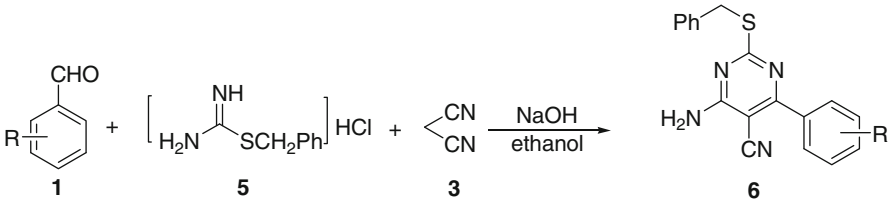
The structures of all the products were confirmed on the basis of spectroscopic data, particularly nuclear magnetic resonance (^{1}H NMR) spectroscopy and high-



Scheme 1 Synthesis of 4-amino-6-aryl-2-(methylthio)pyrimidine-5-carbonitrile derivatives

Table 3 Results from synthesis of compounds **4**

Entry	Ar	Product	Yield[a] (%)
1	C_6H_5	**4a**	88
2	4-ClC_6H_4	**4b**	89
3	4-$CH_3C_6H_4$	**4c**	81
4	2-$CH_3OC_6H_4$	**4d**	80
5	3,4-$(CH_3)_2C_6H_3$	**4e**	82
6	2,5-$(CH_3O)_2C_6H_3$	**4f**	80
7	3,4-$(CH_3O)_2C_6H_3$	**4g**	82
8	3,4-$OCH_2OC_6H_3$	**4h**	88
9	3,4,5-$(CH_3O)_3C_6H_2$	**4i**	83
10	1-naphthalenyl	**4j**	84



Scheme 2 Synthesis of 4-amino-6-aryl-2-(benzylthio)pyrimidine-5-carbonitrile derivatives

Table 4 Results from synthesis of compounds **6**

Entry	Ar	Product	Yield[a] (%)
1	C_6H_5	**6a**	85
2	4-FC_6H_4	**6b**	86
3	4-BrC_6H_4	**6c**	84
4	3,4-$Cl_2C_6H_3$	**6d**	83
5	3,4-$(CH_3O)_2C_6H_3$	**6e**	88
6	3,4-$OCH_2OC_6H_3$	**6f**	89

resolution mass spectroscopy (HRMS). We take **4c** and **6f** as examples to analyze their structures. The ^{1}H NMR spectrum of **4c** contained singlet signals at $\delta = 2.43$ (3H) and 2.58 (3H) ppm from CH_3 and SCH_3 protons. Doublet signals at $\delta = 7.42$ (1H, $J = 8.0$ Hz) and 7.92 (1H, $J = 8.4$ Hz) and a triplet signal at $\delta = 7.33$ (2H, $J = 8.4$ Hz) were ascribed to four phenyl protons. A singlet signal at $\delta = 5.70$ (2H) should be the amino protons. In the infrared (IR) spectrum, amino peaks were observed at 3,480 and 3,346 cm^{-1} and a nitrile peak at 2,212 cm^{-1}. In the HRMS spectrum, the calculated m/z ($C_{13}H_{12}N_4S$ $[M + Na]^+$) of **4c** is 279.0680 and the found m/z is 279.0661.

The ^{1}H NMR spectrum of **6e** contained singlet signals at $\delta = 3.78$ (3H), 3.82 (3H), and 4.54 (2H) ppm from $2 \times OCH_3$ and $PhCH_2$ protons. Singlet signals at $\delta = 7.11$ (2H) and 7.18 (1H) ppm, triplet signals at $\delta = 7.26$ (1H, $J = 7.2$ Hz) and

7.33 (2H, $J = 6.8$), and a doublet at $\delta = 7.52$ (2H, $J = 6.8$ Hz) were attributed to eight phenyl protons. A singlet signal at $\delta = 8.10$ (2H) was attributed to amino protons. In the IR spectrum, the amino peaks appear at 3,474 and 3,330 cm^{-1} and the nitrile peak at 2,216 cm^{-1}. In the HRMS spectrum, the calculated *m/z* ($C_{20}H_{18}N_4O_2S$ $[M + H]^+$) of **6e** is 379.1229 and the found *m/z* is 379.1284.

Conclusions

We report a facile and efficient one-pot reaction for synthesis of 4-amino-6-aryl-2-alkylthiopyrimidine-5-carbonitrile derivatives from aromatic aldehydes, malononitrile, and methyl carbamimidothioate sulfate or *S*-benzylisothiourea hydrochloride. Because of the simple work-up procedure, low cost, and, especially, high product yield, this method is a useful and attractive procedure for synthesis of these thiosubstituted pyrimidine compounds.

Experimental

Melting points were determined on an XT-5 microscopic melting-point apparatus and were uncorrected. IR spectra were recorded on an FT IR-8101 spectrometer. ^1H NMR spectra were obtained from solution in DMSO-d_6, with Me_4Si as internal standard, using a Bruker-400 spectrometer. HRMS spectra were obtained with a Bruker micrOTOF-Q 134 instrument.

General procedure for synthesis of 4-amino-6-aryl-2-alkylthiopyrimidine-5-carbonitrile derivatives

A mixture of aromatic aldehyde **1** (2 mmol), methyl carbamimidothioate sulfate (or *S*-benzylisothiourea hydrochloride) **2** (2 mmol), malononitrile **3** (3 mmol), sodium hydroxide (1 mmol), and ethanol (10 mL) was reacted under reflux conditions for approximately 2 h. When the reaction was complete, the reaction mixture was poured into water, then washed thoroughly with water. The product was isolated by filtration, dried, and recrystallized from 95 % ethanol.

*4-Amino-2-methylthio-6-phenylpyrimidine-5-carbonitrile (**4a**)*

m.p. >280 °C; IR (KBr) *v*: 3460, 3324, 3218, 1625, 1533, 1526, 1428, 1300, 1269, 1238, 1045, 756, 707 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 2.59 (3H, s, SCH_3), 7.54 (2H, t, $J = 4.0$ Hz, ArH), 7.57 (3H, t, $J = 3.6$ Hz, ArH), 8.07 (2H, s, NH_2). HRMS *m/z* calculated for $C_{12}H_{10}N_4S$ $[M + Na]^+$: 265.0524, found: 265.0533.

*4-Amino-6-(4-chlorophenyl)-2-(methylthio)pyrimidine-5-carbonitrile (**4b**)*

m.p. 228–230 °C; IR (KBr) *v*: 3469, 3329, 3214, 2930, 2812, 2225, 2210, 1620, 1525, 1477, 1385, 1350, 1300, 1235, 1158, 1124, 1033, 993, 965, 860, 761, 703,

667 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 2.61 (3H, s, SCH_3), 7.54 (2H, d, $J = 4.4$ Hz, ArH), 7.58–7.62 (1H, m, ArH), 7.70 (1H, d, $J = 7.6$ Hz, ArH), 8.19 (2H, s, NH_2). HRMS *m/z* calculated for $C_{12}H_9ClN_4S$ $[M]^+$: 276.0236, found: 276.0263.

*4-Amino-2-methylthio-6-p-tolylpyrimidine-5-carbonitrile (**4c**)*

m.p. 195–196 °C; IR (KBr) *v*: 3480, 3346, 2927, 2212, 1624, 1542, 1513, 1329, 1300, 1239, 1190, 1153, 1040, 994, 864, 811, 774 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 2.43 (3H, s, CH_3), 2.58 (3H, s, SCH_3), 5.70 (2H, s, NH_2), 7.33 (2H, t, $J = 8.4$ Hz, ArH), 7.42 (1H, d, $J = 8.0$ Hz, ArH), 7.92 (1H, d, $J = 8.4$ Hz, ArH). HRMS *m/z* calculated for $C_{13}H_{12}N_4S$ $[M + Na]^+$: 279.0680, found: 279.0661.

*4-Amino-6-(2-methoxyphenyl)-2-(methylthio)pyrimidine-5-carbonitrile (**4d**)*

m.p. 269–270 °C; IR (KBr) *v*: 3450, 3343, 2812, 2214, 1632, 1545, 1496, 1384, 1349, 1249, 1118, 1014, 824, 756 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 2.58 (3H, s, SCH_3), 3.80 (3H, s, OCH_3), 7.11 (1H, t, $J = 7.6$ Hz, ArH), 7.21 (1H, d, $J = 8.4$ Hz, ArH), 7.32 (1H, d, $J = 7.6$ Hz, ArH), 7.53 (1H, t, $J = 8.0$ Hz, ArH), 8.00 (2H, s, NH_2). HRMS *m/z* calculated for $C_{13}H_{12}N_4OS$ $[M + H]^+$: 273.0810, found: 273.0896.

*4-Amino-6-(3,4-dimethylphenyl)-2-(methylthio)pyrimidine-5-carbonitrile (**4e**)*

m.p. 223–225 °C; IR (KBr) *v*: 3324, 3217, 2225, 2210, 1637, 1542, 1527, 1428, 1306, 1264, 1241, 670 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 2.29 (3H, s, CH_3), 2.30 (3H, s, CH_3), 2.58 (3H, s, SCH_3), 7.23 (1H, d, $J = 7.6$ Hz, ArH), 7.31 (2H, t, $J = 5.6$ Hz, ArH), 7.95 (2H, s, NH_2). HRMS *m/z* calculated for $C_{14}H_{14}N_4S$ $[M + H]^+$: 271.1017, found: 271.1055.

*4-Amino-6-(2,5-dimethoxyphenyl)-2-(methylthio)pyrimidine-5-carbonitrile (**4f**)*

m.p. >280 °C; IR (KBr) *v*: 3447, 3343, 3220, 2932, 2837, 2213, 1638, 1625, 1541, 1491, 1221, 1157, 1049, 1015, 846, 809, 731, 669 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 2.59 (3H, s, SCH_3), 3.75 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 6.94 (1H, dd, $J = 2.8$ Hz, $J = 14.8$ Hz, ArH), 7.09 (1H, dd, $J = 2.8$ Hz, $J = 8.8$ Hz, ArH), 7.16 (1H, d, $J = 9.2$ Hz, ArH), 7.95 (2H, s, NH_2). HRMS *m/z* calculated for $C_{14}H_{14}N_4O_2S$ $[M]^+$: 302.0837, found: 302.0840.

*4-Amino-6-(3,4-dimethoxyphenyl)-2-(methylthio)pyrimidine-5-carbonitrile (**4g**)*

m.p. >280 °C; IR (KBr) *v*: 3421, 3329, 3234, 2933, 2835, 2212, 1639, 1547, 1500, 1466, 1428, 1260, 1224, 1141, 1024, 855, 814, 782, 756, 669 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 2.58 (3H, s, SCH_3), 3.80 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 7.10–7.15 (2H, m, ArH), 7.18 (1H, s, ArH), 7.95 (2H, s, NH_2). HRMS *m/z* calculated for $C_{14}H_{14}N_4O_2S$ $[M]^+$: 302.0837, found: 302.0823.

*4-Amino-6-(benzo[d][1,3]dioxol-5-yl)-2-(methylthio)pyrimidine-5-carbonitrile (**4h**)*

m.p. >280 °C; IR (KBr) *v*: 3461, 3219, 2850, 2220, 1633, 1593, 1540, 1506, 1417, 1386, 1350, 1248, 669 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 2.57 (3H, s, SCH_3), 6.15 (2H, s, CH_2), 7.03 (1H, d, $J = 8.0$ Hz, ArH), 7.10 (1H, d, $J = 8.0$ Hz, ArH), 7.16 (1H, s, ArH), 8.02 (2H, s, NH_2). HRMS *m/z* calculated for $C_{13}H_{10}N_4O_2S$ $[M + H]^+$: 287.0603, found: 287.0629.

*4-Amino-2-methylthio-6-(3,4,5-trimethoxyphenyl)pyrimidine-5-carbonitrile (**4i**)*

m.p. >280 °C; IR (KBr) *v*: 3480, 3337, 3223, 2960, 2842, 2219, 1638, 1544, 1509, 1473, 1417, 1253, 1131, 1005, 840, 778, 669 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 2.59 (3H, s, SCH_3), 3.75 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 6.90 (2H, s, ArH), 8.30 (2H, s, NH_2). HRMS *m/z* calculated for $C_{15}H_{16}N_4O_3S$ $[M - H]^+$: 331.0865, found: 331.0870.

*4-Amino-2-methylthio-6-(naphthalen-1-yl)pyrimidine-5-carbonitrile (**4j**)*

m.p. 237–239 °C; IR (KBr) *v*: 3458, 3329, 3213, 3054, 2929, 2215, 1621, 1551, 1525, 1455, 1385, 1258, 1239, 1059, 1026, 958, 809, 723, 621 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 2.65 (3H, s, SCH_3), 7.59 (3H, t, $J = 5.6$ Hz, ArH), 7.62 (1H, s, ArH), 7.68 (1H, t, $J = 7.6$ Hz, ArH), 8.07 (1H, d, $J = 8.0$ Hz, ArH), 8.13 (1H, d, $J = 8.0$ Hz, ArH). HRMS *m/z* calculated for $C_{16}H_{12}N_4S$ $[M + Na]^+$: 315.0602, found: 315.0626.

*4-Amino-2-benzylthio-6-phenylpyrimidine-5-carbonitrile (**6a**)*

m.p. 192–193 °C; IR (KBr) *v*: 3441, 3329, 3217, 2220, 1644, 1633, 1539, 1495, 1455, 1263, 669 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 4.52 (2H, s, SCH_2), 7.26 (1H, t, $J = 7.6$ Hz, ArH), 7.33 (2H, t, $J = 7.6$ Hz, ArH), 7.52-7.56 (7H, m, ArH), 8.29 (2H, s, NH_2). HRMS *m/z* calculated for $C_{18}H_{14}N_4S$ $[M + H]^+$: 319.1017, found: 319.1022.

*4-Amino-2-benzylthio-6-(4-fluorophenyl)pyrimidine-5-carbonitrile (**6b**)*

m.p. 191–193 °C; IR (KBr) *v*: 3469, 3329, 3214, 2930, 2812, 2225, 2210, 1620, 1525, 1477, 1385, 1350, 1300, 1235, 1158, 1124, 1033, 993, 965, 860, 761, 703, 667 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 4.04 (2H, s, SCH_2), 7.25(1H, t, $J = 7.6$ Hz, ArH), 7.31(2H, t, $J = 7.2$ Hz, ArH), 7.40 (2H, t, $J = 7.6$ Hz, ArH), 7.45(2H, d, $J = 7.6$ Hz, ArH), 7.92 (2H, t, $J = 7.2$ Hz, ArH), 8.22 (2H, s, NH_2). HRMS *m/z* calculated for $C_{18}H_{13}FN_4S$ $[M + H]^+$: 337.0923, found: 337.0940.

*4-Amino-2-benzylthio-6-(4-bromophenyl)pyrimidine-5-carbonitrile (**6c**)*

m.p. 195–196 °C; IR (KBr) *v*: 3459. 3120, 2210, 1641, 1590, 1573, 1538, 1493, 1397, 1312, 1243, 1067, 995, 839, 792, 768, 701 cm^{-1}; ^1H NMR (400 MHz,

DMSO-d_6) δ: 4.40 (2H, s, SCH_2), 7.24 (1H, t, $J = 7.2$ Hz, ArH), 7.31 (2H, t, $J = 7.6$ Hz, ArH), 7.44 (2H, d, $J = 7.2$ Hz, ArH), 7.72 (4H, dd, $J = 8.8$ Hz, $J = 12.0$ Hz, ArH), 8.27 (2H, s, NH_2). HRMS *m/z* calculated for $C_{18}H_{13}BrN_4S$ [M]: 396.0044, found: 396.0082.

*4-Amino-2-benzylthio-6-(3,4-dichlorophenyl)pyrimidine-5-carbonitrile (**6d**)*

m.p. 197–199 °C; IR (KBr) *v*: 3458, 3345, 3231, 2213, 1640, 1523, 1475, 1396, 1308, 1245, 1150, 1031, 892, 788, 711, 696 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 4.39 (2H, s, SCH_2), 7.25 (2H, t, $J = 7.6$ Hz, ArH), 7.32 (3H, t, $J = 7.2$ Hz, ArH), 7.45 (2H, t, $J = 7.2$ Hz, ArH), 8.03 (1H, s, ArH), 8.52 (2H, s, NH_2). HRMS *m/z* calculated for $C_{18}H_{12}Cl_2N_4S$ $[M + H]^+$: 387.0238, found: 387.0246.

*4-Amino-2-benzylthio-6-(3,4-dimethoxyphenyl)pyrimidine-5-carbonitrile (**6e**)*

m.p. 194–196 °C; IR (KBr) *v*: 3474, 3330, 3211, 2216, 1616, 1595, 1545, 1454, 1420, 1261, 1227, 1141, 1017, 818, 778, 720 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 3.78 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 4.51 (2H, s, SCH_2), 7.11 (2H, s, ArH), 7.18 (1H, s, ArH), 7.26 (1H, t, $J = 7.2$ Hz, ArH), 7.33 (2H, t, $J = 7.6$ Hz, ArH), 7.52 (2H, d, $J = 6.8$ Hz, ArH), 8.10 (2H, s, NH_2). HRMS *m/z* calculated for $C_{20}H_{18}N_4O_2S$ $[M + H]^+$: 379.1229, found: 379.1284.

*4-Amino-6-(benzo[d][1,3]dioxol-5-yl)-2-(benzylthio)pyrimidine-5-carbonitrile (**6f**)*

m.p. 214–215 °C; IR (KBr) *v*: 3476, 3331, 2906, 2218, 1618, 1549, 1487, 1443, 1349, 1249, 1033, 920, 776, 720, 677 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 4.50 (2H, s, SCH_2), 6.14 (2H, s, CH_2), 7.02 (1H, d, $J = 8.0$ Hz, ArH), 7.09 (1H, d, $J = 8.0$ Hz, ArH), 7.16 (1H, s, ArH), 7.25 (1H, t, $J = 7.2$ Hz, ArH), 7.32 (2H, t, $J = 7.6$ Hz, ArH), 7.52 (2H, d, $J = 7.2$ Hz, ArH), 7.95 (2H, s, NH_2). HRMS *m/z* calculated for $C_{19}H_{14}N_4O_2S$ $[M + H]^+$: 363.0916, found: 363.0920.

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