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FULL-LENGTH PAPER

An efficient three-component, one-pot synthesis of 2-alkylthio-4-amino-5-cyano-6-aryl(alkyl)pyrimidines in water

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Abstract A convenient and practical method for the synthesis of 2-alkylthio-4-amino-5-cyano-6-aryl(alkyl)pyrimidines has been developed via a three-component, one-pot reaction from aldehydes, malononitrile and *S*-alkylisothiouronium salts in water at room temperature. A series of polysubstituted pyrimidines were prepared by this method in moderate to excellent yields. In addition, two kinds of pyrimidine-fused heterocyclic derivatives with potential pharmacological activity were constructed from our 2-alkylthio-4-amino-5-cyano-6-arylpyrimidines.

Keywords Pyrimidines · Multicomponent reaction (MCR) · Pyrimidine-fused · Environmentally friendly

Introduction

Pyrimidine is an important heterocyclic scaffold that has attracted considerable attention in medicinal chemistry. Many pyrimidines and pyrimidine-fused heterocyclic derivatives have shown diverse biological activities, such as adenosine kinase inhibitors[1], selective dihydrofolate reductase (from *Mycobacterium tuberculosis* and *Plasmodium falciparum*) inhibitors[2–4], SecA inhibitors [5], VEGF-R2 inhibitors [6], SARS-CoV 3CL protease inhibitors [7], HIV-1 reverse transcriptase inhibitors [8], adenosine receptor and growth hormone secretagogue receptor antagonists [9,10], and antimicrobial activity [11–13]. In addition to their pharmacological activities, some of them also exhibit interesting fluorescent properties [14].

Polyfunctional-substituted pyrimidines (PFSPs) play an important role in the preparation of substituted pyrimidine and pyrimidine-fused heterocyclic derivatives through the transformation of functional substituents on the pyrimidine scaffold. Therefore, many methods have been developed for the synthesis of PFSPs, and various substituted pyrimidine and pyrimidine-fused heterocyclic derivatives have been prepared from these PFSPs [3–13,15].

2-Alkylthio-4-amino-5-cyano-6-aryl(alkyl) pyrimidines represent one kind of the important PFSPs, and their pyrimidine and pyrimidine-fused heterocyclic derivatives were found to have special pharmacological activities. For example, derivatives of **A** exhibit topoisomerase II inhibitory activity against filarial parasite *Setaria Cervi* [16], compounds **B** show DPP-IV inhibitory activity against type 2 diabetes [17,18], and compounds **C** display adenosine A2a receptor agonistic activity for treating glaucoma [19]. The pyrimidine-fused heterocyclic compounds **D** and **E** are PDK1 inhibitors and TLR modulators, respectively (Fig. 1) [20–22]. To the best of our knowledge, there are mainly two methods for the synthesis of 2-alkylthio-4-amino-5-cyano-6-aryl(alkyl)pyrimidines [23–29], as shown in Scheme 1. Both require at least 2–3 synthetic steps using organic solvents under heating, which requires a tedious work-up, there is a limitation in reactant/substrates, and the method offers unsatisfactory yields. To alleviate all these drawbacks, a more efficient PFSPs synthesis is highly desirable.

Multicomponent one-pot reaction represents an attractive alternative for the formation of multiple bonds in a single reaction giving access to complex molecules without the

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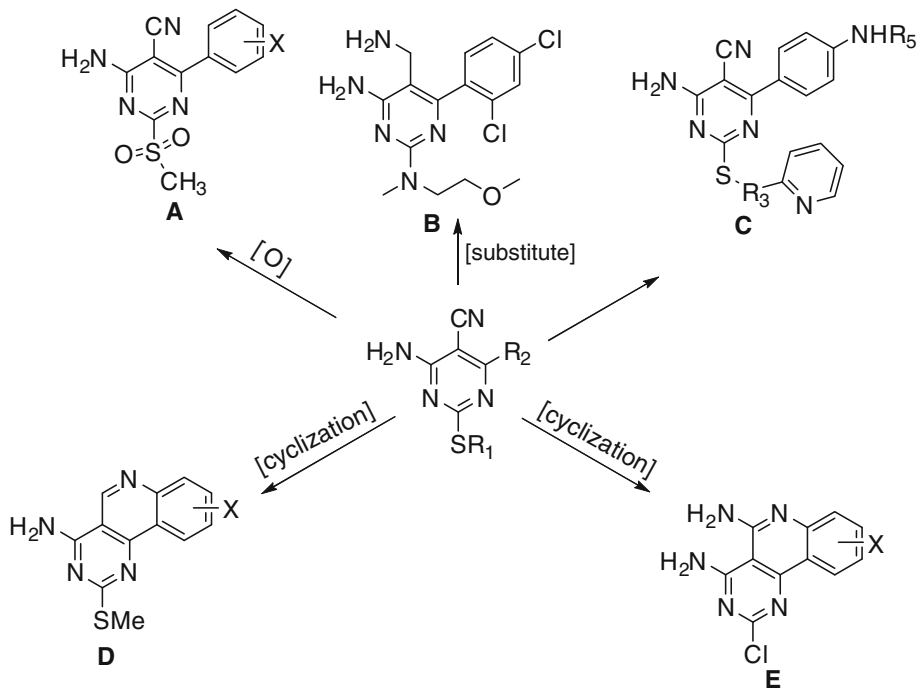
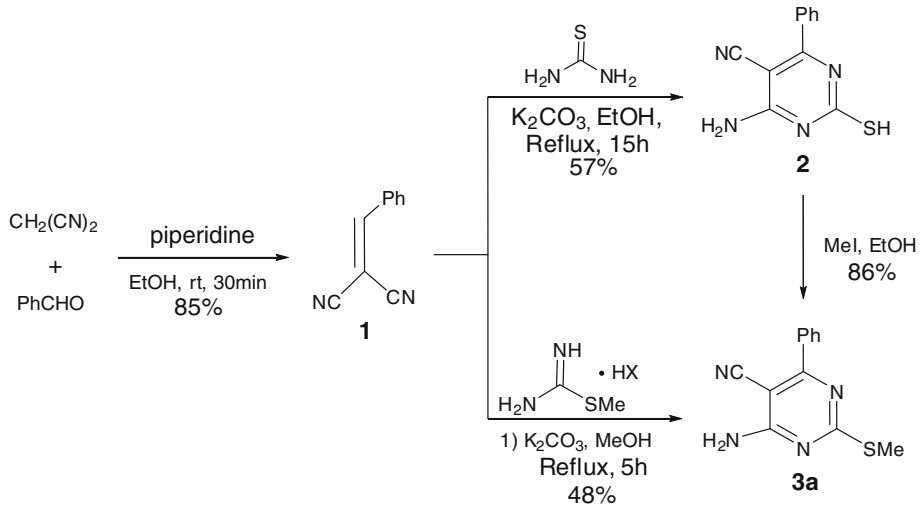


Fig. 1 Pharmacologically active 2-alkylthio-4-amino-5-cyano-6-aryl(alkyl)-pyrimidine derivatives



Scheme 1 Reported synthesis of 2-alkylthio-4-amino-5-cyano-6-aryl(alkyl)-pyrimidines

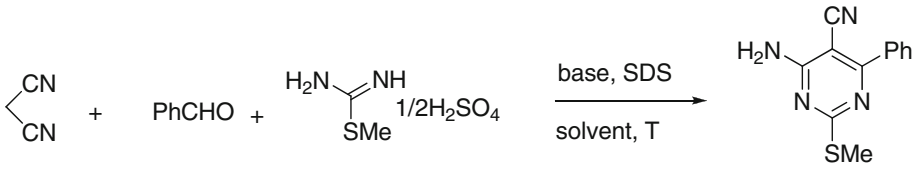
need of isolation or purification of reaction intermediates [30,31]. In our continuing efforts to develop multicomponent one-pot synthesis of various heterocycles [32–34], we here report an efficient synthesis of 2-alkylthio-4-amino-5-cyano-6-aryl(alkyl)pyrimidine derivatives from the one-pot three-component condensation of aldehydes, malononitrile, and *S*-alkylisothiouronium salts in water.

Results and discussion

In our previous study, we developed an efficient synthesis of highly substituted pyridines via a three-component, one-pot reaction of aldehydes, malononitrile, and *S*-alkylisothiouronium salts in water [32,33]. Interestingly, we also obtained minor amounts of 2-alkylthio-4-amino-5-cyano-6-aryl(alkyl)pyrimidine as a byproduct in the above reaction. This discovery prompted us to explore the possibility of developing this side reaction into a more optimized method to synthesize 2-alkylthio-4-amino-5-cyano-6-aryl (alkyl)pyrimidines.

We first studied the model reaction of benzaldehyde, malonoitrile, and *S*-methylisothiourea sulfate to optimize the reaction conditions and the results are listed in Table 1. Referring to the reaction conditions in our previous study [32–34], when equal amounts of each reactant were reacted in water at room temperature using sodium dodecyl sulfate (SDS) as the additive, we found that a strong base (e.g., NaOH) was unfa-

Table 1 One-pot synthesis of 2-alkylthio-4-amino-5-cyano-6-aryl(alkyl)-pyrimidines: optimization of reaction conditions



Entry	Base (equiv)	Solvent	Aldehyde (equiv)	SDS (equiv)	T(°C)	Yield (%)
1	NaOH (3)	H_2O	1.0	0.01	rt	30
2	Et_3N (3)	H_2O	1.0	0.01	rt	50
3	Piperidine (3)	H_2O	1.0	0.01	rt	40
4	K_3PO_4 (3)	H_2O	1.0	0.01	rt	33
5	K_2CO_3 (3)	H_2O	1.0	0.01	rt	32
6	Et_3N (4)	H_2O	1.0	0.01	rt	55
7	Et_3N (4)	H_2O	1.0	0	rt	65
8	Et_3N (5)	H_2O	1.0	0	rt	45
9	Et_3N (4)	DMF	1.0	0	rt	–
10	Et_3N (4)	DMF/H_2O	1.0	0	rt	60
11	Et_3N (4)	EtOH	1.0	0	rt	62
12	Et_3N (4)	MeOH	1.0	0	rt	63
13	Et_3N (4)	H_2O	1.0	0	60	45
14	Et_3N (4)	H_2O	1.0	0	90	42
15	Et_3N (4)	H_2O	1.1	0	rt	70
16	Et_3N (4)	H_2O	1.2	0	rt	61

vorable for the reaction (entry 1), organic amines (entries 2 and 3) worked better than weak inorganic bases (entries 4 and 5), and that using triethylamine as the base gave the best yield (entry 2, 50 % yield). The presence of SDS was not necessary in this reaction (entries 2 and 6). The stoichiometry of Et_3N was essential and 4 equivalents of Et_3N gave the best yield (entries 2, 7, 8). Increasing the reaction temperature decreased the yield significantly, which may be due to the decomposition of the intermediates at higher temperature (entries 13 and 14). Using organic solvents in the reaction did not increase yields (entries 9–12), due to poor solubility of the *S*-alkylisothiouronium salts. Fortunately, it was found that when the amount of aldehyde was increased slightly from 1 to 1.1 equivalent better yields were achieved (entries 14–17).

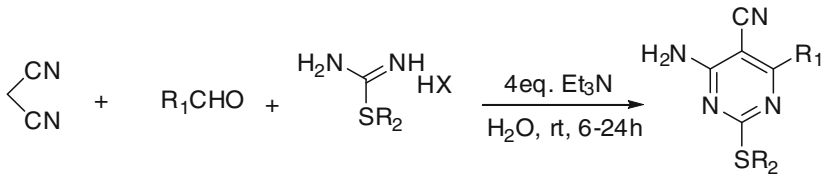
Having optimized the reaction conditions for the model system (Table 1, entry 15), we then proceeded to explore the scope and limitations of this three-component, one-pot reaction (Table 2). We first examined the influence of different aromatic heterocyclic aldehydes, with malononitrile and *S*-methylisothiouronium sulfate to give the corresponding 2-methylthio-4-amino-5-cyano-6-aryl(alkyl)pyrimidines in moderate to good yields (entries 1–17). The electronic property and position of the substituents on the aldehydes had an impact on the reaction. In general, substitution at 3- or 4-position with electron withdrawing groups was more favorable for the reaction than that at 3- or 4-position with electron donating groups, and substitution at 2-position was unfavorable for the reaction (entries 8, 10). Using acetaldehyde as an example of an aliphatic aldehyde was also examined, which afforded the desired product **3r** in 35 % yield (entry 18).

The scope of this method was further investigated through the reaction of pyridine-3-carboxaldehyde and malononitrile with various *S*-alkylisothiouronium salts under the same reaction conditions(entries 19–23). The results showed that all reactions proceeded smoothly to afford the 2-alkylthio-4-amino-5- cyano-6-(3-pyridinyl)pyrimidines in 54–74 % yield.

It is worth pointing out that due to the mild reaction conditions, this reaction can tolerate a wide range of functional groups, including nitro, amino, cyano, hydoxyl, methoxy, halide, and alkene. This advantage makes our method a very powerful tool for the synthesis of PFSPs, which could be transformed into structurally diverse substituted pyrimidines and pyrimidine-fused heterocyclic derivatives. Furthermore, this procedure does not require the separation and purification of intermediates and uses water as the reaction medium, which is environmentally friendly.

To demonstrate the application of 2-alkylthio-4-amino-5-cyano-6-(3-pyridinyl)pyrimidines in the synthesis of pyrimidine derivatives, we have successfully constructed two

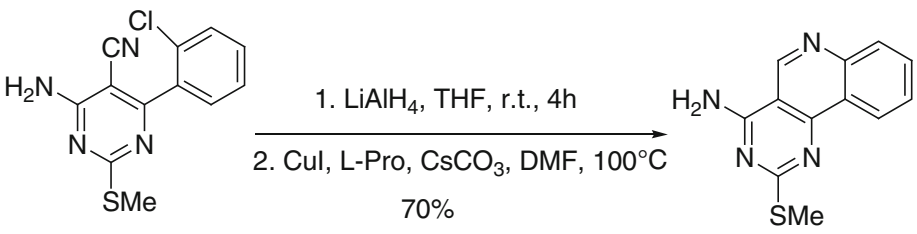
Table 2 One-pot synthesis of 2-alkylthio-4-amino-5-cyano-6-aryl(alkyl)-pyrimidines



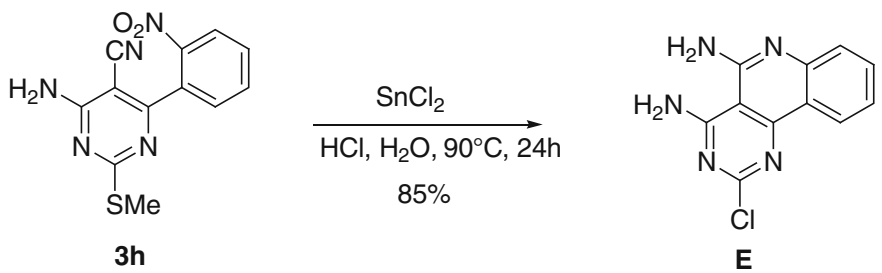
3a-3w

Entry	R_1	R_2	Time (h)	Product	Yield (%)
1	Ph	Me	24	**3a**	70
2	4-F–Ph	Me	24	**3b**	75
3	4-Cl–Ph	Me	24	**3c**	67
4	4-Br–Ph	Me	24	**3d**	82
5	4-CF_3–Ph	Me	24	**3e**	69
6	4-CN–Ph	Me	24	**3f**	74
7	4-OCH_3–Ph	Me	24	**3g**	40
8	2-NO_2–Ph	Me	24	**3h**	40
9	3-NO_2–Ph	Me	24	**3i**	93
10	2-Cl–Ph	Me	24	**3j**	54
11	3-Cl–Ph	Me	24	**3k**	65
12	2,4-Cl–Ph	Me	24	**3l**	89
13	3-OH–Ph	Me	24	**3m**	60
14	3-OCH_3–Ph	Me	24	**3n**	60
15	3-F–Ph	Me	24	**3o**	77
16	3-Pyridine	Me	6	**3p**	82
17	4-Pyridine	Me	6	**3q**	81
18	CH_3	Me	24	**3r**	35
19	3-Pyridine	Et	24	**3s**	63
20	3-Pyridine	$PhCH_2$	24	**3t**	58
21	3-Pyridine	Cyclopentyl	24	**3u**	56
22	3-Pyridine	*n*-Bu	24	**3v**	74
23	3-Pyridine	Allyl	24	**3w**	54

Scheme 2 Synthesis of potential PDK1 inhibitors **D** and **E**



3j **D**



3h **E**

important pyrimidine-fused heterocycles (**D**, **E**) from **3j** and **3h** via reduction and ring closure reactions in 70 % and 85 % yield, respectively (Scheme 2). Both the compounds and their derivatives are potential inhibitors of PDK1 [20–22].

Conclusion

In summary, we have developed a convenient and practical method for the synthesis of 2-alkylthio-4-amino-5-cyano-6-aryl(alkyl) pyrimidines via a three-component, one-pot reaction of aldehyde with malononitrile and *S*-alkylisothiouronium salt in water at room temperature. The environmentally friendly reaction condition and a broad substrate scope will make this method widely applicable in the synthesis of structurally diverse pyrimidines and pyrimidine-fused heterocyclic derivatives.

Experimental

General experimental

Melting point data were recorded on an X-4 micromelting point instrument and uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance III 400 NMR spectrometer in $CDCl_3$ or DMSO-d_6 (^{1}H at 400 MHz and ^{13}C at 101 MHz) using tetramethylsilane (TMS) as internal standard. HRMS were recorded on Bruker Apex IV FTMS. IR were recorded using NEXUS-470 FTIR (Nicolet). Column chromatography was performed on silica gel (zcx.II; 200–300 mesh). All reagents were purchased from commercial suppliers and used without further purification. Tetrahydrofuran was dried over sodium.

General procedure for the synthesis of **3a**–**3w**

Malononitrile (1 mmol) and *S*-alkylisothiouronium salt (2 mmol) were dissolved in 20 mL water and then the aldehyde (1.1 mmol) and Et_3N (4 mmol) were added. The mixture was stirred at room temperature for 6–24 h. The endpoint of the reaction was monitored by TLC. The resulting mixture was extracted with ethyl acetate (1 × 10 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification of the resulting residue by column chromatography (petroleum ether/EtOAc, 8:1–6:1, v/v) afforded the desired products **3a**–**3o** and **3r**–**3w**. To get the products **3p** and **3q**, at the end of the reaction the resulting mixture were filtered, and the precipitates were dried and recrystallized (EtOAc/MeOH, 1:1, v/v). In cases where the reactant aldehyde is solid, a minor amount of ethyl acetate was used to first dissolve it before its addition.

*4-Amino-5-cyano-2-methylthio-6-phenylpyrimidine (**3a**)*

Obtained in 70 % yield; white needle crystal; mp 200–202 °C (MeOH); FT-IR (KBr) ν3364, 3180, 2216, 1652, 1534 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07–7.44 (m, 5H), 5.69 (s, 2H), 2.58 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6)δ 174.33, 167.71, 163.75, 136.51, 131.48, 128.98, 128.94, 116.79, 82.84, 13.96; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{12}H_{11}N_4S$: 243.06989; found: 243.06955.

*4-Amino-5-cyano-2-methylthio-6-(4-fluorophenyl)-pyrimidine (**3b**)*

Obtained in 75 % yield; white needle crsytal; mp 197–200 °C (EtOAc/petrol); FT-IR (KBr) ν 3372, 3179, 2213, 1650, 1541cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (dd, J = 8.6, 5.4 Hz, 2H), 7.20 (t, J = 8.6 Hz, 2H), 5.66 (s, 2H), 2.57 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6)δ 174.33, 166.52, 165.39, 163.70, 162.88, 132.94, 131.58, 116.77, 116.01, 82.71, 13.96; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{12}H_{10}FN_4S$: 261.06047; found: 261.06020.

*4-Amino-5-cyano-2-methylthio-6-(4-chlorophenyl)-pyrimidine (**3c**)*

Obtained in 67 % yield; white needle crystal; mp 216–217 °C (EtOH/petrol); FT-IR (KBr) ν 3388, 3211, 2217, 1661, 1528 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.52 (d, J = 8.6 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 5.72(s, 2H), 2.59 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6)δ 174.42, 166.46, 163.66, 136.39, 135.25, 130.85, 129.06, 116.63, 82.84, 13.97; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{12}H_{10}ClN_4S$: 277.03092; found: 277.03064.

*4-Amino-5-cyano-2-methylthio-6-(4-bromophenyl)-pyrimidine (**3d**)*

Obtained in 82 % yield; yellow needle crystal; mp 228–230 °C (EtOAc/petrol); FT-IR (KBr) ν 3372, 3179, 2214, 1650, 1534 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.89 (d, J = 8.6 Hz, 2H), 7.65 (d, J = 8.5 Hz, 2H), 5.63 (s, 2H), 2.57 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6)δ 174.45, 166.50, 163.67, 135.59, 131.97, 131.00, 125.26, 116.65, 82.79, 14.01; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{12}H_{10}BrN_4S$: 320.98041; found: 320.98056.

*4-Amino-5-cyano-2-methylthio-6-(4-trifluoromethyl-phenyl)-pyrimidine (**3e**)*

Obtained in 69 % yield; white needle crystal; mp 234–235 °C (EtOAc/petrol); FT-IR (KBr) ν 3375, 3184, 2216, 1650, 1535 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$)δ 8.09 (d, J = 8.1 Hz, 1H), 7.78 (d, J = 8.2 Hz, 1H), 5.69 (s, 1H),

2.58 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6)δ 174.60, 166.48, 163.54, 140.37, 131.47, 129.89, 125.85, 123.00, 116.39, 83.40, 13.97; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{10}F_3N_4S$: 311.05728; found: 311.05719.

*4-Amino-5-cyano-2-methylthio-6-(4-cyanophenyl)-pyrimidine (***3f***)*

Obtained in 74 % yield; red needle crystal; mp 258–261 °C (EtOAc/petrol); FT-IR (KBr) ν 3434, 3343, 2213, 1649, 1522 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$)δ 8.09 (d, J = 8.0 Hz, 2H), 7.81 (d, J = 8.0 Hz, 2H), 5.68 (s, 2H), 2.57 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6)δ 166.23, 163.48, 140.73, 132.92, 129.88, 116.30, 113.81, 14.00; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{10}N_5S$: 268.06514; found: 268.06462.

*4-Amino-5-cyano-2-methylthio-6-(4-methoxyphenyl)-pyrimidine (***3g***)*

Obtained in 40 % yield; white crystal; mp 205–207 °C (EtOAc/petrol); FT-IR (KBr) ν 3453, 3334, 2217, 1625, 1557 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6)δ 8.19–7.53 (m, 4H), 7.10 (d, J = 8.9 Hz, 2H), 3.85 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.06, 166.77, 163.91, 162.09, 130.82, 128.59, 117.19, 114.36, 81.79, 55.91, 13.94; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{13}N_4S$: 273.08046; found: 273.08009.

*4-Amino-5-cyano-2-methylthio-6-(2-nitrophenyl)-pyrimidine (***3h***)*

Obtained in 40 % yield; yellow crystal; mp 210–213 °C (EtOAc/petrol); FT-IR (KBr) ν 3439, 3165, 2216, 1643, 1523 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$)δ 8.11 (d, J = 8.1 Hz, 1H), 7.75 (t, J = 7.5 Hz, 1H), 7.68 (t, J = 7.2 Hz, 1H), 7.63 (d, J = 7.5 Hz, 1H), 5.64 (s, 2H), 2.48 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.48, 166.87, 162.78, 148.32, 134.22, 132.02, 131.56, 131.43, 125.26, 115.57, 84.24, 13.87; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{12}H_{10}N_5O_2S$: 288.05497; found: 288.05479.

*4-Amino-5-cyano-2-methylthio-6-(3-nitrophenyl)-pyrimidine (***3i***)*

Obtained in 93 % yield; white powder; mp 225–226 °C (EtOAc/petrol); FT-IR (KBr) ν 3457, 3345, 2221, 1651, 1527 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 1H), 8.40 (d, J = 8.2 Hz, 1H), 8.34 (d, J = 7.8 Hz, 1H), 7.72 (t, J = 8.0 Hz, 1H), 5.70 (s, 2H), 2.59 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.64, 165.35, 163.55, 148.12, 137.83, 135.32, 130.72, 125.97, 123.68, 116.40, 83.29, 14.01; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{12}H_{10}N_5O_2S$: 288.05497; found: 288.05493.

*4-Amino-5-cyano-2-methylthio-6-(2-chlorophenyl)-pyrimidine (***3j***)*

Obtained in 54 % yield; yellow power crystal; mp 187–190 °C (EtOH/petrol); FT-IR (KBr) ν 3381, 3157, 2223, 1650, 1536 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.35 (m, 4H), 5.75 (s, 2H), 2.54 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.58, 167.78, 162.69, 136.11, 131.92, 131.38, 130.78, 130.14, 127.87, 115.51, 85.76, 40.61, 40.40, 40.20, 39.99, 39.78, 39.57, 39.36, 13.98; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{12}H_{10}ClN_4S$: 277.03092; found: 277.03075.

*4-Amino-5-cyano-2-methylthio-6-(3-chlorophenyl)-pyrimidine (***3k***)*

Obtained in 65 % yield; white needle crystal; mp 195–198 °C (EtOH/petrol); FT-IR (KBr) ν 3444, 3146, 2210, 1646, 1539 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.89 (d, J = 7.6 Hz, 1H), 7.50 (t, J = 9.7 Hz, 1H), 7.45(t, J = 7.8 Hz, 1H), 5.67 (s, 2H), 2.59(s, 3H);^{13}C NMR (101 MHz, DMSO-d_6) δ 174.49, 166.19, 163.58, 138.46, 133.66, 131.22, 130.88, 128.65, 127.67, 116.51, 83.15, 14.00; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{12}H_{10}ClN_4S$: 277.03092; found: 277.03057.

*4-Amino-5-cyano-2-methylthio-6-(2,4-dichlorophenyl)-pyrimidine (***3l***)*

Obtained in 89 % yield; yellow crystal; mp 203–205 °C (EtOAc/petrol); FT-IR (KBr) ν 3389, 3204, 2215, 1656, 1527 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 8.36–7.88 (s, 2H), 7.83 (s, 1H), 7.64–7.53 (m, 2H), 2.47 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.69, 166.84, 162.60, 135.85, 135.02, 132.63, 132.20, 129.78, 128.21, 115.42, 85.76, 13.99; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{12}N_5S$: 270.08079; found: 270.08093.

*4-Amino-5-cyano-2-methylthio-6-(3-hydroxylphenyl)-pyrimidine (***3m***)*

Obtained in 60 % yield; white needle crystal; mp 228–230 °C (EtOAc/petrol); FT-IR (KBr) ν 3396, 3174, 2216, 1659, 1531 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.79 (s, 1H), 7.72 (s, 2H), 7.37–7.23 (m, 3H), 6.96 (d, J = 7.9 Hz, 1H), 2.51 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.22, 167.59, 163.81, 157.78, 137.70, 130.03, 119.64, 118.49, 116.76, 115.64, 82.64, 13.95; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{12}N_5S$: 259.06481; found: 259.06468.

*4-Amino-5-cyano-2-methylthio-6-(3-methoxyphenyl)-pyrimidine (**3n**)*

Obtained in 60 % yield; white crystal; mp 176–178 °C (EtOAc/petrol); FT-IR (KBr) ν 3340, 3239, 2212, 1656, 1528 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 2H), 7.43 (m, 3H), 7.15 (d, J = 7.9 Hz, 1H), 3.82 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.29, 167.47, 163.72, 159.52, 137.79, 130.16, 121.20, 117.12, 116.76, 114.36, 82.92, 55.77, 13.97; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{12}N_5S$: 273.08050; found: 273.08046.

*4-Amino-5-cyano-2-methylthio-6-(3-fluorophenyl)-pyrimidine (**3o**)*

Obtained in 77 % yield; white needle crystal; mp 230 °C (EtOAc/petrol); FT-IR (KBr) ν 3466, 3152, 2211, 1650, 1545 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 (d, J = 172.6 Hz, 2H), 7.75–7.57 (m, 3H), 7.44 (td, J = 8.4, 1.9 Hz, 1H), 2.51 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.46, 166.33, 163.59, 163.48, 161.04, 138.68, 131.20, 131.12, 125.19, 118.45, 118.24, 116.53, 115.93, 115.70, 83.13, 13.98; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{12}N_5S$: 261.04047; found: 261.04046.

*4-Amino-5-cyano-2-methylthio-6-(3-pyridineyl)-pyrimidine (**3p**)*

Obtained in 82 % yield; white needle crystal; mp 217–219 °C(CH_3OH/EtOAc); FT-IR (KBr) ν 3391, 3083, 2211, 1679, 1528 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.78 (d, J = 4.7 Hz, 1H), 8.31 (d, J = 8.1 Hz, 1H), 7.45 (dd, J = 7.8, 5.0 Hz, 1H), 5.68 (s, 2H), 2.58 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.65, 165.39, 163.48, 151.98, 149.41, 136.56, 132.40, 123.90, 116.51, 83.36, 49.05, 13.98; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{11}H_{10}N_5S$: 244.06514; found: 244.06497.

*4-Amino-5-cyano-2-methylthio-6-(4-pyridineyl)-pyrimidine (**3q**)*

Obtained in 81 % yield; white crystal; mp 300 °C (CH_3 CN/DMSO); FT-IR (KBr) ν 3423, 2998, 2210, 1657, 1536 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (d, J = 6.0 Hz, 2H), 8.08 (s, 2H), 7.79 (d, J = 6.0 Hz, 2H), 2.52 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.75, 165.78, 163.42, 150.59, 143.71, 123.01, 116.15, 83.49, 14.01; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{12}N_5S$: 244.06514; found: 244.06510.

*4-Amino-5-cyano-2-methylthio-6-methyl-pyrimidine (**3r**)*

Obtained in 35 % yield; white crystal; mp 244–245 °C (EtOAc/petrol); FT-IR (KBr) ν 3427, 3223, 2206, 1636, 1565 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.52 (s, 1H), 2.56 (s, 3H), 2.55 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.31, 159.93, 157.21, 115.75, 86.43, 19.75, 13.02; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{13}N_4S$: 181.05424; found: 181.05379.

*4-Amino-5-cyano-2-ethylthio-6-(3-pyridinyl)-pyrimidine (**3s**)*

Obtained in 63 % yield; white needle crystal; mp 172–173 °C (EtOAc/petrol); FT-IR (KBr) ν 3389, 3053, 2213, 1642, 1537 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (d,J = 1.9 Hz, 1H), 8.81–8.75 (m, 1H), 8.31 (d, J = 7.9 Hz, 1H), 7.46 (dt,J = 7.4, 3.8 Hz, 1H), 7.30–7.24 (m, 1H), 5.76 (s, 2H), 3.23–3.14 (m, 2H), 1.45–1.39 (m, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.25, 165.51, 163.52, 151.99, 149.41, 136.55, 132.44, 123.94, 116.50, 83.43, 25.07, 15.02; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{12}H_{12}N_5S$: 258. 08079; found: 258.08028.

*4-Amino-2-benzylthio-5-cyano-6-(3-pyridinyl)-pyrimidine (**3t**)*

Obtained in 58 % yield; white needle crystal; mp 159–162 °C (EtOAc/petrol); FT-IR (KBr) ν 3472, 3085, 2209, 1642, 1524 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (s, 1H), 8.77 (d, J = 4.7 Hz, 1H), 8.26 (d, J = 7.7 Hz, 1H), 7.46–7.29 (m, 6H), 5.70 (s, 2H), 4.43 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.67, 165.68, 163.50, 152.04, 149.44, 138.26, 136.59, 132.35, 129.52, 128.85, 127.56, 123.93, 116.43, 83.70, 34.71; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{17}H_{14}N_5S$: 320.09644; found: 320.09595.

*4-Amino-5-cyano-2-cyclopentylthio-6-(3-pyridinyl)-pyrimidine (**3u**)*

Obtained in 56 % yield; white needle crystal; mp 197–199 °C (EtOAc/petrol); FT-IR (KBr) ν 3359, 3194, 2221, 1666, 1542 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.77 (d, J = 4.7 Hz, 1H), 8.31 (d, J = 8.0 Hz, 1H), 7.45 (dd, J = 7.9, 4.9 Hz, 1H), 5.81 (s, 2H), 4.09–4.00 (m, 1H), 2.22 (dd, J = 15.4, 8.2 Hz, 2H), 1.78 (d, J = 6.5 Hz, 2H), 1.73–1.60 (m, 4H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.78, 165.43, 163.44, 151.98, 149.40, 136.53, 132.47, 123.95, 116.51, 83.33, 43.56, 33.30, 24.96; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{16}N_5S$: 298.11209; found: 297.11190.

*4-Amino-5-cyano-2-n-butylthio-6-(3-pyridinyl)-pyrimidine (**3v**)*

Obtained in 74 % yield; white needle crystal; mp 140–141 °C (EtOAc/petrol); FT-IR (KBr) ν 3347, 3066, 2213, 1664, 1542 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (d, J = 1.8 Hz, 1H), 8.78 (dd, J = 4.8, 1.5 Hz, 1H), 8.44–8.21 (m, 1H), 7.45 (dd, J = 7.7, 4.8 Hz, 1H), 5.86 (s, 2H), 3.17 (t, J = 7.3 Hz, 2H), 1.81–1.65 (m, 2H), 1.55–1.33 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.95, 164.65, 163.27, 152.03, 149.68, 135.89, 131.66, 123.25, 115.93, 83.21, 30.89, 21.96, 13.66; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{16}N_5S$: 286.11209; found: 286.11237.

*2-Allylthio-4-amino-5-cyano-6-(3-pyridinyl)-pyrimidine (**3w**)*

Obtained in 54 % yield; white needle crystal; mp 182–183 °C (EtOAc/petrol); FT-IR (KBr) ν 3437, 3147, 2214, 1645, 1546 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (m, J = 13.9, 7.1 Hz, 5H), 6.06–5.90 (m, 1H), 5.69 (s, 2H), 5.32 (d, J = 17.0 Hz, 1H), 5.16 (d, J = 10.0 Hz, 1H), 3.91–3.80 (d, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.52, 165.65, 163.49, 152.07, 149.43, 136.60, 134.19, 132.39, 123.97, 118.58, 116.42, 83.64, 33.43; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{12}N_5S$: 270.08079; found: 270.08093.

*Pyrimido[5,4-c]quinoline-2-methylthio-4-amine (**D**)*

Compound **3j** (2 mmol) was dissolved in 20 mL anhydrous THF at room temperature. Lithium aluminum hydride (8 mmol) in 5 mL anhydrous THF was then added slowly, and the mixture was stirred at room temperature for 6 h before the dropwise addition of 10 mL of water at 0 °C. Afterwards, 3 mL 3N hydrochloric acid was added, and the mixture was extracted with ethyl acetate (2 × 20 mL). The solid of sodium hydroxide was added to the aqueous layer to reach pH 11, and then the aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo. The residue was dissolved in 20 mL DMF, and CuI (0.1 equiv), L-proline (0.2 equiv) and Cs_2CO_3 (2 equiv) were added into the solution under nitrogen atmosphere. The mixture was stirred at room temperature for 30 min, then heated at 100 °C for 24 h in an oil bath. The resulting suspension was allowed to cool to room temperature and filtered. The precipitate was washed with ethyl acetate (10 mL) and 30 mL of water were added to the filtrate. The filtrate was then extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried, concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc/petrol, 2:1, v/v) to give compound **D** as the product.

Obtained in 70 % yield; yellow powder; mp > 300 °C; FT-IR (KBr) ν 3320, 3157, 1669, 1593, 1542 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.52 (s, 1H), 8.82 (d, J = 7.4 Hz, 1H), 8.30 (s, 2H), 8.05 (d, J = 8.2 Hz, 1H), 7.93–7.86 (m, 1H), 7.72 (dd, J = 13.4, 6.2 Hz, 1H), 2.65 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.98, 161.37, 152.81, 148.66, 148.47, 131.89, 129.33, 127.40, 124.28, 123.34, 104.07, 13.97; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{12}N_5S$: 243.06989; found: 243.06984.

*Pyrimido[5,4-c]quinoline-2-methylthio-4,5-diamine (**E**)*

Compound **3h** (2 mmol) and $SnCl_2 \cdot H_2O$ (4 mmol) were dissolved in 20 mL 1N hydrochloric acid in a flask. The solution was heated at 100 °C for 48 h in an oil bath. The resulting suspension was allowed to cool to room temperature and filtered. The precipitate was washed with water and dried to afford compound **E** as yellow powder in 85 % yield; mp > 300 °C; FT-IR (KBr) ν 3334, 3216, 1731, 1680, 1637cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.20 (s, 2H), 8.80 (s, 2H), 8.65 (d, J = 8.3 Hz, 1H), 8.06 (d, J = 8.5 Hz, 1H), 7.97–7.89 (t, 1H), 7.55 (t, J = 11.3, 4.0 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 163.67, 150.50, 149.20, 146.43, 139.38, 135.52, 125.37, 125.03, 116.04, 112.16, 94.00; MS (EI): m/z 244 (M^+, 6), 246 (2) 229 (50), 228 (100), 185 (40), 157 (31).

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