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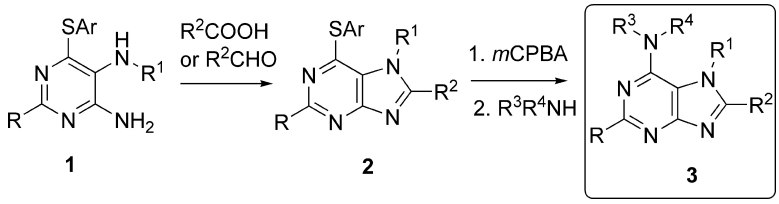

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An Efficient and Regiospecific Strategy to N^7-Substituted Purines and Its Application to a Library of Trisubstituted Purines

Jinglin Liu, Qun Dang, Zhonglin Wei, Fuqiang Shi, and Xu Bai*

The Center for Combinatorial Chemistry and Drug Discovery, Jilin University, 75 Haiwai Street, Changchun, Jilin 130012, P.R. China

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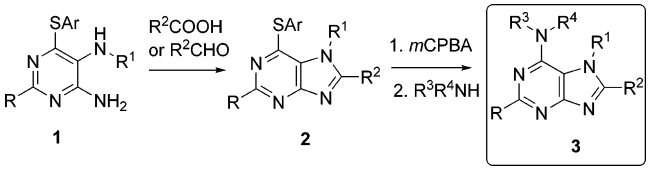
A regiospecific strategy for the preparation of N^7-substituted purines in an efficient manner was devised. This approach to 6,7,8-trisubstituted purines relies on the cyclization reactions of suitably substituted pyrimidines (**1**) with either a carboxylic acid or an aldehyde. The method development for the five-step synthetic strategy outlined here was completed using 5-amino-4,6-dichloropyrimidine (**4**) as the starting material. The utility of this methodology was demonstrated through the preparation of a 40-membered library of 6,7,8-trisubstituted purines (**3**) in good yields and high purity.

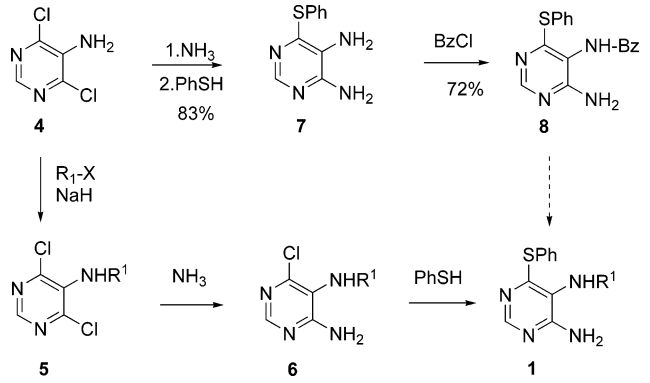
Introduction

Purine derivatives have been explored for many years for their potential therapeutic effects.[1] New strategies for the efficient and selective synthesis of purine derivatives are therefore still of interest to chemists, which is particularly true for less common purine derivatives.[2] As part of our ongoing programs to develop new methodologies that are suitable for efficient generation of large heterocyclic compound libraries, we have reported two synthetic methodologies and their applications to libraries of 2,6,8,9-substituted purines.[3] N^9-Substituted purine derivatives are among the most commonly studied compounds, which is not too surprising since natural purine nucleosides are N^9-substituted. There have been recent interests in N^7-substituted purine derivatives. For example, N^7-substituted purines have been reported as antiviral agents;[4] N^7-substituted guanines are also important DNA adducts formed as a result of exposure to electrophiles.[5] Moreover, N^7-alkylpurines are the main types of DNA adducts excreted in urine and are therefore important markers for the development of diagnostic methods to detect and quantify specific types of DNA damages.[6] Despite the abundance of work reported related to purine derivatives, few studies report libraries of N^7-substituted purine derivatives.[7] Traditionally, N^7-substituted purines are made via alkylation reactions of purines, which often produce both N^7- and N^9-substituted purines as a mixture of regioisomers.[8] Although a regioselective synthesis was reported recently, only low yields of desired products were obtained.[9] We envisioned that cyclization reaction of 5-alkylamino-4-amino-6-arylthiopyrimidine **1** should lead to the desired N^7-substituted purines regiospecifically, and the 6-arylthio group allowed further elaboration of the N^7-substituted purine system to lead to a library of 2,6,7,8-substituted purines with up to five diversity points, Scheme 1. Herein, the demonstration of the strategy in the parallel solution-phase construction of a 40-member library of 6,7,8-trisubstituted purines is reported.

Scheme 1



Scheme 2



Results and Discussions

The key pyrimidine substrates **1** required for the purine ring formation reaction leading to N^7-substituted purines were prepared as shown in Scheme 2. The aryl sulfide group was selected as a transition point in the 6-position of pyrimidines **1** to replace the usual 6-chloro group which was observed to give oxazolopyrimidines during purine ring formation conditions as observed in our previous studies.[3a,3b] Initially, pyrimidine **4** was converted to pyrimidine **7** in good yield. The conversion of compound **7** to the desired **1** was then explored via the reduction of an amidyl group such as pyrimidine **8**. Toward that end, pyrimidine **7** was acylated with benzoyl chloride to give pyrimidine **8** in good yield. Unfortunately, all attempted reduction of the amide group

* To whom correspondence should be addressed. Phone: +86-431-5188955. E-mail: xbai@jlu.edu.cn.

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Table 1. Alkylation Reactions of Pyrimidine **4** Leading to Pyrimidines **5**

entry	R^1X	product	MW	M + 1[a]	yield[b] (%)
1	iodoethane	**5a**	191	192	59
2	1-iodopentane	**5b**	233	234	63
3	allyl bromide	**5c**	203	204	76
4	benzyl bromide	**5d**	253	254	65
5	iodocyclohexane		245		0

[a] Observed by LC-MS. [b] Yields of pure compounds isolated by flash chromatography.

Table 2. Preparation of Pyrimidines **6** and **1** from Pyrimidines **5**

entry	R^1	product	yield (%)	product	yield[a] (%)
1	ethyl	**6a**	70	**1a**	82
2	pentyl	**6b**	66	**1b**	95
3	allyl	**6c**	81	**1c**	87
4	benzyl	**6d**	84	**1d**	94

[a] Purified by flash chromatography on silica gel.

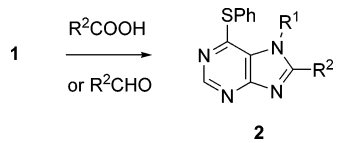
failed to produce the desired 5-benzylaminopyrimidine **1** under standard reduction conditions such as $B_2H_6-SMe_2$ and $LiAlH_4$.

An alternative route was developed which entailed a direct alkylation reaction of pyrimidine **4** with alkyl halides in the presence of sodium hydride to give pyrimidines **5**,[10] Table 1. Amination of pyrimidines **5** followed by substitution reaction with thiophenol to give the desired pyrimidines **1**, Table 2. The alkylation reactions of pyrimidines **4** with primary alkyl halides proceeded smoothly to give the desired pyrimidines **5** in good yields, entries 1−4, Table 1. However, a secondary alkyl halide such as iodocyclohexane failed to yield the desired product (entry 5, Table 1) possibly due to steric hindrance.

The monoamination of pyrimidines **5** using excess amount of ethanolic ammonia produced pyrimidines **6** selectively in good to high yields, Table 2. No over-amination was observed for any of the pyrimidines **5**, which may be attributed to the fact that the strong electron-donating effect of the newly introduced amino group in pyrimidines **6** prevents further nucleophilic substitutions by ammonia. Consequently, it was anticipated that displacement of the final chloro group in pyrimidines **6** may require elevated temperature. Therefore, the conversions of pyrimidines **6** to pyrimidines **1** were accomplished in high yields under the conditions of excess thiophenol and triethylamine in refluxing *n*-butanol, Table 2.

With the suitably substituted pyrimidines **1** in hand, we began to investigate the construction of the purine ring system leading to N^7-substituted purines in a regiospecific manner.[11,7b] First, reaction of pyrimidine **1a** with either a carboxylic acid or an acyl chloride in the presence of PPA (polyphosphoric acid), similar to a method developed for the preparation of N^9-substituted purines,[3a] was attempted. Treatment of pyrimidine **1a** with acetic acid and PPA in refluxing toluene gave 7-ethyl-8-methyl-6-(phenylthio)-7*H*-purine (**2a**) in 84% yield, entry 1, Table 3. Toluene was used to replace $POCl_3$ as the solvent of choice in the original PPA method since retention of chloro group at the 6-position of pyrimidine **1a** was no longer an issue. The toluene/PPA condition could also be applied to those substrates in which R^1 is a simple alkyl group, such as ethyl and pentyl group, (pyrimidines **1a**−**b**) to give the desired products in good to high yields, entries 2−4, Table 3. Furthermore, the milder PPA/tolune cyclization reaction condition was tested with pyrimidine **1c** with a more acid-sensitive allyl group. Treatment of pyrimidine **1c** with acetic acid and PPA in refluxing toluene for 5 h only gave 7-allyl-8-methyl-6-(phenylthio)-7*H*-purine (**2e**) in 12% yield, entry 5, Table 3. The de-allyl purine product was isolated in 30% yield. This suggested that the current reaction conditions were still not mild enough to tolerate acid-liable groups such as allyl. Consequently, other purine ring formation methods had to be identified in order to broaden the scope of the current series of N^7-substituted purines. For this purpose, the $FeCl_3$-promoted cyclization reaction reported by Dang et al. for the preparation of N^9-substituted purines[12] was considered. Pyrimidine **1c** was reacted with benzaldehyde in the presence of $FeCl_3-SiO_2$ in refluxing dioxane to give 7-allyl-8-phenyl-6-(phenylthio)-7*H*-purine (**2f**) in 61% yield (entry 6, Table 3). This result indicated that the $FeCl_3-SiO_2$ reaction conditions could be suitable to the substrate with an acid-liable allyl group. Moreover, the successful adoption of the $FeCl_3$-promoted cyclization reaction should further broaden the scope of the

Table 3. Cyclization of Pyrimidines **1a**−**d** with Either R^2COOH or R^2CHO Yielding Purines **2**

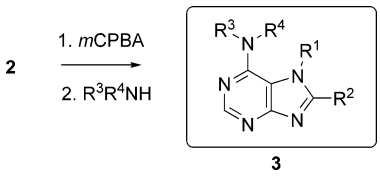


2

entry	R^1	R^2COOH or R^2CHO	product	reaction time (h)	MW	M + 1	yield[a] (%)
1	ethyl	MeCOOH	**2a**	9	270	271	84
2	ethyl	PhCOOH	**2b**	11	332	333	63
3	*n*-pentyl	EtCOOH	**2c**	5	326	327	95
4	*n*-pentyl	PhCOOH	**2d**	36	374	375	81
5	allyl	MeCOOH	**2e**	5	282	283	12
6	allyl	PhCHO	**2f**	54	344	345	61
7	allyl	EtCHO	**2g**	60	296	297	71
8	benzyl	EtCHO	**2h**	40	346	347	64
9	benzyl	PhCHO	**2i**	56	394	395	84

[a] Isolated via flash chromatography.

Table 4. Amine Substitutions of N^7-Substituted 6-Phenylthiopurines **2**



3

entry	R^1	R^2	R^3R^4 amine used	MW	mass found	purity (%)	yield[a] (%)
1	allyl	ethyl	2-aminoethanol	247	248	100	73
2	allyl	ethyl	NH_3	203	204	100	75
3	allyl	ethyl	pyrrolidine	257	258	100	90
4	allyl	ethyl	*n*-butylamine	259	260	100	80
5	allyl	ethyl	cyclohexylamine	285	286	100	37 (35)[b]
6	allyl	phenyl	2-aminoethanol	295	296	100	53
7	allyl	phenyl	NH_3	251	252	95	60
8	allyl	phenyl	pyrrolidine	305	306	99	63
9	allyl	phenyl	*n*-butylamine	307	308	98	62
10	allyl	phenyl	cyclohexylamine	333	334	99	36 (23)
11	benzyl	ethyl	2-aminoethanol	297	298	100	57
12	benzyl	ethyl	NH_3	253	254	100	66
13	benzyl	ethyl	pyrrolidine	307	308	98	47
14	benzyl	ethyl	*n*-butylamine	309	310	95	76
15	benzyl	ethyl	cyclohexylamine	335	336	98	34 (30)
16	benzyl	phenyl	2-aminoethanol	345	346	99	65
17	benzyl	phenyl	NH_3	301	302	90	64
18	benzyl	phenyl	pyrrolidine	355	356	100	50
19	benzyl	phenyl	*n*-butylamine	357	358	98	54
20	benzyl	phenyl	cyclohexylamine	383	384	97	35 (23)
21	ethyl	methyl	2-aminoethanol	221	222	100	76
22	ethyl	methyl	NH_3	177	178	97	71
23	ethyl	methyl	pyrrolidine	231	232	98	81
24	ethyl	methyl	*n*-butylamine	233	234	100	90
25	ethyl	methyl	cyclohexylamine	259	260	98	30 (40)
26	ethyl	phenyl	2-aminoethanol	283	284	100	65
27	ethyl	phenyl	NH_3	239	240	98	66
28	ethyl	phenyl	pyrrolidine	293	294	98	70
29	ethyl	phenyl	*n*-butylamine	295	296	100	69
30	ethyl	phenyl	cyclohexylamine	321	322	94	26 (29)
31	pentyl	ethyl	2-aminoethanol	277	278	98	87
32	pentyl	ethyl	NH_3	233	234	90	53
33	pentyl	ethyl	pyrrolidine	287	288	98	80
34	pentyl	ethyl	*n*-butylamine	289	290	99	86
35	pentyl	ethyl	cyclohexylamine	315	316	100	33 (24)
36	pentyl	phenyl	2-aminoethanol	325	326	100	82
37	pentyl	phenyl	NH_3	281	282	97	61
38	pentyl	phenyl	pyrrolidine	335	336	99	69
39	pentyl	phenyl	*n*-butylamine	337	338	100	72
40	pentyl	phenyl	cyclohexylamine	363	364	100	33 (45)

[a] Purified either by flash chromatography on silica gel or LC-MS. [b] Yield in parentheses indicates the product from *n*-butanol as the nucleophile.

R^2 group since now aldehydes, one of the most readily available classes of compounds, can be used as the preferred reactants to build the purine ring.

The final method development step is the introduction of two additional diversity points, R^3 and R^4, to the N^7-substituted purines **2**. Activation of a sulfide group at the 6-position of a purine toward nucleophilic substitutions has often been reported and applied to preparation of purine libraries using either solution-phase[3b] or solid-phase methodologies.[13] Therefore, *m*CPBA oxidation of compounds **2** gave their corresponding 6-phenylsulfonyl purines in excellent yields and were sufficiently pure for the next reaction without further purification. Substitution of the 6-phenylsulfonyl group by various amines was achieved using an excess amount of primary or secondary amines in *n*-butanol at 100 °C in sealed tubes to give the final target N^7-substituted purines **3**. To demonstrate the utility of the current strategy outlined in Scheme 1, a 40-membered library of 6,7,8-trisubstituted purines were targeted. The final conversion of purines **2** to **3** were carried out in solution phase in a parallel format to give the desired purine derivatives. All final compounds **3** were purified and characterized by LC/MS-ELSD, Table 4. Although the final two steps were not fully optimized, most of these reactions gave the desired products in high purity (>90%) and good to excellent yields (47−90%). However, when R^3R^4NH is cyclohexylamine the final products **3** were obtained (in low yields of 26−37%, entries 5, 10, 15, 20, 25, 30, 35, 40, Table 4) along with a significant amount of *n*-butyloxy replacement products (23−45%). Although *n*-butyloxy-substituted products were ob-

served in other cases as well, they were not sufficiently enough to be isolated, which suggested that nucleophilic substitution by cyclohexylamine was slower compared to other amines used.

Conclusion

An efficient synthetic strategy to N^7-substituted purines was devised and carried out in a regiospecific manner. Method development was completed starting 5-amino-4,6-dichloropyrimidine (**4**) as a model compound. A key step of this synthetic sequence entails the cyclization of designated 4-amino-5-alkylaminopyrimidines with either a carboxylic acid or an aldehyde to produce the desired N^7-substituted purines in good to excellent yields. Another key feature is the strategically placed phenylthio group in place of the usual 6-chloro group in pyrmidines **1**. The phenylthio group is stable enough to last through all required reactions, but it can be readily activated for replacement by nucleophiles (e.g. conversion of **2** to **3**) such as primary and secondary amines. Moreover, the chemistry worked out with the sulfide group for the current synthesis should also serve as a prelude of using sulfur-linked Merrifield resin as a traceless linker in solid-phase synthesis of N^7-substituted purines. The successful construction of a 40-membered library of 6,7,8-trisubstituted purines further demonstrated the potential utility of this regiospecific strategy toward the preparation of a large compound library.

Experimental Section

General Methods. Commercial reagents were used without purification. The melting points were determined on a XT5 melting point apparatus and are uncorrected. Unless otherwise stated, ^{1}H NMR data were recorded on a 300 MHz Varian VXR-300S NMR spectrometer with $CDCl_3$ as solvent and TMS as the internal standard. The following abbreviations were used to designate the multiplicities: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. Purity of compounds was assessed by LC-MS-ELSD (Agilent 1100 series) with an API-ES ionization source operating in positive mode.

General Procedure for the Preparation of Compounds 5. A solution of 5-amino-4,6-dichloropyrimidine (**4**) (3.28 g, 20 mmol) in THF (100 mL) was treated with 65% NaH (0.89 g, 24 mmol) at 0 °C. Then the mixture was warmed to ambient temperature, and appropriate RX (24 mmol) and tetrabutylammonium bromide (7.7 g, 24 mmol) were added. The mixture was stirred for 2 h, concentrated in vacuo, and chromatographed (EtOAc−hexane, 1:4) to give the desired product **5**.

4,6-Dichloro-*N*-ethylpyrimidin-5-amine (5a, R^1 = Ethyl). Brown oil; yield 2.27 g (59%). ES-MS: 192 (M + H$^+$). ^{1}H NMR: δ 8.25 (s, 1H), 4.06 (br, 1H), 3.50−3.59 (m, 2H), 1.26 (t, 3H, J = 7.2 Hz).

4,6-Dichloro-*N*-pentylpyrimidin-5-amine (5b, R^1 = Pentyl). Brown oil; yield 2.9 g (63%). ES-MS: 234 (M + H$^+$). ^{1}H NMR: δ 8.24 (s, 1H), 4.13 (br, 1H), 3.45−3.51 (m, 2H), 1.56−1.63 (m, 2H), 1.28−1.40 (m, 4H), 0.92 (t, 3H, J = 7.2 Hz).

***N*-Allyl-4,6-dichloropyrimidin-5-amine (5c, R^1 = Allyl).** Yellow oil; yield 3.1 g (76%). ES-MS: 204 (M + H$^+$). ^{1}H NMR: δ 8.28 (s, 1H), 5.85−5.96 (m, 1H), 5.24−5.31 (m, 1H), 5.18−5.23 (m, 1H), 4.09−4.12 (m, 2H).

***N*-Benzyl-4,6-dichloropyrimidin-5-amine (5d, R^1 = Benzyl).** Yellow oil; yield 3.3 g (65%). ES-MS: 254 (M + H$^+$). ^{1}H NMR: δ 8.27 (s, 1H), 7.27−7.39 (m, 5H), 4.64 (s, 2H), 4.44 (br, 1H).

General Procedure for the Preparation of Compounds 6. A solution of compound **5** (10 mmol) in 7 M ethanolic ammonia (10 mL) and 2.5 mL of triethylamine in a sealed reactor was heated for 24 h at 120 °C. The solvent was evaporated in vacuo, and the residue was dissolved with ethyl acetate and washed with water, saturated $NaHCO_3$, and brine in sequel. The organic phase was dried over anhydrous $MgSO_4$, concentrated in vacuo to white solid, and purified by flash chromatography.

6-Chloro-*N*^{5}-ethylpyrimidine-4,5-diamine (6a, R^1 = Ethyl). White solid; yield 1.34 g (70%); mp 102.1−103.0 °C. ES-MS: 173 (M + H$^+$). ^{1}H NMR: δ 8.10 (s, 1H), 5.52 (br, 2H), 2.95−3.02 (m, 2H), 1.21 (t, 3H, J = 7.2 Hz). ^{13}C NMR: δ 15.90, 41.26, 123.61, 151.48, 152.38, 160.12.

6-Chloro-*N*^{5}-pentylpyrimidine-4,5-diamine (6b, R^1 = Pentyl). White solid; yield 1.42 g (66%); mp 105.9−106.7 °C. ES-MS: 215 (M + H$^+$). ^{1}H NMR: δ 8.09 (s, 1H), 5.54 (br, 2H), 3.10 (br, 1H), 2.90−2.94 (m, 2H), 1.53−1.62 (m, 2H), 1.29−1.42 (m, 4H), 0.92 (t, 3H, J = 7.2 Hz). ^{13}C NMR: δ 13.95, 22.42, 29.08, 30.40, 46.69, 123.96, 151.24, 152.32, 159.91.

***N*^{5}-Allyl-6-chloropyrimidine-4,5-diamine (6c, R^1 = Allyl).** Pale yellow solid; yield 1.49 g (81%); mp 85.1−87.1 °C. ES-MS: 185 (M + H$^+$). ^{1}H NMR: δ 8.06 (s, 1H), 5.86−5.99 (m, 1H), 5.75 (br, 2H), 5.24−5.31 (m, 1H), 5.12−5.17 (m, 1H), 3.51−3.53 (m, 2H), 3.20 (br, 1H). ^{13}C NMR: δ 48.65, 117.00, 123.27, 135.17, 151.30, 152.34, 159.88.

***N*^{5}-Benzyl-6-chloropyrimidine-4,5-diamine (6d, R^1 = Benzyl).** Yellow solid; yield 1.97 g (84%); mp 104.6−106.1 °C. ES-MS: 235 (M + H$^+$). ^{1}H NMR: δ 8.13 (s, 1H), 7.30−7.40 (m, 5H), 5.40 (br, 2H), 4.07−4.11 (m, 2H), 3.44 (br, 1H). ^{13}C NMR: δ 50.47, 123.28, 127.72, 127.81, 128.71, 138.45, 151.95, 152.67, 160.06.

6-(Phenylthio)pyrimidine-4,5-diamine (7). A solution of 5-amino-4,6-dichloropyrimidine (**4**) (11.48 g, 70 mmol) in 8 M ethanolic ammonia (60 mL) and 14.7 mL of triethylamine (105 mmol) in a sealed reactor was heated for 20 h at 120 °C. The solvent was evaporated in vacuo, and the residue was dissolved with ethyl acetate and washed with water, saturated $NaHCO_3$, and brine in sequel. The organic phase was dried over anhydrous $MgSO_4$ and concentrated in vacuo to a white solid. The crude product was dissolved in *n*-butanol (100 mL), thiophenol (7.9 mL, 77 mmol), and triethylamine (14.7 mL, 105 mmol). The mixture was stirred under reflux for 5 h, then concentrated in vacuo, diluted with water, and extracted with ethyl acetate. The combined ethyl acetate layer was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to the crude product. Purification by flash chromatography (elution with hexane followed by 30% ethyl acetate in hexane) yielded **7**. Yield 12.65 g (83%); mp 197.0−198.1 °C. ES-MS: 219 (M + H$^+$). ^{1}H NMR (DMSO-d_6): δ 7.71 (s, 1H), 7.27−7.34 (m, 5H), 6.59 (s, 2H), 4.87 (s, 2H).

***N*-(4-Amino-6-(phenylthio)pyrimidin-5-yl)benzamide (8).** To a solution of compound **7** (1.09 g, 5 mmol) and diisopropylethylamine (1.4 mL, 8 mmol) in anhydrous THF (25 mL) was added dropwise benzoyl chloride (1.1 g, 8 mmol). The mixture was stirred for 5 h in an ice bath (TLC showed complete consumption of **8**). The reaction mixture was concentrated in vacuo, diluted with water, and extracted with CH_2Cl_2. The organic phase was washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to yield a yellow solid, which was purified by flash chromatography (CH_2Cl_2:CH_3OH = 97:3) to yield **8** as a white solid. Yield 1.15 g (72%); mp 227.9−229.9 °C. ES-MS: 323 ($M + H^+$). ^1H NMR (DMSO-d_6): δ 9.76 (s, 1H), 8.05−8.06 (m, 2H), 8.03 (s, 1H), 7.53−7.60 (m, 3H), 7.39−7.46 (m, 5H), 6.91 (s, 2H).

General Procedure for the Preparation of Compounds 1. N^5-Alkyl-6-chloropyrimidine-4,5-diamine (**6**) (10 mmol), thiophenol (12 mmol), and triethylamine (2.2 mL, 20 mmol) were dissolved in normal butyl alcohol (25 mL), and the mixture was stirred under reflux for 9 h. The reaction mixture was concentrated in vacuo, diluted with water, and extracted with ethyl acetate. The combined ethyl acetate layer was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to the crude product. Purification by flash chromatography yielded product **1**.

N^5-Ethyl-6-(phenylthio)pyrimidine-4,5-diamine (1a, R^1 = Ethyl). Pale yellow solid; yield 2.02 g (82%); mp 81.1−82.3 °C. ES-MS: 247 ($M + H^+$). ^1H NMR (DMSO-d_6): δ 9.02 (br, 2H), 8.23 (s, 1H), 7.43 (m, 5H), 3.18−3.25 (m, 2H), 1.14 (t, 3H, J = 7.2 Hz). ^{13}C NMR (DMSO-d_6): δ 16.08, 39.37, 127.31, 129.31, 130.28, 130.80, 132.76, 144.49, 155.93, 157.73.

N^5-Pentyl-6-(phenylthio)pyrimidine-4,5-diamine (1b, R^1 = Pentyl). White solid; yield 2.74 g (95%); mp 96.5−97.8 °C. ES-MS: 289 ($M + H^+$). ^1H NMR: δ 8.12 (s, 1H), 7.45−7.50 (m, 2H), 7.35−7.41 (m, 3H), 5.31 (br, 2H), 2.89−2.93 (m, 2H), 1.54−1.61 (m, 2H), 1.32−1.41 (m, 4H), 0.92 (t, 3H, J = 7.2 Hz). ^{13}C NMR: δ 13.96, 22.44, 29.10, 30.48, 46.75, 124.64, 128.37, 129.08, 130.20, 133.57, 153.08, 157.64, 158.59.

N^5-Allyl-6-(phenylthio)pyrimidine-4,5-diamine (1c, R^1 = Allyl). Yellow solid; yield 2.24 g (87%); mp 61.9−63.5 °C. ES-MS: 259 ($M + H^+$). ^1H NMR: δ 8.13 (s, 1H), 7.36−7.56 (m, 5H), 5.93−6.06 (m, 1H), 5.35 (br, 2H), 5.28−5.34 (m, 1H), 5.06−5.23 (m, 1H), 3.51−3.54 (m, 2H), 2.66 (br, 1H). ^{13}C NMR: δ 48.24, 117.07, 124.27, 128.79, 129.49, 130.39, 134.13, 136.01, 153.51, 158.50, 158.87.

N^5-Benzyl-6-(phenylthio)pyrimidine-4,5-diamine (1d, R^1 = Benzyl). Yellow solid; yield 2.90 g (94%); mp 100.2−101.3 °C. ES-MS: 309 ($M + H^+$). ^1H NMR: δ 8.14 (s, 1H), 7.28−7.45 (m, 10H), 5.31 (br, 2H), 4.07−4.09 (m, 2H), 3.22 (br, 1H). ^{13}C NMR: δ 50.54, 123.59, 125.52, 127.53, 127.97, 128.62, 129.06, 129.49, 133.87, 138.88, 153.46, 158.65, 158.87.

General Procedure for the Preparation of Compounds 2. Method a. A mixture of compound **1** (5 mmol) and an appropriate carboxyl acid (10 mmol) and PPA (15 mmol) in toluene was stirred under reflux for 7−9 h. The resulted mixture was diluted with water, treated with saturated $NaHCO_3$, and extracted with ethyl acetate (3 × 10 mL). The combined ethyl acetate layer was washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), concentrated in vacuo, and purified by flash chromatography (5% methanol in DCM) to give **2a**−**e**.

Method b. A solution of **1** (4 mmol) and appropriate aldehyde (8 mmol) in anhydrous dioxane (50 mL) was treated with 15% $FeCl_3/SiO_2$ (2 equiv) at 100 °C under nitrogen for 48∼72 h. The cooled reaction mixture was filtered through a pad of Celite and washed with EtOAc (3 × 20 mL), and the filtrate was concentrated in vacuo. The residue was dissolved with EtOAc, washed with saturated $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to a dark oil. Purification by parallel flash chromatography (eluting with a gradient of EtOAc in hexane) yielded the product as **2f**−**i**.

7-Ethyl-8-methyl-6-(phenylthio)-7*H*-purine (2a, R^1 = Ethyl, R^2 = Methyl). White solid; yield 1.13 g (84%); mp 110.3−112.2 °C. ES-MS: 271 ($M + H^+$). ^1H NMR: δ 8.70 (s, 1H), 7.59−7.62 (m, 2H), 7.46−7.49 (m, 3H), 4.49−4.56 (m, 2H), 2.70 (s, 3H), 1.56 (t, 3H, J = 7.2 Hz). ^{13}C NMR: δ 13.91, 16.67, 41.00, 123.88, 126.94, 129.21, 129.37, 134.97, 150.15, 152.15, 156.53, 158.23.

7-Ethyl-8-phenyl-6-(phenylthio)-7*H*-purine (2b, R^1 = Ethyl, R^2 = Phenyl). Pale yellow solid; yield 1.05 g (63%); mp 146.1−151.2 °C. ES-MS: 333 ($M + H^+$). ^1H NMR: δ 8.76 (s, 1H), 7.73−7.79 (m, 2H), 7.53−7.66 (m, 5H), 7.47−7.51 (m, 3H), 4.56−4.64 (m, 2H), 1.56 (t, 3H, J = 7.2 Hz). ^{13}C NMR: δ 17.74, 41.88, 126.94, 128.85, 128.95, 129.11, 129.38, 129.49, 129.63, 130.75, 133.76, 135.27, 152.79, 152.94, 158.24.

8-Ethyl-7-pentyl-6-(phenylthio)-7*H*-purine (2c, R^1 = *n*-Pentyl, R^2 = Ethyl). Pale yellow solid; yield 1.54 g (95%); mp 49.4−51.2 °C. ES-MS: 327 ($M + H^+$). ^1H NMR: δ 8.68 (s, 1H), 7.58−7.61 (m, 2H), 7.45−7.48 (m, 3H), 4.42 (t, 2H, J = 8.1 Hz), 2.91−2.99 (m, 2H), 1.86−1.92 (m, 2H), 1.44−1.54 (m, 7H), 0.95 (t, 3H, J = 6.9 Hz). ^{13}C NMR: δ 11.47, 13.78, 20.84, 22.12, 28.50, 31.61, 45.74, 123.64, 127.15, 129.24, 129.40, 135.00, 150.36, 152.10, 158.29, 161.12.

7-Pentyl-8-phenyl-6-(phenylthio)-7*H*-purine (2d, R^1 = *n*-Pentyl, R^2 = Phenyl). Pale yellow solid; yield 1.51 g (81%); mp 110.0−111.8 °C. ES-MS: 375 ($M + H^+$). ^1H NMR: δ 8.76 (s, 1H), 7.73−7.77 (m, 2H), 7.47−7.65 (m, 5H), 7.36−7.39 (m, 3H), 4.53 (t, 2H, J = 7.8 Hz), 1.86−1.96 (m, 2H), 1.23−1.38 (m, 4H), 0.86 (t, 3H, J = 7.2 Hz). ^{13}C NMR: δ 13.71, 21.85, 28.18, 31.91, 46.86, 124.11, 126.92, 128.79, 128.99, 129.34, 129.48, 130.66, 133.65, 135.25, 151.99, 152.67, 152.73, 158.37.

7-Allyl-8-methyl-6-(phenylthio)-7*H*-purine (2e, R^1 = Allyl, R^2 = Methyl). Yellow solid; yield 0.17 g (12%). ES-MS: 283 ($M + H^+$). ^1H NMR: δ 8.69 (s, 1H), 7.55−7.62 (m, 2H), 7.41−7.47 (m, 3H), 6.04−6.14 (m, 1H), 5.29−5.33 (m, 1H), 5.11−5.13 (m, 2H), 4.85−4.91 (m, 1H), 2.65 (m, 3H).

7-Allyl-8-phenyl-6-(phenylthio)-7*H*-purine (2f, R^1 = Allyl, R^2 = Phenyl). White solid; yield 0.84 g (61%); mp 144.5−146 °C. ES-MS: 345 ($M + H^+$). ^1H NMR: δ 8.78 (s, 1H), 7.82−7.86 (m, 2H), 7.46−7.62 (m, 8H), 6.16−6.26

(m, 1H), 5.41−5.45 (m, 1H), 5.18−5.21 (m, 2H), 4.95−5.02 (m, 1H). ^{13}C NMR: δ 48.78, 117.61, 127.37, 128.59, 128.83, 129.40, 129.52, 129.58, 131.03, 133.67, 135.20, 152.11, 153.01, 158.58.

7-Allyl-8-ethyl-6-(phenylthio)-7*H*-purine (2g, R^1 = Allyl, R^2 = Ethyl). Orange solid; yield 0.84 g (71%); mp 108.2−110.3 °C. ES-MS: 297 (M + H^+). ^{1}H NMR: δ 8.71 (s, 1H), 7.56−7.59 (m, 2H), 7.44−7.46 (m, 3H), 6.03−6.16 (m, 1H), 5.29−5.33 (m, 1H), 5.13−5.15 (m, 2H), 4.85−4.91 (m, 1H), 2.89−2.96 (m, 2H), 1.50 (t, 3H, J = 7.2 Hz). ^{13}C NMR: δ 11.20, 20.70, 47.35, 117.17, 123.75, 127.26, 129.17, 129.27, 132.19, 134.83, 150.38, 152.17, 158.23, 161.65.

7-Benzyl-8-ethyl-6-(phenylthio)-7*H*-purine (2h, R^1 = Benzyl, R^2 = Ethyl). Pale yellow solid; yield 0.89 g (64%); mp 112.5−114.4 °C. ES-MS: 347 (M + H^+). ^{1}H NMR: δ 8.74 (s, 1H), 7.30−7.51 (m, 8H), 7.01−7.03 (m, 2H), 5.77 (s, 2H), 2.81−2.91 (m, 2H), 1.43 (t, 3H, J = 7.2 Hz). ^{13}C NMR: δ 11.22, 21.11, 48.83, 125.72, 127.31, 128.05, 129.08, 129.23, 129.40, 134.98, 135.72, 150.64, 152.47, 158.50, 162.09.

7-Benzyl-8-phenyl-6-(phenylthio)-7*H*-purine (2i, R^1 = Benzyl, R^2 = Phenyl). Yellow solid; yield 1.32 g (84%); mp 174.8−176.6 °C. ES-MS: 395 (M + H^+). ^{1}H NMR: δ 8.79 (s, 1H), 7.66−7.72 (m, 2H), 7.31−7.57 (m, 11H), 7.02−7.05 (m, 2H), 5.84 (s, 2H). ^{13}C NMR: δ 50.17, 125.57, 128.01, 128.50, 128.89, 129.11, 129.26, 129.56, 131.03, 135.18, 136.71, 153.13, 159.02, 161.16.

General Procedure for the Preparation of Compounds 3. A solution of *m*-chloroperbenzoic acid (3 equiv) in dichloromethane (15 mL) was added to 6-(phenylthio)-7,8-disubstituted purine **2** (1 equiv), and the resulting mixture was stirred for 4 h in an ice−water bath. The mixture was stirred until disappearance of starting **2** as judged by TLC on silica gel in EtOAc/hexane 3/10 (4 h). It was diluted by H_2O and extracted with CH_2Cl_2. The organic layer was washed with H_2O and saturated $NaHSO_3$, dried over $MgSO_4$, and concentrated in vacuo. The residue was divided into five portions, and each portion was transferred to a glass tube reactor with 2 mL of *n*-butanol and excess of an appropriate amine (>3 equiv). The tube was sealed, kept in 110 °C for 12 h, and then cooled to room temperature. The mixture was evaporated under reduced pressure, and the residue was purified by LC.

7-Pentyl-8-phenyl-6-(pyrrolidin-1-yl)-7*H*-purine (3a). Yellow solid; yield 69%; mp 122.6−124.6 °C. ES-MS: 336 (M + H^+). ^{1}H NMR: 8.55 (s, 1H), 7.76−7.79 (m, 2H), 7.51−7.55 (m, 3H), 4.38 (t, 2H, J = 7.2 Hz), 3.76−3.80 (m, 4H), 1.98−2.02 (m, 4H), 1.45−1.53 (m, 2H), 0.98−1.05 (m, 2H), 0.70−0.80 (m, 2H), 0.66 (t, 3H, J = 7.2 Hz).

7-Ethyl-8-phenyl-6-(pyrrolidin-1-yl)-7*H*-purine (3b). Yellow solid; yield 70%; mp 140.9−142.8 °C. ES-MS: 294 (M + H^+). ^{1}H NMR: 8.54 (s, 1H), 7.76−7.80 (m, 2H), 7.52−7.54 (m, 3H), 4.41−4.48 (m, 2H), 3.76−3.81 (m, 4H), 1.98−2.05 (m, 4H), 1.09 (t, 3H, J = 7.2 Hz).

7-Benzyl-*N*-butyl-8-phenyl-7*H*-purin-6-amine (3c). Pale yellow solid; yield 54%; mp 85.3−87.1 °C. ES-MS: 358 (M + H^+). ^{1}H NMR: 8.54 (s, 1H), 7.66−7.73 (m, 2H), 7.42−7.54 (m, 5H), 7.28−7.29 (m, 3H), 5.54 (s, 2H), 4.44−4.50 (m, 1H), 3.28−3.34 (m, 2H), 1.14−1.25 (m, 2H), 0.94−1.07 (m, 2H), 0.79 (t, 3H, J = 7.2 Hz).

***N*-Butyl-7-ethyl-8-methyl-7*H*-purin-6-amine (3d).** Pale yellow solid; yield 90%; mp 156.9−158.7 °C. ES-MS: 234 (M + H^+). ^{1}H NMR: 8.45 (s, 1H), 5.04 (br, 1H), 4.20−4.27 (s, 2H), 3.57−3.63 (m, 2H), 2.54 (s, 3H), 1.62−1.71 (m, 2H), 1.39−1.51 (m, 5H), 0.96 (t, 3H, J = 7.2 Hz).

7-Ethyl-8-methyl-6-(pyrrolidin-1-yl)-7*H*-purine (3e). Yellow solid; yield 81%; mp 97.7−99.4 °C. ES-MS: 232 (M + H^+). ^{1}H NMR: 8.46 (s, 1H), 4.27−4.35 (m, 2H), 3.67−3.71 (m, 4H), 2.62 (s, 3H), 1.95−2.02 (m, 4H), 1.38 (t, 3H, J = 7.2 Hz).

***N*-Cyclohexyl-7-ethyl-8-phenyl-7*H*-purin-6-amine (3f).** Pale yellow solid; yield 26%; mp 180.4−184.6 °C. ES-MS: 322 (M + H^+). ^{1}H NMR: 8.55 (s, 1H), 7.62−7.66 (m, 2H), 7.48−7.55 (m, 3H), 4.79 (d, 1H, J = 7.2 Hz), 4.23−4.34 (m, 2H), 2.13−2.18 (m, 1H), 1.66−1.81 (m, 4H), 1.51 (t, 3H, J = 7.2 Hz), 1.26−1.35 (m, 6H).

***N*-Butyl-7-pentyl-8-phenyl-7*H*-purin-6-amine (3g).** Pale yellow solid; yield 72%; mp 98.6−100.4 °C. ES-MS: 338 (M + H^+). ^{1}H NMR: 8.55 (s, 1H), 7.60−7.63 (m, 2H), 7.47−7.50 (m, 3H), 5.06 (br, 1H), 4.27 (t, 2H, J = 7.5 Hz), 3.61−3.68 (m, 2H), 1.64−1.80 (m, 4H), 1.42−1.50 (m, 2H), 1.07−1.19 (m, 4H), 0.98 (t, 3H, J = 7.2 Hz), 0.80 (t, 3H, J = 7.2 Hz).

7-Allyl-*N*-butyl-8-ethyl-7*H*-purin-6-amine (3h). Pale yellow solid; yield 80%; mp 113.5−115.6 °C. ES-MS: 260 (M + H^+). ^{1}H NMR: 8.49 (s, 1H), 6.09−6.21 (m, 1H), 5.40−5.45 (m, 1H), 5.01−5.08 (m, 1H), 4.86 (br, 1H), 4.81−4.83 (m, 2H), 3.49−3.56 (m, 2H), 2.79−2.87 (m, 2H), 1.55−1.64 (m, 2H), 1.36−1.45 (m, 5H), 0.95 (t, 3H, J = 7.2 Hz).

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