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An efficient synthesis of substituted cytosines and purines under focused microwave irradiation

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Abstract—A rapid nucleophilic displacement reaction of 6-chloropurine, 2-amino-6-chloropurine and 5-bromocytosine with various nucleophiles under focused microwave irradiation is described. Using this method, the desired products were obtained with the yields up to 99% in a short reaction time.

1. Introduction

Nucleosides play important roles in various biological processes. Many nucleoside analogues with modifications on the heterocyclic bases have been investigated for their antiviral and anticancer activities. There are extensive interests in the study of cytosine, purine and guanine derivatives. Surprisingly, the synthesis of 5-substituted cytosines has not yet been reported. To our best knowledge, there are few reports on the amination of guanine by a conventional method.[1] Among various synthetic routes to purine derivatives, conversion of the oxo group in hypoxanthine to amino groups is the most widely used.[2] However, this synthetic route often requires vigorous reaction conditions and prolonged reaction time to give low yields of the desired products. Taking the beneficial effect of microwave irradiation in the promotion of organic syntheses,[3] we carried out a novel and efficient synthesis of a series of cytosine and purine derivatives.

2. Results and discussion

In order to find the optimized conditions for the synthesis of cytosine and purine derivatives, the reactions of 5-bromocytosine, 6-chloroguanine and 2-amino-6-chloropurine with nucleophiles were investigated in detail with varied amounts of substrates and reaction conditions including reaction times, temperatures and solvents. We first studied the nucleophilic displacement reactions of 5-bromocytosine with amines. The substitution reaction of 5-bromocytosine with 4 equiv of 1-naphthylmethylamine in *N*-methylpyrrolidone (NMP) proceeded smoothly at 175 °C by microwave irradiation for 20 min to give the corresponding 5-(1-naphthylmethylamino)cytosine in 75% yield (entry 1, Table 1). No solvent is required for the substitution reaction with *N*-methylbenzylamine (20 equiv), giving 5-(*N*-methylbenzylamino)cytosine in 90% yield by microwave irradiation at 175 °C for 25 min (entry 3, Table 1). The nucleophilic substitution with morpholine is better conducted in NMP by comparison of the results in entries 4 and 5 (Table 1). The reaction of 5-bromocytosine with piperidine occurred in similar conditions (entry 7, Table 1) to afford a 70% yield of 5-piperidylcytosine. The substitution reaction of 5-bromocytosine with PhSNa was also realized to afford 40–70% yields of the desired product under microwave irradiation for 1–5 min in the solvent NMP, DMSO or HMPA (entries 8–11, Table 1). Attempted substitution reaction of 5-fluorocytosine with PhSNa in NMP and HMPA failed (entries 12 and 13, Table 1). It is obvious that 5-bromocytosine is more reactive than 5-fluorocytosine in the substitution reaction with sodium thiophenoxide.

We then studied the substitution reactions of 6-chloropurine and 2-amino-6-chloropurine. When 6-chloropurine was treated with 10 equiv of primary amines, including benzylamine, butylamine and aniline in the absence of solvent, by microwave irradiation in less than 6 min, the corresponding 6-substituted purines were obtained in high yields (86–95%, entries 1–3, Table 2). The microwave assisted substitution reactions of 6-chloropurine with secondary amines, such as piperidine and morpholine, also took place to afford 94% yield of the desired products (entries 4 and 5, Table 2). However, the reaction with diphenylamine failed (entry 6, Table 2), presumably due to the steric hindrance of this

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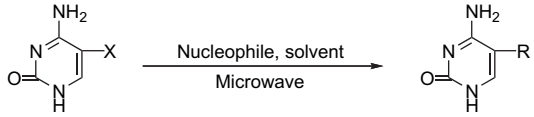
Table 1. Reactions of 5-halocytosine with nucleophiles



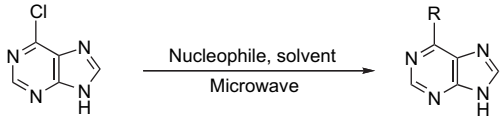
Entry	–X	Nucleophile	Solvent	Molar proportions of nucleophile	Temp (°C)	Time (min)	Product, R=	Yield (%)
1	Br	NH_2CH_2-1-naphthalyl	NMP	4	175	20	$NHCH_2$-1-naphthalyl	75
2	Br	$NH(CH_3)CH_2Ph$	[a]	15	170	20	$N(CH_3)CH_2Ph$	65
3	Br	$NH(CH_3)CH_2Ph$	[a]	20	175	25	$N(CH_3)CH_2Ph$	90
4	Br	Morpholine	[a]	40	120	25	N-morpholyl	69
5	Br	Morpholine	NMP	20	150	25	N-morpholyl	84
6	Br	Piperidine	NMP	20	140	20	Piperidyl	55
7	Br	Piperidine	NMP	20	140	25	Piperidyl	70
8	Br	PhSNa	NMP	4	150	1	SPh	70
9	Br	PhSNa	NMP	4	150	5	SPh	63
10	Br	PhSNa	DMSO	4	150	5	SPh	40
11	Br	PhSNa	HMPA	4	150	5	SPh	58
12	F	PhSNa	NMP	4	160	10	SPh	0
13	F	PhSNa	HMPA	4	180	5	SPh	0

[a] No solvent was used.

bulky amine. The displacement reactions of 6-chloropurine with *O*- and *S*-nucleophiles, including MeONa, EtONa, $PhCH_2OH$, PhONa, MeSNa and PhSNa, also proceeded to give the corresponding 6-substituted purines in high yields (entries 7–16, Table 2). In the cases using benzyl alcohol and sodium phenoxide, DMSO is the solvent of choice in comparison with NMP or HMPA (entries 10–14, Table 2). Because sodium phenoxide is a relatively weak nucleophile, elevated reaction temperature (150 °C) and prolonged reaction time (10 min) are applied to improve the yield (entry 13, Table 2). The substitution reaction with PhSeH was achieved in NMP in the presence of a base (*t*-BuOK) to provide 6-phenylselenylpurine in 76% yield (entry 17, Table 2). Interestingly, the microwave assisted substitution reaction with PhSeH occurred in aqueous media using $Ba(OH)_2$ or KOH as the base to give quantitative product (entries 18 and 19, Table 2). We also investigated the possibility in the substitution reactions of 6-chloropurine with the nucleophiles of glycine (NH_2CH_2COOH), thioglycolic acid sodium salt ($HSCH_2COONa$), phenylacetonitrile ($PhCH_2CN$) and malononitrile ($CH_2(CN)_2$), but no desired products could be isolated even in strenuous reaction conditions.

Intrigued by our above-described results, a more electron-rich 2-amino-6-chloropurine was chosen as the substrate to probe whether the nucleophilic displacement reactions could be easily accessed. To our expectation, the microwave assisted substitution reactions proceeded smoothly with various

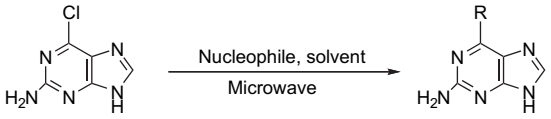
Table 2. Reactions of 6-chloropurine with nucleophiles



Entry	Nucleophile	Solvent	Molar proportions of nucleophile	Temp (°C)	Time (min)	Product, R=	Yield (%)
1	NH_2CH_2Ph	[a]	10	100	5	$NHCH_2Ph$	95
2	$NH_2(CH_2)_3CH_3$	[a]	10	80	6	$NH(CH_2)_3CH_3$	87
3	$PhNH_2$	[a]	10	130	1	NHPh	86
4	Morpholine	[a]	10	80	1	N-morpholyl	94
5	Piperidine	[a]	10	80	1	Piperidyl	94
6	$NH(Ph)_2$	NMP	3	150	15	$N(Ph)_2$	0
7	MeONa	DMF	2.5	90	1	OMe	99
8	EtONa	DMF	4	100	2	OEt	90
9	EtONa	NMP	4	100	2	OEt	99
10	$PhCH_2OH$	DMSO	3	100	3	OCH_2Ph	92
11	$PhCH_2OH$	NMP	3	100	3	OCH_2Ph	88
12	$PhCH_2OH$	HMPA	3	100	3	OCH_2Ph	81
13	PhONa	DMSO	4	150	10	OPh	91
14	PhONa	NMP	4	150	5	OPh	83
15	MeSNa	DMF	3	80	1	SMe	99
16	PhSNa	DMF	1	80	1	SPh	99
17	PhSeH/*t*-BuOK	NMP	4	90	1	SePh	76
18	PhSeH/$Ba(OH)_2$	H_2O	3	90	2	SePh	99
19	PhSeH/KOH	H_2O	3	90	2	SePh	98

[a] No solvent was used.

Table 3. Reactions of 2-amino-6-chloropurine with nucleophiles



Entry	Nucleophile	Solvent	Molar proportions of nucleophile	Temp (°C)	Time (min)	Product, R=	Yield (%)
1	NH_2CH_2Ph	[a]	10	110	15	$NHCH_2Ph$	93
2	$NH_2(CH_2)_3CH_3$	[a]	20	80	15	$NH(CH_2)_3CH_3$	84
3	Cyclohexylamine	[a]	30	130	1	Cyclohexylamino	94
4	$PhNH_2$	[a]	10	130	5	NHPh	96
5	$PhNH_2$	[a]	10	130	5	NHPh	48[b]
6	Morpholine	[a]	10	90	1	N-morpholyl	99
7	Piperidine	[a]	10	90	1	Piperidyl	93
8	MeONa	NMP	3	100	1	OMe	99
9	EtONa	DMSO	3	100	2	OEt	83
10	EtONa	NMP	3	100	3	OEt	98
11	$PhCH_2OH$	DMSO	3	100	1	OCH_2Ph	74
12	PhONa	DMSO	4	150	10	OPh	96
13	MeSNa	DMF	2.2	90	1	SMe	91
14	MeSNa	NMP	3	90	1	SMe	99
15	PhSNa	DMF	2	80	1	SPh	99

[a] No solvent was used.
[b] Heating in oil bath.

primary and secondary aliphatic amines (benzylamine, butylamine, cyclohexylamine, morpholine and piperidine), and even the less basic aromatic amine (aniline). These reactions were performed in the absence of solvent to give 84–99% yields of the substitution products (entries 1–4, 6 and 7, Table 3). In order to compare the efficacy of microwave irradiation with conventional heating, 2-amino-6-chloropurine was heated with 10 equiv of aniline at 130 °C in an oil bath for 5 min to give only 48% of 2-amino-6-anilinopurine (entry 5, Table 3), far less than 96% in microwave irradiation (entry 4, Table 3). Under microwave irradiation, 2-amino-6-chloropurine also reacted with the nucleophiles of MeONa, EtONa, $PhCH_2OH$, PhONa, MeSNa and PhSNa to afford 74–99% yields of the 2-amino-6-substituted purines (entries 8–15, Table 3).

In summary, we have established a novel and efficient route to the synthesis of various derivatives of cytosine and purines. In connection with our investigation of new chemotherapeutic agents of nucleoside antimetabolites, our synthetic method using microwave irradiation is definitely valuable for the rapid access of these bioactive heterocyclic bases. Our current results also show that the relative aptitude of heterocyclic substrates for the nucleophilic substitution reactions follows 6-chloropurine∼2-amino-6-chloropurine> 5-bromocytosine ≫ 5-fluorocytosine.

3. Experimental section

3.1. General

^{1}H NMR spectra were measured in DMSO-d_6 or $CDCl_3$ solutions on a Bruker 300 spectrometer. Reactions were monitored by analytical thin-layer chromatography using silica gel 60 F_{254} (0.2 mm layer thickness). Flash chromatography was carried out by utilizing silica gel 60 (70–230 mesh ASTM).

3.2. General procedure for reaction of halocytosines and halopurines with nucleophile

In a reaction vessel (12 mL) were placed a nucleophile and a halocytosine (0.1 mmol) in an appropriate solvent (1 mL). A base [*t*-BuOK, $Ba(OH)_2$ or KOH (1.1 equiv vs nucleophile)] could be added in appropriate cases. The reaction vessel was then placed into the cavity of a focused monomode microwave reactor (CEM Discover), and irradiated for the period listed in the tables. The reaction temperature was maintained by modulating the power level of the reactor. The desired product precipitated when the pH was adjusted to 6 with 6 N HCl. The product was collected, washed with H_2O and then purified by recrystallization. Products **11**–**15** and **24**–**28** were purified by silica gel chromatography eluting with a mixture of hexane, ethyl acetate and acetone.

3.2.1. 5-(1-Naphthalylmethylamino)cytosine. Pale white solid, mp 315 °C; IR (KBr): 3405, 1707, 1529, 1381, 1248 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.18 (br, 1H, 1-NH), 10.07 (br, 1H, 4-NH), 8.15–7.44 (m, 7H), 6.25 (s, 1H, 6-H), 4.87 (t, J=5.7 Hz, 1H, –NH), 4.54 (d, J=5.7 Hz, 2H, $-NCH_2Ph$); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.3, 149.2, 134.2, 133.9, 131.0, 128.5, 127.4, 126.1, 125.7, 125.4, 124.7, 123.7, 123.5, 113.2, 45.8; MS *m/e* 267 (M^++H), 155, 141; HRMS *m/e* calcd for 267.1255, found 267.3059. Anal. Calcd for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04. Found: C, 67.67; H, 4.96; N, 20.95.

3.2.2. 5-(Benzylmethylamino)cytosine. Yellow solid, mp 250–252 °C; IR (KBr) 3415, 1653, 1458, 1231 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.19 (s, 1H, NH), 7.31–7.22 (m, 5H, Ph), 7.11 (s, 1H, 4-NH), 6.73 (s, 1H, 6-H), 3.90 (s, 2H, $-NH_2Ph$), 2.41 (s, 3H, N–CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 164.2, 155.5, 137.8, 134.1, 128.6 (2C), 128.1 (2C), 127.0, 119.1, 58.9, 42.3; MS *m/e* 230 (M^+), 139, 120, 91; HRMS *m/e* calcd for 230.2688, found

230.1160. Anal. Calcd for $C_{12}H_{14}N_4O$: C, 62.59; H, 6.13; N, 24.33. Found: C, 62.20; H, 6.13; N, 23.90.

3.2.3. 5-Morpholinocytosine. Pale yellow solid, mp 245 °C (dec); IR (KBr) 3455, 1651, 1454, 1230 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 10.23 (br, 1H, 1-NH), 7.13 (s, 2H, $-NH_2$), 6.56 (s, 1H, 6-H), 3.66 (t, J=4.5 Hz, 4H), 2.65 (t, J=4.5 Hz, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.7, 155.5, 132.8, 119.8, 66.3 (2C), 52.0 (2C); MS *m/e* 196 (M^+), 180, 111, 86; HRMS *m/e* calcd for 196.1284, found 196.0968. Anal. Calcd for $C_8H_{12}N_4O_2$: C, 48.97; H, 6.16; N, 28.56. Found: C, 49.09; H, 6.25; N, 28.05.

3.2.4. 5-Piperidylcytosine. Pale yellow solid, mp 290 °C (dec); IR (KBr) 3465, 1649, 1453, 1226 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 10.11 (br, 1H, 1-NH), 7.04 (s, 2H, $-NH_2$), 6.33 (s, 1H, 6-H), 2.60 (m, 4H), 1.59 (m, 4H), 1.44 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.9, 160.0, 155.5, 132.2, 121.0, 53.0 (2C), 25.8 (2C), 23.5; MS *m/e* 194 (M^+), 177, 110, 84; HRMS *m/e* calcd for 194.2376, found 194.1163. Anal. Calcd for $C_9H_{14}N_4O$: C, 55.65; H, 7.27; N, 28.85. Found: C, 55.54; H, 7.02; N, 28.70.

3.2.5. 5-Phenylthiocytosine. Colourless solid, mp 308 °C (dec); IR (KBr) 3447, 1684, 1456, 1235 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.00 (s, 1H, NH), 7.84 (s, 1H, 4-NH), 7.50 (s, 1H, 4-NH), 7.33–7.15 (m, 5H, SPh), 6.78 (s, 2H, $-NH_2$); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.3, 160.0, 153.3, 135.4, 129.0 (2C), 128.2 (3C), 88.7, 58.1, 39.4, 33.4, 27.9; MS *m/e* 219 (M^+), 142, 110, 77; HRMS *m/e* calcd for 219.2262, found 219.0459. Anal. Calcd for $C_{10}H_9N_3OS$: C, 41.60; H, 4.07; N, 8.09; S, 18.50. Found: C, 41.70; H, 4.15; N, 8.11; S, 18.60.

3.2.6. 6-Benzylaminopurine.[2] Pale yellow solid, mp 237–238 °C (lit. 236–237 °C); ^1H NMR (300 MHz, DMSO-d_6) δ 12.79 (s, 1H, NH), 8.36 (s, 1H, 2-H), 8.10 (s, 1H, 8-H), 7.46–7.17 (m, 5H, Ph), 4.76 (br, 2H, $-CH_2Ph$).

3.2.7. 6-Butylaminopurine.[2] White solid, mp 230–232 °C (lit. 223–234 °C); ^1H NMR (300 MHz, DMSO-d_6) δ 12.84 (s, 1H, 9-NH), 8.14 (s, 1H, 2-H), 8.05 (s, 1H, 8-H), 3.46 (br, 2H), 1.61–1.49 (m, 2H), 1.38–1.26 (m, 2H), 0.88 (t, J=7.2 Hz, 3H).

3.2.8. 6-Anilinopurine.[2] Pale yellow solid, mp 290–291 °C (lit. 284–286 °C); ^1H NMR (300 MHz, DMSO-d_6) δ 13.15 (s, 1H, 9-NH), 9.74 (s, 1H, NHPh), 8.37 (s, 1H), 8.22 (s, 1H), 7.93–6.99 (m, 5H, Ph).

3.2.9. 6-Morpholinopurine.[2] White solid, mp 315–316 °C (lit. 300–301 °C); ^1H NMR (300 MHz, DMSO-d_6) δ 13.00 (br, 1H, 9-NH), 8.22 (s, 1H, 2-H), 8.13 (s, 1H, 8-H), 4.19 (m, 4H), 3.70 (m, 4H).

3.2.10. 6-Piperidylpurine.[2] White solid, mp 286–287 °C (lit. 274–275 °C); ^1H NMR (300 MHz, DMSO-d_6) δ 12.89 (br, 1H, 9-NH), 8.18 (s, 1H, 2-H), 8.07 (s, 1H, 8-H), 4.18 (m, 4H), 1.66–1.63 (m, 2H), 1.57–1.48 (m, 4H).

3.2.11. 6-Methoxypurine.[4] White solid, mp 195–196 °C (lit. 197–199 °C); ^1H NMR (300 MHz, DMSO-d_6) δ 8.49 (s, 1H), 8.36 (s, 1H), 4.07 (s, 3H, OCH_3).

3.2.12. 6-Ethoxypurine.[5] White solid, mp 220–222 °C (lit. 223–224 °C); ^1H NMR (300 MHz, DMSO-d_6) δ 13.38 (s, 1H, 9-NH), 8.46 (s, 1H), 8.35 (s, 1H), 4.57 (q, J=7.2 Hz, 2H), 1.40 (t, J=7.2 Hz, 3H).

3.2.13. 6-Benzyloxypurine.[6] Light brown solid, mp 173–175 °C (lit. 171–172 °C); ^1H NMR (300 MHz, DMSO-d_6) δ 13.44 (s, 1H, 9-NH), 8.51 (s, 1H), 8.35 (s, 1H), 7.53–7.32 (m, 5H, Ph), 5.61 (s, 2H, OCH_2Ph).

3.2.14. 6-Phenoxypurine.[7] White solid, mp 213–216 °C (lit. 217–218 °C); ^1H NMR (300 MHz, DMSO-d_6) δ 13.56 (s, 1H, 9-NH), 8.50 (s, 1H), 8.41 (s, 1H), 7.49–7.27 (m, 5H, OPh).

3.2.15. 6-Methylthiopurine.[7] White solid, mp 222–224 °C (lit. 220–223 °C); ^1H NMR (300 MHz, DMSO-d_6) δ 8.69 (s, 1H), 8.41 (s, 1H), 2.88 (s, 3H, SCH_3).

3.2.16. 6-Phenylthiopurine. White solid, mp 261–262 °C; IR (KBr) 3085, 1240 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 13.56 (s, 1H, 9-NH), 8.53 (s, 1H), 8.50 (s, 1H), 7.51–7.48 (m, 5H, SPh); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.9, 155.9, 151.2, 136.6, 136.4, 129.1 (4C), 126.2, 125.9; MS *m/e* 228 (M^+), 119, 109, 77; HRMS *m/e* calcd for 228.2710, found 228.0475. Anal. Calcd for $C_{11}H_8N_4S$: C, 57.88; H, 3.53; N, 24.54. Found: C, 57.59; H, 4.05; N, 24.60.

3.2.17. 6-Phenylselenylpurine. Pale yellow solid, mp 240–242 °C; IR (KBr) 3078, 1227 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 13.59 (s, 1H, 9-NH), 8.53 (s, 1H), 8.51 (s, 1H), 7.71–7.43 (m, 5H, SePh); ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.9, 151.7, 150.2, 144.3, 136.3, 131.6 (4C), 129.4, 129.0, 124.8; MS *m/e* 276 (M^+), 157, 119, 77; HRMS *m/e* calcd for 275.9914, found 275.9921. Anal. Calcd for $C_{11}H_8N_4Se$: C, 48.01; H, 2.93; N, 20.36. Found: C, 48.27; H, 2.82; N, 20.16.

3.2.18. 2-Amino-6-benzylaminopurine.[1a] White solid, mp 247–248 °C (lit. 228–230 °C); ^1H NMR (300 MHz, DMSO-d_6) δ 12.06 (s, 1H, 9-NH), 7.63 (s, 1H, 8-H), 7.34–7.16 (m, 5H, Ph), 5.67 (s, 2H, $-NH_2$), 4.64 (br, 2H, $-NCH_2Ph$).

3.2.19. 2-Amino-6-butylaminopurine.[1b] White solid, mp 181–182 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 11.99 (br, 1H, 9-NH), 7.62 (s, 1H, 8-H), 6.97 (br, 1H, NH), 5.60 (s, 2H, $-NH_2$), 3.42 (m, 2H), 1.58–1.48 (m, 2H), 1.38–1.25 (m, 2H), 0.89 (t, J=7.2 Hz, 3H).

3.2.20. 2-Amino-6-cyclohexylaminopurine.[1c] Pale yellow solid, mp 204–205 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 12.00 (s, 1H, 9-NH), 7.61 (s, 1H, 8-H), 6.70 (d, J=8.1 Hz, 1H, NH), 5.60 (s, 2H, $-NH_2$), 4.06 (m, 1H), 1.82–1.12 (m, 10H).

3.2.21. 2-Amino-6-anilinopurine.[1d] Pale yellow solid, mp 330–331 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 13.10 (br, 1H, 9-NH), 10.61 (br, 1H, NHPh), 8.17 (s, 1H, 8-H), 7.99–7.08 (m, 5H, Ph).

3.2.22. 2-Amino-6-morpholinopurine.[1e] White solid, mp 274–275 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 12.18 (br,

1H, 9-NH), 7.67 (s, 1H, 8-H), 5.74 (s, 2H, $-NH_2$), 4.09 (m, 4H), 3.66 (m, 4H).

3.2.23. 2-Amino-6-piperidylpurine.[1f] White solid, mp 262–263 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.06 (br, 1H, 9-NH), 7.63 (s, 1H, 8-H), 5.64 (s, 2H, $-NH_2$), 4.09 (m, 4H), 1.64–1.62 (m, 2H), 1.53–1.52 (m, 4H).

3.2.24. 2-Amino-6-methoxypurine.[8] White solid, mp 253 °C (dec) (lit. 260 °C, dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.37 (br, 1H, 9-NH), 7.78 (s, 1H, 8H), 6.22 (s, 2H, $-NH_2$), 3.94 (s, 3H, OCH_3).

3.2.25. 2-Amino-6-ethoxypurine.[9] White solid, mp 260 °C (dec) (lit. 293 °C, dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.35 (s, 1H, 9-NH), 7.77 (s, 1H, 8H), 6.17 (s, 2H, $-NH_2$), 4.43 (q, J=7.0 Hz, 2H), 1.34 (t, J=7.0 Hz, 3H).

3.2.26. 2-Amino-6-benzyloxypurine.[10] White solid, mp 205–206 °C (lit. 204–206 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.41 (s, 1H, 9-NH), 7.80 (s, 1H, 8-H), 7.59–7.25 (m, 5H, Ph), 6.29 (s, 2H, $-NH_2$), 5.47 (s, 2H, OCH_2Ph).

3.2.27. 2-Amino-6-phenoxypurine. Pale white solid, mp 226–231 °C (dec); IR (KBr): 3480, 1282 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.55 (s, 1H, 9-NH), 7.94 (s, 1H, 8H), 7.45–7.21 (m, 5H, OPh), 6.25 (s, 2H, $-NH_2$); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.7, 159.5, 156.1, 152.7, 138.8, 129.5, 124.9, 121.7, 113.8; MS *m/e* 227 (M^+), 211, 134, 93, 77; HRMS *m/e* calcd for 227.2250, found 227.0812. Anal. Calcd for $C_{11}H_9N_5O$: C, 58.14; H, 3.99; N, 30.82. Found: C, 57.96; H, 4.45; N, 30.54.

3.2.28. 2-Amino-6-methylthiopurine.[11] Pale white solid, mp 239–241 °C (lit. 238–241 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.50 (s, 1H, 9-NH), 7.88 (s, 1H, 8H), 6.32 (s, 2H, $-NH_2$), 2.54 (s, 3H, SCH_3).

3.2.29. 2-Amino-6-phenylthiopurine.[12] White solid, mp 205–206 °C (dec) (lit. 205 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.56 (s, 1H, 9-NH), 7.93 (s, 1H, 8-H), 7.60–7.41 (m, 5H, SPh), 6.18 (s, 2H, $-NH_2$).

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