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One-pot synthesis of *N*-alkyl purine and pyrimidine derivatives from alcohols using TsIm: a rapid entry into carboacyclic nucleoside synthesis

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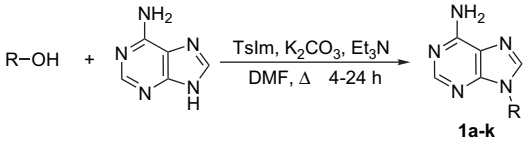
Abstract

A convenient and efficient one-pot N-alkylation of nucleobases from alcohols using *N*-(*p*-toluenesulfonyl)imidazole (TsIm) is described. In this method, treatment of alcohols with a mixture of purine or pyrimidine nucleobase, TsIm, K_2CO_3, and triethylamine in refluxing DMF regioselectively furnishes the corresponding *N*-alkyl nucleobases in good yields. This methodology is highly efficient for various structurally diverse primary alcohols.

Keywords: Nucleobase; Alcohol; N-Alkylation; *N*-(*p*-Toluenesulfonyl)imidazole (TsIm); Triethylamine; K_2CO_3

1. Introduction

The N-alkylation of nucleobases has great significance since it is a direct and appealing route into nucleosides synthesis.[1] The N-alkylation of purine and pyrimidine nucleobases is usually achieved using different sources of carbon electrophiles including: alkyl halides,[2] alkyl tosylates,[3] alkyl mesylates,[4] epoxides,[5] Michael acceptors,[6] carbonates,[7] and allylic esters catalyzed by Pd(0).[8] Furthermore, the N-alkylation of nucleobases can also be achieved using active ethers including: acetoxyethyl acetoxymethyl ether and its analogues,[9] methylthiomethyl ether,[10] and cyclic acetals.[11] Due to the advantageous and attractive strategy of the direct synthesis of acyclic nucleosides from alcohols, some limited methods have been developed. Along this line, methods based on Mitsunobu conditions are widely applied.[12] However, this method is accompanied by several drawbacks including: utilizing toxic, expensive, and explosive reagents such as diethyl azodicarboxylate (DEAD) and diisopropyl azodicarboxylate (DIAD); the presence of unreacted PPh_3 and formation of $O{=}PPh_3$, which requires a tedious work up and cumbersome separation process. Recently, we have reported the *N*-(*p*-toluenesulfonyl)imidazole (TsIm) as an efficient, cheap, and stable reagent for the one-pot conversion of alcohols into alkyl azides[13] and nitriles.[14] In this context, herein; we report TsIm as an appropriate reagent for the one-pot N-alkylation of nucleobases using alcohols in the presence of a K_2CO_3/triethylamine mixture in anhydrous DMF (Schemes 1 and 2).



Scheme 1.

2. Results and discussion

The first step of this synthetic approach consists of finding out the optimized reaction conditions. The optimization was

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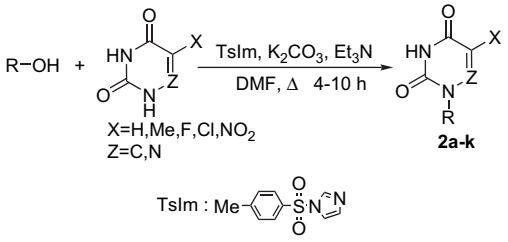


Scheme 2.

begun with studying the effect of various solvents on the model reaction of adenine, 2-phenylethanol, and freshly prepared TsIm (1.5–2.0 equiv) in the presence of an equimolar mixture of K_2CO_3/Et_3N. As the data in Table 1 indicates, through the examined solvents, anhydrous DMF (Table 1, entry 3) afforded the best result and hence it was solvent of choice for all reactions. Using DMSO and wet DMF afforded a moderate yield of the corresponding 9-phenethyl-9*H*-purin-6-amine (**1a**) while other solvents were inefficient even when the reaction time was prolonged.

The choice of the reaction base for activation of the alcohol to react with TsIm and nucleobase was of great significance. In this case, we investigated the effect of miscellaneous organic and inorganic bases on the reaction model (Table 2). The results in Table 2 demonstrate that among the employed bases, an equimolar mixture of K_2CO_3/Et_3N (Table 2, entry 10) was the most efficient base for the progress of reaction. Furthermore, using K_2CO_3 (1 equiv) (Table 2, entry 7) or Et_3N (2 equiv) (Table 2, entry 8) alone in reaction is not as efficient as an equimolar mixture of K_2CO_3/Et_3N. DBN, DBU (Table 2, entries 1 and 2), and Cs_2CO_3 (Table 2, entry 6) afforded **1a** in moderate yields while other bases were nearly inefficient. Interestingly, comparing the results of the base's role in our previous research into synthesis of alkyl azides[13] and nitriles[14] with this recent work, shows that Et_3N is more responsible for activation of alcohol than K_2CO_3.

In other experiments, we have investigated the effect of various phase transfer catalysts on the model reaction. In this case, tetra-*n*-butylammonium halides (TBAX; X=F, Cl, Br, and I) were employed. In contrary with azidation[13] and cyanidation[14] of alcohols using TsIm, TBAX had a negligible effect in the enhancement of reaction efficiency. This can be attributed to solubility of nucleobases in comparison with sodium azide and cyanide in DMF.

We also examined other TsIm analogues (Table 3). As the data in Table 3 indicates, higher yield of 9-phenethyl-9*H*-purin-6-amine (**1a**) and short reaction time were obtained with TsIm (Table 4, entry 3) in comparison with other sulfonyl analogues. Replacing the tolyl in TsIm with methyl, trifluromethyl, and phenyl gave no improvement in reaction yield (Table 3, entries 1, 2, and 4). Furthermore, changing the imidazole residue to other azole derivatives did not affect the reaction efficiency (Table 3, entries 5 and 6). *N*-Tosyl phthalimide (Table 3, entry 7) was inactive for the conversion of 2-phenylethanol to the corresponding 9-phenethyl-9*H*-purin-6-amine, even after reflux for 48 h.

Various sulfonyl chlorides were examined instead of TsIm to attain **1a** (Table 4). Lower yields of **1a** were obtained when

Table 1
Effect of various solvents on conversion of 2-phenylethanol into **1a**

Entry	Solvent	Time (h)	Yield[b] (%)
1	DMSO	6	57
2	DMF	6	63
3	DMF[a]	4	81
4	MeCN	12	22
5	HMPA	12	10
6	NMP	48	NR[c]
7	THF	12	15
8	Toluene	48	NR
9	Acetone/H_2O[d]	12	10
10	H_2O	48	NR

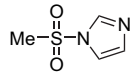
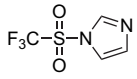
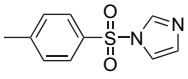
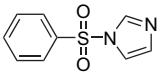
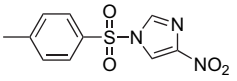
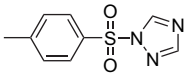
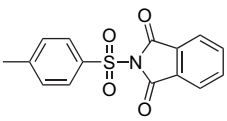
[a] Anhydrous DMF.
[b] Isolated yield.
[c] No reaction.
[d] Ratio (1:1).

Table 2
Effect of various bases on conversion of 2-phenylethanol into 9-phenethyl-9*H*-purin-6-amine in anhydrous DMF

Entry	Base	Time (h)	Yield[a] (%)
1	DBN	12	48
2	DBU	12	54
3	DABCO	24	14
4	DMAP	24	20
5	MgO	24	16
6	Cs_2CO_3	6	67
7	K_2CO_3	6	58
8	Et_3N	24	18
9	NaH	24	13
10	K_2CO_3/Et_3N[b]	4	81

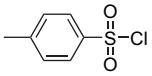
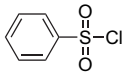
[a] Isolated yield.
[b] Ratio (1:1).

Table 3
Comparison of TsIm reactivity with analogues in reaction of adenine with 2-phenylethanol

Entry	Reagent	Time (h)	Yield[a] (%)
1		6	54
2		10	32
3		10	81
4		4	69
5		12	60
6		12	51
7		48	NR[b]

[a] Isolated yield.
[b] No reaction.

Table 4
Effect of various sulfonyl chlorides in reaction of adenine with 2-phenylethanol

Entry	Sulfonyl chloride	Time (h)	Yield[a] (%)
1		12	18
2		12	10
3		12	27
4		12	22

[a] Isolated yield.

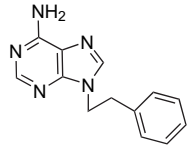
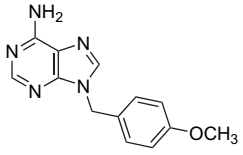
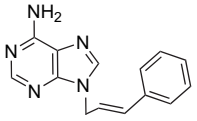
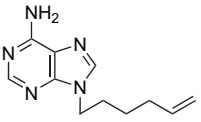
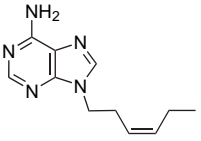
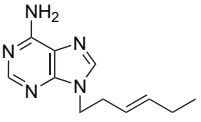
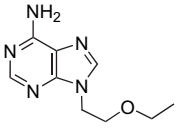
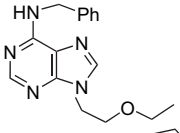
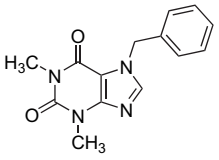
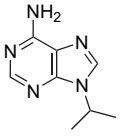
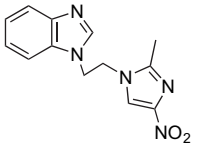
sulfonyl chlorides were employed for sulfonylation of 2-phenylethanol instead of TsIm. Additionally, the extension of these reactions to sulfonyl chlorides, uracil, and 2-phenylethanol led to complicated mixtures of side products. This probably results from the fact that, highly reactive sulfonyl chlorides have less selectivity for individual reactions with alcohols. While adenine and uracil are ambident nucleophiles that can readily react with sulfonyl chlorides at various *N*-sites to afford the complicated mixture of products.

To evaluate the general applicability and versatility of the method, the optimized conditions were applied to various structurally diverse alcohols and nucleobases (Tables 5 and 6). As the results in Tables 5 and 6 indicate, various alcohols reacted with purine and pyrimidine nucleobases to afford products **1a**–**k** and **2a**–**k**, respectively. Depicted data in Tables 5 and 6 indicate this method is suitable for primary alcohols including: aliphatic, benzylic, and allylic while the secondary and tertiary types rarely react with nucleobases. For instance, the N-alkylation of adenine with isopropyl alcohol afforded **1j** in 23% yield. This method is also applicable for the alkylation of other *N*-heterocycles. For example, the N-alkylation of benzimidazole (purine-like scaffold) was achieved with 2-(2-methyl-4-nitro-1*H*-imidazol-1-yl) ethanol, which attained **1k** in a good yield. Interestingly, good regioselectivity was observed for the site of N-alkylation in nucleobases.[15] In the case of purine nucleobases, the *N*9 isomers were almost the dominant products and *N*7 isomers were produced in trace amounts (<4–7%). The N-alkylation of pyrimidines was achieved chiefly from *N*1 site and *N*1,*N*3-dialkyl derivatives were also produced in trace amounts (<10–12%). Furthermore, O-alkylation of pyrimidine nucleobases was not observed.

To study the regioselectivity of described method, we compared the TsIm mediated N-alkylation of adenine and uracil with 1-(2-chloroethyl) benzene using a method applied by Lazrek and co-workers.[16] The results are summarized in Table 7.

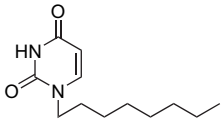
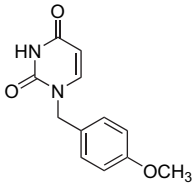
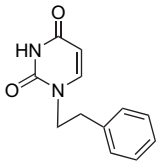
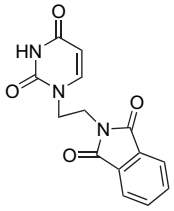
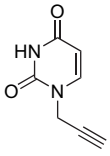
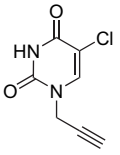
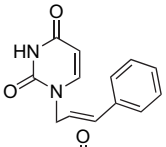
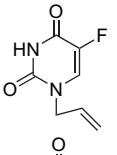
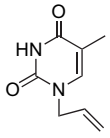
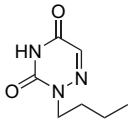
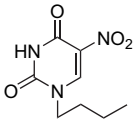
Mechanistically, it is interesting to note, there is a considerable tendency for alcohols to react with TsIm in comparison to the reaction of nucleobases with TsIm. To demonstrate this experience, we conducted two reactions. In the first experiment, the reaction was achieved in the absence of adenine with all components including TsIm, Et_3N, K_2CO_3, and 2-phenylethanol. The obtained product was an alkyl tosylate.

Table 5
One-pot N-alkylation of purines via alcohols using TsIm/Et_3N/K_2CO_3 in refluxing DMF

Compound	Structure	Mp (°C)	Time (h)	Yield[a] (%)
1a		180.1	4	81
1b		161.1	6	72
1c		237.3	10	68
1d		140.0	5	83
1e		98.1	5	61
1f		127.3	6	75
1g		148.7	5	78
1h		124.1	4	58
1i		158.6	9	61
1j		234.8	24	23
1k		223.7	10	65

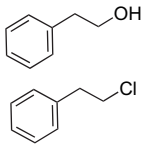
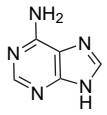
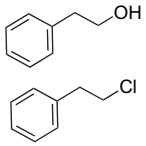
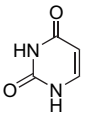
[a] Isolated yield.

Table 6
One-pot N-alkylation of pyrimidines via alcohols using TsIm/Et_3N/K_2CO_3 in refluxing DMF

Compound	Structure	Mp (°C)	Time (h)	Yield[a] (%)
2a		61.2	6	63
2b		118.9	4	60
2c		150.1	5	71
2d		263.0	6	80
2e		154.6	7	66
2f		169.4	6	59
2g		198.1	10	62
2h		101.3	8	54
2i		123.2	6	58
2j		136.4	10	60
2k		146.3	10	76

[a] Isolated yield.

Table 7
Comparison of the regioselectivity of N-alkylation for nucleobases

Compound	A.S.[a]	Nucleobase	Method	Ratio[d]
1a			TsIm/Et_3N/K_2CO_3	95:5[b]
			K_2CO_3/DMF[16]	61:39[b]
2c			TsIm/Et_3N/K_2CO_3	92:8[c]
			K_2CO_3/DMF[16]	58:42[c]

[a] Alkylating source.
[b] *N*9/*N*7.
[c] *N*1-alkyl/*N*1,*N*3-dialkyl.
[d] Isomers were separated by column chromatography.

In the second reaction, the same condition was established but in the presence of adenine and absence of alcohol. Interestingly, no tosylation of nucleobase was achieved even when the reflux time was prolonged to 48 h. The same result was also observed when the uracil was used.

3. Conclusion

A convenient method for the one-pot N-alkylation of purines and pyrimidines using alcohols in the presence of TsIm, Et_3N, and K_2CO_3 in refluxing DMF has been established. In this method various primary alcohols including: aliphatic, benzylic, and allylic underwent reaction with purines and pyrimidines to afford *N*-alkyl derivatives in reasonable to good yields. However, this method was not effective enough for N-alkylation of nucleobases with secondary and tertiary alcohols. Good regioselectivities were observed for both purines and pyrimidines in the case of site of N-alkylation using this method.

4. Experimental

4.1. General

All chemicals were purchased from *Fluka* or *Merck* chemical companies except for TsIm, which was freshly prepared according to, published methods.[13] Solvents were purified and dried due to reported methods [17] and stored over 3 Å molecular sieves.[12] The progress of the reactions was followed with TLC using silica gel *SILG/UV 254* plates. Silica gel 60, 0.063–0.200 mm (70–230 mesh ASTM) was used for column chromatography. IR spectra were run on a *Shimadzu FTIR-8300* spectrophotometer. The ^1H NMR (250 MHz) and ^{13}C NMR (62.5 MHz) were run on a *Brüker Avanced DPX-250*, FT-NMR spectrometer; δ in parts per million, J in hertz. Mass spectra were recorded on a *Shimadzu GC–MS-QP 1000 EX* apparatus. Microanalyses were performed on a *Perkin–Elmer 240-B* microanalyzer. Melting points (mp) were recorded on a *Büchi 510* apparatus in open capillary tubes and are uncorrected.

4.2. General procedure for one-pot N-alkylation of nucleobases using alcohols

In a double-necked round bottom flask (100 mL) equipped with a condenser was added a mixture, consisting of alcohol (0.01 mol), TsIm (0.012 mol), Et_3N (0.02 mol), K_2CO_3 (0.01 mol), and nucleobase (0.01 mol) in DMF (30 mL). The mixture was heated at reflux, and in most cases, darkening occurred. Heating was continued until TLC indicated no further improvement in the conversion (Tables 5 and 6). The solvent was evaporated under vacuum and the remaining foam was dissolved in $CHCl_3$ (100 mL) and subsequently washed with water (2×100 mL). The organic layer was dried (Na_2SO_4) and evaporated. The crude product was purified by column chromatography on silica gel eluting with proper solvents described below.

4.2.1. 9-Phenethyl-9H-purin-6-amine (**1a**)

Column chromatography on SiO_2, eluted with EtOAc afforded white needle crystals (1.93 g, 81%). Mp=180.1 °C; R_f (EtOAc)=0.24; δ_H (250 MHz, DMSO-d_6) 3.14 (2H, t, J 7.2 Hz, PhCH_2), 4.37 (2H, t, J 7.2 Hz, NCH_2), 7.09–7.28 (7H, m, aryl and NH_2), 7.78 (1H, s, C(2)–H, adenine), 8.18 (1H, s, C(8)–H, adenine); δ_C (62.5 MHz, DMSO-d_6) 35.1, 44.2, 118.7, 126.4, 127.9, 128.3, 137.9, 140.6, 149.4, 152.3, 155.8; IR (KBr) ν cm^{-1}: 3335 (NH_2), 3142, 2928; MS [m/z (%)]: 239 (35). Anal. Calcd for $C_{13}H_{13}N_5$: C, 62.25; H, 5.48; N, 29.27%. Found: C, 62.31; H, 5.45; N, 29.32%.

4.2.2. 9-(4-Methoxybenzyl)-9H-purin-6-amine (**1b**)

Column chromatography on SiO_2, eluted with EtOAc afforded white needle crystals (1.84 g, 72%). Mp=161.1 °C; R_f (EtOAc)=0.22; δ_H (250 MHz, DMSO-d_6) 3.67 (3H, s, OMe), 5.37 (2H, s, NCH_2), 6.87 (2H, d, J 8.6 Hz, C(2,6)–H, aryl), 7.01 (1H, s, C(2)–H, adenine), 7.22 (2H, d, J 8.6 Hz, C(3,5)–H, aryl), 7.29 (2H, s, NH_2, adenine), 8.48 (1H, s, C(8)–H, adenine); δ_C (62.5 MHz, DMSO-d_6) 45.6, 54.9, 113.9, 118.6, 121.6, 135.1, 140.5, 149.3, 152.5, 155.9, 158.7; IR (KBr) ν cm^{-1}: 3315 (NH_2), 3155, 2930; MS [m/z (%)]: 255 (40). Anal. Calcd for $C_{13}H_{13}N_5O$: C, 61.17; H, 5.13; N, 27.43%. Found: C, 61.22; H, 5.10; N, 27.44%.

4.2.3. (E)-9-Cinnamyl-9H-purin-6-amine (**1c**)

Column chromatography on SiO_2, eluted with EtOAc afforded pale yellow needle crystals (1.71 g, 68%). Mp= 237.3 °C; R_f (EtOAc)=0.32; δ_H (250 MHz, DMSO-d_6) 4.93 (2H, d, J 5.0 Hz, NCH_2), 6.43 (1H, d, J 16.4 Hz, =CH–Ph), 7.21–7.31 (6H, complex, CH_2–CH, aryl), 7.37 (1H, s, C(2)–H, adenine), 7.40 (2H, s, NH_2, exchangeable with D_2O), 8.15 (1H, s, C(8)–H, adenine); δ_C (62.5 MHz, DMSO-d_6) 44.5, 118.6, 124.5, 126.3, 127.8, 128.5, 132.3, 135.8, 140.5, 149.3, 152.4, 155.9; IR (KBr) ν cm^{-1}: 3355 (NH_2), 3130, 2950; MS [m/z (%)]: 251 (29.8). Anal. Calcd for $C_{14}H_{13}N_5$: C, 66.92; H, 5.21; N, 27.87%. Found: C, 66.88; H, 5.25; N, 27.91%.

4.2.4. 9-(Hex-5-enyl)-9H-purin-6-amine (**1d**)

Column chromatography on SiO_2, eluted with EtOAc afforded white prism crystals (1.80 g, 83%). Mp=140.0 °C; R_f (EtOAc)=0.36; δ_H (250 MHz, DMSO-d_6) 1.34 (2H, m, CH_2), 1.84 (2H, m, CH_2), 2.06 (2H, m, CH_2), 4.20 (2H, t, J 7.0 Hz, NCH_2), 4.93 (2H, dd, J 1.3, 9.2 Hz, =CH_2), 5.78 (1H, m, =CH), 7.32 (2H, br s, NH_2, exchangeable with D_2O), 8.22 (1H, s, C(2)–H, adenine), 8.25 (1H, s, C(8)–H, adenine); δ_C (62.5 MHz, DMSO-d_6) 25.1, 29.0, 32.4, 42.6, 114.8, 118.6, 138.1, 140.7, 149.4, 152.3, 155.9; IR (KBr) ν cm^{-1}: 3330 (NH_2), 3115, 2948; MS [m/z (%)]: 217 (21.0). Anal. Calcd for $C_{11}H_{15}N_5$: C, 60.81; H, 6.96; N, 32.23%. Found: C, 60.86; H, 7.00; N, 32.20%.

4.2.5. (Z)-9-(Hex-3-enyl)-9H-purin-6-amine (**1e**)

Column chromatography on SiO_2, eluted with EtOAc afforded pale yellow prism crystals (1.3 g, 61%). Mp=98.1 °C; R_f (EtOAc)=0.19; δ_H (250 MHz, DMSO-d_6) 0.64 (3H, t, J 7.6 Hz, Me), 1.70 (2H, m, MeCH_2), 2.58 (2H, m, NCH_2CH_2), 4.14 (2H, t, J 6.7 Hz, NCH_2), 5.37 (2H, m, 2(=CH)), 7.23 (2H, br s, NH_2, exchangeable with D_2O), 8.12 (1H, s, C(2)–H, adenine), 8.19 (1H, s, C(8)–H, adenine); δ_C (62.5 MHz, DMSO-d_6) 13.6, 19.7, 27.0, 42.5, 118.6, 124.3, 134.2, 140.8, 149.4, 152.2, 155.8; IR (KBr) ν cm^{-1}: 3300 (NH_2), 3110, 2950; MS [m/z (%)]: 217 (22.3). Anal. Calcd for $C_{11}H_{15}N_5$: C, 60.81; H, 6.96; N, 32.23%. Found: C, 60.80; H, 7.01; N, 32.35%.

4.2.6. (E)-9-(Hex-3-enyl)-9H-purin-6-amine (**1f**)

Column chromatography on SiO_2, eluted with EtOAc afforded white prism crystals (1.62 g, 75%). Mp=127.3 °C; R_f (EtOAc)=0.27; δ_H (250 MHz, DMSO-d_6) 0.51 (3H, t, J 7.4 Hz, Me), 1.03 (2H, m, MeCH_2), 1.64 (2H, m, NCH_2CH_2), 4.46 (2H, t, J 4.0 Hz, NCH_2), 5.37 (2H, m, 2(=CH)), 7.07 (2H, s, NH_2, exchangeable with D_2O), 7.83 (1H, s, C(2)–H, adenine), 7.91 (1H, s, C(8)–H, adenine); δ_C (62.5 MHz, DMSO-d_6) 13.6, 21.4, 33.3, 44.3, 118.6, 124.7, 134.0, 140.3, 149.2, 152.4, 155.9; IR (KBr) ν cm^{-1}: 3310 (NH_2), 3110, 2950; MS [m/z (%)]: 217 (21.7). Anal. Calcd for $C_{11}H_{15}N_5$: C, 60.81; H, 6.96; N, 32.23%. Found: C, 60.81; H, 7.00; N, 32.20%.

4.2.7. 9-(2-Ethoxyethyl)-9H-purin-6-amine (**1g**)

Column chromatography on SiO_2, eluted with EtOAc afforded white needle crystals (1.6 g, 78%). Mp=148.7 °C; R_f (EtOAc)=0.12; δ_H (250 MHz, DMSO-d_6) 0.98 (3H, t, J 6.9 Hz, Me), 3.36 (2H, q, J 6.9 Hz, MeCH_2), 3.69 (2H, t, J 5.2 Hz, NCH_2), 4.27 (2H, t, J 5.2 Hz, OCH_2), 7.24 (2H, s, NH_2, exchangeable with D_2O), 8.06 (1H, s, C(2)–H, adenine), 8.48 (1H, s, C(8)–H, adenine); δ_C (62.5 MHz, DMSO-d_6) 14.8, 65.2, 67.5, 67.6, 118.5, 141.1, 149.4, 152.3, 155.8; IR (KBr) ν cm^{-1}: 3310 (NH_2), 3160, 2985; MS [m/z (%)]: 207 (23). Anal. Calcd for $C_9H_{13}N_5O$: C, 52.16; H, 6.32; N, 33.79%. Found: C, 52.21; H, 6.27; N, 33.83%.

4.2.8. Benzyl-[9-(2-ethoxyethyl)-9H-purin-6-yl]-amine (**1h**)

Column chromatography on SiO_2, eluted with EtOAc afforded white needle crystals (1.72 g, 58%). Mp=124.1 °C; R_f (EtOAc)=0.41; δ_H (250 MHz, DMSO-d_6) 1.00 (3H, t, J

6.9 Hz, *Me*), 3.36 (2H, q, *J* 6.9 Hz, MeCH_2), 3.69 (2H, t, *J* 5.2 Hz, NCH_2), 4.28 (2H, t, *J* 5.2 Hz, OCH_2), 4.72 (2H, br s, PhCH_2), 7.13–7.66 (5H, m, aryl), 8.09 (1H, s, C(2)–H, adenine), 8.21 (1H, s, C(8)–H, adenine) 8.51 (1H, br s, NH); δ_C (62.5 MHz, DMSO-d_6) 15.3, 40.9, 43.2, 65.8, 68.0, 119.4, 126.9, 127.5, 128.5, 140.6, 141.5, 149.3, 152.7, 154.8; IR (KBr) ν cm^{-1}: 3300 (NH_2), 3130, 2900; MS [*m*/*z* (%)]: 297 (20.1). Anal. Calcd for $C_{16}H_{19}N_5O$: C, 64.63; H, 6.44; N, 23.55%. Found: C, 64.68; H, 6.46; N, 23.60%.

4.2.9. 7-Benzyl-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione (**1i**)

Column chromatography on SiO_2, eluted with EtOAc/*n*-hexane (50:50) afforded white needle crystals (1.65 g, 61%). Mp=158.6 °C; R_f (EtOAc)=0.48; δ_H (250 MHz, $CDCl_3$) 3.31 (3H, s, N(3)–*Me*), 3.49 (3H, s, N(1)–*Me*), 5.53 (2H, s, N(7)–CH_2), 7.12–7.31 (5H, m, aryl), 7.62 (1H, s, C(8)–H); δ_C (62.5 MHz, $CDCl_3$) 27.9, 29.6, 50.1, 106.8, 127.3, 127.8, 128.6, 135.3, 140.8, 148.7, 151.5, 155.1; IR (KBr) ν cm^{-1}: 3100, 2980, 2895, 1720 (C═O), 1705 (C═O); MS [*m*/*z* (%)]: 270 (31.4). Anal. Calcd for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N, 20.73%. Found: C, 62.26; H, 5.26; N, 20.70%.

4.2.10. 9-Isopropyl-9H-purin-6-amine (**1j**)

Column chromatography on SiO_2, eluted with EtOAc afforded white cube crystals (0.41 g, 23%). Mp=234.8 °C; R_f (EtOAc)=0.26; δ_H (250 MHz, DMSO-d_6) 1.46 (6H, d, *J* 6.6 Hz, 2*Me*), 4.66 (1H, m, C*H*), 7.16 (2H, br s, NH_2, exchangeable with D_2O), 8.08 (1H, s, C(2)–H, adenine): 8.17 (1H, s, C(8)–H, adenine); δ_C (62.5 MHz, DMSO-d_6) 22.0, 46.3, 119.0, 138.7, 148.9, 152.0, 155.8; IR (KBr) ν cm^{-1}: 3310 (NH_2), 3160, 2985, 2850; MS [*m*/*z* (%)]: 177 (31.9). Anal. Calcd for $C_8H_{11}N_5$: C, 54.22; H, 6.26; N, 39.52%. Found: C, 54.20; H, 6.30; N, 39.48%.

4.2.11. 1-(2-(2-Methyl-4-nitro-1H-imidazol-1-yl)ethyl)-1H-benzo[d]imidazole (**1k**)

Column chromatography on SiO_2, eluted with EtOAc afforded pale yellow cube crystals (1.76 g, 65%). Mp=223.7 °C; R_f (MeOH/EtOAc) (1:10)=0.30; δ_H (250 MHz, DMSO-d_6) 1.82 (3H, s, *Me*), 4.43 (2H, t, *J* 6.2 Hz, NCH_2), 4.68 (2H, t, *J* 6.2 Hz, NCH_2), 7.19 (m, 2H, aryl), 7.20 (1H, d, *J* 7.5 Hz, aryl), 7.65 (1H, d, *J* 7.5 Hz, aryl), 8.01 (1H, s, C(5)–H, imidazole), 8.16 (1H, s, C(2)–H, benzimidazole); δ_C (62.5 MHz, DMSO-d_6) 12.0, 44.0, 46.1, 109.8, 119.4, 121.7, 122.1, 122.5, 133.5, 143.1, 143.8, 145.0, 145.4; IR (KBr) ν cm^{-1}: 3210, 3100, 2980, 2895; MS [*m*/*z* (%)]: 271 (33.2). Anal. Calcd for $C_{13}H_{13}N_5O_2$: C, 57.56; H, 4.83; N, 25.82%. Found: C, 57.51; H, 4.89; N, 25.83%.

4.2.12. 1-Octylpyrimidine-2,4(1H,3H)-dione (**2a**)

Column chromatography on SiO_2, eluted with EtOAc/*n*-hexane (50:50) afforded pale yellow needle crystals (1.4 g, 63%). Mp=61.2 °C; R_f (EtOAc)=0.55; δ_H (250 MHz, $CDCl_3$) 0.87 (3H, t, *J* 6.2 Hz, *Me*), 1.26–1.31 (10H, m, 5CH_2), 1.49–1.52 (2H, m, CH_2), 3.73 (2H, t, *J* 7.2 Hz, NCH_2), 5.74 (1H, d, *J* 7.8 Hz, C(5)–H uracil), 7.20 (1H, d, *J* 7.8 Hz, C(6)–H uracil), 10.48 (1H, s, N3–H, exchangeable with D_2O); δ_C (62.5 MHz, $CDCl_3$) 14.0, 22.5, 26.9, 29.0, 29.1, 31.7, 40.5, 48.8, 102.0, 144.5, 151.0, 164.4; IR (KBr) ν cm^{-1}: 3200 (NH), 3100, 2895, 1735 (C═O), 1710 (C═O); MS [*m*/*z* (%)]: 224 (34.9). Anal. Calcd for $C_{12}H_{20}N_2O_2$: C, 64.26; H, 8.99; N, 12.49%. Found: C, 64.20; H, 9.03; N, 12.44%.

4.2.13. 1-(4-Methoxybenzyl)pyrimidine-2,4(1H,3H)-dione (**2b**)

Column chromatography on SiO_2, eluted with EtOAc/*n*-hexane (50:50) afforded white cube crystals (1.4 g, 60%). Mp=118.9 °C; R_f (EtOAc)=0.38; δ_H (250 MHz, DMSO-d_6) 3.70 (3H, s, O*Me*), 3.73 (2H, s, NCH_2), 5.58 (1H, d, *J* 7.8 Hz, C(5)–H uracil), 6.84 (2H, d, *J* 8.6 Hz, C(2,6)–H, aryl), 6.90 (2H, d, *J* 8.6 Hz, C(3,5)–H, aryl), 7.72 (1H, d, *J* 7.8 Hz, C(6)–H uracil), 11.17 (1H, s, N3–H, exchangeable with D_2O); δ_C (62.5 MHz, DMSO-d_6) 49.6, 54.9, 101.1, 113.5, 128.6, 129.1, 145.3, 150.9, 158.7, 163.6; IR (KBr) ν cm^{-1}: 3250 (NH), 3100, 2895, 1728 (C═O), 1715 (C═O); MS [*m*/*z* (%)]: 232 (55.4). Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06%. Found: C, 62.00; H, 5.25; N, 12.04%.

4.2.14. 1-Phenethylpyrimidine-2,4(1H,3H)-dione (**2c**)

Column chromatography on SiO_2, eluted with EtOAc/*n*-hexane (50:50) afforded white cube crystals (1.53 g, 71%). Mp=150.1 °C; R_f (EtOAc)=0.29; δ_H (250 MHz, DMSO-d_6) 2.83 (2H, t, *J* 7.2 Hz, PhCH_2), 3.89 (2H, t, *J* 7.2 Hz, NCH_2), 5.45 (1H, d, *J* 7.8 Hz, C(5)–H uracil), 7.16–7.30 (5H, m, aryl), 7.50 (1H, d, *J* 7.8 Hz, C(6)–H uracil), 11.23 (1H, s, N3–H, exchangeable with D_2O); δ_C (62.5 MHz, DMSO-d_6) 34.1, 48.7, 100.4, 126.2, 128.3, 128.5, 137.7, 145.5, 150.7, 163.6; IR (KBr) ν cm^{-1}: 3250 (NH), 3110, 2895, 1730 (C═O), 1720 (C═O); MS [*m*/*z* (%)]: 216 (27). Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96%. Found: C, 66.70; H, 5.63; N, 12.90%.

4.2.15. 2-(2-(2,4-Dioxo-3,4-dihydropyrimidin-1(2H)-yl)-ethyl)isoindoline-1,3-dione (**2d**)

Column chromatography on SiO_2, eluted with EtOAc/*n*-hexane (60:40) afforded white cube crystals (2.28 g, 80%). Mp=263.0 °C; R_f (EtOAc)=0.29; δ_H (250 MHz, DMSO-d_6) 3.83–3.87 (4H, m, 2NCH_2), 5.45 (1H, d, *J* 7.8 Hz, C(5)–H uracil), 7.52 (1H, d, *J* 7.8 Hz, C(6)–H uracil), 7.78–7.86 (4H, m, aryl), 11.15 (1H, s, N3–H, exchangeable with D_2O); δ_C (62.5 MHz, DMSO-d_6) 36.4, 46.4, 101.0, 123.0, 131.4, 134.3, 145.4, 151.1, 163.6, 167.6; IR (KBr) ν cm^{-1}: 3200 (NH), 3210, 2895, 1730–1710 (C═O); MS [*m*/*z* (%)]: 285 (40). Anal. Calcd for $C_{14}H_{11}N_3O_4$: C, 58.96; H, 3.89; N, 14.73%. Found: C, 59.00; H, 3.91; N, 14.75%.

4.2.16. 1-(Prop-2-ynyl)pyrimidine-2,4(1H,3H)-dione (**2e**)[16]

Column chromatography on SiO_2, eluted with EtOAc/*n*-hexane (70:30) afforded white cube crystals (1.0 g, 66%). Mp=154.6 °C, Lit.[16] (154–166 °C); R_f (EtOAc)=0.28; δ_H (250 MHz, DMSO-d_6) 3.13 (1H, s, ≡C*H*), 4.28 (2H, s, NCH_2), 5.41 (1H, d, *J* 7.8 Hz, C(5)–H uracil), 7.64 (1H, d, *J* 7.8 Hz, C(6)–H uracil), 11.13 (1H, s, N3–H, exchangeable with D_2O); δ_C (62.5 MHz, DMSO-d_6) 36.5, 75.6, 78.3, 101.6, 144.4, 150.3, 163.5; IR (KBr) ν cm^{-1}: 3290 (≡CH), 3200

(NH), 3100, 2895, 2145 (C≡C), 1740 (C=O), 1715 (C=O); MS [*m/z* (%)]: 150 (55.7). Anal. Calcd for $C_7H_6N_2O_2$: C, 56.00; H, 4.03; N, 18.66%. Found: C, 56.05; H, 3.99; N, 18.60%.

*4.2.17. 5-Chloro-1-(prop-2-ynyl) pyrimidine-2,4(1H,3H)-dione (**2f**)*[16]

Column chromatography on SiO_2, eluted with EtOAc/*n*-hexane (70:30) afforded white cube crystals (1.1 g, 59%). Mp=169.4 °C, lit.[16] (168–170 °C); R_f (EtOAc)=0.29; δ_H (250 MHz, DMSO-d_6) 3.18 (1H, s, ≡C*H*), 4.26 (2H, s, NCH_2), 8.23 (1H, s, C(6)–H uracil), 11.56 (1H, s, N3–H, exchangeable with D_2O); δ_C (62.5 MHz, DMSO-d_6) 36.3, 75.4, 78.6, 102.7, 145.4, 150.8, 163.2; IR (KBr) ν cm^{-1}: 3310 (≡CH), 3250 (NH), 3100, 2890, 2150 (C≡C), 1735 (C=O), 1715 (C=O); MS [*m/z* (%)]: 184 (51.8). Anal. Calcd for $C_7H_5ClN_2O_2$: C, 45.55; H, 2.73; Cl, 19.21; N, 15.18%. Found: C, 45.62; H, 2.78; Cl, 19.17; N, 15.17%.

*4.2.18. (E)-1-Cinnamylpyrimidine-2,4(1H,3H)-dione (**2g**)*

Column chromatography on SiO_2, eluted with EtOAc/*n*-hexane (50:50) afforded white cube crystals (1.42 g, 62%). Mp=198.1 °C; R_f (EtOAc)=0.65; δ_H (250 MHz, DMSO-d_6) 4.51 (2H, d, *J* 5.6 Hz, NCH_2), 5.67 (1H, d, *J* 7.8 Hz, C(5)–H uracil), 6.36 (1H, m, CH_2–C*H*), 6.64 (1H, d, *J* 16.0 Hz, =C*H*–Ph), 7.26–7.68 (5H, m, aryl), 7.71 (1H, d, *J* 7.8 Hz, C(6)–H uracil), 11.36 (1H, s, N3–H, exchangeable with D_2O); δ_C (62.5 MHz, DMSO-d_6) 48.6, 101.2, 124.2, 126.3, 127.8, 128.5, 132.4, 135.8, 145.2, 150.7, 163.7; IR (KBr) ν cm^{-1}: 3250 (NH), 3050, 2895, 1730 (C=O), 1710 (C=O); MS [*m/z* (%)]: 228 (31.4). Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27%. Found: C, 68.38; H, 5.26; N, 12.30%.

*4.2.19. 1-Allyl-5-fluoropyrimidine-2,4(1H,3H)-dione (**2h**)*[8a,b,18]

Column chromatography on SiO_2, eluted with EtOAc/*n*-hexane (70:30) afforded white needle crystals (0.92 g, 54%). Mp=101.3 °C, lit.[8b] (101 °C); R_f (EtOAc)=0.27; δ_H (250 MHz, $CDCl_3$) 4.33 (2H, d, *J* 5.8 Hz, NCH_2), 5.35 (2H, dd, *J* 11.0, 16.3 Hz, =CH_2), 5.80 (1H, m, C*H*), 7.27 (1H, d, $^3J_{HF}$ 5.4 Hz, C(6)–H uracil), 9.65 (1H, s, N3–H, exchangeable with D_2O); δ_C (62.5 MHz, $CDCl_3$) 51.4, 121.4, 128.2, 131.0, 141.0, 150.9, 158.8; IR (KBr) ν cm^{-1}: 3220 (NH), 3050, 2895, 1725 (C=O), 1715 (C=O); MS [*m/z* (%)]: 170 (38.0). Anal. Calcd for $C_7H_7FN_2O_2$: C, 49.41; H, 4.15; F, 11.17; N, 16.46%. Found: C, 49.46; H, 4.10; F, 11.14; N, 16.52%.

*4.2.20. 1-Allyl-5-methylpyrimidine-2,4(1H,3H)-dione (**2i**)*[8a,b,19]

Column chromatography on SiO_2, eluted with EtOAc/*n*-hexane (60:40) afforded white cube crystals (0.96 g, 58%). Mp=123.2 °C, lit.[8b] (122 °C); R_f (EtOAc)=0.25; δ_H (250 MHz, $CDCl_3$) 1.89 (3H, s, *Me*), 4.31 (2H, d, *J* 5.5 Hz, NCH_2), 5.24 (2H, dd, *J* 10.8, 16.1 Hz, =CH_2), 5.82 (1H, m, =C*H*), 6.96 (1H, s, C(6)–H uracil), 10.23 (1H, br s, N3–H, exchangeable with D_2O); δ_C (62.5 MHz, $CDCl_3$) 13.8, 51.8, 112.3, 121.4, 133.2, 141.6, 152.2, 166.9; IR (KBr) ν cm^{-1}: 3200 (NH), 3100, 2980, 1734 (C=O), 1720 (C=O); MS [*m/z* (%)]: 166 (43.2). Anal. Calcd for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86%. Found: C, 57.86; H, 6.00; N, 16.91%.

*4.2.21. 2-Butyl-1,2,4-triazine-3,5(2H, 4H)-dione (**2j**)*

Column chromatography on SiO_2 eluted with EtOAc/*n*-hexane (40:60) afforded white needle crystals (1.02 g, 60%). Mp 136.4 °C; R_f (EtOAc:*n*-hexane) (4:1) 0.77; δ_H (250 MHz, DMSO-d_6) 0.63 (3H, t, *J* 6.2 Hz, CH_3), 1.01 (2H, m, CH_2CH$_3$), 1.26 (2H, m, NCH$_2$CH_2), 3.48 (2H, t, *J* 6.5 Hz, NCH_2), 7.20 (1H, s, C(5)–H azauracil), 12.29 (1H, s, N3–H exchangeable with D_2O); δ_C (62.5 MHz, DMSO-d_6) 13.4, 19.4, 28.6, 38.3, 134.5, 148.9, 156.1; IR (KBr) ν cm^{-1}: 3200 (NH), 3210, 2985, 2895, 1725–1715 (C=O); MS [*m/z* (%)]: 169 (35). Anal. Calcd for $C_7H_{11}N_3O_2$: C, 49.70; H, 6.55; N, 24.84%. Found: C, 49.76; H, 6.51; N, 24.87%.

*4.2.22. 1-Butyl-5-nitropyrimidine-2,4(1H,3H)-dione (**2k**)*

Column chromatography on SiO_2 eluted with EtOAc/*n*-hexane (60:40) afforded pale yellow needle crystals (1.43 g, 76%). Mp 146.3 °C; R_f (EtOAc:*n*-hexane) (4:1) 0.68; δ_H (250 MHz, DMSO-d_6) 0.83 (3H, t, *J* 6.7 Hz, CH_3), 1.26 (2H, m, CH_2CH$_3$), 1.59 (2H, m, NCH$_2$CH_2), 3.81 (2H, t, *J* 6.5 Hz, NCH_2), 9.23 (1H, s, C(6)–H uracil), 11.96 (1H, s, N3–H uracil exchangeable with D_2O); δ_C (62.5 MHz, DMSO-d_6) 18.6, 24.1, 35.6, 54.1, 129.7, 154.4, 155.8, 160.1; IR (KBr) ν cm^{-1}: 3250 (NH), 3210, 2985, 2890, 1730–1715 (C=O); MS [*m/z* (%)]: 213 (25). Anal. Calcd for $C_8H_{11}N_3O_4$: C, 45.07; H, 5.20; N, 19.71%. Found: C, 45.03; H, 5.21; N, 19.73%.

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