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An Efficient Synthesis of 7,8-Dihydropyrimido[5,4-*d*]pyrimidines

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7,8-Dihydropyrimido[5,4-*d*]pyrimidines **4** were isolated in very good yields by treatment of 9-aryl-6-cyanopurines **1** with primary amines. Nucleophilic attack of the amine on C8 of the purine ring was followed by ring-opening of the imidazole unit, and subsequent intramolecular cyclization involving the newly formed amidine group and the cyano substituent in the pyrimidine ring produced the 7,8-dihydropyrimido[5,4-*d*]pyrimidine structure **4**. When ammonia was used instead of primary amines, compound **4** rapidly reacted further to afford the more stable pyrimido[5,4-*d*]pyrimidine **6** as a result of tautomeric equilibration. The aromatic structure **6** was also isolated when purine **1a** and an excess of ethanolamine were heated at reflux in methanol, and also when purine **1c** was combined with an excess of (4-methoxyphenyl)-hydrazine in THF at room temperature in the presence of a catalytic amount of DBU. In both cases the product is formed by a Dimroth rearrangement of the precursor 7,8-dihydropyrimido[5,4-*d*]pyrimidine **4**.

Introduction

Pyrimido[5,4-*d*]pyrimidines are an important class of biologically active compounds. Dipyridamole, a 2,4,6,8-tetrasubstituted pyrimido[5,4-*d*]pyrimidine, shows cardiovascular and antithrombotic activity,[1,2] and is currently prescribed as a medication to prevent excessive blood clotting. A number of these structures have also been reported to be active as antiviral and antitumour agents,[3–13] as inhibitors of tyrosine kinase activity,[7,9,12] or as bronchodilators and antiallergenic agents.[14] Most of the substituted pyrimido[5,4-*d*]pyrimidines have been prepared by nucleophilic substitution of the chlorine atoms in the 2,4,6,8-tetrasubstituted derivative, by treatment with amines.[5,10,11,15] The synthesis of the fused heterocycle from a substituted pyrimidine has also been carried out under appropriate reaction conditions.[12,16,17] Treatment of 6-cyanopurines with a large excess of methanolic ammonia caused rearrangement of the purine ring, also resulting in the formation of pyrimido[5,4-*d*]pyrimidines.[3,4,6,18–20]

In our research group we have developed a simple and efficient method by which to prepare 9-substituted 6-cyanopurines **1** by treatment of 5-amino-4-(cyanoformimidoyl)-imidazole with dimethylformamide diethyl acetal or triethyl orthoformate in the presence of acid catalysis.[21,22] When these compounds were treated with methylamine, 7,8-dihydropyrimido[5,4-*d*]pyrimidine structures **4** were formed exclusively.[22] These products were considered to arise from nucleophilic attack of the amine on C8 of the purine ring, by an ANRORC-type mechanism. However, the results reported in the literature concerning reactions between 6-cyanopurines and substituted amines are confusing and somewhat contradictory. Higashino[23] reported the formation of 6-amidinopurines **2** (Scheme 1) when 9-phenyl-6-cyanopurine (**1a**) was treated with *n*-butylamine, piperidine, hydrazine and hydroxylamine, in methanol or ethanol as solvent, whilst our previous results on the reaction behaviour of 6-cyanopurines in methanol in the presence of DBU[24] showed nucleophilic attack of the solvent on the cyano carbon atom to be the major pathway, resulting in a 6-imidatopurine **3** (Scheme 1). Imidates are useful precursors of amidines, and compound **3** was efficiently transformed into a 6-amidinopurine **2** on treatment with methylammonium chloride.[24] Currently available information on the reactivity of 6-cyanopurines with amine nucleophiles indicates that the reaction can follow two different pathways, affording either pyrimido[5,4-*d*]pyrimidines[22] or 6-amidinopurines,[23,24] depending on a delicate balance of the reaction conditions.

In order to clarify this matter, a careful investigation into the reactions between three different 9-aryl-6-cyanopurines and ammonia or primary amines was carried out under different experimental conditions. Three of the reactions reported by Higashino[23] were repeated under the conditions reported in the literature.

Results and Discussion

A careful analysis of Higashino's results on the reactions between 9-phenyl-6-cyanopurine (**1a**) and *n*-butylamine, piperidine, hydrazine and hydroxylamine suggests that his structure assignments (Scheme 1) may not be entirely correct.

Higashino assumed that all these reactions were producing 6-amidinopurines (**2a**–**d**), and the possibility of nucleo-

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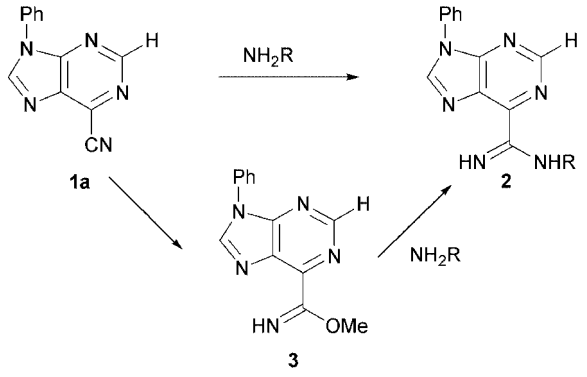
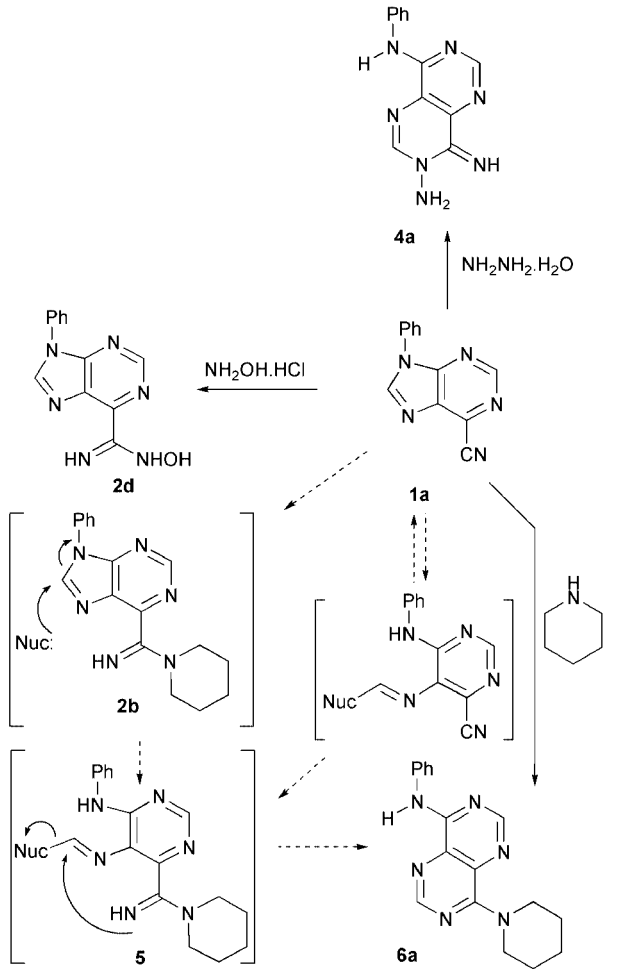


Compound	NH_2R	Reaction Conditions	Yield (%)
2a	$NH_2(CH_2)_3CH_3$	methanol; amine (4 equiv.); 1 h (reflux)	50[a]
2b	NHC_5H_{10}	methanol; amine (2 equiv.); 4 h (reflux)	52[a]
2c	$NH_2NH_2.H_2O$	ethanol; amine (2.5 equiv.); 1 h (reflux)	79[a]
		acetonitrile; amine (1.5 equiv.); anilinium chloride (cat.); 8 h (r.t.)	85[b]
2d	$NH_2OH.HCl$	methanol; amine (4 equiv.); AcONa (4 equiv.); 45 min. (reflux)	71[a]
2e	NH_3	dichloromethane:methanol (1:1); $AcONH_4$(2.5 equiv.; 2 h (reflux)	70[b]

[a] Cited reference 23; [b] From 6-alkoxyformimidoylpurine **3**

Scheme 1.



Compound	NH_2R	Reaction Conditions	Yield (%)
2d	$NH_2OH.HCl$	methanol; amine (4 equiv.); AcONa (4 equiv.); 50 min. (reflux)	76
4a	$NH_2NH_2.H_2O$	ethanol; amine (2.5 equiv.); 1 h (reflux)	84
6a	NHC_5H_{10}	methanol; amine (2 equiv.); 21 h (reflux)	72

Scheme 2.

philic attack on C8 of the purine ring was never envisaged. In the current work, these reactions were repeated with 9-phenylpurine **1a**, and the results are compiled in Scheme 2. The reaction between purine **1a** and hydroxylamine did indeed provide the 6-amidinopurine **2d** in a comparable yield (71[23] vs. 76%), the values reported in the literature for the ^{1}H NMR chemical shifts of compound **2d**[23] being in good agreement with those obtained for the same product in the current work, whilst a careful study using NMR correlation techniques (HMQC and HMBC) also confirmed the structure proposed for this compound. Use of hydrazine hydrate, however, resulted in the 7,8-dihydropyrimido[5,4-*d*]pyrimidine structure **4a**, isolated in 84% yield (Scheme 2).

The structure of this compound was confirmed by NMR correlation spectroscopy. In this case, nucleophilic attack on C8 of the purine ring is the major pathway, as was previously reported for the reaction with methylamine.[22] The only spectroscopic data reported in the literature for this compound, identified there as **2c**,[23] amount to one signal in the infrared spectrum (KBr) at 3360 cm^{-1}, assigned to the N–H stretching vibration. A similar, medium intensity band at 3364 cm^{-1} is also present in the infrared spectrum (Nujol mull) of the solid that we isolated, and this is the major evidence that we are dealing with the same product. The reported value for the melting point (219 °C with decomposition)[23] is also similar to that registered for **4a** (222–224 °C with decomposition). In the reaction between **1a** and piperidine, a complex mixture was present after 4 h under reflux conditions. Tlc indicated that the starting material was still present, and the reaction mixture was heated at reflux for a further 17 h. A major compound was clearly present, and this was isolated and identified as the pyrimido[5,4-*d*]pyrimidine **6a**. The ^{1}H NMR spectrum obtained for this product (δC2–H 8.62 ppm and δC6–H 8.52 ppm, δN–H 9.0 ppm) compares well with that reported in the literature for the compound identified as **2b** (δC2–H 8.50 ppm

and δC8–H 8.40 ppm, δN–H 8.9 ppm).[23] The formation of compound **6a** can be explained if the 6-amidinopurine **2b** is initially formed and reacts further to afford **6a** through ring-opening at C8, followed by intramolecular cyclization (Scheme 2). The same intermediate species **5** can be generated if ring-opening of the 6-cyanopurine precedes the nucleophilic attack on the cyano group to generate the amidine substituent in the 6-position.

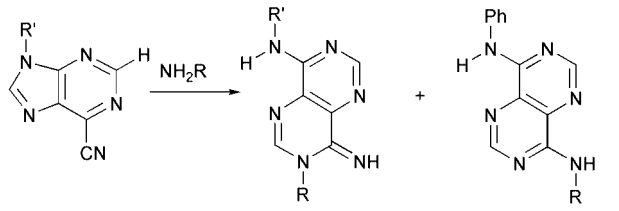
The 6-amidinopurines **2c** and **2e** were actually prepared by an alternative synthetic method, based on the reactions between the 6-alkoxyformimidoylpurine **3**[24] and either hydrazine hydrate or ammonium acetate, respectively (Scheme 1). The reactions occurred smoothly in the presence of acid and the products were isolated in very good yield. These compounds were fully characterized by spectroscopic techniques and it is clear that **2c** shows three intense bands for the N–H signals in its infrared spectrum (3454, 3329 and 3231 cm^{-1}), rather than a single band at 3360 cm^{-1} as reported in the literature.[23] The melting point of 170 °C (dec.) is also different from the previously reported value (215 °C).[23]

These results prompted us to carry out a wider study on reactions between 6-cyanopurines and amine nucleophiles in order to understand the circumstances that favour nucleophilic attack on C8 over addition to the cyano group in the 6-position. Since the major pathway for nucleophilic attack on C-8 could be influenced by the electronic effect of the substituent at N9 in the purine ring, this study was performed with 6-cyanopurines possessing 9-aryl substituents incorporating electron-donating (4-methoxy, purine **1b**) and electron-withdrawing (4-cyano, purine **1c**) groups. The results of this study are compiled in Scheme 3, Scheme 4 and Scheme 5.

The reactions were carried out in dichloromethane or chloroform (medium polarity solvents with no H-bonding acceptor properties), tetrahydrofuran (a medium polarity solvent with H-bonding acceptor properties) and methanol or ethanol (polar amphiprotic solvents) and the temperature was varied from 0 °C to reflux conditions. All these different experimental conditions resulted in the formation of the 7,8-dihydropyrimido[5,4-*d*]pyrimidine structures **4**, isolated in very good yields (60–99%).

The presence of an electron-withdrawing substituent in the aromatic ring on N9 (purine **1c**) does not seem either to influence the reaction pathway or to accelerate the 7,8-dihydropyrimido[5,4-*d*]pyrimidine formation. The products are isolated in higher yields, possibly as a result of poor solubility in organic solvents (Scheme 3 and Scheme 4).

The reaction between purine **1c** and aniline, a less nucleophilic amine, required an excess of amine (7 molar equivalents) and one equivalent of base (DBU). The 7,8-dihydropyrimido[5,4-*d*]pyrimidine **4h** was isolated in 60% yield after 2 d at room temperature (Scheme 4). Under the same reaction conditions, purine **1b** (Scheme 3) produced a lower isolated yield of the product **4e** after 13 h at reflux, due to the difficulty in separating the solid from the reaction mixture, in which it is more soluble. In order to overcome this problem, two equivalents of the amine were used, together



1a R'= C_6H_5
1b R'= 4-$MeOC_6H_5$

4a R'= C_6H_5; R= NH_2
4b R'= C_6H_5; R= CH_2CH_2OH
4c R'= C_6H_5; R= CH_2CH_3
4d R'= 4-$MeOC_6H_4$; R= CH_3
4e R'= 4-$MeOC_6H_4$; R= Ph
4f R'= 4-$MeOC_6H_4$; R= NH_2

6b R= CH_2CH_2OH

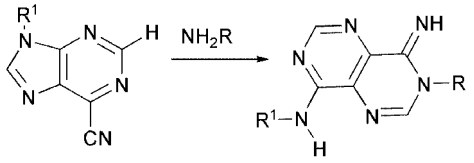
R'	NH_2R	Reaction Conditions	Yield (%) **4**	**6**
C_6H_5	$NH_2(CH_2)_2OH$	dichloromethane; amine (2.5 equiv.); DBU(cat.); 2 h (reflux)	73	-
		methanol; amine (2.5 equiv.);DBU(cat.); 2 h (reflux)	21	41
		methanol; amine (2.5 equiv.);DBU(cat.); 18 h (r.t.)	62	-
		methanol;amine (1.5 equiv.); H_2SO_4(cat.);15 days (r.t.)	35[a]	56[a]
	$NH_2CH_2CH_3$	methanol; amine (aq., 4 equiv.); 1 h (reflux)	62	-
4-$MeOC_6H_4$	NH_2Me	dichloromethane; amine (aq., 7 equiv.); 17 h (r.t.)	86[b]	-
	NH_2Ph	THF; amine (7 equiv.); DBU (1equiv.);13 h (reflux),14 h (r.t.)	49	-
		THF; amine (2 equiv.); DBU(cat.); 12 days (reflux)	86	-
		THF; amine (2 equiv.); DBU(cat.); 24 h (reflux)	38	-
	$NH_2NH_2.H_2O$	ethanol:dichloromethane(3:5); amine (2 equiv.); DBU(cat.); 20 h (r.t).	91	-
		ethanol:dichloromethane(3:5); amine (2 equiv.); 4 days (r.t.)	84	-
		ethanol; amine (2 equiv.); 1 h (reflux)	81	-
		methanol; amine (2 equiv.); DBU(cat.); 1 h (r.t.)	88	-

[a] From 6-imidatopurine **3**; [b] Cited reference 22

Scheme 3.

with a catalytic amount of DBU, and the time at reflux was increased to 12 d. Under these conditions, compound **4e** was isolated in 86% yield. The reactivities of the other amines (alkyl primary amines and hydrazine) were comparable, and the differences in the basicity and nucleophilicity parameters[25] did not affect the yields of the products when the reactions were carried out under similar conditions. The reaction with ammonia (Scheme 5) must follow the same pathway (attack on C8), but the 7,8-dihydropyrimido[5,4-*d*]-pyrimidine **4** rapidly tautomerizes to the more stable aro-

matic structure **6**, the only compound isolated in this case. In the reaction between 9-phenyl-6-cyanopurine (**1a**) and hydroxylamine hydrochloride (Scheme 2), nucleophilic attack on the cyano group was the major pathway, on heating at reflux in methanol in the presence of an equimolar amount of sodium acetate. In this case, it is possible that only a low concentration of free hydroxylamine is present in solution, and that this might considerably reduce attack on C-8. The use of methanol as solvent and an acidic medium may be responsible for the transformation of the cyano group into an imidate function, at which nucleophilic attack would be facilitated. When the reaction between purine **1a** and ethanolamine (2.5 molar equivalents) was carried out under reflux in methanol in the presence of a catalytic amount of DBU, the solid isolated after 2 h was a mixture of pyrimido[5,4-*d*]pyrimidines **4b** and **6b** in a 1:2 ratio (Scheme 3). When this solid mixture was combined with 1.5 molar equivalents of ethanolamine, a catalytic amount of DBU and methanol, and the solution was heated at reflux for another 7 h, the product isolated was again a mixture of **4b** and **6b**, but now in a 1:4 ratio. In this case, the transformation of **4b** into **6b** can only be explained by a Dimroth rearrangement (Scheme 6).



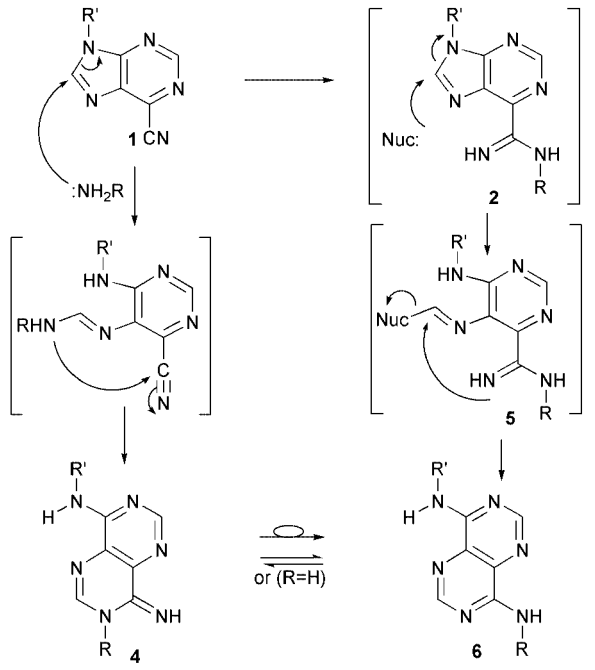
1c R^1 =4-NCC_6H_4

4g R= CH_3
4h R= Ph
4i R= NH_2
4j R= NHC_6H_4(4-OMe)
4k R= CH_2CH_2OH

NH_2R	Reaction Conditions	Yield (%) **4**
NH_2Me	dichloromethane; amine (aq., 7 equiv.); 18 h (r.t.)	94[a]
	ethanol; amine (aq.,7 equiv.); 36 h (r.t.)	99[a]
NH_2Ph	ethanol; amine (2 equiv.); DBU(cat.); 29 days (r.t.)	[b]
	THF; amine (7 equiv.); DBU(1 equiv.); 2 days (r.t.)	60
$NH_2NH_2.H_2O$	ethanol; amine (2 equiv.); DBU(cat.); 16 h (r.t.)	99
$NH_2NHC_6H_4$(4-OMe)	THF; amine (7 equiv.); DBU(cat.); 2.5 h (r.t.)	38[c]
$NH_2(CH_2)_2OH$	ethanol:ethyl acetate (1:1);amine (2 equiv.); DBU(cat.); 17 h (r.t.)	97

[a] Cited reference 22; [b] Purine **1c** was quantitatively recovered; [c] The 2nd crop (42%) was a mixture of compounds **4** and **6** in a 4:3 ratio

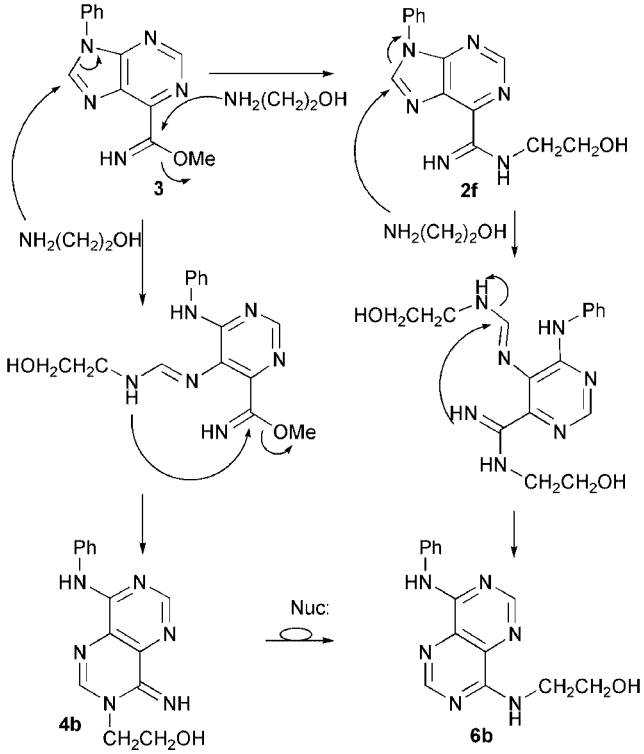
Scheme 4.



Compound	R'	R	Reaction Conditions	Yield (%)
6c	C_6H_5	H	methanol; $AcONH_4$ (4 equiv.); AcONa (4 equiv.); 8 h (reflux).	60
6d	4-$MeOC_6H_4$	H	chloroform; amine (gas, excess);DBU(cat.); 1.5 h (0 °C), 36 h (4 °C)	64
			methanol; amine (aq., 7 equiv.); 5 days (r.t.)	61
6e	4-NCC_6H_4	H	ethanol; amine (aq., 7 equiv.); 36 h (r.t.)	96
			dichloromethane; amine (aq., 7 equiv.); 6 days (r.t.)	96
6f		NHC_6H_4(4-OMe)	THF; amine (7 equiv.); DBU(cat.); 1 day (r.t.)	77

Scheme 5.

The presence of a nucleophile causes ring-opening of the pyrimidine ring **4b** with the exocyclic double bond, and the ring-closure that follows affords the more stable aromatic heterocyclic system **6b**. Ethanolamine was also treated with 6-alkoxyformimidoylpurine **3** in methanol as solvent and with sulfuric acid catalysis (Scheme 6). The starting material had only been completely consumed after 15 d at room temperature, the solid product, isolated in 91% yield, being a mixture of **4b** and **6b** in a 2:3 ratio. Structure **4b** can only arise from nucleophilic attack of ethanolamine on C8 of purine **3**, followed by ring-opening and ring-closure. Structure **6b** can result from **4b** by Dimroth rearrangement or can be formed from the 6-amidinopurine **2f** after a reaction sequence involving nucleophilic attack on C8, followed by ring-opening and ring-closure.



Scheme 6.

The reaction between purine **1c** and 4-methoxyphenylhydrazine was carried out in tetrahydrofuran in the presence of 7 molar equivalents of the amine and with DBU catalysis (Scheme 4). After 2.5 h at room temperature, the solid suspension was filtered off and identified as compound **4j** (38%). The second crop, obtained from the mother liquor after concentration of the solvent, was a mixture of structures **4j** and **6f** (42%) in a 4:3 molar ratio (by ^{1}H NMR spectroscopy). When the same reaction mixture was stirred at room temperature for one day, the aromatic pyrimido[5,4-*d*]pyrimidine **6f** was the only product isolated, in 77% yield (Scheme 5). In this case the 7,8-dihydropyrimido[5,4-*d*]pyrimidine **4** can only be isolated as a pure product if it precipitates from the reaction mixture. Once in solution, it rapidly reacts further to form the pyrimido[5,4-*d*]-pyrimidine **6** by a Dimroth rearrangement, and the heteroaromatic compound is isolated as a pure solid after a longer reaction time.

Compounds **2**, **4** and **6** share common empirical formulas and the only way to identify each structure is by careful analysis of its spectroscopic data. Compounds **2**, isolated from the reactions between 6-imidatopurine **3** and primary amines, each show a medium/intense band at around 1650 cm^{-1} in the infrared spectrum. The signals for C2–H and C8–H in the ^{1}H NMR spectrum ([D$_6$]DMSO solution) are both visible at δ = 8.9–9.0 ppm, whilst signals in the ^{13}C NMR for C2 at δ = 151–152 ppm and for C8 at δ = 145–146 ppm are also typical features (Table 1).

In compounds **4**, the infrared spectra each show a medium/intense band in the 1630–1640 cm^{-1} region and an intense band around 1600 cm^{-1}. In the NMR spectra ([D$_6$]-DMSO solution), the C2–H proton is in the δ = 8.4–8.7 ppm region and the signal for the adjacent carbon is at δ = 154–157 ppm. The C6–H proton, at δ = 8.1–8.2 ppm, shows the adjacent carbon around δ = 147–149 ppm.

Table 1. Relevant ^{1}H and ^{13}C NMR spectroscopic data for compounds **2c–e**, **4a–k** and **6a–f**.

Compound	H2	H8[a]/H6[b]	C2	C8[a]/C6[b]
2c	8.88	8.92	151.58	144.98
2d	8.98	9.00	151.74	145.80
2e	9.27	9.42	152.29	149.33
4a	8.53	8.18	154.78	148.22
4b	8.52	8.04	154.61	149.06
4c	8.52	8.21	154.73	148.29
4e	8.50	8.06	155.21	147.24
4f	8.46	8.16	156.78	147.14
4h	8.69	8.11	154.72	147.80
4i	8.65 8.89[c]	8.22 8.72[c]	– 156.44[c]	– 147.69[c]
4j	8.66	8.29	–	–
4k	8.64	8.07	154.05	149.21
6a	8.56	8.55	151.56	153.65
6b	8.60	8.53	–	–
6c	8.58	8.47	153.55	154.93
6d	8.52	8.44	153.53	154.58
6e	8.73	8.53	155.02[c]	148.93[c]
6f	8.75	8.53	153.49	154.92

[a] For compounds **2**. [b] For compounds **4** and **6**. [c] [D$_6$]DMSO/TFA.

The aromatic pyrimido[5,4-*d*]pyrimidine structures **6** each show an intense band around 1600 cm^{-1} in the infrared spectrum. In the NMR spectrum ([D$_6$]DMSO solution), the signals for C2–H and C6–H are usually present in the δ = 8.4–8.8 ppm region and the corresponding carbon atoms C2 and C6 can be identified around δ = 153–155 ppm.

Conclusions

The reactions between 9-aryl-6-cyanopurines and primary amines described in this work proved to be an efficient method for the preparation of 7,8-dihydropyrimido[5,4-*d*]pyrimidines **4**. Good isolated yields are obtained with dichloromethane, THF, methanol or ethanol as solvents, and an excess of the amine (2 to 7 equiv.), together with a catalytic amount of DBU. The major synthetic pathway involves nucleophilic attack of the amine at C8 of the purine, followed by ring-opening and ring-closure on the cyano group in the 6-position. The presence of electron-donating or electron-withdrawing groups on the aromatic substituent at N9 of the purine ring does not influence the yield of the product. Use of ammonia results in the isolation of pyrimido[5,4-*d*]pyrimidines **6**, stable tautomers of compounds **4**. The aromatic structures **6** are also formed by Dimroth rearrangements of the precursor 7,8-dihydropyrimido[5,4-*d*]pyrimidines **4**, which occur after longer reaction times at room temperature or under reflux conditions, in methanol as solvent and with either acid or base catalysis.

This synthetic approach can be envisaged as a versatile method for the regioselective synthesis of libraries of this

important class of biologically active compounds, through the appropriate combination of *N*-substituted-6-cyanopurine and primary amine. The compounds prepared have been submitted to TAACF[26] for screening of their tuberculostatic activity, and studies on their antioxidant properties are also in progress.

Experimental Section

General Remarks: NMR spectra, including the ^1H–^{13}C correlation spectra (HMQC and HMBC), were recorded with a Varian Unity Plus (^1H: 300 MHz, ^{13}C: 75 MHz) instrument, and deuterated DMSO was used as solvent. IR spectra were recorded with a FT-IR Bomem MB 104 instrument as Nujol mulls or in NaCl cells. The reactions were monitored by thin-layer chromatography (TLC; Merck 60 F_{254} silica gel). The melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Elemental analyses were performed on a LECO CHNS-932 instrument.

Reaction between 6-Cyanopurine 1a and Hydroxylamine Hydrochloride: The hydrochloride salt of hydroxylamine (0.27 g, 3.86 mmol) and sodium acetate (0.31 g, 3.84 mmol) were added to a suspension of 6-cyanopurine **1a** (0.21 g, 0.96 mmol) in methanol (10 mL), and the suspension was heated at reflux for 50 min to afford a white solid. Water (3 mL) was added to the reaction mixture, which was cooled in an ice bath. The solid was filtered and washed with water and ethanol, and the product was identified as *N′*-hydroxy-9-phenyl-9*H*-purine-6-carboximidamide (**2d**; 0.19 g, 0.73 mmol, 76%), m.p. 278–279 °C. ^1H NMR ([D$_6$]DMSO, 300 MHz): δ = 10.64 (s, 1 H), 9.00 (s, 1 H), 8.98 (s, 1 H), 7.90 (d, J = 7.5 Hz, 2 H), 7.63 (t, J = 7.5 Hz, 2 H), 7.51 (t, J = 7.5 Hz, 1 H), 6.13 (s, 2 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 151.95, 151.74, 148.67, 148.04, 145.80, 134.25, 130.24, 129.60, 128.16, 123.75 ppm. IR (Nujol mull): $\tilde{\nu}$ = 1650, 1578, 1507 cm^{-1}. $C_{12}H_{10}N_6O$ (254.25): calcd. C 56.69, H 3.94, N 33.07; found: C 56.45, H 4.06, N 32.83.

General Procedure for the Reactions between the 6-(Alkoxyformimidoyl)purine 3 and Primary Amines: The amine or ammonium acetate (1.5 molar equivalents) was added to a suspension of the 6-(alkoxyformimidoyl)purine **3** in acetonitrile (for **2c**) or methanol/dichloromethane 1:1 (for **2e**). A catalytic amount of anilinium chloride (for **2c**) was added and the mixture was stirred at room temperature (for **2c**) or heated at reflux (for **2e**) until all the starting material had been consumed (TLC evidence). The solvent was partially removed in the rotary evaporator and the solid was filtered and washed with cold diethyl ether. The product was identified as the 6-amidinopurine **2**.

9-Phenyl-9*H*-purine-6-carbohydrazonamide (2c): Yield 0.50 mmol, 85%, m.p. 170 °C (dec.). ^1H NMR ([D$_6$]DMSO, 300 MHz): δ = 8.92 (s, 1 H), 8.88 (s, 1 H), 7.90 (d, J = 7.5 Hz, 2 H), 7.62 (t, J = 7.5 Hz, 2 H), 7.49 (t, J = 7.5 Hz, 1 H), 6.80 (br s, 1 H), 5.91 (br s, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 151.70, 151.58, 149.11, 144.98, 141.41, 134.38, 129.66, 129.58, 129.03, 123.64 ppm. IR (Nujol mull): $\tilde{\nu}$ = 1645, 1624, 1575, 1511 cm^{-1}. HRMS: calcd. for $C_{12}H_{12}N_7$ [M + H]$^+$ 254.1154; found: 254.1158.

Acetate Salt of 9-Phenyl-9*H*-purine-6-carboximidamide (2e): Yield 0.46 mmol, 70%, m.p. 221–223 °C (dec.). ^1H NMR ([D$_6$]DMSO, 300 MHz): δ = 10.11 (s, 2 H), 9.71 (s, 2 H), 9.42 (s, 1 H), 9.27 (s, 1 H), 7.91 (d, J = 7.5 Hz, 2 H), 7.67 (t, J = 7.5 Hz, 2 H), 7.56 (t, J = 7.5 Hz, 1 H), 1.89 (s, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 172.23, 160.13, 153.50, 152.29, 149.33, 140.17, 133.67, 132.03, 129.91, 129.01, 124.08, 21.16 ppm. IR (Nujol mull): $\tilde{\nu}$ = 1693, 1595, 1568, 1538, 1511 cm^{-1}. $C_{14}H_{14}N_6O_2$ (298.30): calcd. C 56.38, H 4.70, N 28.19; found: C 56.67, H 4.85, N 28.26.

Reaction between 6-Cyanopurine 1a and Ethylamine: An aqueous solution of ethylamine (0.16 mL, 1.92 mmol) was added to a suspension of 6-cyanopurine **1a** (0.11 g, 0.48 mmol) in methanol (3 mL). The reaction mixture was heated, resulting in a homogeneous solution that was further heated at reflux for 60 min, after which the starting material was no longer present (TLC evidence). Addition of diethyl ether (4 mL) and cooling at –5 °C for 18 h produced an off-white solid that was filtered and washed with diethyl ether. The product was identified as 7-ethyl-8-imino-*N*-phenyl-7,8-dihydropyrimido[5,4-*d*]pyrimidin-4-amine (**4c**; 0.08 g, 0.29 mmol, 62%), m.p. 214–216 °C. ^1H NMR ([D$_6$]DMSO, 300 MHz): δ = 9.59 (s, 1 H), 8.52 (s, 1 H), 8.42 (s, 1 H), 8.21 (s, 1 H), 7.89 (d, J = 7.5 Hz, 2 H), 7.35 (t, J = 7.5 Hz, 2 H), 7.09 (t, J = 7.5 Hz, 1 H), 4.04 (q, J = 6.9 Hz, 2 H), 1.30 (t, J = 6.9 Hz, 3 H) ppm. ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.67 (s, 1 H), 8.63 (s, 1 H), 8.39 (s, 1 H), 7.82 (s, 1 H), 7.78 (d, J = 8.4 Hz, 2 H), 7.41 (t, J = 8.4 Hz, 2 H), 7.15 (t, J = 8.4 Hz, 1 H), 4.10 (q, J = 7.2 Hz, 2 H), 1.46 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 156.52, 154.73, 148.29, 138.62, 138.27, 128.46, 127.72, 127.53, 125.45, 42.78, 13.33 ppm. IR (Nujol mull): $\tilde{\nu}$ = 1635, 1603, 1594, 1575, 1576, 1525, 1498, 1489 cm^{-1}. $C_{14}H_{14}N_6$ (266.30): calcd. C 63.16, H 5.26, N 31.58; found: C 63.21, H 5.40, N 31.48.

Reactions between 6-Cyanopurines 1a or 1c and Ethanolamine: Ethanolamine (2–2.5 molar equivalents) was added to a suspension of 6-cyanopurine **1** in dichloromethane or methanol (for **4b**) or ethanol/ethyl acetate 1:1 (for **4k**). A catalytic amount of DBU (10–50 μL) was added and the reaction mixture was heated at reflux (for **4b**) or stirred at room temperature (for **4b** or **4k**). When the starting material was no longer present (TLC evidence), the reaction mixture was cooled and the suspension was filtered and washed with dichloromethane or ethanol and diethyl ether. The solid was identified as the 7,8-dihydropyrimido[5,4-*d*]pyrimidine **4**.

General Procedure for the Reactions between 6-Cyanopurines 1b or 1c and Aniline: Aniline (2–7 molar equivalents) was added to a suspension of the 6-cyanopurine in tetrahydrofuran (5–20 mL). A catalytic amount of DBU (or a molar equivalent) was added and the mixture was heated at reflux or stirred at room temperature. When the starting material was no longer present (TLC evidence), the solvent was partially removed in the rotary evaporator. Addition of ethanol gave a solid product that was filtered and washed with ethanol and diethyl ether. The solid was identified as the 7,8-dihydropyrimido[5,4-*d*]pyrimidine **4**.

General Procedure for the Reactions between 6-Cyanopurines 1 and Hydrazine Hydrate: Hydrazine hydrate (2–2.5 molar equivalents) was added to a suspension of the 6-cyanopurine **1** in methanol or ethanol (or a solution in dichloromethane). The reaction mixture was stirred at room temperature (or at reflux in ethanol) until the starting material had been completely consumed (TLC evidence). Catalytic amounts of DBU (10 μL) were used in some of these reactions, as indicated in the tables in Scheme 3 and Scheme 4. The solvent was partially removed in the rotary evaporator and the solid suspension was filtered and washed with diethyl ether. The product was identified as compound **4**.

4-Imino-*N*^{8}-phenylpyrimido[5,4-*d*]pyrimidine-3,8(4*H*)-diamine (4a): Yield 0.40 mmol, 84%, m.p. 222–224 °C. ^1H NMR ([D$_6$]DMSO, 300 MHz): δ = 9.63 (s, 1 H), 8.53 (s, 1 H), 8.38 (s, 1 H), 8.18 (s, 1 H), 7.90 (d, J = 8.1 Hz, 2 H), 7.34 (t, J = 8.1 Hz, 2 H), 7.09 (t, J = 8.1 Hz, 1 H), 5.79 (s, 2 H) ppm. ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.64 (s, 1 H), 8.58 (s, 1 H), 8.44 (s, 1 H), 8.08 (s, 1 H), 7.81 (d, J = 7.5 Hz, 2 H), 7.42 (t, J = 7.5 Hz, 2 H), 7.16 (t, J = 7.5 Hz, 1 H),

4.87 (s, 2 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 156.61, 156.07, 154.78, 148.22, 138.60, 138.23, 128.48, 125.46, 123.47, 121.37 ppm. IR (Nujol mull): $\tilde{\nu}$ = 1644, 1603, 1579, 1557 cm^{-1}. $C_{12}H_{11}N_7$ (253.27): calcd. C 56.92, H 4.35, N 38.74; found: C 57.11, H 4.43, N 38.46.

2-(8-Anilino-4-iminopyrimido[5,4-*d*]pyrimidin-3(4*H*)-yl)ethanol (4b): Yield 1.08 mmol, 73%, m.p. 228–230 °C. ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 9.61 (brs, 1 H), 8.52 (s, 1 H), 8.40 (s, 1 H), 8.04 (s, 1 H), 7.90 (d, J = 7.8 Hz, 2 H), 7.35 (t, J = 7.8 Hz, 2 H), 7.09 (t, J = 7.8 Hz, 1 H), 4.99 (s, 1 H), 4.07 (m, 2 H), 3.71 (m, 2 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 156.50, 155.10, 154.61, 149.06, 138.65, 138.31, 128.45, 125.49, 123.31, 121.24, 56.89, 50.19 ppm. IR (Nujol mull): $\tilde{\nu}$ = 1633, 1599, 1573, 1555, 1520, 1498 cm^{-1}. $C_{14}H_{13}N_6O{\cdot}0.25\,H_2O$ (285.80): calcd. C 58.84, H 4.73, N 29.42; found: C 58.75, H 5.05, N 29.17.

8-Imino-*N*-(4-methoxyphenyl)-7-phenyl-7,8-dihydropyrimido[5,4-*d*]-pyrimidin-4-amine (4e): Yield 0.67 mmol, 86%, m.p. 242–243 °C. ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 9.65 (s, 1 H), 8.50 (s, 1 H), 8.45 (s, 1 H), 8.06 (s, 1 H), 7.77 (d, J = 8.7 Hz, 2 H), 7.55 (m, 4 H), 7.50 (m, 1 H), 6.93 (d, J = 8.7 Hz, 2 H), 3.75 (s, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 156.52, 156.06, 155.69, 155.21, 142.24, 138.75, 138.66, 131.49, 129.12, 128.46, 127.56, 124.62, 123.18, 113.61, 55.18 ppm. IR (Nujol mull): $\tilde{\nu}$ = 1634, 1608, 1584, 1576, 1558, 1534, 1507 cm^{-1}. $C_{19}H_{16}N_6O$ (344.37): calcd. C 66.28, H 4.65, N 24.42; found: C 66.18, H 4.81, N 24.45.

4-Imino-N^8-(4-methoxyphenyl)pyrimido[5,4-*d*]pyrimidine-3,8(4*H*)-diamine (4f): Yield 0.53 mmol, 91%, m.p. 197–198 °C. ^{1}H NMR ([D$_6$]-DMSO, 300 MHz): δ = 9.58 (s, 1 H), 8.46 (s, 1 H), 8.33 (s, 1 H), 8.16 (s, 1 H), 7.76 (d, J = 9.0 Hz, 2 H), 6.92 (d, J = 9.0 Hz, 2 H), 5.78 (s, 2 H), 3.74 (s, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 156.78, 156.35, 156.44, 155.44, 147.14, 134.09, 130.71, 127.94, 124.03, 113.71, 55.28 ppm. IR (Nujol mull): $\tilde{\nu}$ = 1640, 1619, 1606, 1579, 1561, 1535, 1510 cm^{-1}. $C_{13}H_{13}N_7O$ (283.29): calcd. C 55.12, H 4.59, N 34.63; found: C 55.26, H 4.85, N 34.59.

4-[(8-Imino-7-phenyl-7,8-dihydropyrimido[5,4-*d*]pyrimidin-4-yl)amino]benzonitrile (4h): Yield 0.41 mmol, 60%, m.p. above 274–275 °C (dec.). ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 10.22 (s, 1 H), 8.69 (s, 1 H), 8.59 (s, 1 H), 8.24 (d, J = 9.0 Hz, 2 H), 8.11 (s, 1 H), 7.82 (d, J = 9.0 Hz, 2 H), 7.55 (m, 5 H) ppm. ^{13}C NMR([D$_6$]DMSO, 75 MHz): δ = 156.23, 155.82, 154.72, 147.80, 143.06, 139.70, 138.54, 132.71, 129.14, 128.55, 127.56, 120.91, 119.03, 104.74 ppm. IR (Nujol mull): $\tilde{\nu}$ = 2229, 1630, 1592, 1581, 1534, 1515 cm^{-1}. $C_{19}H_{13}N_7$ (339.36): calcd. C 66.38, H 3.93, N 28.53; found: C 66.48, H 4.03, N 28.70.

4-[(7-Amino-8-imino-7,8-dihydropyrimido[5,4-*d*]pyrimidin-4-yl)amino]benzonitrile (4i): Yield 1.06 mmol, 99%, m.p. above 350 °C (dec.). ^{1}H NMR ([D$_6$]DMSO/TFA, 300 MHz): δ = 10.78 (s, 1 H), 10.63 (s, 1 H), 10.08 (s, 1 H), 8.89 (s, 1 H), 8.72 (s, 1 H), 8.24 (d, J = 8.7 Hz, 2 H), 7.87 (d, J = 8.7 Hz, 2 H), 6.80 (s, 2 H) ppm. ^{1}H NMR ([DMSO, 300 MHz): δ = 10.13 (s, 1 H), 8.65 (s, 1 H), 8.48 (s, 1 H), 8.22 (s, 1 H), 8.23 (d, J = 8.7 Hz, 2 H), 7.80 (d, J = 8.7 Hz, 2 H), 6.82 (s, 2 H) ppm. ^{13}C NMR ([D$_6$]DMSO/TFA, 75 MHz): δ = 156.57, 156.44, 155.59, 147.69, 142.45, 134.81, 132.96, 128.35, 121.93, 119.06, 106.04 ppm. IR (Nujol mull): $\tilde{\nu}$ = 2221, 1642, 1601, 1553, 1519 cm^{-1}. $C_{13}H_{10}N_8$ (278.28): calcd. C 56.12, H 3.60, N 40.28; found: C 56.19, H 3.77, N 40.28.

4-({8-Imino-7-[(4-methoxyphenyl)amino]-7,8-dihydropyrimido[5,4-*d*]-pyrimidin-4-yl}amino)benzonitrile (4j): Yield 0.47 mmol, 38%. ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 10.25 (brs, 1 H), 8.89 (s, 1 H), 8.66 (s, 1 H), 8.57 (s, 1 H), 8.29 (s, 1 H), 8.23 (d, J = 7.5 Hz, 2 H), 7.82 (d, J = 7.5 Hz, 2 H), 6.78 (m, 4 H), 3.66 (s, 3 H) ppm. IR (Nujol mull): $\tilde{\nu}$ = 2215, 1641, 1605, 1557, 1525 cm^{-1}.

4-{[7-(2-Hydroxyethyl)-8-imino-7,8-dihydropyrimido[5,4-*d*]pyrimidin-4-yl]amino}benzonitrile (4k): Yield 0.93 mmol, 97%, m.p. 265–266 °C (dec.). ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 10.09 (s, 1 H), 8.64 (s, 1 H), 8.51 (s, 1 H), 8.22 (d, J = 9.0 Hz, 2 H), 8.07 (s, 1 H), 7.80 (d, J = 9.0 Hz, 2 H), 5.00 (brs, 1 H), 4.07 (m, 2 H), 3.71 (m, 2 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 156.07, 154.76, 154.05, 149.21, 142.97, 138.83, 132.59, 127.79, 120.70, 118.91, 104.60, 56.83, 50.02 ppm. IR (Nujol mull): $\tilde{\nu}$ = 2219, 1631, 1597, 1555, 1515 cm^{-1}. $C_{15}H_{13}N_7O$ (307.31): calcd. C 58.63, H 4.24, N 31.92; found: C 58.86, H 4.38, N 31.55.

General Procedure for the Reactions between 6-Cyanopurines 1 and Ammonia

Method A: A solution of 6-cyanopurine **1** in chloroform was kept in a round-bottomed flask fitted with a serum cap and a magnetic bar and stirred in an ice-salt bath. Ammonia was bubbled through the reaction mixture for 1.5 h, and stirring at 4 °C was continued until all the starting material was no longer present (TLC evidence). The solvent was partially removed in the rotary evaporator and the solid was filtered and washed several times with diethyl ether.

Method B: An aqueous solution of ammonia (25%, 7 molar equiv.) was added to a suspension of 6-cyanopurine **1** in methanol, ethanol or dichloromethane. The round-bottomed flask was fitted with a serum cap and a magnetic bar and stirred at room temperature. When TLC indicated that all the purine had been consumed, the solvent was partially removed in the rotary evaporator and the solid suspension was filtered and washed with ethanol and diethyl ether.

Reaction between 6-Cyanopurine 1a and Piperidine: Piperidine (0.14 mL, 1.44 mmol) was added to a suspension of 6-cyanopurine **1a** (0.15 g, 0.72 mmol) in methanol (5 mL). The solution was heated at reflux for 21 h, after which the TLC indicated that all the starting material had been consumed. White crystals were formed on cooling and were filtered and washed with methanol and diethyl ether. The product was identified as *N*-phenyl-8-(piperidin-1-yl)pyrimido[5,4-*d*]pyrimidin-4-amine (**6a**, 0.16 g, 0.52 mmol, 72%). Characterization: m.p. 105–108 °C (dec.). ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 9.92 (s, 1 H), 8.56 (s, 1 H), 8.55 (s, 1 H), 7.99 (d, J = 7.5 Hz, 2 H), 7.31 (t, J = 7.5 Hz, 2 H), 7.10 (t, J = 7.5 Hz, 1 H), 4.35 (brs, 4 H), 1.67 (m, 6 H) ppm. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.03 (s, 1 H), 8.62 (s, 1 H), 8.53 (s, 1 H), 7.88 (d, J = 7.5 Hz, 2 H), 7.42 (t, J = 7.5 Hz, 2 H), 7.15 (t, J = 7.5 Hz, 1 H), 4.40 (brs, 4 H), 1.77 (brs, 6 H) ppm. ^{13}C NMR([D$_6$]DMSO, 75 MHz): δ = 157.45, 156.95, 153.65, 151.56, 138.55, 134.37, 133.07, 128.51, 123.55, 121.11, 48.07 (br), 26.00, 24.16 ppm. IR (Nujol mull): $\tilde{\nu}$ = 1604, 1551, 1518 cm^{-1}. HRMS: calcd. for $C_{17}H_{19}N_6$ [M + H]$^+$ 307.1671; found: 307.1668.

Reaction between 6-(Methoxyformimidoyl)purine 3 and Ethanolamine: Ethanolamine (0.08 mL, 1.34 mmol) was added to a suspension of 6-methoxyformimidoylpurine **3** (0.23 g, 0.89 mmol) in methanol (2 mL). Sulfuric acid (50 μL) was added and the suspension was stirred at room temperature until the starting material was no longer present (15 d). The suspension was filtered and washed with methanol and diethyl ether, and the solid was identified as a mixture of **4b** and **6b** in a 1:2 molar ratio (0.23 g, 8.81 mmol, 91%). Characterization of 2-[(8-anilinopyrimido[5,4-*d*]pyrimidin-4-yl)-amino]ethanol **6b**: ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 9.93 (brs, 1 H), 8.60 (s, 1 H), 8.53 (s, 1 H), 8.24 (brs, 1 H), 7.90 (d, J = 8.1 Hz, 2 H), 7.37 (t, J = 7.5 Hz, 2 H), 7.11 (t, J = 7.5 Hz, 1 H), 4.86 (brs, 1 H), 3.61 (m, 4 H) ppm.

Reaction between 6-Cyanopurine 1c and (4-Methoxyphenyl)hydrazine: The hydrochloride salt of (4-methoxyphenyl)hydrazine (1.50 g,

8.61 mmol) was neutralized by the addition of aqueous sodium hydroxide solution (1 M, 1 molar equivalent) and the hydrazine was extracted with dichloromethane (4 × 25 mL). The solvent was almost completely removed in the rotary evaporator and the 6-cyanopurine **1c** (0.31 g, 1.27 mmol) in THF (5 mL) was added. A catalytic amount of DBU (10 μL) was added and the reaction mixture was stirred at room temperature. After 24 h, TLC indicated the absence of the starting material and the suspension was filtered off and washed with ethanol and diethyl ether. The solid was identified as the pyrimido[5,4-*d*]pyrimidine **6f** (0.38 g, 0.99 mmol, 77%). Characterization: m.p. 249–251 °C. ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 10.44 (brs, 1 H), 10.38 (brs, 1 H), 8.75 (s, 1 H), 8.53 (s, 1 H), 8.32 (d, J = 8.7 Hz, 2 H), 7.84 (d, J = 8.7 Hz, 2 H), 7.77 (s, 1 H), 6.76 (s, 4 H), 3.64 (s, 3 H) ppm. ^{13}C NMR ([D$_6$]-DMSO, 75 MHz): δ = 159.05 (br), 156.26, 154.92 (br), 153.49, 152.81, 143.02, 142.42, 132.84, 131.76 (br), 121.11, 119.16, 114.26, 113.93, 104.93, 55.23 ppm. IR (Nujol mull): $\tilde{\nu}$ = 2224, 1604, 1592, 1579, 1558, 1525, 1509 cm^{-1}. $C_{20}H_{16}N_8O$ (384.40): calcd. C 62.50, H 4.17, N 29.17; found: C 62.51, H 4.38, N 29.11. When this reaction was repeated and the mixture was stirred at room temperature for 2 h, the solid suspension that was filtered off and washed with ethanol and diethyl ether was identified as compound **4j** (0.18 g, 0.47 mmol, 38%). A second crop was obtained from the mother liquor after partial removal of the solvent in the rotary evaporator. This solid was a mixture of compounds **4j** and **6f** in a 1:1.3 molar ratio (0.20 g, 0.53 mmol, 42%).

***N*-Phenylpyrimido[5,4-*d*]pyrimidine-4,8-diamine (6c):** Yield 0.70 mmol, 60%, m.p. 243–245 °C. ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 9.91 (s, 1 H), 8.58 (s, 1 H), 8.47 (s, 1 H), 8.05 (brs, 1 H), 7.90 (d, J = 7.8 Hz, 2 H), 7.86 (s, 1 H), 7.36 (t, J = 7.8 Hz, 2 H), 7.10 (t, J = 7.8 Hz, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 161.27, 156.56, 154.93, 153.55, 138.59, 132.29, 131.41, 128.55, 123.71, 121.41 ppm. IR (Nujol mull): $\tilde{\nu}$ = 1664, 1644, 1605, 1561, 1538, 1495 cm^{-1}. HRMS: calcd. for $C_{12}H_{11}N_6$ [M + H]$^+$ 239.1045; found: 239.1042.

***N*-(4-Methoxyphenyl)pyrimido[5,4-*d*]pyrimidine-4,8-diamine (6d):** Yield 0.54 mmol, 64%, m.p. 256–257 °C. ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 9.88 (s, 1 H), 8.52 (s, 1 H), 8.44 (s, 1 H), 8.02 (s, 1 H), 7.86 (d, J = 6.9 Hz, 2 H), 7.82 (brs, 1 H), 6.94 (d, J = 6.9 Hz, 2 H), 3.75 (s, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 161.07, 156.27, 155.54, 154.58, 153.53, 132.12, 131.46, 131.08, 122.98, 113.60, 55.15 ppm. IR (Nujol mull): $\tilde{\nu}$ = 1660, 1616, 1606, 1580, 1561, 1546 cm^{-1}. $C_{13}H_{12}N_6O$ (268.28): calcd. C 58.21, H 4.48, N 31.34; found: C 58.17, H 4.56, N 31.32.

4-[(8-Aminopyrimido[5,4-*d*]pyrimidin-4-yl)amino]benzonitrile (6e): Yield 0.82 mmol, 96%, m.p. 338–341 °C (dec.). ^{1}H NMR ([D$_6$]-DMSO/TFA, 300 MHz): δ = 10.46 (brs, 2 H), 8.83 (d, J = 6.9 Hz, 2 H), 8.73 (s, 1 H), 8.55 (brs, 1 H), 8.53 (s, 1 H), 8.44 (s, 1 H), 8.30 (d, J = 6.9 Hz, 2 H) ppm. ^{13}C NMR ([D$_6$]DMSO/TFA, 75 MHz): δ = 162.7, 140.1, 134.0, 132.3, 129.6, 128.9, 126.4, 115.3, 38.6 ppm. IR (Nujol mull): $\tilde{\nu}$ = 2231, 1659, 1604, 1532, 1503 cm^{-1}. $C_{13}H_9N_7 \cdot 0.5\,H_2O$ (272.27): calcd. C 57.35, H 3.67, N 36.03; found: C 57.10, H 3.85, N 35.77.

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