

Facile Synthesis of 9-Substituted 9-Deazapurines as Potential Purine Nucleoside Phosphorylase Inhibitors

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A facile synthesis of 9-substituted 9-deazapurines as potential inhibitors of purine nucleoside phosphorylase has been achieved by the direct Friedel–Crafts arylation or arylmethylation of 9-deazapurines using trifluoromethanesulfonic acid as catalyst. The aroylated 9-deazapurines could be transformed into the corresponding 9-arylmethyl derivatives by the Wolff–Kishner reaction. A novel synthesis of 9-deazahypoxanthine was also developed by treatment of 4-hydroxy-5-phenylazo-6-methylpyrimidin-2-thione with triethyl orthoformate in trifluoroacetic acid (TFA) to yield 8-oxo-7H-2-phenylpyrimido[5,4-c]pyridazin-6-thione followed by Raney nickel reduction.

Key words 9-deazahypoxanthine; 9-deazapurine; 9-aryol-9-deazapurine; 9-arylmethyl-9-deazapurine; purine nucleoside phosphorylase inhibitor

Purine nucleoside phosphorylase (PNP) catalyzes reversibly the phosphorylation of guanosine, inosine, and their 2'-deoxyribonucleoside derivatives to the corresponding free base, α -ribose-1-phosphate, or 2-deoxy- α -ribose-1-phosphate. Inhibition of PNP may cause the selective accumulation of dGTP,¹⁾ selective depletion of T lymphocytes, and inhibition of cellular immune response.²⁾ Thus, a potent PNP inhibitor may provide a new and effective immunosuppressive agent in the treatment of T-cell dependent diseases such as rheumatoid arthritis, psoriasis, T-cell leukemia and lymphoma. Various derivatives of 9-substituted 9-deazaguanine and 9-deazahypoxanthine as potent competitive inhibitors of purine nucleoside phosphorylase based on the application of crystallographic and modeling methods have been described.^{3–7)} All these derivatives were prepared by multi-step synthesis without using a common building block. Usually, the last step in these processes was the construction of the pyrimidine or pyrrole ring of the deazapurine base.^{3–7)} In order to find a simple and effective method to explore more PNP inhibitors, a facile synthesis of these analogues was developed based on the strategy of the direct arylation or arylmethylation of available building blocks, such as 9-deazaxanthine (**1**),⁸⁾ 9-deazaguanine (**2**),^{8,9)} or 9-deazahypoxanthine (**3**).⁹⁾ The aroylated compounds could be converted to the corresponding arylmethyl derivatives or *vice versa*. These approaches would be much more efficient than the previously reported multi-step synthesis which employed no common building blocks. Herein, we report a facile synthesis of 9-substituted 9-deazapurines and an improved method to prepare 9-deazahypoxanthine.

Results and Discussion

Synthesis of 9-Substituted 9-Deazaxanthine As C-deoxyribonucleosides¹⁰⁾ had been prepared by the direct C-glycosylation of 7- and 9-deazaguanine using stannic chloride as catalyst, it was possible to synthesize 9-substituted 9-deazapurines by a direct arylation or arylmethylation of available 9-deazaxanthine (**1**), 9-deazaguanine (**2**) or 9-deazahypoxanthine (**3**). In our initial attempts, the Friedel–Crafts benzylation of **1** in the presence of Lewis acid catalysts gave a mixture of 9-deazaxanthine benzylation at N-1, N-3, and N-7 as major products. As acylation of olefins could pro-

ceed through carbocation intermediate in the presence of strong acids,¹¹⁾ treatment of **1** with benzoyl chloride in polyphosphoric acid at 100 °C gave unsatisfactory results. However, acylation of **1** with benzoyl chloride using triflic acid as catalyst in nitromethane, provided the desired 9-benzoyl-9-deazaxanthine, **4**, in low yield. Optimization of the reaction conditions for benzylation was achieved upon the reaction of **1** with benzoyl chloride (1.2 eq), using triflic acid (>10 eq) as catalyst and solvent at temperatures higher than 60 °C for 48 h providing 75% yield of **4**. A similar procedure was applied to yield 9-(*p*-methylbenzoyl)- and 9-(3',4'-dichlorobenzoyl)-9-deazaxanthine, **5** and **6**, respectively. In these reactions, one major aroylated product at the C-9 position was isolated. 8-Aroyl or 8,9-diaroyl derivatives were not found. The lack of these side products indicated the exclusive arylation at C-9. The electron-withdrawing aroyl substituent at C-9 might play an important role to deactivate further arylation at the C-8 position of 9-deazaxanthine. However, a limitation in the scope of this electrophilic substitution was observed. We found that reactions involving aroyl chlorides bearing electron-withdrawing groups at the para position, proceeded with great difficulty due to the limited availability of *in-situ* generated carbocation. We then investigated several procedures to convert the aroyl substituent to arylmethyl derivatives. Attempts to reduce **4** by the Clemmensen reduction or by catalytic hydrogenation using 10% palladium on carbon under acidic or basic conditions, failed to give product. However, it was found that **4** could be reduced to 9-benzyl-9-deazaxanthine, **7** (56% yield), by the Wolff–Kishner reaction, using 10 eq of NaOH and 10 eq of hydrazine in ethylene glycol at 100 °C. Similarly, 9-(*p*-methylbenzoyl)-9-deazaxanthine, **8**, was obtained from **5** by the Wolff–Kishner reaction. The successful synthesis of 9-aryol-9-deazaxanthine led us to turn our attention to the preparation of 9-arylmethyl derivatives by the direct Friedel–Crafts alkylation of **1**. Previously, the Friedel–Crafts alkylation of **1** with benzyl bromide using a Lewis acid catalyst such as stannic chloride, or aluminum chloride in nitromethane, or acetonitrile, produced a mixture of 9-deazaxanthines benzylation at C-8, C-9, N-1, or N-7. Attempts to prepare the desired compound using silver oxide as catalyst,¹²⁾ which had been successfully used in an indole system,

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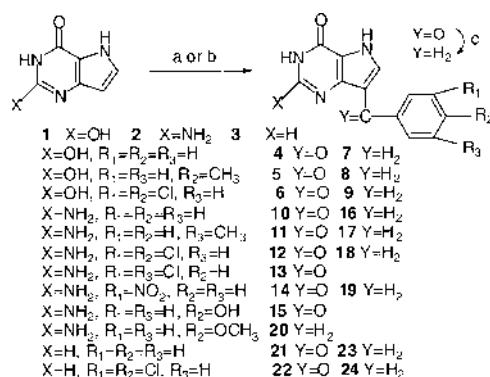
resulted in benzylation at N-7 and C-8 positions. Treatment of **1** with benzyl alcohol, a good source of benzyl cation,^{13,14} in triflic acid at room temperature yielded 8,9-dibenzylated derivatives. The reaction of **1** with benzyl bromide in triflic acid as catalyst and solvent at 60–100 °C also gave 8,9-dibenzyl derivatives. In an effort to solve the problem, treatment of **1** with benzyl bromide using triflic acid (>4 eq) as catalyst in glacial acetic acid at 100 °C or TFA at 80 °C for 48 h, resulted in **7** as a major product. Similar results were obtained by the same approach to yield **8** and **9**, respectively. However, the better result of **9** was obtained when aluminum chloride, a Lewis acid, was added as the second catalyst to increase the formation of 3,4-dichlorobenzyl cation. In these reactions, acetic acid or TFA not only helped to dissolve 9-deazaxanthine but also increased the formation of benzyl cation for alkylation. We isolated 8,9-diarylmethylated compounds as a minor product. However, we observed no 8-arylmethyl-9-deazaxanthin. It was postulated that arylmethylation occurred first at C-9, followed by further electrophilic substitution at C-8 to yield 8,9-diarylmethyl derivatives.

Synthesis of 9-Substituted 9-Deazaguanine Unlike **1**, acylation of **2** can occur at 2-amino and C-9 positions. Thus, reaction of **2** with 2.2 eq of benzoyl chloride in triflic acid (>20 eq) at 60 °C resulted in dibenzoyl derivative at 2-amino and C-9 positions, which could be converted to the desired 9-benzoyl-9-deazaguanine, **10**, by treatment of the reaction mixture with excess NaOH (>40 eq) for 2 h at 60 °C, followed by neutralization. However, at a higher temperatures (>80 °C), 2-acylamide of dibenzoyl derivative was further hydrolyzed by triflic acid to give **10**. Similar procedure by treatments of **2** with *p*-methylbenzoyl chloride, 3,4-dichlorobenzoyl chloride, 3,5-dichlorobenzoyl chloride, or 3-nitrobenzoyl chloride resulted in **11**, **12**, **13**, or **14**, respectively. However, treatment of **2** with *p*-methoxybenzoyl chloride at 80 °C for 40 h resulted in 9-(*p*-hydroxybenzoyl)-9-deazaguanine, **15**, because *p*-methoxyl substituent was further hydrolyzed by triflic acid. We found that the reaction gave a major product of 9-(*p*-methoxybenzoyl)-9-deazapurine (ms, 285, MH⁺) at a lower temperature (60 °C) for 20 h, but failed to give a product at higher temperature (>100 °C) for 24 h, due to the early cleavage of the methoxyl group of *p*-methoxybenzoyl chloride by triflic acid before it could be acylated at C-9. The chemistry of electrophilic substitution of 9-deazaguanine under strong acidic condition was similar to that of 9-substituted 9-deazaxanthine. Accordingly, treatment of **2** with 1.2 eq of benzyl, *p*-methylbenzyl, 3,4-dichlorobenzyl, 3-nitrobenzyl bromide, or *p*-methoxybenzyl chloride and 5 eq of triflic acid in glacial acetic acid or TFA offered **16**, **17**, **18**, **19**, or **20** as a major product, respectively.

Synthesis of 9-Deazahypoxanthine and Its 9-Substituted Derivatives Previously, **3** had been prepared by dichlorination of **1** with phosphorus oxychloride followed by partial alkaline hydrolysis of 6-chloro substituent and the subsequent removal of 2-chloro by hydrogenation with palla-

dium on carbon,⁹ or by the condensation of isoxazole and diethyl aminomalonate to form pyrrole derivative followed by reaction with formamidine acetate,¹⁵ or by palladium-catalyzed cross-coupling of 4-methoxy-5-nitro-6-iodopyridine and trimethyl(tributylstannylolethynyl)silane to form 4-methoxy-5-nitro-6-trimethylsilylolethynylpyridine followed by construction of an annulated pyrrole ring.¹⁶ However, in the routes to synthesize intermediates of **1** and **2**, 6,8-dioxo-7*H*-2-phenylpyrimido[5,4-*c*]pyridazine⁸) and 6-amino-8-oxo-2-phenylpyrimido[5,4-*c*]pyridazine,⁸) respectively, by modifying Klein's procedure⁸) using TFA as solvent, we found a simple two-step synthesis of **3** with an overall yield of 50%. This new method involved the reaction of 4-hydroxy-5-phenylazo-6-methylpyrimidin-2-thione, **25**,¹⁷) with triethyl orthoformate in TFA at 70 °C to give 8-oxo-7*H*-2-phenylpyrimido[5,4-*c*]pyridazin-6-thione, **26**. The subsequently concomitant ring constriction and removal of the 2-thione of this intermediate with Raney-nickel in methanol offered **3** (Chart 2). In this reaction, hydrazine or NaOH could be used as base catalyst. The chemistry of **3** toward the Friedel-Crafts acylation or alkylation was expected to be the same as **1**. Accordingly, 9-benzoyl-9-deazahypoxanthine (**21**), 9-(3',4'-dichlorobenzoyl)-9-deazahypoxanthine (**22**), 9-benzyl-9-deazahypoxanthines (**23**) and 9-(3',4'-dichlorobenzyl)-9-deazahypoxanthine (**24**) were obtained by the same procedures used in the preparations of 9-substituted 9-deazaxanthines.

Summary We had developed a novel synthesis of 9-deazahypoxanthine and demonstrated more efficient and concise approaches to prepare 9-substituted 9-deazapurines *via* the Friedel-Crafts acylation or alkylation, using triflic acid as catalyst. These approaches were based on the *in-situ* generation of available carbocation or arylmethyl cation, so that arylation or arylmethylation could occur at the C-9 of 9-deazapurine. The aryolated compounds could be transformed into the corresponding arylmethyl analogues by the Wolff-Kishner reaction or *visé versa* as evidenced by the



a. ArCOCl, triflic acid, 60–100 °C; b. ArCH₂Br, triflic acid, 80–100 °C; c. NH₂NH₂, KOH

Chart 1

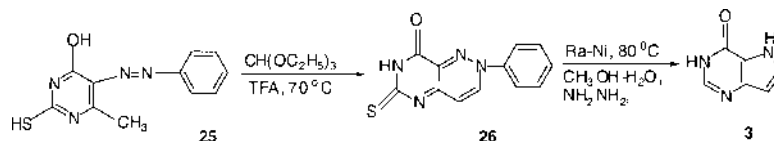


Chart 2

conversion of **16** to **10** using CrO_3 in acetic acid.¹⁸⁾ We are currently applying these methods to synthesize 7-substituted 7-deazapurines.

Experimental

All solvents and chemicals were of analytical grade. Melting points were determined by the capillary method with a MEL-Temp II apparatus, and uncorrected. NMR spectra in $\text{DMSO}-d_6$ were recorded at 500 MHz. Mass spectrum was obtained by FAB-MS.

General Procedures. Method A. Aroylation of 9-Deazapurines 1: The mixture of **1** (200–300 mg as 1.0 eq) or **3** (100 mg as 1.0 eq), and aroyl chloride (1.2 eq) in triflic acid (10 eq) was stirred at 60–100 °C for 48 h. After cooling, water was added to the reaction mixture. The resulting precipitate was filtered and washed with solvent several times such as methylene chloride, ethyl acetate, acetone, or methanol, to give desired product. Further purification can be done by repeatedly boiling the product in methanol and then filtered several times.

2: The mixture of **2** (200–300 mg) and aroyl chloride (2.2 eq) in triflic acid (>20 eq) was stirred at 80–120 °C for 48 h. After cooling, water was added to the reaction mixture. The resulting precipitate was filtered and washed several times with solvent such as methylene chloride, ethyl acetate, acetone, or methanol, to give desired product. Further purification can be done by repeatedly boiling the product in methanol and then filtered several times.

B. Arylmethylation of 9-Deazapurines The mixture of 9-deazapurine (100–300 mg), arylmethyl bromide (1.2 eq) and triflic acid (4–10 eq) in acetic acid (10 ml) or TFA (10 ml) was stirred at 80–100 °C for 48 h. The reaction mixture was concentrated under *vacuo*. The residue was added with water, neutralized and then extracted with ethyl acetate twice. The combined organic phase was dried and evaporated. The residue was purified by flash column chromatography using 5% methanol in methylene chloride as an eluent to give product. For the synthesis of 9-(3',4'-dichlorobenzyl)-9-deazapurines, a modification was made by adding aluminum chloride (2.2 eq) as the second catalyst to increase the formation of 3,4-dichlorobenzyl cation.

C. The Wolff-Kishner Reaction The mixture of 9-deazapurine (100–150 mg), NaOH (10 eq) and hydrazine (10 eq) in ethylene glycol (10 ml) was stirred at 100–120 °C for 16 h. The reaction mixture was diluted with water and then neutralized with acetic acid. The mixture was then extracted with ethyl acetate twice. The combined organic phase was dried and evaporated. The residue was chromatographed using 10% methanol in methylene chloride as an eluent to give the product.

3H,5H-Pyrrolo[3,2-*d*]pyrimidin-4-one (3): The mixture of 4-hydroxy-5-phenylazo-6-methylpyrimid-2-thione¹⁰⁾ (12 g), triethyl orthoformate (100 ml) in TFA (60 ml) was stirred at 70 °C overnight. After cooling, the reaction mixture was filtered and washed with CH_2Cl_2 to give 7.0 g of crude 8-oxo-7H-2-phenylpyrimido[5,4-*c*]pyridazin-6-thione [NMR, δ 7.70 (m, 3H, aromatic H), 7.90 (m, 2H, aromatic H), 8.15 (bs, 1H, C-4H), 9.2 (bs, 1H, C-3H), 9.57 (d, 1H, NH)]. This crude intermediate in 120 ml of 50% methanol-water and 5 ml of hydrazine was added Ra-Ni (wet, 40 g) with stirring at 80 °C overnight. The reaction mixture was filtered and the filtrate was evaporated to give almost pure product (3.22 g, 49%), which was recrystallized from hot water to give pure compound. mp >300 °C (lit.⁹⁾ >300 °C; MS *m/z*, 136 (MH^+); ¹H-NMR ($\text{DMSO}-d_6$) δ 6.36 (d, 1H, C-7H), 7.37 (t, 1H, *J*=2.5 Hz, C-6H), 7.78 (s, 1H, C-2H), 11.86 (s, 1H), 12.08 (s, 1H).

7-Benzoyl-1H,3H,5H-pyrrolo[3,2-*d*]pyrimidin-2,4-dione (4): 75% yield from method A-1; mp 340 °C (decomposed); MS *m/z*, 255 (M^+); ¹H-NMR ($\text{DMSO}-d_6$) δ 7.55 (t, 2H, *J*=7.5 Hz, C'-3H, C'-5H), 7.64 (t, 1H, *J*=6.5 Hz, C'-4H), 7.68 (d, 1H, *J*=4 Hz, C-6H), 7.82 (d, 2H, *J*=7 Hz, C'-2H, C'-6H), 10.0 (b, 1H, OH), 10.9 (b, 1H, OH), *Anal.* Calcd for $\text{C}_{13}\text{H}_9\text{N}_3\text{O}_3 \cdot 1/2\text{H}_2\text{O}$: C, 59.03; H, 3.78; N, 15.90. Found: C, 59.00; H, 3.57; N, 15.92.

7-(*p*-Methylbenzoyl)-1H,3H,5H-pyrrolo[3,2-*d*]pyrimidin-2,4-dione (5): 79% yield from method A-1; mp >300 °C; MS *m/z*, 270 (M^+); ¹H-NMR ($\text{DMSO}-d_6$) δ 2.37 (s, 3H, CH_3), 7.33 (d, 2H, *J*=8 Hz, C'-3H, C'-5H), 7.68 (s, 1H, C-6H), 7.73 (d, 2H, *J*=8 Hz, C'-2H, C'-6H), 10.3 (s, 1H, OH), 11.0 (s, 1H, OH), 12.85 (b, 1H, NH). *Anal.* Calcd for $\text{C}_{14}\text{H}_{11}\text{N}_3\text{O}_3 \cdot 1/3\text{CF}_3\text{SO}_3\text{H}$: C, 53.87; H, 3.76; N, 13.16. Found: C, 54.11; H, 3.93; N, 12.93.

7-(3',4'-Dichlorobenzoyl)-1H,3H,5H-pyrrolo[3,2-*d*]pyrimidin-2,4-dione (6): 90% yield from method A-1; mp 326 °C (decomposed); MS *m/z*, 324 (MH^+); ¹H-NMR ($\text{DMSO}-d_6$) δ 7.77 (m, 3H, C-6H, C'-5H, C'-6H), 7.95 (s, 1H, C'-4H), 10.19 (s, 1H, OH), 11.05 (s, 1H, OH), 12.9 (s, 1H, NH); *Anal.* Calcd for $\text{C}_{13}\text{H}_6\text{Cl}_2\text{N}_3\text{O}_3 \cdot 2/3\text{H}_2\text{O}$: C, 46.41; H, 2.47; N, 12.50. Found: C, 46.20; H, 2.53; N, 12.24.

7-Benzyl-1H,3H,5H-pyrrolo[3,2-*d*]pyrimidin-2,4-dione (7): 11% yield from method B, 77.6% yield from method C; mp 257 °C (decomposed); MS *m/z*, 241 (M^+); ¹H-NMR ($\text{DMSO}-d_6$) δ 3.79 (s, 2H, CH_2), 6.93 (d, 1H, *J*=6 Hz, C-6H), 7.15 (t, 1H, *J*=6.5 Hz, C'-4H), 7.26 (m, 4H, C'-2H, C'-3H, C'-5H, C'-6H), 10.58 (s, 1H, OH), 10.87 (s, 1H, OH), 11.65 (s, 1H, NH). *Anal.* Calcd for $\text{C}_{13}\text{H}_{11}\text{N}_3\text{O}_2 \cdot 1/15\text{CF}_3\text{SO}_3\text{H}$: C, 62.41; H, 4.40; N, 16.72. Found: C, 62.37; H, 4.12; N, 16.37.

7-(*p*-Methylbenzyl)-1H,3H,5H-pyrrolo[3,2-*d*]pyrimidin-2,4-dione (8): 58% yield from method C, 17% yield from method B; mp 283 °C (decomposed); MS *m/z*, 256 (MH^+); ¹H-NMR ($\text{DMSO}-d_6$) δ 2.22 (s, 3H, CH_3), 3.72 (s, 2H, CH_2), 6.88 (s, 1H, C-6H), 7.0–7.2 (m, 5H, aromatic H), 10.57 (s, 1H, OH), 10.82 (s, 1H, OH), 11.62 (s, 1H, NH). *Anal.* Calcd for $\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}_2 \cdot 1/2\text{H}_2\text{O}$: C, 63.57; H, 5.30; N, 15.90. Found: C, 63.95; H, 4.94; N, 15.64.

7-(3',4'-Dichlorobenzyl)-1H,3H,5H-pyrrolo[3,2-*d*]pyrimidin-2,4-dione (9): 8% yield from method B; mp 278 °C (decomposed); MS *m/z*, 310 (MH^+); ¹H-NMR ($\text{DMSO}-d_6$) δ 3.79 (s, 2H, CH_2), 7.07 (d, 1H, *J*=3 Hz, C-6H), 7.23 (dd, 1H, *J*=1.5 Hz, C'-6H), 7.51 (s, 1H, C'-2H), 7.53 (d, 1H, *J*=1.5 Hz, C'-5H), 10.60 (s, 1H, OH), 10.88 (s, 1H, OH), 11.76 (s, 1H, NH). *Anal.* Calcd for $\text{C}_{13}\text{H}_6\text{Cl}_2\text{N}_3\text{O}_2 \cdot 1/9\text{H}_2\text{O}$: C, 50.02; H, 2.98; N, 13.46. Found: C, 50.33; H, 2.96; N, 13.07.

2-Amino-3H,5H-7-benzoylpyrrolo[3,2-*d*]pyrimidin-4-one (10): 54% yield from A-2; mp 287 °C (decomposed, lit.¹⁸⁾ mp >250 °C); MS *m/z*, 255 (MH^+); ¹H-NMR ($\text{DMSO}-d_6$) δ 6.4 (b, 2H, NH_2), 7.49 (t, 2H, *J*=7.5 Hz, C'-3H, C'-5H), 7.56 (s, 1H, C-6H), 7.6 (t, 1H, C'-4H), 7.79 (d, 2H, *J*=7.0 Hz, C'-2H, C'-6H). *Anal.* Calcd for $\text{C}_{13}\text{H}_{10}\text{N}_4\text{O}_2 \cdot 1/6\text{CF}_3\text{SO}_3\text{H}$: C, 56.18; H, 3.94; N, 19.91. Found: C, 56.58; H, 3.64; N, 20.06.

2-Amino-3H,5H-7-(*p*-methylbenzoyl)pyrrolo[3,2-*d*]pyrimidin-4-one (11): 55% yield from method A-2; mp 267 °C (decomposed); MS *m/z*, 269 (MH^+); ¹H-NMR ($\text{DMSO}-d_6$) δ 6.4 (b, 2H, NH_2), 7.30 (d, 2H, *J*=8 Hz, C'-3H, C'-5H), 7.55 (s, 1H, C-6H), 7.71 (d, 2H, *J*=8 Hz, C'-2H, C'-6H), 10.9 (b, 1H, OH), 12.46 (b, 1H, NH). *Anal.* Calcd for $\text{C}_{14}\text{H}_{12}\text{N}_4\text{O}_2 \cdot 1/5\text{CF}_3\text{SO}_3\text{H}$: C, 57.12; H, 4.09; N, 18.78. Found: C, 57.21; H, 4.44; N, 18.44.

2-Amino-3H,5H-7-(3',4'-dichlorobenzoyl)pyrrolo[3,2-*d*]pyrimidin-4-one (12): 91% yield from method A-2; mp 310 °C (decomposed); MS *m/z*, 323 (M^+); ¹H-NMR ($\text{DMSO}-d_6$) δ 6.8 (s, 2H, NH_2), 7.6 (s, 1H, C-6H), 7.78 (d, 2H, C'-5H, C'-6H), 7.96 (s, 1H, C'-2H), 10.18 (s, 1H, OH), 11.03 (s, 1H, NH); *Anal.* Calcd for $\text{C}_{13}\text{H}_8\text{Cl}_2\text{N}_4\text{O}_2 \cdot 1.6\text{H}_2\text{O}$: C, 44.36; H, 3.21; N, 15.92. Found: C, 44.27; H, 2.82; N, 15.66.

2-Amino-3H,5H-7-(3',5'-dichlorobenzoyl)pyrrolo[3,2-*d*]pyrimidin-4-one (13): 57% yield from method A-2; mp 308 °C (decomposed); MS *m/z*, 324 (MH^+); ¹H-NMR ($\text{DMSO}-d_6$) δ 6.41 (b, 2H, NH_2), 7.70 (s, 1H, C-6H), 7.75 (s, 2H, C'-2H, C'-6H), 7.94 (s, 1H, C'-4H), 11.03 (b, 1H, OH), 12.6 (s, 1H, NH). *Anal.* Calcd for $\text{C}_{13}\text{H}_8\text{Cl}_2\text{N}_4\text{O}_2 \cdot 2/3\text{CH}_3\text{OH} \cdot 1/15\text{CF}_3\text{SO}_3\text{H}$: C, 46.49; H, 3.02; N, 15.79. Found: C, 46.22; H, 2.91; N, 15.61.

2-Amino-3H,5H-7-(*m*-nitrobenzoyl)pyrrolo[3,2-*d*]pyrimidin-4-one (14): 72% yield from method A-2; mp >300 °C; MS *m/z*, 300 (MH^+); ¹H-NMR ($\text{DMSO}-d_6$) δ 6.36 (b, 2H, NH_2), 7.57 (s, 1H, C-6H), 7.77 (t, 1H, *J*=7.5 Hz, C'-5H), 8.19 (d, 1H, *J*=7.5 Hz, C'-6H), 8.39 (d, 1H, *J*=8.0 Hz, C'-4H), 8.51 (s, 1H, C'-2H). *Anal.* Calcd for $\text{C}_{13}\text{H}_9\text{N}_5\text{O}_4 \cdot 0.4\text{CH}_3\text{OH} \cdot 0.15\text{CF}_3\text{SO}_3\text{H}$: C, 48.60; H, 3.21; N, 20.93. Found: C, 48.57; H, 2.91; N, 20.67.

2-Amino-3H,5H-7-(*p*-hydroxybenzoyl)pyrrolo[3,2-*d*]pyrimidin-4-one (15): 75% yield from method A-2 at 100 °C for 3 d; mp >300 °C; MS *m/z*, 271 (MH^+); ¹H-NMR ($\text{DMSO}-d_6$) δ 6.85 (d, 2H, *d*=8.5 Hz, C'-3H, C'-5H), 7.62 (s, 1H, C-6H), 7.75 (d, 2H, *J*=8 Hz, C'-2H, C'-6H), 10.27 (s, 1H, OH), 12.54 (b, 1H, NH). *Anal.* Calcd for $\text{C}_{13}\text{H}_9\text{N}_4\text{O}_3 \cdot \text{CH}_3\text{COCH}_3 \cdot 0.65\text{CF}_3\text{SO}_3\text{H}$: C, 46.95; H, 3.94; N, 13.16. Found: C, 47.32; H, 3.81; N, 12.94.

2-Amino-3H,5H-7-benzylpyrrolo[3,2-*d*]pyrimidin-4-one (16): 20% yield from method B, 53% yield from method C; mp 255 °C (decomposed, lit.³⁾ 269–270 °C); MS *m/z*, 240 (M^+); ¹H-NMR ($\text{DMSO}-d_6$) δ 3.77 (s, 2H, CH_2), 5.79 (b, 2H, NH_2), 6.90 (s, 1H, C-6H), 7.0–7.3 (m, 5H, aromatic H), 10.25 (b, 1H, OH), 11.2 (b, 1H, NH).

2-Amino-3H,5H-7-(*p*-methylbenzyl)pyrrolo[3,2-*d*]pyrimidin-4-one (17): 12% yield from method B; mp 175 °C (decomposed); MS *m/z*, 254 (M^+); ¹H-NMR ($\text{DMSO}-d_6$) δ 2.22 (s, 3H, CH_3), 3.75 (s, 2H, CH_2), 5.8 (b, 2H, NH_2), 6.90 (d, 1H, *J*=3 Hz, C-6H), 7.04 (d, 2H, *J*=7.5 Hz, C'-3H, C'-5H), 7.10 (d, 2H, *J*=8 Hz, C'-2H, C'-6H), 10.32 (s, 1H, NH), 11.2 (1H, NH). *Anal.* Calcd for $\text{C}_{14}\text{H}_{14}\text{N}_4\text{O} \cdot 2/3\text{CH}_3\text{COOH}$: C, 62.52; H, 5.66; N, 19.03. Found: C, 62.40; H, 5.62; N, 19.20.

2-Amino-3H,5H-7-(3',4'-dichlorobenzyl)pyrrolo[3,2-*d*]pyrimidin-4-one (18): 14% yield from method B; mp 245 °C (decomposed, lit.³⁾ 278–280 °C); MS *m/z*, 309 (MH^+); ¹H-NMR ($\text{DMSO}-d_6$) δ 3.79 (s, 2H, CH_2), 5.82 (b, 2H, NH_2), 6.99 (d, 1H, C-6H), 7.21 (m, 1H, C'-6H), 7.43 (m, 1H, C'-2H), 7.46 (m, 1H, C'-5H), 10.38 (s, 1H, OH), 11.28 (s, 1H, OH).

2-Amino-3H,5H-7-(*m*-nitrobenzyl)pyrrolo[3,2-*d*]pyrimidin-4-one (19): 15%

yield from method B in the solvent of triflic acid; mp 190 °C; MS m/z , 285 (M^+); 1H -NMR (DMSO- d_6) δ 4.05 (s, 2H, CH₂), 7.33 (s, 2H, C-6H), 7.57 (t, 1H, C'-5H), 7.70 (d, 1H, $J=6.9$ Hz, C'-6H), 8.06 (d, 1H, $J=7.5$ Hz, C'-4H), 8.11 (s, 1H, C'-2H), 12.4 (s, 1H, NH). *Anal.* Calcd for C₁₃H₁₁N₅O₃·1.4CF₃COOH·0.5H₂O: C, 41.81; H, 3.28; N, 15.43. Found: C, 41.80; H, 3.15; N, 15.27.

2-Amino-3*H*,5*H*-7-(*p*-methoxybenzyl)pyrrolo[3,2-*d*]pyrimidin-4-one (**20**): 21% yield from method B using *p*-methoxybenzyl bromide as alkylating agents at 80 °C for 24 h; mp 275 °C, decomposed; 1H -NMR (DMSO- d_6) δ 3.68 (s, 3H, OCH₃), 3.71 (s, 2H, CH₂), 5.82 (s, 2H, NH₂), 6.78 (d, 2H, $J=8.5$ Hz, C'-3, C'-5H), 6.86 (d, 1H, $J=2.5$ Hz, C-6H), 7.13 (d, 2H, $J=9$ Hz, C'-2H, C'-6H), 10.4 (b, 1H, NH), 11.19 (s, 1H, NH). *Anal.* Calcd for C₁₄H₁₄N₄O₂·0.8CH₃COOH: C, 58.85; H, 5.46; N, 17.60. Found: C, 59.22; H, 5.17; N, 17.27.

7-Benzoyl-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (**21**): 13% yield from method A-1; mp >300 °C; MS m/z , 239 (M^+); 1H -NMR (DMSO- d_6) δ 7.49 (t, 2H, $J=7$ Hz, C'-3H, C'-5H), 7.59 (t, 1H, $J=7.5$ Hz, C'-4H), 7.79 (d, 2H, $J=7.5$ Hz, C'-2H, C'-6H), 7.86 (d, 1H, $J=3.5$ Hz, C-6H), 7.91 (s, 1H, C-2H). *Anal.* Calcd for C₁₃H₉N₃O₂·0.1CF₃SO₃H: C, 61.88; H, 3.61; N, 16.53. Found: C, 62.18; H, 3.58; N, 16.31.

7-(3',4'-Dichlorobenzoyl)-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (**22**): 15% yield from method A-1; mp 290 °C (decomposed); MS m/z , 308 (MH^+); 1H -NMR (DMSO- d_6) δ 7.75 (m, 2H, C'-5H, C'-6H), 7.90 (s, 1H, C-6H), 7.95 (s, 1H, C-2H), 7.98 (s, 1H, C'-2H). *Anal.* Calcd for C₁₃H₇N₃O₂Cl₂·0.12CF₃SO₃H: C, 48.31; H, 2.20; N, 12.88. Found: C, 48.29; H, 2.24; N, 12.51.

7-Benzyl-9-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (**23**): 20% yield from method B; mp 249 °C (decomposed, lit.⁶) 340 °C, decomposed; MS m/z , 226 (MH^+); 1H -NMR (DMSO- d_6) δ 3.91 (s, 2H, CH₂), 7.3 (m, 6H, C-6H, aromatic H), 7.78 (s, 1H, C-2H).

7-(3',4'-Dichlorobenzoyl)-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (**24**): 19% yield from method B; mp 275 °C (decomposed); MS m/z , 294 (MH^+); 1H -NMR (DMSO- d_6) δ 3.93 (s, 2H, CH₂), 7.26 (m, 2H, C-6H, C'-6H), 7.50 (m, 2H, C'-2H, C'-5H), 7.78 (s, 1H, C-2H). *Anal.* Calcd for C₁₃H₉Cl₂N₃O·1/2H₂O: C, 53.30; H, 3.17; N, 13.34. Found: C, 52.94; H, 3.09; N, 13.69.

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