Regiospecific Solid-Phase Strategy to N7-Substituted Purines and Its Application to 8-Azapurines and [i]-Condensed Purines

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A highly regioselective and traceless solid-phase route to 1,7,8-trisubstituted purines has been developed. This methodology could be extended to the preparation of 8-azapurines and [i]-condensed purines. A representative set of 17 purines, azapurines, and [i]-condensed purines was synthesized. This paper also describes a mild method to prepare the *p*-benzyloxybenzylamine (BOBA) resin.

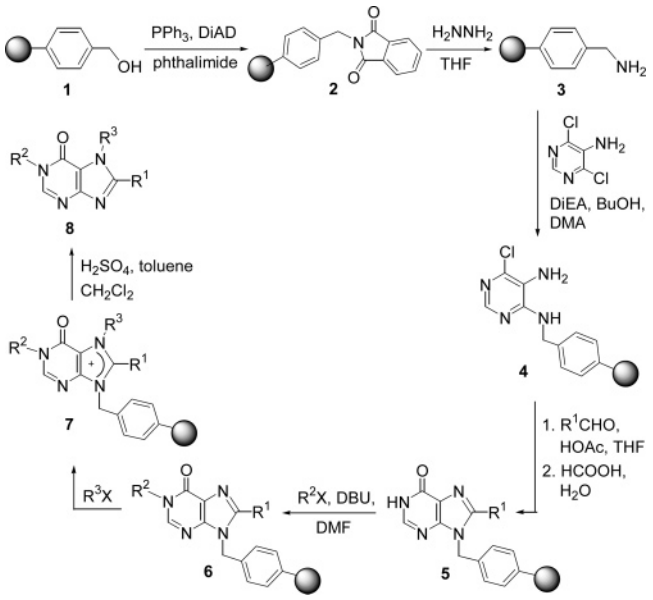
Introduction

The study of N7-substituted purines is of special interest as these isomers have found applications as antiviral agents[1] and, more recently, have been shown to possess stronger antiproliferative properties than the N9 isomers.[2] In addition, N7-substituted guanines are capable of inhibiting telomerase activity and possess the ability to enhance the efficacy of other chemotherapeutic agents in the treatment of cancer.[3] They are also important DNA adducts formed as a result of exposure to electrophiles.[4] Consequently, 7-alkylguanines are the main types of DNA adducts excreted in urine and are therefore important markers for the development of diagnostic methods to detect and quantitate specific types of DNA damages.[5] Despite the abundance of work produced on purines, few studies report libraries of N7-substituted purines.[6] We have recently reported a regiospecific traceless solid-phase route for the synthesis of N1,N7-disubstituted guanines using 6-chloropurine.[6c] Although the reaction was highly efficient and allowed a variety of disubstituted purines to be prepared, attempts to functionalize C8 did not yield the desired C8-substituted product. To circumvent this problem, we herein present the results of a new synthetic procedure utilizing substituted pyrimidines as precursors to the purine scaffold (Scheme 1). The linkage strategy involves the use of the *p*-benzyloxybenzylamine (BOBA) resin which was coupled to the pyrimidine frame to give a resin bound diamine as the key intermediate. An advantage here is that the purine ring formation could be carried out using different reagents which provided the flexibility for introducing various substituents on C8 while leaving the N7 position as the steric priority for subsequent alkylation, thus allowing a highly regiocontrolled N7 synthesis to be achieved.

Results and Discussion

Solution-Phase Synthesis of 1,7,8-Trisubstituted Purines. Prior to the solid-phase synthesis (SPS), preliminary solution-phase studies were carried out to survey the requisite reaction conditions and establish the modifications required

Scheme 1. SPS of 1,7,8-Trisubstituted Purines



for solid-phase synthesis. In the first step, 4-benzyloxybenzylamine **9** was used to mimic the BOBA resin **3**. Treatment of **9** with 5-amino-4,6-dichloropyrimidine in the presence of a base yielded the diamine **10**. $NaHCO_3$ and *N*,*N*-diisopropylethylamine (DiEA) were examined as possible bases for this reaction, and between these two bases, DiEA provided a better yield (75%) than $NaHCO_3$ (60%). The purine ring formation was then facilitated by treating diamine **10** with heptanal in the presence of acetic acid. During this reaction, two products were obtained and identified as 6-chloropurine and 6-oxopurine **11**. This encouraged us to perform the cyclization and hydrolysis in a one-pot reaction. Thus, **10** was first treated overnight with heptanal and acetic acid in THF and then concentrated to dryness. The residue obtained was then stirred with 85% aqueous formic acid at 70 °C for another 3 h which provided **11** in 81% overall yield. It is worth noting that attempts to use formic acid for both the cyclization and hydrolysis failed to provide a complete disappearance of **10**.

We next proceeded to N1-alkylate **11** with propargyl bromide. The reaction occurred readily with DBU at room

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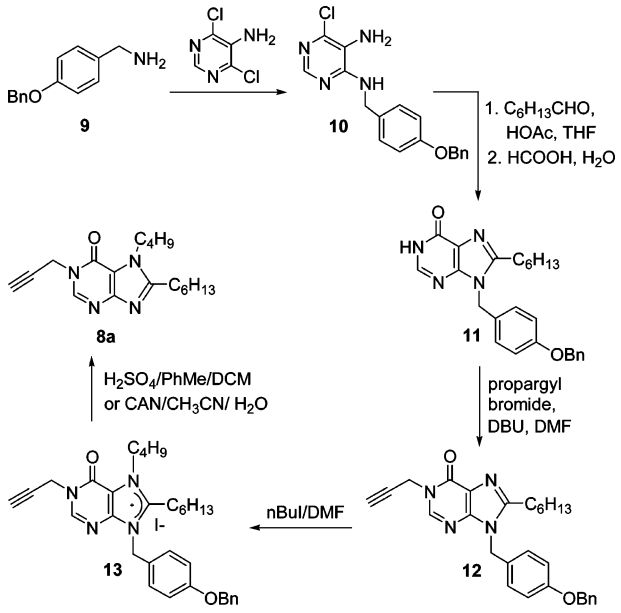
Scheme 2. Solution-Phase Study



temperature to give **12** in quantitative yield. Subsequent quarternization of **12** was initially carried out with 20 equiv of iodobutane. However, despite heating the reaction mixture at 70 °C for 48 h, thin-layer chromatography (TLC) monitoring did not show a complete disappearance of **12**. By increasing the amount of iodobutane to 40 equiv, the quaternization reaction was completed after sitting overnight at 70 °C. Having accomplished the quaternization, we proceeded to N9-debenzylation which mimics the traceless cleavage from the resin. Treatment of **13** with 10 equiv of 96% H_2SO_4 at room temperature in the presence of toluene provided the final product **8a** in 95% yield. This debenzylative cleavage proceeded via a carbonium formation, and toluene was used as a carbonium trap which drives the reaction to completion.[7] We have also investigated the cleavage reaction via oxidative debenzylation[8] in which treatment of **13** with 4 equiv of CAN in CH_3CN/H_2O (4/1) gave **8a** in high yield (see Scheme 2).

Solid-Phase Synthesis of 1,7,8-Trisubstituted Purines. Having validated the synthetic approach in solution, we proceeded to adapt the strategy on solid support. *p*-benzyloxybenzylamine (BOBA) resin **3** was initially prepared using a reported procedure whereby bromo Merrifield resin was treated with 4-hydroxybenzamide in the presence of NaOH followed by reduction with 1 M borane in THF.[9] Since the borane solution was difficult to handle and harsh reaction conditions were needed for the reaction to proceed, we decided to explore a simpler and milder method to prepare resin **3** (Scheme 1). Since the Mitsunobu reaction is known to convert an alcohol to a primary amine, the Wang resin (1.6 mmol/g) **1** was chosen as the starting resin and was reacted with PPh_3, diisopropyl azodicarboxylate (DiAD), and phthalimide to give resin **2** which was amenable to Fourier transform infrared (FTIR) monitoring (i.e., the appearance of C═O stretching at 1770 and 1714 cm^{-1}). This was followed by hydrazinolysis with 1 M hydrazine in THF to give resin **3** which showed the disappearance of the C═O stretching. Meanwhile, the loading of resin **3** was calculated from the loading of its FMOC derivative as determined by the FMOC release UV assay.[10] The result showed near quantitative conversion from resin **1** to resin **3** (1.55 mmol/g).

With resin **3** on hand, we carried out an S_NAr displacement with 5-amino-4,6-dichloropyrimidine by adapting the procedure established in our solution-phase study. In the solid-phase reaction, DMA was added as a cosolvent to ensure good swelling of the resin. DMF could not be used as a cosolvent because it decomposed at high temperature under basic conditions. Since resin **4** could not be reliably analyzed, we proceeded to the purine ring formation by treating resin **4** with various aldehydes in THF under reflux followed by hydrolysis with 85% formic acid. This transformation was monitored by FTIR for the appearance of a new C═O stretch (ν_{max} 1720 cm^{-1}). Subsequent N1 alkylation of resin **5** provided resin **6** which was further functionalized by N7 quaternization with different alkyl halides. It is noted that when an alkyl bromide is used in the quaternization reaction, the addition of NaI to the reaction mixture provided a marked improvement in the reaction. The final product **8** was eventually released from resin **7** by treatment with 96% sulfuric acid at room temperature for 3 h in the presence of toluene and CH_2Cl_2 as a cosolvent (to enhance resin swellability). Using this synthetic strategy, a representative set of 9 compounds (**8a**−**8i**) was prepared (Figure 1). The overall yields obtained were 8−12% (purities of >95% by NMR), indicating an average yield of over 70% for each step of the reaction. To illustrate the versatility of this methodology, we have extended this synthetic procedure to the preparation of 1,7-disubstituted purines, 8-azapurines, and [i]-condensed purines.

Solid-Phase Synthesis of 1,7-Disubstituted Purines, 8-Azapurines, and [i]-Condensed Purines. Treatment of resin **4** with trimethyl orthoformate facilitated the formation of the purine imidazole ring to give resin **14a** (Scheme 3). Subsequent hydrolysis of the chloride followed by N1-alkylation, regioselective N7-alkylation, and debenzylative cleavage using the procedure described earlier provided compounds **16a**−**16d** in ∼18% overall yield. This implies that an average 81% yield was obtained for each step of the reaction.

We next examined the solid-phase syntheses of 8-azapurines and [i]-condensed purines which to the best of our knowledge have not been reported previously. Reaction of resin **4** with sodium nitrite in the presence of 50% acetic acid in CH_2Cl_2 gave resin **14b** which was then hydrolyzed and N1-alkylated using various halides to provide resin **15b**. Treatment of resin **15b** with 96% H_2SO_4 or ceric ammonium nitrate (CAN)/CH_3CN/H_2O gave 8-azapurines **17a**−**17d** (Figure 1) in good yields.

On the other hand, [i]-condensed purines could be prepared by first treating resin **14** with ethanolamine to give resin **18**. Attempts to carry out the internal cyclization of resin **18** by using traditional solution-phase methods such as CH_3SO_2-Cl/tetraethylamine (TEA) at room temperature[11a] or $SOCl_2$ under reflux[11b] gave either very low overall yield of the [i]-condensed purine or decomposition of the resin. To circumvent this problem, we carried out a systematic study of the reaction by varying the solvent, reaction temperature,

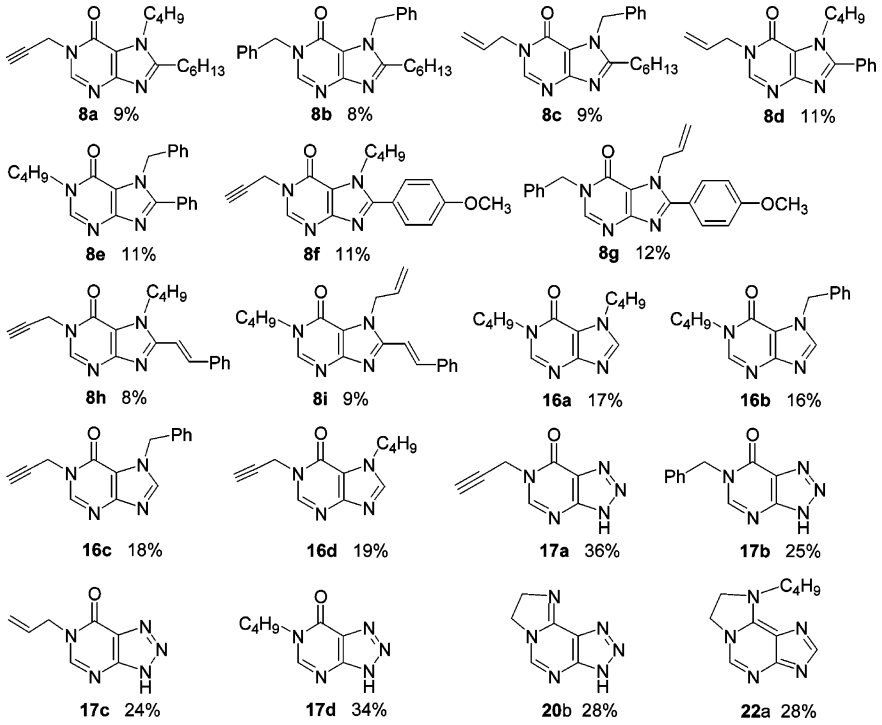
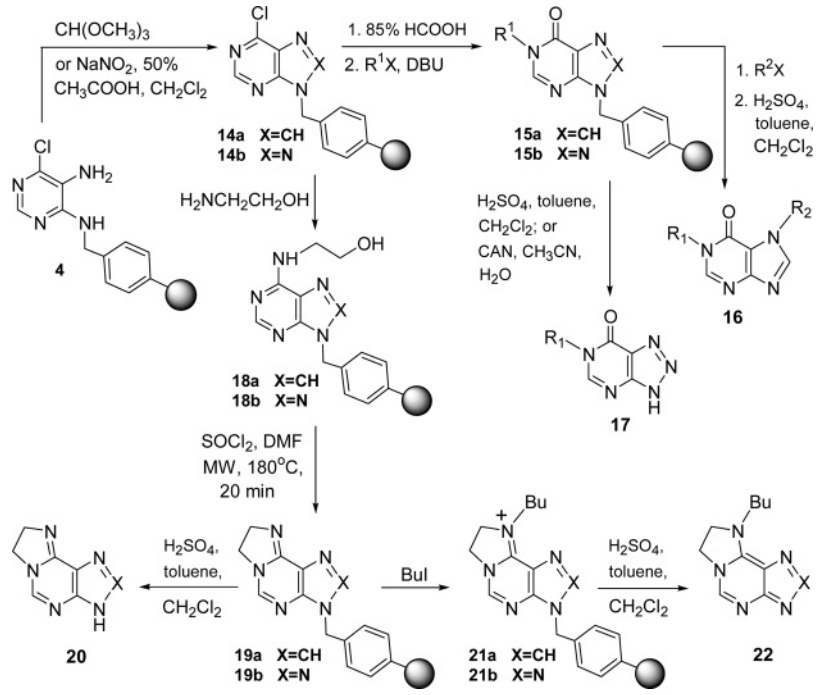


Figure 1. Library of **8**, **16**, **17**, **20**, and **22**.

Scheme 3. SPS of 1,7-Disubstituted Purines, 8-Azapurines, and [i]-Condensed Purines



and concentrations of $SOCl_2$ and TEA. We were pleased to find that internal cyclization occurred readily when resin **18** was treated with $SOCl_2$ in DMF at 180 °C for 20 min under microwave conditions. The [i]-condensed purine **19** obtained could be directly cleaved from the resin to yield **20** or quarternized and cleaved to give **22**.

In the internal cyclization of resin **18**, it is possible for the pendant alcohol to react with N1 or N7. To obtain experimental evidence for the direction of cyclization, we attempted a nuclear Overhauser enhancement spectroscopy (NOESY) experiment on **22a** (X═CH). However, the protons on C2 and C8 of **22a** could not be clearly differentiated from the ^{1}H NMR spectrum. Thus, we synthesized **23** (Figure 2) as a mimic of resin **21a** and carried out a NOESY experiment with it. The positions of the protons on C2 and C8 were determined by examining their interactions with $N9CH_2$.

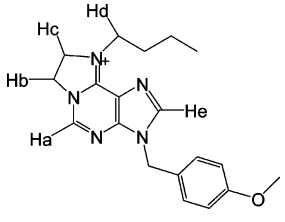


Figure 2. Compound **23**.

From the NOESY spectrum, only one of the two protons displayed the interaction with $N9CH_2$ and this proton was assigned as C8H. The NOESY spectrum also showed the interaction between H_a and H_b which confirmed that the pendant alcohol had cyclized at the N1 position. In addition, it showed interaction between H_c and H_d and the absence of interaction between H_d and H_e. This provides evidence for the location of the butyl group after quaternization and confirms the structures of **20** and **22**.

In conclusion, we have demonstrated a traceless solid-phase synthetic route to various substituted purines using the BOBA resin and 5-amino-4,6-dichloropyrimidine. This approach offers various advantages such as (i) regioselective N7 alkylation, (ii) the key intermediate **4** enables different combinatorial modifications to be made on the purine C8 position, and (iii) the synthetic procedure could be extended to the preparation of 8-azapurines and [i]-condensed purines. To our knowledge, this is the first example of the synthesis of 8-azapurines and [i]-condensed purines on the solid-phase format.

Experimental Section

General Procedures. ^{1}H NMR and ^{13}C NMR spectra were measured at 298 K on a Bruker DPX 300 Fourier transform spectrometer. Chemical shifts were reported in δ (ppm), relative to the internal standard of tetramethylsilane (TMS). All infrared (IR) spectra were recorded on a Bio-Rad FTS 165 spectrometer. Mass spectra were performed on VG Micromass 7035 spectrometer under electron impact (EI). All chemical reagents were obtained from commercial suppliers and used without further purification. Analytical TLC was carried out on precoated plates (Merck silica gel 60, F254) and visualized with UV light. Flash column chromatography was performed with silica (Merck, 70-230 mesh). Microwave reactions were performed on the Initiator microwave synthesizer.

4-(Benzyloxy)benzamide. To a solution of 4-hydroxybenzamide (3.09 g, 22.5 mmol) in DMSO (40.0 mL) was added NaOH (1.50 g, 37.5 mmol). The reaction mixture was stirred at 90 °C for 1 h before benzyl bromide (2.57 g, 15 mmol) was added. The reaction mixture was then stirred at 90 °C for another 3 h and extracted with ethyl acetate and water. The combined organic layer was washed with brine, dried with $MgSO_4$, concentrated to dryness, and purified by column chromatography (ethyl acetate:hexane = 2:1) to give 4-(benzyloxy)benzamide as a white solid (3.00 g, 87%). ^{1}H NMR (DMSO-d_6): δ 5.16 (s, 2H, $PhCH_2$), 7.05 (m, 2H, ArH), 7.33−7.47 (m, 5H, ArH), 7.84 (m, 2H, ArH). ^{13}C NMR (DMSO-d_6): δ 68.76, 113.64, 136.18, 127.13, 127.32, 127.85, 128.73, 136.16, 160.06, 166.79. HRMS(EI) calcd for $C_{14}H_{13}NO_2$ 227.0946; found 227.0946.

(4-(Benzyloxy)phenyl)methanamine (9). To a solution of BH_3 (0.6 mmol) in THF (1.0 mL) was added 4-(benzyloxy)benzamide (67 mg, 0.3 mmol) in THF (2.0 mL). The reaction mixture was stirred under reflux overnight and then concentrated to dryness. The white solid obtained was extracted with ethyl acetate and water. The combined organic layer was washed with brine, dried with $MgSO_4$, concentrated to dryness, and purified by column chromatography (ethyl actate followed by MeOH:CH_2Cl_2 = 1:8) to give **9** as a white solid (55 mg, 88%). ^{1}H NMR (MeOD): δ 4.43 (s, 4H, $2CH_2$), 6.49−6.97 (m, 9H, ArH). ^{13}C NMR (DMSO-d_6): δ 45.59, 70.99, 116.11, 128.50, 128.81, 129.45, 130.07, 132.32, 138.69, 159.53. MS(EI): *m*/*z* 213.1.

N4-(4-(Benzyloxy)benzyl)-6-chloropyrimidine-4,5-diamine (10). A solution of **9** (1.00 g, 4.7 mmol), 5-amino-4,6-dichloropyrimidine (1.50 g, 9.4 mmol), and DiEA (4.2 mL) in 1-butanol (70.0 mL) was stirred under reflux for 24 h and then evaporated to dryness. The residue obtained was extracted with ethyl acetate and water. The combined organic layer was washed with brine, dried with $MgSO_4$, concentrated to dryness, and purified by column chromatography (ethyl actate:hexane = 1:4) to give **10** as a white solid (1.20 g, 75%). ^{1}H NMR ($CDCl_3$): δ 3.62 (s, 2H, NH_2), 4.57 (d, J = 5.2 Hz, 2H, $NHCH_2$), 5.03 (s, 2H, OCH_2), 5.45 (s, 1H, NH), 6.90−7.43 (m, 9H, ArH), 8.03 (s, 1H, C2H). ^{13}C NMR (DMSO-d_6): δ 45.00, 69.96, 114.94, 121.96, 127.34, 127.93, 128.52, 129.23, 130.36, 136.76, 142.00, 149.09, 154.32, 158.18. HRMS(EI) calcd for $C_{18}H_{17}N_4OCl$ 340.1091; found 340.1087.

9-(4-(Benzyloxy)benzyl)-8-hexyl-1H-purin-6(9H)-one (11). To a solution of **10** (66 mg, 0.2 mmol) and 1-heptanal (0.11 mL, 0.8 mmol) in THF (2.0 mL) was added acetic acid (0.50 mL). The reaction mixture was stirred under reflux for 24 h and then concentrated to dryness. The residue was dissolved in 85% formic acid (2.1 mL), stirred at 70 °C for 3 h, and then evaporated to dryness and chromatographed on silica gel column using ethyl acetate:hexane = 1:1 followed by EtOH:CH_2Cl_2 = 1:10 as eluent to give **11** as a pale yellow solid (65 mg, 81%). ^{1}H NMR (DMSO-d_6): δ 0.83 (t, J = 6.6 Hz, 3H, CH_3), 1.19−1.59 (m, 8H, $4CH_2$), 2.67 (t, J = 7.7 Hz, 2H, $C8CH_2$), 5.05 (s, 2H, $N9CH_2$), 5.28 (s, 2H, OCH_2), 6.96 (m, 2H, ArH), 7.11−7.42 (m, 7H, ArH), 8.02 (s, 1H, C2H), 12.25 (s, 1H, N1H). ^{13}C NMR (DMSO-d_6): δ 13.29, 21.34, 25.81, 26.04, 27.60, 30.34, 73.94, 68.68, 114.44, 122.13, 127.03, 127.23, 127.73, 127.82, 128.23, 136.38, 144.49, 148.60, 150.54, 155.71, 157.27. HRMS(EI) calcd for $C_{25}H_{28}N_4O_2$ 416.2212; found 416.2200.

9-(4-(Benzyloxy)benzyl)-8-hexyl-1-(prop-2-ynyl)-1H-purin-6(9H)-one (12). Propargyl bromide (142 mg, 1.2 mmol) and DBU (177 mg, 1.2 mmol) were added to a solution of **11** (110 mg, 0.3 mmol) in DMF (2.0 mL). The reaction mixture was stirred at room temperature overnight and then extracted with ethyl acetate and brine. The combined organic layer was washed with brine, dried with $MgSO_4$, concentrated to dryness, and purified by column chromatography (ethyl acetate:hexane = 1:1 followed by acetone:hexane = 1:4) to provide **12** as a yellow oil (125 mg, 98%). ^{1}H NMR ($CDCl_3$): δ 0.84 (t, J = 6.4 Hz, 3H, CH_3), 1.22−1.76 (m, 8H, $4CH_2$), 2.49 (t, J = 2.4 Hz, 1H, CH), 2.68 (t, J = 7.8 Hz, 2H, $C8CH_2$), 4.86 (d, J = 2.0 Hz, 2H, $N1CH_2$), 5.01 (s, 2H, $N9CH_2$), 5.24 (s, 2H, OCH_2), 6.89 (m, 2H, ArH), 7.05 (m, 2H, ArH), 7.30−7.39 (m, 5H, ArH), 8.25 (s, 1H, C2H). ^{13}C NMR ($CDCl_3$): δ 13.93, 22.40, 27.05, 27.72, 28.92, 31.35, 34.87, 45.39, 70.02, 75.38, 76.58, 115.24, 127.33, 127.94 (× 2), 127.98, 128.21, 128.53, 136.63, 145.17, 148.46, 152.88, 155.65, 158.57. HRMS(EI) calcd for $C_{28}H_{30}N_4O_2$ 454.2369; found 454.2360.

9-(4-(Benzyloxy)benzyl)-7-butyl-8-hexyl-1-(prop-2-ynyl)-8,9-dihydro-1H-purin-6(7H)-one salt (13). Iodobutane (0.80 mL, 7 mmol) was added to a solution of **12** (80 mg, 0.18 mmol) in DMF (2.0 mL). The reaction mixture was stirred at 70 °C for 24 h and then evaporated to dryness. The residue was purified by column chromatography (EtOH:CH_2Cl_2 = 1:15) to give **13** (104 mg, 93%). ^{1}H NMR ($CDCl_3$): δ 0.77 (t, J = 7.0 Hz, 3H, CH_3), 0.92 (t, J = 7.3 Hz, 3H, CH_3), 1.04−1.94 (m, 12H, $6CH_2$), 2.53 (t, J = 2.4 Hz, 1H, CH), 3.22 (t, J = 8.0 Hz, 2H, $C8CH_2$), 4.36 (t, J = 8.0 Hz, 2H, $N7CH_2$), 4.91 (d, J = 2.4 Hz, 2H, $N1CH_2$), 4.97 (s, 2H, $N9CH_2$), 5.64 (s, 2H, OCH_2), 6.88 (m, 2H, ArH), 7.21 (m, 2H, ArH), 7.24−7.32 (m, 5H, ArH), 8.69 (s, 1H, C2H). ^{13}C NMR ($CDCl_3$): δ 13.32, 13.82, 19.83, 22.14, 26.81, 27.37, 29.01, 30.91, 32.50, 36.27, 48.27, 48.86, 70.07, 75.42, 76.45, 113.36, 115.57, 125.55, 127.32, 128.07, 128.56, 129.51, 136.31, 146.74, 150.27, 151.36, 153.43, 159.26. HRMS(ESI) calcd for $C_{32}H_{39}N_4O_2$ 511.3073; found 511.3070.

7-Butyl-8-hexyl-1-(prop-2-ynyl)-1H-purin-6(7H)-one (8a). Method A. In this approach, 96% sulfuric acid (0.50 mL) and toluene (0.50 mL) were added to a solution of **13** in dichloromethane (1.0 mL). The reaction mixture was stirred vigorously at room temperature for 3 h, neutralized with saturated $NaHCO_3$ to pH 8, and then extracted with ethyl acetate and water. The combined organic layer was washed with brine, dried with $MgSO_4$, concentrated to dryness, and purified by column chromatography (ethyl acetate:hexane = 1:1 followed by acetone:hexane = 1:2) to provide **8a** as a yellow oil (0.13 g, 95%). ^{1}H NMR ($CDCl_3$): δ 0.87 (t, J = 7.0 Hz, 3H, CH_3), 0.90 (t, J = 7.4 Hz, 3H, CH_3), 1.29−1.91 (m, 12H, $6CH_2$), 2.46 (t, J = 2.6 Hz, 1H, CH), 2.78 (t, J = 7.8 Hz, 2H, $C8CH_2$), 4.33 (t, J = 7.4 Hz, 2H, N7CH2), 4.79 (d, J = 2.8 Hz, 2H, $N1CH_2$), 8.23 (s, 1H, C2H). ^{13}C NMR ($CDCl_3$): δ 13.63, 13.95, 19.75, 22.45, 27.04, 27.56, 29.03, 31.43, 33.48, 34.63, 45.25, 74.82, 76.58, 114.70, 114.93, 147.38, 153.19, 156.34. HRMS(EI) calcd for $C_{18}H_{26}N_4O$314.2107; found 314.2103.

Method B. CAN (4 equiv) was added protionwise to a stirred solution of compound **13** and in acetonitrile/H_2O (4:1). The reaction mixture was stirred rapidly at room temperature for 8 h and then quenched with $NaHCO_3$(aq). The quenched mixture was stirred vigorously for 10 min and then extracted with ethyl acetate and brine. The combined organic layer was washed with brine, dried with $MgSO_4$, concentrated to dryness, and purified by column chromatography (ethyl acetate:hexane = 1:1 followed by acetone:hexane = 1:2) to provide **8a**.

Preparation of BOBA Resin (3). DiAD (3 equiv) was added dropwise to a mixture of Wang resin (loading 1.6 mmol/g), phthalimide (3 equiv), and triphenylphosphine (3 equiv) in THF under ice−water bath temperature. The reaction mixture was shaken at room temperature overnight, and the resin was filtered and washed sequentially with DMF (20 mL × 2), H_2O (20 mL × 2), EtOH (20 mL × 2), CH_2Cl_2 (20 mL × 2), and ether (20 mL × 2) and dried overnight in a vacuum oven at 40 °C. The dried resin was then subjected to hydrazinolysis using a solution of hydrazine (15 equiv) in THF at room temperature overnight. Thereafter, the resin was washed sequentially with DMF (20 mL × 2), H_2O (20 mL × 2), EtOH (20 mL × 2), CH_2Cl_2 (20 mL × 2), and ether (20 mL × 2) and dried overnight in a vacuum oven at 40 °C.

Preparation of Resin Bound N4-(4-(Benzyloxy)benzyl)-6-chloropyrimidine-4,5-diamine (4). Resin **3** was swollen in DMA for 30 min. 1-Butanol, 5-amino-4,6-dichloropyrimidine (2 equiv), and DiEA (5 equiv) were added, and the reaction mixture was stirred slowly at 140 °C for 24 h. Thereafter, the resin was filtered and washed sequentially with DMF (20 mL × 2), H_2O (20 mL × 2), EtOH (20 mL × 2), CH_2Cl_2 (20 mL × 2), and ether (20 mL × 2) and dried overnight in a vacuum oven at 40 °C.

General Procedure for the Preparation of Resin Bound 9-(4-(Benzyloxy)benzyl)-8-substituted-1H-purin-6(9H)-one (5). Resin **4** was swollen in THF for 30 min. Acetic acid (40 equiv) and the respective aldehyde (8 equiv) were added, and the reaction mixture was slowly stirred under reflux for 24 h. After which, the resin was filtered, treated with 85% aqueous formic acid (150 equiv) and DMF as cosolvent, and stirred at 70 °C for an additional 3 h. The resin was then filtered and washed with DMF (20 mL × 2), EtOH (20 mL × 2), and CH_2Cl_2 (20 mL × 2) and dried in vacuum.

General Procedure for the Preparation of Resin Bound N1-Substituted-9-(4-(benzyloxy)benzyl)-8-substituted-1-(prop-2-ynyl)-1H-purin-6(9H)-one (6). Resin **5** was swollen in DMF for 30 min and the respective alkylating reagent (3 equiv) and DBU (3 equiv) were added. The reaction mixture was shaken at room temperature overnight. Thereafter, the resin was filtered and washed with DMF (20 mL × 2), EtOH (20 mL × 2), and CH_2Cl_2 (20 mL × 2) and dried in a vacuum oven at 40 °C.

General Procedure for the Preparation of Resin Bound *N*1,*N*7-Disubstituted-9-(4-(benzyloxy)benzyl)-8-substituted-1-(prop-2-ynyl)-1H-purin-6(9H)-one salt (7). Resin **6** was swollen in DMF for 30 min. The respective alkyl halide (40 or 50 equiv) was added and the mixture was stirred slowly at 70 °C for 36 h. Thereafter, the resin was filtered and washed with DMF (20 mL × 2), H_2O (20 mL × 2), EtOH (20 mL × 2), and CH_2Cl_2 (20 mL × 2) and dried in a vacuum oven at 40 °C.

General Procedure for the Preparation of Resin Bound 9-(4-(Benzyloxy)benzyl)-6-chloro-9H-purine (14a). Resin **4** was swollen in DMF for 30 min, and then, trimethyl orthoformate (50 equiv) was added. The reaction mixture was then cooled in an ice−water bath and HCl (cat) was added. The reaction mixture was then shaken at room temperature overnight. Thereafter, the resin was filtered and washed with DMF (20 mL × 2), H_2O (20 mL × 2), EtOH (20 mL × 2), and CH_2Cl_2 (20 mL × 2) and dried in a vacuum oven at 40 °C.

General Procedure for the Preparation of Resin Bound 3-(4-(Benzyloxy)benzyl)-7-chloro-3*H*-[1,2,3]triazolo-[4,5-*d*]pyrimidine (14b). Resin **4** was swollen in DCM for 30 min, and 50% aqueous acetic acid (50 equiv) and $NaNO_2$ (2 equiv) were added. After shaking vigorously at room temperature for 30 min, the resin was filtered and washed with EtOH (20 mL × 2) and CH_2Cl_2 (20 mL × 2) and dried in a vacuum oven at 40 °C.

Synthesis of Resin 18 via Amination at C6 with Ethanolamine. Resin **14** was swollen in THF for 30 min, and then, ethanolamine (5 equiv) was added. The reaction mixture was stirred slowly at 60 °C for 4 h. Thereafter, the resin was filtered and washed sequentially with EtOH (20 mL × 2), CH_2Cl_2 (20 mL × 2), and Et_2O (20 mL × 2) and dried overnight in a vacuum oven at 40 °C.

Cyclization of Resin 18 (19). Resin **18** was swollen in DMF for 30 min, and then, $SOCl_2$ (2 equiv) was added. The reaction mixture was stirred at 180 °C under microwave irradiation for 20 min. Thereafter, the resin was filtered and washed sequentially with EtOH (20 mL × 2), saturated $NaHCO_3$ (20 mL × 2), H_2O (20 mL × 2), EtOH (20 mL × 2), CH_2Cl_2 (20 mL × 2), and ether (20 mL × 2) and dried overnight in a vacuum oven at 40 °C.

General Cleavage Procedure. Resin was swollen in DCM for 30 min. Toluene (60 equiv) and 96% sulfuric acid (20 equiv) were added, and the reaction mixture was shaken at room temperature for 4 h. The resin was then filtered and washed with ethyl acetate. The filtrate was neutralized with saturated $NaHCO_3$ and extracted with ethyl acetate and water. The combined organic layer was washed with brine, dried with $MgSO_4$, concentrated to dryness, and purified by column chromatography.

7-Butyl-8-hexyl-1-(prop-2-ynyl)-1*H*-purin-6(7*H*)-one (8a). ^{1}H NMR ($CDCl_3$): δ 0.87 (t, J = 7.0 Hz, 3H, CH_3), 0.90 (t, J = 7.4 Hz, 3H, CH_3), 1.29−1.91 (m, 12H, $6CH_2$), 2.46 (t, J = 2.6 Hz, 1H, CH), 2.78 (t, J = 7.8 Hz, 2H, $C8CH_2$), 4.33 (t, J = 7.4 Hz, 2H, $N7CH_2$), 4.79 (d, J = 2.8 Hz, 2H, $N1CH_2$), 8.23 (s, 1H, C2H). ^{13}C NMR ($CDCl_3$): δ 13.63, 13.95, 19.75, 22.45, 27.04, 27.56, 29.03, 31.43, 33.48, 34.63, 45.25, 74.82, 76.58, 114.70, 114.93, 147.38, 153.19, 156.34. HRMS(EI) calcd for $C_{18}H_{26}N_4O$314.2107; found 314.2103.

1,7-Dibenzyl-8-hexyl-1*H*-purin-6(7*H*)-one (8b). ^{1}H NMR ($CDCl_3$): δ 0.84 (t, J = 6.6 Hz, 3H, CH_3), 1.24−1.31 (m, 6H, $3CH_2$), 1.71−1.75 (m, 2H, CH_2), 2.71 (t, J = 7.7 Hz, 2H, $N7CH_2$), 5.2 (s, $N1CH_2$), 5.66 (s, 1H, $N7CH_2$), 7.12−7.34 (m, 10H, ArH), 8.09 (s, 1H, C2H). ^{13}C NMR ($CDCl_3$): δ 13.96, 22.40, 27.22, 27.26, 28.92, 31.36, 48.37, 49.03, 115.25, 126.72 (× 2), 127.84, 127.92, 128.22 (× 2), 128.90, 128.97, 135.96, 136.25, 146.19, 154.10, 156.05, 156.98. HRMS(EI) calcd for $C_{25}H_{28}N_4O$400.2263; found 400.2257.

1-Allyl-7-benzyl-8-hexyl-1*H*-purin-6(7*H*)-one (8c). ^{1}H NMR ($CDCl_3$): δ 0.84 (t, J = 6.6 Hz, 3H, CH_3), 1.24−1.34 (m, 6H, $3CH_2$), 1.71−1.76 (m, 2H, CH_2), 2.72 (t, J = 7.7 Hz, 2H, $C8CH_2$), 4.63 (d, J = 5.6 Hz, $N1CH_2$), 5.24 (m, 2H, CH_2), 5.65 (s, 2H, $N7CH_2$), 5.93−6.02 (m, 1H, CH), 7.11−7.33 (m, 5H, ArH), 8.00 (s, 1H, C2H). ^{13}C NMR ($CDCl_3$): δ 13.96, 22.40, 27.22, 27.26, 28.92, 31.36, 48.37, 49.03, 115.25, 126.72, 127.84, 127.92, 128.22, 128.90, 128.97, 135.96, 136.25, 146.19, 154.10, 156.05, 156.98. HRMS(EI) calcd for $C_{21}H_{26}N_4O$350.2107; found 350.2111.

1-Allyl-7-butyl-8-phenyl-1*H*-purin-6(7*H*)-one (8d). ^{1}H NMR ($CDCl_3$): δ 0.82 (t, J = 7.5 Hz, 3H, CH_3), 1.19−1.27 (m, 2H, CH_2), 1.73−1.81 (m, 2H, CH_2), 4.43 (t, J = 7.5 Hz, 2H, $N7CH_2$), 4.65 (d, J = 6.0 Hz, $N1CH_2$), 5.23 (m, 2H, $CHCH_2$), 5.93−6.03 (m, 1H, CH), 7.48−7.69 (m, 5H, ArH), 8.01 (s, 1H, C2H). ^{13}C NMR ($CDCl_3$): δ 13.37, 19.47, 33.57, 46.34, 47.80, 116.00, 118.53, 128.72, 129.21, 129.27, 130.17, 132.15, 146.39, 153.88, 154.13, 156.35. HRMS(EI) calcd for $C_{18}H_{20}N_4O$308.1637; found 308.1637.

7-Benzyl-1-butyl-8-phenyl-1*H*-purin-6(7*H*)-one (8e). ^{1}H NMR ($CDCl_3$): δ 0.95 (t, J = 7.3 Hz, 3H, CH_3), 1.32−1.42 (m, 2H, CH_2), 1.69−1.79 (m, 2H, CH_2), 4.00 (t, J = 7.3 Hz, 2H, $N1CH_2$), 5.74 (s, 2H, $N7CH_2$), 6.99−7.64 (m, 10H, 2ArH), 8.05 (s, 1H, C2H). ^{13}C NMR ($CDCl_3$): δ 13.57, 19.76, 31.87, 46.34, 49.54, 126.33, 127.72, 127.81, 128.23, 128.77, 128.96, 129.37, 130.35, 136.95, 146.80, 154.19, 154.58, 156.36. HRMS(EI) calcd for $C_{22}H_{22}N_4O$358.1794; found 308.1788.

7-Butyl-8-(4-methoxyphenyl)-1-(prop-2-ynyl)-1*H*-purin-6(7*H*)-one (8f). ^{1}H NMR ($CDCl_3$): δ 0.86 (t, J = 7.3 Hz, 3H, CH_3), 1.24−1.31 (m, 2H, CH_2), 1.77−1.84 (m, 2H, CH_2), 2.49 (t, J = 2.6 Hz, 2H, $N1CH_2$), 3.88 (s, 3H, OCH_3), 4.44 (t, J = 7.7 Hz, $N7CH_2$), 4.83 (d, J = 2.6 Hz, CH), 7.02 (m, 2H, ArH), 7.64(m, 2H, ArH), 8.30 (s, 1H, C2H). ^{13}C NMR ($CDCl_3$): δ 13.47, 19.59, 33.58, 34.83, 46.48, 55.39, 74.99, 76.70, 114.26, 121.36, 130.79, 145.48, 153.40, 154.38, 156.42, 161.14. HRMS(EI) calcd for $C_{19}H_{20}N_4O_2$ 336.1586; found 336.1588.

7-Allyl-1-benzyl-8-(4-methoxyphenyl)-1*H*-purin-6(7*H*)-one (8g). ^{1}H NMR ($CDCl_3$): δ 3.88 (s, 3H, CH_3), 5.04 (m, 2H, $N7CH_2$), 5.17 (dd, J = 13.7 Hz, J = 81.2 Hz, $CHCH_2$), 5.23 (s, 2H, $N1CH_2$), 6.09−6.20 (m, 1H, CH), 7.02−7.23 (m, 2H, ArH), 7.34−7.36 (m, 5H, ArH), 7.74 (m, 2H, ArH), 8.16 (s, 1H, C2H). ^{13}C NMR ($CDCl_3$): δ 48.47, 49.03, 55.29, 114.11, 115.98, 116.98, 120.95, 127.79, 128.14, 128.89, 130.69, 133.68, 135.89, 146.62, 153.92, 154.29, 156.20, 161.19. HRMS(EI) calcd for $C_{22}H_{20}N_4O_2$ 372.1586; found 372.1578.

7-Butyl-1-(prop-2-ynyl)-8-styryl-1*H*-purin-6(7*H*)-one (8h). ^{1}H NMR ($CDCl_3$): δ 0.97 (t, J = 7.3 Hz, 3H, CH_3), 1.35−1.48 (m, 2H, CH_2), 1.79−1.89 (m, 2H, CH_2), 2.49 (t, J = 2.4 Hz, 1H, CH), 4.53 (t, J = 7.3 Hz, 2H, $N7CH_2$), 4.81 (d, J = 2.8 Hz, 2H, $N1CH_2$), 6.95 (d, J = 15.7 Hz, 1H, CH), 7.36−7.60 (m, 5H, ArH), 8.04 (d, J = 15.7 Hz, 1H, CH), 8.29 (s, 1H, C2H). ^{13}C NMR ($CDCl_3$): δ 13.66, 19.72 (× 2), 33.67 (× 2), 34.78, 45.09, 75.07, 111.31, 127.47, 128.91 (× 2), 129.56, 135.49, 145.67, 151.62, 153.17, 156.34. HRMS(EI) calcd for $C_{20}H_{20}N_4O$332.1637; found 332.1621.

7-Allyl-1-butyl-8-styryl-1*H*-purin-6(7*H*)-one (8i). ^{1}H NMR ($CDCl_3$): δ 0.96 (t, J = 7.3 Hz, 3H, CH_3), 1.36−1.44 (m, 2H, CH_2), 1.73−1.78 (m, 2H, CH_2), 3.99 (t, J = 7.4 Hz, 2H, $N1CH_2$), 5.05−5.28 (m, 2H, CH_2), 5.23 (d, J = 5.0 Hz, $N7CH_2$), 5.99−6.10 (m, 1H, CH), 6.92 (d, J = 15.8 Hz, 1H, CH), 7.36−7.57 (m, 5H, ArH), 7.99 (d, J = 15.7 Hz, 1H, CH), 8.04 (s, 1H, C2H). ^{13}C NMR ($CDCl_3$): δ 13.56, 19.79, 31.85, 46.29, 46.92, 111.63, 117.53, 127.41, 128.39, 128.83, 129.44, 132.68, 135.50, 139.38, 146.71, 151.71, 153.91, 156.24. HRMS(EI) calcd for $C_{20}H_{22}N_4O$ 334.1794; found 334.1777.

1,7-Dibutyl-1*H*-purin-6(7*H*)-one (16a). ^{1}H NMR ($CDCl_3$): δ 0.92−0.98 (m, 6H, $2CH_3$), 1.31−1.43 (m, 4H, $2CH_2$), 1.70−1.92 (m, 4H, $2CH_2$), 4.00 (t, 3H, J = 7.3 Hz, CH_2), 4.40 (t, 3H, J = 7.3 Hz, CH_2), 7.81 (s, 1H, C8H), 7.99 (s, 1H, C2H). ^{13}C NMR ($CDCl_3$): δ 13.44, 13.55, 19.54, 19.81,

31.86, 33.34, 46.32, 47.21, 115.41, 143.15, 146.38, 154.25, 156.94. HRMS(ESI) calcd for $C_{13}H_{20}N_4O$248.1637; found 248.1637.

7-Benzyl-1-butyl-1*H*-purin-6(7*H*)-one (16b). ^{1}H NMR ($CDCl_3$): δ 0.95 (t, J = 7.3 Hz, 3H, CH_3), 1.35−1.43 (m, 2H, CH_2), 1.69−1.79 (m, 2H, CH_2), 4.00 (t, J = 7.5 Hz, 2H, N1CH_2), 5.60 (s, 2H, N7CH_2), 7.30−7.34 (m, 5H, ArH), 7.84 (s, 1H, C8H), 7.99 (s, 1H, C2H). ^{13}C NMR ($CDCl_3$): δ 13.57, 19.77, 31.84, 46.30, 50.55, 127.92, 128.48, 129.02, 135.64, 143.17, 143.29, 146.51, 154.38, 156.86. HRMS(EI) calcd for $C_{16}H_{18}N_4O$282.1481; found 282.1467.

7-Benzyl-1-(prop-2-ynyl)-1*H*-purin-6(7*H*)-one (16c). ^{1}H NMR ($CDCl_3$): δ 2.48 (t, J = 2.4 Hz, 1H, CH), 4.80 (d, J = 2.8 Hz, 2H, N1CH_2), 5.58 (s, 2H, N7CH_2), 7.32−7.36 (m, 5H, ArH), 7.87 (s, 1H, C8H), 8.27 (s, 1H, C2H). ^{13}C NMR ($CDCl_3$): δ 34.75, 50.62, 75.13, 114.73, 127.91, 128.55 (× 2), 129.04, 135.41, 143.45, 145.46, 153.63, 156.92. HRMS(EI) calcd for $C_{15}H_{12}N_4O$264.1.11; found 264.1.11.

7-Butyl-1-(prop-2-ynyl)-1*H*-purin-6(7*H*)-one (16d). ^{1}H NMR ($CDCl_3$): δ 0.89 (t, J = 7.3 Hz, 3H, CH_3), 1.25−1.35 (m, 2H, CH_2), 1.77−1.86 (m, 2H, CH_2), 2.46 (dt, J = 0.7 Hz, J = 2.4 Hz, 1H, CH_3), 4.32 (t, J = 7.3 Hz, 2H, N1CH_2), 4.77 (dd, J = 0.7 Hz, J = 2.6 Hz, 2H, N1CH_2), 7.81 (s, 1H, C8H), 8.23(s, 1H, C2H). ^{13}C NMR ($CDCl_3$): δ 12.90, 18.95, 32.70, 34.22, 46.71, 74.48, 76.07, 114.45, 142.95, 144.87, 152.94, 156.40. HRMS(EI) calcd for $C_{12}H_{14}N_4O$230.1168; found 230.1162.

6-(Prop-2-ynyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (17a). ^{1}H NMR ($CDCl_3$): δ 3.42 (t, J=2.5 Hz, 1H, CH), 4.85 (d, J=2.6 Hz, 2H, N1CH_2), 8.55 (s, 1H, C2H). ^{13}C NMR ($CDCl_3$): δ 34.49, 75.38, 77.94, 126.91, 149.86, 151.95, 153.73. HRMS(EI) Calcd for $C_7H_7N_5O$175.0494; Found: 175.0494.

6-Benzyl-3*H*-[1,2,3]triazolo-[4,5-*d*]pyrimidin-7(6*H*)-one (17b). ^{1}H NMR (DMSO-d_6): δ 5.22 (s, 2H, CH_2), 7.29−7.34 (m, 5H, ArH), 8.59 (s, 1H, C2H). ^{13}C NMR (DMSO-d_6): δ 47.85, 127.05, 127.17 (× 2), 128.14, 136.44, 149.76, 152.74, 154.61. HRMS(EI) calcd for $C_{11}H_9N_5O$227.0807; found 227.0805.

6-Allyl-3*H*[1,2,3]triazolo-[4,5-*d*]pyrimidin-7(6*H*)-one (17c). ^{1}H NMR (DMSO-d_6): δ 4.64 (d, J = 5.2 Hz, 2H, N1CH_2), 5.13 (m, 2H, CH_2), 5.92−6.05 (m, 1H, CH), 8.40 (s, 1H, C2H). ^{13}C NMR (DMSO-d_6): δ 46.70, 116.95, 126.97, 132.69, 149.99, 152.36, 154.23. HRMS(EI) calcd for $C_7H_7N_5O$177.0651; found 177.0646.

6-Butyl-3*H*-[1,2,3]triazolo-[4,5-*d*]pyrimidin-7(6*H*)-one (17d). ^{1}H NMR (MeOD): δ 0.95 (t, J = 7.3 Hz, 3H, CH_3), 1.32−1.45 (m, 2H, CH_2), 1.69−1.79 (m, 2H, CH_2), 4.09 (t, J = 7.5 Hz, 2H, N1CH_2), 8.38 (s, 1H, C2H). ^{13}C NMR (MeOD): δ 13.94, 20.75, 32.60, 47.51, 128.75, 152.23, 153.80, 156.91. HRMS(EI) calcd for $C_8H_{11}N_5O$193.0964; found 193.0956.

7,8-Dihydro-3*H*-imidazo[1,2-c] [1,2,3]triazolo-[4,5-*e*]pyrimidine (20b). ^{1}H NMR (DMSO-d_6): δ 4.17 (t, J = 9.4 Hz, 2H, CH_2), 4.69 (t, J = 9.5 Hz, 2H, CH_2), 8.81 (s, 1H, C2H). ^{13}C NMR (MeOD): δ 45.32 (× 2), 114.84, 148.25, 148.53, 159.58. HRMS(EI) calcd for $C_6H_6N_6$ 162.0654; found 162.0651.

9-Butyl-8,9-dihydro-7*H*-imidazo[1,2-c] [1,2,3]triazolo-[4,5-*e*]pyrimidine (22a). ^{1}H NMR (MeOD): δ 1.00 (t, J = 7.3 Hz, 3H, CH_3), 1.44−1.54 (m, 2H, CH_2), 1.79−1.86 (m, 2H, CH_2), 4.11−4.22 (m, 4H, 2CH_2), 4.80 (t, J = 7.3 Hz, 2H, N1CH_2), 8.35 (s, 1H, C8H), 8.51 (s, 1H, C2H). ^{13}C NMR (MeOD): δ 12.99, 19.66, 29.28, 47.04, 47.84, 48.41, 117.07, 144.52, 145.45, 151.08, 152.81. HRMS(EI) calcd for $C_{11}H_{15}N_5$ 217.1327; found 217.1324.

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Supporting Information Available. ^{1}H and ^{13}C NMR spectra of all compounds, crystallographic data in CIF format of **8i**, **16c**, and **16d**, and NOESY spectrum of **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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