JOC Article

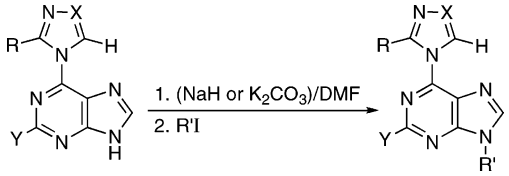
Regiospecific N9 Alkylation of 6-(Heteroaryl)purines: Shielding of N7 by a Proximal Heteroaryl C−H[1]

Minghong Zhong and Morris J. Robins*

Department of Chemistry and Biochemistry, Brigham Young University, Provo, Utah 84602-5700

morris_robins@byu.edu

Received August 25, 2006



Purine alkylations have been plagued with formation of mixtures of N9 (usually desired), N7, and other regioisomers. We have developed methods for synthesis of 6-(azolyl)purine derivatives whose X-ray crystal structures show essentially coplanar conformations of the linked azole−purine rings. Such ring orientations position the C−H of the azole above N7 of the purine, which results in protection of N7 from alkylating agents. Treatment of 6-(2-butylimidazol-1-yl)-2-chloropurine (**9**) with sodium hydride in DMF followed by addition of ethyl iodide resulted in exclusive formation of 6-(2-butylimidazol-1-yl)-2-chloro-9-ethylpurine (**10**), whereas identical treatment of 2-chloro-6-(4,5-diphenylimidazol-1-yl)-purine (**11**) produced a regioisomeric mixture **12**/**13** (N9/N7, ∼5:1). The linked imidazole and purine rings are coplanar in **9** (the butyl side chain is extended away from the purine ring and C−H is over N7) but are rotated ∼57° in **11**, and the more bulky azole substituent in **11** did not prevent formation of the minor N7 regioisomer **13**. Access to various regioisomerically pure 9-alkylpurines is now readily available.

Introduction

Acyclic analogues of nucleosides (acyclonucleosides) have remained major biomedical research targets since the discovery of the potent antiviral activity of 9-[(2-hydroxyethoxy)methyl]-guanine (acyclovir, ACV),[2] the standard drug for the treatment of herpes viral infections. Additional acyclonucleosides have been prepared and found to have such activity including 2-amino-9-(4-hydroxybutyl)purine (substrate for HSV-1 and HSV-2 thymidine kinases),[3] 9-[4-acetoxy-3-(acetoxymethyl)-butyl]-2-aminopurine, and 2-amino-9-[4-hydroxy-3-(hydroxymethyl)butyl]purine.[4] More recently, the potent antiherpetic activity of 9-{[(1*S*,2*R*)-1,2-bis(hydroxymethyl)cycloprop-1-yl]-methyl}guanine was reported.[5] A requisite step for the preparation of all of these compounds is alkylation at N9 of a purine ring. Polypeptide nucleic acids (PNAs) have good chemical and enzymatic stability and bind strongly with oligonucleotides to produce double- and triple-stranded structures with potential applications in antisense and related diagnosis and therapeutic strategies.[6] The polypeptide backbone units of PNAs also are linked to N9 of the purine bases.

Alkylation of purine nucleobases and analogues is rarely regiospecific, and mixtures of N9 and N7 isomers are usually obtained. The desired N9 compound is normally the major product, but formation of significant amounts of the N7 isomer,[7] as well as other alkylation products,[8] is often observed. Ratios of regioisomers formed can vary with different purine substrates

(1) Nucleic Acid Related Compounds. 140. (Patent application filed.) Paper 139 is: Nowak, I.; Robins, M. J. *J. Org. Chem.*, in press.

(2) Schaeffer, H. J.; Beauchamp, L.; de Miranda, P.; Elion, G. B.; Bauer, D. J.; Collins, P. *Nature* **1978**, *272*, 583−585.

(3) Keller, P. M.; Fyfe, J. A.; Beauchamp, L.; Lubbers, C. M.; Furman, P. A.; Schaeffer, H. J.; Elion, G. B. *Biochem. Pharmacol.* **1981**, *30*, 3071−3077.

(4) (a) Harnden, M. R.; Jarvest, R. L.; Bacon, T. H.; Boyd, M. R. *J. Med. Chem.* **1987**, *30*, 1636−1642. (b) Harnden, M. R.; Jarvest, R. L.; Boyd, M. R.; Sutton, D.; Vere Hodge, R. A. *J. Med. Chem.* **1989**, *32*, 1738−1743.

(5) Sekiyama, T.; Hatsuya, S.; Tanaka, Y.; Uchiyama, M.; Ono, N.; Iwayama, S.; Oikawa, M.; Suzuki, K.; Okunishi, M.; Tsuji, T. *J. Med. Chem.* **1998**, *41*, 1284−1298.

(6) Nielsen, P. E.; Haaima, G. *Chem. Soc. Rev.* **1997**, *26*, 73−78.

(7) Ogilvie, K. K.; Cheriyan, U. O.; Radatus, B. K.; Smith, K. O.; Galloway, K. S.; Kennell, W. L. *Can. J. Chem.* **1982**, *60*, 3005−3010.

(8) Estep, K. G.; Josef, K. A.; Bacon, E. R.; Carabateas, P. M.; Rumney, S., IV; Pilling, G. M.; Krafte, D. S.; Volberg, W. A.; Dillon, K.; Dugrenier, N.; Briggs, G. M.; Canniff, P. C.; Gorczyca, W. P.; Stankus, G. P.; Ezrin, A. M. *J. Med. Chem.* **1995**, *38*, 2582−2595.

10.1021/jo061759h CCC: $33.50
Published on Web 10/18/2006

and also with the nature of the alkylating species.[9] It has been noted that N9/N7 alkylation ratios were influenced significantly by the size of the substituent at C6 on purine rings. Increased N9/N7 ratios were observed with larger groups at C6,[10] and bulky protecting groups have been installed to improve the N9 alkylation selectivity.[11] Geen et al. reported that N9/N7 alkylation ratios changed from 1.8:1 with 2-amino-6-methoxypurine to 25:1 with the more sterically demanding 2-amino-6-isopropoxypurine (in DMF with K_2CO_3 as the base),[10] and Reese and co-workers found that treatment of 2-amino-6-[(4-chlorophenyl)-sulfanyl]purine with 4-acetoxy-3-(acetoxymethyl)butyl mesylate (K_2CO_3/DMF) gave the N9 isomer in 80% yield (with 89% regioselectivity).[12] We had developed a methodology for regiospecific N9 glycosylation (and alkylation with a reactive α-bromoether) of 2-acetamido-6-(*N*,*N*-diphenylcarbamoyloxy)-purine,[13] but others noted that its alkylation with methyl bromoacetate (DIPEA as base) gave limited regioselectivity (N9/N7, ~71:15).[14] Efficient N9 alkylation with potassium *tert*-butoxide/18-crown-6/DMF at 0 °C was achieved with our carbamoyloxy derivative,[15] and problems reported with other reagents and conditions[16,17] can be attributed to the limited stability of the diphenylcarbamoyloxy group at C6.[18]

Lewis acid catalyzed alkylations (S_N1-type) are an alternative to S_N2-type methods. Alkylation at N7 occurs more rapidly than at N9 under S_N1 conditions, but the N7 compounds can undergo isomerization to the more thermodynamically stable N9 products. Thus, TMSOTf-catalyzed alkylation of silylated guanine derivatives with 2-acetoxy-4-(benzyloxymethyl)tetrahydrofuran gave increased N9/N7 ratios (from 1:1 to 15:1) with extended reaction times.[19] Treatment with (2-acetoxyethoxy)methyl acetate at 100−110 °C for 80 h gave a ratio of ~24:1 (N9/N7), but it was suggested that the high regioselectivity might have resulted from the combination of specific reagents.[20]

We have elaborated 6-amino groups on the purine base and nucleoside derivatives into the readily displaced 6-(1,2,4-triazol-4-yl) substituent[21] and developed alternative methods for the synthesis of 6-(imidazol-1-yl)purine derivatives.[22,23] Mintas[24] and others[25] used pyrrol-1-yl[24] and 1,2,4-triazol-4-yl[25] rings as sterically demanding 6-substituents to inhibit alkylation at N7 of 2-aminopurine. However, a minor amount of the N7 isomer was formed (in addition to the desired N9 product) upon alkylation of the sodium salt of 6-(pyrrol-1-yl)purine with propylene carbonate in hot DMF,[24a] and alkylation of 6-(thien-2-yl)purine with an epoxide in DMSO (or its sodium salt in DMF) produced the N3 isomer as well as the N9 product.[8] Our 6-(imidazol-1-yl)purine derivatives are more stable than the 6-(1,2,4-triazol-4-yl)purine counterparts, but both triazole and imidazole substituents are more readily displaced (much less basic) than a pyrrole anion. Favorable π-electron interactions (and possibly nonclassical hydrogen bonding, C−H···N7) stabilize coplanar orientations of azole−aromatic ring-linked systems.[26] We reasoned that such preferred conformations of 6-(azolyl)purines (with C−H on the azole ring positioned above N7 of the purine ring) would provide more effective shielding of N7 than time-averaged steric interference by bulky substituents at C6. In addition, any contribution of nonclassical hydrogen bonding (C−H···N7) would decrease the nucleophilicity of N7. Our X-ray crystal structures of 6-(azolyl)purine derivatives[23] are consistent with the calculations,[26] and we are pleased to report that alkylations of sodium (NaH/DMF) and potassium (K_2CO_3/DMF) salts of 6-(imidazol-1-yl)- and 6-(1,2,4-triazol-4-yl)purines under controlled conditions produce N9 alkyl products exclusively. The N7 regioisomers were not contaminants in purified products, and they were not detected in crude reaction mixtures (TLC, NMR).

Results and Discussion

The sodium salt of 6-(1,2,4-triazol-4-yl)purine[21] (**1**) (Scheme 1) was generated with sodium hydride in dried DMF at ambient temperature. Treatment of the sodium purinate with methyl iodide gave a single isomer (^{1}H NMR, TLC) that was purified by filtration through silica gel to give 9-methyl-6-(1,2,4-triazol-4-yl)purine (**2a**) (90%) (identical to the compound obtained by triazole ring elaboration with 9-methyladenine[21]). Similar treatment with other primary (ethyl, butyl, and benzyl) iodoalkanes gave the respective 9-alkyl products **2b** (93%), **2c** (84%), and **2d** (98%) exclusively. Because **2d** was obtained in 64% yield with benzyl chloride, benzyl iodide was generated in situ by stirring a solution of sodium iodide and benzyl chloride in DMF prior to addition of the purinate salt. Regiospecific alkylation of the sodium purinate also occurred efficiently with secondary iodides (iodocyclopentane, 2-iodopropane, and 2-iodooctane) to give the 9-cyclopentyl **2e** (87%), 9-(1-methylethyl) **2f** (99%),

(9) Hockova, D.; Budesinsky, M.; Marek, R.; Marek, J.; Holy, A. *Eur. J. Org. Chem.* **1999**, 2675−2682. In this paper, it was reported that alkylation of 6-*N*-[(dimethylamino)methylene]adenine with chloroacetonitrile, ethyl bromoacetate, and 1,1,1-trifluoro-2-iodoethane (with NaH or DBU as basic promoters) gave 7-alkyl derivatives (32−51% isolated yields). X-Ray crystal structures showed that conformations of the electron-donating amidine group [$(CH_3)_2$NCH═N−] at C6 were distal to N7, and the enhanced basicity of N7 with this substituent at C6 was indicated by ^{13}C NMR.

(10) Geen, G. R.; Grinter, T. J.; Kincey, P. M.; Jarvest, R. L. *Tetrahedron* **1990**, *46*, 6903−6914.

(11) Breipohl, G.; Will, D. W.; Peyman, A.; Uhlmann, E. *Tetrahedron* **1997**, *53*, 14671−14686.

(12) Brand, B.; Reese, C. B.; Song, Q.; Visintin, C. *Tetrahedron* **1999**, *55*, 5239−5252.

(13) (a) Zou, R.; Robins, M. J. *Can. J. Chem.* **1987**, *65*, 1436−1437. (b) Robins, M. J.; Zou, R.; Guo, Z.; Wnuk, S. F. *J. Org. Chem.* **1996**, *61*, 9207−9212.

(14) Timar, Z.; Kovacs, L.; Kovacs, G.; Schmel, Z. *J. Chem. Soc., Perkin Trans. 1* **2000**, 19−26.

(15) Lazrek, H. B.; Taourirte, M.; Barascut, J. L.; Imbach, J. L. *Bull. Soc. Chim. Belg.* **1996**, *105*, 391−395.

(16) Onishi, T.; Matsuzawa, T.; Nishi, S.; Tsuji, T. *Tetrahedron Lett.* **1999**, *40*, 8845−8847.

(17) Cheung, A. W.-H.; Sidduri, A.; Garofalo, L. M.; Goodnow, R. A., Jr. *Tetrahedron Lett.* **2000**, *41*, 3303−3307.

(18) Zhong, M.; Robins, M. J. *Tetrahedron Lett.* **2003**, *44*, 9327−9330 and references therein.

(19) Geen, G. R.; Kincey, P. M.; Spoors, P. G. *Tetrahedron Lett.* **2001**, *42*, 1781−1784.

(20) Singh, D.; Wani, M. J.; Kumar, A. *J. Org. Chem.* **1999**, *64*, 4665−4668.

(21) (a) Samano, V.; Miles, R. W.; Robins, M. J. *J. Am. Chem. Soc.* **1994**, *116*, 9331−9332. (b) Miles, R. W.; Samano, V.; Robins, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 5951−5957.

(22) (a) Lin, X.; Robins, M. J. *Org. Lett.* **2000**, *2*, 3497−3499. (b) Janeba, Z.; Lin, X.; Robins, M. J. *Nucleosides, Nucleotides, Nucleic Acids* **2004**, *23*, 137−147.

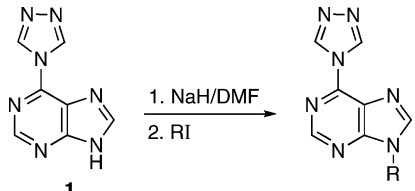
(23) Zhong, M.; Nowak, I.; Cannon, J. F.; Robins, M. J. *J. Org. Chem.* **2006**, *71*, 4216−4221.

(24) (a) Raic, S.; Pongracic, M.; Vorkapic-Furac, J.; Vikic-Topic, D.; Hergold-Brundic, A.; Nagl, A.; Mintas, M. *Nucleosides Nucleotides* **1996**, *15*, 937−960. (b) Dzolic, Z.; Kristafor, V.; Cetina, M.; Nagl, A.; Hergold-Brundic, A.; Mrvos-Sermek, D.; Burgemeister, T.; Grdisa, M.; Slade, N.; Pavelic, K.; Balzarini, J.; De Clercq, E.; Mintas, M. *Nucleosides, Nucleotides, Nucleic Acids* **2003**, *22*, 373−389.

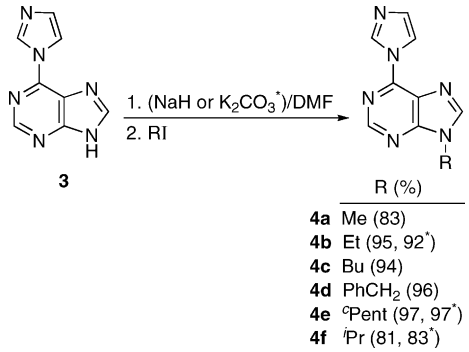
(25) Alarcon, K.; Martelli, A.; Demeunynck, M.; Lhomme, J. *Tetrahedron Lett.* **2000**, *41*, 7211−7215.

(26) Carra, C.; Bally, T.; Albini, A. *J. Am. Chem. Soc.* **2005**, *127*, 5552−5562.

SCHEME 1. Alkylation of 6-(1,2,4-Triazol-4-yl)purine



SCHEME 2. Alkylation of 6-(Imidazol-1-yl)purine

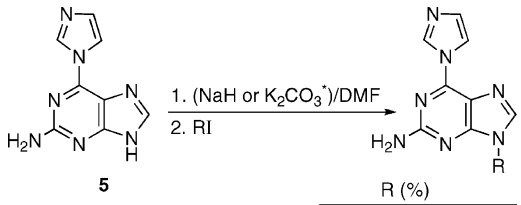


and 9-(1-methylheptyl) **2g** (83%) derivatives, respectively. Formation of byproduct 6-alkoxy-9-alkylpurines was observed (and byproducts were isolated in some cases). Extended reaction times and/or excess alkyl iodide resulted in greater byproduct formation [displacement of iodide by OH^- (from adventitious H_2O and NaH) would produce an alcohol, which would react with NaH to generate an alkoxide nucleophile].

Alkylation yields with 6-(imidazol-1-yl)purine[23] (**3**) (Scheme 2) were comparable to those with **1**. Selective alkylation at N9 of the purinate salt was effected with 1.5 equiv of benzyl iodide, but both the imidazole N3 and the purine N9 positions were benzylated with 4.5 equiv. NMR and mass spectral data were consistent with a 3′,9-dibenzyl structure.[27] Dialkylated byproducts were not observed with 3 equiv of other alkyl iodides (or even with 5 equiv of cyclopentyl iodide). Anhydrous potassium carbonate is a much more convenient base than sodium hydride dispersed in mineral oil, and K_2CO_3/DMF was equivalent or superior to NaH/DMF for some alkylations. The 6-(imidazol-1-yl)purines have lower S_NAr reactivity than their triazole analogues, which makes them less sensitive to byproduct formation and purification procedures. Benzylation of the appended imidazole produces an imidazolium cation that is more readily displaced by nucleophiles.[27] Exclusive N9 alkylation followed by S_NAr displacements[21,22] or cross-coupling reactions[28] makes a wide range of regiochemically pure 9-alkylpurines readily available.

We then probed access to 9-alkyl-2-(substituted)purines with 2-amino-6-(imidazol-1-yl)purine (**5**) (Scheme 3). Treatment of **5** with NaH/DMF followed by addition of excess butyl iodide

SCHEME 3. Alkylation of 2-Amino-6-(imidazol-1-yl)purine



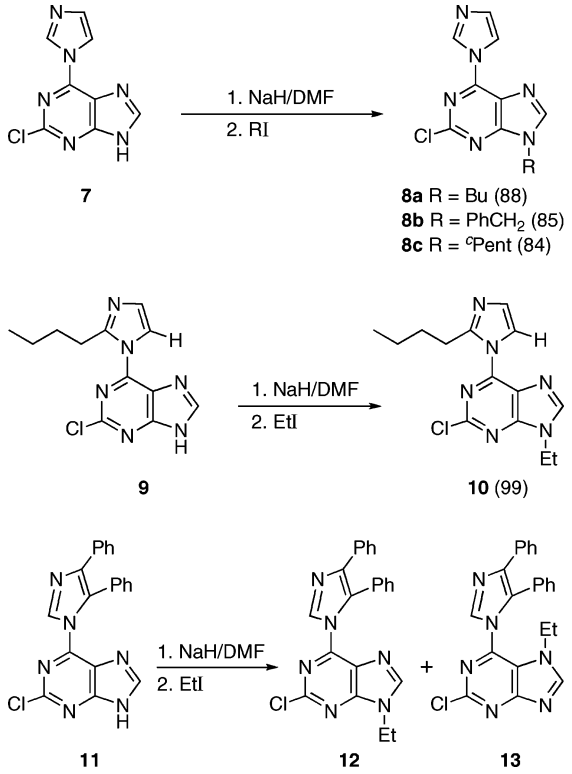
gave 2-amino-9-butyl-6-(imidazol-1-yl)purine (**6a**) (62%) plus a 9-butyl-2-butylamino-6-(imidazol-1-yl)purine byproduct (8%). More of that byproduct was formed with larger excesses of butyl iodide and/or longer reaction times, and purified **6a** was converted into the dibutyl compound under the same conditions. Treatment of the sodium purinate with benzyl iodide (generated in situ from benzyl chloride and sodium iodide in acetonitrile) gave 2-amino-9-benzyl-6-(imidazol-1-yl)purine (**6b**) (77%) as the only detected monobenzyl product, and minor byproducts were removed by chromatography. Standard treatment of the purinate with cyclopentyl iodide gave 2-amino-9-cyclopentyl-6-(imidazol-1-yl)purine (**6c**) (58% after chromatography). Because NaH-mediated alkylations of **5** did not proceed to completion and were not as clean as parallel reactions of **1** or **3**, we tried K_2CO_3/DMF. Treatment of a suspension of **5**/K_2CO_3/DMF with butyl iodide gave **6a** as the only observed product (81% after chromatography). Cyclopentyl iodide/**5**/K_2CO_3/DMF gave **6c** (99% after chromatography). Benzylation of **5** gave **6b** (68%) as the only regioisomer but did not proceed to completion with this procedure. Treatment of the sodium salt of **5** with the reactive (2-acetoxyethoxy)methyl bromide gave 9-[(2-acetoxyethoxy)methyl]-2-amino-6-(imidazol-1-yl)purine (**6d**) (56% after chromatography), and the K_2CO_3/DMF system also produced bis(2-acetoxyethoxy)methyl byproducts in addition to **6d** (50%).

Regiospecific alkylation of 2-chloro-6-(imidazol-1-yl)purine (**7**) (Scheme 4) with butyl iodide, benzyl iodide, and cyclopentyl iodide (NaH/DMF) gave 9-butyl-2-chloro-6-(imidazol-1-yl)-purine (**8a**) (88%), 9-benzyl-2-chloro-6-(imidazol-1-yl)purine (**8b**) (85%), and 2-chloro-9-cyclopentyl-6-(imidazol-1-yl)purine (**8c**) (84%), respectively. Treatment of 6-(2-butylimidazol-1-yl)-2-chloropurine (**9**) with NaH/DMF followed by addition of ethyl iodide resulted in quantitative conversion to 2-chloro-9-ethyl-6-(2-butylimidazol-1-yl)purine (**10**). In contrast, identical treatment of 2-chloro-6-(4,5-diphenylimidazol-1-yl)purine (**11**) produced the ethylated regioisomers **12** and **13** (N9/N7, ~5:1). The 4,5-diphenylimidazole moiety in **11** is more bulky and would be expected to shield the proximal N1 and N7 regions of space more effectively if conformationally averaged steric effects were more important. However, the phenyl groups on the imidazole ring in **11** impede coplanar orientations of the linked imidazole−purine system (a departure of 56.5° from coplanarity was measured in an X-ray crystal structure[23]), which also would disrupt nonclassical hydrogen bonding. In contrast, the alkyl substituent at C2 of the imidazole ring in **9** does not interfere with coplanarity of the imidazole−purine system because the butyl group is extended away from the purine N1 region of space (a deviation of only 3.4° between the planes of the imidazole and purine rings was measured in our X-ray crystal structure[23] of **9**). The C−H of the coplanar imidazole moiety in **9** is held above N7 of the purine ring, which would

(27) Zhong, M.; Nowak, I.; Robins, M. J. *J. Org. Chem.*, **2006**, *71*, 7773−7779.

(28) Liu, J.; Robins, M. J. *Org. Lett.* **2004**, *6*, 3421−3423.

SCHEME 4. Alkylation of 2-Chloro-6-(imidazol-1-yl)purines



effectively shield this volume of space and also might decrease the nucleophilicity of N7. Thus, our alkylation results, X-ray crystal structures,[23] and theoretical calculations[26] are in harmony with the coplanar conformation-restriction hypothesis.

Summary and Conclusions

Treatment of 6-(1,2,4-triazol-4-yl)purine, 6-(imidazol-1-yl)-purine, 2-amino-6-(imidazol-1-yl)purine, and 2-chloro-6-(imidazol-1-yl)purine with NaH/DMF followed by alkyl iodides gave regiospecific N9 alkylation (N7 isomers were not detected, even in crude reaction mixtures). Anhydrous K_2CO_3/DMF was a convenient alternative to NaH/DMF in some cases. Byproduct 6-alkoxy-9-alkylpurines were presumably formed by displacement of iodide from the iodoalkanes by hydroxide (adventitious H_2O and NaH) to give alcohols, deprotonation by NaH to give alkoxides, and alkoxide displacement of the azole at C6. Larger excesses of alkyl iodides and/or longer reaction times increased byproduct formation. We attribute the N9 regiospecificity to the coplanarity of the linked azole−purine rings, which positions the C−H of the azole above N7 of the purine. Treatment of the sodium salt of 6-(2-butylimidazol-1-yl)-2-chloropurine (coplanar azole−purine rings) with ethyl iodide gave the 9-ethyl isomer exclusively, whereas identical treatment of sodium 2-chloro-6-(4,5-diphenylimidazol-1-yl)purinate (greater steric bulk, but rotated ∼57° from coplanarity) gave both N9 and N7 regioisomers (∼5:1). A broad array of regioisomerically pure 6-substituted-9-alkylpurines and 9-alkylpurines with substituents at both C2 and C6 are now readily accessible. Although not investigated, 6-(heteroaryl)-8-(substituted)purines also would be expected to undergo alkylation regiospecifically at N9 because steric effects of groups at C8 should disfavor reactions at N7 that would generate products with three contiguous substituents (at C6, N7, and C8).

Experimental Section[29]

The 6-(1,2,4-triazol-4-yl)purine[21] (**1**), 6-(imidazol-1-yl)purine[23] (**3**), 2-amino-6-(imidazol-1-yl)purine[23] (**5**), 2-chloro-6-(imidazol-1-yl)purine[23] (**7**), 2-chloro-6-(2-butylimidazol-1-yl)purine[23] (**9**), and 2-chloro-6-(4,5-diphenylimidazol-1-yl)purine[23] (**11**) were prepared and characterized as described.

General Method 1. Sodium hydride (60% w/w dispersion in mineral oil) was added to a stirred solution of the 6-(azolyl)purine in DMF (5 mL) under N_2, and stirring was continued at ambient temperature for ∼1 h. The respective iodoalkane was added, and stirring was continued until conversion of the starting was essentially complete (TLC). For alkylations of: **1** (190 mg, 1.02 mmol) and NaH (60 mg of 60% dispersion, 1.5 mmol); **3** (93 mg, 0.50 mmol) and NaH (23 mg of 60% dispersion, 0.58 mmol); **5** (100 mg, 0.5 mmol) and NaH (25 mg of 60% dispersion, 0.63 mmol); and **7** (110 mg, 0.50 mmol) and NaH (25 mg of 60% dispersion, 0.63 mmol).

Traces of 6-alkoxy-9-alkylpurine byproducts resulting from nucleophilic replacement of triazole by the alkoxide derived from the respective iodoalkane were observed.

General Method 2. Anhydrous potassium carbonate (230 mg, 1.67 mmol) and the 6-(azolyl)purine (0.5 mmol) in DMF (5 mL) were stirred under N_2. The respective iodoalkane was added to the suspension, and stirring was continued at ambient temperature overnight.

9-Methyl-6-(1,2,4-triazol-4-yl)purine[21] **(2a).** Treatment of **1** by general method 1 with MeI (0.09 mL, 210 mg, 1.5 mmol), evaporation of volatiles in vacuo, and chromatography of the residue ($MeOH/CH_2Cl_2$, 1:14) gave a solid. This material was washed (H_2O) to give **2a** (180 mg, 90%): UV max 210, 277 nm (ϵ 27 300, 12 700), min 235 nm (ϵ 2600); ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.67 (s, 2H), 8.95 (s, 1H), 8.79 (s, 1H), 3.93 (s, 3H); LRMS (EI) m/z 201 (M^+ [$C_8H_7N_7$] = 201).

A solution of **2a** in Me_2NH/H_2O (40% w/w, 20 mL) was stirred at ambient temperature until the displacement was complete (TLC). Volatiles were evaporated in vacuo, and the residue was chromatographed ($MeOH/CH_2Cl_2$, 1:40) to give 9-methyl-6-dimethylaminopurine[21] (150 mg, 86%): ^{1}H NMR δ 8.30 (s, 1H), 7.64 (s, 1H), 3.74 (s, 3H), 3.47 (br s, 6H); LRMS (EI) m/z 177 (M^+ [$C_8H_{11}N_5$] = 177).

9-Ethyl-6-(1,2,4-triazol-4-yl)purine (2b). Treatment of **1** by general method 1 with EtI (0.12 mL, 230 mg, 1.4 mmol), evaporation of volatiles in vacuo, and chromatography of the residue ($MeOH/CH_2Cl_2$, 1:40 → 1:30 → 1:20) gave a solid (228 mg) that was dissolved in CH_2Cl_2 and washed (H_2O). The aqueous phase was back-extracted with CH_2Cl_2, and the combined organic phase was dried (Na_2SO_4). Volatiles were evaporated in vacuo to give a solid (205 mg, 93%) that was recrystallized (CH_2Cl_2/hexanes) to give **2b**: mp 218.5−220.5 °C; UV max 212, 277 nm (ϵ 25 400, 13 100), min 235 nm (ϵ 2600); ^{1}H NMR δ 9.67 (s, 2H), 8.88 (s, 1H), 8.25 (s, 1H), 4.46 (q, J = 7.3 Hz, 2H), 1.66 (t, J = 7.3 Hz, 3H); ^{13}C NMR δ 154.2, 152.4, 145.3, 143.4, 141.2, 122.8, 39.8, 15.6; HRMS (EI) m/z 215.0911 (M^+ [$C_9H_9N_7$] = 215.0919). Anal. Calcd for $C_9H_9N_7$: C, 50.23; H, 4.22; N, 45.56. Found: C, 50.45; H, 4.32; N, 45.70.

9-Benzyl-6-(1,2,4-triazol-4-yl)purine (2d). A. Treatment of **1** by general method 1 with BnCl (0.17 mL, 190 mg, 1.5 mmol) and evaporation of volatiles in vacuo gave a residue that was partitioned (H_2O/CH_2Cl_2). The aqueous layer was extracted (CH_2Cl_2), and the combined organic phase was dried (Na_2SO_4). Volatiles were evaporated, and the residue was dissolved in a small amount of CH_2Cl_2. Precipitation with Et_2O gave solid **2d** (180 mg, 64%).

B. BnCl (0.17 mL, 190 mg, 1.5 mmol) was added to a stirred solution of NaI (450 mg, 3.0 mmol) in CH_3CN (3 mL). Precipitation of NaCl occurred, and stirring was continued for ∼1 h at ambient temperature (the resulting solution of BnI was used without

(29) General experimental items are in the Supporting Information.

purification). Treatment of **1** by general method 1 with the crude BnI, evaporation of volatiles in vacuo, and chromatography of the residue (MeOH/CH_2Cl_2, 1:20) gave a solid (276 mg, 98%) that was recrystallized (CH_2Cl_2/hexanes) to give **2d**: mp 218−218.8 °C; UV max 211, 277 nm (ϵ 33 300, 13 700), min 238 nm (ϵ 3200); ^{1}H NMR δ 9.66 (s, 2H), 8.91 (s, 1H), 8.20 (s, 1H), 7.42−7.29 (m, 5H), 5.55 (s, 2H); ^{13}C NMR δ 154.4, 152.8, 145.6, 143.5, 141.1, 134.7, 129.6, 129.5, 129.3, 128.3, 122.6, 48.1; HRMS (EI) *m*/*z* 277.1075 (M^+ [$C_{14}H_{11}N_7$] = 277.1076). Anal. Calcd for $C_{14}H_{11}N_7$: C, 60.64; H, 4.00; N, 35.36. Found: C, 60.81; H, 3.98; N, 35.30.

9-Cyclopentyl-6-(1,2,4-triazol-4-yl)purine (2e). Treatment of **3** by general method 1 with iodocyclopentane (0.3 mL, 509 mg, 2.6 mmol) (conversion not complete, TLC), evaporation of volatiles in vacuo, and chromatography of the residue (MeOH/CH_2Cl_2, 1:40) gave a solid (226 mg, 87%) that was recrystallized (CH_2Cl_2/hexanes) to give **2e**: mp 181−182.5 °C; UV max 211, 278 nm (ϵ 28 900, 13 700), min 236 nm (ϵ 3000); ^{1}H NMR δ 9.66 (s, 2H), 8.86 (s, 1H), 8.26 (s, 1H), 5.10 (quint, J = 7.3 Hz, 1H), 2.46−2.34 (m, 2H), 2.17−1.84 (m, 6H); ^{13}C NMR δ 154.4, 152.1, 144.2, 143.3, 141.2, 123.1, 57.1, 32.9, 24.2; HRMS (EI) *m*/*z* 255.1228 (M^+ [$C_{12}H_{13}N_7$] = 255.1232). Anal. Calcd for $C_{12}H_{13}N_7$: C, 56.46; H, 5.13; N, 38.41. Found: C, 56.70; H, 5.18; N, 38.40.

9-Ethyl-6-(imidazol-1-yl)purine (4b). A. Treatment of **3** by general method 1 with EtI (0.06 mL, 117 mg, 0.75 mmol), evaporation of volatiles in vacuo, and chromatography of the residue (MeOH/CH_2Cl_2, 1:40) gave a solid (101 mg, 95%) that was recrystallized (CH_2Cl_2/hexanes) to give **4b** (97 mg, 91%): mp 125.5−127 °C; UV max 212, 282, 292 nm (ϵ 24 000, 15 900, 11 800), min 235, 290 nm (ϵ 2900, 11 700); ^{1}H NMR δ 9.18 (s, 1H), 8.79 (s, 1H), 8.40 (t, J = 1.2 Hz, 1H), 8.13 (s, 1H), 7.25 (d, J = 0.5 Hz, 1H), 4.39 (q, J = 7.3 Hz, 2H), 1.61 (t, J = 7.3 Hz, 3H); ^{13}C NMR δ 153.8, 152.3, 145.9, 144.2, 137.9, 130.9, 122.8, 117.6, 39.6, 15.6; HRMS *m*/*z* 214.0959 (M^+ [$C_{10}H_{10}N_6$] = 214.0967). Anal. Calcd for $C_{10}H_{10}N_6$: C, 56.07; H, 4.70; N, 39.23. Found: C, 56.31; H, 4.52; N, 39.08.

Extended reaction times and/or more iodoethane resulted in the formation of 6-ethoxy-9-ethylpurine: ^{1}H NMR δ 8.55 (s, 1H), 7.94 (s, 1H), 4.68 (q, J = 7.1 Hz, 2H), 4.32 (q, J = 7.3 Hz, 2H), 1.57 (t, J = 7.3 Hz, 3H), 1.54 (t, J = 7.3 Hz, 3H); LRMS *m*/*z* 192 (M^+ [$C_9H_{12}N_4O$] = 192), 177 (M − CH_3 [$C_8H_9N_4O$] = 177).

B. Treatment of **3** (98 mg, 0.5 mmol) by general method 2 with EtI (80 μL, 159 mg, 1.0 mmol) and workup as in A gave **4b** (98 mg, 92%).

9-Benzyl-6-(imidazol-1-yl)purine (4d). A. Treatment of **3** by general method 1 with BnI [prepared from BnCl (0.086 mL, 95 mg, 0.75 mmol) and NaI (0.25 g, 1.67 mmol) in CH_3CN (2 mL)], evaporation of volatiles in vacuo, and chromatography of the residue (MeOH/CH_2Cl_2, 1:40) gave a solid (133 mg, 96%) that was recrystallized (CH_2Cl_2/hexanes) to give **4d**: mp 195.5−196.5 °C; UV max 282, 292 nm (ϵ 16 800, 12 700), min 238, 290 nm (ϵ 3600, 12 300); ^{1}H NMR δ 9.21 (s, 1H), 8.86 (d, J = 1.2 Hz, 1H), 8.85 (s, 1H), 8.11 (s, 1H), 7.29−7.43 (m, 6H), 5.52 (s, 2H); ^{13}C NMR δ 154.0, 152.7, 146.0, 144.5, 137.9, 135.0, 131.0, 129.5, 129.1, 128.2, 122.6, 117.6, 47.9; HRMS *m*/*z* 276.1122 (M^+ [$C_{15}H_{12}N_6$] = 276.1123). Anal. Calcd for $C_{15}H_{12}N_6$: C, 65.21; H, 4.38; N, 30.42. Found: C, 65.22; H, 4.31; N, 30.66.

B. Increasing the ratio of BnI/**3** from 1.5:1 (in A) to 3:1 (in B) gave **4d** (20 mg, 14%) plus 3-benzyl-1-(9-benzylpurin-6-yl)-imidazolium iodide (179 mg, 73%): ^{1}H NMR δ 10.57−10.59 (m, 1H), 8.76 (s, 1H), 8.66 (s, 1H), 8.60−8.61 (m, 1H), 8.06−8.08 (m, 1H), 7.64−7.69 (m, 2H), 7.24−7.41 (m, 8H), 6.01 (s, 2H), 5.57 (s, 2H); ^{13}C NMR δ 154.8, 151.9, 147.9, 141.5, 135.6, 134.7, 132.5, 129.8−128.5 (overlap), 124.4, 122.8, 120.0, 54.4, 48.1. The second benzylation could be driven to completion with BnI/**3** ratios of ≥5:1.

9-Cyclopentyl-6-(imidazol-1-yl)purine (4e). A. Treatment of **3** by general method 1 with iodocyclopentane (290 μL, 492 mg, 2.5 mmol), evaporation of volatiles in vacuo, and chromatography of the residue (MeOH/CH_2Cl_2, 1:40) gave a solid (123 mg, 97%) that was recrystallized (CH_2Cl_2/hexanes) to give **4e**: mp 117.5−119 °C; UV max 283, 293 nm (ϵ 16 500, 12 300), min 240, 291 nm (ϵ 3800, 11 700); ^{1}H NMR δ 9.21 (s, 1H), 8.80 (d, J = 1.5 Hz, 1H), 8.43 (s, 1H), 8.17 (s, 1H), 7.28 (s, 1H), 5.07 (quint, J = 7.1 Hz, 1H), 2.41−2.35 (m, 2H), 1.86−2.13 (m, 6H); ^{13}C NMR δ 154.0, 152.1, 145.9, 143.0, 137.9, 130.9, 123.1, 117.6, 56.8, 32.9, 24.1; HRMS *m*/*z* 254.1291 (M^+ [$C_{13}H_{14}N_6$] = 254.1280). Anal. Calcd for $C_{13}H_{14}N_6$: C, 61.40; H, 5.55; N, 33.05. Found: C, 61.21; H, 5.32; N, 33.13.

B. Treatment of **3** (98 mg, 0.5 mmol) by general method 2 with iodocyclopentane (174 μL, 295 mg, 1.5 mmol) and workup as in A gave **4e** (123 mg, 97%).

2-Amino-9-butyl-6-(imidazol-1-yl)purine (6a). A. Treatment of **5** by general method 2 (complete in 28 h, TLC) with BuI (0.25 mL, 404 mg, 2.20 mmol), evaporation of volatiles in vacuo, and chromatography (MeOH/CH_2Cl_2, 1:60) of the residue gave **6a** (103 mg, 81%; the only product eluted): mp 156.5−157 °C; UV max 227, 321 nm (ϵ 33 800, 9000), min 281 nm (ϵ 1400); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.92 (s, 1H), 8.24−8.23 (m, 2H), 7.19−7.18 (m, 1H), 6.80 (s, 2H), 4.08 (t, J = 7.3 Hz, 2H), 1.78 (quint, J = 7.3 Hz, 2H), 1.27 (sext, J = 7.3 Hz, 2H), 0.90 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.6, 156.5, 145.6, 143.8, 137.2, 130.6, 117.7, 115.7, 43.3, 31.8, 20.0, 14.1; HRMS *m*/*z* 257.1378 (M^+ [$C_{12}H_{15}N_7$] = 257.1389). Anal. Calcd for $C_{12}H_{15}N_7$: C, 56.02; H, 5.88; N, 38.11. Found: C, 55.82; H, 6.01; N, 37.88.

B. Treatment of **5** by general method 1 (complete in 5.5 h, TLC) with BuI (0.25 mL, 404 mg, 2.20 mmol), evaporation of volatiles in vacuo, and chromatography of the residue (MeOH/CH_2Cl_2, 1:96 → 1:60) gave **6a** (80 mg, 62%) plus 9-butyl-2-butylamino-6-(imidazol-1-yl)purine (12 mg, 8%): mp 134.5−135 °C; UV max 232, 333 nm (ϵ 35 400, 7600), min 212, 287 nm (ϵ 13 600, 3200); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.08 (s, 1H), 8.33 (s, 1H), 7.72 (s, 1H), 7.22 (s, 1H), 5.13 (s, 1H), 4.13 (t, J = 7.3 Hz, 2H), 3.50 (q, J = 7.0 Hz, 2H), 1.88 (quint, J = 7.3 Hz, 2H), 1.67 (quint, J = 7.3 Hz, 2H), 1.47 (sext, J = 7.3 Hz, 2H), 1.40 (sext, J = 7.3 Hz, 2H), 0.98−1.01 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 156.2, 146.1, 141.4, 137.7, 130.4, 117.6, 116.4, 43.4, 41.9, 31.99, 31.97, 20.4, 20.1, 14.1, 13.8; HRMS *m*/*z* 313.2007 (M^+ [$C_{16}H_{23}N_7$] = 313.2015). Anal. Calcd for $C_{16}H_{23}N_7$: C, 61.32; H, 7.40; N, 31.28. Found: C, 61.16; H, 7.46; N, 31.14.

Greater excesses of BuI produced more of the dibutylated product, and treatment of **6a** with BuI by general method 1 also produced the dibutyl compound.

2-Amino-9-cyclopentyl-6-(imidazol-1-yl)purine (6c). A. Treatment of **5** by general method 2 with iodocyclopentane (0.30 mL, 0.509 g, 2.57 mmol), evaporation of volatiles in vacuo, and chromatography of the residue (MeOH/CH_2Cl_2, 1:30) gave **6c** (133 mg, 99%): mp 183.5−184.5 °C; UV max 228, 320 nm (ϵ 31 900, 8500), min 210, 281 nm (ϵ 12 800, 1800); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.08 (s, 1H), 8.32 (s, 1H), 7.84 (s, 1H), 7.22 (s, 1H), 5.01 (s, 2H), 4.85 (quint, J = 7.3 Hz, 1H), 2.27−2.32 (m, 2H), 1.92−2.03 (m, 4H), 1.79−1.87 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 156.0, 146.3, 140.2, 137.7, 130.5, 117.6, 117.5, 55.9, 32.8, 24.1; HRMS *m*/*z* 269.1383 (M^+ [$C_{13}H_{15}N_7$] = 269.1389). Anal. Calcd for $C_{13}H_{15}N_7$: C, 57.98; H, 5.61; N, 36.41. Found: C, 57.91; H, 5.87; N, 36.28.

B. Treatment of **5** by general method 1 (incomplete; minor byproducts, TLC) with iodocyclopentane (0.30 mL, 0.509 g, 2.59 mmol), and workup as in A gave **6b** (80 mg, 59%).

9-Butyl-2-chloro-6-(imidazol-1-yl)purine (8a). Treatment of **7** by general method 1 (4 h; complete, TLC) with BuI (0.35 mL, 566 mg, 3.1 mmol), evaporation of volatiles in vacuo, and chromatography of the residue (MeOH/CH_2Cl_2, 1:60) gave **8a** (122 mg, 88%): mp 150−150.5 °C; UV max 220, 290, 300 nm (ϵ 29 000, 15 600, 12 600), min 239, 297 nm (ϵ 2900, 11 100); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.15 (t, J = 1.1 Hz, 1H), 8.35 (t, J = 1.4 Hz, 1H), 8.07 (s, 1H), 7.25 (dd, J = 1.5, 0.9 Hz, 1H), 4.29

(t, J = 7.4 Hz, 2H), 1.93 (quint, J = 7.5 Hz, 2H), 1.41 (sext, J = 7.3 Hz, 2H), 0.99 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 155.4, 153.9, 146.5, 145.1, 138.0, 131.2, 121.6, 117.6, 44.4, 32.1, 20.1, 13.7; HRMS *m/z* 276.0889 (M^+ [$C_{12}H_{13}ClN_6$] = 276.0890). Anal. Calcd for $C_{12}H_{13}ClN_6$: C, 52.08; H, 4.74; N, 30.37. Found: C, 51.96; H, 4.86; N, 30.12.

2-Chloro-9-cyclopentyl-6-(imidazol-1-yl)purine (8c). Treatment of **7** by general method 1 (7 days; incomplete, TLC) with iodocyclopentane (0.3 mL, 509 mg, 2.6 mmol), evaporation of volatiles in vacuo, and chromatography of the residue (MeOH/CH_2Cl_2, 1:60) gave **8c** as a solid (121 mg, 84%): mp 182−182.5 °C; UV max 221, 290, 301 nm (ϵ 30 800, 15 600, 12 700), min 242, 298 nm (ϵ 3600, 12 200); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.85 (s, 1H), 8.33 (s, 1H), 7.27 (s, 1H), 4.97 (quint, J = 7.3 Hz, 1H), 2.20−2.26 (m, 2H), 2.00−2.07 (m, 2H), 1.87−1.95 (m, 2H), 1.70−1.78 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.7, 152.2, 146.9, 146.0, 137.7, 131.5, 122.2, 118.1, 56.9, 32.6, 24.2; HRMS *m/z* 288.0888 (M^+ [$C_{13}H_{13}ClN_6$] = 288.0890). Anal. Calcd for $C_{13}H_{13}ClN_6$: C, 54.08; H, 4.54; N, 29.11. Found: C, 54.30; H, 4.65; N, 29.14.

6-(2-Butylimidazol-1-yl)-2-chloro-9-ethylpurine (10). A mixture of **9** (50 mg, 0.18 mmol) and NaH (11.2 mg, 60% w/w dispersion in mineral oil, 0.28 mmol) in DMF was stirred at ambient temperature under N_2 for 1 h. EtI (0.09 mL, 179 mg, 1.15 mmol) was added, and stirring was continued (4 h; complete, TLC). Volatiles were evaporated in vacuo, and the residue was chromatographed (MeOH/CH_2Cl_2, 1:30) to give **10** (quantitative): mp 104.5−105 °C; UV max 218, 289 nm (ϵ 23 700, 13 300), min 240 nm (ϵ 1500); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.77 (d, J = 1.0 Hz, 1H), 8.45 (t, J = 1.3 Hz, 1H), 7.07 (t, J = 1.5 Hz, 1H), 4.31 (q, J = 7.3 Hz, 2H), 3.12 (t, J = 7.3 Hz, 3H), 1.68 (quint, J = 7.3 Hz, 2H), 1.47 (t, J = 7.3 Hz, 2H), 4.31 (sext, J = 7.3 Hz, 2H), 0.91 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 154.8, 150.9, 149.6, 146.8, 146.7, 128.2, 122.3, 120.3, 38.9, 29.5, 29.4, 21.9, 14.7, 13.6; HRMS *m/z* 327.1105 (MNa^+ [$C_{14}H_{17}ClN_6Na$ = 327.1101]). Anal. Calcd for $C_{14}H_{17}ClN_6$: C, 55.17; H, 5.62; N, 27.57. Found: C, 55.01; H, 5.72; N, 27.57.

2-Chloro-9-ethyl-6-(4,5-diphenylimidazol-1-yl)purine (12) and 2-Chloro-7-ethyl-6-(4,5-diphenylimidazol-1-yl)purine (13). A mixture of 2-chloro-6-(4,5-diphenylimidazol-1-yl)purine (**11**) (54 mg, 0.145 mmol) and NaH (8.6 mg, 60% w/w dispersion in mineral oil, 0.21 mmol) in DMF was stirred at ambient temperature under N_2 for 1 h. EtI (0.05 mL, 98 mg, 0.63 mmol) was added, and stirring was continued (3 h; incomplete, TLC). Volatiles were evaporated in vacuo, and the residue was chromatographed (MeOH/CH_2Cl_2, 1:30) to give **12** and **13** (~5:1). Compound **12**: UV max 278 nm (ϵ 16 300), min 268 nm (ϵ 15 700); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.86 (s, 1H), 8.78 (s, 1H), 7.20−7.48 (m, 10H), 4.28 (q, J = 7.3 Hz, 2H), 1.45 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 154.7, 150.8, 147.6, 145.9, 139.0, 138.8, 133.4, 130.6, 130.4, 128.23, 128.16, 128.1, 127.2, 127.0, 126.8, 124.1, 40.0, 14.6; NOESY cross peaks were present for (CH_2, H8), (CH_2, CH_3), (CH_2, Ph), (CH_3, H8), and (CH_3, Ph); HRMS *m/z* 400.1207 (M^+ [$C_{22}H_{17}ClN_6$] = 400.1203). Anal. Calcd for $C_{22}H_{17}ClN_6$: C, 65.92; H, 4.27; N, 20.96. Found: C, 66.00; H, 4.50; N, 20.83. Compound **13**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.95 (s, 1H), 8.46 (s, 1H), 7.20−7.52 (m, 10H), 4.05 (q, J = 7.3 Hz, 2H), 1.20 (t, J = 7.3 Hz, 3H); NOE difference effects when CH_2 was irradiatied, H8 (1.9%), H2 of 6-(imidazol-1-yl) (3.6%), Ph (2.9%), and CH_3 (4.8%); NOESY cross peaks were present for (CH_2, H8), [CH_2, H2 of 6-(imidazol-1-yl)], (CH_2, CH_3), (CH_2, Ph), (CH_3, H8), [CH_3, H2 of 6-(imidazol-1-yl)], and (CH_3, Ph); ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.1, 153.6, 151.7, 147.6, 142.1, 139.3, 139.0, 134.2, 130.8, 129.5, 129.2, 129.0, 127.9, 127.5, 120.6, 42.9, 15.8; HRMS *m/z* 400.1212 (M^+ [$C_{22}H_{17}ClN_6$ = 400.1203]).

Acknowledgment. We gratefully acknowledge pharmaceutical company unrestricted gift funds (M.J.R.) and Brigham Young University for financial support including a Roland K. Robins Graduate Research Fellowship (M.Z.). We thank Dr. Ireneusz Nowak for helpful discussions and for reviewing the manuscript.

Supporting Information Available: General experimental items, procedures, and characterization data for **2c**, **2f**, **2g**, **4a**, **4c**, **4f**, **6b**, **6d**, and **8b** and NMR spectra of compounds for which elemental analyses were not obtained. This material is available free of charge via the Internet at http://pubs.acs.org.

JO061759H