Facile Preparation of 2,6-Disubstituted Purines Using Solid-Phase Chemistry

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Screening small molecule libraries prepared by combinatorial chemistry methods has become an indispensable tool for discovering novel therapeutic leads. Many new and useful reactions have been applied to solid-phase chemistry,[1] but only one example involving the vast literature of purine chemistry.[2] Various physiological and pharmacological effects of purine analogs have been observed.[3] A recent disclosure showed that the purine derivative olomoucine (**1**) was a potent and selective inhibitor of a cyclin dependent kinase complex $p33^{cdk2}$/cyclin A (IC_{50} = 7 μM).[4] These protein kinases have generated much interest of late, considering their critical role in regulating the cell cycle.[5] Specific inhibitors of cyclin dependent kinases may have potential therapeutic utility in retarding tumor cell proliferation. This prompted us to investigate a method for generating a large and diverse set of purine analogs using solid-phase chemistry. In addition, this method was used to prepare olomoucine (**1**) in 62% yield over three steps.

Our approach to generating purine analogs using solid-phase chemistry is shown in Scheme 1. Two key facts guided our design: (1) the known purine tetrahydropyranyl (THP) protecting group[6] can be easily removed using mild acid and (2) a THP linker-based solid support[7] was recently disclosed by Ellman. The starting material used in Ellman's synthesis to prepare 3,4-dihydro-2*H*-pyran-2-methanol was no longer commercially available and motivated us to devise a new approach to this highly versatile linker. Lithium aluminum hydride reduction of 3,4-dihydro-2*H*-pyran-2-carboxylic acid, sodium salt gave essentially a quantitative yield of the alcohol **2** needed to prepare the THP linker. This alcohol could be purified by chromatography or distillation, but we found that similar results were obtained in the subsequent alkylation of the resin using the crude material. The crude alcohol was converted to its sodium salt using NaH in DMF at 25 °C for 30 min and then treated with Merrifield resin[8] in one portion to give the desired THP-linked resin **3**. We routinely performed this reaction on multigram quantities of Merrifield resin with excellent results regardless of the initial chlorine loading level. This reaction proceeded in quantitative yield as determined by elemental analysis.[9] Loading 2,6-dichloropurine onto this resin was accomplished using 0.5 equiv of camphorsulfonic acid in 1,2-dichloroethane at 65 °C for 16 h. Only 2 equiv of 2,6-dichloropurine were needed to give a 0.47 mmol/g loading level.[10] The excess 2,6-dichloropurine could be recovered and recycled by simple extraction and chromatography. Introducing the different substituents could be accomplished sequentially owing to the chlorine substituents' different reactivities to nucleophilic displacement. The 6-chloro position was the more reactive site and was easily displaced with 5 equiv of benzylamine and 5 equiv of triethylamine at 80 °C in 1-butanol after 3 h. The purity of the crude product was 98% as determined by HPLC. The 2-chloro substituent was much less reactive and required more severe reaction conditions. This was accomplished using the amine as a solvent and heating the resin at 150 °C for 2.5 h.[11] The severe reaction conditions demonstrate the THP-linked Merrifield resin's versatility. The final product was cleaved from the resin using a standard acidic cleavage protocol. Treating the resin with CH_2Cl_2:TFA (8:1) at 25 °C for 10 min and washing with methanol provided compound **7** in 90% yield for the two steps.

This reaction sequence gave consistently good yields and recoveries for a variety of examples as shown in Table 1. Both primary and secondary amines and anilines were employed with good results. A variety of substituents are tolerated in this reaction sequence (primary alcohols, phenols, amides, and imidazole) without interfering in the desired reaction pathway. A slightly modified protocol was used to introduce the alcohol and sulfonamide nucleophiles exemplified by compounds **11** and **15**. Generating the sodium salt of these nucleophiles with sodium hydride was required prior to treating with the resin.[12] Oxygen- and hydrazine-based nucleophiles could be successfully introduced into the 6-position of the purine core as exemplified by compounds **15** and **16**. Unfortunately, these substituents did not tolerate the subsequent step's elevated temperatures, and the desired 2-substituted purines **24** and **25** were not isolated.

The synthesis of olomoucine was completed (Scheme 1) by selective alkylation of the N-9 imidazole nitrogen of compound **7** using sodium hydride and methyl iodide to give the final product in 70% yield after chromatography.[13] Judicious choice of substituents at the 2- and

(1) Ellman, J. A. *Acc. Chem. Res.* **1996**, *29* (3), 132−43. Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1996**, 52 (13), 4527−54. Terret, N. K.; Gardner, M.; Gordon, D. W.; Kobylecki, R. J.; Steele, J. *Tetrahedron* **1995**, *51* (30), 8135−73. Gordon, E. M.; Barret, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. *J. Med. Chem.* **1994**, *37*, 1233−51.

(2) During the preparation of this paper, a library approach to purine analogs was published. See: Norman, T. C.; Gray, N. S.; Koh, J. T.; Schultz, P. G. *J. Am. Chem. Soc.* **1996**, *118*, 7430−1. For a comprehensive review of purine chemistry, see: Lister, J. H., Ed. *The Purines, Suppl. 1*; Wiley: Chichester, U.K., 1996.

(3) Hurst, D. T. *The Chemistry and Biology of Pyrimidines, Purines, and Pteridines*; Wiley: Chichester, U.K., 1980. Store, T. W., Ed. *Purines, Pharmacology and Physiological Roles*; Macmillan: London, 1985.

(4) Vesely, J.; Havlicek, L.; Strnad, M.; Blow, J.; Donella-Deana, A.; Pinna, L.; Letham, D.; Kato, J.; Detivaud, L.; Leclerc, S.; Meijer, L. *Eur. J. Biochem.* **1994**, *224*, 771−86. Glab, N.; Labidi, B.; Qin, L.-X.; Trehin, C.; Bergounioux, C.; Meijer, L. *FEBS Lett.* **1994**, *353* (2), 207−11. Mistelli, T.; Warren, G. *J. Cell Sci.* **1995**, *108*, 2715−27.

(5) Hartwell, L. H.; Kastan, M. B. *Science*, **1994**, *266*, 1821−28. Pines, J. *Semin. Cancer Biol.* **1994**, *5*, 305−13. Nigg, E. A. *Trends Cell Biol.* **1993**, *3*, 296−301. Sherr, C. S. *Cell* **1993**, *73*, 1059−65.

(6) Robins, R. K.; Godefroi, E. F.; Taylor, E. C.; Lewis, L. R.; Jackson, A. *J. Am. Chem. Soc.* **1961**, *83*, 2574.

(7) Thompson, L. A.; Ellman, J. A. *Terahedron Lett.* **1994**, *35* (50), 9333−6.

(8) Obtained from Advanced ChemTech (Louisville, KY) with a loading level of 0.76 mmol/g.

(9) No trace of chlorine was detected at a 100 ppm sensitivity level, indicating all resin bound chlorine was displaced as shown in Scheme 1.

(10) The loading level was determined by mass balance after cleavage of the compound from the resin using CH_2Cl_2:TFA (8:1).

(11) These are similar reaction conditions to those found in the original preparation of olomoucine. See: Parker, C.; Entsch, B.; Letham, D. *Phytochemistry* **1986**, *25*, 303−10. Hocart, C.; Letham, D.; Parker, C. *Phytochemistry* **1991**, *30*, 2477−86.

(12) 3-(Benzyloxy)benzyl alcohol was treated with NaH in THF at 25 °C for 30 min. Benzenesulfonamide was treated with NaH in DMA and heated to 80 °C for 45 min.

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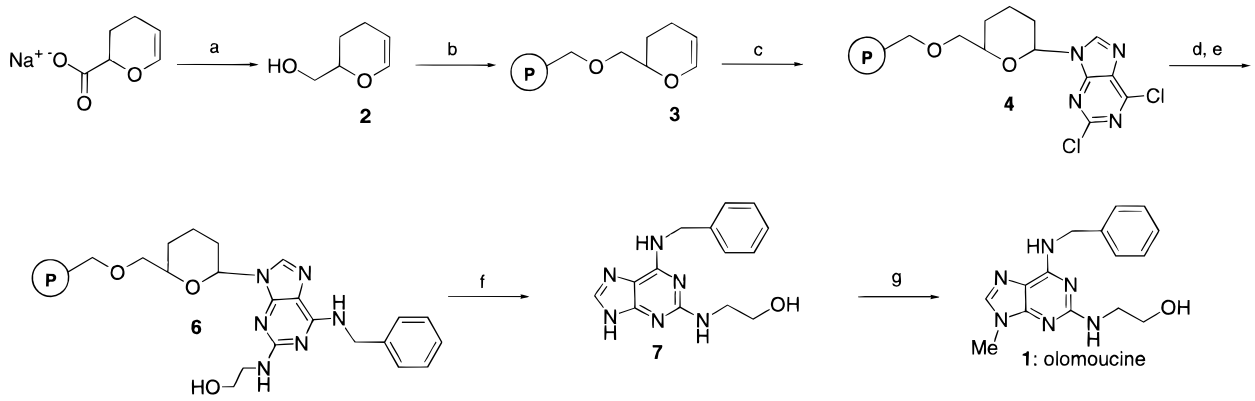
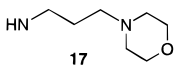
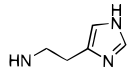
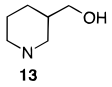
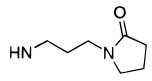
Scheme 1[a]



[a] Reagents and conditions: (a) LAH, THF, rt; (b) NaH, DMF, Merrifield resin, rt; (c) 2,6-dichloropurine, CSA, 1,2-dichloroethane, 65 °C; (d) benzylamine, *n*-BuOH, Et_3N, 80 °C; (e) ethanolamine, neat, 150 °C; (f) TFA:CH_2Cl_2, (1:8), rt; (g) NaH, MeI, rt.

Table 1.

R_1	yield[a] (%)	R_2	yield[a,b] (%)
8: $C_6H_5CH_2NH$	95 (97%)	**7**: $NHCH_2CH_2OH$	90 (92%)
		 **17**	90 (94%)
9: 3,4-$(HO)_2C_6H_3CH_2NH$	90 (97%)	 **18**	71 (91%)
10: 3-$MeOC_6H_3CH_2NH$	94 (99%)	**19**: $NHCH_2CH_2OH$	90 (95%)
11: $C_6H_5SO_2NH$	91 (94%)	**20**: $NHCH_2CH_2OH$	91 (89%)
12: 3-$O_2NC_6H_4CH_2NH$	94 (97%)	**21**: $NH(CH_2)_5OH$	81 (93%)
 **13**	96 (99%)	 **22**	53 (91%)
14: C_6H_5NH	90 (90%)	**23**: $NHCH_2CH_2OH$	85 (95%)
15: 3-benzyloxy-$C_6H_4CH_2O$	94 (95%)	**24**: $NHCH_2CH_2OH$	c
16: C_6H_5NHNH	92 (97%)	**25**: $NHCH_2CH_2OH$	c

[a] Crude yield based on 0.47 mmol/g loading level of 2,6-dichloropurine. Values in parentheses correspond to the crude product's purity by HPLC. [b] Crude yield for two-step protocol: 2-chloropurine displacement and acid cleavage from resin. [c] Desired product not isolated.

6-positions of the purine core should allow for selective introduction of other substituents at the 9-position, enhancing this approach's utility.

Using a solid-phase approach to these purine analogs was critical in obtaining good recoveries of the final product. In particular, these compounds are water soluble and have low R_f values on thin layer chromatography. Since the second displacement required using one of the reagents as solvent, it would be extremely difficult to purify the final product from the excess amine. The use of a solid support alleviates these purification problems because the excess amine was removed from the polymer bound purine by filtration and subsequent washings.

In summary, we presented a novel, solid-phase approach to generating diverse purine structures with the potential for creating combinatorial libraries of these biologically interesting compounds. The purine's 2- and 6-positions can be selectively differentiated to introduce a variety of nucleophiles. Once the products are cleaved from the resin, the 9-position can be further modified, introducing an additional element of diversity. Several other chemical manipulations of the 2- and 6-positions of purines are known.[14] These are currently under investigation and will be reported in due course.

Experimental Section

General. All reactions were carried out with continuous stirring under an atmosphere of dry nitrogen. Commercial reagents were used as received without additional purification. Merrifield resin was purchased from Advanced ChemTech, Louisville, KY (0.76 mmol Cl/g resin, 1% DVB, 100−200 mesh). THF was distilled from sodium benzophenone ketyl. ^1H NMR (300 MHz) spectra were recorded using tetramethylsilane as an internal standard. Melting points are uncorrected. TLC was performed on E. Merck 15719 silica gel plates. Flash chromatography was carried out using EM Science silica gel 60, 230−400 mesh. UV spectra were measured in 70% EtOH. High-pressure liquid chromatography (HPLC) was performed using a DYNAMX 300-A C_{18} column with UV detection at 240 nm. Elemental analysis was performed by Quantitative Technologies, Inc., Bound Brook, NJ.

3,4-Dihydro-2*H*-pyran-2-methanol (2). A suspension of 3,4-dihydro-2*H*-pyran-2-carboxylic acid, sodium salt (2.0 g, 13.3 mmol) in THF (10 mL), cooled to 0 °C on an ice bath, was treated with LAH (13.5 mL, 13.5 mmol, 1.0 M in THF) dropwise over 10 min. After the addition was complete, the cooling bath was removed and the reaction mixture was allowed to reach rt. After 30 min, the mixture was recooled to 0 °C and the reaction quenched by the slow addition of 1 N NaOH (2 mL). The mixture was diluted with ether (30 mL), and anhydrous $MgSO_4$ was added. After being stirred for 10 min, the mixture was filtered (Celite) and the solvent removed at reduced pressure. (*Caution! Product is volatile.*) The desired product was obtained as a clear oil and was used without further purification (1.45 g, 97%). **2**: NMR ($CDCl_3$) δ 6.3 (d, J = 6 Hz, 1 H), 4.6 (bs, 1 H), 3.8 (m, 1 H), 3.6 (bs, 2 H), 2.85 (s, 1 H), 2.0 (m, 2 H), 1.6 (m, 2 H); CIMS (NH_3) m/z 115 ($M + H^+$, 100).

(13) The compound was identical (mp, NMR, MS, UV, and HPLC) to a sample prepared according to ref 11.

(14) For Stille coupling reactions with chloropurines, see: Langli, G.; Gundersen, L.-L.; Rise, F. *Tetrahedron* **1996**, *52* (15), 5625−38. Gundersen, L.-L. *Terahedron Lett.* **1994**, *35* (19), 3153−58. For Heck coupling reactions with chloropurines, see: Koyama, S.; Kumazawa, Z.; Kashimura, N. *Nucleic Acids Res., Symp. Ser.* **1982**, *11*, 41−44.

((3,4-Dihydro-2*H*-pyran-2-ylmethyl)oxy)-Linked Merrifield Resin (3). A solution of 3,4-dihydro-2*H*-pyran-2-methanol **(2)** (0.75 g, 6.6 mmol) in DMF (15 mL) at rt was treated with NaH (0.28 g, 6.8 mmol, 60% suspension in oil) in one portion. After 30 min, Merrifield resin (3 g, 2.28 mmol, 0.76 mmol Cl/g) was added in one portion and the mixture stirred for 16 h. The reaction was quenched by the addition of water (1 mL), and the resin was collected on a Buchner funnel, washed with DMF (3 × 10 mL), methanol (3 × 10 mL), and CH_2Cl_2 (3 × 10 mL), and dried in a vacuum oven at 60 °C overnight to give the desired product **3** (3.0 g, 92%). Elemental analysis did not detect the presence of chlorine at a sensitivity level of 100 ppm.

Support Bound 2,6-Dichloropurine (4). A solution of 2,6-dichloropurine (0.29 g, 1.52 mmol), resin **3** (1.0 g, 0.76 mmol), and camphorsulfonic acid (0.08 g, 0.34 mmol) in 1,2-dichloroethane (10 mL) was stirred at 60 °C for 16 h. The mixture was filtered, and the resin was collected on a Buchner funnel, washed with CH_2Cl_2 (2 × 10 mL), DMF (3 × 10 mL), and CH_2Cl_2 (3 × 10 mL), and dried in a vacuum oven at 60 °C overnight to give the desired product **4** (1.13 g). The loading level of 2,6-dichloropurine was determined to be 0.47 mmol/g by gravimetric methods.

Support Bound 2-Chloro-6-(benzylamino)purine (5). A suspension of resin **4** (0.5 g, 0.235 mmol), benzylamine (0.13 mL, 1.18 mmol), and triethylamine (0.17 mL, 1.18 mmol) in 1-butanol (5 mL) was heated to 80 °C for 3 h. The mixture was cooled to rt and filtered, and the resin was washed with MeOH (3 × 10 mL) and CH_2Cl_2 (3 × 10 mL) and dried in a vacuum oven at 60 °C to give the desired product **5** (0.55 g).

2-Chloro-6-(benzylamino)purine (8). Resin **5** (0.1 g, 0.47 mmol) was suspended in CH_2Cl_2:TFA (8:1) (2 mL) and stirred for 10 min at rt. The solution was filtered and the resin washed with methanol (2 × 10 mL). The filtrate was concentrated at reduced pressure to give the crude product **8** as a foam (11.5 mg, 95%). An analytical sample was purified by chromatography (silica, 5% MeOH/CH_2Cl_2). **8**: mp 254−255 °C; NMR (DMSO-d_6) δ 13.1 (bs, 1 H), 8.75 (bs, 1 H), 8.1 (s, 1 H), 7.3 (m, 5 H), 4.6 (d, J = 6.8 Hz, 2 H); ESIMS m/z 260 (M + H^+, 100). Anal. Calcd for $C_{12}H_{10}N_5Cl$: C, 55.50; H, 3.88; N, 26.97. Found: C, 55.22; H, 3.78; N, 27.00.

Support Bound 2-[(2-Hydroxyethyl)amino]-6-(benzylamino)purine (6). A suspension of resin **5** (0.1 g, 0.047 mmol) in ethanolamine (0.5 mL) was heated to 150 °C for 2.5 h. The mixture was then cooled and filtered, and the resin was washed with MeOH (3 × 10 mL), DMF (3 × 10 mL), MeOH (3 × 10 mL), and CH_2Cl_2 (3 × 10 mL) and dried at 60 °C in a vacuum oven overnight to give the desired product **6** (0.1 g).

2-[(2-Hydroxyethyl)amino]-6-(benzylamino)purine (7). Resin **6** (0.1 g, 0.47 mmol) was subjected to the same acid cleavage protocol described for compound **8** to give the crude product **7** as a foam (8 mg, 90%). An analytical sample was purified by chromatography (silica, 10% MeOH/CH_2Cl_2). **7**: mp 184−186 °C; NMR (DMSO-d_6) δ 12.15 (bs, 1 H), 7.6 (s, 1 H), 7.3 (m, 5 H), 6.0 (bs, 1 H), 4.6 (m, 2 H), 3.4 (m, 2 H), 3.2 (m, 2 H); ESIMS m/z 285 (M + H^+, 100). Anal. Calcd for $C_{14}H_{16}N_6O$: C, 59.14; H, 5.67; N, 29.56. Found: C, 59.01; H, 5.78; N, 29.32.

2-[(2-Hydroxyethyl)amino]-6-(benzylamino)-9-methylpurine (Olomoucine) (1). A solution of purine **7** (20 mg, 0.07 mmol) in dimethylacetamide (1 mL) at rt was treated with sodium hydride (4 mg, 0.08 mmol, 60% oil dispersion) in one portion. After the solution was stirred for 30 min, methyl iodide (8 μL, 0.08 mmol) was added. After the reaction mixture was stirred an additional 30 min, the reaction was quenched with MeOH (40 μL) and the solvent removed at reduced pressure. Chromatography (silica, 2.5−5% MeOH/CH_2Cl_2) gave the desired product as a white solid (14.5 mg, 70%). **1**: mp 125−126 °C (lit.[11] mp 125−126 °C); λ_{max} 232 (ϵ 23 260), 290 (ϵ 12 878); NMR (DMSO-d_6) δ 7.6 (s, 1 H), 7.3 (m, 5 H), 6.1 (bs, 1 H), 4.6 (m, 2 H), 3.5 (s, 3 H), 3.45 (m, 2 H), 3.25 (m, 2 H); ESIMS m/z 299 (M + H^+, 100). Anal. Calcd for $C_{15}H_{18}N_6O$: C, 60.39; H, 6.08; N, 28.17. Found: C, 60.32; H, 6.01; N, 27.92.

2-Chloro-6-[(3,4-dihydroxybenzyl)amino]purine (9): mp 205−208 °C; NMR (CD_3OD) δ 8.0 (s, 1 H), 6.8 (s, 1 H), 6.75 (s, 2 H), 4.6 (bs, 2 H); ESIMS m/z 292 (M + H^+, 100). Anal. Calcd for $C_{12}H_{10}N_5O_2Cl$: C, 49.41; H, 3.46; N, 24.01. Found: C, 49.49; H, 3.55; N, 23.80.

2-Chloro-6-[(3-methoxybenzyl)amino]purine (10): mp 238−239 °C; NMR (DMSO-d_6) δ 13.1 (bs, 1 H), 8.7 (bs, 1 H), 8.0 (s, 1 H), 7.2 (t, J = 8 Hz, 1 H), 6.9 (m, 1 H), 6.75 (d, J = 8 Hz, 2 H), 4.6 (bs, 2 H), 3.7 (s, 3 H); ESIMS m/z 290 (M + H^+, 100). Anal. Calcd for $C_{13}H_{12}N_5OCl$: C, 53.89; H, 4.17; N, 24.17. Found: C, 53.52; H, 3.88; N, 23.81.

2-Chloro-6-[(phenylsulfonyl)amino]purine (11): amorphous solid; NMR (DMSO-d_6) δ 13.2 (bs, 1 H), 8.4 (bs, 1 H), 8.1 (s, 1 H), 8.0 (d, J = 8 Hz, 2 H), 7.6 (m, 3 H); ESIMS m/z 310 (M + H^+, 100); HRMS calcd for $C_{11}H_9N_5O_2SCl$ (M + H^+) 310.0165, found 310.0144.

2-Chloro-6-[(3-nitrobenzyl)amino]purine (12): mp >300 °C; NMR (DMSO-d_6) δ 13.1 (bs, 1 H), 8.9 (bs, 1 H), 8.2 (s, 1 H), 8.1 (m, 2 H), 7.8 (d, J = 8 Hz, 1 H), 7.6 (t, J = 6.5 Hz, 1 H), 4.8 (bs, 2 H); ESIMS m/z 305 (M + H^+, 100). Anal. Calcd for $C_{12}H_9N_6O_2Cl$: C, 47.30; H, 2.98; N, 27.58. Found: C, 47.06; H, 3.20; N, 27.55.

2-Chloro-6-[3-(hydroxymethyl)-1-piperidyl]purine (13): mp 206−207 °C; NMR (DMSO-d_6) δ 13.1 (bs, 1 H), 8.1 (s, 1 H), 4.55 (t, J = 5.5 Hz, 2 H), 3.3 (m, 4 H), 1.8−1.2 (m, 5 H); ESIMS m/z 268 (M + H^+, 100). Anal. Calcd for $C_{11}H_{14}N_5OCl$: C, 49.35; H, 5.27; N, 26.16. Found: C, 49.31; H, 5.10; N, 26.49.

2-Chloro-6-(phenylamino)purine (14): mp 320 °C dec; NMR (DMSO-d_6) δ 10.15 (bs, 1 H), 8.3 (s, 1 H), 7.8 (d, J = 8 Hz, 1 H), 7.35−7.3 (m, 2 H), 7.1−7.0 (m, 2 H); ESIMS m/z 246 (M + H^+, 100); HRMS calcd for $C_{11}H_9N_5Cl$ (M + H^+) 246.0546, found 246.0543. Anal. Calcd for $C_{11}H_8N_5Cl$: C, 53.78; H, 3.28; N, 28.51. Found: C, 53.88; H, 3.44; N, 28.36.

2-Chloro-6-[[3-(benzyloxy)benzyl]oxy]purine (15): mp 161−162 °C; NMR ($CDCl_3$) δ 11.5 (bs, 1 H), 8.1 (s, 1 H), 7.5−7.1 (m, 8 H), 6.95 (d, J = 8 Hz, 1 H), 5.6 (s, 2 H), 5.1 (s, 2 H); ESIMS m/z 367 (M + H^+, 100). Anal. Calcd for $C_{19}H_{15}N_4O_2Cl$: C, 62.21; H, 4.12; N, 15.27. Found: C, 62.02; H, 3.80; N, 15.05.

2-Chloro-6-(phenylhydrazino)purine (16): mp 249−250 °C dec; NMR (DMSO-d_6) δ 13.2 (bs, 1 H), 8.3 (s, 1 H), 7.6 (d, J = 7 Hz, 1 H), 7.4 (t, J = 6 Hz, 1 H), 7.2 (m, 3 H), 6.9 (d, J = 7 Hz, 1 H), 6.8 (d, J = 7 Hz, 1 H); ESIMS m/z 261 (M + H^+, 100). Anal. Calcd for $C_{11}H_9N_6Cl$: C, 50.68; H, 3.48; N, 32.24. Found: C, 50.31; H, 3.10; N, 32.59.

2-[[3-(1,4-oxazin-4-yl)propyl]amino]-6-(benzylamino)purine (17): amorphous solid; NMR (CD_3OD) δ 8.0 (bs, 1 H), 7.3 (m, 5 H), 3.8 (bs, 2 H), 3.5 (m, 4 H), 3.3−3.1 (m, 8 H), 2.0 (m, 2 H); ESIMS m/z 368 (M + H^+, 100); HRMS calcd for $C_{19}H_{26}N_7O$ (M + H^+) 368.2199, found 368.2190.

2-[[2-(1*H*-4-Imidazolyl)ethyl]amino]-6-[(3,4-dihydroxybenzyl)amino]purine (18): amorphous solid; NMR (CD_3OD) δ 8.85 (s, 1 H), 8.8 (s, 1 H), 8.2 (bs , 1 H), 7.5 (m, 1 H), 7.3 (s, 1 H), 6.85 (s, 1 H), 6.75 (s, 2 H), 4.7 (s, 2 H), 3.8 (m, 2 H), 3.1 (m, 2 H); ESIMS m/z 367 (M + H^+, 23), 184 (M + 2H^+, 100); HRMS calcd for $C_{17}H_{18}N_8O_2$ (M + H^+) 367.1631, found 367.1620.

2-[(2-Hydroxyethyl)amino]-6-[(3-methoxybenzyl)amino]-purine (19): mp 161−162 °C; NMR (DMSO-d_6) δ 12.15 (bs, 1 H), 7.6 (s, 1 H), 7.2 (t, J = 8 Hz, 1 H), 6.8 (m, 2 H), 6.75 (m, 1 H), 6.0 (m, 1 H), 4.6 (m, 3 H), 3.7 (s, 3 H), 3.45 (m, 2 H), 3.2 (m, 2 H); ESIMS m/z 315 (M + H^+, 100). Anal. Calcd for $C_{15}H_{18}N_6O_2$: C, 57.31; H, 5.77; N, 26.74. Found: C, 57.22; H, 5.78; N, 27.01.

2-[(2-Hydroxyethyl)amino]-6-[(phenylsulfonyl)amino]-purine (20): amorphous solid; NMR (CD_3OD) δ 8.6 (bs, 1 H), 8.1 (s, 1 H), 8.0 (s, 1 H), 7.5 (m, 5 H), 3.7 (m, 2 H), 3.5 (m, 2 H); ESIMS m/z 335 (M + H^+, 100); HRMS calcd for $C_{13}H_{15}N_6O_3S$ (M + H^+) 335.0926, found 335.0901.

2-[(5-Hydroxypentyl)amino]-6-[(3-nitrobenzyl)amino]-purine (21): amorphous solid; NMR (DMSO-d_6) δ 12.15 (bs, 1 H), 8.2 (s, 1 H), 8.05 (d, J = 8 Hz, 1 H), 7.9 (m, 1 H), 7.75 (d, J = 8 Hz, 1 H), 7.6 (s, 1 H), 6.2 (bs, 1 H), 4.3 (s, 2 H), 3.2 (m, 4 H), 1.6−1.2 (m, 6 H); ESIMS m/z 372 (M + H^+, 100); HRMS calcd for $C_{17}H_{22}N_7O_3$ (M + H^+) 372.1784, found 372.1759.

2-[[3-(2-Oxopyrrolidinyl)propyl]amino]-6-[3-(hydroxymethyl)-1-piperidyl]purine (22): amorphous solid; NMR (CD_3OD) δ 7.6 (s, 1 H), 3.5−3.3 (m, 10 H), 2.4 (t, J = 6 Hz, 2 H), 2.0 (m, 2 H), 1.9−1.4 (m, 9 H); ESIMS m/z 374 (M + H^+, 100); HRMS calcd for $C_{18}H_{28}N_7O_2$ (M + H^+) 374.2304, found 374.2300.

2-[(2-Hydroxyethyl)amino]-6-(phenylamino)purine (23): mp 230−231 °C; NMR (DMSO-d_6) δ 12.35 (bs, 1 H), 9.3 (s, 1 H), 8.0 (m, 2 H), 7.8 (s, 1 H), 7.25 (m, 2 H), 7.0−6.9 (m, 1 H), 6.4 (bs, 1 H), 3.5 (m, 2 H), 3.2−3.05 (m, 2 H); ESIMS m/z 270 (M + H^+, 100); HRMS Calcd for $C_{13}H_{14}N_6O$ (M + H^+) 270.1307, found 270.1306.

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