2-Amino-4-oxo-6-substituted-pyrrolo[2,3-*d*]pyrimidines as Potential Inhibitors of Thymidylate Synthase [1]

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Classical, antifolate inhibitors of thymidylate synthase often suffer from a number of potential disadvantages when used as antitumor agents. These include impaired uptake due to an alteration of the active transport system required for cellular uptake, as well as the formation of long acting, non-effluxing polyglutamates *via* folypolyglutamate synthetase, which are responsible for toxicity to normal cells. To overcome some of the disadvantages of classical thymidylate synthase inhibitors, there has been considerable interest in the synthesis and evaluation of nonclassical inhibitors, which could enter cells *via* passive diffusion and are not substrates for folypolyglutamate synthetase. A series of eight nonclassical 6-substituted 2-amino-4-oxo-pyrrolo[2,3-*d*]pyrimidines **2a-2h** were designed as potential inhibitors of thymidylate synthase. The synthesis of the target compounds **2a-2h** was achieved *via* regioselective iodination at the 6-position of **5**, palladium-catalyzed coupling with the appropriate phenylacetylenes, reduction of the C8-C9 triple bond followed by saponification. Preliminary biological results indicated that none of the target compounds showed inhibitory activities against thymidylate synthase from *Escherichia coli*, *Lactobacillus casei*, rat or human thymidylate synthase at the concentrations tested. None of the target compounds showed inhibitory activity against dihydrofolate reductase from *Escherichia coli, Lactobacillus casei*, rat or human at 3.0 x 10^{-5} *M*. However, 50% inhibition of dihydrofolate reductase from *Pneumocystis carinii* and from *Toxoplasma gondii* was achieved with compound **2d** and with compound **2g** at 3.0 x 10^{-5} *M*.

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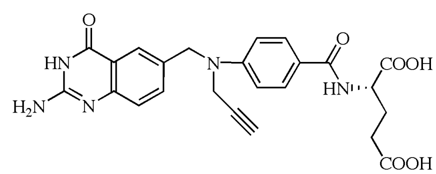
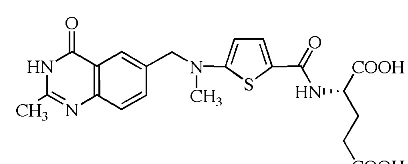
Thymidylate synthase catalyzes a two-step conversion of deoxyuridylate (dUMP) to deoxythymidylate (dTMP) utilizing 5,10-methylenetetrahydrofolate (5,10-CH_2-FH_4) as the cofactor [2]. This enzyme is unique among those which utilize tetrahydrofolate cofactors in that 5,10-methylenetetrahydrofolate serves the dual function of both a one-carbon donor and reductant, by concomitant transfer of its methylene group and the 6-hydrogen atom to form the methyl group at the 5-position of deoxythymidylate. In the process, the cofactor is oxidized to 7,8-dihydrofolate. Tetrahydrofolate is regenerated from 7,8-dihydrofolate by dihydrofolate reductase in a NADPH-dependent reaction. The conversion of 7,8-dihydrofolate to deoxythymidylate catalyzed by thymidylate synthase represents the sole *de novo* source of deoxythymidylate, and hence thymidylate synthase plays a pivotal role in DNA biosynthesis and cell replication. In the absence of an exogenous supply of thymidine, inhibition of thymidylate synthase leads to "thymineless cell death" [3,4]. Thus inhibition of thymidylate synthase is an attractive target for the development of antitumor agents.

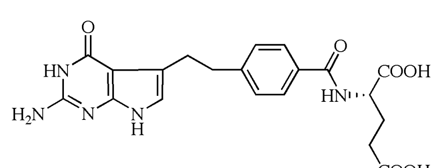
Thymidylate synthase inhibitors that are clinically used as antitumor agents include 5-fluorouracil,[5] a deoxyuridylate substrate analogue which is rapidly metabolized within the cell to a number of fluorinated nucleotides. One of these metabolites, 5-fluorodeoxyuridine monophosphate (FdUMP) is a potent inhibitor of thymidylate synthase [6]. 5-Fluorouracil also has other biochemical sites of action which result from nucleotide metabolites of 5-fluorouracil being incorporated into RNA [7]. Among the folate-based thymidylate synthase inhibitors that were synthesized and entered clinical trials the first was CB3717, which displayed promising clinical activity [8-10]. However, its development was abandoned because of sporadic and unpredictable nephrotoxicity and myelotoxocity. A successor of CB3717, ZD1694, a clinically used antitumor agent in Europe (Tomudex^{TM}), [11] has been shown to be non-nephrotoxic [12] and is currently used for the treatment of metastatic colorectal cancer. LY231514, also a thymidylate synthase inhibitor, has entered clinical trials and is currently in Phase III as an antitumor agent.



CB3717



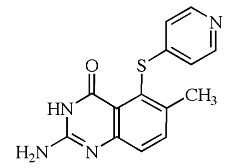
ZD1694



LY231514

All of the folate-based classical antifolates contain a terminal glutamate moiety. A major drawback of these classical antifolates is that they enter cells *via* the reduced folate uptake system, which when impaired can lead to drug resistance [13-16]. In addition the antitumor activities of classical thymidylate synthase inhibitors are, in part, determined by their ability to function as substrates of the enzyme folypolyglutamate synthetase (FPGS) [17,18]. Although polyglutamylation is necessary for the cytotoxicity to tumor cells, it has also been implicated as a possible cause of detrimental side effects, such as renal and hepatic toxicities in the host. These toxicities arise because of their polyionic nature which allows retention in normal cells [19]. The problem of tumor resistance of classical antifolates which is, in part, a result of low or defective folypolyglutamate synthetase activity is also a potential limitation of these classical antifolates that depend on polyglutamylation for their antitumor effects [20-22].

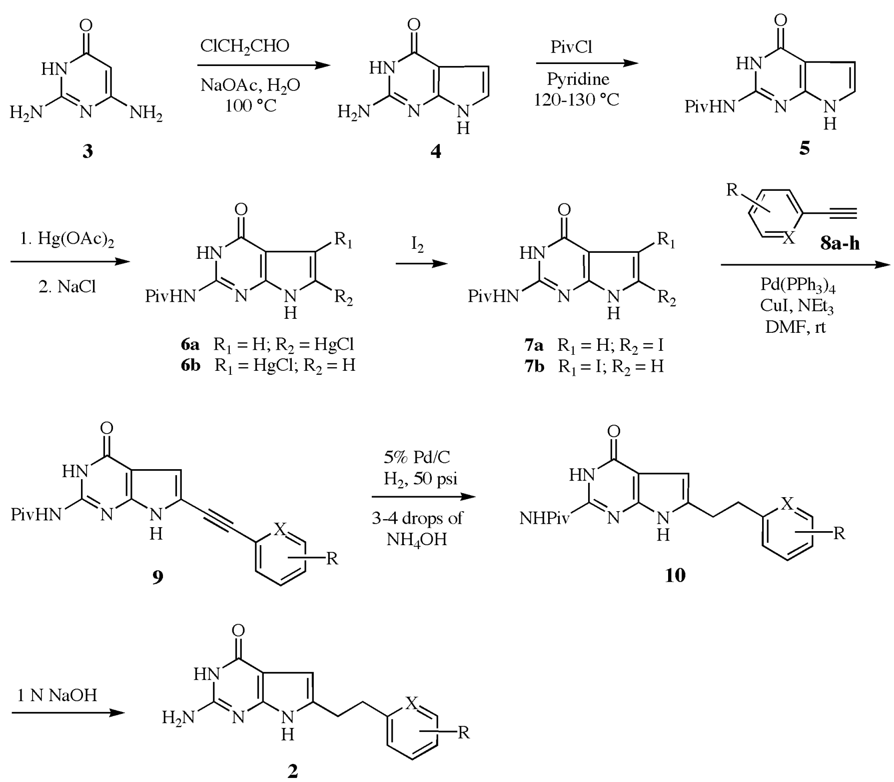
To circumvent these disadvantages associated with classical antifolates, there has recently been considerable interest in lipophilic, nonclassical antifolates as thymidylate synthase inhibitors which lack the L-glutamic acid side chain found in classical antifolates thus allowing for passive uptake of these inhibitors, independent of the folate transport system(s) [23-27]. Nolatrexate dihydrochloride (Thymitaq^{TM}, AG337), a lipophilic inhibitor of thymidylate synthase, was designed using X-ray crystallographic structures and molecular modeling, and is the first potent lipophilic thymidylate synthase inhibitor (human thymidylate synthase IC_{50} = 3.4 x 10^{-7} *M*) currently in clinical trials [23].



AG337

Molecular modeling of the 6-5 ring-fused analogues superimposed on 6-6 ring-fused analogues indicated that the 5-substituents are closely positioned in both ring systems and the 6-substituent of the 6-5 system lies in between the 6- and 7- substituent of the 6-6 system (Figure 1) [28]. Examples of potent thymidylate synthase inhibitors in the 5-substituted 6-6 system, include AG337 [23] and in 5-substituted 6-5 systems, LY231514 [29]. The

Scheme 1



2a R = H; X = CH **2b** R = *p*-CH_3; X = CH
2c R = *p*-OCH_3; X = CH **2d** R = *o*-Cl; X = CH
2e R = H; X = N **2f** R = 2',3'-C_4H_4; X = CH
2g R = 3',4'-C_4H_4; X = CH **2h** R = 2',5'-diOMe; X = CH

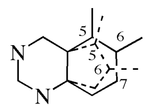
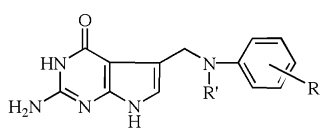


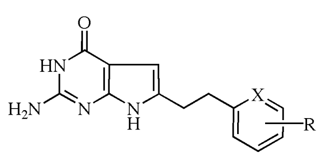
Figure 1. Superimposition of 6-6 fused ring system with 6-5 fused ring system (dash line)

6-6 fused systems that have been found to be potent inhibitors of thymidylate synthase are usually 6-substituted [30]. A recent report by Gangjee *et al.*[27] showed that a series of 5-substituted nonclassical analogues **1** were inactive against thymidylate synthase and were also poor inhibitors of *Pneumocystis carinii* dihydrofolate reductase and rat liver dihydrofolate reductase. It was therefore of interest to synthesize 6-substituted analogues in the 6-5 fused system to mimic the 6-substituted 6-6 fused system as inhibitors of thymidylate synthase. With these objectives in mind, we synthesized analogues **2a-2h**.

The syntheses of analogues of **2a-2h** were envisioned through the formation of the key intermediate **7a** which was initially reported by Taylor *et al.* [31] (Scheme 1). Using a method similar to that reported by Secrist and Liu, [32] intermediate **4** was synthesized from commercially available 2,4-diamino-6-hydroxypyrimidine **3** and chloroacetaldehyde in sodium acetate-water solution. The cyclocondensation was regiospecific and afforded **4** in 82% yield. Due to the poor solubility of **4** in organic solvent, the 2-amino group was pivaloyated using pivaloyl chloride in the presence of pyridine, which resulted in the formation of **5**. Chloromercuration of **5** was carried out by adding mercuric acetate in glacial acetic acid, followed by the addition of saturated sodium chloride solution. The precipitated white solid was filtered and washed thoroughly with water to give a 10:1 mixture of the 6-chloromercuri derivative **6a** and 5-chloromercuri derivative **6b** in 50% overall yield. The resulting mixture of chloromercuri derivatives was treated with iodine in dichloromethane to afford the corresponding iodo derivatives **7a** and **7b** from which the desired 6-iodo compound **7a** was readily separated by column chromatography in 64% yield.



1 (R' = H; CH_3)

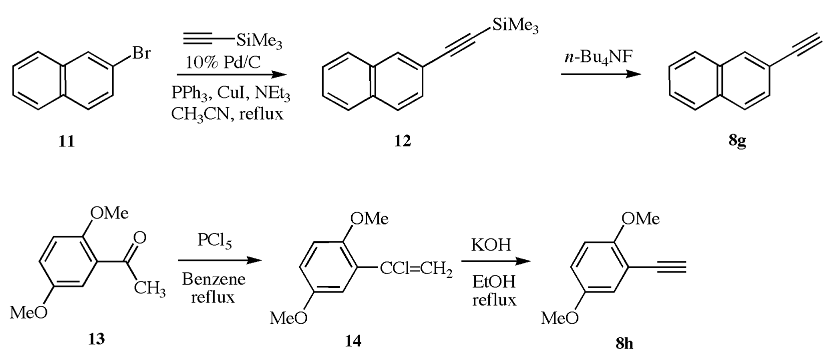


2

2a R = H; X = CH **2b** R = *p*-CH_3; X = CH
2c R = *p*-OCH_3; X = CH **2d** R = *o*-Cl; X = CH
2e R = H; X = N **2f** R = 2',3'-C_4H_4; X = CH
2g R = 3',4'-C_4H_4; X = CH **2h** R = 2',5'-diOMe; X = CH

The next step was the Sonogashira coupling reaction [33] of **7a** with an appropriately substituted phenylacetylene. Of the desired phenylacetylenes necessary for the Sonogashira reaction, only phenylacetylene **8a**, *p*-methylphenylacetylene **8b**, *p*-methoxyphenylacetylene **8c**, *o*-chlorophenylacetylene **8d** and 2-ethynylpyridine **8e** were commercially available. 1-Ethynylnaphthalene **8f**, 2-ethynylnaphthalene **8g** and (2,5-dimethyoxyphenyl)-ethyne **8h** were synthesized. Compounds **8f** and **8g** were synthesized using the method reported by Guzman *et al.* [34] using a palladium charcoal-catalyzed coupling reaction which was the most convenient and economical for large-scale synthesis of the various available methods. Thus 2-bromonaphthalene **11** was coupled with trimethysilylacetylene in the presence of palladium charcoal, triphenylphosphine and copper(I) iodide to afford **12** in 63% yield (Scheme 2). Intermediate **12** was readily desilylated by stirring with a 1 *M* solution of a tetra-*n*-butylammonium fluoride to afford the terminal acetylene **8h** in almost quantitative yield. Compound **8f** was also prepared in a similar method. An alternate method [35] from commercially available (2,5-dimethoxyphenyl)acetone **13** which reacted with phosphorous pentachloride followed by treat-

Scheme 2



ment with potassium hydroxide afforded **8h** in 65% yield (over two steps).

With both **7a** and **8a-8h** in hand, intermediates **9a-9h** were synthesized *via* palladium-catalyzed coupling reactions in the presence of tetrakis(triphenylphosphine)-palladium(0), copper(I) iodide and triethylamine. The desired products **9a-9h** were separated and isolated by carefully increasing the polarity of the mobile phase during flash chromatography. Reduction of the C8-C9 triple bonds of **9a-9h** were accomplished by hydrogenation at 50 psi using 5% palladium on charcoal as catalyst, along with 3-4 drops of concentrated ammonium hydroxide to prevent reduction of the pyrrole ring [36]. Finally, the depivaloylation of the 2-amino group of **10a-10h** were accomplished with 1 *N* sodium hydroxide to afford **2a-2h** in yields ranging from 44-80%.

Compounds **2a-2h** were evaluated as inhibitors against thymidylate synthase from *Escherichia coli*, *Lactobacillus casei*, rat and human [37]. None of the target compounds inhibited any of the thymidylate synthase at the concentrations tested (>1.0 x 10^{-5} *M*). These results along with observations reported for analogues of general structure **1** suggest that nonclassical analogues with a two-atom side chain substituent at the 5- or 6-position of 2-amino-4-oxo-pyrrolo[2,3-*d*]pyrimidine systems are not conducive to thymidylate synthase inhibitory activity. However, 50% inhibition of dihydrofolate reductase from *Pneumocystis carinii* and from *Toxoplasma gondii* was achieved with **2d** and with **2g** as well as with *Escherichia coli* (**2c**) and with *Toxoplasma gondii* (**2a**) (Table 1). None of the target compounds reached the IC_{50} level with human dihydrofolate reductase (Table 1).

EXPERIMENTAL

All evaporations were carried out *in vacuo* with a rotary evaporator. Analytical samples were dried *in vacuo* (0.2 mmHg) in an Abderhalden drying apparatus over P_2O_5 and refluxing ethanol. Thin layer chromatography (TLC) was performed on silica gel plates with fluorescent indicator. Spots were visualized by UV light (254 and 365 nm). All analytical samples were homogeneous on TLC in at least two different solvent systems. Purification by column and flash chromatography was carried out using Merck silica gel 60 (200-400 mesh). The amount (weight) of silica gel for column chromatography was in the range of 50-100 times the amount (weight) of the crude compounds being separated. Columns were dry packed unless specified otherwise. Solvent systems are reported as volume percent mixture. Melting points were determined on a Mel-Temp II melting point apparatus with a digital thermometer and are uncorrected. ^{1}H nmr spectra were recorded on a Bruker WH-300 (300 MHz) nmr spectrometer. The chemical shift (δ) values are reported as parts per million (ppm) relative to tetramethylsilane as internal standard; s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet, exch = protons exchangeable by addition of D_2O. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA. Elemental compositions were within ± 0.4% of the calculated values. Fractional moles of water or organic solvents frequently found in some analytical samples of antifolates could not be removed despite 24 hours of drying *in vacuo* and were confirmed, where possible, by their presence in the ^{1}H nmr spectrum. All solvents and chemicals were purchased from Aldrich Chemical Co. and Fisher Scientific and were used as received except anhydrous solvents, which were freshly dried in the laboratory.

2-(Naphthyl)trimethylsilylacetylene (**12**).

A mixture of 2-bromonaphthalene **11** (2.07 g, 10.0 mmol), trimethylsilylacetylene (1.03 g, 10.5 mmol), 10% palladium on charcoal (0.43 g, 0.4 mmol), triphenylphosphine (0.42 g, 1.6 mmol), copper iodide (0.08 g, 1.6 mmol) and triethylamine (25

Table 1

Inhibition of Dihydrofolate Reductases from *Escherichia coli, Pneumocystis carinii, Toxoplasma gondii* and Human by Compounds **2a-2h**.

	IC_{50} M			
Compound	E. coli [a]	P. carinii [b]	T. gondii [c]	Human [d]
2a	> 3.9 x 10^{-5} (0) [e]	> 1.9 x 10^{-5} (20)	3.9 x 10^{-5}	> 3.9 x 10^{-5} (0)
2b	> 3.7 x 10^{-5} (0)	> 1.8 x 10^{-5} (24)	> 3.7 x 10^{-5} (23)	> 3.7 x 10^{-5} (0)
2c	3.7 x 10^{-5}	> 1.8 x 10^{-5} (16)	> 3.7 x 10^{-5} (0)	> 3.7 x 10^{-5} (0)
2d	> 3.4 x 10^{-5} (0)	2.0 x 10^{-5}	3.4 x 10^{-5}	> 3.4 x 10^{-5} (0)
2e	> 3.8 x 10^{-5} (0)	> 1.9 x 10^{-5} (17)	> 3.8 x 10^{-5} (0)	> 3.8 x 10^{-5} (20)
2f	> 3.3 x 10^{-5} (0)	> 1.7 x 10^{-5} (17)	> 3.3 x 10^{-5} (26)	> 3.3 x 10^{-5} (16)
2g	> 3.3 x 10^{-5} (0)	> 1.7 x 10^{-5}	3.3 x 10^{-5}	> 3.3 x 10^{-5} (31)
2h	> 3.0 x 10^{-5} (0)	> 1.5 x 10^{-5} (0)	> 3.0 x 10^{-5} (21)	> 3.0 x 10^{-5} (19)
Trimethoprim	2.0 x 10^{-8}	1.5 x 10^{-5}	3.4 x 10^{-6}	3.4 x 10^{-4}
Methotrexate	6.0 x 10^{-9}	1.1 x 10^{-9}	2.2 x 10^{-8}	2.2 x 10^{-8}
Trimetrexate	7.0 x 10^{-9}	1.0 x 10^{-8}	5.1 x 10^{-9}	1.8 x 10^{-8}

[a] Kindly provided by Dr. R. L. Blakley, St. Jude Children's Hospital, Memphis, TN. [b] Kindly provided by Dr. D. Borhani, Southern Research Institute, Birmingham, AL. [c] Kindly provided by Dr. D. V. Santi, University of California, San Francisco, CA. [d] Kindly provided by Dr. J. H. Freisheim, Medical College of Ohio, Toledo, OH. [e] Numbers in parenthese indicate the % inhibition at the given concentration.

mL) in dry acetonitrile (15 mL) were heated at reflux under nitrogen for 24 hours. After cooling, the reaction mixture was filtered through a celite pad and the solid washed with methylene chloride. Silica gel (10 g) was added to the filtrate, and the solvent evaporated to afford a plug. The silica gel plug obtained was loaded onto a silica gel column and eluted with hexanes followed by crystallization from hexanes to afford 1.40 g (63%) of **12** as a pale yellow solid: ^{1}H nmr ($CDCl_3$): δ 0.29 (s, 9 H, $Si(CH_3)_3$), 7.49 (m, 3 H, $C_{10}H_7$), 7.77 (m, 3 H, $C_{10}H_7$), 7.99 (s, 1 H, $C_{10}H_7$).

2-Ethynylnaphthalene (**8g**).

To a solution of **12** (2.2 g, 10.0 mmol) in THF (15 mL) was added a 1 *M* solution of tetrabutylammonium fluoride in THF (3 mL, 3.0 mmol), and the solution was stirred under nitrogen at room temperature for 2 hours. Silica gel (10 g) was added, and the solvent evaporated to afford a plug which was loaded onto a silica gel column and eluted with hexanes. Fractions containing the product (TLC) were pooled and the solvent evaporated to afford 1.2 g (81%) of **8f** as a white solid: mp 39-40.5 °C (lit.,[34] no mp reported); ^{1}H nmr (DMSO-d_6): δ 4.29 (s, 1 H, CH), 7.51-7.57 (m, 3 H, $C_{10}H_7$), 7.91-7.94 (m, 3 H, $C_{10}H_7$), 8.11 (s, 1 H, $C_{10}H_7$).

(2,5-Dimethoxyphenyl)ethyne (**8h**).

A solution of **13** (6.25 g, 35.0 mmol) in dry benzene (5 mL) was added dropwise with stirring to phosphorous pentachloride (3.98 g, 18.5 mmol) in dry benzene (15 mL) and the initial exothermic reaction was allowed to subside. The mixture was then heated to reflux for 5 hours to complete the reaction. The reaction mixture was cooled and poured into water (40 mL). The organic material was extracted into ether and the ether extracts were thoroughly washed with brine, separated and dried over $MgSO_4$. Evaporation and chromatography with 1:4 methylene chloride/hexanes on silica gel afforded 5.60 g (80%) of **14** (1-chloro-1-(2,5-dimethoxyphenyl)ethane) which was used without further purification. To **14** (5.60 g, 28.2 mmol) was added a solution of potassium hydroxide (2.30 g, 39.0 mmol) in ethanol (25 mL) and the resulting solution was refluxed for 48 hours and then cooled. After dilution with water (40 mL), the product was extracted into ether and the ether extracts dried over $MgSO_4$. Silica gel (10 g) was added to the organic solvent, and the solvent evaporated to afford a plug, which was loaded onto a silica gel column and eluted with 1:4 methylene chloride/hexanes. Fractions containing the product (TLC) were pooled and the solvent evaporated to afford 3.28 g (81%) of **8h** as a brown solid: mp 38-40 °C (lit., [35] mp 39-40 °C); ^{1}H nmr ($CDCl_3$): δ 3.30 (s, 1 H, CH), 3.78 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 6.78-7.02 (m, 3 H, C_6H_3).

General Procedure for the Synthesis of Compounds **9a**-**9h**.

To a 50-mL round-bottom flask covered with aluminum foil were added **7a**, the appropriate (substituted)phenylacetylene **8a**-**8h**, copper(I) iodide and tetrakis(triphenyl phosphine)palladium (0) dissolved in anhydrous DMF, followed by the addition of triethylamine. The dark brown solution was stirred at room temperature under nitrogen for 3 days. The solvents were removed *in vacuo* and the crude residue was flash chromatographed on silica gel and eluted with 1.5% MeOH in $CHCl_3$ to afford the product.

2-Pivaloylamino-4-oxo-6-phenylethynylpyrrolo[2,3-*d*]pyrimidine (**9a**).

Using the general procedure described above, **7a** (0.12 g, 0.33 mmol), phenylacetylene **8a** (0.05 g, 0.50 mmol), copper(I) iodide (0.01 g, 0.07 mmol), tetrakis(triphenyl phosphine)palladium (0) (0.04 g, 0.03 mmol) and triethylamine (0.5 mL) afforded 0.05 g (45%) of **9a** as a white solid: mp >310 °C (dec); ^{1}H nmr (DMSO-d_6): δ 1.25 (s, 9 H, $C(CH_3)_3$), 6.79 (s, 1 H, 5-H), 7.55 (m, 5 H, C_6H_5), 10.99 (s, 1 H, 2-N*H*Piv or 3-NH, exch), 11.96 (s, 1 H, 2-N*H*Piv or 3-NH, exch), 12.25 (bs, 1 H, 7-NH, exch).

Anal. Calcd. For $C_{19}H_{18}N_4O_2$•$0.3H_2O$: C, 67.16; H, 5.52; N, 16.49. Found: C, 67.23; H, 5.49; N, 16.40.

2-Pivaloylamino-4-oxo-6-[(*p*-methylphenyl)ethynyl]pyrrolo-[2,3-*d*]pyrimidine (**9b**).

Using the general procedure described above, **7a** (0.12 g, 0.33 mmol), *p*-methylphenylacetylene **8b** (0.17 g, 1.5 mmol), copper(I) iodide (0.04 g, 0.20 mmol), tetrakis(triphenyl phosphine)palladium (0) (0.01 g, 0.07 mmol) and triethylamine (0.5 mL) afforded 0.06 g (52%) of **9b** as a white solid: mp >250 °C (dec); ^{1}H nmr (DMSO-d_6): δ 1.24 (s, 9 H, $C(CH_3)_3$), 2.34 (s, 3 H, 4'-CH_3), 6.76 (s, 1 H, 5-H), 7.24 (d, 2 H, J = 8.0 Hz, C_6H_4), 7.44 (d, 2 H, J = 8.0 Hz, C_6H_4), 10.97 (s, 1 H, 2-N*H*Piv or 3-NH, exch), 11.95 (s, 1 H, 2-N*H*Piv or 3-NH, exch), 12.20 (bs, 1 H, 7-NH, exch).

Anal. Calcd. For $C_{20}H_{20}N_4O_2$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.73; H, 5.63; N, 15.79.

2-Pivaloylamino-4-oxo-6-[(*p*-methoxyphenyl)ethynyl]pyrrolo-[2,3-*d*]pyrimidine (**9c**).

Using the general procedure described above, **7a** (0.36 g, 1.0 mmol), *p*-methoxyphenylacetylene **8c** (0.26 g, 2 mmol), copper(I) iodide (0.04 g, 0.10 mmol), tetrakis(triphenyl phosphine)-palladium (0) (0.12 g, 0.10 mmol) and triethylamine (0.5 mL) afforded 0.05 g (17%) of **9c** as a gray solid: mp >300 °C (dec); ^{1}H nmr (DMSO-d_6): δ 1.24 (s, 9 H, $C(CH_3)_3$), 3.79 (s, 3 H, 4'-OCH_3), 6.73 (s, 1 H, 5-H), 7.00 (d, 2 H, J = 8.4 Hz, C_6H_4), 7.49 (d, 2 H, J = 8.4 Hz, C_6H_4), 10.95 (s, 1 H, 2-N*H*Piv or 3-NH, exch), 11.95 (s, 1 H, 2-N*H*Piv or 3-NH, exch), 12.17 (bs, 1 H, 7-NH, exch).

Anal. Calcd. For $C_{20}H_{20}N_4O_2$•$0.5H_2O$: C, 64.33; H, 5.67; N, 15.00. Found: C, 64.42; H, 5.56; N, 14.64.

2-Pivaloylamino-4-oxo-6-[(2'-chlorophenyl)ethynyl]pyrrolo[2,3-*d*]pyrimidine (**9d**).

Using the general procedure described above, **7a** (0.12 g, 0.33 mmol), *o*-chlorophenylacetylene **8d** (0.07 g, 0.50 mmol), copper(I) iodide (0.01 g, 0.03 mmol), tetrakis(triphenyl phosphine)palladium (0) (0.02 g, 0.02 mmol) and triethylamine (0.5 mL) afforded 0.12 g (93%) of **9d** as a pale yellow solid: mp >250 °C (dec); ^{1}H nmr (DMSO-d_6): δ 1.24 (s, 9 H, $C(CH_3)_3$), 6.84 (s, 1 H, 5-H), 7.40-7.68 (m, 4 H, C_6H_4), 10.97 (s, 1 H, 2-N*H*Piv or 3-NH, exch), 11.97 (s, 1 H, 2-N*H*Piv or 3-NH, exch), 12.29 (bs, 1 H, 7-NH, exch).

Anal. Calcd. For $C_{19}H_{17}N_4O_2Cl$: C, 61.57; H, 4.71; N, 15.12; Cl: 9.57. Found: C, 61.41; H, 4.86; N, 15.35, Cl: 9.53.

2-Pivaloylamino-4-oxo-6-[(2'-pyridin)ethynyl]pyrrolo[2,3-*d*]-pyrimidine (**9e**).

Using the general procedure described above, **7a** (0.36 g, 1.0 mmol), 2-ethynylpyridine **8e** (0.16 g, 1.5 mmol), copper(I) iodide (0.04 g, 0.20 mmol), tetrakis(triphenyl phosphine)palladium (0) (0.12 g, 0.10 mmol) and triethylamine (0.5 mL) afforded 0.17 g (49%) of **9e** as a grey solid: mp >270 °C (dec); ^{1}H nmr (DMSO-d_6): δ 1.25 (s, 9 H, $C(CH_3)_3$), 6.90 (s, 1 H, 5-H), 7.41 (d, 1 H, C_5-

H_4), 7.61 (d, 1 H, C_5H_4), 7.85 (t, 1 H, C_5H_4), 8.61 (d, 1 H, C_5H_4), 10.99 (s, 1 H, 2-N*H*Piv or 3-NH, exch), 11.98 (s, 1 H, 2-N*H*Piv or 3-NH, exch), 12.37 (bs, 1 H, 7-NH, exch).

Anal. Calcd. For $C_{18}H_{17}N_5O_2$•$0.3H_2O$: C, 63.44; H, 5.21; N, 20.55. Found: C, 63.29; H, 5.12; N, 20.58.

Pivaloylamino-4-oxo-6-[(1'-naphthlene)ethynyl]pyrrolo[2,3-*d*]-pyrimidine (**9f**).

Using the general procedure described above, **7a** (0.36 g, 1.0 mmol), 1-ethynylnaphthalene **8f** (0.18 g, 1.2 mmol), copper(I) iodide (0.04 g, 0.20 mmol), tetrakis(triphenyl phosphine)palladium (0) (0.07 g, 0.06 mmol) and triethylamine (1.0 mL) afforded 0.34 g (89%) of **9f** as a pale-yellow solid: mp >280 °C dec; ^{1}H nmr (DMSO-d_6): δ 1.26 (s, 9 H, $C(CH_3)_3$), 6.94 (s, 1 H, 5-H), 7.54-7.67 (m, 3 H, $C_{10}H_7$), 7.80 (d, 1 H, J = 6.9 Hz, $C_{10}H_7$), 8.02 (dd, 2 H, J = 7.8 Hz & 3.0 Hz, $C_{10}H_7$), 8.40 (d, 1 H, J = 8.2 Hz, $C_{10}H_7$), 10.96 (s, 1 H, 2-N*H*Piv or 3-NH, exch), 11.99 (s, 1 H, 2-N*H*Piv or 3-NH, exch), 11.34 (bs, 1 H, 7-NH, exch).

Anal. Calcd. For $C_{23}H_{20}N_4O_2$•$0.3H_2O$: C, 70.86; H, 5.33; N, 14.37. Found: C, 70.70; H, 5.22; N, 14.45.

2-Pivaloylamino-4-oxo-6-[(2'-naphthlene)ethynyl]pyrrolo[2,3-*d*]-pyrimidine (**9g**).

Using the general procedure described above, **7a** (0.36 g, 1.0 mmol), 2-ethynylnaphthalene **8g** (0.18 g, 1.2 mmol), copper(I) iodide (0.04 g, 0.20 mmol), tetrakis(triphenyl phosphine)palladium (0) (0.07 g, 0.06 mmol) and triethylamine (1.0 mL) afforded 0.12 g (31%) of **9g** as a brown solid: mp 195-197 °C; ^{1}H nmr (DMSO-d_6): δ 1.25 (s, 9 H, $C(CH_3)_3$), 6.84 (s, 1 H, 5-H), 7.56-7.99 (m, 6 H, $C_{10}H_7$), 8.17 (s, 1 H, $C_{10}H_7$), 10.99 (s, 1 H, 2-N*H*Piv or 3-NH, exch), 11.97 (s, 1 H, 2-N*H*Piv or 3-NH, exch), 12.29 (bs, 1 H, 7-NH, exch).

Anal. Calcd. For $C_{23}H_{20}N_4O_2$•$0.2H_2O$: C, 71.19; H, 5.30; N, 14.44. Found: C, 71.04; H, 5.18; N, 14.68.

2-Pivaloylamino-4-oxo-6-[(2',5'-dimethoxyphenyl)ethynyl]-pyrrolo[2,3-*d*]pyrimidine (**9h**).

Using the general procedure described above, **7a** (0.12 g, 0.33 mmol), (2,5-dimethoxyphenyl)ethyne **8h** (0.08 g, 0.50 mmol), copper(I) iodide (0.02 g, 0.10 mmol), tetrakis(triphenyl phosphine)palladium (0) (0.02 g, 0.02 mmol) and triethylamine (1.0 mL) afforded 0.13 g (36%) of **9h** as a off-white solid: mp >250 °C (dec); ^{1}H nmr (DMSO-d_6): δ 1.25 (s, 9 H, $C(CH_3)_3$), 3.73 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 6.75 (s, 1 H, 5-H), 6.95-7.05 (m, 3 H, C_6H_3), 10.98 (s, 1 H, 2-N*H*Piv or 3-NH, exch), 11.95 (s, 1 H, 2-N*H*Piv or 3-NH, exch), 12.22 (bs, 1 H, 7-NH, exch).

Anal. Calcd. For $C_{21}H_{22}N_4O_4$•$0.5H_2O$: C, 62.52; H, 5.75; N, 13.89. Found: C, 62.84; H, 5.63; N, 13.58.

General Procedure for the Synthesis of Compounds **10a**-**10h**.

To a Parr hydrogenation bottle was added **9a-9h** dissolved in a mixture of DMF and THF followed by the addition of 5% Pd/C (same as the weight of **9**) and 3-4 drops of concentrated ammonium hydroxide. The reaction mixture was then shaken at 50 psi for 20 hours, filtered through a celite pad, and washed with hot THF (15 mL x 2). Silica gel (10 g) was added to the filtrate and the solvent evaporated to form a plug which was dried, loaded on top of a silica gel column and eluted with 1.5% MeOH in $CHCl_3$. Fractions containing the product (TLC) were pooled, and the solvent evaporated to afford the solid, which was further washed with hexanes to afford the pure product.

2-Pivaloylamino-4-oxo-6-(2-phenethyl)pyrrolo[2,3-*d*]pyrimidine (**10a**).

Compound **10a** was obtained from **9a** (0.16 g, 0.50 mmol) using the general procedure described above to afford 0.16 g (97%) of **10a** as a white solid: mp 250-251.5 °C; ^{1}H nmr (DMSO-d_6): δ 1.24 (s, 9 H, $C(CH_3)_3$), 2.91 (m, 4 H, CH_2CH_2), 6.09 (s, 1 H, 5-H), 7.24 (m, 5 H, C_6H_5), 10.76 (s, 1 H, 2-N*H*Piv or 3-NH, exch), 11.42 (s, 1 H, 2-N*H*Piv or 3-NH, exch), 11.79 (bs, 1 H, 7-NH, exch).

Anal. Calcd. For $C_{19}H_{22}N_4O_2$•$0.2C_6H_{14}$: C, 68.22; H, 7.03; N, 15.75. Found: C, 68.21; H, 6.79; N, 16.11.

2-Pivaloylamino-4-oxo-6-[2-(*p*-methylphenyl)ethyl]pyrrolo[2,3-*d*]pyrimidine (**10b**).

Compound **10b** was obtained from **9b** (0.24 g, 0.69 mmol) using the general procedure described above to afford 0.20 g (80%) of **10b** as a white solid: mp 255-257 °C; ^{1}H nmr (DMSO-d_6): δ 1.24 (s, 9 H, $C(CH_3)_3$), 2.25 (s, 3 H, 4'-CH_3), 2.88 (m, 4 H, CH_2CH_2), 6.07 (s, 1 H, 5-H), 7.09 (s, 4 H, C_6H_4), 10.72 (s, 1 H, 2-N*H*Piv or 3-NH, exch), 11.38 (s, 1 H, 2-N*H*Piv or 3-NH, exch), 11.78 (bs, 1 H, 7-NH, exch).

Anal. Calcd. For $C_{20}H_{24}N_4O_2$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.19; H, 6.89; N, 15.85.

2-Pivaloylamino-4-oxo-6-[2-(*p*-methoxyphenyl)ethyl]pyrrolo-[2,3-*d*]pyrimidine (**9c**).

Compound **10c** was obtained from **9c** (0.16 g, 0.43 mmol) using the general procedure described above to afford 0.12 g (74%) of **10c** as a off-white solid: mp 232-233 °C; ^{1}H nmr (DMSO-d_6): δ 1.24 (s, 9 H, $C(CH_3)_3$), 2.87 (s, 4 H, CH_2CH_2), 3.71 (s, 3 H, OCH_3), 6.08 (s, 1 H, 5-H), 6.85 (d, 2 H, J = Hz, C_6H_4), 7.13 (d, 2 H, J = Hz, C_6H_4), 10.73 (s, 1 H, 2-N*H*Piv or 3-NH, exch), 11.39 (s, 1 H, 2-N*H*Piv or 3-NH, exch), 11.79 (bs, 1 H, 7-NH, exch).

Anal. Calcd. For $C_{20}H_{24}N_4O_3$: C, 65.20; H, 6.57; N, 15.20. Found: C, 64.98; H, 6.51; N, 15.07.

2-Pivaloylamino-4-oxo-6-[2-(2'-chlorophenyl)ethyl]pyrrolo[2,3-*d*]-pyrimidine (**10d**).

Compound **10d** was obtained from **9d** (0.10 g, 0.27 mmol) using the general procedure described above to afford 0.07 g (64%) of **10d** as a white solid: mp 215-218 °C; ^{1}H nmr (DMSO-d_6): δ 1.24 (s, 9 H, $C(CH_3)_3$), 2.90 (t, 2 H, CH_2CH_2), 3.06 (t, 2 H, CH_2CH_2), 6.10 (s, 1 H, 5-H), 7.21-7.43 (m, 4 H, C_6H_4), 10.74 (s, 1 H, 2-N*H*Piv or 3-NH, exch), 11.44 (s, 1 H, 2-N*H*Piv or 3-NH, exch), 11.74 (bs, 1 H, 7-NH, exch).

Anal. Calcd. For $C_{19}H_{21}N_4O_2Cl$: C, 61.21; H, 5.68; N, 15.03; Cl, 9.51. Found: C, 61.58; H, 5.42; N, 15.31; Cl, 9.27.

2-Pivaloylamino-4-oxo-6-[2-(2'-pyridin)ethyl]pyrrolo[2,3-*d*]-pyrimidine (**10e**).

Compound **10e** was obtained from **9e** (0.16 g, 0.48 mmol) using the general procedure described above to afford 0.14 g (87%) of **10e** as a off-white solid: mp 217-218 °C; ^{1}H nmr (DMSO-d_6): δ 1.22 (s, 9 H, $C(CH_3)_3$), 3.04 (m, 4 H, CH_2CH_2), 6.08 (s, 1 H, 5-H), 7.21 (m, 1 H, C_5H_4), 7.27 (d, 1 H, C_5H_4), 7.68 (t, 1 H, J = 4.8 Hz, C_5H_4), 8.49 (d, 1 H, J = 4.8 Hz, C_5H_4), 10.77 (s, 1 H, 2-N*H*Piv or 3-NH, exch), 11.44 (s, 1 H, 2-N*H*Piv or 3-NH, exch), 11.79 (bs, 1 H, 7-NH, exch).

Anal. Calcd. For: $C_{18}H_{21}N_5O_2$•$0.2H_2O$: C, 63.03; H, 6.29; N, 20.42. Found: C, 63.00; H, 6.27; N, 20.30.

2-Pivaloylamino-4-oxo-6-[2-(1'-naphthlene)ethyl]pyrrolo[2,3-*d*]-pyrimidine (**10f**).

Compound **10f** was obtained from **9f** (0.88 g, 2.3 mmol) using the general procedure described above to afford 0.65 g (73%) of **10f** as a pale yellow solid: mp 228-230 °C; ^{1}H nmr (DMSO-d_6): δ 1.18 (s, 9 H, CH_3), 3.00 (t, 2 H, J = 9.0 Hz, CH_2CH_2), 3.41 (t, 2 H, J = 9.0 Hz, CH_2CH_2), 6.20 (s, 1 H, 5-H), 7.39-7.60 (m, 4 H, $C_{10}H_7$), 7.80 (d, 1 H, J = 3.0 Hz, $C_{10}H_7$), 7.95 (d, 1 H, J = 8.1 Hz, $C_{10}H_7$), 8.21 (d, 1 H, J = 7.1 Hz, $C_{10}H_7$), 10.74 (s, 1 H, 2-NH, exch), 11.50 (s, 1 H, 3-NH, exch), 11.81 (bs, 1 H, 7-NH, exch).

Anal. Calcd. For $C_{23}H_{24}N_4O_2$: C, 70.40; H, 6.28; N, 14.28. Found: C, 70.40; H, 6.24; N, 14.27.

2-Pivaloylamino-4-oxo-6-[2-(2'-naphthlene)ethyl]pyrrolo[2,3-*d*]pyrimidine (**10g**).

Compound **10g** was obtained from **9g** (0.28 g, 0.73 mmol) using the general procedure described above to afford 0.20 g (71%) of **10g** as a white solid: mp 248.5-249.5 °C; ^{1}H nmr (DMSO-d_6): δ 1.23 (s, 9 H, $C(CH_3)_3$), 2.99 (t, 2 H, J = 7.5 Hz, CH_2CH_2), 3.1 (t, 2 H, J = 7.5 Hz, CH_2CH_2), 6.12 (s, 1 H, 5-H), 7.40-7.87 (m, 7 H, $C_{10}H_7$), 10.75 (s, 1 H, 2-N*H*Piv or 3-NH, exch), 11.45 (s, 1 H, 2-N*H*Piv or 3-NH, exch), 11.79 (bs, 1 H, 7-NH, exch).

Anal. Calcd. For $C_{23}H_{24}N_4O_2$•$0.1CHCl_3$: C, 69.29; H, 6.07; N, 13.99. Found: C, 69.23; H, 6.01; N, 14.11.

2-Pivaloylamino-4-oxo-6-[2-(2',5'-dimethoxyphenyl)ethyl]-pyrrolo[2,3-*d*]pyrimidine (**10h**).

Compound **10h** was obtained from **9h** (0.35 g, 0.89 mmol) using the general procedure described above to afford 0.33 g (93%) of **10h** as a pale yellow solid: mp 195-197 °C; ^{1}H nmr (DMSO-d_6): δ 1.23 (s, 9 H, $C(CH_3)_3$), 2.85 (s, 4 H, CH_2CH_2), 3.67 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 6.09 (s, 1 H, 5-H), 6.74 (m, 2 H, C_6H_3), 6.86 (d, 1 H, J = 8.2 Hz, C_6H_3), 10.74 (s, 1 H, 2-N*H*Piv or 3-NH, exch), 11.38 (s, 1 H, 2-N*H*Piv or 3-NH, exch), 11.79 (bs, 1 H, 7-NH, exch).

Anal. Calcd. For $C_{21}H_{26}N_4O_4$: C, 63.30; H, 6.58; N, 14.04. Found: C, 63.34; H, 6.66; N, 13.82.

General Procedure for the Synthesis of Compounds **2a**-**2h**.

To a 25-mL round-bottomed flask was added **10a-10h** dissolved in THF (10 mL) followed by the addition of 1 *N* NaOH (3 mL). The mixture was refluxed at 70 °C for 24 hours. The solvent evaporated and the residue was flash chromatographed on silica gel and eluted with 1:19 MeOH/$CHCl_3$ to afford the product.

2-Amino-4-oxo-6-(2-phenethyl)pyrrolo[2,3-*d*]pyrimidine (**2a**).

Compound **2a** was obtained from **10a** (0.10 g, 0.29 mmol) using the general procedure described above to afford 0.06 g (80%) of **2a** as a white solid: mp >280 °C (dec); ^{1}H nmr (DMSO-d_6): δ 2.76 (t, 2 H, J = 6.9 Hz, CH_2CH_2), 2.91 (t, 2 H, J = 6.9 Hz, CH_2CH_2), 5.85 (s, 1 H, 5-H), 5.98 (s, 2 H, 2-NH_2, exch), 7.24 (m, 5 H, C_6H_5), 10.14 (s, 1H, 3-NH, exch), 10.90 (bs, 1H, 7-NH, exch).

Anal. Calcd. For $C_{14}H_{14}N_4O$: C, 66.13; H, 5.55; N, 22.03. Found: C, 66.51; H, 5.72; N, 22.08.

2-Amino-4-oxo-6-[2-(*p*-methylphenyl)ethyl]pyrrolo[2,3-*d*]-pyrimidine (**2b**).

Compound **2b** was obtained from **10b** (0.08 g, 0.23 mmol) using the general procedure described above to afford 0.04 g (62%) of **2b** as a pale yellow solid: mp >290 °C (dec); ^{1}H NMR (DMSO-d_6): δ 2.25 (s, 3 H, CH_3), 2.76 (t, 2 H, J = 6.6 Hz, CH_2CH_2), 2.85 (t, 2 H, J = 6.6 Hz, CH_2CH_2), 5.83 (s, 1 H, 5-H), 5.98 (s, 2 H, 2-NH_2, exch), 7.08 (m, 4 H, C_6H_4), 10.14 (s, 1 H, 3-NH, exch), 10.88 (bs, 1 H, 7-NH, exch).

Anal. Calcd. For $C_{15}H_{16}N_4O_2$•$0.1H_2O$: C, 66.70; H, 6.05; N, 20.74. Found: C, 66.68; H, 6.09; N, 20.51.

2-Amino-4-oxo-6-[2-(*p*-methoxyphenyl)ethyl]pyrrolo[2,3-*d*]pyrimidine (**2c**).

Compound **2c** was obtained from **10c** (0.09 g, 0.24 mmol) using the general procedure described above to afford 0.04 g (62%) of **2c** as a pale yellow solid: mp 278.5-280 °C; ^{1}H nmr (DMSO-d_6): δ 2.76 (t, 2 H, J = 7.5 Hz, CH_2CH_2), 2.82 (t, 2 H, J = 7.5 Hz, CH_2CH_2), 3.70 (s, 3 H, OCH_3), 5.83 (s, 1 H, 5-H), 5.98 (s, 2 H, 2-NH_2, exch), 6.82 (d, 2 H, J = 8.4 Hz, C_6H_4), 7.12 (d, 2 H, J = 8.4 Hz, C_6H_4), 10.14 (s, 1 H, 3-NH, exch), 10.87 (bs, 1 H, 7-NH, exch).

Anal. Calcd. For $C_{15}H_{16}N_4O$: C, 63.37; H, 5.67; N, 19.71. Found: C, 63.26; H, 5.78; N, 19.56.

2-Amino-4-oxo-6-[2-(2'-chlorophenyl)ethyl]pyrrolo[2,3-*d*]-pyrimidine (**2d**).

Compound **2d** was obtained from **10d** (0.06 g, 0.15 mmol) using the general procedure described above to afford 0.03 g (79%) of **2d** as a white solid: mp 264-266 °C; ^{1}H nmr (DMSO-d_6): δ 2.78 (t, 2 H, J = 7.0 Hz, CH_2CH_2), 3.00 (t, 2 H, J = 7.0 Hz, CH_2CH_2), 5.80 (s, 1 H, 5-H), 5.98 (s, 2 H, 2-NH_2, exch), 7.22-7.42 (m, 4 H, C_6H_4), 10.14 (s, 1 H, 3-NH, exch), 10.92 (bs, 1 H, 7-NH, exch).

Anal. Calcd. For $C_{14}H_{13}N_4OCl$•$0.2H_2O$: C, 57.52; H, 4.62; N, 19.16; Cl 12.13. Found: C, 57.82; H, 4.98; N, 18.80; Cl, 12.29.

2-Amino-4-oxo-6-[2-(2'-pyridin)ethyl]pyrrolo[2,3-*d*]pyrimidine (**2e**).

Compound **2e** was obtained from **10e** (0.09 g, 0.27 mmol) using the general procedure described above to afford 0.03 g (44%) of **2e** as a white solid: mp >265 °C dec; ^{1}H nmr (DMSO-d_6): δ 2.89 (t, 2 H, J = 6.9 Hz, CH_2CH_2), 3.04 (t, 2 H, J = 6.9 Hz, CH_2CH_2), 5.83 (s, 1 H, 5-H), 5.98 (s, 2 H, 2-NH_2, exch), 7.22 (m, 2 H, C_5H_4), 7.67 (t, 1 H, J = 7.5 Hz, C_5H_4), 8.48 (d, 1 H, J = 4.5 Hz, C_5H_4), 10.14 (s, 1 H, 3-NH, exch), 10.90 (bs, 1 H, 7-NH, exch).

Anal. Calcd. For $C_{13}H_{13}N_5O$•$0.5H_2O$: C, 59.04; H, 5.34; N, 26.56. Found: C, 59.35; H, 5.52; N, 26.45.

2-Amino-4-oxo-6-[2-(1'-naphthlene)ethyl]pyrrolo[2,3-*d*]pyrimidine (**2f**).

Compound **2f** was obtained from **10f** (0.11 g, 0.28 mmol) using the general procedure described above to afford 0.05 g (57%) of **2f** as a yellow solid: mp >220 °C dec; ^{1}H nmr (DMSO-d_6): δ 2.88 (t, 2 H, J = 9.0 Hz, CH_2CH_2), 3.35 (t, 2 H, J = 9.0 Hz, CH_2CH_2), 5.95 (s, 1 H, 5-H), 5.98 (s, 2 H, NH_2, exch), 7.40-7.57 (m, 4 H, $C_{10}H_7$), 7.78 (d, 1 H, J = 9.0 Hz, $C_{10}H_7$), 7.93 (d, 1 H, J = 6.0 Hz, $C_{10}H_7$), 8.20 (d, 1 H, J = 9.0 Hz, $C_{10}H_7$), 10.15 (s, 1 H, 3-NH, exch), 11.02 (bs, 1 H, 7-NH, exch).

Anal. Calcd. For $C_{18}H_{16}N_4O$•$0.8H_2O$: C, 68.21; H, 5.53; N, 17.16. Found: C, 67.99; H, 5.57; N, 17.32.

2-Amino-4-oxo-6-[2-(2'-naphthlene)ethyl]pyrrolo[2,3-*d*]pyrimidine (**2g**).

Compound **2g** was obtained from **10g** (0.07 g, 0.18 mmol) using the general procedure described above to afford 0.08 g

(55%) of **2g** as a yellow solid: mp 165-168 °C; ^{1}H nmr (DMSO-d_6): δ 2.96 (t, 2 H, J = 7.5 Hz, CH_2CH_2), 3.06 (t, 2 H, J = 7.5 Hz, CH_2CH_2), 5.88 (s, 1 H, 5-H), 5.99 (s, 2 H, NH_2, exch), 7.43 (m, 3 H, $C_{10}H_7$), 7.72 (s, 1 H, $C_{10}H_7$), 7.98 (m, 3 H, $C_{10}H_7$), 10.16 (s, 1 H, 3-NH, exch), 10.94 (bs, 1 H, 7-NH, exch).

Anal. Calcd. For $C_{18}H_{16}N_4O$: C, 71.04; H, 5.30; N, 18.41. Found: C, 71.29; H, 5.63; N, 18.28.

2-Amino-4-oxo-6-[2-(2',5'-dimethoxyphenyl)ethyl]pyrrolo[2,3-*d*]-pyrimidine (**2h**).

Compound **2h** was obtained from **10h** (0.11 g, 0.27 mmol) using the general procedure described above to afford 0.05 g (52%) of **2h** as a yellow solid: mp 225-227 °C; ^{1}H nmr (DMSO-d_6): δ 2.71 (t, 2 H, J = 6.0 Hz, CH_2CH_2), 2.80 (t, 2 H, J = 6.0 Hz, CH_2CH_2), 3.68 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 5.84 (s, 1 H, 5-H), 5.97 (s, 2 H, NH_2, exch), 6.80 (m, 3 H, C_6H_3), 10.14 (s, 1 H, 3-NH, exch), 10.86 (bs, 1 H, 7-NH, exch).

Anal. Calcd. For $C_{16}H_{18}N_4O_3$•0.5MeOH: C, 59.99; H, 6.10; N, 16.96. Found: C, 60.38; H, 6.29; N, 16.70.

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