Synthesis of Three Carbon Atom Bridged 2,4-Diaminopyrrolo[2,3-*d*]-pyrimidines as Nonclassical Dihydrofolate Reductase Inhibitors

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A series of seven nonclassical three carbon atom bridged 2,4-diamino-5-substituted-pyrrolo[2,3-*d*]-pyrimidines **1a**-**g** were synthesized as potential inhibitors of dihydrofolate reductase. Selective oxidation of diols **7a**-**g** affords α-hydroxy ketones **8a**-**g**. Subsequent condensation with malononitrile gave the requisite 2-amino-3-cyano-4-substituted furan precursors **9a**-**g**. Cyclocondensation with guanidine in refluxing ethanol in one step affords the three carbon atom bridged 2,4-diamino-5-substituted-pyrrolo[2,3-*d*]-pyrimidines **1a-g**. Preliminary biological results indicated that these compounds showed moderate inhibitory activities against dihydrofolate reductases from *Pneumocystis carinii, Toxoplasma gondii*, *Mycobacterium avium* and rat liver with IC_{50} values in the 0.66 μM - 70.1 μM range and some compounds had marginal selectivity for *T. gondii* dihydrofolate reductase.

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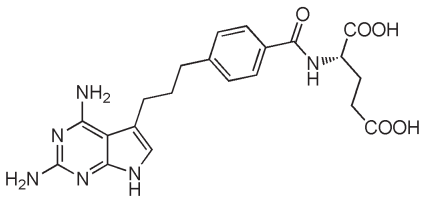
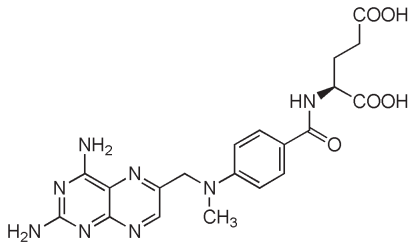
Dihydrofolate reductase is an essential enzyme in the biosynthesis of purines and pyrimidines and therefore DNA. Inhibition of dihydrofolate reductase interrupts the recycling of dihydrofolate back to tetrahydrofolate and thus has a deleterious effect on cell growth. Methotrexate, a classical dihydrofolate reductase inhibitor, is clinically used in cancer chemotherapy [1]. Miwa *et al.* [2] reported the synthesis of a classical 2,4-diamino-5-substituted pyrrolo[2,3-*d*]pyrimidine (TNP351) with a three carbon atom bridge, as an inhibitor of dihydrofolate reductase and an antitumor agent. Inhibitory IC_{50} values for TNP351 against the growth of KB and A549 tumor cells in culture were 27 and 4.5 ng/ml while those for methotrexate were 5.0 and 35 ng/ml respectively. Thus TNP351 demonstrated that truncation of the 6-6 ring system to a 6-5 ring system can be more than compensated for by increasing the bridge length from two to three carbon atoms. Classical antifolates, like methotrexate and TNP351, utilize folate transport mechanisms to gain entry into cells. Further, classical antifolates are unable to penetrate pathogenic cells which lack the folate transport systems. A decrease in the efficiency of transport of classical antifolates leads to drug resistance in some tumor cells.

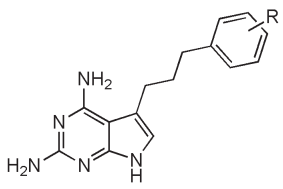
An important determinant of the antitumor activity of some classical antifolates is their ability to function as substrates for the enzyme folypolyglutamate synthetase (FPGS)



TNP351



MTX



1a-g

1a R = 2,5-diCl; **1b** R = 2,5-diOMe; **1c** R = 3,4,5-triOMe; **1d** R = 4-benzyloxy; **1e** R = 2,3-$(CH)_4$; **1f** R = 3,4-$(CH)_4$; **1g** R = H

which converts the monoglutamate forms of classical antifolates into long chain noneffluxing poly-γ-glutamates within the cell [3]. The ineffectiveness of some classical antifolates against resistant tumor cells has been attributed, in part, to both reduced uptake [4-7] and/or inefficient polyglutamylation [8-11]. Although polyglutamylation of certain classical antifolates appears necessary for cytotoxicity, it has also been implicated as a possible cause of toxicity to host cells due to the prolonged retention of polyanionic forms of polyglutamates of these antifolates [12].

Lipophilic, nonclassical antifolates which lack the glutamate moiety do not require the reduced folate transport systems to gain access to tumor cells and hence are useful where resistance is attributable to inefficient uptake systems. In addition, such nonclassical dihydrofolate reductase inhibitors are also useful in the treatment of opportunistic infections in acquired immunodeficiency syndrome (AIDS) patients, such as those caused by *Pneumocystis carinii* and *Toxoplasma gondii*. These opportunistic infections are responsible for significant morbidity and mortality in AIDS patients [13]. These organisms lack the transport systems for classical antifolates and thus are only accessible *via* nonclassical antifolates.

Selectivity of inhibitors for dihydrofolate reductase from *Pneumocystis carinii* and/or *Toxoplasma gondii* over mammalian dihydrofolate reductase, such as rat liver along with high potency against these pathogenic dihydrofolate reductases, is a desirable goal. It was thus of interest to design and synthesize the nonclassical analogs **1a-g** of TNP351 which contain a three carbon atom bridge as selective inhibitors of pathogen dihydrofolate reductase or as potential antitumor agents.

2-Amino-3-cyanofurans can be readily cyclized to annulated 2,4-diaminopyrrolo[2,3-*d*]pyrimidine ring systems by reaction with guanidine. These 2-amino-3-cyanofurans can be prepared by condensation of malononitrile with the appropriate α-hydroxy ketones [14]. With this in mind, the appropriate α-hydroxy ketones were synthesized by selective oxidation of triol precursors (Scheme 1) [15]. Thus 1,2,4-butanetriol was converted to its acetonide **3** in 97% yield. The ^{1}H nmr supported the five-membered ring structure **3** [16]. The protected alcohol **3** was oxidized with pyridinium chlorochromate in dichloromethane under a nitrogen atmosphere for 10 hours to afford the corresponding aldehyde **4**, in 68% yield. Wittig reaction of the corresponding triphenylphosphine bromide and **4** in tetrahydrofuran afforded **5a-g** as a mixture of *E*- and *Z*- isomers in 38-85% yields. Hydrogenation of **5a-g** over 5% palladium on activated carbon for 10 hours gave **6a-g** in quantitative yield. Shorter reaction times of 5 hours or 2 hours afford **6a-g** in 98% or 95% yields respectively. Deprotection of **6a-g** with aqueous acetic acid afforded **7a-g** in 82%-99% yields. The key α-hydroxy ketones **8a-g** were obtained by selective oxidation of diols **7a-g** using bis(tributyltin) oxide (HBD) and bromine. Attempted oxidation of unprotected **5g** resulted in an inseparable mixture. A possible reason for the failure of the reaction with unprotected **5g** might be that the double bond is also susceptible to oxidation with bromine. Condensation of malononitrile with the appropriate α-hydroxy ketones **8a-g** gave the corresponding 2-amino-3-cyano-4-substituted-furans which were cyclized to 2,4-diaminopyrrolo[2,3-*d*]pyrimidines **1a-g** with guanidine in 47%-88% yields.

The compounds were evaluated as inhibitors of dihydrofolate reductase from *Pneumocystis carinii*, *Toxoplasma gondii*, rat liver and *Mycobacterium avium* using established methods [17]; the results are listed in Table 1. The compounds were moderately inhibitory but there was no selectivity for *Pneumocystis* or *Mycobacterium* dihydrofolate reductase and only marginal selectivity for *Toxoplasma gondii* dihydrofolate reductase. The most potent compound was **1d** with an IC_{50} in the submicromolar range against rat liver dihydrofolate reductase. Thus the three atom bridged nonclassical analogs synthesized are not particularly

Scheme 1

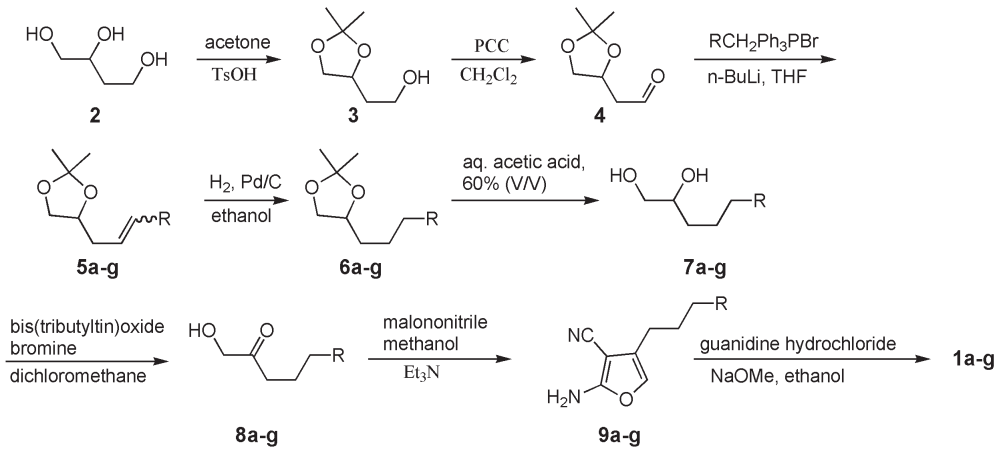


Table 1

Inhibition of Dihydrofolate Reductase from *Pneumocystis carinii*, *Toxoplasma gondii*, *Mycobacterium avium* and Rat liver by compounds **1a-g**

IC_{50} 10^{-6} *M* (Selectivity *)

Compound	*P. carinii*	*T. gondii*	*M. avium*	Rat Liver
1a	13.5 (0.4)	1.24 (3.9)	20.2 (0.24)	4.8
1b	28.9 (0.4)	4.05 (2.9)	24.6 (0.5)	11.8
1c	14.9 (0.3)	1.03 (4.7)	38.5 (0.12)	4.8
1d	11.5 (0.1)	1.6 (0.4)	4.3 (0.15)	0.66
1e	6.9 (0.2)	1.3 (1.2)	8.2 (0.18)	1.5
1f	4.93 (0.2)	1.01 (1.1)	14.2 (0.08)	1.09
1g	42.9 (0.2)	2.7 (3.2)	70.1 (0.12)	8.6
TMQ[a]	0.047 (0.17)	0.016 (0.5)	0.0015 (5.3)	0.008
PTX[a]	0.013 (0.26)	0.0043 (0.76)	0.00061 (5.4)	0.0015

* Selectivity is the ratio of IC_{50} for rat liver enzyme/IC_{50} for pathogen enzyme; this ratio is in parentheses following each IC_{50} for the pathogen enzymes. These assays were carried out at 37 ∞C, under conditions of substrate (90 mM dihydrofolic acid) and cofactor (119 mM nicotinamide diphosphate) in the presence of 150 mM potassium chloride and 2-mercaptoethanol (8.9 mM), in a sodium phosphate buffer (pH 7.4) [17]. [a] Data for TMQ and PTX assayed under the same conditions are from reference [18].

potent or selective against dihydrofolate reductase. Compared to the unsubstituted analog **1g** all of the substituted analogs were more potent inhibitors (except **1b** for *T. gondii* and rat liver). The most potent inhibitors were those with bulky substituents. Thus for *P. carinii* and *T. gondii* **1f** was the most potent and for rat liver and *M. avium* **1d** was the most potent.

EXPERIMENTAL

All evaporations were carried out *in vacuo* with a rotary evaporator. Analytical samples were dried *in vacuo* (0.2 Torr) in a Chem-Dry apparatus over phosphorous pentoxide. Melting points were determined on a Mel-Temp apparatus and are uncorrected. Nuclear magnetic resonance spectra for proton (^{1}H nmr) were recorded on a Bruker WH-300 (300 MHz) spectrometer. The chemical shift values are expressed in ppm (parts per million) relative to tetramethylsilane as internal standard; s = singlet, d = doublet, dd = doublet of doublet, dt = doublet of triplet, t = triplet, q = quartet, quin = quintet, m = multiplet, bs = broad singlet. The relative integrals of peak areas agreed with those expected for the assigned structures. High resolution mass spectra (HRMS) were recorded on a VG-7070E-HF instrument. Thin layer chromatography (tlc) was performed on POLYGRAM Sil G/UV_{254} silica gel plates with fluorescent indicator, and the spots were visualized under 254 and 366 nm illumination. Proportions of solvents used for thin layer chromatography are by volume. Elemental analyses were performed by Atlantic Microlabs Inc., Norcoss, GA. Analytical results indicated by element symbols are within ±0.4% of the calculated values. Fractional moles of water or organic solvents frequently found in some analytical samples of antifolates were not removed in spite of 24-48 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.

General Procedure for the Synthesis of Compounds **5a-g**.

To a solution of the corresponding substituted triphenylphosphine bromide (1.0 equivalent) in dry tetrahydrofuran was added dropwise *n*-butyl lithium (1 *M*, 1.1 equivalents) at –78 °C under a nitrogen atmosphere. After 10 minutes, a solution of **4** in 2 ml of tetrahydrofuran was added to the solution, and the solution was slowly allowed to come to room temperature. The stirring was continued for an additional 10 hours. The solvent was evaporated under reduced pressure to dryness. To the residue was added hot hexane to precipitate the triphenylphosphine oxide which was filtered. The filtrate was evaporated to dryness to afford a residue which was chromatographed on silica gel with hexane-ethyl acetate (V/V). Appropriate fractions (tlc) that contained the product spots were pooled and the solvent evaporated to afford **5a-g**.

Z- and *E-O*-Isopropylidene-1-(2',5'-dichlorophenyl)-1-pentene-4,5-diol (**5a**).

Compound **5a** was synthesized using the general procedure with **4** (1.50 g, 10.4 mmol) and 2,5-dichlorobenzyltriphenylphosphine bromide (5.23 g, 10.4 mmol) to give 1.14 g (38% yield) of a yellow liquid; R_f=0.25 (hexane-ethyl acetate, 35:1). ^{1}H nmr (DMSO-d_6): δ 1.26 (s, 3H), 1.33 (s, 3H), 2.37 (m, 2H, *J*=6.5 Hz), 3.34 (m, 1H), 3.99 (m, 1H), 4.19 (m, 1H), 5.90 (dt, 0.6H, *J*=11.6 Hz, and *J*=7.3 Hz), 6.38 (dt, 0.4H, *J*=15.9 Hz, *J*=7.3 Hz), 6.51 (d, 0.6H, *J*=11.6 Hz), 6.70 (d, 0.4H, *J*=15.9 Hz), 7.34-7.72 (m, 3H); HRMS: *m/e* calcd for (M+) $C_{14}H_{16}O_2Cl_2$ 286.0527; found 286.0535.

Z- and *E-O*-Isopropylidene-1-(2',5'-dimethoxyphenyl)-1-pentene-4,5-diol (**5b**).

Compound **5b** was synthesized using the general procedure with **4** (1.0 g, 6.9 mmol) and 2,5-dimethoxybenzyltriphenylphosphine bromide (3.42 g, 6.9 mmol) to give 0.93 g (48% yield) of a yellow liquid; R_f=0.30 (hexane-ethyl acetate, 9:2); ^{1}H nmr (DMSO-d_6) δ 1.26 (s, 3H), 1.33 (s, 3H), 1.42 (m, 2H), 3.53 (m, 1H), 3.66 (s, 3H), 3.69 (s, 3H), 3.98 (m, 1H), 4.15 (m, 1H), 5.70 (dt, 0.3H, *J*=7.0 and *J*=11.6 Hz), 6.22 (dt, 0.7H, *J*=7.0 and 16.1 Hz), 6.53 (d, 0.3H, *J*=11.6 Hz) 6.65 (d, 0.7H, *J*=16.1 Hz), 6.70-7.08 (m, 3H); HRMS: *m/e* calcd for (M+) $C_{16}H_{22}O_4$ 278.1518; found 278.1527.

Z- and *E-O*-Isopropylidene-1-(3',4',5'-trimethoxyphenyl)-1-pentene-4,5-diol (**5c**).

Compound **5c** was synthesized using the general procedure with **4** (1.60 g, 11.1 mmol) and 3,4,5-trimethoxybenzyltriphenylphosphine bromide (5.81 g, 11.1 mmol) to give 1.92 g (56% yield) of a colorless liquid; R_f=0.30, 0.28 (hexane-ethyl acetate, 10:3). ^{1}H nmr (DMSO-d_6): δ 1.27 (s, 3H), 1.40 (s, 3H), 2.30-2.61 (m, 2H), 3.44 (s, 3H), 3.52 (m, 1H), 3.58 (s, 3H), 3.76 (s, 3H), 3.96 (m, 1H), 4.10 (m, 1H), 5.60 (dt, 0.7H, *J*=7.0 and 11.6 Hz), 6.18 (dt, 0.3H, *J*=7.0 and 15.9 Hz), 6.25 (d, 0.7H, *J*=11.6 Hz), 6.40 (d, 0.3H, *J*=15.9 Hz), 6.69 (s, 2H); HRMS: *m/e* calcd for (M+) $C_{17}H_{24}O_5$ 308.1623; found 308.1633.

Z- and *E-O*-Isopropylidene-1-(4'-benzyloxyphenyl)-1-pentene-4,5-diol (**5d**).

Compound **5d** was synthesized using the general procedure with **4** (2.00 g, 13.9 mmol) and benzyloxyphenyltriphenyl-

phosphine bromide (6.85 g, 13.9 mmol) to give 3.70 g (82% yield) of a colorless oil, R_f=0.31, 0.29 (hexane-ethyl acetate, 10:1). ^{1}H nmr (DMSO-d_6): δ 1.26 (s, 3H), 1.31 (s, 3H), 2.35-2.42 (m, 2H), 3.53 (m, 1H), 4.00 (m, 1H), 4.14 (m, 1H), 5.09 (s, 2H), 5.50-6.50 (m, 2H), 6.69 (d, 2H), 7.00 (d, 2H), 7.24-7.45 (m, 5H).

Z- and *E*-*O*-Isopropylidene-1-(1'-naphthyl)-1-pentene-4,5-diol (**5e**).

Compound **5e** was synthesized using the general procedure with **4** (2.00 g, 13.9 mmol) and 1-naphthalenemethyltriphenylphosphine chloride (6.33 g, 14.44 mmol) to give 2.40 g (64% yield) of a colorless liquid; R_f=0.34, 0.32 (hexane-ethyl acetate, 15:1). ^{1}H nmr (DMSO-d_6): δ 1.29 (s, 3H), 1.36 (s, 3H), 2.60 (m, 2H), 3.65 (m, 1H), 4.05 (m, 1H), 4.25 (m, 1H), 5.95-7.30 (m, 2H), 7.35-8.25 (m, 7H).

Z- and *E*-*O*-Isopropylidene-1-(2'-naphthyl)-1-pentene-4,5-diol (**5f**).

Compound **5f** (*E*- and *Z*-isomers) were synthesized using the general procedure with **4** (1.76 g, 12.5 mmol) and 2-naphthalenemethyltriphenylphosphine bromide (6.05 g, 12.52 mmol) to give 1.04 g (*Z*-isomer, 27% yield) of a colorless liquid; R_f =0.20 (hexane-ethyl acetate, 20:1). ^{1}H nmr (DMSO-d_6): δ 1.32 (s, 3H), 1.39 (s, 3H), 2.64 (m, 2H), 3.56 (m, 1H), 4.03 (m, 1H), 4.21 (m, 1H), 5.78 (dt, 1H, *J*=7.2 and 11.6 Hz), 6.68 (d, 1H, *J*=11.6 Hz), 7.49-8.04 (m, 7H); HRMS: *m/e* calcd for (M+) $C_{18}H_{20}O_2$ 268.1463; found 268.1469; and 2.21 g (*E*-isomer, 58 % yield) of a white solid; R_f =0.18 (hexane-ethyl acetate, 20:1); mp 42-45° C (hexane). ^{1}H nmr (DMSO-d_6): δ 1.35 (s, 3H), 1.42 (s, 3H), 2.50 (m, 2H), 3.58 (m, 1H), 4.04 (m, 1H), 4.19 (m, 1H), 6.40 (dt, 1H, *J*=7.0 and 15.9 Hz), 6.64 (d, 1H, *J*=15.9 Hz), 7.47-7.86 (m, 7H); HRMS: *m/e* calcd for (M+) $C_{18}H_{20}O_2$ 268.1463; found 268.1462.

Z- and *E*-*O*-Isopropylidene-1-phenyl-1-pentene-4,5-diol (**5g**).

Compound **5g** was synthesized using the general procedure with **4** (2.00 g, 13.9 mmol) and benzyltriphenylphosphine bromide (6.52 g, 14.43 mmol) to give 2.30 g (76% yield) of a colorless oil; R_f=0.35, 0.32 (hexane-ethyl acetate, 12:1); ^{1}H nmr (DMSO-d_6): δ 1.26 (s, 3H), 1.33 (s, 3H), 2.40 (m, 2H), 3.55 (m, 1H), 4.00 (m, 1H), 4.15 (m, 1H), 5.60-6.55 (m, 2H), 7.17-7.55 (m, 5H).

General Procedure for the Synthesis of Compounds **6a-g.**

To a solution of **5a-g** in anhydrous ethanol was added palladium on activated carbon (10%). Hydrogenation was carried out in a Paar hydrogenator for 10 hours with hydrogen at 50 Psi. The reaction mixture was filtered to remove the catalyst and the filtrate evaporated at reduced pressure to give the crude product which was chromatographed on silica gel with hexane-ethyl acetate at an appropriate ratio to afford **6a-g**.

5-(2'-5'-Dichlorophenyl)-*O*-isopropylidenepentane-1,2-diol (**6a**)

Compound **6a** was synthesized using the general procedure with **5a** (1.14 g, 3.97 mmol) to give 1.14 g (100% yield) of a colorless oil; R_f=0.35 (hexane-ethyl acetate, 35:1); ^{1}H nmr (DMSO-d_6): δ 1.17 (s, 3H), 1.24 (s, 3H), 1.40-1.80 (m, 4H), 2.70 (t, 2H), 3.21-3.24 (m, 1H), 3.94-4.05 (m, 2H), 7.27-7.45 (m, 3H); HRMS: *m/e* calcd for (M+) $C_{14}H_{18}O_2Cl_2$ 288.0683; found 288.0686.

5-(2',5'-Dimethoxyphenyl)-*O*-isopropylidenepentane-1,2-diol (**6b**).

Compound **6b** was synthesized using the general procedure with **5b** (0.55 g, 1.96 mmol) to give 0.55 g (100% yield) of a colorless liquid; R_f=0.28 (hexane-ethyl acetate, 5:1); ^{1}H nmr (DMSO-d_6) δ 1.24 (s, 3H), 1.28 (s, 3H), 1.47-1.53 (m, 4H), 2.50 (t, 2H), 3.20 (m, 1H), 3.71 (s 3H), 3.77 (s, 3H), 3.94-4.01 (m, 2H), 6.71-6.86 (m, 3H); HRMS: *m/e* calcd for (M+) $C_{16}H_{24}O_4$ 280.1674; found 280.1685.

5-(3',4',5'-Trimethoxyphenyl)-*O*-isopropylidenepentane-1,2-diol (**6c**).

Compound **6c** was synthesized using the general procedure with **5c** (1.40 g, 44.54 mmol) to give 1.40 g (100% yield) of a colorless liquid; R_f=0.34 (hexane-ethyl acetate, 10:3); ^{1}H nmr (DMSO-d_6): δ 1.24 (s, 3H), 1.28 (s, 3H), 1.40-1.60 (m, 4H), 2.50 (t, 2H), 3.24-3.38 (m, 1H), 3.44 (s, 3H), 3.52 (s, 3H), 3.73 (s, 3H), 3.90-4.05 (m, 2H), 6.48 (s, 2H); HRMS: *m/e* calcd for (M+) $C_{17}H_{26}O_5$ 310.1780; found 310.1773.

5-(4'-Benzyloxyphenyl)-*O*-isopropylidenepentane-1,2-diol (**6d**).

Compound **6d** was synthesized using the general procedure with **5d** (3.70 g, 11.4 mmol) to give 3.70 g (100% yield) of a colorless liquid; R_f=0.33 (hexane-ethyl acetate, 5:1); ^{1}H nmr (DMSO-d_6): δ 1.20 (s, 3H), 1.24 (s, 3H), 1.42-1.58 (m, 4H), 2.54 (t, 2H), 3.39 (m, 1H), 3.98 (m, 2H), 5.06 (s, 2H), 6.91 (d, 2H), 7.10 (d, 2H), 7.32-7.45 (m, 5H); HRMS: *m/e* calcd for (M+) $C_{21}H_{26}O_3$ 326.1881; found 326.1897.

5-(1'-Naphthyl)-*O*-isopropylidenepentane-1,2-diol (**6e**).

Compound **6e** was synthesized using the general procedure with **5e** (2.4 g, 8.94 mmol) to give 2.35 g (98% yield) of a colorless liquid, R_f=0.32 (hexane-ethyl acetate, 6:1); ^{1}H nmr (DMSO-d_6): δ 1.24 (s, 3H), 1.27 (s, 3H), 1.52-1.75 (m, 4H), 3.06 (t, 2H), 3.40 (m, 1H), 3.96 (m, 1H), 4.03 (m, 1H), 7.34-8.08 (m, 7H); HRMS: *m/e* calcd for (M+) $C_{18}H_{22}O_2$ 270.1619; found 270.1607.

5-(2'-Naphthyl)-*O*-isopropylidenepentane-1,2-diol (**6f**).

Compound **6f** was synthesized as in the general procedure with **5f** (1.00 g, 3.73 mmol) to give 1.00 g (100% yield) of a colorless liquid; R_f=0.22 (hexane-ethyl acetate, 20:1); ^{1}H nmr (DMSO-d_6): δ 1.19 (s, 3H), 1.23 (s, 3H), 1.47-1.74 (m, 4H), 2.72 (t, 2H, *J*=7.0 Hz), 3.36-3.43 (m, 1H), 3.93-4.37 (m, 2H), 7.35-7.85 (m, 7H); HRMS: *m/e* calcd for (M+) $C_{18}H_{22}O_2$ 270.1619; found 270.1617.

5-Phenyl-*O*-isopropylidenepentane-1,2-diol (**6g**).

Compound **6g** was synthesized using the general procedure with **5g** (2.3 g, 10.5 mmol) to afford 2.3 g (100% yield) of a colorless liquid; R_f=0.37 (hexane- ethyl acetate, 12:1); ^{1}H nmr (DMSO-d_6): δ 1.24 (s, 3H), 1.28 (s, 3H), 1.46-1.54 (m, 4H), 2.58 (t, 2H), 3.39 (m, 1H), 3.96 (m, 1H), 4.01 (m, 1H), 7.17-7.27 (m, 5H); HRMS: *m/e* calcd for (M-CH_3+) $C_{13}H_{17}O_2$ 205.1228; found 205.1233.

General Procedure for the Synthesis of Compounds **7a-g**.

A mixture of **6a-g** and 60% AcOH (V:V) (10 ml) was stirred for 18 hours at room temperature. Water and AcOH were evaporated under reduced pressure. To the residue was added 20 ml of water. The solution was extracted with ethyl acetate (3x20 ml). The combined organic phase was dried with anhydrous sodium

sulfate and filtered and the filtrate was evaporated to afford a residue which was chromatographed on silica gel with hexane-ethyl acetate (appropriate ratio) to give **7a-g** and the *Z*- and *E*-isomers of 1- (2'- naphthyl)-1-pentane-4,5-diol.

5-(2',5'-Dichlorophenyl)-1,2-pentanediol (**7a**).

Compound **7a** was synthesized as in the general procedure with **6a** (1.1 g, 3.67 mmol) to give 0.91 g (99% yield) of **7a** as a colorless liquid; R_f=0.55 (hexane-ethyl acetate, 1:5); ^{1}H nmr (DMSO-d_6): δ 1.15-1.30 (m, 1H), 1.40-1.65 (m, 2H), 1.65-1.81 (m, 1H), 2.65 (t, 2H), 3.23 (m, 2H), 3.41 (m, 1H), 4.44 (d, 1H, D_2O exchangeable), 4.46 (t, 1H, D_2O exchangeable), 7.31-7.45 (m, 3H); HRMS: *m/e* calcd for (M+) $C_{11}H_{14}O_2Cl_2$ 248.0370; found 248.0368.

5-(2',5'-Dimethoxyphenyl)-1,2-pentanediol (**7b**).

Compound **7b** was synthesized as in the general procedure with **6b** (0.50 g, 1.78 mmol) to afford 0.84 g (90% yield) of a colorless liquid; R_f=0.30 (hexane-ethyl acetate, 1:4); ^{1}H nmr (DMSO-d_6): δ 1.12-1.25 (m, 1H), 1.30-1.55 (m, 2H), 1.59-1.71 (m, 1H), 2.60 (t, 2H), 3,23 (m, 2H), 3.40 (m, 1H), 3.67 (s, 3H), 3.72 (s, 3H), 4.71 (d, 1H, D_2O exchangeable), 4.43 (t, 1H, D_2O exchangeable), 6.70-6.88 (m, 3H); HRMS: *m/e* calcd for (M+) $C_{13}H_{20}O_4$ 240.1361; found 240.1368.

5-(3',4',5'-Trimethoxyphenyl)-1,2-pentanediol (**7c**).

Compound **7c** was synthesized as in the general procedure with **6c** (1.30 g, 6.12 mmol) to give 1.01 g (89% yield) of a colorless liquid; R_f=0.28 (hexane-ethyl acetate, 1:5); ^{1}H nmr (DMSO-d_6): δ 1.29 (m, 1H), 1.40-1.80 (m, 3H), 2.52 (t, 2H), 3.23 (m, 2H), 3.41 (m, 1H), 3.61 (s, 3H), 3.81 (s, 6H), 4.39 (d, 1H, D_2O exchangeable), 4.44 (t, 1H, D_2O exchangeable), 6.47 (s, 2H); HRMS: *m/e* calcd for (M+) $C_{14}H_{22}O_5$ 270.1467; found 270.1464.

5-(4'-Benzyloxyphenyl)-1,2-pentanediol (**7d**).

Compound **7d** was synthesized using the general procedure with **6d** (3.60 g, 11.03 mmol) to give 3.05 g (97% yield) of a white solid; R_f=0.27 (hexane- ethyl acetate, 1:5), mp 64-67 °C (hexane-ethyl acetate). ^{1}H nmr (DMSO-d_6): δ 1.15-1.70 (m, 4H), 2.50 (t, 2H), 3.22 (m, 2H), 3.40 (m, 1H), 3.60 (d, 1H, D_2O exchangeable), 4.41 (t, 1H, D_2O exchangeable), 5.05 (s, 2H), 6.90 (d, 2H), 7.08 (d, 2H), 7.31-7.44 (m, 5H).

Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.50; H, 7.74. Found: 75.42; H, 7.62.

5-(1'-Naphthyl)-1,2-pentanediol (**7e**).

Compound **7e** was synthesized as in the general procedure with **6e** (2.15 g, 7.95 mmol) to give 1.8 g (98% yield) of a colorless liquid; R_f=0.26 (hexane-ethyl acetate, 1:4); ^{1}H nmr (DMSO-d_6): δ 1.35-1.82 (m, 4H), 3.02 (t, 2H), 3.24 (m, 2H), 3.45 (m, 1H), 4.42 (d, 1H, D_2O exchangeable), 4.45 (t, 1H, D_2O exchangeable), 7.34-8.09 (m, 7H).

5-(2'-Naphthyl)-1,2-pentanediol (**7f**).

Compound **7f** was synthesized as in the general procedure with **6f** (0.80 g, 2.96 mmol) to give 0.666 g (82% yield) of a white solid; R_f=0.26 (hexane-ethyl acetate, 1:4), m.p. 72-75° C (hexane-ethyl acetate); ^{1}H nmr (DMSO-d_6) δ 1.29 (m, 1H), 1.50 (m, 1H), 1.67 (m, 1H), 1.80 (m, 1H), 2.74 (t, 2H), 3.26 (m, 2H), 3.41 (m, 1H), 4.41 (d, 1H, D_2O exchangeable), 4.43 (t, 1H, D_2O exchangeable), 7.37-7.87 (m, 7H).

Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found C, 78.12; H, 7.85.

5-Phenyl-1,2-pentanediol (**7g**).

Compound **7g** was synthesized as in the general procedure with **6g** (2.3 g, 10.44 mmol) to give 1.65 g (88% yield) of a colorless liquid; R_f=0.25 (hexane- ethyl acetate, 1:3); ^{1}H nmr (DMSO-d_6): δ 1.18-1.80 (m, 4H), 2.56 (t, 2H), 3.24 (m, 2H), 3.45 (m, 1H), 4.38 (d, 1H, D_2O exchangeable), 4.42 (t, 1H, D_2O exchangeable), 7.15-7.29 (m, 5H).

General Procedure for the Synthesis of Compounds **8a**-**g**.

To a mixture of the diol in dry dichloromethane (6 ml), **7a**-**g** (1 equivalent) and bis(tributyltin) oxide (1.3 equivalents) was added dropwise a solution of bromine (1.3 equivalents) in 10 ml of dichloromethane at room temperature with stirring under a nitrogen atmosphere. The mixture was stirred at this temperature for additional 10 hours. The resulting solution was evaporated to dryness to give a crude product which was chromatographed on silica gel with hexane-ethyl acetate to afford **8a-g**.

5-(2',5'-Dichlorophenyl)-1-hydroxy-2-pentanone (**8a**).

Compound **8a** was synthesized as in the general procedure with **7a** (0.86 g, 3.44 mmol) to give 0.72 g (84% yield) of a colorless liquid; R_f=0.29 (hexane-ethyl acetate, 2:1); ^{1}H nmr (DMSO-d_6): δ 1.70-1.81 (m, 2H), 2.45 (t, 2H), 2.65 (t, 2H, *J*=6.5 Hz), 4.03 (d, 2H), 5.08 (t, 1H), 7.31-7.45 (m, 3H); HRMS: *m/e* calcd for (M+) $C_{11}H_{12}O_2Cl_2$ 246.0214; found 246.0206.

5-(2',5'-Dimethoxyphenyl)-1-hydroxy-2-pentanone (**8b**).

Compound **8b** was synthesized as in the general procedure with **7b** (0.35 g, 1.46 mmol) to give 0.26 g (75% yield) of a colorless oil; R_f=0.26 (hexane-ethyl acetate, 1:1). ^{1}H nmr (DMSO-d_6): δ 1.65-1.85 (m, 2H), 2.39 (t, 2H), 2.50 (t, 2H), 3.71 9 (s, 3H), 3.78 (s, 3H), 4.02 (d, 2H), 5.05 (t, 1H), 6.71-6.92 (m, 3H); HRMS: *m/e* calcd for (M+) $C_{13}H_{18}O_4$ 238.1205; found 238.1196.

5-(3',4',5'-Trimethoxyphenyl)-1-hydroxy-2-pentanone (**8c**).

Compound **8c** was synthesized as in the general procedure with **7c** (0.97 g, 3.59 mmol) to give 0.89 g (92% yield) of a colorless oil; R_f=0.54 (hexane-ethyl acetate,1:5); ^{1}H nmr (DMSO-d_6): δ 1.73 (quin, 2H, *J*=7.2 Hz), 2.45 (t, 2H, *J*=7.3 Hz), 2.60 (t, 2H, *J*=7.0 Hz), 3.13 (s, 3H), 3.75 (s, 3H), 3.78 (s, 3H), 4.11 (d, 2H, *J*=5.8 Hz), 5.07 (t, 1H, *J*=5.8 Hz, D_2O exchangeable), 6.80 (s, 2H).

5-(4'-Benzyloxyphenyl)-1-hydroxy-2-pentanone (**8d**).

Compound **8d** was synthesized using the general procedure with **7d** (2.97 g, 10.37 mmol) to give 2.30 g (78% yield) of a white solid; R_f=0.48 (hexane-ethyl acetate, 1:1); m.p. 65-68° C (hexane-ethyl acetate); ^{1}H nmr (DMSO-d_6): δ 1.72 (quin, 2H), 2.38 (t, 2H), 2.48 (t, 2H), 4.01 (d, 2H), 5.05 (s, 3H, one proton D_2O exchangeable), 6.91 (d, 2H), 7.10 (d, 2H), 7.25-7.49 (m, 5H).

Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09; Found: C, 75.88; H, 7.12.

5-(1'-Naphthyl)-1-hydroxy-2-pentanone (**8e**).

Compound **8e** was synthesized as in the general procedure with **7e** (0.87 g, 3.91 mmol) to give 0.83 g (96% yield) of a colorless oil; R_f=0.50 (hexane-ethyl acetate, 1:1). ^{1}H nmr (DMSO-

d$_6$): δ 1.86 (quin, 2H), 2.52 (t, 2H), 3.01 (t, 2H), 4.12 (d, 2H), 5.09 (t, 1H, D_2O exchangeable), 7.33-8.13 (m, 7H); HRMS: *m/e* calcd for (M+) $C_{15}H_{16}O_2$ 228.1150; found 228.1143.

5-(2'-Naphthyl)-1-hydroxy-2-pentanone (**8f**).

Compound **8f** was synthesized as in the general procedure with **7f** (1.20 g, 5.21 mmol) to give 1.02 g (86% yield) of a white solid; R_f=0.52 (hexane-ethyl acetate, 1:1); mp 64-67° C (hexane). ^{1}H nmr (DMSO-*d*$_6$): δ 1.84-1.92 (m, 2H), 2.45 (t, 2H, *J*=7.3 Hz), 2.73 (t, 2H, *J*=7.3 Hz), 4.02 (d, 2H, *J*=5.9 Hz), 5.07 (t, 1H, *J*=5.9 Hz), 7.36-7.87 (m, 7H).

Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.07; Found: C, 78.85; H, 7.11.

5-Phenyl-1-hydroxy-2-pentanone (**8g**).

Compound **8g** was synthesized using the general procedure with **7g** (1.55 g, 8.60 mmol) to give 1.27 g (83% yield) of a colorless oil; R_f =0.48 (hexane-ethyl acetate, 1:1); ^{1}H nmr (DMSO-*d*$_6$) δ 1.75 (quin, 2H), 2.40 (t, 2H), 2.54 (t, 2H), 4.02 (d, 2H), 5.06 (t, 1H, D_2O exchangeable), 7.17-7.30 (m, 5H); HRMS: *m/e* calcd for (M+) $C_{11}H_{14}O_2$ 178.0993; found 178.0990.

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

To a solution of the hydroxy ketones (1 equivalent) in methanol (3 ml) at room temperature was added a mixture of malononitrile (1 equivalent) and triethylamine (1 equivalent) in methanol (1 ml), and the solution was stirred at room temperature for an additional 20 hours. The solvent was evaporated under reduced pressure and the residue was chromatograghed on silica gel with hexane-ethyl acetate at appropriate ratios to give **9a-g**.

2-Amino-3-cyano-4-[3'-(2',5'-dichlorophenyl)propyl]-furan (**9a**).

Compound **9a** was synthesized as in the general procedure with **8a** (0.71 g, 2.85 mmol) to give 0.69 g (82% yield) of a white solid; R_f=0.28 (hexane-ethyl acetate, 3:1); mp 137-140 °C (hexane-ethyl acetate). ^{1}H nmr (DMSO-*d*$_6$): δ 1.77-1.82 (m, 2H), 2.33 (t, 2H, *J*=7.3 Hz), 2.71 (t, 2H, *J*=7.3 Hz), 6.80 (s, 1H), 7.23 (s, 2H, D_2O exchangeable), 7.32-7.45 (m, 3H).

Anal. Calcd. for $C_{14}H_{12}ON_2Cl_2$: C, 56.97; H, 4.10; N, 9.49; Cl, 24.02; Found: C, 56.69; H, 3.98; N, 9.32; Cl, 24.08.

2-Amino-3-cyano-4-[3'-(2',5'-dimethoxyphenyl)propyl]-furan (**9b**).

Compound **9b** was synthesized as in the general procedure with **8b** (253 mg, 1.06 mmol) to afford 193 mg (64% yield) of a light yellow liquid; R_f=0.20 (hexane-ethyl acetate, 2:1). ^{1}H nmr (DMSO-*d*$_6$): δ 1.70-1.85 (m, 2H), 2.29 (t, 2H), 2.51 (t, 2H), 3.68 (s, 3H), 3.72 (s, 3H), 6.77 (s, 1H), 6.73-7.14 (m, 3H), 7.21 (2H, D_2O exchangeable); HRMS: *m/e* calcd for (M+) $C_{16}H_{18}N_2O_3$ 286.1317; found 286.1321.

2-Amino-3-cyano-4-[3'-(3',4',5'-trimethoxyphenyl)propyl]-furan (**9c**).

Compound **9c** was synthesized as in the general procedure with **8c** (683 mg, 2.54 mmol) to yield 690 mg (86% yield) of a brown-red solid; R_f=0.50 (hexane-ethyl acetate, 2:1); mp 111-113 °C (hexane-ethyl acetate); ^{1}H nmr (DMSO-*d*$_6$): δ 1.81 (m, 2H), 2.34 (t, 2H), 2.68 (t, 2H), 3.74 (s, 3H), 3.77 (s, 3H), 3.79 (s, 3H), 6.80 (s, 2H), 6.83 (s, 1H), 7.22 (s, 2H, D_2O exchangeable).

2-Amino-3-cyano-4-[3'-(4'-benzyloxyphenyl)propyl]-furan (**9d**).

Compound **9d** was synthesized as in the general procedure with **8d** (900 mg, 3.17 mmol) to yield 1.00 g (95% yield) of a white solid; R_f=0.28 (hexane-ethyl acetate, 2:1); mp 98-102° C (hexane-ethyl acetate); ^{1}H nmr (DMSO-*d*$_6$): δ 1.74 (quin, 2H), 2.27 (t, 2H), 2.53 (t, 2H), 5.06 (s, 2H), 6.75 (s, 1H), 6.90 (d, 2H), 7.10 (d, 2H), 7.20 (s, 2H, D_2O exchangeable), 7.30-7.45 (m, 5H).

Anal. Calcd for $C_{21}H_{20}N_2O_2 \bullet 0.1H_2O$: C, 75.47; H, 6.09; N, 8.38; Found: C, 75.38; H, 6.08; N, 8.23.

2-Amino-3-cyano-4-[3'-(1'-naphthyl)propyl]-furan (**9e**).

Compound **9e** was synthesized using the general procedure with **8e** (500 mg, 2.19 mmol) to give 500 mg (87% yield) of a colorless oily liquid; R_f=0.18 (hexane-ethyl acetate, 2:1); ^{1}H nmr (DMSO-*d*$_6$): δ 1.92 (m, 2H), 2.42 (t, 2H), 3.08 (t, 2H), 6.81 (s, 1H), 7.24 (s, 2H , D_2O exchangeable), 7.30-8.11 (m, 7H).

2-Amino-3-cyano-4-[3'-(2'-naphthyl)propyl]-furan (**9f**).

Compound **9f** was synthesized as in the general procedure with **8f** (856 mg, 3.75 mmol) to give 880 mg (89% yield) of a white solid; R_f=0.28 (hexane-ethyl acetate, 2:1). The solid was recrystallized from hexane-ethyl acetate to afford light yellow crystals; mp 113-115 °C. ^{1}H nmr (DMSO-*d*$_6$): δ 1.88-1.93 (m, 2H), 2.33 (t, 2H, *J*=7.3 Hz), 2.78 (t, 2H, *J*=7.3 Hz), 6.80 (s, 1H), 7.24 (s, 2H, D_2O exchangeable), 7.38-7.87 (m, 7H).

Anal. Calcd. for $C_{18}H_{16}N_2O$: C, 78.24; H, 5.84; N, 10.14; Found: C, 77.96; H, 5.86; N, 10.16.

2-Amino-3-cyano-4-[3-(phenyl)-propyl]-furan (**9g**).

Compound **9g** was synthesized as in the general procedure with **8g** (1.23 g, 6.90 mmol) to give 1.23 g (79% yield) of a light yellow solid; R_f=0.30 (hexane-ethyl acetate, 5:2); mp 82-84 °C (hexane-ethyl acetate); ^{1}H nmr (DMSO-*d*$_6$): δ 1.80 (quin, 2H), 2.29 (t, 2H), 2.60 (t, 2H), 6.77 (s, 1H), 7.18-7.30 (m, 5H), 7.22 (s, 2H, D_2O exchangeable).

Anal. Calcd. for $C_{14}H_{14}N_2O \bullet 0.1H_2O$: C, 73.73; H, 6.28; N, 12.28; Found: C, 73.59; H, 6.21; N, 12.23.

General Procedure for the Synthesis of Compounds **1a**-**g**.

To a solution of **9a**-**g** (1 equivalent) in ethanol (1.7 ml) was added 1.5 equivalents of guanidine hydrochloride and then 1.5 equivalents of $NaOCH_3$. The mixture was refluxed at 100-110° C for 3 days. The solvent was evaporated under reduced pressure to give a residue which was chromatographed on silica gel with methanol-chloroform to give **1a-g**.

2,4-Diamino-5-[3-(2',5'-dichlorophenyl)propyl]-pyrrolo[2,3-*d*]-pyrimidine (**1a**).

Compound **1a** was synthesized as in the general procedure with **9a** (0.57 g, 1.93 mmol) to give 0.44 g (68% yield) of a light yellow solid; R_f = 0.12 (chloroform-methanol, 20:1); mp 202-204 °C (decomposition); ^{1}H nmr (DMSO-*d*$_6$): δ 1.81-1.91 (m, 2H), 2.73 (t, 2H), 2.80 (t, 2H), 5.34 (s, 2H, D_2O exchangeable), 5.93 (s, 2H, D_2O exchangeable), 6.44 (s, 1H), 7.30-7.44 (m, 3H), 10.38 (s, 1H, D_2O exchangeable).

Anal. Calcd for $C_{15}H_{15}N_5Cl_2 \bullet 0.2H_2O$: C, 53.28; H, 4.65; N, 20.44; Cl, 20.69; Found: C, 53.68; H, 4.60; N, 20.10; Cl, 20.66.

2,4-Diamino-5-[3-(2',5'-dimethoxyphenyl)propyl]-pyrrolo[2,3-*d*]-pyrimidine (**1b**).

Compound **1b** was synthesized as in the general procedure with **9b** (175 mg, 0.612 mmol) to give 106 mg (53% yield) of a light yellow solid; R_f =0.39 (chloroform-methanol, 10:1); mp 144-146°

C (dec.); ^{1}H nmr (-DMSO-d_6): δ 1.75-1.86 (m, 2H), 2.59 (t, 2H), 2.64 (t, 2H), 3.56 (s, 3H), 3.60 (s, 3H), 5.34 (s, 2H, D_2O exchangeable), 5.87 (s, 2H, D_2O exchangeable), 6.43 (s, 1H), 6.73-7.13 (m, 3H), 10.36 (s, 1H, D_2O exchangeable); HRMS: *m/e* calcd for (M+) $C_{17}H_{21}N_5O_2$ 327.1695; found 327.1691.

2,4-Diamino-5-[3-(3',4',5'-trimethoxyphenyl)propyl]-pyrrolo[2,3-*d*]pyrimidine (**1c**).

Compound **1c** was synthesized as in the general procedure with **9c** (859 mg, 2.72 mmol) to give 895 mg (88% yield) of a light yellow solid; R_f =0.28 (chloroform-methanol,10:1); mp 160-161.5 °C (hexane-chloroform). ^{1}H nmr (DMSO-d_6): δ 1.81 (m, 2H), 2.72 (m, 4H), 3.73 (s, 3H), 3.75 (s, 3H), 3.78 (s, 3H), 5.37 (s, 2H, D_2O exchangeable), 5.94 (s, 2H, D_2O exchangeable), 6.45 (s, 1H), 6.81 (s, 2H), 10.39 (s, 1H, D_2O exchangeable).

Anal. Calcd for $C_{18}H_{23}N_5O_3$•1.0$CHCl_3$: C, 47.86; H, 5.07; N, 14.69; Found: C, 47.87; H, 5.12; N, 14.82.

2,4-Diamino-5-[3-(4'-benzyloxyphenyl)propyl]-pyrrolo[2,3-*d*]pyrimidine (**1d**).

Compound **1d** was synthesized as in the general procedure with **9d** (606 mg, 1.82 mmol) to give 550 mg (78% yield) of a light yellow solid; R_f =0.31 (chloroform-methanol, 10:1); mp 174-176 °C (dec. methanol-chloroform). ^{1}H nmr (DMSO-d_6): δ 1.78 (quin, 2H), 2.57 (t, 2H), 2.65 (t, 2H), 5.05 (s, 2H), 5.38 (s, 2H, D_2O exchangeable), 5.92 (s, 2H, D_2O exchangeable), 6.41 (s, 1H), 6.90 (d, 2H), 7.10 (d, 2H), 7.31-7.44 (m, 5H), 10.39 (s, 1H, D_2O exchangeable).

Anal. Calcd for $C_{22}H_{23}N_5O$•0.3 H_2O: C, 69.75; H, 6.28; N, 18.49; Found: C, 69.86; H, 6.12; N, 18.43.

2,4-Diamino-5-[3-(1'-naphthyl)propyl]-pyrrolo[2,3-*d*]pyrimidine (**1e**).

Compound **1e** was synthesized as in the general procedure with **9e** (475 mg, 1.81 mmol) to give 320 mg (78% yield) of a light yellow solid; R_f=0.29 (chloroform-methanol, 10:1); mp 78-80 °C (dec.). ^{1}H nmr (DMSO-d_6): δ 1.94 (m, 2H), 2.79 (t, 2H), 3.11 (t, 2H), 5.42 (s, 2H, D_2O exchangeable), 6.05 (s, 2H, D_2O exchangeable), 6.47 (s, 1H), 7.38-8.02 (m, 7H), 10.44 (s, 1H, D_2O exchangeable).

Anal. Calcd for $C_{19}H_{19}N_5$•0.7H_2O: C, 69.15; H, 6.23; N, 21.22; Found: C, 69.05; H, 5.92; N, 21.18.

2,4-Diamino-5-[3-(2'-naphthyl)propyl]-pyrrolo[2,3-*d*]pyrimidine (**1f**).

Compound **1f** was synthesized as in the general procedure with **9f** (740 mg, 2.82 mmol) to give 580 mg (65% yield) of a light yellow solid; R_f=0.25 (chloroform-methanol, 10:1); mp 214-216 °C (dec.). ^{1}H nmr (DMSO-d_6): δ 1.85-2.01 (m, 2H), 2.72 (t, 2H, *J*=7.3 Hz), 2.82 (t, 2H, *J*=7.5 Hz), 5.36 (s, 2H, D_2O exchangeable), 5.94 (s, 2H, D_2O exchangeable), 6.45 (s, 1H), 7.35-7.86 (m, 7H), 10.40 (s, 1H, D_2O exchangeable).

Anal. Calcd for $C_{19}H_{19}N_5$•0.3H_2O: C, 70.70; H, 6.12; N, 21.70; Found: C, 70.88; H, 6.23; N, 21.32.

2,4-Diamino-5-[(3'-phenyl)propyl]-pyrrolo[2,3-*d*]pyrimidine (**1g**).

Compound **1g** was synthesized as in the general procedure with **9g** (725 mg, 3.20 mmol) to give 400 mg (47% yield) of a light yellow solid; R_f =0.35 (chloroform-methanol, 10:1); mp 159-161 °C (hexane-chloroform); ^{1}H nmr (DMSO-d_6): δ 1.82 (quin, 2H), 2.62 (m, 4H), 5.32 (s, 2H, D_2O exchangeable), 5.87 (s, 2H, D_2O exchangeable), 6.41 (s, 1H), 7.18-7.27 (m, 5H), 10.35 (s, 1H, D_2O exchangeable).

Anal. Calcd for $C_{15}H_{17}N_5$•0.1H_2O: C, 66.94; H, 6.44; N, 26.02; Found: C, 66.78; H, 6.36; N, 25.78.

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