Formation of Aryl-bis (6-Amino-1,3-Dimethyluracil-5-yl) Methanes by reaction of 6-Amino-1, 3-Dimethyluracil with Aromatic Aldehydes

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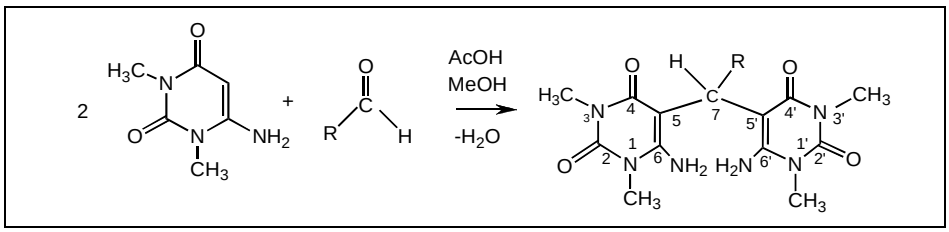

The synthesis of aryl-bis(6-amino-1,3-dimethyluracil-5-yl)-methanes **3a-m** by condensation of 6-amino-1,3-dimethyluracil (**1**) with aromatic aldehydes **2a-m** at room temperature is reported. The structures of the compounds were established using various spectroscopic analyses and X-ray crystallography. The crystal structures of two aryl-bis (6-amino-1,3-dimethyluracil-5-yl) methanes are presented.

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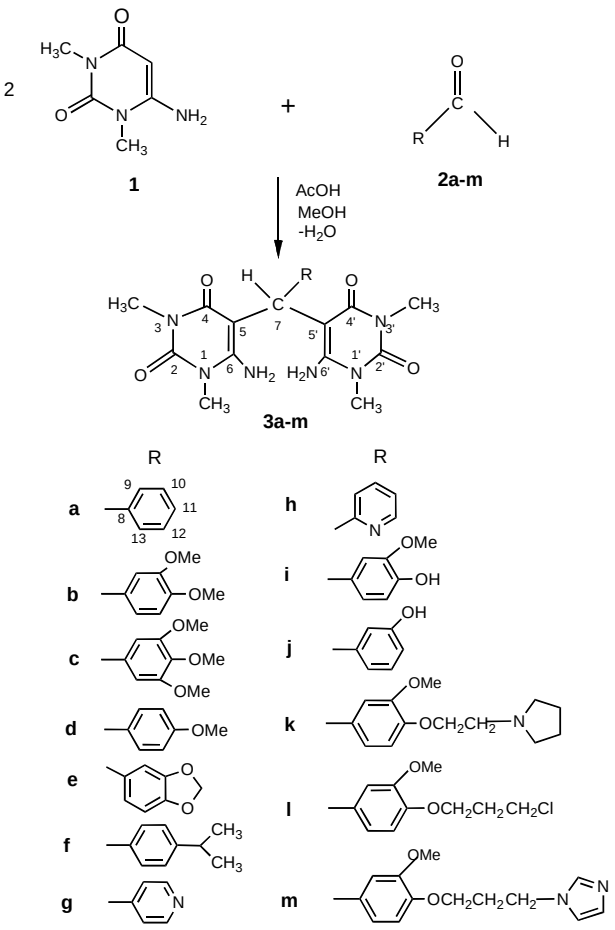
INTRODUCTION

The role of methylxanthines as phosphodiesterase (PDE) inhibitors is well established and theophylline is now routinely used as a phosphodiesterase inhibitor for the treatment of asthma [1–5]. In order to investigate the minimal structural requirements for inhibiting phosphodiesterases by xanthines, a series of uracil derivatives have been synthesized and studied by Garst *et al.* [6]. The uracil ring of the xanthine nucleus plays a vital role in phosphodiesterase inhibition and the imidazole portion is insufficient to maintain inhibition of phosphodiesterase [7]. The present study was also aimed at the synthesis of a new series of 6-amino-1,3-dimethyluracil derivatives in order to investigate their PDE inhibitory effects. However, during the synthesis of these compounds some interesting bis-products were obtained, which we report herein.

RESULTS AND DISCUSSION

While synthesizing a series of 6-amino-1,3-dimethyluracil derivatives, condensation of 6-amino-1,3-dimethyluracil (**1**) [8] with various aromatic aldehydes such as benzaldehyde, veratraldehyde, 3,4,5-trimethoxybenzaldehyde, *p*-anisaldehyde, piperonal, cuminaldehyde, pyridine-4-carboxaldehyde, pyridine-2-carboxaldehyde, vanillin and 3-hydroxybenzaldehyde (**2a-j**) in the presence of glacial acetic acid and methanol at room temperature led to the formation of the respective aryl-*bis*(6-amino-1,3-dimethyluracil-5-yl)methanes **3a-j** as outlined in Scheme I.

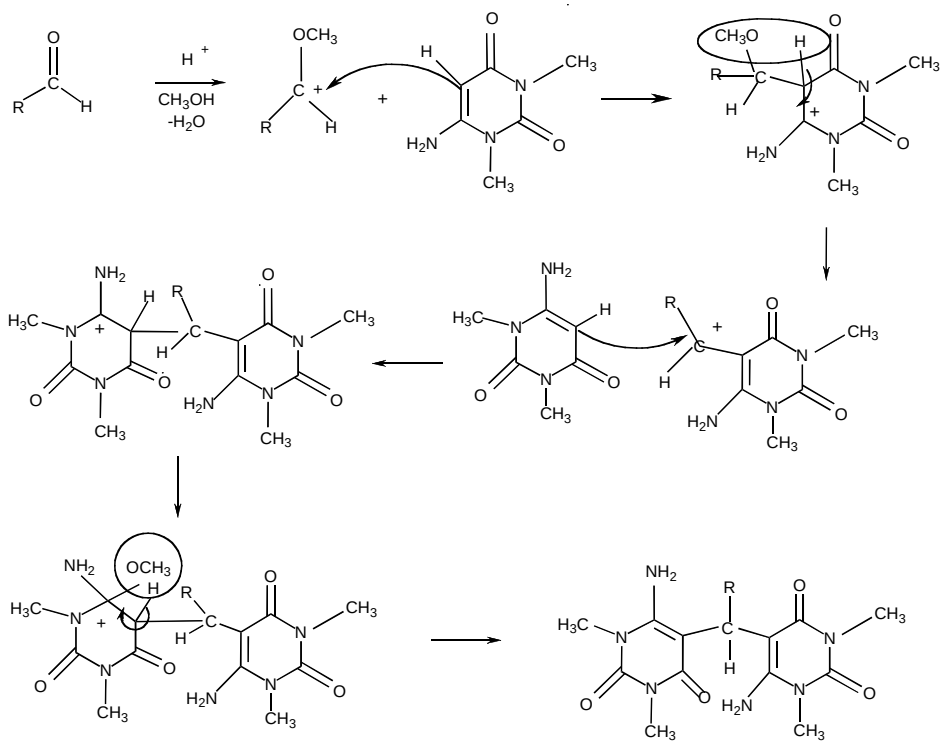
Scheme I



For the preparation of **3k** and **3l**, vanillin was condensed with 1-(2-chloroethyl)pyrrolidine hydrochloride and 1-bromo-3-chloropropane in ethyl methyl ketone in the presence of anhydrous potassium carbonate to get oily residues, which were used as such and treated with 6-amino-1,3-dimethyluracil by using a similar procedure. Further fusion of chloro derivative **3l** with imidazole at 110 °C for 2 h yielded the target imidazole derivative **3m**. Most of the bis-methanes were isolated as crystalline materials in good yields by stirring the reactants overnight at room temperature.

substituents in the compounds **3a-m** were also observed at the appropriate places. In order to further confirm the carbon skeleton, ^{13}C NMR spectra of some of the bis-products were also studied. The ^{13}C NMR spectra showed characteristic peaks near δ 27.7 (C(7)), 29.4 (*Me*-N(3, 3'), 34.4 (*Me*-N(1,1'), 153.5 (C(2,2'), C=O), 162.9 (C(4,4'), C=O) and for aromatic carbons between 125-126 ppm. The proposed structures were also confirmed by X-ray crystallographic studies for **3a** and **3i**. The formation of the bis-methanes could be explained by the mechanism illustrated in Scheme II. The electrophile generated by

Scheme II Mechanism illustrating the formation of bis-methanes



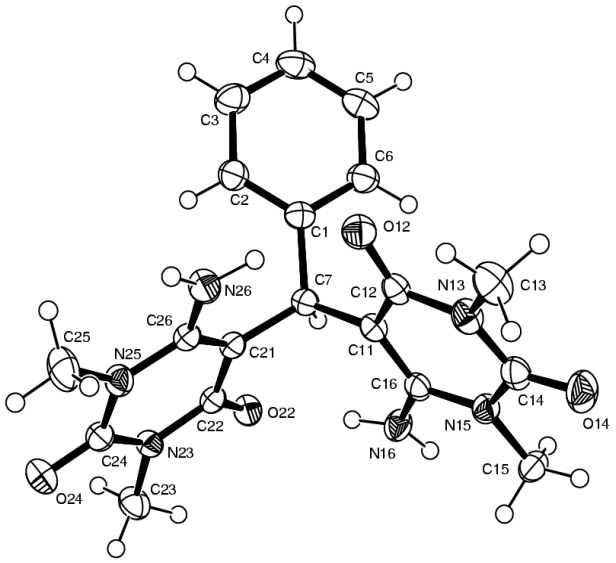
However pyridyl substituted derivatives **3g** and **3h** could be obtained within 2 h of stirring the corresponding reactants but in lower yields. Detailed spectroscopic studies of the obtained bis-products confirmed their structures. Characteristic asymmetrical and symmetrical stretching for free amino groups were observed at 3470 and 3350 cm^{-1}, respectively, in the infrared spectra of all the bis-products **3a-m**. Proton NMR spectra of **3a-m** showed four singlets, each integrating for 3 protons of four *N*-methyls, which indicated the presence of two uracil nuclei. A singlet appeared at δ 5.75 ppm for the *H*–C(7) of bis-methanes through which the two nuclei are connected to each other. Two exchangeable free amino groups appeared as broad singlets ranging from δ 6.50 - 7.25 ppm in the proton NMR spectra of all of the products. Signals for various protons of the respective

acid catalysed reaction of aldehyde with methanol attacks the electron rich center of 6-aminouracil, which is stabilized by free amino and carbonyl group. Removal of methanol followed by rearrangement leads to the formation of another electron deficient carbonium ion, which combines with one more nucleophilic uracil nucleus to form bis-methanes.

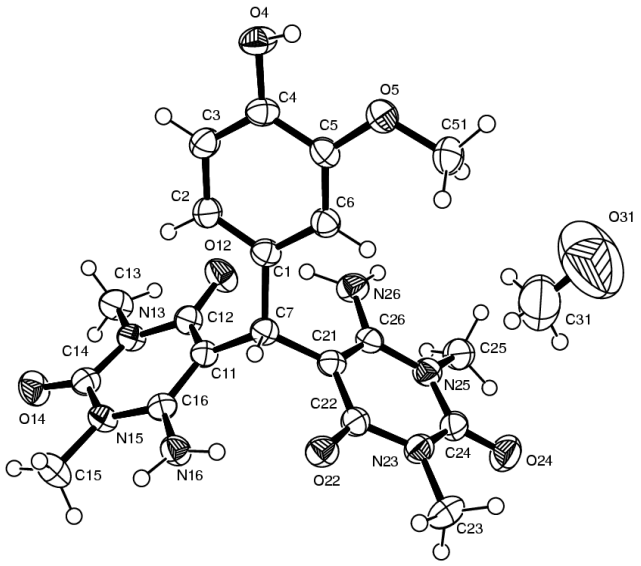
6-Aminouracils are key intermediates in the synthesis of a number of xanthine based drug molecules and also act as starting compounds for the synthesis of new condensed heterocycles exhibiting intriguing pharmacological activities [9-11], the formation of interesting aryl-bis (6-amino-1,3-dimethyluracil-5-yl) methanes by acid catalysed condensation of 6-amino-1,3-dimethyluracil with aromatic aldehydes with stirring at room temperature in methanol could be a key step for the

formation of novel pharmacologically attractive heterocyclic structures.

Crystallography. Views of the asymmetric units in the structures of **3a** and **3i**, with atomic numbering schemes, are shown in Figures 1a and 1b, respectively.



1a



1b

Figure 1. ORTEP representation of the asymmetric unit in the structure of compound **3a** (a) compound **3i**.0.5MeOH (b), showing the atom-labeling scheme (Displacement ellipsoids are drawn at the 50% probability level and H atoms are represented by circles of arbitrary radii).

Compound **3i** crystallizes as a methanol hemisolvate, in which the methanol molecule is disordered over two positions close to an inversion center. The bond lengths and angles in **3a** and **3i** have normal values in each structure; the orientations of the pyrimidinedione rings relative to the phenyl rings are different. The dihedral angles between the plane of the phenyl ring and those of the two-pyrimidinedione rings are 76.6(1) and 66.2(1)° in **3a**. The corresponding angles in **3i** are 69.1(1) and 80.7(1)°. The dihedral angle between the planes of the two-pyrimidine rings is 64.4(1)° in **3a** and 54.2(1)° in **3i**.

The structures of **3a** and **3i** are stabilized by series of N–H…O hydrogen bonds (Table 1 & 2). In **3a**, atoms N(16) and N(26) act as donors for intramolecular hydrogen bonds with carbonyl atoms O(22) and O(12), respectively. Each interaction can be described by a graph-set motif of *S*(8) [12]. In addition, atom N(16) [*via* H(162)] is involved in an intermolecular N–H…O hydrogen bond with carbonyl atom O(22) of a neighboring centro- symmetrically related molecule. Taken together, the intra- and intermolecular hydrogen bonds involving N(16)…O(22) interactions generate dimers across an inversion center and create a ring motif which can be described by a graph-set motif of $R_4^2(8)$ (Figure 2).

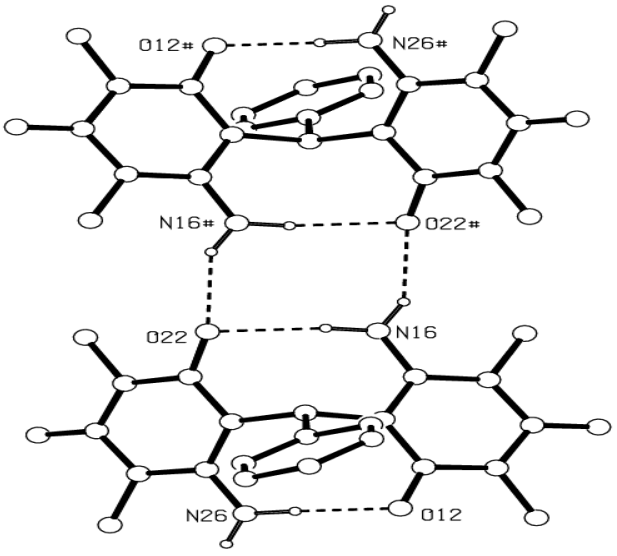


Figure 2. The hydrogen bonding in **3a**, showing the formation of a centrosymmetric dimmer and the $R_4^2(8)$ ring motif (Atoms marked with a hash (#) are at the symmetry positions (-x,1-y,1-z)).

Table 1

Hydrogen-bond parameters (Å, °)

D–H…A	d(D–H)	d(H…A)	d(D…A)	∠D–H…A
Compound 3a				
N16–H161…O22	0.92(2)	2.04(2)	2.951(2)	171(2)
N16–H162…O22^{i}	0.88(2)	2.06(2)	2.863(2)	151(2)
N26–H261…O12	0.95(2)	1.82(2)	2.749(2)	164(2)
Compound 3i.0.5MeOH				
O4–H4…O22^{ii}	0.89(3)	1.91(3)	2.737(3)	154(3)
N16–H161…O22	0.86(3)	2.04(3)	2.883(3)	168(2)
N16–H162…O4^{iii}	0.89(3)	2.40(3)	3.276(3)	167(3)
N26–H261…O12^{iv}	0.85(3)	2.55(3)	3.338(3)	155(3)
N26–H261…O12	1.00(4)	1.81(4)	2.755(3)	156(3)
C25–H251…O12^{iv}	0.98	2.34	3.154(3)	140
C51–H512…O24^{v}	0.98	2.56	3.409(4)	145

Symmetry codes: (i) -x,-y+1,-z+1; (ii) -x,-y,-z+2; (iii) x+1/2,-y-1/2,z+1/2; (iv) -x+1/2,y+1/2,-z+3/2; (v) -x,-y+1,-z+2

Table 2

Crystallographic Data of compounds **3a** and **3i**

		3a	**3i**
Empirical formula		$C_{19}H_{22}N_6O_4$	$C_{20}H_{24}N_6O_6$, 0.5(CH_3OH)
M_r		398.4	460.5
Crystal color, habit		colourless, prism	colourless, prism
Crystal dimensions [mm]		0.25 x 0.25 x 0.18	0.25 x 0.20 x 0.18
Temperature [K]		160(2)	160(2)
Crystal system		Monoclinic	Monoclinic
Space group		$P2_1/n$	$P2_1/n$
Z		4	4
Reflections for cell determination		4565	3879
2θ Range for cell determination [°]		4–55	4–50
Unit cell parameters	a [Å]	12.2918(3)	14.3616(5)
	b [Å]	8.1130(2)	9.4789(3)
	c [Å]	19.3728(4)	15.1782(5)
	β [°]	105.5443(15)	94.463(2)
V [Å^3]		1861.26(8)	2059.98(12)
Dx [g cm^{-3}]		1.422	1.485
μ [mm^{-1}]		0.103	0.113
Scan type		ϕ and ω	ϕ and ω
$2\theta_{(max)}$ [°]		55	50
Total reflections measured		47241	26753
Symmetry-independent reflections		4263	3642
Reflections with (I > 2σ(I))		3248	2724
Reflections used in refinement		4263	3642
Parameters refined		282	334
Final	*R(F)* (I > 2σ(I) reflections	0.0492	0.0548
	wR(F^2) (all data)	0.1348	0.1603
Goodness of fit		1.066	1.026
Final Δ_{max}/σ		0.000	0.000
$\Delta\rho$ (max; min) [e Å^3]		0.26; -0.27	0.27; -0.27

Weights: For **3a** w = $[\sigma^2(F_o^2)+(0.0687P)^2+0.4769P)]^{-1}$; for **3i** w = $[\sigma^2(F_o^2)+(0.0856P)^2+1.0009P)]^{-1}$; where $P = (F_o^2+2F_o^2)/3$

Surprisingly, the second H-atom on atom N(26) is not involved in any hydrogen bonds, thus precluding the presence of an anticipated ladder structure. In case of **3i**, one of the amino groups [N(26)] forms bifurcated hydrogen bonds. One of these is intramolecular and involves the carbonyl O-atom, O(12), of one of the pyrimidine rings. The second interaction is also with O(12), but in an adjacent molecule. The intramolecular interaction generates an *S*(8) motif, while the intermolecular interaction links the molecules into which run parallel to the crystallographic *b* axis (Fig. 3) and can be described by a graph-set motif of *C*(8). One H atom of the other amino group (N16) forms an intramolecular hydrogen bond with the carbonyl O atom, O(22), to give

an *S*(8) motif. The other H atom forms an intermolecular hydrogen bond with the hydroxyl O atom, O(4), of a neighboring molecule and thereby links the molecules into chains which run parallel to the crystallographic *c* axis and can be described by a graph-set motif of *C*(10). Atom C(25) is involved in a weak intermolecular C–H…O interaction with carbonyl atom O(12). This weak interaction links the molecules into a chain, which runs parallel to the axis and has a graph-set motif of *C*(9).

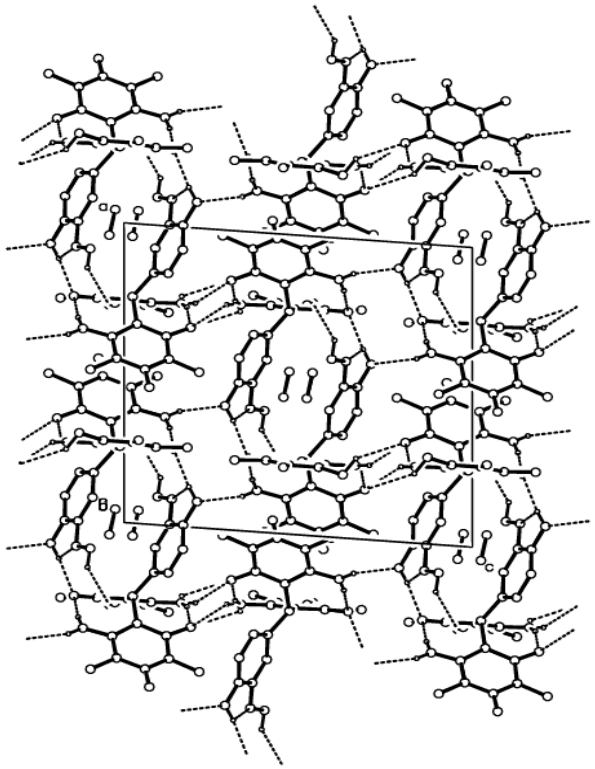


Figure 3. The crystal structure of **3i.** 0.5 MeOH projected onto the ac plane, showing the hydrogen bonding (for clarity, H atoms not involved in the hydrogen bonding have been omitted).

Atom C(51) has also weak intermolecular C–H…O interaction with atom O(24) of a neighboring centro-symmetrically-related molecule. This interaction produces a $R_2^2(24)$ loop.

EXPERIMENTAL

Materials obtained from the commercial suppliers were used without further purification. Anhydrous Na_2SO_4 was used as a drying agent. The purity of the compounds was established by TLC and elemental analyses. TLC: plates (*E. Merck*, Darmstadt, Germany) were prepared according to *Stahl* (activated at 110°C for 30 min.); AcOEt as a solvent; visualization by I_2 vapors. M.p.*: MP1-Veego* instrument (*Veego Instruments*, Mumbai, India); uncorrected. IR spectra: *Perkin-Elmer* spectrum RX 1, FT-IR spectrophotometer (Huenenberg, Switzerland). KBr pellets; ν_{max} in cm^{-1}. ^1H- and ^{13}C-NMR spectra: *Bruker AC-300F* (300 MHz) instrument (*Bruker AG*, Fällanden, Switzerland); Me_4Si as the internal standard; chemical shifts δ in ppm, *J* in Hz. Elemental analyses (C, H, N): *Perkin-Elmer-2400* apparatus.

General Procedure. Compounds **3a-l** were prepared by treating equimolar quantities (2.58 mmol) of 6-amino-1,3-dimethyluracil and the requisite aromatic aldehyde in methanol (16.0 mL) and glacial acetic acid (4.0 mL) with constant stirring. Although pyridyl substituted derivatives **3g** and **3h** could be isolated within 2 h of stirring the corresponding reactants, formation of rest of the bis-products required overnight stirring. The completion of the reaction was monitored by TLC. The reaction was worked up by addition of water and further basification with aqueous sodium hydroxide. The precipitate obtained was collected by filtration, washed thoroughly with water, dried and recrystallized using appropriate solvents. For the synthesis of **3h** and **3l**, aromatic aldehydes, 3-methoxy-4-(2-pyrrolidin-1yl-ethoxy) benzaldehyde and 3-methoxy-4-(3-chloropropoxy) benzaldehyde were prepared by adding 1-(2-chloroethyl) pyrrolidine hydrochloride (1.0 g) and 1-bromo-3-chloropropane (1.0 mL, 9.76 mmol) to a magnetically stirred slurry of vanillin (1.0 g, 6.57 mmol) and anhydrous potassium carbonate (2.0 g) in ethyl methyl ketone (50.0 mL) and further stirring and refluxing the reaction mixture for 6 h. The completion of the reaction was monitored by TLC. The cooled reaction mixture was filtered and the solvent was removed under reduced pressure to obtain the oily residue of the corresponding aldehyde, which was used as such for further reaction. Compound **3m** was obtained by thermally fusing chloro-derivative **3l** with imidazole.

6-Amino-5-[6'-amino-1',3'-dimethyl-2',4'-dioxo-1',2',3',4'-tetrahydro-5'-pyrimidinyl(phenyl)-methyl]-1,3-dimethyl-1,2,3,4-tetrahydro-2,4-pyrimidinedione (3a). Recrystallization (chloroform and methanol); Yield 0.38 g (74.5%). mp 260-262 °C. ir (KBr): 3457.0, 3386.2, 3001.3, 1694.6, 1586.2, 1502.5, 1375.7, 1247.6, 1051.6, 835.5. ^1H nmr (300 MHz, $CDCl_3$): 3.27 (s, 6H, 2 N-CH_3), 3.44 (s, 6H, 2 N-CH_3), 5.75 (s, 1H, 7-H), 7.11 (m, 4H, ArH), 7.15-7.22 (m, 3H, ArH and NH_2), 7.24 (br, 2H, NH_2). *Anal*. Calcd. for $C_{19}H_{22}N_6O_4$ (398.42) : C, 57.2; H, 5.57; N, 21.0. Found: C, 56.9; H, 5.4; N, 20.9.

6-Amino-5-[6'-amino-1',3'-dimethyl-2',4'-dioxo-1',2',3',4'-tetrahydro-5'-pyrimidinyl(3,4-di-methoxyphenyl)methyl]-1,3-dimethyl-1,2,3,4-tetrahydro-2,4-pyrimidinedione (3b). Recrystallization (ether and methanol); Yield 0.37 g (62.71%). mp 220-222 °C. ir (KBr): 3450.2, 3373.7, 3050.0, 1680.0, 1601.0, 1502.0, 1249.4, 762.1. ^1H nmr (300 MHz, $CDCl_3$): 3.35 (s, 6H, 2 N-CH_3), 3.76 (6H, 2 N-CH_3), 3.76 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 5.75 (s, 1H, 7-H), 6.50 (br, 2H, NH_2), 6.67 (br, 2H, NH_2), 6.67 (d, 1H, J_o=10.1 Hz, ArH), 6.75 (d, 2H, J_o =8.1 Hz, ArH); *Anal*. Calcd. for $C_{21}H_{26}N_6O_6$ (458.47): C, 55.0; H, 5.72; N, 18.3. Found: C, 54.8; H, 5.5; N, 17.9.

6-Amino-5-[6'-amino-1',3'-dimethyl-2',4'-dioxo-1',2',3',4'-tetrahydro-5'-pyrimidinyl(3,4,5-trimethoxy-phenyl)methyl]-1,3-dimethyl-1,2,3,4-tetrahydro-2,4-pyrimidinedione (3c). Recrystallization (ether and acetone); Yield 0.28 g (45.16%). mp 268-270 °C. ir (KBr): 3354.5, 3100.0, 1685.2, 1594.4, 1498.0, 1234.8. ^1H nmr (300 MHz, $CDCl_3$): 3.37 (s, 6H, 2 N-CH_3), 3.47 (s, 6H, 2 N-CH_3), 3.76 (s, 6H, OCH_3), 3.82(s, 3H, OCH_3), 5.75 (s, 1H, 7-H), 6.36 (s, 2H, ArH), 6.48 (br, 2H, NH_2), 6.71 (br, 2H, NH_2). *Anal*. Calcd. for $C_{22}H_{28}N_6O_7$ (488.49): C, 54.09; H, 5.78; N, 17.21. Found: C, 54.19; H, 5.39; N, 17.33.

6-Amino-5-[6'-amino-1',3'-dimethyl-2',4'-dioxo-1',2',3',4'-tetrahydro-5'-pyrimidinyl(4-methoxyphenyl)methyl]-1,3-dimethyl-1,2,3,4-tetrahydro-2,4-pyrimidinedione (3d). Recrystallization (chloroform and methanol); Yield 0.37g (67.27%), mp 256-258 °C. ir (KBr): 3352.0, 3050.0, 1686.5, 1592.6, 1502.3, 1242.2, 788.7. ^{1}H nmr (300 MHz, $CDCl_3$): 3.33 (s, 6H, 2 N-CH_3), 3.46 (s, 6H, 2 N-CH_3), 3.77 (s, 3H, OCH_3)), 5.74 (s, 1H, 7-H), 6.49 (br, 2H, NH_2), 6.70 (br, 2H, NH_2), 6.79 (d, 2H, J_o=8.6 Hz, ArH), 7.03 (d, 2H, J_o=8.6 Hz, ArH), ^{13}C nmr ($CDCl_3$, 300 MHz): 27.77 (7-C), 29.47 (2 N-CH_3), 34.42 (2 N-CH_3), 54.53 (O-CH_3), 85.87 (5,5'-C), 112.68 (2ArC), 127.17 (2ArC), 130.57 (ArC), 150.52 (6,6'-C), 153.47 (2,2'-C, C=O), 156.69 (ArC) and 162.9 (4,4'-C, C=O). *Anal*. Calcd. for $C_{20}H_{24}N_6O_5$ (428.44): C, 56.1; H, 5.6; N, 19.62. Found: C, 55.8; H, 5.3; N, 19.28.

6-Amino-5-[6'-amino-1',3'-dimethyl-2',4'-dioxo-1',2',3',4'-tetrahydro-5'-pyrimidinyl(benzo-[*d*][1,3]dioxol-5-yl)methyl]-1,3-dimethyl-1,2,3,-tetra-hydro-2,4-pyrimidinedione (3e). Recrystallization (chloroform and methanol); Yield 0.35 g (61.4%), mp 238-240°C. ir (KBr): 3357.4, 3050.0, 1686.6, 1596.8, 1239.2, 931.6, ^{1}H nmr (300 MHz, $CDCl_3$): 3.27 (s, 6H, 2 N-CH_3), 3.45 (s, 6H, 2 N-CH_3), 5.70 (s, 1H, 7-H), 5.91 (s, 2H, O-CH_2-O), 6.46 (br, 2H, NH_2), 6.58 (m, 2H, ArH), 6.59 (m, 3H, ArH and NH_2). *Anal*. Calcd. for $C_{20}H_{22}N_6O_6$ (442.43): C, 58.5; H, 5.4; N, 20.48. Found: C, 58.16; H, 5.3; N, 20.19.

6-Amino-5-[6'-amino-1',3'-dimethyl-2',4'-dioxo-1',2',3',4'-tetrahydro-5'-pyrimidinyl(4-isopropylphenyl)methyl]-1,3-dimethyl-1,2,3,4-tetrahydro-2,4-pyrimidinedione (3f). Recrystallization (chloroform and methanol); Yield 0.32 g (56.3%), mp 255-257°C. ir (KBr): 3377.6, 3115.0, 2957.3, 1691.4, 1593.5, 1498.2, 1360.0, 1055.4, 928.9. ^{1}H nmr (300 MHz, $CDCl_3$): 1.21 (d, 6H, -CH(C*H*$_3$)$_2$), 2.58 (q, 1H, -C*H*(CH$_3$)$_2$), 3.27 (s, 3H, N-CH_3), 3.38-3.45 (br, 9H, 3 N-CH_3), 5.73 (s, 1H, 7-H), 6.63 (br, 2H, NH_2), 6.85 (br, 2H, NH_2), 7.03 (d, 2H, J_o=8.2 Hz, ArH), 7.12 (d, 2H, J_o=8.3 Hz, ArH). ^{13}C nmr ($CDCl_3$, 300 MHz,): 23.86 (2 CH_3), 29.26 (4 N-CH_3), 33.35 (7-C), 35.24 (CH), 86.60 (5 or 5'-C), 88.16 (5 or 5'-C), 125.97 (2 ArC), 126.54 (2 ArC), 135.59 (ArC), 145.90 (ArC), 150.65 (6,6'-C), 153.47 (2 or 2'-C, C=O), 154.75 (2 or 2'-C, C=O), 162.66 (4 or 4'-C, C=O) and 164.50 (4 or 4'-C, C=O). ^{13}C nmr DEPT 90: 33.35 (7-C), 35.24 (CH), 125.97 (2 ArC), 126.54 (2 ArC). ^{13}C nmr DEPT 135: 23.86 (2 CH_3), 29.26 (4 N-CH_3), 33.35 (7-C), 35.24 (CH), 125.97 (2 ArC), 126.54 (2 ArC). EI-MS: 440.4 [M^+]. *Anal*. Calcd. for $C_{22}H_{28}N_6O_4$ (440.49): C, 59.98; H, 6.41; N, 19.08. Found: C, 59.66; H, 6.05; N, 18.83.

6-Amino-5-[6'-amino-1',3'-dimethyl-2',4'-dioxo-1',2',3',4'-tetrahydro-5'-pyrimidinyl(4-pyridyl)methyl]-1,3-dimethyl-1,2,3,4-tetrahydro-2,4-pyrimidinedione (3g). Recrystallization (ether and acetone); Yield 0.09 g (17.6%), mp 260-262°C. ir (KBr): 3390.9, 3151.1, 1690.1, 1595.2, 1500.0, 1213.5, 1054.7, 852.1, 765.5. ^{1}H nmr (300 MHz, $CDCl_3$): 3.18-3.39 (m, 12H, 4 N-CH_3), 5.73 (s, 1H, 7-H); 7.16 (d, 2H, J_o =5.1 Hz, pyrid H); 7.25 (br, 2H, NH_2); 7.43 (br, 2H, NH_2); 8.44 (d, 2H, J_o=4.2 Hz, pyrid H); *Anal*. Calcd. for $C_{18}H_{21}N_7O_4$ (399.41): C, 54.12; H, 5.30; 24.55. Found: C, 54.69; H, 4.93; N, 24.25.

6-Amino-5-[6'-amino-1',3'-dimethyl-2',4'-dioxo-1',2',3',4'-tetrahydro-5'-pyrimidinyl(2-pyridyl)methyl]-1,3-dimethyl-1,2,3,4-tetrahydro-2,4-pyrimidinedione (3h). Recrystallization (ether and acetone); Yield 0.12g (23.52%), mp 262-264°C. ir (KBr): 3550.0, 3365.1, 3159.7, 1680.9, 1594.9, 1500.9, 1058.9, 843.6, 768.5. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.33 (s, 6H, 2 N-CH_3), 3.42 (s, 6H, 2 N-CH_3), 5.87 (s, 1H, CH), 6.52 (br, 4H, 2 NH_2), 7.11 (t, 1H, J_o=6.1 Hz, pyrid H), 7.19 (d, 1H, J_o =6.2 Hz, pyrid H), 7.60 (t, 1H, J_o =1.6 Hz, pyrid H), 8.53 (d, 1H, J_o =3.8 Hz, pyrid H). *Anal*. Calcd. for $C_{18}H_{21}N_7O_4$ (399.41): C, 54.13; H, 5.30; N, 24.55; Found: C, 53.93; H, 5.21; N, 24.25.

6-Amino-5-[6'-amino-1',3'-dimethyl-2',4'-dioxo-1',2',3',4'-tetrahydro-5'-pyrimidinyl(4-hydroxy-3-methoxyphenyl)-methyl]-1,3-dimethyl-1,2,3,4-tetrahydro-2,4-pyrimidinedione (3i). Recrystallization (chloroform and methanol); Yield 0.42 g (73.68%), mp 240-242°C. ir (KBr): 3432.9, 3050.0, 1694.2, 1599.8, 1504.6, 1377.7, 1259.9, 1031.3, 936.7 785.6. ^{1}H nmr (300 MHz, $CDCl_3$): 3.18 (s, 6H, 2 N-CH_3), 3.40 (s, 6H, 2 N-CH_3), 3.72 (s, 3H, O-CH_3), 5.62 (s,1H, 7-H), 6.54 (d, 1H, J_o=8.2 Hz, ArH), 6.61 (s, 1H, ArH), 6.66 (d, 1H, J_o=8.1Hz, ArH), 7.41 (br, 4H, 2 NH_2); *Anal.* Calcd. for $C_{20}H_{24}N_6O_6$ (444.44): C, 54.05; H, 5.44; N, 18.91. Found: C, 53.85; H, 5.55; N, 18.63.

6-Amino-5-[6'-amino-1',3'-dimethyl-2',4'-dioxo-1',2',3',4'-tetrahydro-5'-pyrimidinyl(3-hydroxyphenyl)methyl]-1,3-dimethyl-1,2,3,4-tetrahydro-2,4-pyrimidinedione (3j). Recrystallization (acetone and petroleum ether); Yield 0.30 g (56.6%), mp 262-264°C. ir (KBr): 3395.5, 3100.0, 1690.0, 1611.8, 1500.0, 1210.5, 810.5, 791.5, 695.9. ^{1}H nmr ($CDCl_3$): 3.28 (s, 6H, (s, 6H, 2 N-CH_3), 3.45 (s, 6H, 2 N-CH_3), 5.71 (s,1H, 7-H), 6.62 (m, 3H, ArH), 7.03 (t, 1H, ArH), 7.25 (br, 4H, 2 NH_2); *Anal*. Calcd. for $C_{19}H_{22}N_6O_5$ (414.42): C, 55.06; H, 5.35; N, 20.28. Found: C, 54.86; H, 4.91; N, 19.92.

6-Amino-5-[6'-amino-1',3'-dimethyl-2',4'-dioxo-1',2',3',4'-tetrahydro-5'-pyrimidinyl{4-[2-(1-pyrrolidinyl)ethoxy]-3-methoxyphenyl}methyl)-1,3-dimethyl-1,2,3,4-tetrahydro-2,4-pyrimidinedione (3k). Recrystallization (acetone); Yield 0.20 g (28.98%), M.p. 235-238°C. ir (KBr): 3423.7, 2952.9, 1688.0, 1614.3, 1498.1, 1261.5, 1214.6, 757.9. ^{1}H nmr ($CDCl_3$+DMSO-d_6): 1.95 (s, 4H, 2 CH_2), 2.97 (s, 4H, N(CH_2)$_2$), 3.16 (s, 2H, NCH_2), 3.38 (s, 6H, 2 N-CH_3), 3.48 (s, 6H, 2 N-CH_3), 3.73 (s, 3H, O-CH_3), 4.27 (s, 2H, O-CH_2), 5.75 (s, 1H, 7-H), 6.5 (br, 2H, NH_2), 6.67 (m, 4H, 2 ArH and NH_2), 6.81 (d, 1H, J_o =8.92 Hz, ArH). Calcd. for $C_{26}H_{35}N_7O_6$ (541.60): C, 57.65; H, 6.51; N, 18.11; Found: C, 57.38; H, 6.36; N, 17.90.

6-Amino-5-[6'-amino-1',3'-dimethyl-2',4'-dioxo-1',2',3',4'-tetrahydro-5'-pyrimidinyl[4-(3-chloropropoxy)-3-methoxyphenyl]methyl]-1,3-dimethyl-1,2,3,4-tetrahydro-2,4-pyrimidinedione (3l). Recrystallization (ethylacetate) ; Yield 0.54 g (80.59%), mp 155-157°C . ir (KBr): 3392.5, 3111.5, 2980.0, 1680.4, 1499.2, 1252.7, 787.8. ^{1}H nmr ($CDCl_3$+DMSO-d_6): 2.33 (p, 2H, -$OCH_2CH_2CH_2Cl$), 3.33 (s, 6H, 2 N-CH_3), 3.46 (s, 6H, 2 N-CH_3), 3.61 (t, 2H, -CH_2Cl), 3.73 (s, 3H, O-CH_3), 4.11 (t, 2H, O-CH_2), 5.75 (s, 1H, 7-H), 6.48 (br, 2H, NH_2), 6.66 (m, 4H, 2 ArH and NH_2), 6.79 (d, 1H, J_o=8.9 Hz, ArH). Calcd. for $C_{23}H_{29}N_6O_6Cl$ (520.96): C, 53.02; H, 5.61; N, 16.13; Found: C, 52.85; H, 5.32; N, 16.24.

6-Amino-5-[6'-amino-1',3'-dimethyl-2',4'-dioxo-1',2',3',4'-tetrahydro-5'-pyrimidinyl{4-[3-(1*H*-1-imidazolyl)propoxy]-3-methoxyphenyl}methyl]-1,3-dimethyl-1,2,3,4-tetrahydro-2,4-pyrimi-dinedione (3m). The chloro derivative 3l (0.5 g, 0.96 mmol) and imidazole (0.1 g, 1.47 mmol) were fused together at 110° for 2 h. The completion of reaction was monitored by TLC. To the fused mixture, ice cold water was added and the mixture was kept in the freezer for complete precipitation. The precipitate obtained was collected by filtration, washed thoroughly with water and dried. Recrystallization (ether); Yield 0.2 g (37.70%), mp 180-182 °C. ir (KBr): 3422.0, 3350.0, 1686.8, 1600.2, 1501.3, 1248.7, 1141.2, 787.3, 753.0. ^{1}H nmr ($CDCl_3$+DMSO-d_6): 2.22 (p, 2H, $OCH_2CH_2CH_2N$), 3.32 (s, 6H,

2 N-CH_3), 3.47 (s, 6H, 2 N-CH_3), 3.76 (s, 3H, -O-CH_3), 3.92 (t, 2H, N-CH_2), 4.20 (t, 2H, O-CH_2), 5.75 (s, 1H, 7-H), 6.56 (br, 2H, NH_2), 6.72 (m, 5H, 3 ArH and NH_2), 6.93 (s, 1H, imid-H), 7.04 (1H, s, imid-H), 7.49 (1H, s, imid-H). Calcd. for $C_{26}H_{32}N_8O_6$ (552.59): C, 56.51; H, 5.84; N, 20.28; Found: C, 56.26; H, 5.45; N, 20.07.

Data Collection, Structure Solution and Refinement. X-ray intensity data were collected for compounds **3a** and **3i** at 160 K on a *Nonius Kappa CCD* diffractometer [13] using graphite-monochromated Mo$K\alpha$ radiation (λ = 0.71073 Å) and an Oxford Cryosystems Cryostream 700 cooler. The data reduction was performed with HKL Denzo and Scalepack [14]. The intensities were corrected for Lorentz and polarization effects, but not for absorption.

Both structures were solved by direct methods using SIR92 [15]. The non-hydrogen atoms were refined anisotropically using SHELXL-97 [16]. In **3a** and **3i**, the positions of the amino H atoms were determined from a difference Fourier map and refined freely along with their isotropic displacement parameters. The methyl H atoms were constrained to an ideal geometry (C–H=0.98 Å), with U_{iso}(H)=1.5U_{eq}(C), but were allowed to rotate freely about the C–C bonds. All remaining H atoms were placed in geometrically calculated positions and refined using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to 1.2U_{eq} of its parent C-atom. The asymmetric unit of **3i** includes a MeOH molecule, which is disordered across two positions close to a center of inversion. The site occupation factors of the MeOH atoms were fixed at 0.5. The position of the hydroxy H atom of the MeOH molecule could not be located from a difference map. The reflection 002 in both **3a** and **3i** was partially obscured by the beam stop and was omitted during the final refinement. Figures were prepared using ORTEP-3 [17] and PLATON [18].

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