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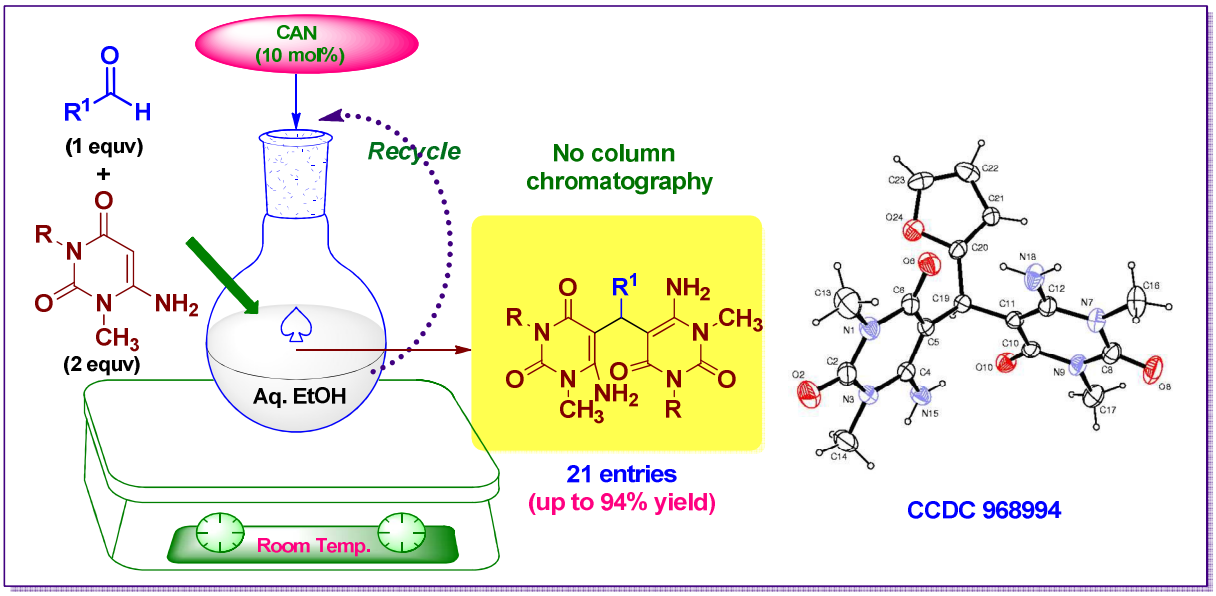
Graphical Abstract

Cerric Ammonium Nitrate (CAN): An Efficient and Eco-friendly Catalyst for the One-Pot Synthesis of Aryl/Alkyl/Heteroaryl-Substituted *Bis*(6-aminouracil-5-yl)methanes at Room Temperature

Goutam Brahmachari* and Bubun Banerjee

Laboratory of Natural products & Organic Synthesis, Department of Chemistry, Visva-Bharati University, Santiniketan-731 235, West Bengal, India

E-mail: brahmg2001@yahoo.co.in; brahmg2001@gmail.com
Tel./Fax: 91-3463-261526



Ceric ammonium nitrate (CAN)-catalyzed one-pot synthesis of alkyl/aryl/heteroaryl-substituted *bis*(6-aminouracil-5-yl)methane scaffolds (**3a-3u**) has been developed *via* a *pseudo* three-component reaction between aldehydes and 6-aminouracils in aqueous ethanol at room temperature.

Ceric Ammonium Nitrate (CAN): An Efficient and Eco-friendly Catalyst for the One-Pot Synthesis of Alkyl/Aryl/Heteroaryl-Substituted *Bis*(6-aminouracil-5-yl)methanes at Room Temperature

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E-mail: brahmg2001@yahoo.co.in; brahmg2001@gmail.com
Tel./Fax: 91-3463-261526

Abstract
A simple, facile and convenient practical method for one-pot synthesis of biologically relevant alkyl/aryl/heteroaryl-substituted *bis*(6-aminouracil-5-yl)methane scaffolds (**3a-3u**) has been developed using ceric ammonium nitrate (CAN) as a commercially available and eco-friendly catalyst *via pseudo* three-component condensation reaction between aldehydes and 6-aminouracils in aqueous ethanol at room temperature The salient features of the present protocol are mild reaction conditions, good to excellent yields, high atom-economy, environmentally benign, easy isolation of products, no column chromatographic separation and reusability of reaction media.

Introduction

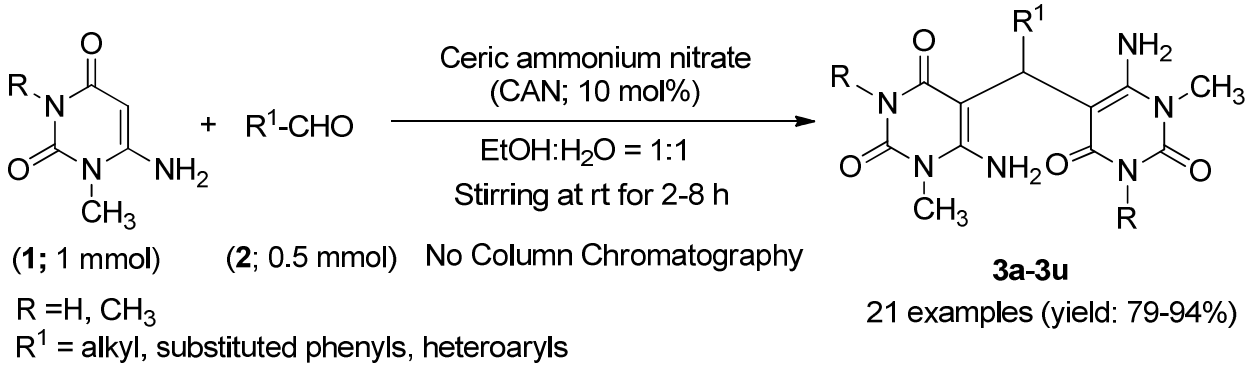
6-Aminouracil is a '*privileged*' structural motif, very much common in bioactive natural products, and regarded as a versatile building block for the several bioactive nitrogen-containing heterocycles.[1] This scaffold acts as an intermediate for the synthesis of many purine-based drugs, such as caffeine, theobromine, penciclovir, and theophylline.[2] In medicinal chemistry, 6-aminouracils are the important starting compounds for the synthesis of xanthenes and theophylline-related compounds[3] which are now routinely used as a phosphodiesterase inhibitor for the treatment of asthma.[4] Pyrimidine-containing organic scaffolds are known to exhibit diverse biological and pharmaceutical activities as well.[5] Heterocycles, particularly bearing a pyrimidine moiety, such as dihydropyrimidines,[6] furopyrimidines,[7] and pyrazolopyrimidines,[8] are regarded as scaffolds of pharmaceutical promise due to their several biological efficacies.[9]

In spite of a handful of diverse applications of alkyl/aryl/heteroaryl-substituted *bis*(6-aminouracil-5-yl)methanes in medicinal chemistry, there are only a few methods are available so far for their synthesis involving a *pseudo* three-component tandem reaction between uracils and aldehydes in the presence of catalysts such as acetic acid,[10] TEBAC,[11] sulfuric acid functionalized silica (SSA)[12] and also using microwave irradiation.[13]Although these protocols reported by others find certain merits of their own, still they suffer from a number of demerits such as long reaction time, heating reaction conditions, and use of toxic organic solvents. Therefore, a search for more general, clean, efficient, and high yielding routes for the synthesis of alkyl/aryl/ heteroaryl-substituted *bis*(6-aminouracil-5-yl)methanes remains a valid exercise.

Ceric ammonium nitrate (CAN) is a commercially available, inexpensive, and eco-friendly substance that has found huge applications in organic transformations in recent years due to its Lewis acidic property, high reactivity, excellent solubility in water and easy work-up procedures. This unique catalyst has been found to be effective in the synthesis of a variety of biologically relevant heterocycles, *viz.* 2,4,5-triaryl-1*H*-imidazoles,[14] indeno[1,2-*b*]pyridines,[15] pyrano[2,3-*d*]pyrimidine-2,4,7-triones,[16] *N*-substituted decahydroacridine-1,8-diones,[17] pyrrole-2,3,4,5-tetracarboxylates[18] and many more.[19] Such successful catalytic performance of CAN has encouraged us to investigate on its further application in other carbon-carbon bond forming reactions. In this paper, we wish to extend the synthetic applicability of this unique catalyst in the one-pot synthesis of alkyl/aryl/ heteroaryl-substituted *bis*(6-aminouracil-5-yl)methanes (**3**).

In recent times, multicomponent reactions (MCRs) have gained eminence as a synthetic tool for producing structurally complex molecular entities with attractive biological features through the formation and breakage of several carbon-carbon and carbon-heteroatom bonds in one-pot.[20] It is becoming increasingly important both in academia and in industry to design less toxic and more environmentally friendly MCRs. In addition, implementation of several transformations in a single manipulation in MCR strategy is highly compatible with the goals of sustainable and "*green*" chemistry.[21]

In continuation of our sincere efforts to develop green synthetic methodologies for organic transformations,[22] we have recently developed a straightforward and efficient *pseudo* three-component one-pot synthesis of alkyl/aryl/heteroaryl-substituted *bis*(6-aminouracil-5-yl)methane derivatives in good yields using commercially available CAN as inexpensive and environmentally benign catalyst from the reaction of aldehydes and 6-aminouracil derivatives in aqueous ethanol at room temperature. The present method is not only cost-effective and environmentally benign, but also experimentally safe and simple, easy to handle, clean and efficient. The results are summarized in Scheme 1 and Table 2.

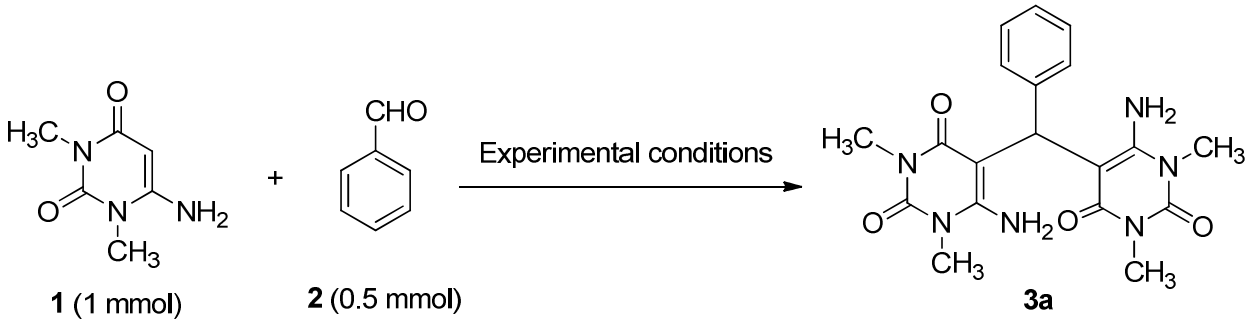


Scheme 1. One-pot synthesis of substituted *bis*(6-aminouracil-5-yl)methanes

Results and discussion

We herein report on a straightforward energy-efficient and high yielding protocol for the one-pot synthesis of a series of biologically relevant alkyl/aryl/heteroaryl-substituted *bis*(6-aminouracil-5-yl)methanes (**3a-3u**) in aqueous ethanol at room temperature under the catalysis of CAN (**Scheme 1**). First, we conducted a series of trial reactions using 6-amino-1,3-dimethyluracil (**1**; R = CH_3; 1 mmol) and benzaldehyde (**2**; 0.5 mmol) in the absence or presence of different catalysts in aqueous ethanol (1:1 v/v) at room temperature for obtaining the best yield of the desired product, 5,5'-(phenylmethylene)*bis*(6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione) (**3a**). It appeared that 10 mol% of CAN in aqueous ethanol (1:1 v/v) at room temperature provides the best result in terms of yield and time (Table 1, entry 6) to obtain **3a**, which was characterized by its physical and spectral properties.[11] Under solvent-free conditions with 10 mol% of CAN, the product was obtained in low yield of 36% at 10 h. The overall results are summarized in Table 1.

Table 1: Optimization of reaction conditions

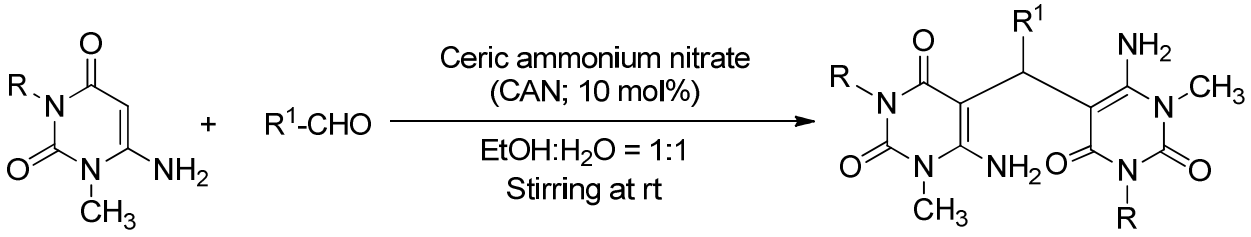


Entry	Catalyst (mol%)	Solvent	Time (h)	Yield(%)[a,b]
1	No catalyst	No solvent	24	Trace
2	No catalyst	H_2O	24	38
3	No catalyst	EtOH	10	42
4	CAN (10 mol%)	EtOH	4	71
5	CAN (10 mol%)	H_2O	10	56
6	**CAN (10 mol%)**	**EtOH:H_2O (1:1 v/v)**	**2**	**89**
7	CAN (10 mol%)	No solvent	10	36
8	CAN (15 mol%)	EtOH:H_2O (1:1 v/v)	2	91
9	CAN (5 mol%)	EtOH:H_2O (1:1 v/v)	3.5	84
10	I_2 (10 mol%)	EtOH:H_2O (1:1 v/v)	2	59
11	NaCl (10 mol%)	EtOH:H_2O (1:1 v/v)	2	0
12	CH_3COONa (10 mol%)	EtOH:H_2O (1:1 v/v)	2	0
13	NH_4Cl (10 mol%)	EtOH:H_2O (1:1 v/v)	2	0
14	$Fe(NO_3)_3.6H_2O$ (10 mol%)	EtOH:H_2O (1:1 v/v)	2	52
15	$NiCl_2.6H_2O$ (10 mol%)	EtOH:H_2O (1:1 v/v)	2	44
16	$CuCl_2.2H_2O$ (10 mol%)	EtOH:H_2O (1:1 v/v)	2	34
17	$(NH_4)_4Ce(SO_4)_4.2H_2O$ (10 mol%)	EtOH:H_2O (1:1 v/v)	2	48

[a]Experimental conditions: 6-amino-1,3-dimethyluracil (**1**, 1 mmol) and benzaldehyde (**2**, 0.5 mmol) in the presence or absence of different catalysts in neat/4 mL of various solvent systems at room temperature. [b]Isolated yields.

After optimizing the reaction conditions, the reaction of 4-chlorobenzaldehyde with 6-amino-1,3-dimethyluracil was carried out under the same reaction conditions and it furnished the product **3b** in 92% yield with CAN within 4 h (Table 2, entry 2). To check the generality as well as the effectiveness of our newly developed protocol, a number of aromatic aldehydes having substituents such as hydroxy, methoxy, nitro, halogens, aliphatic and heteroaryl aldehydes such as isobutaraldehyde and furfural, respectively, were reacted with 6-amino-1,3-dimethyluracil using identical reaction conditions, and all of them underwent the reaction smoothly affording the corresponding *bis*(6-amino-1,3-dimethyluracil-5-yl)methanes (**3c-3s**) (Table 2, entries 3-20) in good to excellent yields (79-94%) at room temperature. Encouraged by these results, we attempted to extend the present protocol with 6-amino-1-methyluracil (**1**; R = H) which also underwent smooth reactions with aldehydes under the same optimized reaction conditions affording the corresponding products **3t-3u** (Table 2, entries 20-21) in excellent yields (86-89%). The overall results are summarized in Table-2.

Table 2
Synthesis of substituted *bis*(6-aminouracil-5-yl)methanes (**3a-3u)**



Entry	Product	R	Substituent (R^1)	CAN (10 mol%)		Melting point (^{0}C)	
				Time (h)	Yield (%)[a,b]	Found	Reported
1	**3a**	CH_3	C_6H_5	2.0	89	257-259	260-262[11]
2	**3b**	CH_3	4-Cl-C_6H_4	4.0	92	260-262	<300[13]
3	**3c**	CH_3	4-F-C_6H_4	8.0	81	263-265	264-265[23]
4	**3d**	CH_3	4-Br-C_6H_4	4.0	91	264-266	–
5	**3e**	CH_3	4-CH_3-C_6H_4	3.0	86	274-276	<300[10]
6	**3f**	CH_3	4-CN-C_6H_4	5.0	87	286-287	–
7	**3g**	CH_3	4-OCH_3-C_6H_4	6.0	89	270-272	–
8	**3h**	CH_3	4-NO_2-C_6H_4	7.0	86	282-283	<300[13]
9	**3i**	CH_3	3-NO_2-C_6H_4	2.0	90	244-246	248-250[13]
10	**3j**	CH_3	2-NO_2-C_6H_4	5.0	82	261-263	–
11	**3k**	CH_3	2-Cl-C_6H_4	7.0	87	259-260	–
12	**3l**	CH_3	3,4,5-$(OCH_3)_3$-C_6H_2	6.0	88	270-272	268-270[11]
13	**3m**	CH_3	3,4-OCH_2O-C_6H_3	8.0	94	236-237	238-240[11]
14	**3n**	CH_3	3-OCH_3-4-OH-C_6H_3	5.0	90	237-238	240-242[11]
15	**3o**	CH_3	3,4-$(OH)_2$-C_6H_3	3.0	87	246-248	–
16	**3p**	CH_3	2-furfuryl	2.0	94	245-246	–
17	**3q**	CH_3	2-OH-5-Cl-C_6H_3	8.0	79	251-253	–
18	**3r**	CH_3	4-OH-C_6H_4	6.0	82	232-234	–
19	**3s**	CH_3	$(CH_3)_2CH$	6.0	84	231-233	–
20	**3t**	H	C_6H_5	2.0	86	293-295	–
21	**3u**	H	3,4,5-$(OCH_3)_3$-C_6H_2	4.0	89	299-300	–

[a]Experimental conditions: 6-aminouracil (**1**, 1 mmol), aldehyde (**2**, 0.5 mmol) and 10 mol% CAN as catalyst in 4 mL of aqueous ethanol (1:1 v/v) at room temperature; [b]Isolated yields.

All the products were isolated pure just by washing with cold aqueous ethanol followed by recrystallization from ethanol; no tedious chromatographic purification was required. The isolated products were fully characterized on the basis of their analytical data and detailed spectral studies including FT-IR, ^{1}H NMR, ^{13}C NMR and TOF-MS. All the known compounds had physical and spectroscopic data identical to those reported in literature.[10,11,13,23] Single crystal X-ray analysis for 5,5'-(furan-2-ylmethylene)*bis*(6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione) (**3p**) (Table 2, entry 16) was also documented in this present communication (Figure 2).[24]

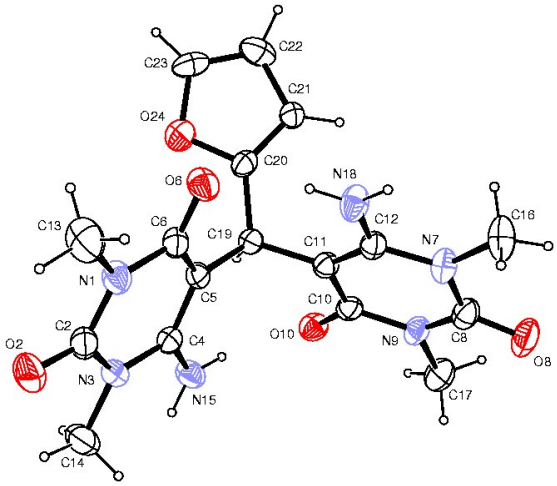


Figure 1a. ORTEP diagram of compound **3p** (CCDC **968994**)

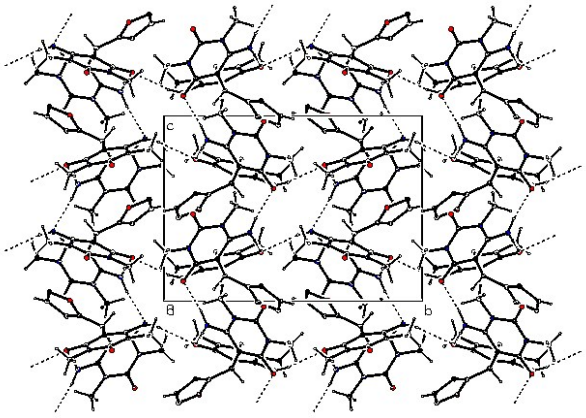
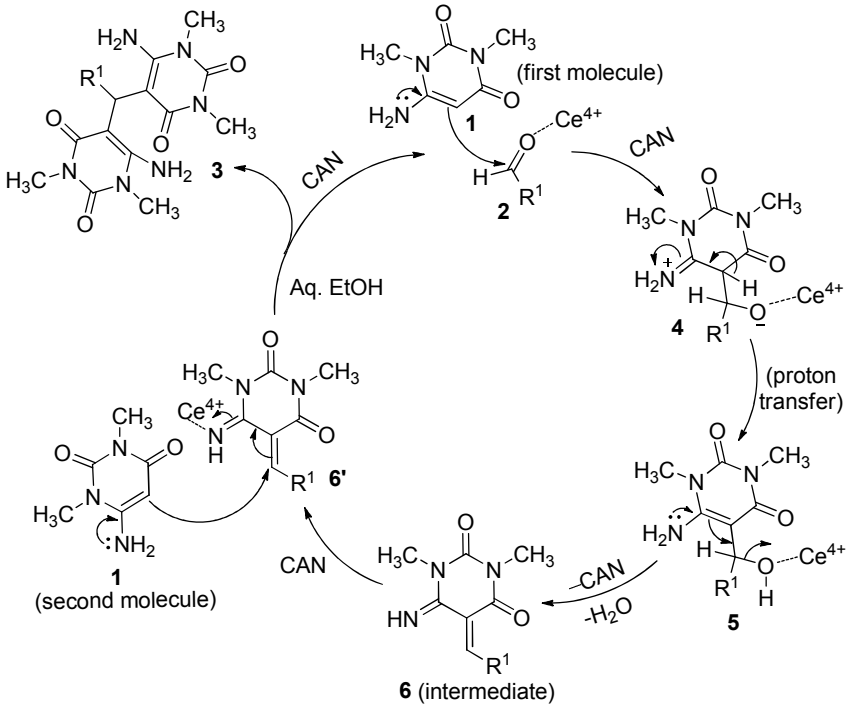


Figure 1b. The packing arrangement of molecules viewed down the b-axis

We herein propose a mechanism for the formation of substituted *bis*(6-aminouracil-5-yl)methane entity. CAN as a Lewis acid activates aldehyde molecule (**2**) and thus facilitates a nucleophilic attack by 6-aminouracil (**1**) to the electron-deficient carbonyl centre of **2** through electron-rich C-5 position, thereby generating an intermediate **6**, which then reacts with the second molecule of **1** under the influence of CAN in aqueous ethanol to afford the desired product **3** (Scheme 2).



Scheme 2. Proposed mechanism for the synthesis of substituted *bis*(6-aminouracil-5-yl)methanes

It is worth-noting that we reused the filtrate containing residual solvent, catalyst and substrates obtained upon filtration of the reaction mixture after completion of the reaction up to 3rd times in case of a representative entry (entry 1; Table 2); addition of reactants directly into the

filtrate without adding further catalyst resulted in the formation of expected product **3a** without appreciable loss of catalytic activity at least up to 3rd run (with respective isolated yields of 89%, 81% and 74%). However, each filtrate can only be used for the particular entry due to the presence of residual starting materials.

Conclusions

In conclusion, we have developed a very simple, facile and convenient practical method for one-pot synthesis of biologically relevant alkyl/aryl/heteroaryl-substituted *bis*(6-aminouracil-5-yl)methane scaffolds (**3a-3u**) in the presence of CAN as a commercially available and eco-friendly catalyst *via pseudo* three-component condensation reaction between aldehydes and 6-aminouracils in aqueous ethanol at room temperature. Mild reaction conditions, good to excellent yields, operational simplicity and absence of tedious separation procedures, clean reaction profile, high atom-economy as well as the use of inexpensive and environmentally benign catalyst are the key advantages of the present method. Moreover, reusability of the reaction media without significant loss of activity is an added advantage. Keeping in view of the synthetic importance of such *bis*(6-aminouracil-5-yl)methane derivatives of pharmaceutical potential, the current methodology with mild reaction conditions and operational simplicity offers the possibility of its use with cost-effective and environmentally friendlier ways for large-scale syntheses.

Experimental

General. Infrared spectra were recorded using a Shimadzu (FT-IR 8400S) FT-IR spectrophotometer using KBr disc. ^{1}H and ^{13}C NMR spectra were obtained at 400 MHz and 100 MHz respectively, using Bruker DRX- 400 spectrometer and DMSO-d_6 as the solvent. Mass spectra (TOF-MS) were measured on a QTOF Micro mass spectrometer. Elemental analyses were performed with an Elementar Vario EL III Carlo Erba 1108 micro-analyzer instrument. Melting point was recorded on a Chemiline CL-726 melting point apparatus and is uncorrected. Thin Layer Chromatography (TLC) was performed using silica gel 60 F_{254} (Merck) plates.

General procedure for the synthesis of aryl/alkyl/heteroaryl-substituted *bis*(6-aminouracil-5-yl)methane derivatives: An oven-dried screw cap test tube was charged with a magnetic stir bar, 6-aminouracils (**1**, 1 mmol) and aldehydes (**2**, 0.5 mmol), CAN (10 mol%) and EtOH: H_2O (1:1 v/v; 4 mL) in a sequential manner; the reaction mixture was then stirred vigorously at room temperature. The progress of the reaction was monitored by TLC. On completion of the reaction, a solid mass precipitated out, filtered off and washed with cold aq. ethanol to obtain crude product (**3**) which was then purified by crystallization from ethanol. The filtrate containing residual solvent, catalyst and substrates obtained upon filtration of the reaction mixture after completion of reaction could be successfully reused for a particular entry up to 3rd times without appreciable loss of the catalytic activity. The structure of each purified product was confirmed by its analytical as well as spectral studies including FT-IR, ^{1}H NMR, ^{13}C NMR and TOF-MS.

Characterization data of all new compounds

5,5'-((4-Bromophenyl)methylene)*bis*(6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione) (3d): White solid, yield 91%. mp: 264-266 °C. IR (ν_{max}/cm^{-1}, KBr): = 3344, 3163, 3049, 2975, 1699, 1680, 1597, 1501, 1447, 1381, 1337, 1246, 1065, 929, 845, 779; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 7.36 (s, 6H, 2 × -N*H*$_2$, 2 × -Ar-*H*), 7.07 (m, 2H, ArH), 5.56 (s, 1H, -C*H*-), 3.34 (s, 6H, 2 × NC*H*$_3$), 3.16 (s, 6H, 2 × NC*H*$_3$). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 162.62 (2C), 155.07 (2C), 150.85 (2C), 139.69, 130.83 (2C), 129.44 (2C), 118.29, 85.27 (2C), 35.43 (2C), 30.38 (2C), 28.40. TOF-MS: 499.0701 [M + Na]$^+$. *Anal*. Calcd for $C_{19}H_{21}BrN_6O_4$: C 47.81, H 4.43, N 17.61; found: C 47.78, H 4.39, N 17.64.

4-(*Bis*(6-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)methyl) benzonitrile (3f): White solid, yield 87%; mp 286-287 °C; IR (ν_{max}/cm^{-1}, KBr): = 3323, 3115, 2945, 2893, 2228, 1684, 1601, 1499, 1379, 1337, 1252, 1144, 1059, 939, 872, 714; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 7.63 (br s, 4H, 2 × -N*H*$_2$), 7.35 (m, 4H, ArH), 5.63 (s, 1H, -C*H*-), 3.39 (s, 6H, 2 × NC*H*$_3$), 3.17 (s, 6H, 2 × NC*H*$_3$). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 163.85 (2C), 155.27 (2C), 150.84 (2C), 146.82, 132.00 (2C), 128.21 (2C), 119.65, 108.13, 86.44, 84.93, 36.23 (2C), 30.42 (2C), 28.40. TOF-MS: 446.1549 [M + Na]$^+$. *Anal*. Calcd for $C_{20}H_{21}N_7O_4$: C 56.73, H 5.00, N 23.16; found: C 56.77, H 4.98, N 23.22.

5,5'-((4-Methoxyphenyl)methylene)*bis*(6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione) (3g): White solid, Yield 89%. Mp: 270-272 °C; IR (ν_{max}/cm^{-1}, KBr): = 3408, 3196, 3045, 3026, 2953, 2829, 2799, 1691, 1655, 1578, 1504, 1466, 1452, 1375, 1348, 1248, 1213, 1161, 1115, 1057, 1038, 928, 835, 793, 750; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H 7.39 (br s, 4H, 2 × -N*H*$_2$), 6.97 (br s, 2H, ArH), 6.76 (br s, 2H, ArH), 5.53 (s, 1H, -C*H*-), 3.67 (s, 3H, -OC*H*$_3$), 3.32 (s, 6H, 2 × NC*H*$_3$), 3.14 (s, 6H, 2 × NC*H*$_3$); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 164.00, 162.58, 157.21, 155.06, 154.12, 150.87 (2C), 131.55, 127.94 (2C), 113.46 (2C), 87.09, 85.95, 55.26, 34.94 (2C), 30.34 (2C), 28.36; TOF-MS: 451.1701 [M + Na]$^+$; *Anal*. Calcd for $C_{20}H_{24}N_6O_5$: C, 56.07; H, 5.65; N, 19.62; found: C, 56.01; H, 5.68; N, 19.59.

5,5'-((2-Nitrophenyl)methylene)*bis*(6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione) (3j): Yellowish solid, yield 82%; mp 261-263 °C; IR (ν_{max}/cm^{-1}, KBr): = 3448, 3174, 2953, 1690, 1668, 1603, 1505, 1455, 1380, 1248, 1160, 1061, 913, 861, 784, 760; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 7.56 (br s, 2H, ArH), 7.52 (br s, 2H, ArH), 7.39 (br s, 4H, 2 × -N*H*$_2$), 7.21 (br s, 2H, ArH), 6.09 (s, 1H, -C*H*-), 3.31 (s, 6H, 2 × NC*H*$_3$), 3.23 (s, 3H, NC*H*$_3$), 2.99 (s, 3H, NC*H*$_3$). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 163.75, 162.24, 154.86, 154.52, 150.70, 150.06, 133.75, 131.85, 129.09 (2C), 127.14 (2C), 123.89 (2C), 86.14, 84.06, 32.58, 30.59, 30.32, 28.70, 28.04. TOF-MS: 466.1447 [M + Na]$^+$. *Anal*. Calcd for $C_{19}H_{21}N_7O_6$: C 51.47, H 4.77, N 22.11; found: C 51.46, H 4.79, N 22.13.

5,5'-((2-Chlorophenyl)methylene)*bis*(6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione) (3k): White solid, yield 87%; mp 259-260 °C; IR (ν_{max}/cm^{-1}, KBr): = 3397, 3374, 3145, 2996,

2948, 1668, 1651, 1609, 1582, 1498, 1450, 1380, 1287, 1263, 1149, 1045, 963, 931, 825, 789; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 7.53 (br s, 2H, ArH), 7.35-7.19 (m, 4H, -NH_2 + ArH), 6.99 (2H, br s, -NH_2), 5.55 (s, 1H, -C*H*-), 3.35 (s, 6H, 2 × NCH_3), 3.19 (s, 3H, NCH_3), 3.07 (s, 3H, NCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 163.44, 162.35, 154.60, 154.10, 150.78 (2C), 138.75, 132.83, 129.81, 129.55, 127.58, 126.84, 86.94, 85.51, 35.11 (2C), 30.44, 28.62, 28.05; TOF-MS: 455.1207 [M + Na]$^+$; *Anal*. Calcd for $C_{19}H_{21}ClN_6O_4$: C 52.72, H 4.89, N 19.42; found: C 52.57, H 4.91, N 19.39.

5,5'-((3,4-Dihydroxyphenyl)methylene)*bis*(6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione) (3o): White solid, yield 87%; mp 246-248 ^{o}C; IR (ν_{max}/cm^{-1}, KBr): = 3383, 2978, 1676, 1595, 1511, 1384, 1348, 1215, 1151, 1056, 870, 790; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 8.52 (s, 2H, -OH), 7.60 (s, 2H, -NH_2), 7.30 (s, 2H, -NH_2), 6.55 (d, 1H, *J* = 8.0 Hz, ArH), 6.48 (s, 1H, ArH), 6.33 (d, 1H, *J* = 7.6 Hz, ArH), 5.46 (s, 1H, -C*H*-), 3.32 (s, 6H, 2 × NCH_3), 3.15 (s, 6H, 2 × NCH_3). ^{13}C NMR (100 MHz, DMSO-d_6):δ_C 163.81, 162.54, 154.81 (2C), 150.89 (2C), 145.01, 142.91, 130.56, 117.56, 115.39, 114.54, 87.27, 86.02, 34.94 (2C), 30.35 (2C), 28.34. TOF-MS: 453.1492 [M + Na]$^+$. *Anal*. Calcd for $C_{19}H_{22}N_6O_6$: C 53.02, H 5.15, N 19.53; found: C 53.05, H 5.12, N 19.49.

5,5'-(Furan-2-ylmethylene)*bis*(6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione) (3p): White solid, yield 94%; mp 245-246 ^{o}C; IR (ν_{max}/cm^{-1}, KBr): = 3356, 2918, 2876, 1685, 1584, 1499, 1359, 1276, 772; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 7.41 (5H, br s, ArH + 2 × -NH_2), 6.28 (1H, s, ArH), 6.03 (1H, d, *J* = 1.2 Hz, ArH), 5.47 (1H, s, -C*H*-), 3.33 (6H, s, 2 × NCH_3), 3.15 (6H, s, 2 × NCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 163.06 (2C), 154.17 (2C), 153.56, 150.78 (2C), 141.32, 110.30, 105.68, 85.76 (2C), 31.70 (2C), 30.30 (2C), 28.30; TOF-MS: 411.1389 [M + Na]$^+$; *Anal*. Calcd for $C_{17}H_{20}N_6O_5$: C, 52.57; H, 5.19; N, 21.64; found: C, 52.58; H, 5.22; N, 21.67.

5,5'-((5-Chloro-2-hydroxyphenyl)methylene)*bis*(6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione) (3q): White solid, yield 89%; mp 251-253 ^{o}C; IR (ν_{max}/cm^{-1}, KBr): = 3381, 3356, 3219, 3072, 2951, 1695, 1601, 1493, 1256, 1119, 1047, 968, 933, 798, 758; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 9.35 (s,1H, -OH), 7.26-7.09 (m, 4H, ArH + -NH_2), 6.99 (s, 2H, -NH_2), 6.64 (s, 1H, ArH), 5.47 (s, 1H, -C*H*-), 3.35 (s, 3H, NCH_3), 3.11 (s, 6H, 2 × NCH_3), 2.91 (s, 3H, NCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 162.97, 161.61, 153.94, 153.56, 151.20, 150.81 (2C), 150.45, 129.72, 126.29, 122.28, 117.93, 90.19, 87.21, 32.32, 30.39 (2C), 29.26, 29.14; TOF-MS: 471.1157 [M + Na]$^+$; *Anal*. Calcd for $C_{19}H_{21}ClN_6O_5$: C 50.84, H 4.72, N 18.72; found: C 50.81, H 4.69, N 18.75.

5,5'-((4-Hydroxyphenyl)methylene)*bis*(6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione) (3r): Yellow solid, yield 82%; mp 232-234 ^{o}C; IR (ν_{max}/cm^{-1}, KBr): = 3420, 3171, 2964, 1682, 1599, 1499, 1379, 1258, 1161, 1055, 960, 775; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 9.06 (s, 1H, -

OH), 7.37 (br s, 4H, 2 × -NH_2), 6.85 (d, 2H, J = 8.0 Hz, ArH), 6.59 (d, 2H, J = 8.4 Hz, ArH), 5.48 (s, 1H, -CH-), 3.32 (s, 6H, 2 × NCH_3), 3.13 (s, 6H, 2 × NCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.47, 163.21, 161.30, 156.79, 155.04, 150.89 (2C), 138.65, 129.70, 127.82 (2C), 115.91, 114.96 (2C), 87.12, 86.13, 34.89 (2C), 30.34 (2C), 28.40; TOF-MS: 437.1544 [M + Na]$^+$; *Anal*. Calcd for $C_{19}H_{22}N_6O_5$: C 55.07, H 5.35, N 20.28; found: C 55.05, H 5.37, N 20.22.

5,5'-(2-Methylpropane-1,1-diyl)*bis*(6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione) (3s): White solid, yield 84%; mp 231-233 ^{o}C; IR (ν_{max}/cm^{-1}, KBr): = 1684, 1595, 1504, 1373, 1246, 1169, 931, 843, 773; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 7.25 (br s, 4H, 2 × -NH_2), 3.56 (d, 1H, J = 11.2 Hz, -CH-), 3.23-3.19 (m, 1H, -CH-), 3.28 (s, 3H, -NCH_3), 3.27 (s, 3H, -NCH_3), 3.16 (s, 3H, -NCH_3), 3.15 (s, 3H, -NCH_3), 0.77 (d, 3H, J = 6.0 Hz, -CH_3), 0.72 (d, 3H, J = 6.4 Hz, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 164.17, 163.16, 154.99, 153.13, 150.82, 150.73, 88.02, 86.93, 30.43, 30.03, 28.57, 28.08, 25.39, 22.57, 21.94; TOF-MS: 387.1752 [M + Na]$^+$; *Anal*. Calcd for $C_{16}H_{24}N_6O_4$: C 52.74, H 6.64, N 23.06; found: C 52.72, H 6.68, N 23.09.

5,5'-(Phenylmethylene)*bis*(6-amino-1-methylpyrimidine-2,4(1*H*,3*H*)-dione) (3t): White solid, yield 86%,, mp 293-295 ^{o}C; IR (ν_{max}/cm^{-1}, KBr): = 3373, 3180, 2989, 1709, 1591, 1504, 1389, 1304, 1236, 1068, 986, 839, 770; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 10.81 (s, 2H, -NH), 7.62-7.32 (m, 3H, -NH_2 + ArH), 7.20 (t, 2H, J = 8.0 & 7.2 ArH), 7.09 (d, 3H, J = 7.2 ArH), 5.45 (s, 1H, -CH-), 3.26 (s, 6H, 2 × -NCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 162.91 (2C), 156.87 (2C), 151.69 (2C), 150.56, 140.01, 128.05 (2C), 126.94 (2C), 125.28, 75.60 (2C), 34.35, 29.32, 28.63; TOF-MS: 393.1284 [M + Na]$^+$; *Anal*. Calcd for $C_{17}H_{18}N_6O_4$: C, 55.13; H, 4.90; N, 22.69; found: C, 55.11; H, 4.88; N, 22.71.

5,5'-((3,4,5-Trimethoxyphenyl)methylene)*bis*(6-amino-1-methylpyrimidine-2,4(1*H*,3*H*)-dione) (3u): White solid, yield 89%; mp 299-300 ^{o}C; IR (ν_{max}/cm^{-1}, KBr): = 3373, 3188, 2962, 2829, 1711, 1585, 1508, 1393, 1308, 1238, 1132, 1065, 999, 859, 783, 725; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 10.84 (s, 1H, -NH), 10.34 (s, 1H, -NH), 7.62 (s, 2H, -NH_2), 7.22 (s, 1H, ArH), 6.82 (s, 2H, -NH_2), 6.36 (s, 1H, ArH), 4.58 (s, 1H, -CH-), 3.65 (s, 6H, 2 × -OCH_3), 3.61 (s, 3H, -OCH_3), 3.26 (s, 3H, -NCH_3), 3.17 (s, 3H, -NCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 162.98 (2C), 156.90 (2C), 152.72 (2C), 151.69, 150.56, 135.88, 135.64, 104.67 (2C), 75.59 (2C), 60.38, 56.24 (2C), 34.45, 28.63 (2C); TOF-MS: 483.1601 [M + Na]$^+$; *Anal*. Calcd for $C_{20}H_{24}N_6O_7$: C 52.17, H 5.25, N 18.25; found: C 52.14, H 5.23, N 18.29.

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24 Complete crystallographic data of 5,5'-(furan-2-ylmethylene)bis(6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione) (**3p**) (Table 2, entry 16) for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 968994. Copies of this information may be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.