

Mandelic acid catalyzed one-pot pseudo three-component synthesis of various trisubstituted methane derivatives at room temperature

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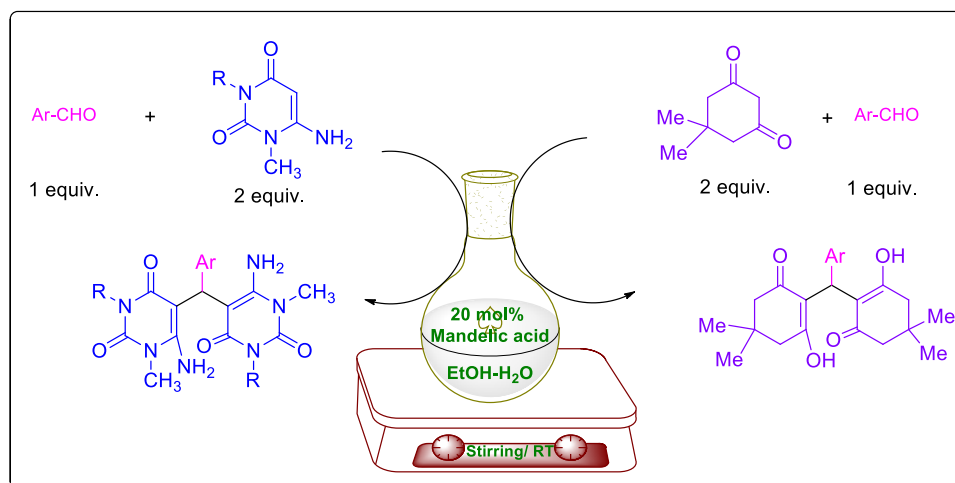
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Abstract

A simple, mild, eco-friendly, general and convenient approach has been developed for the synthesis of various trisubstituted methane derivatives via one-pot pseudo three-component reactions between **one** equivalent of aromatic aldehydes and **two** equivalents of 6-amino-uracils or dimedone respectively using a catalytic amount of mandelic acid as a low cost, commercially available, efficient organo-catalyst in aqueous ethanol at room temperature.



Keywords: 6-Amino-uracil, dimedone, mandelic acid, organocatalysis, room temperature

Introduction

The uracil skeleton is very common in naturally occurring bioactive compounds (Figure 1).¹ Many drug molecules consist of uracil as an important building block (Figure 2).² Recently, in 2021, Awad *et al.* [2] have synthesized some uracil nucleosides which showed better anti-herpes simplex virus 1 (anti-HSV-1) efficacy than the potent anti-viral drug acyclovir. Due to its affection to replicate the bacterial chromosome, uracil skeleton in many occasion showed significant efficacies to treat infectious diseases.³ Figure 3 represents some uracil derivatives with potent anti-cancer efficacies.⁴ 5-Fluorouracil is a well-known drug, which is widely used for the treatment of solid tumors like colon or breast cancer.⁴ Kezin *et al.*⁵ synthesized a series of 5-substituted uracils derivatives which reported to possess a wide spectrum of biological activities. Among other uracil derivatives, 6-amino substituted uracils have been extensively used to prepare various biological active heterocyclic scaffolds (Figure 4).⁶

As an anti-neoplastic agent, uracil itself has been used in combination with tegafur (a chemotherapeutic prodrug of 5-fluorouracil) to treat various cancers, including breast, prostate, and liver cancer.⁷ Very recently, Ramesh *et al.*⁸ synthesized a series of bis-uracil substituted aryl methylene derivatives. *In vitro* study of the synthesized compounds in HIV p24 assay revealed that five compounds, shown in Figure 5, possess promising HIV-1 capsid protein inhibitory efficacy. On the other hand, bis-dimedone substituted aryl/alkyl methylene derivatives are also found to possess significant anti-oxidant and lipoxigenase inhibitory activities (Figure 6).⁹

After noticing the biological efficacy of both bis-uracil/dimedone substituted aryl methylene derivatives, we were motivated to synthesize such derivatives under greener conditions. In the literature, we found a few methods are available for the synthesis of 5,5'-(arylmethylene)*bis*(6-amino-pyrimidine-2,4(1*H*,3*H*)-diones) *via* one-pot pseudo three-component reactions between two equivalents of either *N,N*-dimethyl-6-aminouracil or 1-methyl-6-aminouracil and one equivalent of aldehydes (Table 1; entries 1-7).¹⁰⁻¹⁶ Whereas, 2,2'-(arylmethylene)*bis*(3-hydroxy-5,5-dimethylcyclohex-2-enone) derivatives were synthesized from the reactions of two equivalents of dimedone and one equivalent of aldehydes involving homogeneous as well as heterogeneous catalyst under diverse reaction conditions (Table 2).¹⁷⁻³⁵

Though these reported protocols definitely have some merits but many of them are suffering in terms of green chemistry perspectives such as use of metal containing catalysts, toxic organic solvents, ionic liquids, high heating conditions, long reaction times *etc.* Moreover, in some cases, microwave or ultrasound irradiation was required additionally. Besides, all these reported methods are focused only on a particular scaffold *i.e.*, either synthesis of 5,5'-(arylmethylene)*bis*(6-amino-pyrimidine-2,4(1*H*,3*H*)-diones) or 2,2'-(arylmethylene) *bis*(3-hydroxy-5,5-dimethylcyclohex-2-enone) derivatives. These drawbacks motivated us to rethink and design a mild, efficient, high yielding and common method for the synthesis of both the scaffolds by using a non-toxic organocatalyst at room temperature.

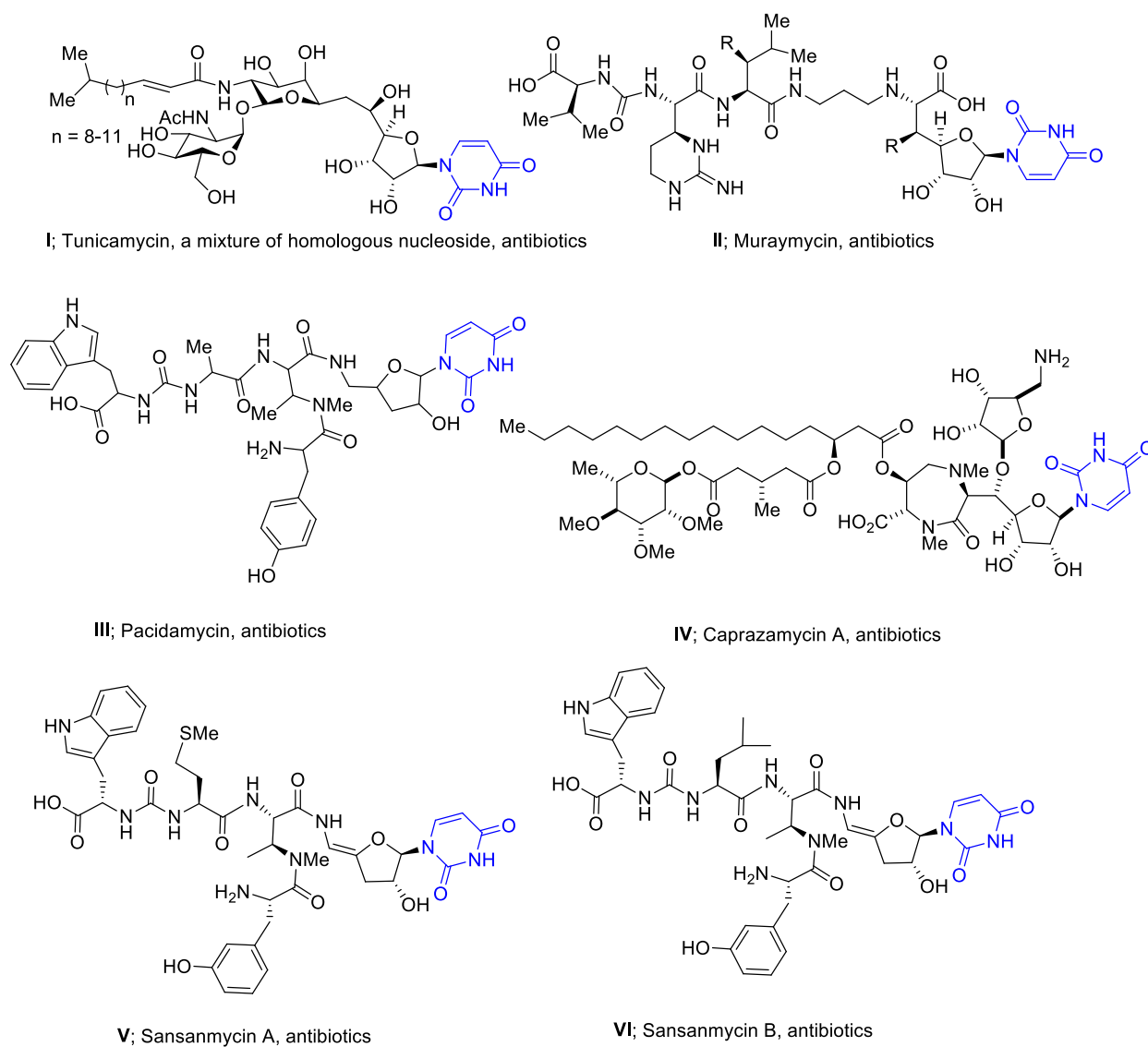


Figure 1. Glimpse of bioactive naturally occurring compounds bearing uracil moiety

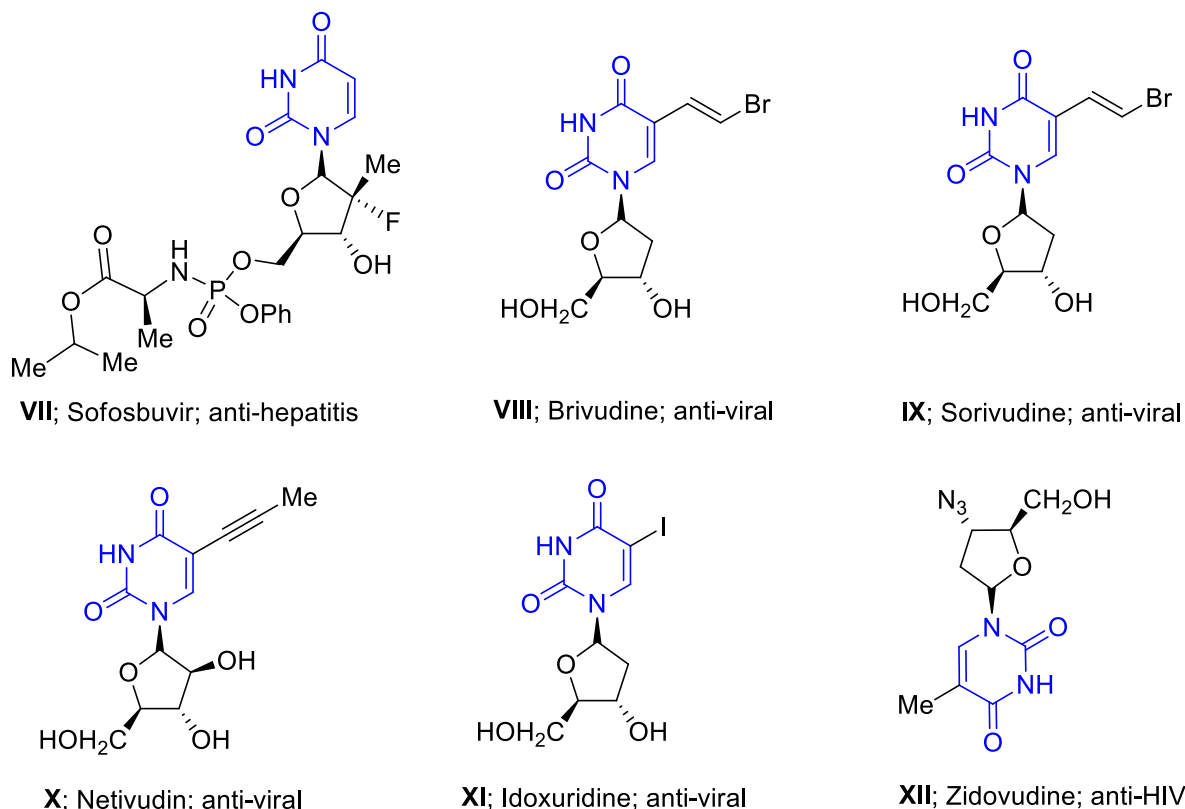


Figure 2. Glimpse of commercially available drug molecules bearing uracil moiety

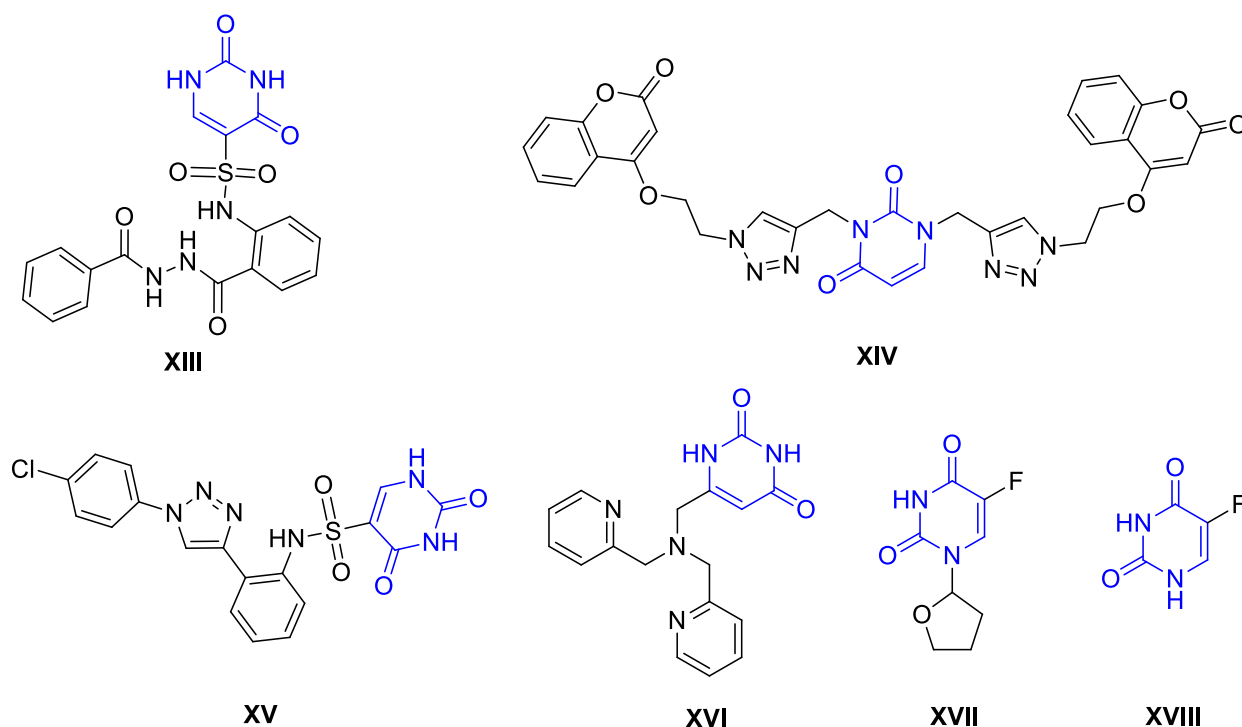


Figure 3. Some uracil derivatives with potent anti-cancer efficacies

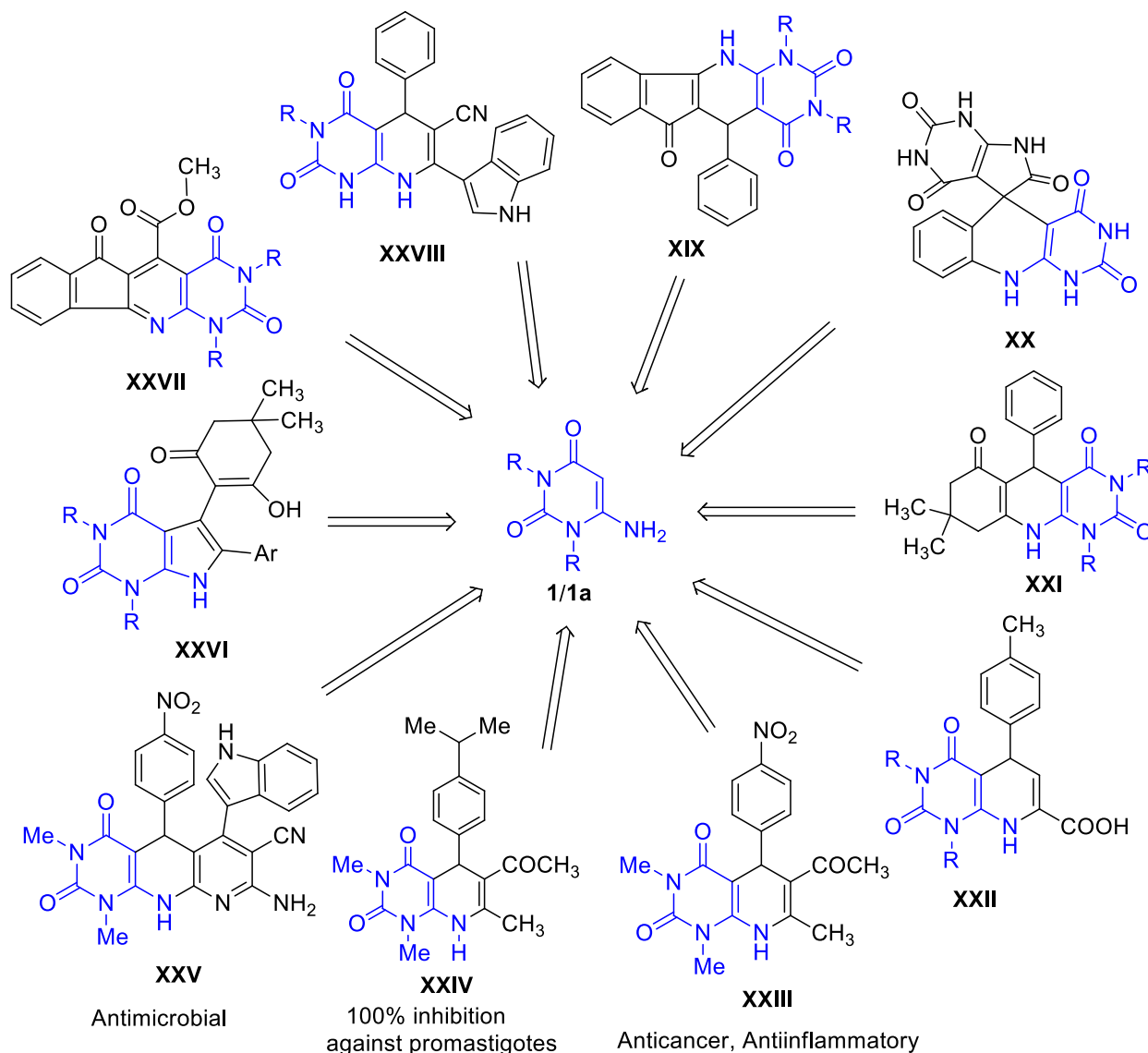


Figure 4. Glimpse of bioactive synthetic heterocyclic compounds synthesized from 6-aminouracil as one of the important starting component

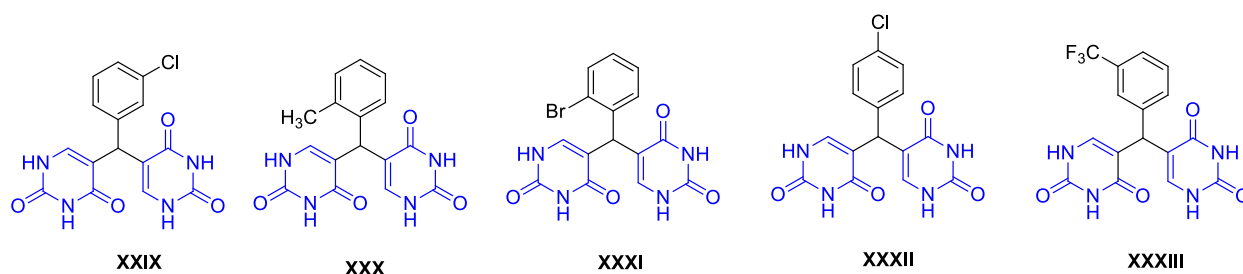


Figure 5. Bisuracil substituted aryl methylene derivatives with promising HIV-1 capsid protein inhibitors

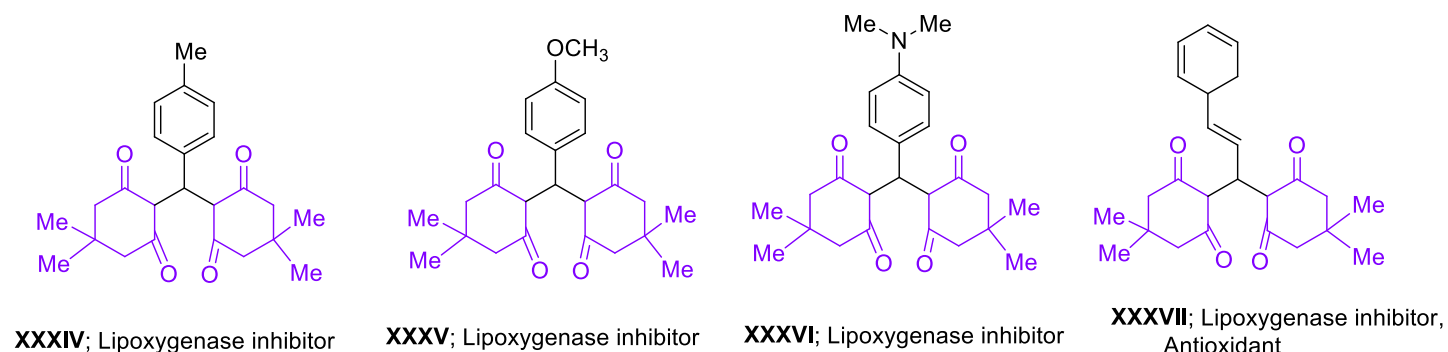
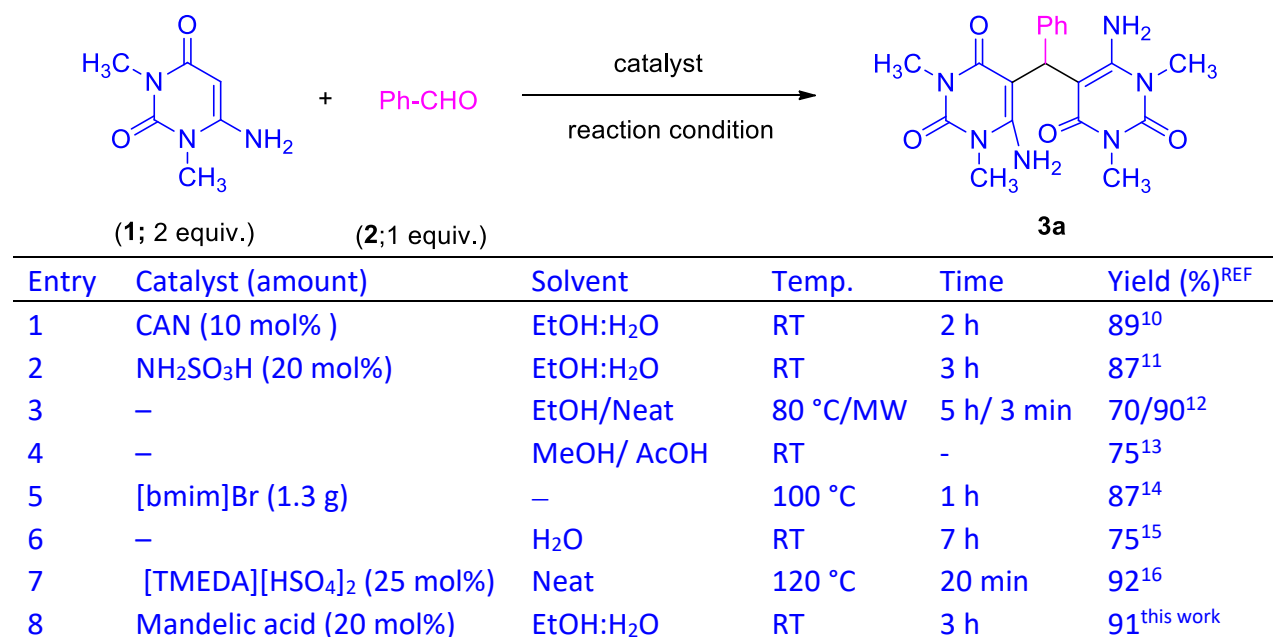


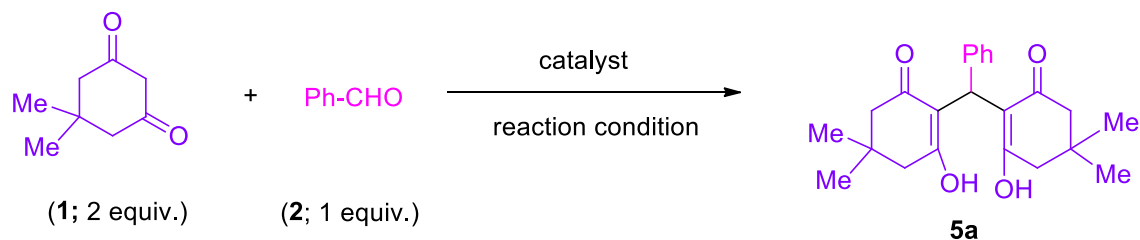
Figure 6. Biologically active bis-dimedone substituted aryl/alkyl methylene derivatives

Under these environmentally conscious days, metal-free organocatalysts have gained significant attention due to their environmental friendliness.³⁶⁻⁴⁵ Recently, our research group has explored the catalytic efficacies of mandelic acid for various organic transformations.⁴⁶⁻⁵⁰ In this communication we wish to report another simple and efficient mandelic acid catalyzed protocol for the synthesis of a series of structurally diverse tri-substituted methane derivatives *viz.*, 5,5'-(arylmethylene)*bis*(6-amino-pyrimidine-2,4(1*H*,3*H*)-diones) and 2,2'-(arylmethylene)*bis*(3-hydroxy-5,5-dimethylcyclohex-2-enones) in aqueous ethanol at room temperature (Scheme 1).

Table 1. Reported protocols for the synthesis of 5,5'-(arylmethylene)*bis*(6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-diones)

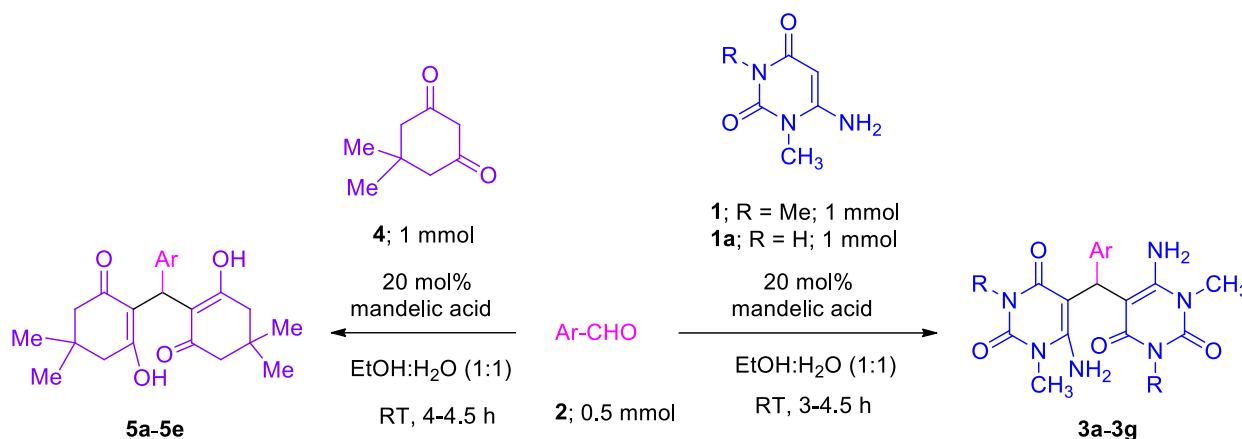


[TMEDA][HSO₄]₂ = *N,N,N',N'*-Tetramethylethylenediaminium bisulfate

Table 2. Reported protocols for the synthesis of 2,2'-(arylmethylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enones) under various reaction conditions

Entry	Catalyst (amount)	Solvent	Temp.	Time	Yield ^a (%) ^{REF}
1	CTMAB ^b (0.18 g)	H ₂ O	RT	24 h	92 ¹⁷
2	PPA-SiO ₂ (10 mol%)	Solvent-free	140 °C	0.5 h	92.8 ¹⁸
3	SiO ₂ @Diphenic acid (0.05 g)	EtOH:H ₂ O	80 °C	0.5 h	90 ¹⁹
4	NaOH (0.125 mmol)	H ₂ O)), 20 °C	1.5 h	68 ²⁰
5	L-Lysine (20 mol%)	H ₂ O	R.T.	7 h	89 ²¹
6	L-Histidine (20 mol%)	[bmim]BF ₄	60 °C	45 min	85 ²²
7	ZrOCl ₂ .8H ₂ O/NaNH ₂ (15 mol%)	THF	R.T.	20 min	88 ²³
8	Nano BiOCl (30 mg)	H ₂ O))), 35 °C	15 min	95 ²⁴
9	Nano-CuFe ₂ O ₄ (0.05 g)	EtOH	R.T.	70 min	94 ²⁵
10	C/TiO ₂ -SO ₃ H (6.4 mol%)	H ₂ O	100 °C	0.25 h	92 ²⁶
11	Ni nanoparticles (25mg/mmol)	H ₂ O	R.T.	3 h	90 ²⁷
12	Et ₄ NBr (0.5 mmol)/NH ₄ Cl (10 mmol)	H ₂ O	R.T.	30 min	98 ²⁸
13	Piperidine (1–2 drops)	Aq. EtOH	R.T.	20 min	98 ²⁹
14	ZnO (30 mol%)	CH ₃ CN	80 °C	12 h	92 ³⁰
15	–	ChCl:Urea	80 °C	-	92 ³¹
16	Fe/NaY (2.5 mg)	EtOH	reflux	105 min	98 ³²
17	SmCl ₃ (10 mol %)	H ₂ O	R.T.	20 min	97 ³³
18	Yb(OTf) ₃ .SiO ₂ (30 mol%)	Solvent-free	R.T.	2 min	81 ³⁴
19	Pd(0)-EDA/SC-2 (2.5 mol%)	H ₂ O	100 °C	2 h	89 ³⁵
20	Mandelic acid (20 mol%)	EtOH:H ₂ O	RT	4 h	92 ^{this work}

CTMAB = cetyltrimethyl ammonium bromide; PPA-SiO₂ = polyphosphoric acid supported on silica; Zr(DP)₂ = Zirconium dodecylphosphonate, THF = Tetrahydrofuran, C/TiO₂-SO₃H = sulfonated carbon/nano-titania, ChCl = Choline chloride, Fe/NaY = Nano Fe/NaY zeolite, Pd(0)-EDA/SC-2 = Pd(0) nanoparticles onto ethylene diamine functionalized silicacellulose. ^aIsolated yields; ^b4-nitrobenzaldehyde was used instead of benzaldehyde.



Scheme 1. Mandelic acid-catalyzed synthesis of 5,5'-(arylmethylene)bis(6-amino-pyrimidine-2,4(1*H*,3*H*)-diones) and 2,2'-(arylmethylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enones) at room temperature

Results and Discussion

To optimize the reaction condition, we carried out a series of trial reactions between *N,N*-dimethyl-6-aminouracil (**1**, 1 mmol) and freshly distilled benzaldehyde (0.5 mmol) under various reaction conditions at ambient temperature. At first, we carried out the reaction under catalyst as well solvent-free conditions which produced only trace amount of the desired product even after 6 hours of stirring at room temperature (Table 3, entry 1). Using water as a solvent, less than 20% yield was observed after 6 hours under catalyst-free conditions at room temperature (Table 3, entry 2). After getting these poor results under catalyst-free conditions we realized that a suitable catalyst is required to promote this reaction. And thus, in continuation of our strong interest with mandelic acid as catalyst, we wanted to evaluate whether mandelic acid can catalyze this reaction or not. Interestingly, when we employed 20 mol% mandelic acid as catalyst under solvent-free conditions, we observed increase in the yield (59%) of the desired product i.e., 5,5'-(phenylmethylene)bis(6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione) (**3a**) after six hours (Table 3, entry 3). Using the same amount of catalyst in water, we obtained **3a** with 53% yield after six hours (Table 3, entry 4). The same reaction in acetonitrile (Table 3, entry 5) or methanol (Table 3, entry 6) as solvent afforded 62% or 59% yields respectively after 6 hours. Slight better yield (88%) was obtained in ethanol though it took six hours (Table 3, entry 7). Interestingly, when we used aqueous-ethanol (1:1 v/v) as solvent with the same amount of catalyst, to our surprise, the same reactions afforded 91% yield of the compound **3a** within just 3 hours. From these preliminary studies it was established that aqueous-ethanol may be the best suitable solvent to carry out this reaction. We then standardized the amount of required catalyst by maintaining other parameters remain fixed. More than 20% less product (70%) was isolated using 15 mol% of mandelic acid (Table 3, entry 9). After 6 hours of stirring, the same reaction yielded 82% (Table 3, entry 10) and 54% (Table 3, entry 11) of the desired product with 15 mol% and 10 mol% mandelic acid as catalyst respectively. On the other hand, no significant improvement in the yield was observed even after increasing the catalyst amount to 25 mol% (Table 3, entry 12). From these results, 20 mol% mandelic acids came out as an optimum catalyst for this transformation in aqueous ethanol at room temperature. We were also interested to check the catalytic efficiency of other few naturally occurring organocatalysts. The same amount of other organocatalysts viz.,

itaconic acid (Table 3, entry 13), palmitic acid (Table 3, entry 14) and shikimic acid (Table 3, entry 15) as catalyst afforded lesser yields (49-66%) in aqueous-ethanol at room temperature after three hours of stirring.

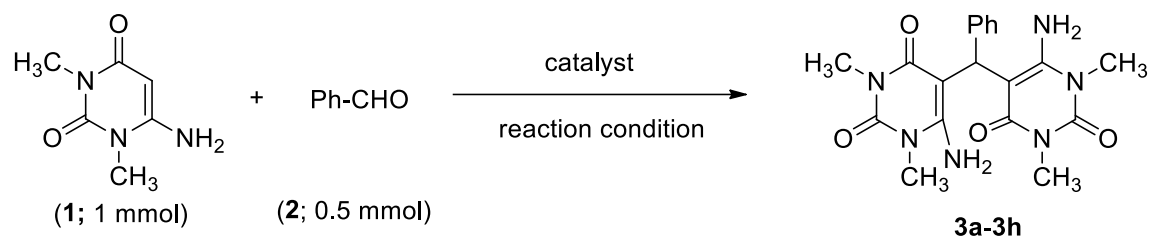
Therefore, it was optimized that a catalytic amount of mandelic acid (20 mol%) is sufficient for the efficient synthesis of 5,5'-(phenylmethylene)bis(6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione) (**3a**) from the one-pot pseudo three-component reactions between two equivalents of *N,N*-dimethyl-6-aminouracil (**1**) and one equivalent of benzaldehyde (**2a**) in aqueous ethanol at room temperature (Table 3, entry 8). To check the generality of our developed protocol, we were keen to synthesize a series of other derivatives of 5,5'-(arylmethylene)bis(6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-diones) under the same optimized reaction conditions. It is our delight to mention that we were successful to synthesize four other derivatives of 5,5'-(arylmethylene)bis(6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-diones) (**3b-3e**) with excellent yields (89-97%) from the reactions of *N,N*-dimethyl-6-aminouracil (**1**; 1 mmol) and various substituted benzaldehydes (**2b-2e**; 0.5 mmol) (Table 4, entries 2-5). Aldehydes with both electron withdrawing as well as donating substituent underwent smoothly and afforded the desired products with excellent yields. Instead of *N,N*-dimethyl-6-aminouracil (**1**), 1-methyl-6-aminouracil (**1a**) is also reacted smoothly with benzaldehyde (**2a**) and 4-fluorobenzaldehyde (**2d**) under the same optimized reaction conditions and afforded the desired products (**3f,3g**) with excellent yields (85-90%).

To extend the scope of our developed protocol, we then planned to carry out the reactions between two equivalents of dimedone (**4**, 1 mmol) instead of 6-aminouracils (**1**) and one equivalent of substituted benzaldehydes (**2a,2c,2f-h**, 0.5 mmol) under the same reaction conditions which afforded the corresponding 2,2'-(arylmethylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enones) (**5a-5e**) with excellent yields (90-94%) within 4.5 hours (Table 5, entries 1-5). Proposed mechanism for the synthesis of aryl-substituted bis(6-aminouracil-5-yl)methane derivatives (**3a-3g**) is shown in Figure 2.

All the synthesized compound were obtained pure just by simple filtration and washing the crude products subsequently with ethanol. No column chromatographic purification was required.

We were successful to synthesize 2,2'-(phenylmethylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (**5a**; 1.54 g, 84%) in gram scale within 4 hours from the reactions of 10 mmol dimedone (**4**; 1.40 g) and freshly distilled 5 mmol benzaldehyde (**2a**; 0.53 g) using 20 mol% mandelic acid (0.15 g) in aqueous ethanol (20 ml) at room temperature. During filtration, the filtrate containing the dissolved catalyst was collected and recycled further for the same gram scale reaction without adding any catalyst which afforded the targeted compound **5a** in 71% yield (1.30 g). All the synthesized compounds were well characterized by the detail physical as well as spectroscopic analyses of ¹H NMR, ¹³C NMR and HRMS. It is also note worthy to mention that we were able to form single crystal of two derivatives *i.e.*, compounds **3d** and **5a**. ORTEP view of the compound **3d** is shown in Figure 3. Figure 4 shows the packing view of molecules down a-axis within the unit cell of compound **3d**. From the X-ray structure it is confirmed that the molecules in the unit cell are bound by the intermolecular N-H...O hydrogen bonds (Figure 4). ORTEP view of the compound **5a** is shown in Figure 5. Figure 6 shows the packing view of molecules down c-axis within the unit cell of compound **5a**.

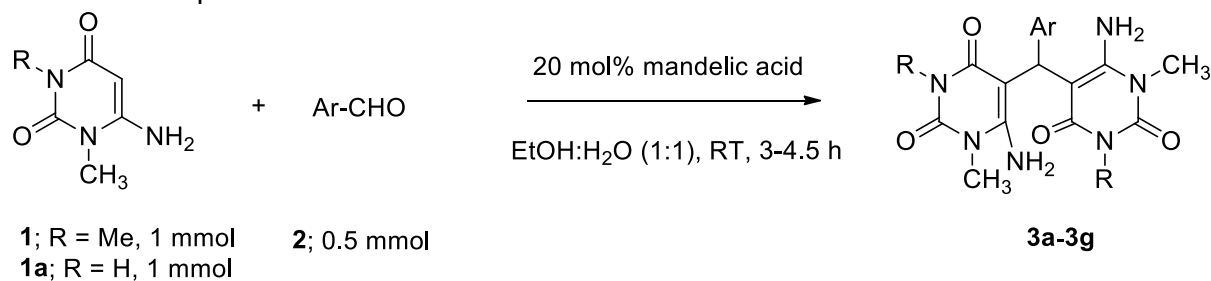
Table 3. Optimization of reaction conditions for the synthesis of 5,5'-(arylmethylene)bis(6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-diones)



Entry	Catalyst (mol%)	Solvent	Time (h)	Yield (%) ^{a,b}
1.	Catalyst-free	neat	6	trace
2	Catalyst-free	H ₂ O	6	>20
3	Mandelic acid (20)	neat	6	56
4	Mandelic acid (20)	H ₂ O	6	73
5	Mandelic acid (20)	CH ₃ CN	6	62
6	Mandelic acid (20)	MeOH	6	59
7	Mandelic acid (20)	EtOH	6	88
8	Mandelic acid (20)	EtOH:H₂O (1:1)	3	91
9	Mandelic acid (15)	EtOH:H ₂ O (1:1)	3	70
10	Mandelic acid (15)	EtOH:H ₂ O (1:1)	6	82
11	Mandelic acid (10)	EtOH:H ₂ O (1:1)	6	54
12	Mandelic acid (25)	EtOH:H ₂ O (1:1)	3	91
13	Itaconic acid (20)	EtOH:H ₂ O (1:1)	3	66
14	Palmitic acid (20)	EtOH:H ₂ O (1:1)	3	54
15	Shikimic acid (20)	EtOH:H ₂ O (1:1)	3	49

^aReaction conditions: *N,N*-dimethyl-6-aminouracil (**1**; 1 mmol) and benzaldehyde (**2a**; 0.5 mmol) in the absence or presence of a catalytic amount of naturally occurring organic acids in neat/4 mL of water/ethanol/methanol/acetonitrile at 28-32 °C. ^bIsolated yields.

Table 4. Synthesis of aryl-substituted bis(6-aminouracil-5-yl)methane derivatives (**3a-3g**) using mandelic acid as catalyst at room temperature

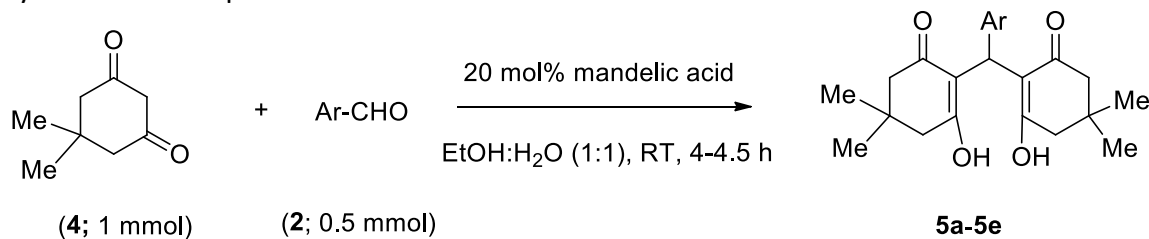


Entry	R	Ar	Product	Time (h)	Yield (%) ^{a,b}	Melting point (°C)	
						Found	Reported ^{REF}
1	CH ₃	C ₆ H ₅ (2a)	3a	3.0	91	290-293	296-299 ¹⁵
2	CH ₃	4-Cl-C ₆ H ₄ (2b)	3b	3.5	95	273-275	268-270 ¹⁵
3	CH ₃	4-NO ₂ -C ₆ H ₄ (2c)	3c	4.0	89	300-302	228-229 ¹⁵

4	CH ₃	4-F-C ₆ H ₄ (2d)	3d	4.0	97	265-267	263-265 ¹⁰
5	CH ₃	3,4-OCH ₂ O-C ₆ H ₃ (2e)	3e	3.0	94	232-235	236-237 ¹⁰
6	H	C ₆ H ₅ (2a)	3f	4.0	90	298-300	293-295 ¹⁰
7	H	4-F-C ₆ H ₄ (2d)	3g	4.5	85	300-303	-

^aReaction conditions: *N,N*-dimethyl-6-aminouracil (**1**; 1 mmol) or 1-methyl-6-aminouracil (**1a**; 1 mmol) and aldehydes (**2a-2d**; 0.5 mmol) in the presence of 20 mol% mandelic acid as catalyst in aqueous ethanol at 28-32 °C. ^bIsolated yields.

Table 5. Synthesis of 2,2'-(arylmethylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (**5a-5e**) using mandelic acid as catalyst at room temperature



Entry	Ar	Product	Time (h)	Yield (%) ^{a,b}	Melting point (°C)	
					Found	Reported ^{REF}
1	C ₆ H ₅ (2a)	5a	4.0	92	190-191	190-192 ²²
2	4-NO ₂ -C ₆ H ₄ (2c)	5b	4.0	90	180-181	169-171 ²²
3	4-OMe-C ₆ H ₄ (2f)	5c	4.0	94	141-143	142-144 ²²
4	3-OMe-4-OH-C ₆ H ₃ (2g)	5d	4.5	92	215-217	191-193 ⁵¹
5	3,5-diOMe-4-OH-C ₆ H ₂ (2h)	5e	4.5	94	192-194	-

^aReaction conditions: dimedone (**4**; 1 mmol) and aldehydes (**2a,2c,2f-2h**; 0.5 mmol) in the presence of 20 mol% mandelic acid as catalyst in aqueous ethanol at 28-32 °C. ^bIsolated yields.

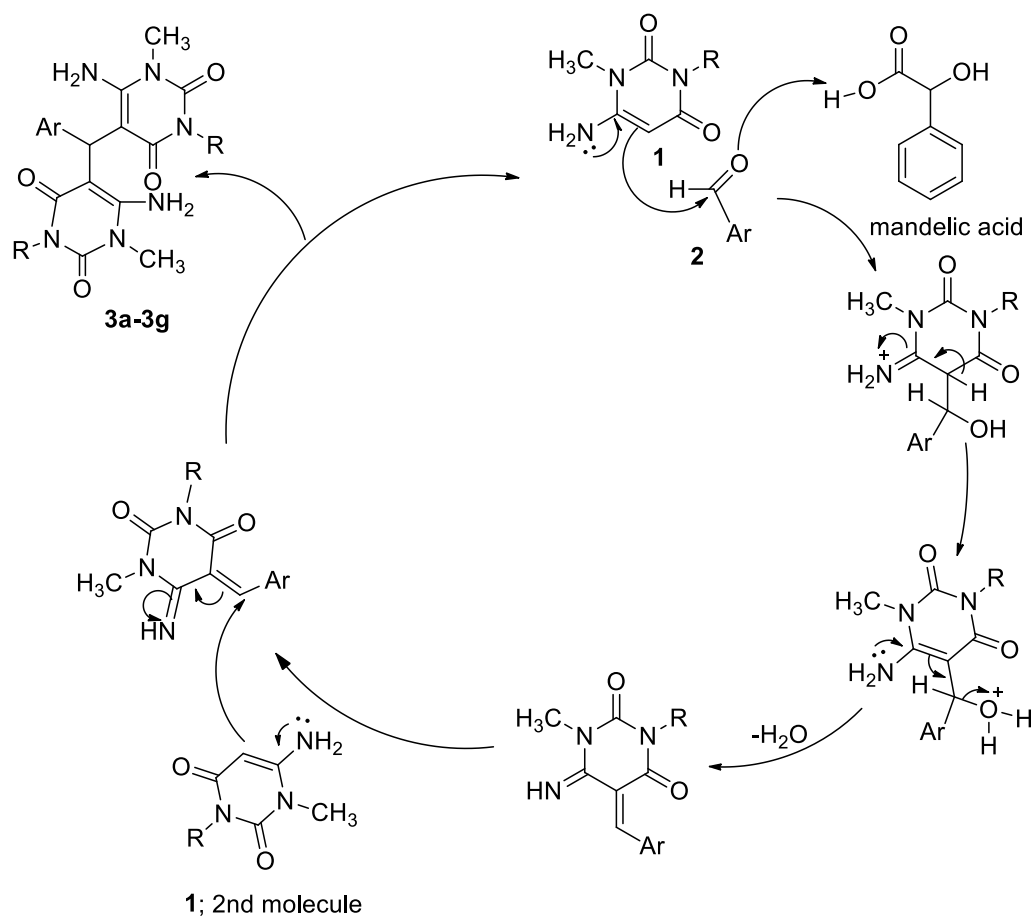


Figure 2. Proposed mechanism for the synthesis of aryl-substituted bis(6-aminouracil-5-yl)methane derivatives

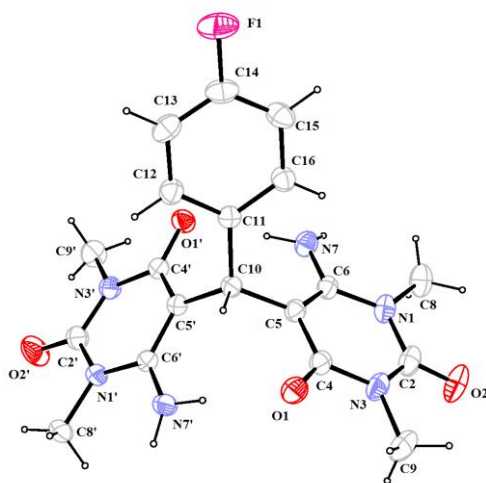


Figure 3. ORTEP view of the molecule 3d with displacement ellipsoids drawn at 40% probability level. Small spheres of arbitrary radii show H (CCDC 1975999)

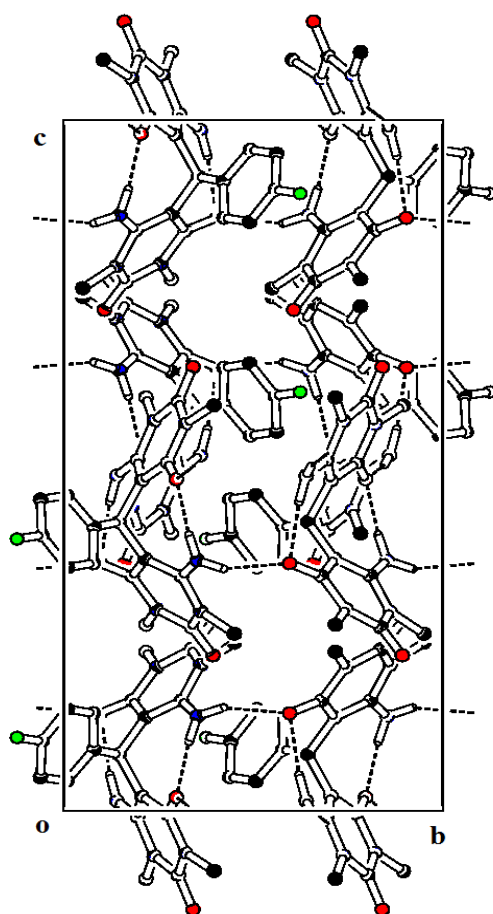


Figure 4. Packing view of the molecules in the unit cell viewed down the a-axis

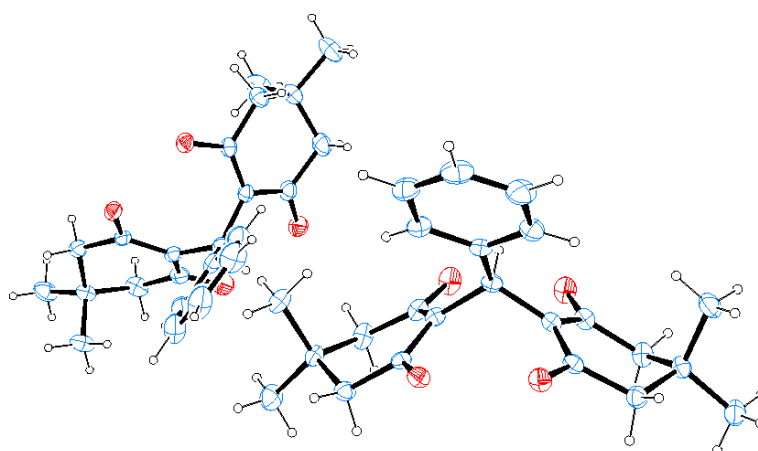


Figure 5. ORTEP view of the molecule **5a** with displacement ellipsoids drawn at 40% probability level. Small spheres of arbitrary radii shows H (CCDC 2157455)

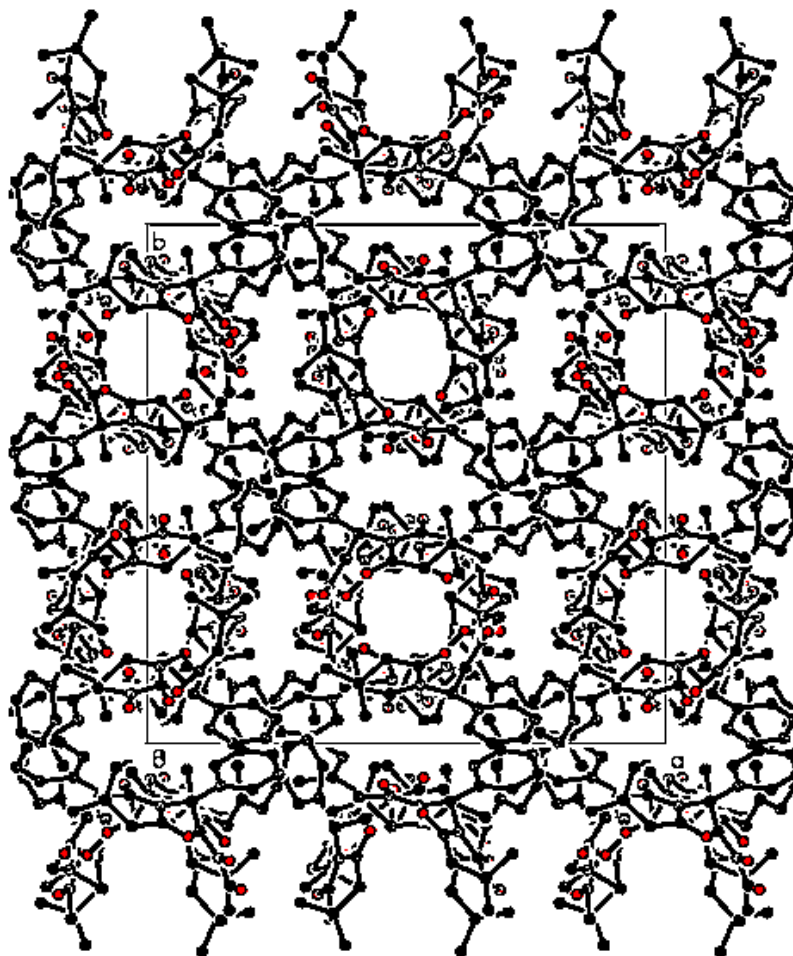


Figure 6. Packing arrangement of molecules viewed down the c-axis.

Experimental Section

General

Melting points were recorded on a Digital Melting Point Apparatus (Model No. MT-934) and are uncorrected. TLC was performed on silica gel 60 F254 (Merck) plates. ^1H and ^{13}C NMR spectra were obtained at 500 MHz Jeol (JNM ECX-500) NMR machines with DMSO-d_6 as the solvent. Mass spectra (TOF-MS ES^+) were measured on a Bruker Impact HD QTOF Micro mass spectrometer.

General procedure for the synthesis of 5,5'-(arylmethylene)bis(6-amino-pyrimidine-2,4(1H,3H)-dione) (3a-3g) and 2,2'-(arylmethylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (5a-5e). In a dry screw-cap test tube a magnetic stir bar, *N,N*-dimethyl-6-aminouracil (**1**; 1 mmol) or 1-methyl-6-aminouracil (**1a**; 1 mmol), substituted benzaldehydes (**2a-2e**; 0.5 mmol), 4 mL aqueous ethanol and a catalytic amount of mandelic acid (20 mol%) were taken sequentially. On a magnetic stirrer, the reaction mixture was then stirred vigorously at room temperature and it was monitored by TLC. After completion of the reaction, the white products of 5,5'-(arylmethylene)bis(6-amino-pyrimidine-2,4(1H,3H)-dione) (**3a-3g**) were isolated pure just by simple filtration and washing the crude products subsequently with ethanol. Under the same optimized reaction conditions, synthesis of 2,2'-(arylmethylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (**5a-5e**) was achieved from the reactions of dimedone (**4**; 1 mmol) and substituted benzaldehydes (**2a,2c,2f-h**; 0.5 mmol) using 20 mol%

mandelic acid as catalyst in aqueous ethanol at room temperature. The structures of the synthesized compounds were confirmed by ^1H NMR, ^{13}C NMR and HRMS analysis.

5,5'-((Phenylmethylene)bis(6-amino-1,3-dimethylpyrimidine-2,4(1H,3H)-dione) (3a). White solid, yield 91%; ^1H NMR (500 MHz, DMSO- d_6): δ_{H} /ppm 7.36 (4H, br s, 2 x NH_2), 7.17 (2H, t, J 8, 7.5 Hz, aromatic H), 7.05 (3H, t, J 7.5, 6.5 Hz, aromatic H), 5.55 (1H, s, $-\text{CH}-$), 3.30 (6H, s, 2 x $-\text{NCH}_3$), 3.11 (6H, s, 2 x $-\text{NCH}_3$); ^{13}C NMR (125 MHz, DMSO- d_6): δ_{C} /ppm 162.99 (2C), 154.93 (2C), 150.99 (2C), 140.10, 128.22 (2C), 127.07 (2C), 125.39, 85.87 (2C), 35.79 (2C), 30.51 (2C), 28.54; HRMS (ESI-TOF) m/z : For $\text{C}_{19}\text{H}_{22}\text{N}_6\text{O}_4$ Calcd. $[\text{M} + \text{Na}]^+$ 421.1600; Found $[\text{M} + \text{Na}]^+$ 421.2078.

5,5'-((4-Chlorophenyl)methylene)bis(6-amino-1,3-dimethylpyrimidine-2,4(1H,3H)-dione) (3b). White solid, yield 95%; ^1H NMR (500 MHz, DMSO- d_6): δ_{H} /ppm 7.35 (4H, br s, 2 x NH_2), 7.20 (2H, d, J = 9 Hz, aromatic H), 7.80 (2H, d, J = 8 Hz, aromatic H), 5.52 (1H, s, $-\text{CH}-$), 3.29 (6H, s, 2 x $-\text{NCH}_3$), 3.10 (6H, s, 2 x $-\text{NCH}_3$); ^{13}C NMR (125 MHz, DMSO- d_6): δ_{C} /ppm 163.31 (2C), 155.37 (2C), 150.95 (2C), 139.32, 129.96, 129.12 (2C), 128.06 (2C), 86.58 (2C), 35.46 (2C), 30.53 (2C), 28.52; HRMS (ESI-TOF) m/z : For $\text{C}_{19}\text{H}_{21}\text{ClN}_6\text{O}_4$ Calcd. $[\text{M} + \text{Na}]^+$ 455.1211; Found $[\text{M} + \text{Na}]^+$ 455.1355.

5,5'-((4-Nitrophenyl)methylene)bis(6-amino-1,3-dimethylpyrimidine-2,4(1H,3H)-dione) (3c). White solid, yield 89%; ^1H NMR (500 MHz, DMSO- d_6): δ_{H} /ppm 8.02 (2H, d, J 9 Hz, aromatic H), 7.37-7.35 (6H, m, aromatic H + 2 x NH_2), 5.62 (1H, s, $-\text{CH}-$), 3.30 (6H, s, 2 x $-\text{NCH}_3$), 3.11 (6H, s, 2 x $-\text{NCH}_3$); ^{13}C NMR (125 MHz, DMSO- d_6): δ_{C} 162.57 (2C), 154.91 (2C), 150.94 (2C), 149.45, 145.75, 128.51 (2C), 123.39 (2C), 84.74 (2C), 36.37 (2C), 30.57 (2C), 28.49; HRMS (ESI-TOF) m/z : For $\text{C}_{19}\text{H}_{21}\text{N}_7\text{O}_6$ Calcd. $[\text{M} + \text{Na}]^+$ 466.1451; Found $[\text{M} + \text{Na}]^+$ 466.1588.

5,5'-((4-Fluorophenyl)methylene)bis(6-amino-1,3-dimethylpyrimidine-2,4(1H,3H)-dione) (3d). White solid, yield 97%; ^1H NMR (500 MHz, DMSO- d_6): δ_{H} /ppm 7.35 (4H, br s, 2 x NH_2), 7.09-7.06 (2H, m, aromatic H), 6.96 (2H, t, J 9 Hz, aromatic H), 5.52 (1H, s, $-\text{CH}-$), 3.29 (6H, s, 2 x $-\text{NCH}_3$), 3.12 (6H, s, 2 x $-\text{NCH}_3$); ^{13}C NMR (125 MHz, DMSO- d_6): δ_{C} /ppm 162.75 (2C), 154.91, 150.94 (2C), 149.45 (2C), 145.75, 128.91 (2C), 123.39 (2C), 84.74 (2C), 36.37 (2C), 30.94 (2C), 28.51; HRMS (ESI-TOF) m/z : For $\text{C}_{19}\text{H}_{21}\text{FN}_6\text{O}_4$ Calcd. $[\text{M} + \text{Na}]^+$ 439.1506; Found $[\text{M} + \text{Na}]^+$ 439.1668.

5,5'-((Benzo[*d*][1,3]dioxol-5-yl)methylene)bis(6-amino-1,3-dimethylpyrimidine-2,4(1H,3H)-dione) (3e). White solid, yield 94%; ^1H NMR (500 MHz, DMSO- d_6): δ_{H} /ppm 7.37 (4H, br s, 2 x $-\text{NH}_2$), 6.68 (1H, d, J 8 Hz, aromatic H), 6.62 (1H, s, aromatic H), 6.53-6.50 (1H, m, aromatic H), 5.91 (2H, s, $-\text{CH}_2$), 5.47 (1H, s, $-\text{CH}-$), 3.28 (6H, s, 2 x $-\text{NCH}_3$), 3.11 (6H, s, 2 x $-\text{NCH}_3$); ^{13}C NMR (125 MHz, DMSO- d_6): δ_{C} /ppm 161.62 (2C), 155.00 (2C), 150.98 (2C), 147.60, 145.16, 134.09, 119.53, 108.09, 107.87, 101.02, 85.85 (2C), 35.56 (2C), 30.48 (2C), 28.48; HRMS (ESI-TOF) m/z : For $\text{C}_{20}\text{H}_{22}\text{N}_6\text{O}_6$ Calcd. $[\text{M} + \text{Na}]^+$ 465.1499; Found $[\text{M} + \text{Na}]^+$ 465.1696.

5,5'-((Phenylmethylene)bis(6-amino-1-methylpyrimidine-2,4(1H,3H)-dione) (3f). White solid, yield 90%; ^1H NMR (500 MHz, DMSO- d_6): δ_{H} /ppm 10.82-10.65 (1H, m, NH), 10.29 (1H, s, $-\text{NH}$), 7.27 (2H, br s, NH_2), 7.16 (1H, t, J 8, 7 Hz, aromatic H), 7.06 (2H, d, J 7.5, 6.5 Hz, aromatic H), 6.77-6.74 (3H, m, aromatic H + $-\text{NH}_2$), 5.41 (1H, s, $-\text{CH}-$), 4.50 (1H, d, J 1.5 Hz), 3.22 (3H, s, $-\text{NCH}_3$), 3.13 (3H, s, $-\text{NCH}_3$); ^{13}C NMR (125 MHz, DMSO- d_6): δ_{C} /ppm 162.86 (2C), 156.90 (2C), 151.81 (2C), 150.65, 140.18, 128.15 (2C), 127.08, 125.37, 75.69 (2C), 34.47, 28.74 (2C); HRMS (ESI-TOF) m/z : For $\text{C}_{17}\text{H}_{18}\text{N}_6\text{O}_4$ Calcd. $[\text{M} + \text{Na}]^+$ 393.1287; Found $[\text{M} + \text{Na}]^+$ 393.1441.

5,5'-((4-Fluorophenyl)methylene)bis(6-amino-1-methylpyrimidine-2,4(1H,3H)-dione) (3g). White solid, yield 85%; ^1H NMR (500 MHz, DMSO- d_6): δ_{H} /ppm 10.83-10.67 (1H, m, NH), 10.30 (1H, br s, NH), 7.28 (2H, br s, $-\text{NH}_2$), 7.06 (1H, t, J 5.5, 2.5 Hz, aromatic H), 6.97 (1H, d, J 9, 8.5 Hz, aromatic H), 6.77-6.71 (3H, m, aromatic H + $-\text{NH}_2$), 5.37 (1H, s, $-\text{CH}-$), 4.50 (1H, d, J 2 Hz, NH_2), 3.21 (3H, s, $-\text{NCH}_3$), 3.13 (3H, s, $-\text{NCH}_3$); ^{13}C NMR (125 MHz, DMSO- d_6): δ_{C} 162.85 (2C), 161.61, 161.53, 159.70, 156.89, 151.81, 150.62, 136.09, 128.84, 114.61 (2C), 75.69 (2C), 39.95, 28.74 (2C); HRMS (ESI-TOF) m/z : For $\text{C}_{17}\text{H}_{17}\text{FN}_6\text{O}_4$ Calcd. $[\text{M} + \text{Na}]^+$ 411.1193; Found $[\text{M} + \text{Na}]^+$ 411.1317.

2,2'-(Phenylmethylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (5a). White solid, yield 92%; ^1H NMR (600 MHz, CDCl_3): δ_{H} /ppm 11.90 (1H, s, OH), 11.56 (1H, br s, OH), 7.27-7.23 (2H, m, aromatic H), 7.17-7.15 (1H, m, aromatic H), 7.09-7.08 (2H, m, aromatic H), 5.53 (1H, s, -CH-), 2.46–2.29 (8H, m, -CH₂-), 1.24 (6H, s, 2 X -CH₃), 1.22 (6H, s, 2 X -CH₃); ^{13}C NMR (150 MHz, CDCl_3): δ_{C} /ppm 190.58 (2C), 189.50 (2C), 138.12, 128.30 (2C), 126.85 (2C), 125.93, 115.66 (2C), 47.12 (2C), 46.51 (2C), 32.81, 31.49 (2C), 29.78 (2C), 27.46 (2C); HRMS (ESI-TOF) m/z : For $\text{C}_{23}\text{H}_{28}\text{O}_4$ Calcd. $[\text{M}]^+$ 368.1988; Found $[\text{M} - \text{H}]^-$ 367.2760.

2,2'-((4-Nitrophenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (5b). White solid, yield 90%; ^1H NMR (600 MHz, CDCl_3): δ_{H} /ppm 11.78 (1H, s, -OH), 11.57 (1H, br s, -OH), 8.13 (2H, t, J 7.2, 1.2 Hz, aromatic), 7.24 (2H, t, J 8.4, 6 Hz, aromatic), 5.53 (1H, s, -CH-), 2.49-2.31 (8H, m, 4x -CH₂), 1.22 (6H, s, 2x -CH₃), 1.10 (6H, s, 2x -CH₃); ^{13}C NMR (150 MHz, CDCl_3): δ_{C} 191.08 (2C), 189.72 (2C), 146.67, 146.29, 127.82 (2C), 123.67 (2C), 115.06 (2C), 47.14 (2C), 46.55 (2C), 33.39, 31.61 (2C), 29.67 (2C), 27.60 (2C); HRMS (ESI-TOF) m/z : For $\text{C}_{23}\text{H}_{27}\text{NO}_6$ Calcd. $[\text{M}]^+$ 413.1838; Found $[\text{M} + \text{H}]^+$ 414.1401.

2,2'-((4-Methoxyphenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (5c). White solid, yield 94%; ^1H NMR (500 MHz, CDCl_3): δ_{H} /ppm; 11.91 (1H, s, -OH), 11.58 (1H, br s, -OH), 6.99 (2H, d, J 9 Hz, aromatic H), 6.80 (2H, d, J 8.5 Hz, aromatic H), 5.47 (1H, s, -CH-), 3.76 (3H, s, -OCH₃), 2.46-2.28 (8H, m, 4x -CH₂), 1.22 (6H, s, 2x -CH₃), 1.09 (6H, s, 2x -CH₃); ^{13}C NMR (125 MHz, CDCl_3): δ_{C} /ppm; 190.53 (2C), 189.48 (2C), 157.65, 129.88, 127.88 (2C), 115.88 (2C), 113.72 (2C), 55.30, 47.14 (2C), 46.51 (2C), 32.10, 31.47 (2C), 29.80 (2C), 27.44 (2C). HRMS (ESI-TOF) m/z : For $\text{C}_{24}\text{H}_{30}\text{O}_5$ Calcd. $[\text{M}]^+$ 398.2093; Found $[\text{M} - \text{H}]^-$ 397.1967.

2,2'-((4-Hydroxy-3-methoxyphenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (5d). White solid, yield 92%; ^1H NMR (500 MHz, CDCl_3): δ_{H} /ppm; 11.97 (1H, s, -OH), 11.61 (1H, br s, -OH), 6.80 (1H, d, J 8 Hz, aromatic H), 6.60 (1H, s, aromatic H), 6.57 (1H, d, J 8.5 Hz, aromatic H), 5.48 (1H, s, -CH-), 5.46 (3H, s, -OH), 3.76 (3H, s, -OCH₃), 2.42-2.33 (8H, m, 4x -CH₂), 1.22 (6H, s, 2x -CH₃), 1.10 (6H, s, 2x -CH₃); ^{13}C NMR (125 MHz, CDCl_3): δ_{C} /ppm; 190.50 (2C), 189.45 (2C), 146.33, 143.61, 129.83, 119.58, 115.86, 114.11, 109.80 (2C), 55.73, 47.15 (2C), 46.46 (2C), 32.39, 31.33 (2C), 29.99 (2C), 27.16 (2C). HRMS (ESI-TOF) m/z : For $\text{C}_{24}\text{H}_{30}\text{O}_6$ Calcd. $[\text{M}]^+$ 414.2042; Found $[\text{M} - \text{H}]^-$ 413.1761.

2,2'-((4-Hydroxy-3,5-dimethoxyphenyl)methylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (5e). White solid, yield 94%; ^1H NMR (600 MHz, CDCl_3): δ_{H} /ppm 12.01 (1H, s, -OH), 11.61 (1H, br s, 2 -OH), 6.33 (2H, s, aromatic H), 5.48 (1H, s, -CH-), 5.335 (1H, s, -OH), 3.76 (6H, s, 2x -OCH₃), 2.44-2.34 (8H, m, 4x -CH₂), 1.23 (6H, s, 2x -CH₃), 1.10 (6H, s, 2x -CH₃); ^{13}C NMR (150 MHz, CDCl_3): δ_{C} /ppm 196.49 (2C), 189.44 (2C), 146.91 (2C), 132.82, 129.21, 115.83 (2C), 104.03 (2C), 56.17 (2C), 47.26 (2C), 46.48 (2C), 32.68, 31.26 (2C), 30.15 (2C), 26.96 (2C); HRMS (ESI-TOF) m/z : For $\text{C}_{25}\text{H}_{32}\text{O}_7$ Calcd. $[\text{M} + \text{Na}]^+$ 467.2046; Found $[\text{M} + \text{Na}]^+$ 467.1732.

Conclusions

In conclusion, we have developed a simple, facile, efficient and general method for the synthesis of 5,5'-(arylmethylene)bis(6-amino-pyrimidine-2,4(1*H*,3*H*)-diones) *via* one-pot pseudo three-component reactions between two equivalents of either *N,N*-dimethyl-6-aminouracil or 1-methyl-6-aminouracil and one equivalent of aldehydes using a catalytic amount of mandelic acid as catalyst in aqueous ethanol at room temperature. Under the same optimized conditions, reactions between two equivalents of dimedone and one equivalent of aromatic aldehydes afforded the corresponding 2,2'-(arylmethylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) derivatives in excellent yields. Mild reaction conditions, use of naturally occurring commercially available low cost organocatalyst, environmentally benign solvent, high yields, short reaction times, gram

scale production and column chromatography-free purification procedure are some of the major advantages of this developed protocol.

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Supplementary Material

Scanned ^1H -NMR, ^{13}C -NMR and HRMS spectra of all the synthesized scaffolds are supplemented in supporting information.

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