The Development of an Ecofriendly Procedure for Alkaline Metal (II) Sulfate Promoted Synthesis of *N*,*N*′-Dimethyl Substituted (Unsubstituted)-4-Aryl-3,4-Dihydropyrimidones (Thiones) and Corresponding Bis-Analogues in Aqueous Medium: Evaluation by Green Chemistry Metrics

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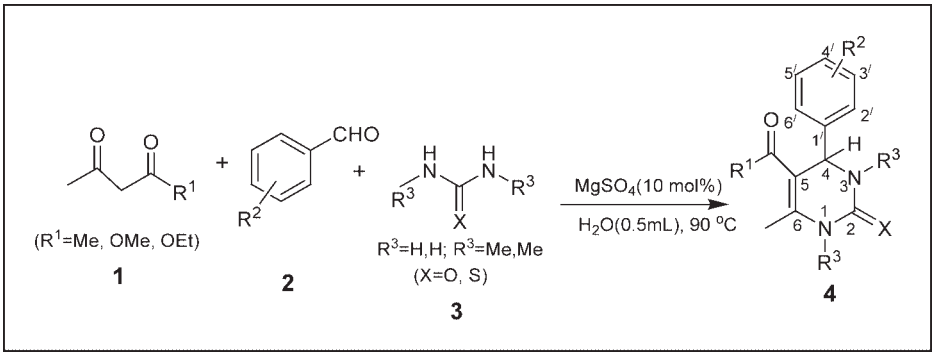

Different alkaline metal (II) sulfates were used as catalysts for the *N*,*N*′-dimethyl substituted as well as unsubstituted 4-aryl-3,4-dihydropyrimidones (thiones) and their corresponding bis-analogues in aqueous medium. Among the various salts, $MgSO_4 \cdot 7H_2O$ (Epsom salt) proved to be the best catalyst giving the desired products in good to excellent yields. This catalyst enables the construction of a series of compound libraries particularly for *N*,*N*′-dimethyl substituted DHPM's whose synthesis is very rare in the literature. The reaction on a wide variety substrates was evaluated by the application of green chemistry metrics and a very good correlation was obtained.

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INTRODUCTION

The actual driving force for the development of new catalysts for the structural motif-*N*,*N*′-disubstituted(unsubstituted)-4-aryl-3,4-dihydropyrimidones being a heterocyclic moiety of remarkable pharmacological importance [1] is to prepare compound libraries for screening in drug discoveries. The appropriately functionalized dihydropyrimidones (DHPMs) are very prominent as mitotic kinesin inhibitors, α_1-adrenergic antagonists and potent hypertensive agents [1]. The importance of the *N*,*N*′-disubstituted DHPMs lies in the fact that *N*,*N*′-disubstitution promotes lipophilicity and advances chemozymatic synthesis of enantiopure DHPMs in organic solvents [2]. When three component coupling (3CC) involving an aldehyde, alkyl acetoacetate, and *N*,*N*′-dimethylurea is performed, the synthesis of the desired dihydropyrimidones often fail or produces the desired products in very low yields due to the formation of multiple side products. Solvent-free conditions also fail to produce them [3]. Till date, the synthesis of *N*,*N*′-disubstituted DHPMs remains a great challenge for organic chemists.

Green Chemistry is a rapidly developing new field that provides a proactive avenue for the sustainable development of future science and technology [4]. Nowadays many reactions are being carried out in water for environmental protection. From this view point, it is desirable, instead of organic solvents, to use water as a reaction medium as, water is safe, easy handling, abundant and an environmentally benign solvent. Therefore, we aimed at the synthesis of the *N*,*N*′-disubstituted and *N*,*N*′-unsubstituted DHPMs in aqueous medium.

RESULTS AND DISCUSSION

Dihydropyrimidones (DHPMs) possess immense biological activity [5] and therefore the synthesis of this nucleus has received much attention. It must be mentioned that the synthesis of the *N*,*N*′-dimethyl substituted DHPMs is rather difficult and there are only few references in the literature. The simple DHPMs, first synthesized by Biginelli [6], have already been prepared by a number of methods. In spite of this, very few reports of the synthesis of this ring system exist in water [7–9]. Thus, exploration for catalysts leading to the synthesis of this extremely important ring system in aqueous medium is still needed. In continuation of our sincere

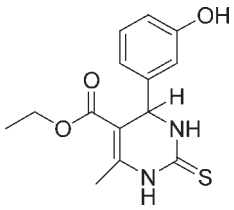


Figure 1. Monastrol.

efforts in carrying out reactions in aqueous medium [10–12], we envisaged the construction of a wide variety of *N*,*N*′-unsubstituted and dimethyl substituted dihydropyrimidones and also bis-dihydropyrimidones in water with variations in all the three components. This catalyst has been efficiently utilized for the synthesis of the mitotic kinesin EG 5 inhibitor Monastrol [13] (Fig. 1) in excellent yield.

For the initial exploration, the condensation of ethylacetoacetate, 4-chlorobenzaldehyde and urea with $MgSO_4$ (10 mol %) was studied in different solvents to optimize the reaction condition and to establish the feasibility of our catalyst (Table 1).

From Table 1, we find that the synthesis of the dihydropyrimidone produced from 4-chlorobenzaldehyde, EAA and urea proceeds best in water at 90°C in water (entry 12). Almost no reaction took place in aqueous medium at lower temperatures (entries 9–11). Use of higher temperature did not increase the yield further (entry 13). The yields were much lower when carried out in organic solvents (entries 1–8). Therefore, water has a definite role for the green reaction medium as it has an unique property of inducing hydrophobic interactions between the substrate and the catalyst.

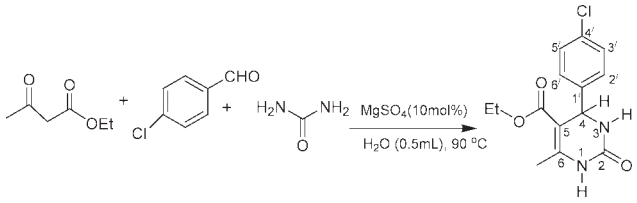
Our next task was the choice of the catalyst for the model reaction with EAA, urea, and 4-chlorobenzaldehyde with 0.5 mL of water at 90°C and the results are summarized in Table 2.

We tried Group IIA metal sulfates as the catalyst for the dihydropyrimidone formation in water at 90°C. It was observed that $MgSO_4 \cdot 7H_2O$ (Epsom salt) produced the desired product in maximum yield. It was also observed that the solubility of the Group IIA metal sulfate decreases down the group in accordance with Fajan's rules, which states that solubility decreases with increasing cationic radius. Therefore, the yield with Epsom salt was maximum probably due to an optimum correlation between its solubility and ionic character. The partial covalent character of Mg^{+2} ion helps to form strong metal-oxygen bonds (similarly as in ref. [5]) thereby increasing the electrophilicity of the carbonyl carbons of the β-keto esters or β-diketones.

Once the optimum reaction conditions were finalized, the catalyst was effectively utilized for the synthesis of a wide variety of *N*,*N*′-unsubstituted-3,4-dihydropyrimidin-2(1H)-ones and thiones (Scheme 1, $R^3 = H$) and the results are summarized in Table 3.

Table 1

Optimization of the reaction conditions of synthesis of dihydropyrimidone from 4-chlorobenzaldehyde, ethylacetoacetate, and urea with $MgSO_4$ (10 mol %).



Entry	Solvent (0.5 mL)	Temperature (°C)	Reaction time (h)	Yield[a] (%) (isolated)
1	CH_2Cl_2	45	5	35
2	THF	65	4	30
3	MeOH	70	4	35
4	EtOH	80	5	30
5	DMF	80	6	40
6	DMF	100	4	45
7	DMSO	80	6	40
8	DMSO	100	5	42
9	H_2O	40	4	00
10	H_2O	60	5	03
11	H_2O	70	6	05
12	H_2O	90	4	90
13	H_2O	100	5	90
14	H_2O	90	8	90

[a] Yields calculated with respect to starting aldehyde.

Table 2

Choice of catalyst for the reaction of EAA, urea, and 4-chlorobenzaldehyde with 0.5 mL water at 90°C.

Entry	Catalyst (10 mol%) (with water of hydration)	Time (h)	Yield % (isolated w. r. t. starting aldehyde)
1	–	10	5
2	$MgSO_4$	4	90
3	$CaSO_4$	6	60
4	$SrSO_4$	7	47
5	$BaSO_4$	10	20

Our next target was the application of our catalyst for the synthesis of the dimethyl substituted DHPM's and hence to synthesize ''drug-like'' molecules. This is because the synthesis of these *N*,*N*′-dimethyl DHPMs are rather difficult and thus references for their synthesis are very rare. To establish the scope and utility of our catalyst, a number of reactions (Table 4) were conducted and the products isolated. It was noted that on scaling up the reaction, the amount of $MgSO_4$ need not be increased proportionately. After lyophilization of the water extract obtained from the filtration of the product, the recovered catalyst could be reused to a maximum of three successive preparations of the DHPMs with almost the same yield of the reaction. The water extract responded to positive tests for both Mg^{+2} and SO_4^{2-} ions indicating that the catalyst remains intact after the reaction. The role of the catalyst is therefore to increase the electrophilicity of the aldehyde carbonyl which is very obvious as with other metal salts and also to coordinate with the carbonyl oxygen of the β-keto ester and the β-diketone.

On analysis of Tables 3 and 4, we find that our catalyst produced the *N*,*N*′-unsubstituted-3,4-dihydropyrimidin-2(1*H*)-ones in excellent yields and the *N*,*N*′-dimethyl DHPMs in good yields. The reaction also accommodated a wide variety of substrates in the aldehyde part, both electron-donating and electron-withdrawing acting equally well. Ethylacetoacetate, methylacetoacetate, and acetylacetone were varied as the β-keto esters or the β-diketone. Again, urea and thiourea were equally effective in carrying out the reaction. Table 3, entry 4 depicts the synthesis of Monastrol (Fig. 1). In all the cases, the pure product was isolated by simple filtration. Recrystallization from aqueous ethanol produced the pure 3, 4-dihydropyrimidin-2(1*H*)-ones. Thus, the products were obtained in pure form without any column chromatography or any cumbersome work-up techniques. In all the cases, 100% conversion was observed as no starting materials were present in thin layer chromatography (TLC) or in ^{1}H NMR (crude) after the reaction. With aliphatic aldehydes, only 10% conversion (by TLC) was observed and the final products cannot be isolated from the reaction mixture. The reaction was also 100% selective as a single product was obtained for all cases for aromatic aldehydes. This is possibly due to the higher stability of the acyl imines (with increasing conjugation) for aromatic aldehydes than with aliphatic ones. This methodology in aqueous medium is obviously a green one as no toxic chemicals or reagents were used and no side products were obtained.

Encouraged by the aforementioned results, we turned our attention toward the utilization of our catalyst toward the construction of the bis-3,4-dihydropyrimidin-2(1*H*)-ones (thiones). We found that the reactions proceeded smoothly in aqueous medium with $MgSO_4$ (10 mol %) to produce the *N*,*N*′-unsubstituted bis-compounds in excellent yields (Scheme 2, Table 5). The reaction generated two new chiral centers at C_4 and C_4'-positions, the relative stereochemistry of which could be either RR or RS. X-ray crystallography of these compounds was not possible due to their amorphous nature. With dimethyl urea and thiourea, the formation of these bis-compounds did not go to completion. These bis-compounds are otherwise quite difficult to achieve and therefore the application of our catalyst provides an easy access to the construction of these compounds.

The mechanism of the dihydropyrimidone formation is similar as proposed by Folkers and Johnson [15]. The

Scheme 1. Synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones (thiones) with $MgSO_4$ (10 mol %) in water at 90°C.

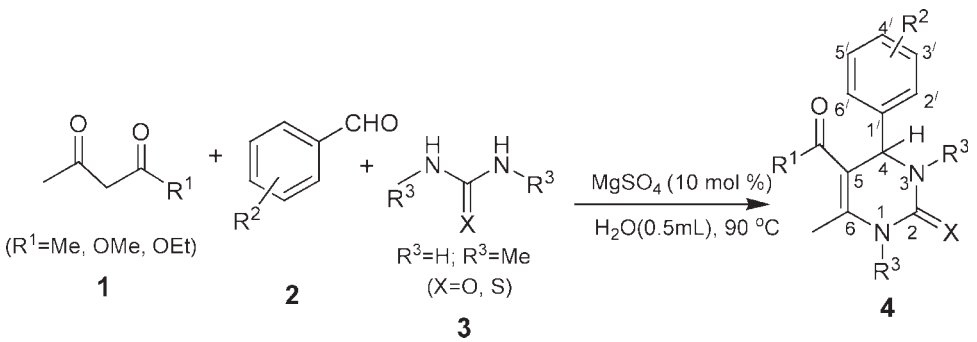


Table 3

Synthesis of *N*,*N*′-unsubstituted-3,4-dihydropyrimidin-2(1*H*)-ones (thiones) (R^3 = H) with $MgSO_4$ (10 mol %) in water at 90°C.

Entry	R^1	R^2	X	Time (h)	Yield (%) (isolated)	References
1	OEt	4-Cl	O	8	90	[10]
2	OMe	4-OMe	O	9	88	[10]
3	OMe	4-OH-3-OMe	S	6	85	[10]
4	OEt	3-OH	S	7	82	[13]
5	OMe	3-NO_2	O	10	80	[10]
6	Me	2,5-$(OMe)_2$	O	5	88	–
7	OMe	2,5-$(OMe)_2$	O	5	87	–
8	OMe	4-CN	O	6	83	–
9	OEt	4-NO_2	O	10	85	[13]
10	Me	H	S	7	82	[13]
11	Me	4-CN	S	8	80	–
12	OEt	2-furanyl	O	4	78	[13]
13	OMe	4-CN	S	8	82	–
14	OEt	4-OH	S	9	78	[13]
15	OEt	4-CN	S	10	81	–
16	Me	2-Cl	S	8	79	[13]
17	OMe	3-OH	S	7	75	–
18	Me	2-NO_2	S	9	80	–
19	Me	3-NO_2	S	9	82	–
20	Me	4-OH-3-OMe	S	8	78	–
21	OEt	H	O	9	75	[13]
22	OEt	H	S	9	78	[13]
23	OMe	4-OH-3-OMe	O	7	79	[13]
24	Me	4-OMe	O	5	82	[13]
25	OEt	4-OMe	S	5	84	[13]
26	Me	3-NO_2	O	10	86	[13]
27	OEt	4-NMe_2	O	4	85	[13]
28	OMe	4-NMe_2	O	4	77	[13]
29	Me	4-NO_2	O	10	73	[13]
30	OEt	3-OH	O	6	76	[13]
31	Me	4-Cl	O	7	77	[13]
32	Me	H	O	8	76	[13]
33	OMe	H	S	8	85	[13]
34	OEt	4-OMe	O	6	84	[13]
35	Me	4-OH	O	7	83	[13]
36	OMe	4-OH	O	8	82	[13]
37	OMe	4-NO_2	O	8	79	[13]

initial formation of the acylimine intermediate takes place which reacts subsequently with the β-diketone or β-ketoester effectively. The partial covalent character of Mg^{+2} helps in forming a strong metal oxygen bond which helps in increasing the electrophilicity of the β-diketone or β-ketoester in the same manner as mentioned in ref. [5]. Finally, a favorable cyclization and dehydration path follows to produce the dihydropyrimidone system.

In a nutshell, our methodology has the following distinct advantages over the earlier reported procedures [6.9]: (a) the reactions are investigated in water and hence avoids the hassles of organic solvents, (b) the catalyst is rather simple and cheap, (c) anhydrous reaction conditions need not be maintained, (d) additional proton sources are not required, (e) the products are obtained by simple filtration without the need for column chromatography, (f) this methodology is particularly useful for the synthesis of the dimethyl dihydropyrimidones and bis-dihydropyrimidones which are otherwise quite rare in the literature, and (g) it is a totally green methodology.

Green metric calculations. The green metrics were calculated using the procedures reported in the literature.[4] Their definitions are given as follows:

Mass Intensity (MI) = Total mass used in a process or process step (g)/mass of product (g)

Reaction mass efficiency (RME) = (Σ mass of products/Σ mass of reactants) × 100

Carbon efficiency (CE) = [(No. of moles of product × No. of carbons in product)/Σ (No. of moles of reactant × No. of carbons in reactant)] × 100

Atom economy (AE) = [molecular weight of product/Σ molecular weight of reactant] ×100

Table 4

Synthesis of *N*,*N*′-dimethyl-4-aryl-dihydropyrimidones (thiones) (R^3 = Me) with $MgSO_4$ (10 mol %) in water at 90°C.

Entry	R^1	R^2	X	Time (h)	Yield[a]	References
1	OMe	4′-OMe	O	10	60	–
2	OEt	4′-OH	O	8	62	–
3	OMe	4′-Cl	O	8	60	–
4	OEt	3′,4′-$(OMe)_2$	O	9	61	–
5	OMe	2′-NO_2	O	9	65	–
6	OMe	2′,5′-$(OMe)_2$	O	9	62	–
7	OEt	2′,5′-$(OMe)_2$	O	10	61	–
8	Me	2′-Cl	O	6	60	–
9	Me	4′-NO_2	O	7	62	–
10	Me	4′-Br	O	9	65	–
11	OMe	4′-Br	O	10	64	–
12	OMe	2′-Cl	O	7	61	–
13	Me	4′-Br	S	12	44	–
14	Me	2′-Cl	S	10	58	–
15	OEt	4′-Cl	O	7	60	–
16	Me	3′-NO_2	O	7	65	–
17	OEt	2′-NO_2	O	8	60	[2]
18	OEt	3′-NO_2	O	9	61	[2]
19	OEt	4′-NO_2	O	9	64	[2]
20	OEt	4′-OMe	O	9	60	[2]

[a] Isolated.

Mass intensity (MI), reaction mass efficiency (RME), carbon efficiency (CE), and atom economy (AE) have been considered as a measure of environmental sustainability in minimizing the amount of theoretical waste. MI considers the yield stoichiometry, the solvent and the RME is the natural measure of greenness that takes into account the yield, excess or catalytic amount of reactants used but it does not account for any solvent use. CE is the percentage of carbon gain or loss, that is, whether all the carbon atoms of the reactant are present in the product. It is a very important parameter in our reaction as our reaction involves carbon atoms. Finally, the AE is a theoretical calculation of the chemical and environmental efficiency of the reaction which allows

Scheme 2. Synthesis of bis-3,4-dihydropyrimidin-2(1*H*)-ones (thiones) at 90°C in aqueous medium with $MgSO_4$ (10 mol %).

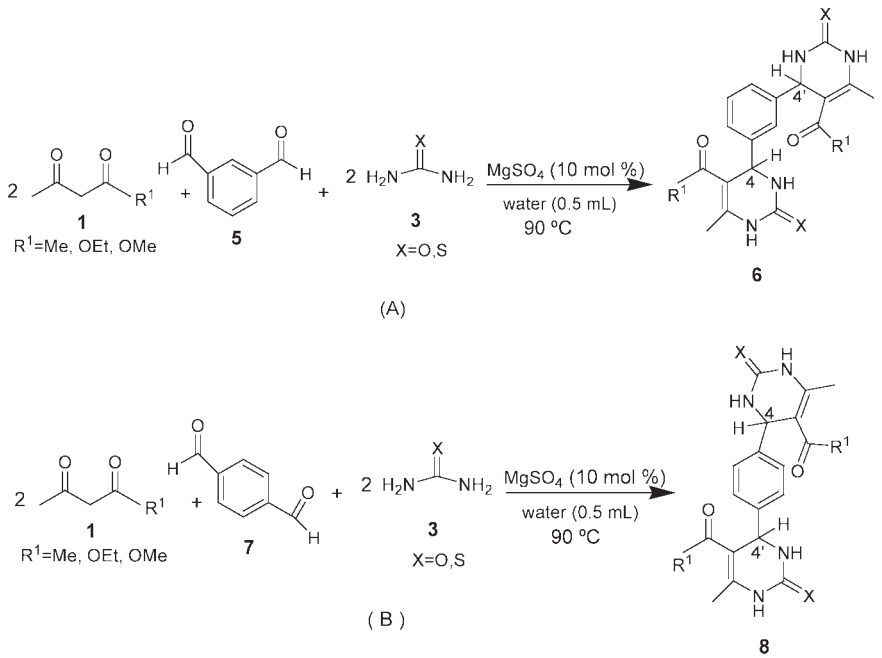


Table 5

Synthesis of bis-3,4-dihydropyrimidin-2(1*H*)-ones (thiones) at 90°C in aqueous medium with $MgSO_4$ (10 mol %).

Entry	R^1	Starting dialdehyde	X	Time (h)	Yield (%) (isolated)	References
1	OMe	**5**	O	10	85	–
2	OEt	**5**	O	11	82	–
3	OMe	**5**	S	15	75	–
4	Me	**5**	O	10	80	[14]
5	OMe	**7**	O	12	84	[14]
6	OEt	**7**	O	11	82	[14]
7	OMe	**7**	S	10	76	[14]
8	OEt	**7**	S	11	74	[14]

for the effect on stoichiometric equation, not considering any solvent, excess of reagents and formation of intermediate or any other side product, etc. So from this aforementioned point, the ideal situation is MI $\approx$ 1, % RME $\approx$ 100, % CE $\approx$ 100, % AE $\approx$ 100.

We have shown the green metrics calculations for some selected compounds using urea, thiourea, or dimethyl urea (Table 6). The results reveal that our reactions have excellent MI values for almost all the compounds (Table 6). MI values of the reactions are very much dependent on solvent. Use of lesser amount of solvent in the reaction will lead to the ideal situation. We use only 0.5 mL of water in our reactions which is the optimum value. Use of lower amount of solvent (water) in the reaction will lead to increase in MI, but lower yield, as the catalyst will not react in lesser amount of solvent used. Thus, the MI values obtained were highly acceptable. Our reactions have excellent CE (for reactions with urea and thiourea) and quite good CE (for reactions with dimethyl counterparts), which in these cases is equal to the yield because all the carbon atoms of the reactant are present in the

Table 6

Green metrics calculations of a wide variety of compounds taken from Tables 3–5.

Entry	Substrates used	% Yield	FW (product)	Yield (g)	MI	% RME	% CE	% AE
1	Table 3, entry 6	88	290.317	0.255	3.32	73.70	88	88.96
2	Table 3, entry 7	87	306.316	0.266	3.43	64.56	87	89.47
3	Table 3, entry 8	83	271.275	0.225	3.90	59.68	83	88.28
4	Table 3, entry 11	80	271.342	0.217	3.81	66.36	80	88.28
5	Table 3, entry 13	82	287.341	0.235	3.80	59.80	82	88.86
6	Table 3, entry 15	81	301.368	0.244	3.72	59.95	81	89.32
7	Table 3, entry 17	75	278.291	0.208	4.25	54.16	75	88.84
8	Table 3, entry 18	80	291.329	0.233	3.64	67.15	80	88.99
9	Table 3, entry 19	82	291.329	0.238	3.56	68.59	82	88.99
10	Table 3, entry 20	78	292.356	0.228	3.72	65.52	78	89.03
11	Table 4, entry 1	60	304.344	0.182	5.00	44.39	60	89.41
12	Table 4, entry 2	62	304.344	0.188	4.80	45.85	62	89.42
13	Table 4, entry 3	60	308.763	0.185	4.94	44.69	60	89.55
14	Table 4, entry 4	61	348.390	0.212	4.50	46.70	61	90.06
15	Table 4, entry 5	65	319.320	0.207	4.47	48.70	65	89.86
16	Table 4, entry 6	62	334.370	0.207	4.54	47.70	62	90.27
17	Table 4, entry 7	61	348.396	0.212	4.50	46.70	61	90.63
18	Table 4, entry 8	60	292.764	0.175	4.85	50.29	60	89.04
19	Table 4, entry 9	62	303.316	0.188	4.75	52.37	62	89.38
20	Table 4, entry 10	65	337.215	0.219	4.08	55.73	65	90.35
21	Table 3, entry 11	64	353.210	0.226	4.24	49.24	64	90.74
22	Table 3, entry 12	61	308.760	0.188	4.87	45.41	61	89.55
23	Table 3, entry 13	44	353.280	0.155	5.87	37.90	44	90.75
24	Table 3, entry 14	58	308.830	0.179	4.83	49.18	58	89.55
25	Table 3, entry 15	60	322.790	0.193	4.81	45.09	60	89.96
26	Table 3, entry 16	65	303.320	0.197	4.36	54.87	65	89.38
27	Table 5, entry 1	85	414.416	0.352	3.14	58.08	85	85.19
28	Table 5, entry 2	82	442.469	0.362	3.13	57.10	82	86.00
29	Table 5, entry 3	75	446.548	0.334	3.41	52.35	75	86.11

product. In the same direction, the excellent yields with the catalyst produced good values of RME while moderate yield produced moderate RME values. Table 6 shows that all our reactions possess excellent AE values mostly being 89–90%. Thus all the reactions carried out using our methodology have very good green metrics correlations.

CONCLUSION

It can be concluded that $MgSO_4 \cdot 7H_2O$ (10 mol %) in 0.5 mL water proves to be the best catalyst amongst all the alkaline Group II metals for dihydropyrimidone, bis-dihydropyrimidone and particularly, *N*,*N*′-dimethyl dihydropyrimidone formation. Since only 10 mol % of the catalyst and 0.5 mL of water are used, the reaction condition meets several green chemistry principles. The isolation of the reaction products is very simple and does not require column chromatography for most cases.

EXPERIMENTAL

General. Ethanol was distilled before use. All the chemicals were purchased from Aldrich Chemical Company and Spectrochem (Mumbai, India). Silica Gel G with binder from Spectrochem was used for thin layer chromatography. $MgSO_4 \cdot 7H_2O$ was purchased from Spectrochem was used as such. ^1H and ^{13}C NMR spectra were obtained on Bruker 300 MHz instrument at 300 and 75 MHz, respectively. $CDCl_3$ and DMSO-d_6 were purchased from Aldrich Chemical Company. Melting points were determined on an electrical melting point apparatus with an open capillary and are uncorrected. IR spectra were recorded on a Perkin-Elmer spectrophotometer RX/FTIR system.

General experimental procedure for dihydropyrimidone/bis-dihydropyrimidone formation. A mixture of aromatic aldehyde (1 mmol), β-keto ester or β-diketone (1.3 mmol/2.6 mmol), urea/thiourea/*N*,*N*′-dimethyl urea/*N*,*N*′-dimethyl thiourea (1.5 mmol/3.0 mmol) and $MgSO_4 \cdot 7H_2O$ (10 mol %) and 0.5 mL water were mixed thoroughly and then taken in a 5 mL conical flask. It was next placed in water bath at 90°C and heated for the specified time as mentioned in Tables 3–5. The reactions were monitored by TLC for the absence of the starting aldehyde. After completion of the reaction, the crude mass was cooled, poured into crushed ice, and stirred for further 10 min, when the dihydropyrimidones (solids) precipitated out. They were directly filtered and crystallized from hot aqueous ethanol to obtain the finally pure products. The liquid DHPMs products were extracted with (2 × 5) mL ethyl acetate, washed with brine, solvent removed to obtain the crude products. The pure products (liquids) were obtained by column chromatography with silica gel (100–200 mesh) and elution with ethyl acetate/petroleum ether (60–80°C). All the products were characterized by their spectral and analytical data.

The data for all the previously unknown compounds are given later:

5-Acetyl-6-methyl-4-(2,5-dimethoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (Table 3, entry 6). Light brown solid; M.p. 252–254°C (MeOH). IR (KBr): 3247, 3107, 1705, 1628, 1495, 1454, and 1235 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ: 9.12 (s, 1H, NH), 7.33 (s, 1H, NH), 6.90 (d, J = 8.7 Hz, 1H, aromatic C_3-H), 6.78 (dd, J = 9.0, 3.0 Hz, 1H, aromatic C_4-H), 6.53 (d, J = 3.3 Hz, 1H, aromatic C_6-H), 5.48 (d, J = 3.0 Hz, 1H, C_4-H), 3.72 (s, 3H, C_2-OMe), 3.61 (s, 3H, C_5-OMe), 2.25 (s, 3H, —$COCH_3$), 2.00 (s, 3H, C_6-CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 194.6 (C=O), 153.2 (C_2=O), 152.3 (aromatic C_2), 150.5 (aromatic C_5), 148.2 (C_6), 132.4 (aromatic C_1), 113.9 (aromatic C_3), 112.3 (aromatic C_4), 112.2 (aromatic C_6), 108.0 (C_5), 56.0 (C_2-OMe), 55.4 (C_5-OMe), 48.9 (C_4), 29.8 (CO*C*H_3), 18.7 (C_6-*C*H_3). *Anal*. calcd. for $C_{15}H_{18}N_2O_4$; C: 62.06, H: 6.25, N: 9.65. Found: C: 62.17, H: 6.02, N: 9.71%.

5-Methoxycarbonyl-6-methyl-4-(2,5-dimethoxyphenyl)-3.4-dihydropyrimidin-2(1H)-one (Table 3, entry 7). Off-white solid; M.p. 240–242°C (MeOH). IR (KBr): 3241, 3106, 2948, 1703, 1646, 1496, 1440, 1235, and 1092 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ: 9.16 (s, 1H, NH), 7.26 (s, 1H, NH), 6.91 (d, J = 9.0 Hz, 1H, aromatic C_3-H), 6.79 (dd, J = 8.9, 3.0 Hz, 1H, aromatic C_4-H), 6.54 (d, J = 3.0 Hz, 1H, aromatic C_6-H), 5.41 (d, J = 3.0 Hz, 1H, C_4-H), 3.73 (s, 3H, C_2-OMe), 3.64 (s, 3H, C_5-OMe), 3.47 (s, 3H, —$COOCH_3$), 2.27 (s, 3H, C_6-CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 165.9 (*CO*OMe), 153.0 (C_2=O), 152.3 (aromatic C_2), 150.8 (aromatic C_5), 149.3 (C_6), 132.6 (aromatic C_1), 113.9 (aromatic C_3), 112.4 (aromatic C_4), 112.0 (aromatic C_6), 97.4 (C_5), 56.1 (C_2-*OMe*), 55.3 (C_5-*OMe*), 50.8 (C_4), 49.0 (CO*OCH*$_3$), 17.8 (C_6-*C*H_3). *Anal*. calcd. for $C_{15}H_{18}N_2O_5$; C: 58.82, H: 5.92, N: 9.15. Found: C: 58.71, H: 5.84, N: 9.22%.

5-Methoxycarbonyl-6-methyl-4-(4-cyanophenyl)-3.4-dihydropyrimidin-2(1H)-one (Table 3, entry 8). White solid; M.p. 176–178°C (MeOH). IR (KBr): 3329, 3120, 2235, 1634, 1223, and 1089 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ: 9.33 (s, 1H, NH), 7.85 (d, J = 1.2 Hz, 1H, NH), 7.80 (d, J = 8.4 Hz, 2H, aromatic C_3-, C_5-H), 7.38 (d, J = 8.1 Hz, 2H, aromatic C_2-, C_6-H), 5.18 (d, J = 3.3 Hz, 1H, C_4-H), 3.49 (s, 3H, —$COCH_3$), 2.22 (s, 3H, C_6-CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 165.7 (*CO*OMe), 152.0 (C_2=O), 149.9 (aromatic C_1), 149.7 (C_6), 132.7 (aromatic C_3, C_5), 127.4 (aromatic C_2, C_6), 118.8 (C_5), 110.3 (aromatic C_4), 98.2 (CN), 53.8 (C_4), 51.0 (CO*OCH*$_3$), 18.0 (C_6-*C*H_3). *Anal*. calcd. for $C_{14}H_{13}N_3O_3$; C: 61.99, H: 4.83, N: 15.49. Found: C: 61.84, H: 4.71, N: 15.63%.

5-Acetyl-6-methyl-4-(4-cyanophenyl)-3.4-dihydropyrimidin-2(1H)-thione (Table 3, entry 11). White solid; M.p. 130–132°C (MeOH). IR (KBr): 3277, 3181, 2228, 1617, 1577, 1455, and 1186 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ: 10.38 (s, 1H, NH), 9.81 (d, J = 2.4 Hz, 1H, NH), 7.80 (d, J = 8.4 Hz, 2H, aromatic C_3-, C_5-H), 7.35 (d, J = 8.1 Hz, 2H, aromatic C_2-, C_6-H), 5.32 (d, J = 3.9 Hz, 1H, C_4-H), 2.31 (s, 3H, $COCH_3$), 2.18 (s, 3H, C_6-CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 194.7 (C=O), 174.6 (C=S), 148.1 (aromatic C_1), 145.5 (C_6), 132.8 (aromatic C_3, C_5), 127.6 (aromatic C_2, C_6), 118.8 (C_5), 110.5 (aromatic C_4), 110.3 (CN), 53.4 (C_4), 30.8 (CO*CH*$_3$), 18.5 (C_6-CH_3). *Anal*. calcd. for $C_{14}H_{13}N_3OS$; C: 61.97, H: 4.83, N: 15.49. Found: C: 61.84, H: 4.75, N: 15.61%.

5-Methoxycarbonyl-6-methyl-4-(4-cyanophenyl)-3.4-dihydropyrimidin-2(1H)-thione (Table 3, entry 13). White solid; M.p. 158–160°C (MeOH). IR (KBr): 3327, 3146, 2926, 2228, 1689, 1526, and 1173 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ: 10.45 (s, 1H, NH), 9.72 (d, J = 2.1 Hz, 1H, NH), 7.80 (d, J = 8.4 Hz, 2H, aromatic C_3-, C_5-H), 7.35 (d, J = 8.1 Hz, 2H, aromatic C_2-, C_6-H), 5.20 (d, J = 3.3 Hz, 1H, C_4-H), 3.51 (s,

3H, $COOCH_3$), 2.25 (s, 3H, C_6-CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 175.1 (C=S), 165.3 (C=O), 147.0 (aromatic C_1), 143.6 (C_6), 132.8 (aromatic C_3, C_5), 127.5 (aromatic C_2, C_6), 118.3 (C_5), 112.4 (aromatic C_4), 102.0 (CN), 55.6 (C_4), 51.7 ($CO\mathit{OCH_3}$), 18.6 (C_6-CH_3). *Anal.* calcd. for $C_{14}H_{13}N_3O_2S$; C: 58.52, H: 4.56, N: 14.62. Found: C: 58.64, H: 4.68, N: 14.74%.

5-Ethoxycarbonyl-6-methyl-4-(4-cyanophenyl)-3.4-dihydropyrimidin-2(1H)-thione (Table 3, entry 15). White solid; M.p. 242–244°C (MeOH). IR (KBr): 3319, 3145, 2229, 1532, 1428, 1172, and 772 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.27 (s, 1H, NH), 7.85 (s, 1H, NH), 7.63 (d, J = 8.1 Hz, 2H, aromatic C_3-, C_5-H), 7.42 (d, J = 8.4 Hz, 2H, aromatic C_2-, C_6-H), 5.46 (d, J = 3.0 Hz, 1H, C_4-H), 4.12 (q, J = 6.8 Hz, 2H, OCH_2CH_3), 2.38 (s, 3H, C_6-CH_3), 1.20 (t, J = 7.2 Hz, 3H, $OCH_2\mathit{CH_3}$). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.7 (C=S), 164.9 (C=O), 147.1 (aromatic C_1), 143.6 (C_6), 132.7 (aromatic C_3, C_5), 127.5 (aromatic C_2, C_6), 118.3 (C_5), 112.2 (aromatic C_4), 102.1 (CN), 60.8 (OCH_2), 55.6 (C_4), 18.4 (C_6-CH_3), 14.1 ($OCH_2\mathit{CH_3}$). *Anal.* calcd. for $C_{15}H_{15}N_3O_2S$; C: 59.78, H: 5.02, N: 13.94. Found: C: 59.64, H: 5.16, N: 14.04%.

4-(3-Hydroxyphenyl)-5-methoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-thione (Table 3, entry 17). Off-white solid; M.p. 220–222°C (EtOH). IR (KBr): 3315, 3189, 1669, 1576, 1478, 1284, 1194, 1117, and 752 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ: 10.32 (s, 1H, NH), 9.62 (brd, J = 1.8 Hz, 1H, NH), 9.47 (s, 1H, OH), 7.12 (t, J = 7.8 Hz, 1H, aromatic C_5-H), 6.65 (d, J = 8.7 Hz, 3H, aromatic C_2-, C_4-, and C_6-H), 5.09 (d, J = 3.6 Hz, 1H, C_4-H), 3.57 (s, 3H, —COOMe), 2.29 (s, 3H, C_6-CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 174.7 (C=S), 166.2 (C=O), 158.0 (aromatic C_3), 145.6 (C_6), 145.1 (aromatic C_1), 130.1 (aromatic C_5), 117.4 (aromatic C_6), 115.2 (aromatic C_2), 113.7 (aromatic C_4), 101.0 (C_5), 54.3 (C_4), 51.6 ($CO\mathit{OCH_3}$), 17.7 (C_6-CH_3). *Anal.* calcd. for $C_{13}H_{14}N_2O_3S$: C: 56.10, H: 5.07, N: 10.06. Found: C: 56.03, H: 5.05, N: 10.10%.

5-Acetyl-6-methyl-4-(2-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-thione (Table 3, entry 18). Brown solid; M.p. 254–256°C (EtOH). IR (KBr): 3419, 2927, 1719, 1607, 1527, 1355, 1268, 1202, 1093, 1013, and 668 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ: 10.41 (s, 1H, NH), 9.60 (s, 1H, NH), 7.92 (dd, J = 9.0, 0.9 Hz, 1H, aromatic C_3-H), 7.72 (td, J = 7.5,1.2 Hz, 1H, C_4-H), 7.54 (td, J = 8.4, 1.2 Hz, 1H, aromatic C_5-H), 7.46 (dd, J = 9.0, 1.2 Hz, 1H, aromatic C_6-H), 5.98 (d, J = 3.0 Hz, 1H, C_4-H), 2.36 (s, 3H, —$COCH_3$), 2.16 (s, 3H, C_6-CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 194.0 (C=O), 173.7 (C=S), 147.0 (aromatic C_2), 144.6 (C_6), 137.0 (aromatic C_1), 133.6 (aromatic C_5), 128.7 (aromatic C_6), 128.6 (aromatic C_4), 123.9 (aromatic C_3), 110.1 (C_5), 48.9 (C_4), 30.3 ($CO\mathit{CH_3}$), 17.9 (C_6-CH_3). *Anal.* calcd. for $C_{13}H_{13}N_3O_3S$: C, 53.60; H,4.50; N, 14.42%. Found: C, 53.53; H, 4.48; N,14.45%.

5-Acetyl-6-methyl-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-thione (Table 3, entry 19). Brown solid; M.p. 280–281°C (EtOH). IR (KBr): 3294, 3183, 2374, 1612, 1576, 1527, 1450, 1346, and 1186 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ: 10.45 (s, 1H, NH), 9.88 (brs, 1H, NH), 8.13–8.17 (m, 1H, aromatic C_4-H), 8.09 (brs, 1H, aromatic C_2-H), 7.63–7.70 (m, 2H, aromatic C_5-, C_6-H), 5.44 (d, J = 3.9 Hz, 1H, C_4-H), 2.37 (s, 3H, —COOMe), 2.28 (s, 3H, C_6-CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 195.1 (C=O), 175.0 (C=S), 148.4 (aromatic C_3), 146.1 (C_6), 145.4 (aromatic C_6), 133.5 (aromatic C_1), 130.8 (aromatic C_5), 123.1 (aromatic C_2), 121.7 (aromatic C_4), 110.8 (C_5), 53.4 (C_4), 31.2 ($CO\mathit{CH_3}$), 18.9 (C_6-CH_3). *Anal.* calcd. for $C_{13}H_{13}N_3O_3S$: C: 53.60, H: 4.50, N: 14.42. Found: C: 53.51, H: 4.54, N:14.39%.

5-Acetyl-4-(4-hydroxy-3-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione (Table 3, entry 20). Yellowish-white solid; M.p. 228–230°C (EtOH). IR (KBr):3485, 3255, 3194, 1589, 1518, 1458, 1193, and 796 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ: 10.20 (s, 1H, NH), 9.65 (brs, 1H, NH), 9.05 (s, 1H, OH), 6.85 (d, J = 1.8 Hz, 1H, aromatic C_2-H), 6.72 (d, J = 7.8 Hz, 1H, aromatic C_5-H), 6.58 (dd, J = 8.1, 1.8 Hz, 1H, aromatic C_6-H), 5.20 (d, J = 3.6 Hz, 1H, C_4-H), 3.74 (s, 3H, aromatic —OMe), 2.32 (s, 3H, —$COCH_3$), 2.11 (s, 3H, C_6-CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 195.6 (C=O), 174.2 (C=S), 148.0 (aromatic C_3), 146.7 (aromatic C_4), 144.6 (C_6), 134.3 (aromatic C_1), 119.2 (aromatic C_6), 115.9 (aromatic C_5), 111.8 (aromatic C_2), 110.6 (C_5), 56.1 (OCH_3), 54.2 (C_4), 30.6 ($COCH_3$), 18.6 (C_6-CH_3). *Anal.* calcd. for $C_{14}H_{16}N_2O_3S$: C: 57.52, H: 5.52, N: 9.58. Found: C: 57.39, H: 5.65, N: 9.47%.

1,3,6-Trimethyl-4-(4-methoxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5 carboxylic acid methyl ester (Table 4, entry 1). Light yellow solid; M.p. 68–70°C (ethylacetate + petroleum ether). IR (KBr): 2949, 1669, 1506, 1431, and 1353 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.13 (td, J = 8.4 Hz and 3 Hz, 2H, C_2-H, C_6-H), 6.81 (td, J = 8.7 Hz and 3 Hz, 2H, C_3-H, C_5-H), 5.17 (s, 1H, C_4-H), 3.77 (s, 3H, –OCH_3), 3.67 (s, 3H, —$COOCH_3$), 3.28 (s, 3H, N_1-CH_3), 2.89 (s, 3H, N_3-CH_3), 2.47 (s, 3H, C_6-CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 166.4 (—$\mathit{C}OOCH_3$), 159.2 (C_2=O), 153.8 (aromatic-C_4), 149.1 (C_1), 133.9 (vinylic C_6), 127.7 (2C, C_2 + C_3), 114.0 (2C, C_3 + C_5), 103.7 (vinylic C_5), 60.2 (C_4), 55.2 (—OCH_3), 51.2 (—$COO\mathit{CH_3}$), 34.3 (N_1-CH_3), 31.0 (N_3-CH_3), 16.6 (C_6-CH_3). *Anal.* calcd. for $C_{16}H_{20}N_2O_4$; C: 63.15, H: 6.62, N: 9.20. Found: C: 63.04, H: 6.77, N: 9.45%.

1,3,6-Trimethyl-4-(4-hydroxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (Table 4, entry 2). Off-white solid; M.p.184–186°C (ethylacetate + petroleum ether). IR (KBr): 3209, 2373, 1704, 1641, and 1449 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.02 (d, J = 8.7 Hz, 2H, C_2-H, C_6-H), 6.68 (d, J = 8.4 Hz, 2H, C_3-H, C_5-H), 5.16 (s, 1H, C_4-H), 4.13 (dq, J = 7.8 Hz and 2.4 Hz, 2H, —OCH_2CH_3), 3.27 (s, 3H, N_1-CH_3), 2.91 (s, 3H, N_3-CH_3), 2.47 (s, 3H, C_6-CH_3), 1.73 (brs, 1H, OH), 1.22 (t, J = 7.2 Hz, 3H, —$OCH_2\mathit{CH_3}$). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 166.1 (—$\mathit{C}OOCH_3$), 156.1 (C_2=O), 154.2 (aromatic C_4), 148.6 (C_1), 132.4 (vinylic C_6), 127.9 (2C, C_2 + C_6), 115.5 (2C, C_3 + C_5), 104.3 (vinylic C_5), 60.4 (C_4), 60.3 (—OCH_2), 34.5 (N_1-CH_3), 31.1 (N_3-CH_3), 16.6 (C_6-CH_3), 14.2 (—$OCH_2\mathit{CH_3}$). *Anal.* calcd. for $C_{16}H_{20}N_2O_4$; C: 63.15, H: 6.62, N: 9.20. Found: C: 63.03, H: 6.88, N: 9.37%.

1,3,6-Trimethyl-4-(4-chlorophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester (Table 4, entry 3). Off-white solid; M.p. 86–88°C (ethylacetate + petroleum ether). IR (KBr): 2927, 1660, 1604, 1464, 1434, and 1268 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.06 (d, J = 8.4 Hz, 2H, C_2-H, C_6-H), 6.96 (d, J = 8.4 Hz, 2H, C_3-H, C_5-H), 5.03 (s, 1H, C_4-H), 3.48 (s, 3H, —OCH_3), 3.06 (s, 3H, N_1-CH_3), 2.71 (s, 3H, N_3-CH_3), 2.28 (s, 3H, C_6-CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 166.0 (—$\mathit{C}OOCH_3$), 153.4 (C_2=O), 149.6 (C_4), 139.3 (vinylic C_6), 133.4 (aromatic C_1), 128.6 (2C, C_2 + C_6), 127.7 (2C, C_3 + C_5), 102.8 (vinylic C_5), 60.0 (C_4), 51.1 (—OCH_3), 34.3 (N_1-CH_3), 30.9 (N_3-CH_3), 16.5 (C_6-CH_3).

Anal. calcd. for $C_{15}H_{17}N_2O_3Cl$; C:58.35, H: 5.55, N: 9.07. Found: C: 58.13, H: 5.83, N: 9.27%.

1,3,6-Trimethyl-4-(3, 4-dimethoxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (Table 4, entry 4). Light brown sticky liquid; IR (KBr): 3499, 2935, 1670, 1511 1031, and 753 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ: 6.77–6.71 (m, 3H, C_2-H, C_5-H, C_6-H), 5.16 (s, 1H,C_4-H), 4.13 (q, $J = 7.2$ Hz, 2H, —OCH_2), 3.82 (s, 3H, —OCH_3), 3.81 (s, 3H —OCH_3), 3.23 (s, 3H, N_1-CH_3), 2.90 (s, 3H, N_3-CH_3), 2.44 (s, 3H, C_6-CH_3), 1.24 (t, $J = 7.2$ Hz, 3H, —CH_2CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 166.0 (—*C*$OOCH_2CH_3$), 153.8 (C_2=O), 148.9, 148.8, 148.6 (3C, aromatic C_4, C_3, C_1), 133.6 (vinylic C_6), 118.6 (C_6), 111.9 (C_2), 109.9 (C_5), 103.9 (vinylic C_5), 60.4 (C_4), 60.1 (—OCH_2), 55.8 (—OCH_3), 55.7 (—OCH_3), 34.3 (N_1-CH_3), 30.9 (N_3-CH_3), 16.5 (C_6-CH_3), 14.2 (—OCH_2*C*H_3). *Anal.* calcd. for $C_{18}H_{24}N_2O_5$; C: 62.05, H: 6.94, N: 8.04, O: 22.96%. Found: C: 62.13, H: 6.73, N: 8.27%.

1,3,6-Trimethyl-4-(2-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester (Table 4, entry 5). Light brown sticky liquid; IR (KBr): 2944, 1670, 1618, 1534, and 1202 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.44 (dd, $J = 9$ Hz and 0.9 Hz, 1H, C_3-H), 7.31–7.23 (m, 2H, aromatic C_4 and C_6H), 7.13 (dt, $J = 7.4$ Hz and 2.4 Hz, 1H, C_5H), 5.71 (s, 1H, C_4-H), 3.24 (s, 3H, N_1-CH_3), 3.08 (s, 3H, —OCH_3), 2.74 (s, 3H, N_3-CH_3), 2.26 (s, 3H, C_6-CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 165.3 (—*C*$OOCH_3$), 152.8 (C_2=O), 150.4 (C_2), 148.8 (C_1) 137.0 (vinylic C_6), 133.2 (C_5), 128.7 (aromatic-C_4+C_6), 123.4 (C_3), 102.1 (vinylic C_5), 54.6 (C_4), 51.0 (—OCH_3), 33.7 (N_1-CH_3), 30.8 (N_3-CH_3), 16.3 (C_6-CH_3). *Anal.* calcd. for $C_{15}H_{17}N_3O_5$; C: 56.42, H: 5.37, N: 13.16, O: 25.05%. Found: C: 56.33, H: 5.43, N: 13.27%.

1,3,6-Trimethyl-4-(2,5-dimethoxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester (Table 4, entry 6). White solid; M.p. 100–102°C (ethylacetate + petroleum ether). IR (KBr): 2940, 2845, 1659, and 1434 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ: 6.76 (d, $J = 8.7$ Hz, 1H, C_3-H), 6.70 (dd, $J = 9$ Hz and 2.7 Hz, 1H, aromatic C_4-H), 6.67 (d, $J = 2.7$ Hz, 1H, C_6-H), 5.55 (s, 1H, C_4-H), 3.73, 3.68 (2S, 6H, 2—OCH_3), 3.57 (S, 3H, N_1-CH_3), 3.25, 3.23 (2s, 6H, N_3-CH_3, —OCH_3), 2.45 (s, 3H, C_6-CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 166.4 (—*C*$OOCH_3$), 153.6 (C_2=O), 151.3 (C_2/C_5), 149.2 (C_5/C_2), 129.7 (vinylic C_6), 115.1 (C_3), 112.8 (aromatic C_4/C_6), 112.0 (C_6/aromatic-C_4), 102.1 (vinylic C_5), 56.2 (C_4), 55.5, 55.4 (2 × OCH_3), 50.9 (*CO*CH_3), 31.0 (N_1-CH_3), 30.8 (N_3-CH_3), 16.4 (C_6-CH_3). *Anal.* calcd. for $C_{17}H_{22}N_2O_5$; C: 61.07, H: 6.63, N: 8.38, O: 23.92%. Found: C: 61.13, H: 6.53, N: 8.27%.

1,3,6-Trimethyl-4-(2,5-dimethoxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (Table 4, entry 7). White solid; M.p. 68–70°C (ethylacetate + petroleum ether). IR (KBr): 2934, 1666, and 1492 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ: 6.78–6.73 (m, 2H, C_3-H, C_4-H), 6.71 (d, $J = 1.2$ Hz, 1H, C_6-H), 5.59 (s, 1H, C_4-H), 4.02 (dq, $J = 7.2$ Hz, 0.9 Hz, —OCH_2), 3.57 (s, 3H, —OCH_3), 3.26 (s, 3H, N_1-CH_3), 2.84 (s, 3H, N_3-CH_3), 2.48 (s, 3H, vinylicC_6), 1.14(t, $J = 7.2$ Hz, 3H, —OCH_2CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 166.1 (—*C*$OOCH_2CH_3$), 153.6 (C_2=O, C_1), 151.3 (C_2/C_5), 149.2 (C_5/C_2), 129.9 (vinylic C_6), 115.5 (C_3), 112.8 (aromatic-C_4/C_6), 111.6 (C_6/aromatic-C_4), 102.3 (vinylic C_5), 59.8 (C_4), 56.0 (—OCH_3), 55.5 (—OCH_3,—OCH_2), 33.9 (N_1-CH_3), 30.8 (N_3-CH_3), 16.4 (C_6-CH_3), 14.0 (—OCH_2-*C*H_3). *Anal.* calcd. for $C_{18}H_{24}N_2O_5$; C: 62.05, H: 6.94, N: 8.04, O: 22.96%. Found: C: 62.13, H: 6.83, N: 8.27%.

1,3,6-Trimethyl-4-(2-chlorophenyl)-5-acetyl-6-methyl-1,2,3,4-tetrahydropyrimidin-2(1H)-one (Table 4, entry 8). Brown solid; M.p. 80–82°C (ethylacetate + petroleum ether). IR (KBr): 2926, 1660, and 1610 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.38–7.33 (m, 1H, aromaticC_4-H), 7.31–7.22 (m, 3H, C_3-H, C_5-H, C_6-H), 5.78 (s, 1H, C_4-H), 3.30 (s, 3H, N_1-CH_3), 2.96, 2.95 (2s, 3H, N_3-CH_3), 2.49 (2s, 3H, C_6-CH_3), 2.14 (S, 3H, —*CO*CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 196.3 (—*C*OCH_3), 152.7 (C_2=O), 148.6 (C_1), 137.7 (C_2), 132.5 (vinylic C_6), (129.8, 129.7, 129.4) (C_3, aromatic C_4, C_6), 128.3 (C_5), 112.1 (vinylic C_5), 57.5 (C_4), 33.9 (N_1-CH_3), 30.9 (N_3-CH_3), 30.1 ($COCH_3$), 17.1 (C_6-CH_3). *Anal.* calcd. for $C_{15}H_{17}N_2O_2Cl$; C: 61.54, H: 5.85, N: 9.57, O: 10.93, Cl: 12.11%. Found: C: 61.33, H: 5.83, N: 9.27%.

1,3,6-Trimethyl-4-(4-nitrophenyl)-5-acetyl-6-methyl-1,2,3,4-tetrahydropyrimidine-2(1H)-one (Table 4, entry 9). Light brown solid; M.p. 142–144°C (ethylacetate + petroleum ether). IR (KBr): 2931, 1675, 1621, and 1518 cm^{-1}. ^1H NMR ($CDCl_3$,300 MHz) δ: 8.16 (td, $J = 8.7$ Hz and 2.4 Hz, 2H, C_2-H, C_6-H), 7.39 (td, 8.7 Hz and 1.8 Hz, 2H, C_3-H, C_5-H), 5.46 (s, 1H, C_4-H), 3.34 (S, 3H, N_1-CH_3), 2.99 (s, 3H, N_3-CH_3), 2.42 (s, 3H, C_6-CH_3), 2.34 (s, 3H, —$COCH_3$). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 194.8 (—*C*OCH_3), 153.5 (C_2=O), 149.0 (aromatic C_4), 147.6 (C_1/vinylic C_6), 147.5 (vinylic C_6/C_1), 127.3 (C_2, C_6), 124.0 (C_3, C_5), 114.2 (vinylic C_5), 59.9 (C_4), 34.8 (N_1-CH_3), 31.4 (N_3-CH_3), 31.4 (—*CO*CH_3), 17.9 (C_6-CH_3). *Anal.* calcd. for $C_{15}H_{17}N_3O_4$; C: 59.40, H: 5.65, N: 13.85, O: 21.10%. Found: C: 59.53, H: 5.83, N: 13.77%.

1,3,6-Trimethyl-4-(4-bromophenyl)-5-acetyl-6-methyl-1,2,3,4-tetrahydropyrimidine-2(1H)-one (Table 4, entry 10). Light brown sticky liquid; IR (KBr): 2929, 1665, 1601, and 1403 cm^{-1}. ^1H NMR ($CDCl_3$,300 MHz) δ: 7.44 (td, $J = 8.4$ Hz and 1.8 Hz, 2H, C_2-H, C_6-H), 7.09 (td, $J = 8.4$ Hz and 1.8 Hz, 2H, C_3-H, C_5-H), 5.23 (s, 1H, C_4-H), 3.26 (s, 3H, N_1-CH_3), 2.95 (s, 3H, N_3-CH_3), 2.42 (s, 3H, vinylic C_6-CH_3), 2.25 (s, 3H, —$COCH_3$). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 195.3 (—$COCH_3$), 153.4 (C_2=O), 148.3 (C_1), 139.1 (vinylic C_6), 131.9 (C_2, C_6), 128.3 (C_3, C_5), 122.0 (C_4), 113.8 (vinylic C_5), 60.5 (C_4), 34.5 (N_1-CH_3), 31.2 (N_3-CH_3), 30.9 (—$COCH_3$), 17.5 (C_6-CH_3). *Anal.* calcd. for $C_{15}H_{17}N_2O_2Br$; C:53.45, H: 5.08, N: 8.31, O: 9.49, Br: 23.69%. Found: C: 53.33, H: 5.13, N: 8.27%.

1,3,6-Trimethyl-4-(4-bromophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester (Table 4, entry 11). Light grey sticky liquid; IR (KBr): 2949, 1672, 1633, and 1415 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.42 (d, $J = 8.4$ Hz, 2H, C_2-H, C_6-H), 7.11 (d, $J = 8.4$ Hz,2H, C_3-H, C_5-H), 5.22 (s, 1H, C_4-H), 3.68 (s, 3H, N_1-CH_3), 3.26 (s, 3H, N_3-CH_3), 2.91 (s, 3H, —OCH_3), 2.48 (s, 3H, C_6-CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 166.0 (—*C*$OOCH_3$), 153.4 (C_2=O), 149.6 (C_1), 139.8 (vinylic C_6), 131.6 (C_2, C_6), 128.1 (C_3, C_5), 121.5 (aromatic C_4), 102.7 (vinylic C_5), 60.1 (C_4), 51.1 (—OCH_3), 34.3 (N_1-CH_3), 30.9 (N_3-CH_3), 16.5 (C_6-CH_3). *Anal.* calcd. for $C_{15}H_{17}N_2O_3Br$; C: 51.01, H: 4.85, N: 7.93, O: 13.59, Br: 22.63%. Found: C: 51.13, H: 4.83, N: 8.17%.

1,3,6-Trimethyl-4-(2-chlorophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester (Table 4, entry 12). Light brown solid; M.p. 54–56°C (ethyl acetate + petroleum ether). IR (KBr): 3596, 1661, 1604, and 1464 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.35–7.28 (m, 2H, aromaticC_4-H, C_6-H), 7.24–7.16 (m, 2H, C_3-H, C_5-H), 5.82 (s, 1H, C_4-H), 3.60 (s, 3H, N_1-CH_3), 3.32, 3.31 (2s, 3H, N_3-CH_3), 2.88 (s, 3H, —OCH_3), 2.57, 2.56 (2s, 3H, C_6-CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 166.1

(—*C*OOCH$_3$), 152.9 (C$_2$=O), 149.9 (C$_1$), 139.0 (C$_2$) 132.0 (vinylic C$_6$), 129.4,129.2, 129.0 (C$_3$, aromatic C$_4$,C$_6$), 127.8 (C$_5$), 102.4 (vinylic C$_5$), 57.1 (C$_4$), 51.1 (—COO*C*H$_3$), 33.7 (N$_1$-CH$_3$), 30.7 (N$_3$-CH$_3$), 16.4 (C$_6$-CH$_3$). *Anal*. calcd. for $C_{15}H_{17}N_2O_3Cl$; C: 58.35, H: 5.55, N: 9.07, O: 15.55, Cl: 11.48%. Found: C: 58.23, H: 5.73, N: 9.27%.

1,3,6-Trimethyl-4-(4-bromophenyl)-5-acetyl-6-methyl-1,2,3,4-tetrahydropyrimidine-2(1H)-thione (Table 4, entry 13). Light yellow sticky liquid; IR (KBr): 3133, 1612, and 1400 cm^{-1}. ^{1}H NMR (CDCl$_3$, 300 MHz) δ: 7.14 (dd, *J* = 9.3 Hz and 1.8 Hz, 2H, C$_2$-H, C$_6$-H), 6.98 (dd, *J* = 8.1 and 1.5 Hz, 2H, C$_3$-H, C$_5$-H), 5.61 (s, 1H, C$_4$-H), 3.56 (s, 3H, N$_1$-CH$_3$), 3.49 (s, 3H, N$_3$-CH$_3$), 2.41 (s, 3H, C$_6$-CH$_3$), 2.39 (s, 3H, —COCH$_3$). ^{13}C NMR (CDCl$_3$, 75 MHz) δ:196.3 (—*C*OCH$_3$), 179.3 (C$_2$=S), 146.4 (C$_1$), 138.2 (vinylic C$_6$), 132.0 (C$_2$, C$_6$), 127.6 (C$_3$,C$_5$), 122.0 (aromatic C$_4$), 116.3 (vinylic C$_5$), 60.6 (C$_4$), 43.1 (N$_1$-CH$_3$), 38.2 (N$_3$-CH$_3$), 31.1 (—CO*C*H$_3$), 17.9 (C$_6$-CH$_3$). *Anal*. calcd. for $C_{15}H_{17}N_2OSBr$; C: 51.00, H: 4.85, N: 7.93, O: 4.53, S: 9.08, Br: 22.62%. Found: C: 51.13, H: 4.93, N: 8.17%.

1,3,6-Trimethyl-4-(2chlorophenyl-5-acetyl-6-methyl-1,2,3,4-tetrahydropyrimidine-2(1H)-thione (Table 4, entry 14). Light yellow sticky liquid; IR (KBr): 3138, 1669, 1625, and 1399 cm^{-1}. ^{1}H NMR (CDCl$_3$, 300 MHz) δ: 7.39–7.36 (m, 1H, aromatic-C$_4$-H), 7.27–7.23 (m, 2H, C$_6$-H, C$_3$-H), 7.17–7.14 (m, 1H, C$_5$-H), 5.95 (s, 1H, C$_4$-H), 3.66 (s, 3H, N$_1$-CH$_3$), 3.50 (s, 3H, N$_3$-CH$_3$), 2.45 (C$_6$-CH$_3$), 2.24 (—COCH$_3$). ^{13}C NMR (CDCl$_3$, 75 MHz) δ: 196.4 (—*C*OCH$_3$), 179.1 (C$_2$=S), 145.3 (C$_1$), 136.4 (C$_2$), 132.2 (vinylic C$_6$), (130.1, 130.0, 128.8, 128.3) (C$_3$, aromatic C$_4$,C$_6$,C$_5$), 114.6 (vinylic C$_5$), 58.5 (C$_4$), 42.5 (N$_1$-CH$_3$), 38.1 (N$_3$-CH$_3$), 30.1 (—CO*C*H$_3$), 17.4 (C$_6$-CH$_3$). *Anal*. calcd. for $C_{15}H_{17}N_2OSCl$; C: 58.34, H: 5.55, N: 9.07, O: 5.18, S: 10.38, Cl: 11.48%. Found: C: 58.23, H: 5.83, N: 9.27%.

1,3,6-Trimethyl-4-(4-chlorophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (Table 4, entry 15). Off-white solid; M.p. 60–62°C (ethylacetate + petroleum ether). IR (KBr): 3500, 1670, and 1427 cm^{-1}. ^{1}H NMR (CDCl$_3$,300 MHz) δ: 7.27 (d, *J* = 8.4 Hz, 2H, C$_2$-H, C$_6$-H), 7.16 (d, *J* = 8.4 Hz, 2H, C$_3$-H,C$_5$-H), 5.22 (s, 1H, C$_4$-H), 4.12 (q, *J* = 7.2 Hz, 2H, —OCH$_2$), 3.26 (s, 3H, N$_1$-CH$_3$), 2.89 (s, 3H, N$_3$-CH$_3$), 2.47 (s, 3H, C$_6$-CH$_3$), 1.24 (t, *J* = 7.2 Hz, 3H, —OCH$_2$C*H*$_3$). ^{13}C NMR (CDCl$_3$, 75 MHz) δ: 164.7 (—*C*OOCH$_2$CH$_3$), 152.6 (C$_2$=O), 148.7 (C$_1$), 138.9 (C$_4$), 132.5 (vinylic C$_6$), 127.9 (C$_2$, C$_6$), 127.3 (C$_3$,C$_5$), 102.2 (vinylic C$_5$), 59.4 (C$_4$), 59.3 (—OCH$_2$), 33.5 (N$_1$-CH$_3$), 30.1 (N$_3$-CH$_3$), 15.2 (C$_6$-CH$_3$), 13.4 (—OCH$_2$*C*H$_3$). *Anal*. calcd. for $C_{16}H_{19}N_2O_3Cl$; C: 59.54, H: 5.93, N: 8.68, O: 14.87, Cl: 10.98%. Found: C: 59.43, H: 5.83, N: 8.77%.

1,3,6-Trimethyl-4-(3-nitrophenyl)-5-acetyl-6-methyl-1,2,3,4-tetrahydropyrimidine-2(1H)-one (Table 4, entry 16). Light brown liquid; IR (KBr): 3485, 1672, 1605, and 1529 cm^{-1}. ^{1}H NMR (CDCl$_3$,300 MHz) δ: 8.14 (qd, *J* = 8.1 Hz and 1.5 Hz, 1H, C$_6$-H), 8.08 (t, *J* = 1.8 Hz, 1H, C$_2$-H), 7.58 (td, *J* = 7.5 Hz and 1.5 Hz, 1H, aromatic-C$_4$-H), 7.50 (t, *J* = 7.8 Hz, 1H, C$_5$-H), 5.41 (s, 1H,C$_4$-H), 3.31 (S, 3H, N$_1$-CH$_3$), 2.99 (s, 3H, N$_3$-CH$_3$), 2.47 (S, 3H, C$_6$-CH$_3$), 2.32 (s, 3H, —COCH$_3$). ^{13}C NMR (CDCl$_3$, 75 MHz) δ:194.8 (—*C*OCH$_3$), 153.2 (C$_2$=O), 149.1 (C$_4$), 148.6 (C$_1$), 142.5 (vinylic-C$_6$), 132.7 (C$_6$), 129.8 (C$_5$), 123.0 (C$_2$/aromatic C$_4$), 121.6 (aromatc C$_4$/C$_2$), 113.9 (vinylic C$_5$), 60.2 (C$_4$), 34.7 (N$_1$-CH$_3$), 31.3 (N$_3$-CH$_3$), 31.2 (C$_6$-CH$_3$), 17.8 (—CO*C*H$_3$). *Anal*. calcd. for $C_{15}H_{17}N_3O_4$; C: 59.40, H: 5.65, N: 13.85, O: 21.10%. Found: C: 59.33, H: 5.83, N: 13.77%.

(RR/RS) 4,4-(1,3-phenylene)-bis[5-methoxycarbonyl-3,4-dihydro-6-methyl]-pyrimidin-2(1H)-one (Table 5, entry 1). White solid; M.p. 309–311°C (MeOH). IR (KBr): 3339, 3304, 1668, 1441, 1343, 1237, and 1091 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ: 9.19 (s, 2H, 2 × NH), 7.71 (s, 2H, 2 × NH), 7.25 (t, *J* = 7.8 Hz, 1H, aromatic C$_5$-H), 7.20–7.05 (m, 3H, aromatic C$_2$, C$_4$, and C$_6$-H), 5.08 (d, *J* = 3.0 Hz, 2H, 2 × C$_4$-H), 3.50 (s, 6H, 2 × OCH$_3$), 2.20 (s, 6H, 2 × C$_6$-CH$_3$). ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ: 165.9 (2 × *C*OOMe), 152.4 (2 × C$_2$=O), 148.6 (aromatic C$_1$, C$_3$), 145.2 (2 × C$_6$), 128.7 (aromatic C$_5$), 125.4 (aromatic C$_4$, C$_6$), 124.1 (aromatic C$_2$), 99.3 (2 × C$_5$), 54.0 (2 × C$_4$), 50.9 (2 × CO*OCH*$_3$), 17.9 (2 × C$_6$-*C*H$_3$). *Anal*. calcd. for $C_{20}H_{22}N_4O_6$; C: 57.97, H: 5.35, N: 13.52. Found: C: 57.84, H: 5.45, N: 13.61%.

(RR/RS) 4,4-(1,3-phenylene)-bis[5-ethoxycarbonyl-3,4-dihydro-6-methyl]-pyrimidin-2(1H)-one (Table 5, entry 2). White solid; M.p. 296–298°C (MeOH). IR (KBr): 3361, 3237, 3114, 1700, 1643, 1457, 1226, and 1093 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ: 9.14 (s, 2H, 2 × NH), 7.72 (s, 2H, 2 × NH), 7.24 (t, *J* = 7.2 Hz, 1H, aromatic C$_5$-H), 7.16–7.03 (m, 3H, aromatic C$_2$, C$_4$-, and C$_6$-H), 5.06 (s, 2H, 2 × C$_4$-H), 3.92 (s, 4H, 2 × —OC*H*$_2$CH$_3$), 2.19 (s, 6H, 2 × C$_6$-CH$_3$), 1.04 (t, *J* = 6.3 Hz, 6H, 2 × —OCH$_2$*C*H$_3$). ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ: 165.3 (2 × *C*OOMe), 152.2 (2 × CO), 148.4 (aromatic C$_1$, C$_3$), 145.2 (2 × C$_6$), 128.6 (aromatic C$_5$), 125.4 (aromatic C$_4$, C$_6$), 124.2 (aromatic C$_2$), 99.4 (2 × C$_5$), 59.3 (2 × OCH$_2$), 54.1 (2 × C$_4$), 17.8 (2 × C$_6$-*C*H$_3$), 14.2 (2 × OCH$_2$*C*H$_3$). *Anal*. calcd. for $C_{22}H_{26}N_4O_6$; C: 59.72, H: 5.92, N: 12.66. Found: C: 59.87, H: 5.85, N: 12.81%.

(RR/RS) 4,4-(1,3-phenylene)-bis[5-methoxycarbonyl-3,4-dihydro-6-methyl]-pyrimidin-2(1H)-thione (Table 5, entry 3). White solid; M.p. 280–282°C (MeOH). IR (KBr):3301, 3186, 2373, 1699, 1567, 1437, 1321, 1186, and 1108 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ: 10.39 (s, 2H, 2 × NH), 9.60 (s, 2H, 2 × NH), 7.31 (t, *J* = 7.8 Hz, 1H, aromatic C$_5$-H), 7.11 (d, *J* = 7.8 Hz, 2H, aromatic C$_4$, C$_6$-H), 7.02 (s, 1H, aromatic C$_2$-H), 5.10 (d, *J* = 3.3 Hz, 2H, 2×C$_4$-H), 3.54 (s, 6H, 2×—OCH$_3$), 2.30 (s, 6H, 2 × -CH$_3$). ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ: 174.4 (2 × C=S), 165.6 (2 × *C*OOMe), 145.3 (aromatic C$_1$, C$_3$), 143.9 (2 × C$_6$), 129.0 (aromatic C$_5$), 125.9 (aromatic C$_4$, C$_6$), 124.2 (aromatic C$_2$), 100.5 (2 × C$_5$), 54.0 (2 × C$_4$), 51.2 (2×CO*OMe*), 17.3 (2×C$_6$-*C*H$_3$). *Anal*. calcd. for $C_{20}H_{22}N_4O_4S_2$; C: 53.80, H: 4.97, N: 12.55. Found: C: 53.94, H: 5.15, N: 12.41%.

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