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Synthesis of 4, 4'-(1, 3 and 1, 4-phenylene) bis (6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate) via a one- pot three-component reaction of Urea with dialdehydes and acetoacetates in the presence of hydrochloric acid and heteropolyacid

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ABSTRACT

A simple and efficient synthesis of 4, 4'-(1, 3 and 1, 4-phenylene) bis (6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate) via a one- pot three-component reaction of Urea with dialdehydes and acetoacetates in the presence of hydrochloric acid and heteropolyacid is described. All synthesized compounds were characterized on the basis of their spectral and microanalytical data. In the first stage we report a convenient synthesis of new 4, 4'-(phenylene) bis tetrahydropyrimidines 4a-4f by a one-pot three-component reaction of Urea 1, dialdehydes 2a-4b, and acetoacetates 3a-3c in refluxing hydrochloric acid. And then, in the second stage, we used heteropolyacids in this reaction. We report reaction conditions (solvent, temperature, reaction time, catalyst type, and concentration) were studied to optimize in this procedure. Melting points were recorded on a Stuart SMP3 melting point apparatus. The IR spectra were obtained using a Bruker Tensor 27 spectrophotometer using KBr discs. The ^{1}H NMR (300 MHz) was recorded with Bruker-300 MHz spectrometers. The ^{13}C-NMR was recorded with Bruker-300 MHz spectrometers at 75 MHz frequencies. The mass spectra were scanned on an Agilent Technologies instrument at 70 eV. Elemental analysis was performed on a Thermo Finnigan Flash EA microanalyzer.

KEY WORDS: BIS (1, 2, 3, 4-TETRAHYDROPYRIMIDINE-5-CARBOXYLATE), HETEROPOLYACID, UREA, ACETOACETATES, DIALDEHYDES, BIGINELLI REACTION

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INTRODUTION

3,4-Dihydropyrimidin-2-(1H)-ones (DHPMs) and their derivatives gained considerable interest from the first reported in 1891 until today both in academia and industry because of their important and promising therapeutic and pharmacological properties (Biginelli *et al.* 1891). For instance, they have emerged as integral backbones of several channel blockers, antihypertensive agent α-1antagonists, neuropeptide Y (NPY) antagonists and anticancer activities (Singh *et al.* 2009; Russowsky *et al.* 2006; Kumar *et al.* 2009; Da Silva *et al.* 2012).

The classical Biginelli reaction involves the strong acid-catalyzed cyclocondensation reaction of ethyl acetoacetate, benzaldehyde and urea in ethanol at reflux temperature for long reaction time. Furthermore, this one-pot three-component procedure often provides with relatively low yields of the dihydropyrimidine derivatives. In order to improve the effiency and synthetic procedure of the classical one-pot Biginelli reaction, using different types of catalysts and conditions have been reported by different research groups. The most of these procedures are all similar, using different acid catalyst such as $BF_3.OEt_2$ (Hu *et al.* 1998), $FeCl_3.6H_2O$ (Xu *et al.* 2004), $MgCl_2.6H_2O$ (Zhang *et al.* 2004), $MgBr_2$ (Gulten, 2013; Salehi, 2004), $BiCl_3$ (Ramalinga *et al.* 2001), $InCl_3$ (Ranu *et al.* 2000), ZnO nano particles (Hassanpour *et al.* 2015), zeolites (Radha *et al.* 2001), $LaCl_3.7H_2O$ (Lu *et al.* 2000), $LiClO_4$ (Yadav *et al.* 2001), $Mn(OAc)_3.2H_2O$ (Kumar *et al.* 2001), $NiCl_2.6H_2O$ (Lu, 2010), and so on, in solvent such as CH_3CN, CH_2Cl_2, THF, EtOH or H_2O. In addition procedures employing ultrasound, microwave (Kappe, 1999), solid and fluorous (Studer *et al.* 1997) phase syntheses have reported.

A number of procedures under solvent free conditions using different acid catalyst have also been reported (Zhang *et al.* 2015). However, despite their potential utility some these procedures use expensive catalysts, strong acidic conditions, higher temperatures, stoichometric amounts of catalyst, toxic reagents, large amount of solvents, unsatisfactory yields, inconvenient prurification techniques, incompatibility with other functional groups and require longer reaction times are not all acceptable in the context of green synthesis.

On the other hand, Polyoxometalates (POMs) are a large class of metal oxide cluster compounds consisting of transi-tion metal atoms bridged by oxygen atoms. POMs can exist in a variety of different size and structure, and compounds belonging to this class have been studied extensively because they possess interesting electronic and molecular properties, such as wide-ranging reduction potentials, acidities, and polarities. Based on their attractive properties, POMs have also been used in a variety of different application, including catalysis, biomedicine, magnetism, nanotechnology, and materials science (Müller *et al.* 1998; Pope and Müller, 2001; Davoodnia *et al.* 2013; Coronado *et al.* 1998; Okuhara *et al.* 1996). The development of methods using heteropolyacids (HPAs) as Catalyst for the synthesis of fine chemicals, such as flavors, pharmaceuticals, and in food industries, has gained attention in the last decade (Chwegler *et al.* 1991).

Catalysts based on heteropolyacids have many advantages over liquid-acid catalysts. They are not corrosive and are environmentally benign and present fewer disposal problems.

Solid heteropolyacids have attracted much attention organic synthesis owing to easy work-up procedures, easyfiltration, and reduction of cost and waste generation through reuse and recycling of the catalysts.

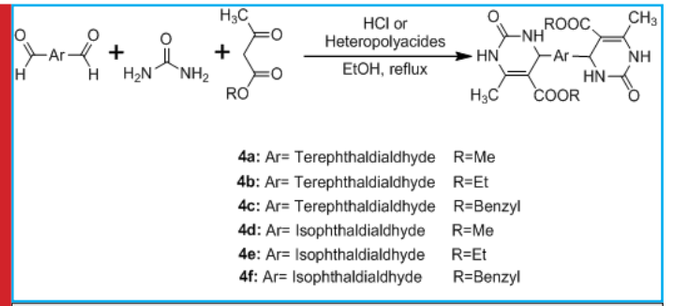
MATERIAL AND METHODS

In spite of much work on the synthesis of substituted tetrahydropyrimidines, to the best of our knowledge, the synthesis of 4, 4'-(1, 3 and 1, 4-phenylene) bis (6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate) has not been reported in the literature. In this paper, in the first stage we report a convenient synthesis of new 4, 4'-(phenylene) bis tetrahydropyrimidines **4a-4f** by a one-pot three-component reaction of Urea **1**, dialdehydes **2a-4b**, and acetoacetates **3a-3c** in refluxing hydrochloric acid. And then, in the second stage, we used heteropolyacids in this reaction. We report reaction conditions (solvent, temperature, reaction time, catalyst type, and concentration) were studied to optimize in this procedure (Scheme 1).

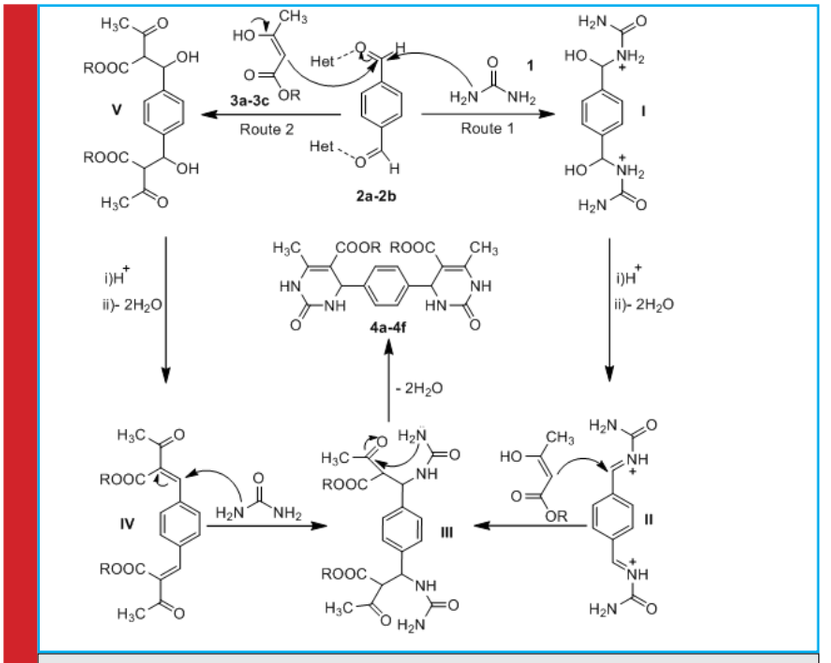
RESULTS AND DISCUSSION

Although we did not investigate the reaction mechanism, two plausible mechanisms for this three-component reaction as have been depicted in Scheme 2. For example in route 1, it is proposed that the reaction occurs via initial formation of the intermediate **I** as a result of a nucleophilic attack of Urea at the carbonyl group of dialdehydes. Dehydration of the intermediate **I** follows the intermediate **II**. Reaction of acetoacetates with this intermediate then gives the intermediate **III** which after cyclization followed by dehydration afforded final products **4a-4f**. As shown in Scheme 2, we propose that Hydrochloric acid and Heteropolyacid ≡ Het activate the reactants and the intermediates in this reaction.

A one-pot three-component reaction of Urea **1**, an dialdehydes **2a-2b** and acetoacetates **3a-3c** in the presence of hydrochloric acid under reflux for 4h leads to the facile formation of 4, 4'-(1, 3 and 1, 4-phenylene)



SCHEME 1. Synthesis of some 4,4'-(phenylene)bis tetrahydropyrimidines in HCI=Het



SCHEME 2. Plausible mechanism for the formation of some 4,4'-(phenylene)bis tetrahydropyrimidines in HCI=Het

bis (6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate) **4a-4f** in 80-90% yields (Table 1).

The structures of the products were deduced from their spectral and microanalytical data. For example, the ^{1}H NMR spectrum of compound **4a** which this is a symmetrical produce, exhibited one sharp signal at δ 2.250 and 3.541ppm for methyl groups, δ 5.109ppm for CH groups, δ 7.736 and 9.231ppm for NH groups, as well as the signals in the aromatic region, δ 7.189 ppm, due to 4 aromatic protons indicating the formation of the compound **4a**. The IR spectrum of **4a** showed strong absorptions at 3430 cm^{-1}for NH absorption, 3028 and 2943 cm^{-1} due to the aromatic and aliphatic protons, two strong absorptions in 1697 and 1661 cm^{-1} for stretching C=O in the pyrimidine ring, two strong absorptions as doublet in 1433 and 1385 cm^{-1} for stretching C=C in rings and a medium absorption in 1238 cm^{-1} for C-N respectively.

The MS (APCI) of 4a showed a peak at m/z 414.1([M]$^{+}$) corresponding to the molecular formula $C_{20}H_{22}N_4O_6$. This product gave also satisfactory proton decoupled ^{13}C NMR data in 18.30, 51.32, 53.99, 99.40, 129.78, 144.25, 149.15, 152.62, 166.28 ppm.

In the second stage, we studied the efficiency using two heteropolyacids contain Keggin-type $H_3[PMo_{12}O_{40}]$ and preyssler $H_{14}[NaP_5W_{30}O_{110}]$. The results are reported in Table1 with the order of efficiency as follows: $H_3[PMo_{12}O_{40}]$> $H_{14}[NaP_5W_{30}O_{110}]$.

Table1. Synthesis of some new 4, 4'-(phenylene) bis tetrahydropyrimidines **4a-4f**

Product[c]	R	Ar	HCl[a]		$H_3[PMo_{12}O_{40}]$[b]		$H_{14}[NaP_5W_{30}O_{110}]$[b]		M.P. (°C)
			Time(hr)	Yield (%)[d]	Time(min)	Yield (%)	Time(min)	Yield (%)	
4a	Me	1,4-phenylene	4	84	30	86	60	84	315 dec.
4b	Et	1,4-phenylene	4	87	30	90	60	86	310 dec.
4c	$PhCH_2$	1,4-phenylene	5	90	30	92	60	88	294-296
4d	Me	1,3-phenylene	6	85	30	88	60	80	279-281
4e	Et	1,3-phenylene	4	80	30	85	60	84	289-291
4f	$PhCH_2$	1,3-phenylene	5	85	30	85	60	82	300 dec.

[a]Reaction conditions : Urea 1 (2 mmol), a dialdhyde **2a-2b** (1 mmol), an acetoacetate **3a-3c** (2 mmol), Ethanol (6 ml), Hydrochloric acid (4-5 drops), reflux.
[b]Reaction conditions : Urea 1 (2 mmol), a dialdhyde **2a-2b** (1 mmol), an acetoacetate **3a-3c** (2 mmol), Ethanol (6 ml), Hydrochloric acid (4-5 drops), $H_3[PMo_{12}O_{40}]$ or $H_{14}[NaP_5W_{30}O_{110}]$ (0.1gr), temperature room.
[c]All the products were characterized according to their spectral and microanalytical data.
[d]Isolated yields.

The effect of varying the reaction duration was studied for the synthesis of **4a** by reaction of Urea **1**, Terephaldialdhyde **2a**, and methyl acetoacetate **3a**.

The effect of solvent on the synthesis of **4a** was studied on solvents including $C_6H_5CH_3$, DMF, DMSO, H_2O, CH_2Cl_2, $CHCl_3$, and EtOH. Ethanol proved to be the best in terms of yield (Table 2).

The effects of temperature, and the amounts of heteropolyacid, had showed respectively Tables 3 and 4.

CONCLUSION

Melting points were recorded on a Stuart SMP3 melting point apparatus. The IR spectra were obtained using a Bruker Tensor 27 spectrophotometer using KBr discs. The ^{1}H NMR (300 MHz) was recorded with Bruker-300 MHz spectrometers. The ^{13}C-NMR was recorded with Bruker-300 MHz spectrometers at 75 MHz frequencies. The mass spectra were scanned on an Agilent Technologies instrument at 70 eV. Elemental analysis was performed on a Thermo Finnigan Flash EA microanalyzer.

Synthesis of bis-1, 2, 3, 4-tetrahydropyrimidines 4a-4f; (general procedure). A mixture of urea **1** (2 mmol), an aldehyde **2a-2b** (1 mmol), β-ketoester **3a-3c** (2 mmol) and conc. HCl (4-6 drops) in EtOH (6mL) was heated under reflux for 4-6 hours. After the completion of the reaction, the solvent was evaporated in vacuo. The crude product was collected and re-crystallized from ethanol to give compounds **4a-4f** in 80-90% yields.

Table 2. Effect of Solvent on the yields of 4a[a]

Entry	Solvent	Time(hr)	Yield (%)
1	H_2O	3	38
2	DMSO	3	32
3	DMF	3	35
4	$C_6H_5CH_3$	3	Trace
5	CH_2Cl_2	3	Trace
6	$CHCl_3$	3	Trace
7	EtOH	**30(min)**	**86**

[a]Reaction conditions : Urea 1 (2 mmol), Terephthaldialdhyde **2a** (1 mmol), methyl acetoacetate **3a** (2 mmol), solvent (6 ml), $H_3[PMo_{12}O_{40}]$ (0.1gr), Hydrochloric acid (4-5 drops), temperature room.

Table 3. Effect of temperature on the yields of 4a[a]

Entry	Temperature (°C)	Product (gr)	Yield (%)
1	Room	0.356	86
2	50	0.228	55
3	110	0.141	34

[a]Reaction conditions : Urea 1 (2 mmol), Terephthaldialdhyde **2a** (1 mmol), methyl acetoacetate **3a** (2 mmol), solvent (6 ml), $H_3[PMo_{12}O_{40}]$ (0.1gr), Hydrochloric acid (4-5 drops).

Table 4. Effect of the amounts of Keggin $H_3[PMo_{12}O_{40}]$ on the yields of 4a[a]

Entry	amounts of Keggin(gr)	Time (min)	Yield (%)
1	0.05	30	28
2	0.07	30	68
3	0.10	30	86
4	0.12	30	63
5	0.15	30	52

[a]Reaction conditions : Urea 1 (2 mmol), Terephthaldialdhyde **2a** (1 mmol), methyl acetoacetate **3a** (2 mmol), solvent (6 ml), Hydrochloric acid (4-5 drops), temperature room.

Table 5. Synthesis of **4a** with recycled Keggin $H_3[PMo_{12}O_{40}]$[a].

	1st run	2nd run	3rd run	4th run
Time (min)	30	30	40	50
Yield (%)	86	78	76	70

[a]Reaction conditions : Urea 1 (2 mmol), Terephthaldialdhyde **2a** (1 mmol), methylacetoacetate **3a** (2 mmol), solvent (6 ml), $H_3[PMo_{12}O_{40}]$ (0.1gr), Hydrochloric acid (4-5 drops).

Synthesis of bis-1, 2, 3, 4-tetrahydropyrimidines 4a-4f in presence of heteropolyacids; (general procedure). To a mixture of urea **1** (2 mmol), a dialdehyde **2a-2b** (1 mmol), and β-ketoester **3a-3c** (2 mmol), a catalytic amount of heteropolyacid (0.1 gr) was added and the resulting mixture was stired in solvent (6 mL). The progress of the reaction was monitored by TLC. On completion, the catalyst was filtered off, the solvent was evaporated and the pure product was collected and recrystallized from ethanol to give compounds **4a-4f** in 85-92 % yields.

Dimethyl 4, 4'-(1, 4-phenylene) bis (6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate) (4a). Yield 84-86%, yellow powder, mp 315°C >decomposed, IR spectrum, ν, cm^{-1}: 3430(N-H), 3028 (arom-CH), 2943 (aliph-CH), 1697(C=O), 1661(C=O), 1433 and 1385 (C=C), 1238(C-N), 1094(C-O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.250(s, 6H, -CH_3); 3.541(s, 6H, -CH_3); 5.109(s, 2H, -CH); 7.189(s, 4H, C_6H_4); 7.736(s, 2H, N-H exchange with D_2O), 9.231(s, 2H, N-H exchange with D_2O). ^{13}C NMR (DMSO-d_6), δ, ppm: 18.30(CH_3), 51.32(CH_3), 53.99(CH), 99.40(C), 126.78(Ar), 144.25(Ar), 149.15(C), 152.62(C=O), 166.28(C=O). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 414.1[M]$^+$ (10), 413.1[M-H]$^+$ (15), 375.1(40), 311.1(20), 260.1(20), 182.9(20), 131.0(25), 97.1(45), 71.0(43), 43.1(100). Elemental Analysis: Found, %: C 55.43; H 5.21; N 12.89; $C_{20}H_{22}N_4O_6$. Calculated, %: C 57.97; H 5.35; N 13.52.

Diethyl 4, 4'-(1, 4-phenylene) bis(6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate) (4b). Yield 86-90% , white powder, mp 310°C decomposed, IR spectrum, ν, cm^{-1}: 3308(N-H), 3019 (arom-CH), 2931 (aliph-CH), 1703(C=O), 1660(C=O), 1453 and 1372 (C=C), 1235(C-N), 1085(C-O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.067-1.128(t, 6H, CH_3); 2.242(s, 6H, -CH_3); 3.949-4.018(q, 4H, -CH_2);5.115(s, 2H, -CH); 7.190(s, 4H, C_6H_4); 7.704(s, 2H,N-H exchange with D2O), 9.197(s, 2H, N-H exchange with D_2O). ^{13}C NMR (DMSO-d_6), δ, ppm: 14.53(CH_3), 22.88(CH_3), 54.06(CH), 59.69(CH_2), 99.69(C), 126.78(Ar), 144.40(Ar), 148.76(C), 152.53(C=O), 165.77(C=O). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 442.3[M]$^+$ (15), 441.2[M-H]$^+$ (22). Elemental Analysis: Found, %: C 58.46; H 5.68; N 12.07; $C_{22}H_{26}N_4O_6$. Calculated, %: C 59.72; H 5.92; N 12.66.

Dibenzyl 4, 4'-(1, 4-phenylene)bis(6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate) (4c). Yield 88-92%, white powder, mp 294-296 °C, IR spectrum, ν, cm^{-1}: 3356(N-H), 3107 (arom-CH), 2958 (aliph-CH), 1693(C=O), 1641(C=O), 1453 and 1380 (C=C), 1223(C-N), 1090(C-O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.281(s, 6H, -CH_3); 5.028(s, 2H, -CH); 5.148(s, 4H, -CH_2); 7.127-7.331(m, 14H, C_6H_4 and C_6H_5); 7.754(s, 2H, N-H exchange with D_2O), 9.301(s, 2H, N-H exchange with D_2O). ^{13}C NMR (DMSO-d_6), δ, ppm: 18.36(CH_3), 54.09(CH), 65.31(CH_2), 99.21(C), 126.85(Ar), 128.06(Ar), 128.20(Ar), 128.76(Ar), 128.78(Ar), 136.96 (Ar), 144.28(Ar), 149.74(C), 152.53(C=O), 165.52 (C=O). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 566.3[M]$^+$ (5), 259.0(20), 183.0(18), 90.9(100), 44.0(95). Elemental Analysis: Found, %: C 66.34; H 5.04; N 9.13; $C_{32}H_{30}N_4O_6$. Calculated, %: C67.83; H5.34; N 9.89.

Dimethyl 4, 4'-(1,3-phenylene)bis(6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate) (4d). Yield 80-88%, white powder, mp 279-281 °C, IR spectrum, ν, cm^{-1}: 3408(N-H), 3031 (arom-CH), 2950 (aliph-CH), 1696(C=O), 1646(C=O), 1436 and 1318 (C=C), 1233(C-N), 1092(C-O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.249(s, 6H, -CH_3); 3.550(s, 6H, -CH3); 5.124(s, 2H, -CH); 7.142-7.169(m, 3H, C_6H_4); 7.280-7.332(m, 1H, C_6H_4); 7.769(s, 2H,N-H exchange with D_2O), 9.249(s, 2H, N-H exchange with D2O). ^{13}C NMR (DMSO-d_6), δ, ppm: 18.24(CH_3), 51.19(CH_3), 54.29(CH), 99.56(C), 124.43(Ar), 125.63(Ar), 129.04(Ar), 145.51(Ar), 149.01(C), 152.65(C=O), 166.18(C=O). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 414.2[M]$^+$ (4), 169.0(100), 137.0(50), 42.1(40). Elemental Analysis: Found, %: C 57.24; H 5.12; N 12.98; $C_{20}H_{22}N_4O_6$. Calculated, %: C 57.97; H5.35; N 13.52.

Diethyl 4, 4'-(1, 3-phenylene)bis(6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate) (4e). Yield 80-85%, yellow powder, mp 289-291 °C, IR spectrum, ν, cm^{-1}: 3360(N-H), 3118 (arom-CH), 2978 (aliph-CH), 1699(C=O), 1649(C=O), 1461 and 1385 (C=C), 1225(C-N), 1093(C-O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.048-1.095(t, 6H, -CH_3); 2.227(s, 6H, -CH_3); 3.913-3.998(q, 4H, -CH_2); 5.101(s, 2H, CH); 7.118-7.138(m, 3H, C_6H_4); 7.256-7.309(m, 1H, C_6H_4); 7.761(s, 2H,N-H exchange with D_2O), 9.182(s, 2H, N-H exchange with D_2O). ^{13}C NMR (DMSO-d_6), δ, ppm: 14.55(CH_3), 18.18(CH_3), 54.41(CH), 59.60(CH2), 99.70(C), 124.55(Ar), 125.78(Ar), 128.93(Ar), 145.53(Ar), 148.80(C), 152.52(C=O), 165.69(C=O). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 442.1[M]$^+$ (6), 441.0[M-H]+(20). Elemental Analysis: Found, %: C 58.91; H 5.38; N 11.96; $C_{22}H_{26}N_4O_6$. Calculated, %: C 59.72; H 5.92; N 12.66.

Dibenzyl 4, 4'-(1, 3-phenylene)bis(6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate) (4f). Yield 82-85%, white powder, mp 300°C decomposed, IR spectrum, ν, cm^{-1}: 3369(N-H), 3048 (arom-CH), 2933 (aliph-CH), 1697(C=O), 1644(C=O), 1451 and 1382 (C=C), 1227(C-N), 1084(C-O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.260(s, 6H, -CH_3); 4.990(s, 2H, CH); 5.179 (s, 4H, -CH_2); 7.153-7.276(m, 3H, C_6H_4); 7.454(m, 1H, C_6H_4); 7.835(s, 2H,N-H exchange with D_2O), 9.310(s, 2H, N-H exchange with D_2O). ^{13}C NMR (DMSO-d_6), δ, ppm: 18.32(CH_3), 54.26(CH), 65.23(CH_2), 99.30(C), 124.61(Ar), 125.79(Ar), 128.79(Ar), 129.57(Ar), 137.03(Ar), 145.39(Ar), 148.83(Ar), 149.75(C), 152.55

(C=O), 165.49(C=O). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 565.9$[M]^+$ (3), 565.0[M-H]+(20), 220.9(15), 137.0(10), 97.1(65), 91.1(100), 43.6(85) . Elemental Analysis: Found, %: C 64.82; H 5.11; N 9.06; $C_{32}H_{30}N_4O_6$. Calculated, %: C 67.83; H 5.34; N 9.89.

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