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Ultrasound-Assisted Synthesis of 6-Methyl-1,2,3,4-tetrahydro-*N*-aryl-2-oxo/thio-4-arylpyrimidine-5-carboxamides Catalyzed by Uranyl Nitrate Hexahydrate

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An efficient and simple method developed for the synthesis of 6-methyl-1,2,3,4-tetrahydro-*N*-aryl-2-oxo/thio-4-arylpyrimidine-5-carboxamide derivatives (**4a-o**) using $UO_2(NO_3)_2.6H_2O$ catalyst under conventional and ultrasonic conditions. The ultrasound irradiation synthesis had shown several advantages such as milder conditions, shorter reaction times and higher yields. The structures of all the newly synthesized compounds have been confirmed by FT-IR, ^{1}H NMR, ^{13}C NMR and mass spectra.

Keywords: Ultrasonic irradiation; $UO_2(NO_3)_2.6H_2O$; Spectral characterization.

INTRODUCTION

The dihydropyrimidinone (DHPM) is the most important ring system in the synthesis of different pharmacologically active agents such as antihypertensive agents, calcium channel blockers, neuropeptide Y (NPY) antagonists, α-1a-antagonists, antiviral, antitumor, antibacterial and anti-inflammatory drugs.[1-7] In addition, the batzelladine alkaloids containing the DHPM core unit inhibit the binding of HIV envelope protein gp-120 to human CD_4 cells and therefore, are potential new leads for AIDS therapy.[8-10] Hence synthesis of dihydropyrimidinones (DHPMs) has always been of great interest to the organic chemists.

The synthetic strategies used to generate DHPMs have been well documented and have typically involved variations of the original Biginelli reaction.[11-14] The one-pot synthesis of 3,4-dihydropyrimidin-2(*1H*)-ones was first reported by Biginelli in 1893, often involves unsatisfactory yields (20–60%), harsh reaction conditions and long reaction times.[15-17] Apart from subtle modifications from the original design, the Biginelli reaction takes place by mixing different substituted aldehydes, urea or thiourea, and an active 1,3-dicarbonyl compound in combination with different catalytic systems such as AcOH,[18] H_2SO_4,[19] lanthanide triflate,[20] KSF clay,[21] $LiClO_4$,[12] $InCl_3$,[22] $LaCl_3$,[23] PPE,[24] $CdCl_2$,[25] $BF_3.OEt_2$,[26] ion-exchange resin,[27] $Mn(OAc)_3$,[28] $InBr_3$,[29] 1-n-butyl-3-methyl imidazolium tetrafluoroborate,[30] $SiO_2/NaHSO_4$,[31] ytterbium triflates,[32] $FeCl_3$,[33] $MgBr_2$,[34] Ceric ammonium nitrate (CAN),[35] $BiCl_3$,[36] $ZrCl_4$,[37] $Cu(OTf)_2$,[38] LiBr,[39] $AlCl_3.H_2O$,[40] p-TSA,[41] $Pb(NO_3)_2$,[42] NaCl,[43] alkaline phosphates[44-46] and sulphates[47] under classical reflux,[48,49] microwave[50-53] or ultrasound irradiation[54] and solvent-free conditions.[20,30,55]

However, insipte of their potential utility, many of these methods require the use of expensive reagents, stoichiometric amounts of catalysts, strongly acidic conditions in combination with bronsted acids, such as hydrochloric acid and acetic acid[56-59] as additives, long reaction times, high temperatures and unsatisfactory yields. Therefore, to avoid these limitations, the development of a mild, efficient and cost effective catalyst with high catalytic activity, short reaction time with simple work-up procedure for the preparation of dihydropyrimidinones is of prime interest and would extend the scope of pyrimidinone chemistry.

Ultrasound has increasingly been employed in organic synthesis for decades with varied success. Chemical applications extend to such varied areas as organic and organometallic chemistry, materials science, aerogels, food chemistry and medicinal research.[60-62] Ultrasound is considered as non-conventional energy source when used to perform chemical reactions and they are regarded as having very interesting results compared to the conventional heating sources. Ultrasonic acceleration effects on chemical processes are widely used both in laboratory and industrial practice.[61,63] Sonication mostly affects reaction rates, yields, and in some cases the ratios of reaction products.

In continuation of our interest on the ultrasonic accelerated reactions and uranyl nitrate hexahydrate ($UO_2(NO_3)_2.6H_2O$) catalyst,[64,65] we wish to report a simple, efficient and practical approach for the synthesis of 6-methyl-1,2,3,4-tetrahydro-*N*-aryl-2-oxo/thio-4-arylpyrimidine-5-carboxamide derivatives catalyzed by $UO_2(NO_3)_2.6H_2O$ using conventional and ultrasonic irradiation methods. The characterization of all the synthesized compounds through

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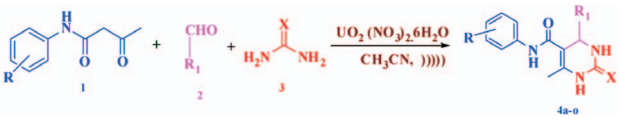
IR, ^{1}H NMR, ^{13}C NMR and mass spectra is also described.

RESULTS AND DISCUSSION

The one-pot there-component reaction for the synthesis of 5-carboxamide-DHPMs was carried out by the reaction between different substituted aldehydes, urea or thiourea and substituted acetoacetanilides using uranyl nitrate hexahydrate catalyst under conventional heating and ultrasonic irradiation conditions (Scheme 1). $UO_2(NO_3)_2.6H_2O$ is relatively cost effective catalyst for the synthesis of 5-carboxamide-DHPMs compared with the other lewis acid catalysts reported for the same in the literature. In order to optimize the reaction conditions, the condensation of benzaldehyde, urea and acetoacetanilide in the presence of catalytic amounts of $UO_2(NO_3)_2.6H_2O$ under conventional and ultrasound conditions using different solvent systems (chloroform, dichloromethane, ethanol, methanol, acetonitrile) was examined as a model reaction (Table 1 & 2).

Scheme 1



The results show that the reaction proceeded more efficiently under ultrasonic irradiation as compared to conventional heating. The reaction was completed within 21 min to furnish the desired 6-methyl-1,2,3,4-tetrahydro-*N*-phenyl-2-oxo-4-(4-hydroxy-3-methoxyphenyl)pyrimidine-5-carboxamide in 88% yield at 16 kHz operating frequency of ultrasonic irradiation in the presence of 5 mol% $UO_2(NO_3)_2.6H_2O$ under acetonitrile solvent (Entry 4, Table 1).

Furthermore, effect of quantity of catalyst loading was examined. The optimum catalyst loading for $UO_2(NO_3)_2.6H_2O$ was found to be about 5 mol%. Larger amounts of the catalyst (Entries 5 and 6, Table 2) did not improve the yield, while lowering the amount of catalyst did not have much effect on the yield. After optimizing the conditions, this method was tried out for synthesis of Beginelli type dihydropyrimidinones by using different heterocyclic and aryl aldehydes with a variety of substitutions at *ortho*-, *meta*-, *para*-positions, urea or thiourea and different substituted acetoacetanilide under conventional heating and ultrasonic irradiation conditions to establish the catalytic importance of $UO_2(NO_3)_2.6H_2O$ for this reaction (Table 3). Generally, the synthetic procedure involves stirring the mixture of aldehyde (1 mmol), acetoacetanilide (1 mmol), urea or thiourea (1.2 mmol) and $UO_2(NO_3)_2.6H_2O$ (5 mol%) for 360 and 21 min in the presence of acetonitrile at reflux temperature and ultrasonic irradiation, respectively. The corresponding results are summarized in Table 3.

Moreover, reaction work-up is simple and the catalyst can be easily separated from the product. After completion of the reaction, the reaction mixture was cooled to room

Table 2. Effect of different catalysts on the formation of compound **4k** in the presence of acetonitrile under ultrasonic irradiation

Entry	Catalyst	Catalyst (mol %)	Time (min.)	Yield (%)[b]
1	$RuCl_3.2H_2O$	5	30	67
2	$RuCl_3.2H_2O$	10	30	65
3	$RuCl_3.2H_2O$	20	30	65
4	$UO_2(NO_3)_2.6H_2O$	5	21	88
5	$UO_2(NO_3)_2.6H_2O$	10	21	88
6	$UO_2(NO_3)_2.6H_2O$	15	21	87
7[a]	Conc. HCl	1 mL	18 h	65

[a] Reaction carried out under reflux condition.
[b] Isolated yields.

Table 1. Effect of the solvent for the synthesis of 6-methyl-1,2,3,4-tetrahydro-*N*-phenyl-2-oxo-4-(4-hydroxy-3-methoxyphenyl)pyrimidine-5-carboxamide (**4k**) catalyzed by $UO_2(NO_3)_2.6H_2O$

Entry	Solvents	Catalyst (mol %)		Time (min.)		Yield (%)[b]	
		$RuCl_3$	$UO_2(NO_3)_2.6H_2O$	$RuCl_3$	$UO_2(NO_3)_2.6H_2O$[a]	$RuCl_3$	$UO_2(NO_3)_2.6H_2O$[a]
1	Chloroform	5	5	900	600/30	20	43/31
2	Dichloromethane	5	5	900	600/30	19	41/28
3	Ethanol	5	5	900	420/21	57	68/71
4	Methanol	5	5	900	420/21	61	76/78
5	Acetonitrile	5	5	900/30[a]	420/21	65/67	85/88

[a] Under conventional and ultrasonic heating.
[b] Isolated yield of product from conventional and ultrasonic heating reaction.

Table 3. Experimental results and physical data of 6-methyl-1,2,3,4-tetrahydro-*N*-aryl-2-oxo/thio-4-arylpyrimidine-5-carboxamide derivatives (**4a-o**)

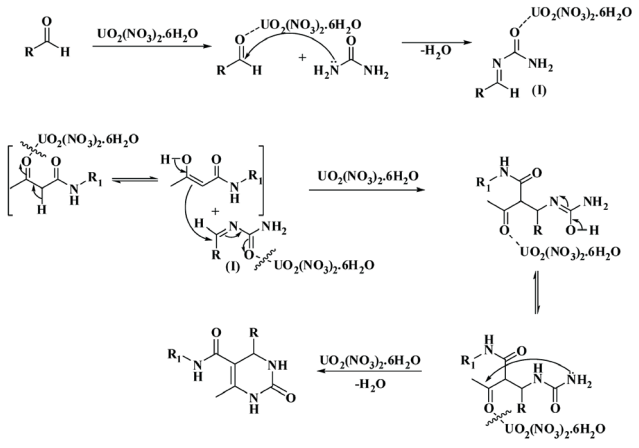
Compd.	R	R1	X	Reaction time (min.)		Yield (%)[a]		M.P. (°C)
				US	Conv.	US	Conv.	
4a	H	Ph H	O	21	450	87	82	225-228[41]
4b	H	Ph H	S	21	450	85	83	214-217[41]
4c	H	Ph 3-OEt-4-OH	O	24	480	83	80	253-256
4d	H	Ph 3-OEt-4-OH	S	24	480	81	78	242-245
4e	H	Ph 2,4-Cl	O	21	480	83	79	206-209
4f	H	Ph 2,4-Cl	S	21	480	80	75	188-191
4g	H	Ph 4-OEt-3-OMe	S	24	480	81	76	123-126
4h	H	2-C_4H_3S	O	21	420	83	77	192-195
4i	H	2-C_4H_3S	S	21	420	79	75	201-204
4j	H	Ph 4-OEt	O	24	450	84	80	235-238
4k	H	Ph 4-OH-3-OMe	O	21	420	88	85	230-233
4l	4-Cl	Ph 2,4-Cl	O	21	480	82	79	205-208
4m	4-Cl	Ph 4-OEt	O	24	480	84	78	248-251
4n	4-Cl	Ph 4-OEt	S	24	480	82	75	228-230
4o	4-Cl	2-C_4H_3S	O	21	420	83	77	239-242

[a] Isolated yields; US = Ultrasonic irradiation; Conv. = Conventional heating; C_4H_3S = Thiophene.

temperature and diluted with ice cold water and kept aside overnight. The separated solid was suction filtered and washed with large amount of water. The catalyst which is highly soluble in water could be easily removed by washing with excess amount of cold water through suction filtration.

Plausible reaction mechanism of Biginelli condensation via formation of acyliminium ion intermediate is presented in Scheme 2, this intermediate is formed by the reaction of the different substituted carbaldehyde **2** and urea or thiourea **3** and then stabilized by $UO_2(NO_3)_2.6H_2O$ through a coordinate bond owing to its empty orbital. Subsequent addition of the acyliminium ion to acetoacetanilide **1** in the presence of $UO_2(NO_3)_2.6H_2O$ as catalyst produces an open chain ureide which subsequently undergo cyclization and dehydration to afford the corresponding 6-methyl-1,2,3,4-tetrahydro-*N*-aryl-2-thio/oxo-4-arylpyrimidine-5-carboxamide **4a-o**.

Scheme 2



The efficiency of $UO_2(NO_3)_2.6H_2O$ was compared with that of other catalyst, $RuCl_3$ reported as a new catalyst in the synthesis of 6-methyl-1,2,3,4-tetrahydro-*N*-phenyl-2-oxo-4-(4-hydroxy-3-methoxyphenyl)pyrimidine-5-carboxamide by one-pot three-component condensation of 4-hydroxy-3-methoxy benzaldehyde, urea and acetoacetanilide in the presence of different solvent systems under reflux and ultrasonic irradiation conditions (Table 1 & 2). The data listed in Table 2 show that $RuCl_3$ can also act as a suitable catalyst for this reaction at different catalytic amounts under ultrasonic irradiation conditions.

In conclusion, we have developed a simple and efficient procedure for the synthesis of 6-methyl-1,2,3,4-tetrahydro-*N*-aryl-2-oxo/thio-4-arylpyrimidine-5-carboxamide derivatives by one-pot three-component condensation of different substituted aldehydes, urea or thiourea and substituted acetoacetanilides under conventional heating and ultrasonic irradiation conditions using $UO_2(NO_3)_2.6H_2O$ as catalyst. The key advantages of this process are mild reaction conditions, shorter reaction times, cost effectiveness of catalyst, easy work-up and high yields. In order to improve the selectivity and yield, the effects of solvents and

mole proportion of catalyst are investigated with $UO_2(NO_3)_2.6H_2O$ and $RuCl_3$ catalysts. The structures of the synthesized compounds have been confirmed through spectral characterization such as IR, ^{1}H NMR, and mass spectra.

EXPERIMENTAL

General: The ^{1}H NMR spectra were obtained on BRUKER AV-(500, 400 and 300) MHz spectrometer with DMSO-d_6 as the solvent using tetramethylsilane (TMS) as the internal standard. Infrared (IR) spectra were recorded at room temperature from 4000 cm^{-1} to 400 cm^{-1} with KBr pellets at a resolution of 4 cm^{-1}, using Avatar 330 equipped with DTGS detector. All reagents were purchased from Aldrich, SD fine Chemicals and Qualigens and used without further purification. Mass spectra were obtained by using HRMS. The melting points were determined by open capillaries and are uncorrected. Sonication was performed in a SONICS, Vibra Cell, VC 130, ultrasonic processor equipped with a 3 mm wide and 140 mm long probe, which was immersed directly into the reaction mixture. The operating frequency was 20 kHz and the output power was 0-130 Watt through manual adjustment.

General procedure for the preparation of compound 6-methyl-1,2,3,4-tetrahydro-*N*-aryl-2-thio/oxo-4-arylpyrimidine-5-carboxamide (4a-o): Conventional method: A mixture of aldehyde (1 mmol), acetoaetanilide (1 mmol), urea or thiourea (1.2 mmol), $UO_2(NO_3)_2.6H_2O$ (5 mol%), and 20 mL acetonitrile was refluxed for the appropriate time mentioned in Table 3. After completion of the reaction as indicated by TLC, the reaction mixture was poured into crushed ice, stirred for 15-20 min. and left overnight. The solid separated was filtered through a funnel, washed with ice-cold water and then recrystallized from hot methanol to afford pure compounds **4a-o**.

Ultrasonic irradiation: A mixture of aldehyde (1 mmol), acetoaetanilide (1 mmol), urea or thiourea (1.2 mmol) and $UO_2(NO_3)_2.6H_2O$ (5 mol%) in 20 mL acetonitrile was subjected to ultrasonic irradiation using ultrasonic processor equipped with a 3 mm wide and 140 mm long probe, which was immersed directly into the reaction mixture varying time periods as shown in Table 3. The operating frequency was 16 kHz and the output power was 104 Watts through manual adjustment. The progress of the reaction was monitored by TLC (ethyl acetate: hexane, 7:3). The reaction mixture was poured into crushed ice, stirred for 15-20 min and left overnight. The solid separated was filtered through a funnel and washed with ice-cold water and then recrystallized from hot methanol to afford pure compounds **4a-o** and their physical data is given in Table 3.

***4-(3-ethoxy-4-hydroxyphenyl)-6-methyl-2-oxo-N-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4c)*:** mp. 253-256 ºC; IR (KBr) ν_{max}: 3542, 3259, 2977, 2931, 1701, 1660, 1609, 1591, 1581, 1518, 1491, 1478, 1436, 1411, 1371, 1336, 1281, 1225, 1212, 1155, 1121, 1093, 1062, 1041 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6, ppm), δ_H = 9.10 (s, 1H, CONH), 8.86 (s, 2H, NH & OH), 7.53 (s, 1H, NH), 6.37–7.28 (m, 8H, ArH of phenyl ring), 5.23 (s, 1H, CH), 3.77–3.84 (m, 2H, OCH_2), 2.48 (s, 3H, CH_3), 1.18–1.32 (m, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6, ppm), δ_C = 164.53, 163.35, 152.70, 152.57, 146.86, 146.76, 146.58, 146.49, 143.16, 142.04, 135.98, 132.26, 128.72, 127.35, 126.03, 125.54, 119.30, 118.02, 115.74, 115.59, 112.66, 102.58, 64.27, 64.17, 63.86, 53.17, 38.83, 15.26, 15.20; HRMS (EI): *m/z* [M+] calcd. for $C_{20}H_{21}N_3O_4$: 367.1532; found: 367.1531. ***4-(3-ethoxy-4-hydroxyphenyl)-6-methyl-N-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4d)*:** mp. 242-245 ºC; IR (KBr) ν_{max}: 3349, 3192, 2975, 2931, 1672, 1625, 1595, 1571, 1512, 1467, 1435, 1400, 1283, 1234, 1217, 1189, 1149, 1120, 1108, 1084, 1039, 1012 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6, ppm), δ_H = 10.29 (s, 1H, CONH), 9.52 (s, 1H, NH), 8.87–8.94 (split peak, 2H, NH & OH), 6.36–7.26 (m, 8H, ArH of phenyl ring), 5.25 (s, 1H, CH proton), 3.56–3.95 (m, 2H, OCH_2), 2.45 (s, 3H, CH_3), 1.18–1.35 (m, 3H, CH_3); HRMS (EI): *m/z* [M+] calcd. for $C_{20}H_{21}N_3O_3S$: 383.1304; found: 383.1302. ***4-(2,4-dichlorophenyl)-6-methyl-2-oxo-N-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4e)*:** mp. 206-209 ºC; IR (KBr) ν_{max}: 3397, 3265, 3168, 3084, 3006, 1669, 1626,1595, 1563, 1525, 1498, 1478, 1436, 1380, 1331, 1236, 1179, 1140, 1101, 1075, 1045 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6, ppm), δ_H =10.11 (s, 1H, CONH), 9.86 (s, 1H, NH), 9.36 (s, 1H, NH), 7.56 (d, 1H, *J* = 2.5 Hz, *m*-ArH of phenyl ring), 7.50 (d, 3H, *J* = 7.5 Hz, *o,o′ & m′*-ArH of phenyl ring), 7.38 (d, 1H, *J* = 8.5 Hz, *o′*-ArH of phenyl ring), 7.25 (t, 2H, *J* = 8.0 Hz, *m,m′*-ArH of phenyl ring), 7.02 (t, 1H, *J* = 7.2 Hz, *p*-ArH of phenyl ring), 5.75 (d, 1H, *J* = 2.0 Hz, CH proton), 2.02 (s, 3H, CH_3 proton); ^{13}C NMR (100 MHz, DMSO-d_6, ppm), δ_C = 174.12, 164.36, 139.35, 138.77, 135.03, 133.08, 132.16, 130.83, 128.86, 128.02, 123.37, 119.47, 106.37, 52.42, 16.20; HRMS (EI): *m/z* [M+] calcd. For $C_{18}H_{15}Cl_2N_3O_2$: 375.0541; found: 375.0541. ***4-(2,4-dichlorophenyl)-1,2,3,4-tetrahydro-6-methyl-N-phenyl-2-thioxopyrimidine-5-carboxamide (4f)*:** mp. 188-191 ºC; IR (KBr) ν_{max}: 3397, 3276, 3088, 2360, 2342, 1672, 1654, 1629, 1598, 1560, 1540, 1523, 1498, 1473, 1438, 1329, 1234,1202, 1180, 1143, 1101, 1076, 1046 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6, ppm), δ_H =10.13 (s, 1H, CONH), 9.87 (s, 1H, NH), 9.37 (s, 1H, NH), 7.56 (d, 1H, *J* = 2.0 Hz, *m*-ArH of phenyl ring), 7.51 (d, 3H, *J* = 8.5 Hz, *o,o′ & m′*-ArH of phenyl ring), 7.39 (d, 1H, *J* = 8.5 Hz, *o′*-ArH of phenyl ring), 7.26 (t, 2H,

J = 8.0 Hz, *m,m′*-ArH of phenyl ring), 7.02 (t, 1H, *J* = 7.2 Hz, *p*-ArH of phenyl ring), 5.75 (d, 1H, *J* = 2.5 Hz, CH proton), 2.03 (s, 3H, CH_3 proton); HRMS (EI): *m/z* [M+] calcd. for $C_{18}H_{15}Cl_2N_3OS$: 391.0313; found: 391.0312. ***4-(4-ethoxy-3-methoxyphenyl)-6-methyl-N-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4g):*** mp. 123-126 ºC; IR (KBr) ν_{max}: 3349, 3291, 3175, 3094, 2977, 2361, 1680, 1635, 1596, 1561, 1513, 1482, 1439, 1394, 1334, 1264, 1229, 1197, 1180, 1139, 1029 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, ppm), δ_H = 9.95 (s, 1H, CONH), 9.72 (s, 1H, NH), 9.38 (s, 1H, NH), 7.54 (d, 2H, *J* = 8.5 Hz, *o,o′*-ArH of phenyl ring), 7.26 (t, 2H, *J* = 7.2 Hz, *m,m′*-ArH of phenyl ring), 7.02 (t, 1H, *J* = 7.2 Hz, *p*-ArH of phenyl ring), 6.91 (d, 1H, *J* = 8.0 Hz, *o*-ArH of phenyl ring), 6.85 (s, 1H, *m′*-ArH of phenyl ring), 6.78 (d, 1H, *J* = 8.0 Hz, *o′*-ArH of phenyl ring), 5.36 (s, 1H, CH proton), 3.96 (q, 2H, *J* = 6.7 Hz, OCH_2), 3.67 (s, 3H, OCH_3), 2.07 (s, 3H, CH_3), 1.29 (t, 3H, *J* = 6.7 Hz, CH_3); HRMS (EI): *m/z* [M+] calcd. for $C_{21}H_{23}N_3O_3S$: 397.1460; found: 397.1459. ***6-methyl-2-oxo-N-phenyl-4-(thiophen-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4h)*:** mp. 192-195 ºC; IR (KBr) ν_{max}: 3249, 2362, 1697, 1640, 1592, 1509, 1492, 1452, 1396, 1307, 1286, 1251, 1208, 1148, 1089, 1040, 1012 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, ppm), δ_H = 9.57 (s, 1H, CONH), 8.85 (s, IH, NH), 7.80 (s, 1H, NH), 7.58 (d, 2H, *J* = 8.0 Hz, *o,o′*-ArH of phenyl ring), 6.93–7.38 (m, 6H, ArH of phenyl & thiophene ring), 5.59 (d, 1H, *J* = 3.0 Hz, CH), 2.06 (s, 3H, CH_3); HRMS (EI): *m/z* [M+] calcd. For $C_{16}H_{15}N_3O_2S$: 313.0885; found: 313.0884. ***6-methyl-N-phenyl-4-(thiophen-2-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4i)*:** mp. 201-204 ºC; IR (KBr) ν_{max}: 3368, 3284, 1679, 1635, 1566, 1548, 1523, 1499, 1477, 1439, 1360, 1328, 1232, 188, 1117, 1076, 1037 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, ppm), δ_H=10.14 (s, 1H, CONH), 9.73 (s, 1H, NH), 9.62 (s, 1H, NH), 6.95–7.68 (m, 8H, ArH of phenyl & thiophene ring), 5.67 (d, 1H, *J* = 3.0 Hz, CH), 2.10 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, ppm), δ_C = 174.19, 164.53, 146.91, 138.94, 136.61, 128.54, 126.78, 125.67, 124.29, 123.34, 119.74, 107.07, 50.36, 16.55; HRMS (EI): *m/z* [M+] calcd. for $C_{16}H_{15}N_3OS_2$: 329.0657; found: 329.0656. ***4-(4-ethoxyphenyl)-6-methyl-2-oxo-N-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4j)*:** mp. 235-238 ºC; IR (KBr) ν_{max}: 3249, 3114, 2981, 2927, 2597, 1736, 1666, 1628, 1611, 1597, 1516, 1440, 1392, 1358, 1328, 1267, 1247, 1176, 1170, 1074, 1048, 1008 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, ppm), δ_H = 9.52 (s, 1H, CONH), 8.70 (s, 1H, NH proton), 7.55 (d, 3H, *J* = 7.5 Hz, NH & *o,o′*-ArH of phenyl ring), 7.17-7.26 (m, 4H, ArH of phenyl ring), 6.99 (t, 1H, *J* = 7.2 Hz, *p*-ArH of phenyl ring), 6.86 (d, 2H, *J* = 8.4 Hz, *m,m′*-ArH of phenyl ring), 5.36 (s, 1H, CH), 3.98 (t, 2H, *J* = 6.9 Hz, OCH_2), 2.04 (s, 3H, CH_3), 1.28 (t, 3H, *J* = 6.9 Hz, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, ppm), δ_C = 172.04, 165.31, 157.75, 152.49, 139.21, 138.15, 136.27, 128.46, 127.47, 123.00, 119.50, 114.19, 105.58, 62.91, 54.46, 16.98, 14.60; HRMS (EI): *m/z* [M+] calcd. for $C_{20}H_{21}N_3O_3$: 351.1583; found: 351.1582. ***4-(4-hydroxy-3-methoxyphenyl)-6-methyl-2-oxo-N-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4k)*:** mp. 230-233 ºC; IR (KBr) ν_{max}: 3411, 3285, 2363, 2341, 1683, 1653, 1628, 1597, 1539, 1521, 1487, 1442, 1386, 1330, 1262, 1241, 1164, 1124, 1074, 1034 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, ppm), δ_H = 9.53 (s, 1H, CONH), 8.93 (s, 1H, OH), 8.67 (s, 1H, NH), 7.55 (d, 3H, *J* = 7.8 Hz, NH & *o,o′*-ArH of phenyl ring), 7.25 (t, 2H, *J* = 7.8 Hz, *m,m′*-ArH of phenyl ring), 7.00 (t, 1H, *J* = 7.35 Hz, *p*-ArH of phenyl ring), 6.82 (s, 2H, *o,m′*-ArH of phenyl ring), 6.71 (s, 1H, *o′*-ArH of phenyl ring), 5.34 (s, 1H, CH), 3.67 (s, 3H, OCH_3), 2.07 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, ppm), δ_C = 165.46, 152.51, 147.32, 145.80, 139.19, 137.88, 135.18, 128.47, 123.04, 119.52, 118.47, 115.21, 110.71, 105.56, 55.46, 54.75, 16.95; HRMS (EI): *m/z* [M+] calcd. for $C_{19}H_{19}N_3O_4$: 353.1376; found: 353.1374. ***N-(4-chlorophenyl)-4-(2,4-dichlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4l)*:** mp. 205-208 ºC; IR (KBr) ν_{max}: 3397, 3195, 1673, 1630,1596, 1565, 1530, 1469, 1439, 1383, 1235, 1202, 1102, 1046 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, ppm), δ_H = 9.84 (s, 1H, CONH), 8.88 (s, 1H, NH), 7.58 (s, 1H, NH), 7.52–7.55 (m, 3H, *o,o′* & *m*-ArH of phenyl ring), 7.45 (d, 2H, *J* = 2.0 Hz, *m,m′*-ArH of phenyl ring), 7.28–7.30 (split peak, 2H, *o′* & *m′*-ArH of phenyl ring), 5.75 (d, 1H, *J* = 2.0 Hz, CH), 2.02 (s, 3H, CH_3); HRMS (EI): *m/z* [M+] calcd. for $C_{18}H_{14}Cl_3N_3O_2$: 409.0152; found: 409.0151. ***N-(4-chlorophenyl)-4-(4-ethoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4m)*:** mp. 248-251 ºC; IR (KBr) ν_{max}: 3293, 2981, 2926, 1702, 1659, 1618, 1585, 1513, 1492, 1477, 1412, 1396, 1376, 1341, 1303, 1272, 1241, 1177, 1137, 1115, 1093, 1049 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, ppm), δ_H = 9.16 (d, 1H, CONH), 7.60 (t, 1H, *J* = 2.2 Hz, NH), 7.30 (q, 2H, *J* = 7.0 Hz, NH, *m*-ArH of phenyl ring), 7.12 (q, 2H, *J* = 7.0 Hz, *o,o′*-ArH of phenyl ring), 7.04 (q, 2H, *J* = 6.5 Hz, *m,m′*-ArH of phenyl ring), 6.63–6.85 (m, 3H, ArH phenyl ring), 5.13–5.29 (split peak, 1H, CH proton), 3.95–4.03 (m, 2H, OCH_2), 2.46–2.51 (m, 3H, CH_3), 1.29–1.35 (m, 3H, CH_3); HRMS (EI): *m/z* [M+] calcd. for $C_{20}H_{20}ClN_3O_3$: 385.1193; found: 385.1192. ***N-(4-chlorophenyl)-4-(4-ethoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4n)*:** mp. 228-230 ºC; IR (KBr) ν_{max}: 3199, 2978, 2925, 1673, 1616, 1560, 1512, 1492, 1464, 1411, 1395, 1338, 1304, 1252, 1197, 1182, 1162, 1111, 1092, 1047, 1014 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, ppm), δ_H = 10.35 (s, 1H, CONH), 9.51 (s, 1H, NH), 7.31–7.33 (split peak, 1H, NH),

7.12–7.14 (split peak, 2H, *o,o′*-ArH of phenyl ring), 7.00 (d, 2H, *J* = 3.5 Hz, *m,m′*-ArH of phenyl ring), 6.81-6.87 (m, 2H, ArH of phenyl ring), 6.64 (d, 3H, *J* = 9.0 Hz, ArH of phenyl ring), 3.94–4.04 (m, 2H, OCH_2), 2.16 (s, 3H, CH_3), 1.30–1.35 (m, 3H, CH_3); HRMS (EI): *m/z* [M+] calcd. for $C_{20}H_{20}ClN_3O_2S$: 401.0965; found: 401.0964. ***N-(4-chlorophenyl)-6-methyl-2-oxo-4-(thiophen-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4o)*:** mp. 239-224 ºC; IR (KBr) ν_{max}: 3245, 3103, 1664, 1594, 1529, 1491, 1427, 1398, 1307, 1240, 1187, 1091, 1042, 1012 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, ppm), δ_H = 10.12 (s, 1H, CONH), 8.95 (s, 1H, NH), 7.95 (s, 1H, NH), 7.63–7.65 (split peak, 2H, *o,o′*-ArH of phenyl ring), 7.51–7.59 (split peak, 2H, *m,m′*-ArH of phenyl ring), 6.95–7.42 (m, 3H, ArH of thiophene ring), 5.73 (d, 1H, *J* = 3.0 Hz, CH), 2.08 (s, 3H, CH_3); HRMS (EI): *m/z* [M+] calcd. for $C_{16}H_{14}ClN_3O_2S$: 347.0495; found: 347.0494.

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