DOI: 10.1002/cjoc.201500862

A General, Efficient and Green Procedure for Synthesis of Dihydropyrimidine-5-carboxamides in Low Melting Betaine Hydrochloride/Urea Mixture

Peng Liu, Jianwu Hao, and Zhanhui Zhang*

College of Chemistry and Material Science, *Hebei Normal University*, *Shijiazhuang*, *Hebei 050024*, *China*

A simple, facile and convenient strategy has been developed for the synthesis of dihydropyrimidine-5-carboxamides in low melting mixture of betaine hydrochloride/urea. In this procedure, the low melting mixture of betaine hydrochloride/urea plays a triple role: as a catalyst, solvent and reactant. The present green protocol has advantages such as high yield of products, short reaction times, operational simplicity, no chromatographic separation, eco-friendliness, and applicability for large-scale synthesis.

Keywords low melting mixture, deep eutectic solvent, dihydropyrimidine-5-carboxamide, green chemistry

Introduction

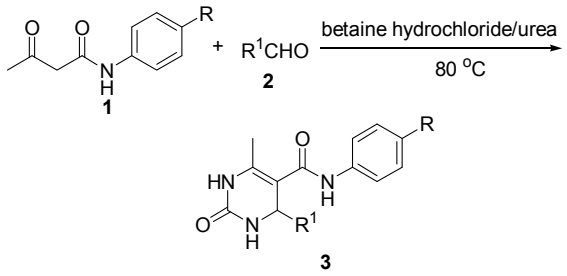
Dihydropyrimidine (DHPM)-5-carboxamides are one of the important class of *N*-heterocycles and have attracted significant attention due to their various biological and pharmacological activities such as antitubercular,[1] antihypertensive,[2] antiinflammatory,[3] anticancer,[4] antimicrobial,[5] anti-HIV-1[6] and antimycobacterial activities.[7] They also show activity specifically against dormant TB bacilli[8] and herpes simplex virus.[9] In addition, DHPM-5-carboxamide analogues have proven to be excellent templates for selective α1a receptor subtype antagonists to warrant further consideration for the treatment of benign prostatic hyperplasia (BPH).[10] In view of their biological importance, several synthetic methods have been developed.[11,12] The most simple and straightforward method for the synthesis of DHPM-5-carboxamides is a one-pot Biginelli condensation of 3-ketoamides, aldehydes and urea under strong acidic conditions.[1-4] Recently, replacement of strong acids by more efficient catalysts such as etidronic acid,[13] chloroacetic acid,[14,15] tangstophosphoric acid ($H_3PW_{12}O_{40}$),[16] uranyl nitrate hexahydrate [$UO_2(NO_3)_2$•$6H_2O$],[17] $ZrCl_4$,[18] and $Yb(OTf)_3$[19] has been developed. Although these catalytic systems are efficient for synthesis of DHPM-5-carboxamides, they possess several disadvantages such as the use of harmful and toxic organic solvents as well as unavailable and costly catalysts, high temperature, long reaction times, cumbersome work up procedures or low yields. Therefore, the further development of simple, efficient, eco-friendly and economically viable processes for the synthesis of DHPM-5-carboxamides is still a challenge in synthetic chemistry.

The replacement of conventional hazardous organic solvents by nontoxic and biodegradable and recyclable media for green synthesis of fine chemicals, particularly in the pharmaceutical industry has become an important research area.[20] In this regard, deep eutectic solvents (DESs) or low melting mixtures (LMMs), have emerged as new generation of solvents in organic transformations.[21,22] DESs do not only share most of advantages of conventional ionic liquids such as low vapor pressure, wide liquid range and tunable physicochemical properties, but also overcome some of their limitations. Compared with ILs, the synthetic process of these eutectic mixtures is relatively simple, which is only by mixing two or more compounds under heating until a homogeneous liquid is formed without any purification with 100% atom utilization rate. From the practical point of view, these solvents are very appealing, especially considering the use of inexpensive and bio-renewable natural compounds as starting materials. In addition, in some procedures, DES played a triple role of being catalyst, solvent and reagent.[23]

With our continuous interest in developing environmentally benign synthetic methodologies,[24] herein, we report a novel and effective protocol for synthesis of dihydropyrimidine-5-carboxamides through a one-pot condensation of *N*-acetoacetanilide with various aldehydes in betaine hydrochloride/urea (Scheme 1).

* E-mail: zhanhui@126.com; Tel.: 0086-0311-80787431
Received December 9, 2015; accepted February 16, 2016; published online March 23, 2016.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cjoc.201500862 or from the author.

Scheme 1 Synthesis of dihydropyrimidine-5-carboxamides in betaine hydrochloride/urea



Results and Discussion

A series of low melting mixtures were prepared by mixing one or two compounds with urea in an appropriate molar ratio. The mixture was heated slowly until forming a homogeneous colorless liquid. Then, it was cooled to room temperature and directly used without any further purification.

Subsequently, the reaction of acetoacetanilide (1 mmol) and benzaldehyde (1 mmol) was investigated in different low melting mixtures and the results are summarized in Table 1. In order to assess the role of low melting mixtures, the reaction was attempted in the absence of solvent but containing urea (1 mmol) at 80 ℃, and it was observed that only trace amount of product was detected (Table 1, Entry 1). The product **3a** could be obtained in 71% yield when the reaction was carried out in choline chloride (ChCl)/urea (Table 1, Entry 2). A noticeable improvement of the yield was observed when the reaction was conducted in low melting mixtures such as $ZnCl_2$/urea or tartaric acid/mannitol/urea. Further studies showed that the yield could be increased to as high as 92% when the reaction was performed in betaine hydrochloride/urea based on DES without the use of any promoter or additional urea (Table 1, Entry 13). In addition, screening indicated that the choice of temperature was also very crucial for the reaction. The yield of product **3a** decreased when the temperature was decreased to 70 ℃. However, no increase in the yield of product was observed when the reaction temperature was raised from 80 to 90 ℃. It is noteworthy that decreasing the amount of solvent resulted in a significant decrease in yield (Table 1, Entries 15—18). It may be because urea is also used as a reactant, with the reduction of the solvent, the amount of urea is also reduced. We found that 1.0 g betaine hydrochloride/urea was necessary in order to achieve the best result.

To illustrate the practical synthetic utility of this method, a 100 gram scale experiment was performed and product **3a** was obtained by recrystallization in 90% yield (Table 1, Entry 19). This satisfying result is very promising and encouraging from practical point of view.

Having established the optimum reaction conditions, we set out to survey the generality and scope of this reaction and the results were summarized in Table 2. In general, aromatic aldehydes containing electron-neutral, electron-rich or electron-poor groups reacted well with acetoacetanilide to afford the desired products in high yields. Halogen atoms such as fluorine, chloride, and bromine on the aromatic ring were unaffected under the present reaction conditions to provide the corresponding products in high yields, which could allow for further synthetic transformation. In addition, more bulky substrate such as 1-naphthaldehyde also reacted well to provide the desired product in high yield (Table 2, Entry 21). It should be noted that the acid-sensitive hetero aromatic aldehyde such as 2-thiophene-carbaldehyde

Table 1 Optimization of reaction conditions[a]

Entry	DES[b]	*t*/℃	Time/min	Yield[c]/%
1[d]	No	80	100	10
2	ChCl/urea (54∶46)	80	90	71
3	$ZnCl_2$/urea (39∶61)	80	60	80
4	Tartaric acid/mannitol/urea (30∶20∶50)	80	60	78
5	Fructose/urea (50∶50)	80	60	21
6	Fructose/urea /NaCl (50∶40∶10)	80	60	30
7	Glucose/urea/NH_4Cl (60∶30∶10)	80	60	41
8	Glucose/urea/$CaCl_2$ (50∶40∶10)	80	60	15
9	Citric acid/mannitol/urea (30∶20∶50)	80	60	83
10	Betaine hydrochloride/urea (39∶61)	50	60	49
11	Betaine hydrochloride/urea (39∶61)	60	60	76
12	Betaine hydrochloride/urea (39∶61)	70	60	82
13	Betaine hydrochloride/urea (39∶61)	80	20	92
14	Betaine hydrochloride/urea (39∶61)	90	20	92
15	Betaine hydrochloride/urea (39∶61) 0.25 g	80	20	44
16	Betaine hydrochloride/urea (39∶61) 0.50 g	80	20	53
17	Betaine hydrochloride/urea (39∶61) 0.75 g	80	20	79
18	Betaine hydrochloride/urea (39∶61) 1.50 g	80	20	93
19[e]	Betaine hydrochloride/urea (39∶61)	80	20	90

[a] Reaction condition: *N*-acetoacetanilide (1 mmol), benzaldehyde (1 mmol), solvent (1.0 g) unless otherwise specified in the Table. [b] The ratio is given in weight%. [c] Isolated yield. [d] Urea (1 mol) was added. [e] The reaction was carried out in 100 g scale.

CHINESE JOURNAL OF CHEMISTRY

Table 2 Synthesis of DHPM-5-carboxamide derivatives in betaine hydrochloride/urea[a]

Entry	Aldehyde	R	Product	Time/min	Yield[b]/%	m.p./℃	
						Found	Reported
1	PhCHO	H	**3a**	20	92	247－249	246－248[25]
2	2-MeO-C_6H_4CHO	H	**3b**	30	86	186－187	
3	3-MeO-C_6H_4CHO	H	**3c**	30	87	184－186	180－185[14]
4	4-MeO-C_6H_4CHO	H	**3d**	30	89	242－244	240－242[17]
3	3,4-$(MeO)_2$-C_6H_3CHO	H	**3e**	40	84	265－268	
6	3-OH-C_6H_4CHO	H	**3f**	25	85	262－263	
7	4-OH-C_6H_4CHO	H	**3g**	25	86	286－288	
8	3-OPh-C_6H_4CHO	H	**3h**	35	90	190－192	
9	4-Me-C_6H_4CHO	H	**3i**	25	90	254－256	
10	4-*t*-Bu-C_6H_4CHO	H	**3j**	30	88	278－279	
11	2-F-C_6H_4CHO	H	**3k**	18	90	227－230	
12	2-Cl-C_6H_4CHO	H	**3l**	20	89	225－228	226－228[25]
13	3-Cl-C_6H_4CHO	H	**3m**	20	90	221－222	
14	4-Cl-C_6H_4CHO	H	**3n**	20	92	245－247	244－246[25]
13	2-Br-C_6H_4CHO	H	**3o**	20	90	140－141	
16	3-Br-C_6H_4CHO	H	**3p**	20	92	118－120	
17	4-Br-C_6H_4CHO	H	**3q**	20	93	294－297	292－294[26]
18	3-NO_2-C_6H_4CHO	H	**3r**	15	92	260－263	262－264[25]
19	4-NO_2-C_6H_4CHO	H	**3s**	15	93	258－259	256－258[25]
20	4-CN-C_6H_4CHO	H	**3t**	15	93	268－271	
21	1-Naphthaldehyde	H	**3u**	25	84	164－166	
22	2-Thiophene-carbaldehyde	H	**3v**	20	85	174－176	174－178[14]
23	Terephthalaldehyde	H	**3w**	30	90	＞330	
24	CH_3CH_2CHO	H	**3x**	120	40	230－232	
25	PhCHO	Me	**3y**	15	92	263－264	
26	4-Me-C_6H_4CHO	Me	**3z**	20	91	256－258	
27	4-NO_2-C_6H_4CHO	Me	**3aa**	30	94	269－271	
28	1-Naphthaldehyde	Me	**3ab**	40	85	226－229	
29	2-Thiophene-carbaldehyde	Me	**3ac**	20	88	245－248	
30	Terephthalaldehyde	Me	**3ad**	20	90	＞330	
31	PhCHO	Cl	**3ae**	15	90	268－269	265－266[27]
32	4-Me-C_6H_4CHO	Cl	**3af**	20	87	249－251	
33	4-NO_2-C_6H_4CHO	Cl	**3ag**	30	91	297－298	294－295[1]
34	1-Naphthaldehyde	Cl	**3ah**	40	82	234－236	
35	2-Thiophene-carbaldehyde	Cl	**3ai**	20	86	221－223	220－222[5]
36	Terephthalaldehyde	Cl	**3aj**	20	89	310－312	

[a] Reaction condition: *N*-acetoacetanilide (1 mmol), aldehyde (1 mmol), betaine hydrochloride/urea (1.0 g). [b] Isolated yield.

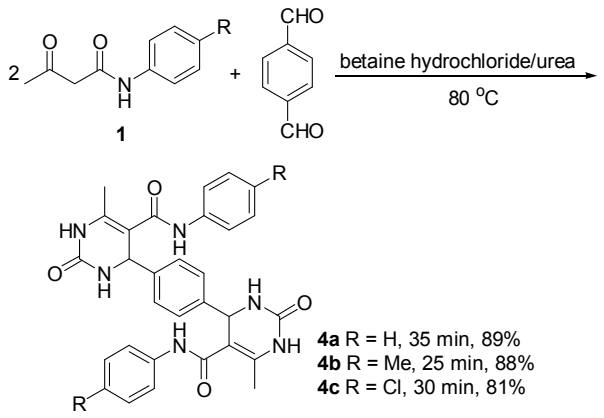
was subjected to the optimized conditions to give expected product in 85% yield (Table 2, Entry 22). However, the yield decreased if aliphatic aldehyde was used as a substrate (Table 2, Entry 24).

Similarly, a variety of *N*-acetoacetanilides containing both electron-rich and electron-poor groups on the phenyl ring were employed under the above conditions and the corresponding DHPM-5-carboxamides were obtained in high yields.

To further explore the generality of the current method, we carried out the reaction of *p*-phthalaldehyde with 2 equiv. of *N*-acetoacetanilide. As expected, the bis-DHPM-5-carboxamides (**4a**－**4c**) could be obtained in high yields under the identical conditions (Scheme 2).

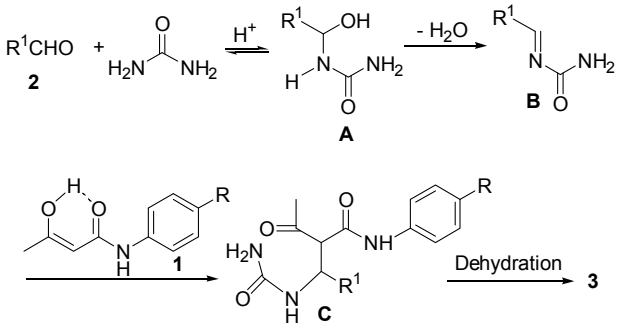
A possible mechanism for the Biginelli reaction of aldehydes, urea and *N*-acetoacetanilide is proposed in Scheme 3. The first step in this reaction involves the acid-catalyzed reaction of the aldehyde (**2**) with urea to form intermediate **A**, which then dehydrates to give acyl imine intermediate **B**. Subsequently, addition of enol

Scheme 2 Synthesis of bis-DHPM-5-carboxamides in betaine hydrochloride/urea



tautomer of *N*-acetoacetanilide (**1**) to the electron-deficient acyl imine intermediate **B** produces an open-chain ureide intermediate **C**, which subsequently cyclizes and dehydrates to obtain the DHPM-5-carboxamide (**3**). As can be seen from Scheme 3, a proton source is necessary for this process. The hydrogen ion not only helps the dehydration of intermediate **A** but also enolizes of *N*-acetoacetanilide to form enolate intermediate. In this procedure, the low melting mixture of betaine hydrochloride/urea plays the triple role of being a reactant, a catalyst, and a solvent.

Scheme 3 Proposed mechanism



Conclusions

In conclusion, we have successfully developed a new, highly efficient and environmentally-benign method for the synthesis of dihydropyrimidine-5-carboxamide derivatives in deep eutectic solvents. This method can be effectively scaled up and a broad spectrum of dihydropyrimidine-5-carboxamides can be rapidly obtained in high to excellent yields. This deep eutectic solvent serves simultaneously as a reactant, a solvent and a catalyst. Notably, mild experiment conditions, short reaction time, high yield and green solvent render this new procedure useful in organic synthesis and industry.

Experimental

All reagents were obtained from commercial suppliers and used without further purification. Melting points were determined on an X-4 apparatus and are uncorrected. IR spectra were obtained on a Thermo Scientific Nicolet 50 spectrometer using KBr disks. NMR spectra were recorded at room temperature on a Bruker DRX-500 spectrometer at 500 MHz (^{1}H), 125 MHz (^{13}C) using DMSO-d_6 as the solvent with TMS as internal standard. Mass spectra were operated at a 3200 Qtrap instrument with an ESI source. High-resolution mass spectra (HRMS) were measured on a Thermo Fisher Scientific LTQ FT Ultra mass spectrometer.

Preparation of betaine hydrochloride/urea

A mixture of betaine hydrochloride (100 mmol) and urea (400 mmol) was added to a round-bottomed flask. The mixture was stirred at 100 ℃ until a clear liquid appeared. It can be directly used without any further purification.

General procedure for synthesis of DHPM-5-carboxamides

N-Acetoacetanilide (1 mmol) and aldehyde (1 mmol) were added in betaine hydrochloride/urea. The mixture was heated with stirring at 80 ℃ for the appropriate time. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature. Then water was added to dissolve DES and the reaction mixture was extracted with ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The resulting crude product was recrystallized using EtOH to obtain the pure DHPM-5-carboxamide derivatives.

6-Methyl-2-oxo-*N*,4-diphenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3a) White solid. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.03 (s, 3H), 5.40 (d, J=2.5 Hz, 1H), 6.99 (t, J=7.5 Hz, 1H), 7.22−7.28 (m, 5H), 7.32 (t, J=7.5 Hz, 2H), 7.53 (d, J=8.5 Hz, 2H), 7.57 (s, 1H), 8.71 (s, 1H), 9.55 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 16.9, 54.9, 105.3, 119.5, 122.9, 126.1, 127.2, 128.3, 128.4, 138.2, 139.1, 144.2, 152.5, 165.2; IR (KBr) v: 3406, 3281, 3117, 1710, 1645, 1629, 1437, 1323, 1246 cm^{-1}; m/z: 308 (M+1)$^+$.

4-(2-Methoxyphenyl)-6-methyl-2-oxo-*N*-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3b) White solid. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.02 (s, 3H), 3.67 (s, 3H), 5.64 (s, 1H), 6.90−6.99 (m, 3H), 7.10 (s, 1H), 7.20−7.26 (m, 4H), 7.17 (d, J=8.0 Hz, 2H), 8.61 (s, 1H), 9.53 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 16.7, 49.4, 55.2, 104.8, 110.9, 119.2, 120.2, 122.7, 126.8, 128.3, 128.5, 131.3, 138.2, 139.3, 153.0, 156.0, 165.2; IR (KBr) v: 3427, 3302, 3101, 1701, 1675, 1631, 1437, 1332, 1244, 1024 cm^{-1}; m/z: 338 (M+1)$^+$.

4-(3-Methoxyphenyl)-6-methyl-2-oxo-*N*-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3c) White solid. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.04 (s, 3H), 3.68 (s, 3H), 5.39 (s, 1H), 6.80−6.87 (m, 3H), 7.00 (t, J=7.0 Hz, 1H), 7.24 (t, J=7.5 Hz, 3H), 7.56 (s,

3H), 8.73 (s, 1H), 9.57 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 16.9, 54.8, 105.2, 112.1, 112.2, 118.2, 119.5, 123.0, 128.4, 129.5, 138.3, 139.1, 145.7, 152.6, 159.2, 165.2; IR (KBr) v: 3394, 3281, 3109, 1712, 1648, 1629, 1437, 1319, 1244, 1037 cm^{-1}; m/z: 338 $(M+1)^+$.

4-(4-Methoxyphenyl)-6-methyl-2-oxo-*N*-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3d) White solid. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.03 (s, 3H), 3.70 (s, 3H), 5.35 (s, 1H), 6.87 (d, J=8.5 Hz, 2H), 6.98 (t, J=7.5 Hz, 1H), 7.18−7.25 (m, 4H), 7.50 (s, 1H), 7.54 (d, J=8.0 Hz, 2H), 8.67 (s, 1H), 9.50 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 16.9, 54.4, 54.9, 105.5, 113.7, 119.4, 122.9, 127.4, 128.4, 136.3, 138.1, 139.1, 152.4, 158.4, 165.2; IR (KBr) v: 3402, 3277, 3117, 1707, 1649, 1627, 1437, 1325, 1246, 1031 cm^{-1}; m/z: 338 $(M+1)^+$.

4-(3,4-Dimethoxyphenyl)-6-methyl-2-oxo-*N*-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3e) White solid. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.03 (s, 3H), 3.65 (s, 3H), 3.69 (s, 3H), 5.35 (s, 1H), 6.80 (d, J=7.0 Hz, 1H), 6.85−6.89 (m, 2H), 6.99 (t, J=7.5 Hz, 1H), 7.24 (t, J=7.5 Hz, 2H), 7.49 (s, 1H), 7.54 (d, J=8.0 Hz, 2H), 8.85 (s, 1H), 9.52 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 16.9, 54.6, 55.3, 55.4, 105.3, 110.3, 111.6, 118.0, 119.4, 122.9, 128.4, 136.6, 138.0, 139.1, 148.0, 148.5, 152.4, 165.3; IR (KBr) v: 3354, 3286, 3117, 1716, 1644, 1629, 1437, 1321, 1247, 1018 cm^{-1}; m/z: 368 $(M+1)^+$; HRMS calcd for $C_{20}H_{22}N_3O_4$ $(M+H)^+$: 368.1604; found 368.1606.

4-(3-Hydroxyphenyl)-6-methyl-2-oxo-*N*-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3f) White solid. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.01 (s, 3H), 5.32 (s, 1H), 6.61 (d, J=8.0 Hz, 1H), 6.67−6.70 (m, 2H), 6.99 (t, J=7.5 Hz, 1H), 7.08 (t, J=7.5 Hz, 1H), 7.24 (t, J=7.5 Hz, 2H), 7.51 (s, 1H), 7.55 (d, J=8.5 Hz, 2H), 8.66 (s, 1H), 9.37 (s, 1H), 9.52 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 16.9, 54.9, 105.5, 113.0, 114.1, 116.6, 119.5, 122.9, 128.3, 129.2, 138.0, 139.1, 145.8, 152.5, 157.3, 165.2; IR (KBr) v: 3371, 3263, 3064, 1707, 1645, 1595, 1437, 1319, 1251, 1155 cm^{-1}; m/z: 324 $(M+1)^+$; HRMS calcd for $C_{18}H_{18}N_3O_3$ $(M+H)^+$: 324.1342; found 324.1343.

4-(4-Hydroxyphenyl)-6-methyl-2-oxo-*N*-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3g) White solid. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.02 (s, 3H), 5.29 (s, 1H), 6.68 (d, J=8.0 Hz, 2H), 6.98 (t, J=7.5 Hz, 1H), 7.07 (d, J=8.0 Hz, 2H), 7.23 (t, J=8.0 Hz, 2H), 7.44 (s, 1H), 7.52 (d, J=8.0 Hz, 2H), 8.62 (s, 1H), 9.33 (s, 1H), 9.47 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 16.9, 54.5, 105.7, 115.0, 119.5, 122.9, 127.4, 128.4, 134.7, 137.8, 139.1, 152.4, 156.5, 165.3; IR (KBr) v: 3429, 3246, 3115, 1701, 1641, 1627, 1442, 1336, 1244, 1170 cm^{-1}; m/z: 324 $(M+1)^+$; HRMS calcd for $C_{18}H_{18}N_3O_3$ $(M+H)^+$: 324.1342; found 324.1344.

6-Methyl-2-oxo-4-(3-phenoxyphenyl)-*N*-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3h) White solid. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.02 (s, 3H), 5.39 (s, 1H), 6.84 (d, J=9.5 Hz, 1H), 6.93 (d, J=8.5 Hz, 2H), 7.01 (t, J=7.5 Hz, 1H), 7.06−7.10 (m, 2H), 7.23−7.29 (m, 4H), 7.34 (t, J=7.5 Hz, 1H), 7.52 (d, J=8.0 Hz, 2H), 7.60 (s, 1H), 8.73 (s, 1H), 9.56 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 16.9, 54.7, 105.1, 116.4, 117.2, 118.3, 119.6, 121.1, 123.0, 123.3, 128.4, 129.8, 130.0, 138.3, 139.0, 146.4, 152.4, 156.2, 156.4, 165.1; IR (KBr) v: 3446, 3290, 3101, 1718, 1655, 1627, 1437, 1327, 1244, 1072 cm^{-1}; m/z: 400 $(M+1)^+$; HRMS calcd for $C_{24}H_{22}N_3O_3$ $(M+H)^+$: 400.1655; found 400.1658.

6-Methyl-2-oxo-*N*-phenyl-4-(*p*-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3i) White solid. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.02 (s, 3H), 2.24 (s, 3H), 5.36 (d, J=2.5 Hz, 1H), 6.99 (t, J=7.5 Hz, 1H), 7.10−7.16 (m, 4H), 7.23 (t, J=7.5 Hz, 2H), 7.52−7.54 (m, 3H), 8.67 (s, 1H), 9.52 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 16.9, 20.5, 54.7, 105.4, 119.4, 122.9, 126.0, 128.3, 128.8, 136.3, 138.0, 139.1, 141.3, 152.4, 165.2; IR (KBr) v: 3402, 3275, 3117, 1707, 1643, 1626, 1437, 1327, 1244, 1101 cm^{-1}; m/z: 322 $(M+1)^+$; HRMS calcd for $C_{19}H_{20}N_3O_2$ $(M+H)^+$: 322.1550; found 322.1553.

4-(4-(*tert*-Butyl)phenyl)-6-methyl-2-oxo-*N*-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3j) White solid. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 1.23 (s, 9H), 2.04 (s, 3H), 5.38 (s, 1H), 6.88 (t, J=7.5 Hz, 1H), 7.19−7.26 (m, 4H), 7.34 (d, J=8.0 Hz, 2H), 7.53 (s, 1H), 7.56 (d, J=8.0 Hz, 2H), 8.69 (s, 1H), 9.56 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 16.9, 31.0, 34.1, 54.5, 105.5, 119.4, 122.9, 125.1, 125.7, 128.4, 138.3, 139.2, 141.3, 149.5, 152.6, 165.3; IR (KBr) v: 3389, 3273, 3124, 1691, 1647, 1624, 1545, 1442, 1249, 1072 cm^{-1}; m/z: 364 $(M+1)^+$; HRMS calcd for $C_{22}H_{26}N_3O_2$ $(M+H)^+$: 364.2019; found 364.2022.

4-(2-Fluorophenyl)-6-methyl-2-oxo-*N*-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3k) White solid. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.02 (s, 3H), 5.65 (s, 1H), 6.98 (t, J=7.0 Hz, 1H), 7.09−7.13 (m, 1H), 7.17 (t, J=7.5 Hz, 1H), 7.22 (t, J=8.0 Hz, 2H), 7.26−7.30 (m, 1H), 7.34 (t, J=7.5 Hz, 1H), 7.48−7.51 (m, 3H), 8.72 (s, 1H), 9.59 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 16.8, 49.7, 104.1, 115.4 (d, $^2J_{CF}$=21.3 Hz), 119.4, 123.0, 124.4, 128.4, 128.6 (d, $^4J_{CF}$=3.9 Hz), 129.3 (d, $^3J_{CF}$=8.1 Hz), 130.8 (d, $^3J_{CF}$=13.6 Hz), 138.4, 139.1, 152.4, 159.2 (d, $^1J_{CF}$=245 Hz), 164.9; IR (KBr) v: 3439, 3296, 3107, 1716, 1645, 1622, 1438, 1321, 1246, 1103 cm^{-1}; m/z: 326 $(M+1)^+$; HRMS calcd for $C_{18}H_{17}FN_3O_2$ $(M+H)^+$: 326.1299; found 326.1302.

4-(2-Chlorophenyl)-6-methyl-2-oxo-*N*-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3l) White solid. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.02 (s, 3H), 5.78 (d, J=2.0 Hz, 1H), 6.98 (t, J=7.5 Hz, 1H), 7.21−7.28 (m, 3H), 7.35 (t, J=7.5 Hz, 2H), 7.45−7.50 (m, 4H), 8.78 (s, 1H), 9.66 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 16.7, 52.6, 104.5, 119.3, 122.9, 127.5, 128.3, 129.0, 129.2, 129.3, 131.3, 138.2, 139.0, 141.0, 152.0, 164.8; IR (KBr) v: 3394, 3232, 3128, 2933,

1693, 1645, 1631, 1531, 1440, 1259, 1041 cm^{-1}; *m/z*: 342 $(M+1)^+$.

4-(3-Chlorophenyl)-6-methyl-2-oxo-*N*-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3m) White solid. ^1H NMR (DMSO-d_6, 500 MHz) δ: 2.04 (s, 3H), 5.38 (s, 1H), 7.00 (t, J=7.5 Hz, 1H), 7.22−7.37 (m, 6H), 7.52 (d, J=8.0 Hz, 2H), 7.61 (s, 1H), 8.76 (s, 1H), 9.57 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 17.0, 54.5, 104.7, 119.6, 123.1, 124.9, 126.1, 127.2, 128.4, 130.3, 133.0, 138.8, 139.0, 146.5, 152.3, 165.1; IR (KBr) *v*: 3410, 3279, 3122, 1712, 1645, 1627, 1438, 1321, 1244, 1103 cm^{-1}; *m/z*: 342 $(M+1)^+$; HRMS calcd for $C_{18}H_{17}ClN_3O_2$ $(M+H)^+$: 342.1003; found 342.1005.

4-(4-Chlorophenyl)-6-methyl-2-oxo-*N*-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3n) White solid. ^1H NMR (DMSO-d_6, 500 MHz) δ: 2.03 (s, 3H), 5.38 (d, J=2.5 Hz, 1H), 7.00 (t, J=7.0 Hz, 1H), 7.22−7.29 (m, 4H), 7.32 (d, J=8.5 Hz, 2H), 7.53 (d, J=8.0 Hz, 2H), 7.61 (s, 1H), 8.77 (s, 1H), 9.56 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 16.9, 54.4, 104.9, 119.5, 123.0, 128.0, 128.3, 128.4, 131.7, 138.6, 139.0, 143.1, 152.3, 165.1; IR (KBr) *v*: 3404, 3273, 3117, 1707, 1645, 1627, 1437, 1321, 1244, 1101 cm^{-1}; *m/z*: 342 $(M+1)^+$.

4-(2-Bromophenyl)-6-methyl-2-oxo-*N*-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3o) White solid. ^1H NMR (DMSO-d_6, 500 MHz) δ: 2.03 (s, 3H), 5.76 (s, 1H), 6.98 (t, J=7.0 Hz, 1H), 7.16−7.23 (m, 3H), 7.39 (t, J=7.5 Hz, 1H), 7.47−7.52 (m, 5H), 8.78 (s, 1H), 9.66 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 16.7, 55.2, 104.9, 119.3, 121.7, 123.0, 128.2, 128.4, 129.4, 129.5, 132.6, 138.0, 139.0, 142.6, 152.0, 164.8; IR (KBr) *v*: 3406, 3246, 3119, 1697, 1665, 1597, 1438, 1323, 1238, 1024 cm^{-1}; *m/z*: 386 $(M+1)^+$; HRMS calcd for $C_{18}H_{17}BrN_3O_2$ $(M+H)^+$: 386.0498; found 386.0501.

4-(3-Bromophenyl)-6-methyl-2-oxo-*N*-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3p) White solid. ^1H NMR (DMSO-d_6, 500 MHz) δ: 2.06 (s, 3H), 5.39 (s, 1H), 7.00 (t, J=7.5 Hz, 1H), 7.23−7.31 (m, 4H), 7.42−7.48 (m, 2H), 7.51−7.56 (m, 3H), 8.71 (s, 1H), 9.52 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 17.0, 54.6, 104.8, 119.6, 121.7, 123.1, 125.3, 128.4, 129.0, 130.1, 130.7, 131.6, 139.0, 146.8, 152.0, 165.1; IR (KBr) *v*: 3446, 3275, 3012, 1716, 1645, 1624, 1437, 1323, 1244, 1047 cm^{-1}; *m/z*: 386 $(M+1)^+$; HRMS calcd for $C_{18}H_{17}BrN_3O_2$ $(M+H)^+$: 386.0498; found 386.0500.

4-(4-Bromophenyl)-6-methyl-2-oxo-*N*-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3q) White solid. ^1H NMR (DMSO-d_6, 500 MHz) δ: 2.03 (s, 3H), 5.37 (d, J=2.5 Hz, 1H), 7.00 (t, J=7.0 Hz, 1H), 7.21−7.25 (m, 4H), 7.52−7.54 (m, 4H), 7.61 (s, 1H), 8.77 (d, J=1.5 Hz, 1H), 9.56 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 16.9, 54.4, 104.8, 119.5, 120.2, 123.0, 128.4, 131.2, 138.5, 139.0, 143.5, 152.3, 165.0; IR (KBr) *v*: 3404, 3271, 3117, 1707, 1653, 1627, 1438, 1321, 1246, 1101 cm^{-1}; *m/z*: 387 $(M+1)^+$.

6-Methyl-4-(3-nitrophenyl)-2-oxo-*N*-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3r) White solid. ^1H NMR (DMSO-d_6, 500 MHz) δ: 2.07 (s, 3H), 5.51 (d, J=2.5 Hz, 1H), 7.01 (t, J=7.5 Hz, 1H), 7.25 (t, J=7.5 Hz, 1H), 7.51 (d, J=8.0 Hz, 2H), 7.65 (t, J=8.0 Hz, 1H), 7.73 (d, J=7.5 Hz, 1H), 7.76 (s, 1H), 8.12−8.15 (m, 2H), 8.90 (s, 1H), 9.62 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 17.6, 55.0, 105.0, 120.2, 121.5, 122.9, 123.7, 129.0, 130.6, 133.6, 139.5, 140.0, 146.9, 148.3, 152.8, 165.5; IR (KBr) *v*: 3409, 3272, 2974, 1710, 1671, 1627,1534, 1346, 1247 cm^{-1}; *m/z*: 353 $(M+1)^+$.

6-Methyl-4-(4-nitrophenyl)-2-oxo-*N*-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3s) White solid. ^1H NMR (DMSO-d_6, 500 MHz) δ: 2.07 (s, 3H), 5.51 (d, J=2.5 Hz, 1H), 7.02 (t, J=7.5 Hz, 1H), 7.26 (t, J=8.0 Hz, 1H), 7.53−7.55 (m, 4H), 7.76 (s, 1H), 8.23 (d, J=9.0 Hz, 1H), 8.89 (s, 1H), 9.63 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 17.6, 55.2, 104.9, 120.2, 123.7, 124.3, 128.0, 129.0, 139.5, 139.8, 147.2, 152.0, 152.8, 165.5; IR (KBr) *v*: 3375, 3267, 3104, 2930, 1723, 1666, 1622, 1517, 1346, 1239 cm^{-1}; *m/z*: 353 $(M+1)^+$.

6-Methyl-4-(4-cyanophenyl)-2-oxo-*N*-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3t) White solid. ^1H NMR (DMSO-d_6, 500 MHz) δ: 2.06 (s, 3H), 5.46 (d, J=2.5 Hz, 1H), 7.01 (t, J=7.5 Hz, 1H), 7.26 (t, J=8.0 Hz, 2H), 7.46 (d, J=8.5 Hz, 2H), 7.54 (t, J=8.0 Hz, 2H), 7.72 (s, 1H), 7.83 (d, J=8.5 Hz, 2H), 8.87 (s, 1H), 9.63 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 17.6, 55.3, 105.0, 110.6, 120.1, 123.7, 127.8, 129.0, 130.0, 139.5, 139.8, 150.0, 153.0, 160.1, 165.6; IR (KBr) *v*: 3308, 3279, 2927, 1707, 1663, 1622, 1429, 1326, 1242, 1150 cm^{-1}; *m/z*: 333 $(M+1)^+$; HRMS calcd for $C_{19}H_{17}N_4O_2$ $(M+H)^+$: 333.1346; found 333.1347.

6-Methyl-4-(naphthalen-1-yl)-2-oxo-*N*-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3u) Yellow solid. ^1H NMR (DMSO-d_6, 500 MHz) δ: 2.11 (s, 3H), 6.25 (d, J=2.5 Hz, 1H), 6.95 (t, J=7.5 Hz, 1H), 7.18 (t, J=8.0 Hz, 2H), 7.45 (d, J=8.0 Hz, 2H), 7.50−7.53 (m, 3H), 7.58 (d, J=8.0 Hz, 2H), 7.84 (d, J=8.5 Hz, 1H), 7.92 (d, J=5.0 Hz, 1H), 8.31 (d, J=5.0 Hz, 1H), 8.81 (s, 1H), 9.61 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 17.5, 52.1, 106.0, 120.0, 123.5, 124.1, 125.6, 126.1, 126.5, 128.5, 128.9, 129.0, 130.6, 134.0, 138.8, 139.5, 140.1, 152.9, 165.7; IR (KBr) *v*: 3404, 3248, 2972, 1707, 1667, 1628, 1442, 1318, 1246, 1047 cm^{-1}; *m/z*: 358 $(M+1)^+$; HRMS calcd for $C_{22}H_{20}N_3O_2$ $(M+H)^+$: 358.1550; found 358.1553.

6-Methyl-4-(thiophen-2-yl)-2-oxo-*N*-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3v) White solid. ^1H NMR (DMSO-d_6, 500 MHz) δ: 2.07 (s, 3H), 5.68 (d, J=3.0 Hz, 1H), 6.93−6.95 (m, 2H), 7.02 (t, J=7.5 Hz, 1H), 7.27 (t, J=8.0 Hz, 2H), 7.38 (dd, J=1.5, 5.0 Hz, 1H), 7.58 (t, J=7.5 Hz, 2H), 7.79 (s, 1H), 8.85 (s, 1H), 9.56 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 17.6, 51.1, 105.8, 120.2, 123.6, 124.0, 125.4, 127.2, 129.0, 139.7, 140.0, 149.2, 152.9, 165.4; IR (KBr) *v*: 3405, 3277, 3115, 1715, 1645, 1627, 1518, 1322, 1248, 1079 cm^{-1}; *m/z*: 314 $(M+1)^+$.

4-(4-Formylphenyl)-6-methyl-2-oxo-*N*-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3w) White solid. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.03 (s, 3H), 5.36 (s, 1H), 5.65 (s, 1H), 7.00 (t, J=7.5 Hz, 1H), 7.22−7.25 (m, 5H), 7.30 (s, 1H), 7.53 (d, J=8.0 Hz, 3H), 8.69 (s, 1H), 9.53 (d, J=4.5 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 17.5, 55.0, 109.1, 117.6, 120.1, 123.5, 126.2, 126.8, 129.0, 139.7, 143.8, 153.1, 161.6, 165.8, 191.7; IR (KBr) v: 3405, 3280, 3110, 1712, 1666, 1624, 1525, 1441, 1245, 1094 cm^{-1}; m/z: 336 (M+1)$^+$; HRMS calcd for $C_{19}H_{18}N_3O_3$ (M + H)$^+$: 336.1342; found 336.1343.

4-Ethyl-6-methyl-2-oxo-*N*-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3x) White solid. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 0.85 (s, 3H), 1.44−1.49 (m, 2H), 1.96 (s, 3H), 4.22 (s, 1H), 7.02−7.07 (m, 2H), 7.28 (t, J=7.5 Hz, 2H), 7.61 (d, J=7.5 Hz, 2H), 8.43 (s, 1H), 9.57 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 8.78, 17.3, 30.1, 53.2, 105.7, 120.2, 123.6, 129.0, 138.4, 139.8, 153.7, 166.4; IR (KBr) v: 3472, 3216, 2921, 1705, 1676, 1632, 1593, 1438, 1249, 1073 cm^{-1}; m/z: 260 (M+1)$^+$; HRMS calcd for $C_{14}H_{18}N_3O_2$ (M+H)$^+$: 260.1393; found 260.1394.

6-Methyl-2-oxo-4-phenyl-*N*-(*p*-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3y) White solid. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.04 (s, 3H), 5.39 (d, J=2.0 Hz, 1H), 7.04 (d, J=8.5 Hz, 2H), 7.21−7.23 (m, 1H), 7.28−7.32 (m, 4H), 7.39 (d, J=8.5 Hz, 3H), 8.52 (s, 1H), 9.32 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 16.8, 20.2, 55.0, 105.4, 119.5, 126.1, 127.1, 128.2, 128.6, 131.8, 136.5, 137.8, 144.1, 152.4, 165.0; IR (KBr) v: 3405, 3277, 3115, 1710, 1645, 1627, 1518, 1320, 1246, 1099 cm^{-1}; m/z: 322 (M+1)$^+$; HRMS calcd for $C_{19}H_{20}N_3O_2$ (M+H)$^+$: 322.1550; found 322.1553.

6-Methyl-2-oxo-*N*,4-di-*p*-tolyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3z) White solid. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.03 (s, 3H), 2.23 (s, 3H), 2.26 (s, 3H), 5.36 (d, J=2.0 Hz, 1H), 7.05 (d, J=8.5 Hz, 2H), 7.12 (d, J=8.0 Hz, 2H), 7.16 (d, J=8.0 Hz, 2H), 7.43 (d, J=8.5 Hz, 2H), 7.48 (s, 1H), 8.82 (s, 1H), 9.41 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 17.5, 20.9, 21.1, 55.3, 106.1, 120.1, 126.7, 129.3, 129.4, 132.4, 136.9, 137.2, 138.4, 141.9, 153.1, 165.6; IR (KBr) v: 3402, 3279, 3115, 1719, 1672, 1626, 1519, 1326, 1245, 1101 cm^{-1}; m/z: 336 (M+1)$^+$; HRMS calcd for $C_{20}H_{22}N_3O_2$ (M+H)$^+$: 336.1706; found 336.1708.

6-Methyl-4-(4-nitrophenyl)-2-oxo-*N*-(*p*-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3aa) Pale yellow solid. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.05 (s, 3H), 2.23 (s, 3H), 5.51 (d, J=2.5 Hz, 1H), 7.06 (d, J=8.5 Hz, 2H), 7.42 (d, J=8.5 Hz, 2H), 7.53 (d, J=9.0 Hz, 2H), 7.74 (s, 1H), 8.23 (d, J=9.0 Hz, 2H), 8.86 (s, 1H), 9.54 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 17.6, 20.9, 55.2, 105.0, 120.2, 124.3, 128.0, 129.4, 132.6, 137.0, 139.6, 147.2, 152.8, 165.3; IR (KBr): v 3409, 3257, 3125, 1715, 1688, 1622, 1516, 1347, 1240, 1107 cm^{-1}; m/z: 367 (M+1)$^+$; HRMS calcd for $C_{19}H_{19}N_4O_4$ (M+H)$^+$: 367.1400; found 367.1401.

6-Methyl-4-(naphthalen-1-yl)-2-oxo-*N*-(*p*-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3ab) Pale yellow solid. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.10 (s, 3H), 2.19 (s, 3H), 6.23 (d, J=1.5 Hz, 1H), 6.99 (d, J=8.0 Hz, 2H), 7.32 (d, J=8.5 Hz, 2H), 7.50−7.53 (m, 4H), 7.57 (d, J=6.5 Hz, 1H), 7.84 (d, J=8.0 Hz, 1H), 7.92 (t, J=5.0 Hz, 1H), 8.31 (t, J=5.0 Hz, 1H), 8.74 (s, 1H), 9.50 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 17.4, 20.8, 52.1, 106.1, 120.0, 124.1, 125.5, 126.0, 126.1, 128.4, 129.3, 130.6, 132.4, 134.0, 137.0, 138.4, 140.1, 152.9, 165.5; IR (KBr) v: 3405, 3283, 3119, 1706, 1655, 1633, 1518, 1349, 1244, 1109 cm^{-1}; m/z: 372 (M+1)$^+$; HRMS calcd for $C_{23}H_{22}N_3O_2$ (M+H)$^+$: 372.1707; found 372.1708.

6-Methyl-2-oxo-4-(thiophen-2-yl)-*N*-(*p*-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3ac) Pale yellow solid. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.06 (s, 3H), 2.24 (s, 3H), 5.67 (d, J=3.0 Hz, 1H), 6.93−6.95 (m, 2H), 7.07 (d, J=8.5 Hz, 2H), 7.38 (dd, J=1.0, 4.5 Hz, 1H), 7.46 (d, J=8.5 Hz, 2H), 7.76 (s, 1H), 8.80 (s, 1H), 9.45 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 17.6, 20.9, 51.1, 105.9, 120.3, 124.0, 125.4, 127.1, 129.3, 132.5, 137.2, 149.2, 152.9, 165.2; IR (KBr) v: 3429, 3250, 3111, 1708, 1645, 1628, 1519, 1332, 1248, 1089 cm^{-1}; m/z: 328 (M + 1)$^+$; HRMS calcd for $C_{17}H_{18}N_3O_2S$ (M+H)$^+$: 328.1114; found 328.1116.

4-(4-Formylphenyl)-6-methyl-2-oxo-*N*-(*p*-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3ad) Pale yellow solid. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.23 (s, 3H), 2.51 (s, 3H), 5.36 (s, 1H), 7.04 (d, J=8.5 Hz, 4H), 7.23 (s, 2H), 7.41 (d, J=8.5 Hz, 3H), 7.50 (s, 1H), 8.63 (s, 1H), 9.42 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 17.5, 20.9, 55.1, 105.9, 106.0, 120.2, 126.7, 126.8, 129.3, 130.4, 132.4, 137.1, 138.7, 143.8, 143.9, 153.2, 165.6, 193.1; IR (KBr) v: 3399, 3265, 3112, 1705, 1665, 1626, 1518, 1327, 1243, 1090 cm^{-1}; m/z: 350 (M + 1)$^+$; HRMS calcd for $C_{20}H_{20}N_3O_3$ (M + H)$^+$: 350.1499; found 350.1501.

***N*-(4-Chlorophenyl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3ae)** White solid. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.05 (s, 3H), 5.40 (s, 1H), 7.21−7.24 (m, 1H), 7.26−7.31 (m, 6H), 7.42 (s, 1H), 7.55 (d, J=8.0 Hz, 2H), 8.57 (s, 1H), 9.54 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 16.9, 66.8, 105.0, 120.9, 126.0, 126.4, 127.1, 128.2, 128.3, 138.0, 138.8, 144.1, 152.4, 165.2; IR (KBr) v: 3446, 3273, 3117, 1712, 1645, 1629, 1458, 1396, 1244, 1089 cm^{-1}; m/z: 342 (M+1)$^+$.

***N*-(4-Chlorophenyl)-6-methyl-2-oxo-4-(*p*-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3af)** White solid. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.01 (s, 3H), 2.23 (s, 3H), 5.34 (d, J=2.0 Hz, 1H), 7.09−7.13 (m, 4H), 7.27 (d, J=9.0 Hz, 2H), 7.52 (s, 1H), 7.55 (d, J=9.0 Hz, 2H), 8.69 (s, 1H), 9.62 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 17.5, 21.1, 55.2, 105.7, 121.5, 126.6, 127.1, 128.8, 129.4, 136.9, 138.7, 139.3, 141.8, 153.0, 165.9; IR (KBr) v: 3406, 3285, 3125, 1759, 1675, 1628, 1539, 1346, 1246, 1109 cm^{-1}; m/z: 356 (M+1)$^+$;

HRMS calcd for $C_{19}H_{19}ClN_3O_2$ $(M+H)^+$: 356.1161; found 356.1163.

***N*-(4-Chlorophenyl)-6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3ag)** Pale yellow solid. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.07 (s, 3H), 5.51 (d, J=2.5 Hz, 1H), 7.31 (d, J=8.5 Hz, 2H), 7.54 (d, J=8.5 Hz, 2H), 7.58 (d, J=9.0 Hz, 2H), 7.78 (s, 1H), 8.23 (d, J=9.0 Hz, 2H), 8.93 (s, 1H), 9.75 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 17.6, 55.1, 104.6, 121.7, 124.3, 127.3, 128.0, 128.9, 138.5, 140.4, 147.3, 151.9, 152.8, 165.6; IR (KBr) v: 3369, 3246, 3110, 1715, 1669, 1625, 1519, 1347, 1239, 1087 cm^{-1}; m/z: 388 $(M+1)^+$.

***N*-(4-Chlorophenyl)-6-methyl-4-(naphthalen-1-yl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3ah)** Pale yellow solid. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.07 (s, 3H), 6.21 (d, J=2.0 Hz, 1H), 7.22 (d, J=9.0 Hz, 2H), 7.45−7.50 (m, 5H), 7.53 (d, J=6.5 Hz, 1H), 7.57 (s, 1H), 7.82 (d, J=8.0 Hz, 1H), 7.89 (t, J=5.0 Hz, 1H), 8.26 (t, J=5.0 Hz, 1H), 8.81 (s, 1H), 9.72 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 17.5, 49.1, 105.7, 121.4, 124.1, 125.5, 126.1, 126.5, 127.1, 128.5, 128.8, 129.0, 130.6, 134.0, 138.5, 139.2, 140.0, 152.9, 165.8; IR (KBr) v: 3400, 3281, 3130, 1707, 1672, 1635, 1503, 1327, 1243, 1089 cm^{-1}; m/z: 392 $(M+1)^+$; HRMS calcd for $C_{22}H_{19}ClN_3O_2$ $(M+H)^+$: 392.1160; found 392.1158.

***N*-(4-Chlorophenyl)-6-methyl-2-oxo-4-(thiophen-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3ai)** Pale yellow solid. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.04 (s, 3H), 5.65 (d, J=3.0 Hz, 1H), 6.89−6.92 (m, 2H), 7.30 (d, J=8.5 Hz, 2H), 7.36 (dd, J=1.0, J=5.0 Hz, 1H), 7.59 (d, J=9.0 Hz, 2H), 7.79 (s, 1H), 8.86 (s, 1H), 9.65 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 17.6, 51.0, 105.6, 121.7, 124.0, 125.4, 127.1, 127.2, 128.9, 138.7, 140.6, 149.2, 152.8, 165.4; IR (KBr) v: 3421, 3283, 3104, 1719, 1654, 1628, 1514, 1247, 1089 cm^{-1}; m/z: 349 $(M+1)^+$.

***N*-(4-Chlorophenyl)-4-(4-formylphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3aj)** Pale yellow solid. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.03 (s, 3H), 5.36 (d, J=2.0 Hz, 1H), 7.21 (s, 2H), 7.27−7.32 (m, 3H), 7.48 (d, J=8.0 Hz, 1H), 7.55 (s, 1H), 7.57 (s, 2H), 7.79 (d, J=8.0 Hz, 1H), 8.73 (s, 1H), 9.66 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 17.6, 55.5, 104.9, 121.6, 126.8, 127.1, 127.2, 127.4, 128.8, 128.9, 130.4, 135.9, 138.5, 138.6, 140.0, 143.8, 151.1, 152.9, 153.0, 165.8, 193.1; IR (KBr) v: 3420, 3269, 2924, 1715, 1627, 1515, 1397, 1240, 1087 cm^{-1}; m/z: 371 $(M+1)^+$.

4,4'-(1,4-Phenylene)bis(6-methyl-2-oxo-*N*-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide) (4a) White solid. m.p. 296−298 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.03 (s, 6H), 5.37 (s, 2H), 7.00 (t, J=7.5 Hz, 2H), 7.23 (s, 8H), 7.53 (d, J=8.5 Hz, 6H), 8.69 (s, 2H), 9.53 (d, J=4.0 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 17.5, 55.0, 55.2, 105.8, 105.9, 120.1, 123.5, 126.7, 126.8, 129.0, 138.9, 139.0, 139.7, 143.8, 143.9, 153.0, 153.1, 165.6, 165.8; IR (KBr) v: 3401, 3273, 3111, 1710, 1670, 1629, 1525, 1440, 1335, 1245, 1049 cm^{-1}; m/z: 537 $(M+1)^+$; HRMS calcd for $C_{30}H_{29}N_6O_4$ $(M+H)^+$: 537.2244; found 537.2248.

4,4'-(1,4-Phenylene)bis(6-methyl-2-oxo-*N*-(*p*-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide) (4b) Pale yellow solid. m.p. >330 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.02 (s, 6H), 2.23 (s, 6H), 5.36 (s, 2H), 7.03 (d, J=8.5 Hz, 4H), 7.23 (s, 4H), 7.41 (d, J=8.5 Hz, 4H), 7.51 (s, 2H), 8.65 (s, 2H), 9.44 (s, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 17.5, 20.9, 55.1, 120.2, 126.7, 126.8, 129.3, 137.2, 138.8, 143.8, 153.1, 165.6; IR (KBr) v: 3450, 3261, 3110, 1705, 1675, 1626, 1519, 1331, 1243, 1090 cm^{-1}; m/z: 565 $(M+1)^+$; HRMS calcd for $C_{32}H_{33}N_6O_4$ $(M+H)^+$: 565.2557; found 565.2559.

4,4'-(1,4-Phenylene)bis(*N*-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide) (4c) Pale yellow solid. m.p. 271−273 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.00 (s, 6H), 5.33 (s, 2H), 7.19 (s, 4H), 7.25 (t, J=7.0 Hz, 4H), 7.49−7.54 (m, 6H), 8.67 (s, 2H), 9.61 (d, J=3.5 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 17.5, 55.0, 55.1, 105.5, 105.6, 121.6, 126.7, 128.9, 138.6, 139.6, 143.8, 143.9, 153.1, 160.1, 165.8; IR (KBr) v: 3454, 3205, 3105, 1710, 1647, 1606, 1552, 1493, 1241, 1109 cm^{-1}; m/z: 605 $(M+1)^+$; HRMS calcd for $C_{30}H_{27}Cl_2N_6O_4$ $(M+H)^+$: 605.1465; found 605.1468.

Acknowledgement

This research was supported by generous grants from the National Natural Science Foundation of China (No. 21272053) and the Natural Science Foundation of Hebei Province (No. B2015205182).

References

[1] Virsodia, V.; Pissurlenkar, R. R. S.; Manvar, D.; Dholakia, C.; Adlakha, P.; Shah, A.; Coutinho, E. C. *Eur. J. Med. Chem.* **2008**, *43*, 2103.
[2] Alam, O.; Khan, S. A.; Siddiqui, N.; Ahsan, W.; Verma, S. P.; Gilani, S. J. *Eur. J. Med. Chem.* **2010**, *45*, 5113.
[3] Sawant, R. L.; Bansode, C. A.; Wadekar, J. B. *Med. Chem. Res.* **2013**, *22*, 1884.
[4] Desai, N. C.; Chhabaria, M. T.; Dodiya, A.; Bhavsar, A. M.; Baldaniya, B. B. *Med. Chem. Res.* **2011**, *20*, 1331.
[5] Sedaghati, B.; Fassihi, A.; Arbabi, S.; Ranjbar, M.; Memarian, H. R.; Saghaie, L.; Omidi, A.; Sardari, A.; Jalali, M.; Abedi, D. *Med. Chem. Res.* **2012**, *21*, 3973.
[6] Zabihollahi, R.; Fassihi, A.; Aghasadeghi, M. R.; Memarian, H. R.; Soleimani, M.; Majidzadeh, K. *Med. Chem. Res.* **2013**, *22*, 1270.
[7] Zalavadiya, P.; Tala, S.; Akbari, J.; Joshi, H. *Arch. Pharm.* **2009**, *342*, 469.
[8] Joshi, R. R.; Barchha, A.; Khedkar, V. M.; Pissurlenkar, R. R. S.; Sarkar, S.; Sarkar, D.; Joshi, R. R.; Joshi, R. A.; Shah, A. K.; Coutinho, E. C. *Chem. Biol. Drug Des.* **2015**, *85*, 201.
[9] Zabihollahi, R.; Fassihi, A.; Aghasadeghi, M. R.; Memarian, H. R.; Soleimani, M.; Majidzadeh, K. *Med. Chem. Res.* **2013**, *22*, 1270.
[10] Barrow, J. C.; Nantermet, P. G.; Selnick, H. G.; Glass, K. L.; Rittle,

K. E.; Gilbert, K. F.; Steele, T. G.; Homnick, C. F.; Freidinger, R. M.; Ransom, R. W.; Kling, P.; Reiss, D.; Broten, T. P.; Schorn, T. W.; Chang, R. S. L.; O'Malley, S. S.; Olah, T. V.; Ellis, J. D.; Barrish, A.; Kassahun, K.; Leppert, P.; Nagarathnam, D.; Forray, C. *J. Med. Chem.* **2000**, *43*, 2703.

[11] Memarian, H. R.; Soleymani, M. *Ultrason. Sonochem.* **2011**, *18*, 745.

[12] Desai, B.; Dallinger, D.; Kappe, C. O. *Tetrahedron* **2006**, *62*, 4651.

[13] Pansuriya, A. M.; Savant, M. M.; Bhuva, C. V.; Singh, J.; Naliapara, Y. T. *Arkivoc* **2009**, (vii), 79.

[14] Couto, I.; Tellitu, I.; Dominguez, E. *Arkivoc* **2011**, (ii), 115.

[15] Couto, I.; Tellitu, I.; Dominguez, E. *J. Org. Chem.* **2010**, *75*, 7954.

[16] Amini, M. M.; Shaabani, A.; Bazgir, A. *Catal. Commun.* **2006**, *7*, 843.

[17] Venkatesan, K.; Satyanarayana, V. S. V.; Sivakumar, A. *J. Chin. Chem. Soc.* **2014**, *61*, 624.

[18] Soleymani, M.; Memarian, H. R. *Z. Naturforsch.* **2010**, *65*, 485.

[19] Stadler, A.; Kappe, C. O. *J. Comb. Chem.* **2001**, *3*, 624.

[20] Gu, Y. L.; Jerome, F. *Chem. Soc. Rev.* **2013**, *42*, 9550.

[21] (a) Zhang, Q. H.; De Oliveira Vigier, K.; Royer, S.; Jérôme, F. *Chem. Soc. Rev.* **2012**, *41*, 7108; (b) Smith, E. L.; Abbott, A. P.; Ryder, K. S. *Chem. Rev.* **2014**, *114*, 11060; (c) Paiva, A.; Craveiro, R.; Aroso, I.; Martins, M.; Reis, R. L.; Duarte, A. R. C. *ACS Sustainable Chem. Eng.* **2014**, *2*, 1063; (d) Russ, C.; König, B. *Green Chem.* **2012**, *14*, 2969; (e) García-Álvarez, J. *Eur. J. Inorg. Chem.* **2015**, 5147; (f) Liu, P.; Hao, J. W.; Mo, L. P.; Zhang, Z. H. *RSC Adv.* **2015**, *5*, 48675; (g) Francisco, M.; van den Bruinhorst, A.; Kroon, M. C. *Angew. Chem., Int. Ed.* **2013**, *52*, 3074; (h) Wang, A.; Zheng, X.; Zhao, Z.; Li, C.; Zheng, X. *Prog. Chem.* **2014**, *26*, 784.

[22] (a) Zhang, Z. H.; Zhang, X. N.; Mo, L. P.; Li, Y. X.; Ma, F. P. *Green Chem.* **2012**, *14*, 1502; (b) Ma, F. P.; Cheng, G. T.; He, Z. G.; Zhang, Z. H. *Aust. J. Chem.* **2012**, *65*, 409; (c) Wang, P.; Ma, F. P.; Zhang, Z. H. *J. Mol. Liq.* **2014**, *198*, 259; (d) Li, P. H.; Ma, F. P.; Wang, P.; Zhang, Z. H. *Chin. J. Chem.* **2013**, *31*, 757; (e) Hu, H. C.; Liu, Y. H.; Li, B. L.; Cui, Z. S.; Zhang, Z. H. *RSC Adv.* **2015**, *5*, 7720; (f) Lu, J.; Li, X. T.; Ma, E. Q.; Mo, L. P.; Zhang, Z. H. *ChemCatChem* **2014**, *6*, 2854; (g) Yan, N.; Xiong, Y. K.; Xia, J. H.; Rui, P. X.; Lei, Z. W.; Liao, W. L.; Xiong, B. *Chin. J. Org. Chem.* **2015**, *35*, 384; (h) Tang, B. K.; Row, K. H. *Monatsh. Chem.* **2013**, *144*, 1427; (i) Jérôme, F.; Ferreira, M.; Bricout, H.; Menuel, S.; Monflier, E.; Tilloy, S. *Green Chem.* **2014**, *16*, 3876; (j) De Oliveira Vigier, K.; Chatel, G.; Jérôme, F. *ChemCatChem* **2015**, *7*, 1250; (k) Ferreira, M.; Jérôme, F.; Bricout, H.; Menuel, S.; Landy, D.; Fourmentin, S.; Tilloy, S.; Monflier, E. *Catal. Commun.* **2015**, *63*, 62; (l) van Osch, D. J. G. P.; Zubeir, L. F.; van den Bruinhorst, A.; Rocha, M. A. A.; Kroon, M. C. *Green Chem.* **2015**, *17*, 4518; (m) Kow, K. K.; Sirat, K. *Chin. Chem. Lett.* **2015**, *26*, 1311; (n) Zhang, L. X.; Yu, H.; Yu, H. B.; Chen, Z.; Yang, L. *Chin. Chem. Lett.* **2014**, *25*, 1132.

[23] (a) Gore, S.; Baskaran, S.; König, B. *Green Chem.* **2011**, *13*, 1009; (b) Gore, S.; Baskaran, S.; Koenig, B. *Adv. Synth. Catal.* **2012**, *354*, 2368; (c) Mahajan, H.; Bhardwaj, M.; Paul, S. *Org. Prep. Proced. Int.* **2014**, *46*, 463; (d) Azizi, N.; Alipour, M. *J. Mol. Liq.* **2015**, *206*, 268; (e) Gore, S.; Chinthapally, K.; Baskaran, S.; König, B. *Chem. Commun.* **2013**, *49*, 5052.

[24] (a) Deng, J.; Mo, L. P.; Zhao, F. Y.; Hou, L. L.; Yang, L.; Zhang, Z. H. *Green Chem.* **2011**, *13*, 2576; (b) Liu, Y. H.; Deng, J.; Gao, J. W.; Zhang, Z. H. *Adv. Synth. Catal.* **2012**, *354*, 441; (c) Guo, R. Y.; Wang, P.; Wang, G. D.; Mo, L. P.; Zhang, Z. H. *Tetrahedron* **2013**, *69*, 2056; (d) Ma, F. P.; Li, P. H.; Li, B. L.; Mo, L. P.; Liu, N.; Kang, H. J.; Liu, Y. N.; Zhang, Z. H. *Appl. Catal. A*: *Gen.* **2013**, *457*, 34; (e) Li, P. H.; Li, B. L.; An, Z. M.; Mo, L. P.; Cui, Z. S.; Zhang, Z. H. *Adv. Synth. Catal.* **2013**, *355*, 2952; (f) Li, B. L.; Zhang, M.; Hu, H. C.; Du, X.; Zhang, Z. H. *New J. Chem.* **2014**, *38*, 2435; (g) Zhao, X. N.; Hu, H. C.; Zhang, F. J.; Zhang, Z. H. *Appl. Catal. A*: *Gen.* **2014**, *482*, 258; (h) Li, P. H.; Li, B. L.; Hu, H. C.; Zhao, X. N.; Zhang, Z. H. *Catal. Commun.* **2014**, *46*, 118; (i) Lu, J.; Ma, E. Q.; Liu, Y. H.; Li, Y. M.; Mo, L. P.; Zhang, Z. H. *RSC Adv.* **2015**, *5*, 59167.

[25] Gein, V. L.; Zamaraeva, T. M.; Kurbatova, A. A.; Vakhrin, M. I. *Chem. Heterocycl. Compd.* **2010**, *46*, 856.

[26] Duburs, G.; Khanina, E. L. *Khim. Geterotsikl. Soedin.* **1976**, *2*, 220.

[27] Baldev, A. D.; Vyas, K. B.; Patel, K. B.; Nimavat, K. S. *J. Chem. Pharm. Res.* **2012**, *4*, 2972.

(Pan, B.; Qin, X.)

