Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-one-5-carboxamides

Mousa Soleymani and Hamid Reza Memarian

Catalysis Division, Department of Chemistry, Faculty of Science, University of Isfahan, Isfahan 81746-73441, Iran

Reprint requests to Prof. Hamid R. Memarian. Fax: +98-311-6689732.
E-mail: memarian@sci.ui.ac.ir

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The synthesis of various dihydropyrimidinone derivatives bearing carbamoyl moieties in 5-position under reflux conditions and microwave irradiation is described. An efficient three-component Biginelli reaction using catalytic amounts of zirconium(IV) chloride as an efficient catalyst leads to the formation of these compounds.

Key words: Biginelli Reaction, 3,4-Dihydropyrimidine-5-carboxamides, Microwave, $ZrCl_4$, Zirconium Salts

Introduction

Dihydropyrimidinones (DHPMs) are important molecules owing to their biological activities as calcium channel blockers [1, 2], anti-hypertensive [3], antiviral [4], anti-tumor [5], anti-inflammatory agents [6], and as neuropeptide Y antagonists [7]. Under this wide range of pharmacological and biological aspects, the synthesis of these compounds is currently under investigation. The first synthesis of DHPMs reported by Biginelli in 1893 involved a three-component one-pot condensation of an aldehyde, a β-ketoester and urea [8, 9]. The reaction was carried out by refluxing a mixture of these components in ethanol solution in the presence of a catalytic amount of HCl. Several improved procedures for the synthesis of DHPMs have since been reported which were recently reviewed [10, 11]. The major part of the reported protocols involves synthesis of DHPMs possessing ester or acetyl groups in 5-position [11], while syntheses of DHPMs with a C5-amide functionality have been less frequently reported. Although in a few studies various simple acetoacetamides have been used in place of alkyl acetoacetate or β-diketones to produce 3,4-dihydropyrimidine-5-carboxamides [12 – 21], the synthesis of these compounds containing various aryl carboxamide groups continues to be of interest.

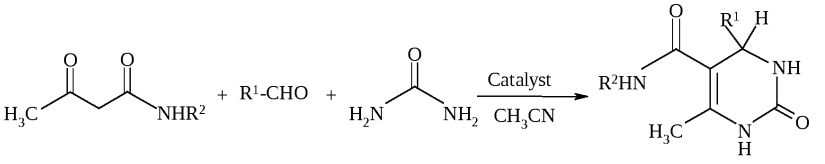
Zirconium tetrachloride ($ZrCl_4$) is an inexpensive, non-toxic (LD_{50}: 1688 mg/kg) and commercially available zirconium salt [22]. Its application as a Lewis acid catalyst or as a reagent in various organic transformations has been reported [23 – 27]. Recently, $ZrCl_4$ has also been used for the synthesis of various 5-alkoxycarbonyl-3,4-dihydropyrimidinones under reflux conditions and microwave irradiation [28, 29]. In continuation of our study of 3,4-dihydropyrimidinones, we have tried the synthesis of these compounds containing carbamoyl moieties in 5-position using various catalysts.

Results and Discussion

Solvent effects and optimization of the reactants

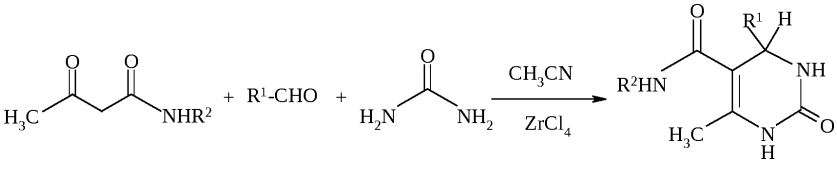
Since the nature of the solvent and also the type of the catalyst influence the yield of the product, the synthesis of 6-methyl-2(1*H*)-oxo-4-phenyl-3,4-dihydropyrimidine-5-(2′-chlorophenyl)carboxamide (**5**) as a model substrate was performed in the presence of 7.5 mol-% (relative to used aldehyde) of various catalysts such as zirconium(IV) chloride, zirconium(IV) acetylacetonate, zirconyl chloride, bismuth nitrate and phosphotungstic acid in dry acetonitrile (Scheme 1). According to the data presented in Table 1, the best yield was obtained by using $ZrCl_4$ as catalyst.

In continuation of this work the synthesis of 6-methyl-2-(1*H*)-oxo-4-(2-chlorophenyl)-3,4-dihydropyrimidine-5-(2′-chlorophenyl)carboxamide (**9**) was carried out in acetonitrile, ethanol and methanol under reflux conditions. The results presented in Table 2 indicate that the best yield was obtained in acetonitrile.



5: R^1 = Phenyl, R^2 = 2-Chlorophenyl
9: R^1 = R^2 = 2-Chlorophenyl

Scheme 1.



Scheme 2.

Table 1. Dependence of the yield[a] of **5** on the applied catalyst.

Catalyst[b]	Yield (%)[c]
Zirconium(IV) chloride	48
Zirconium(IV) acetylacetonate	38
Zirconium oxychloride	40
Bismuth nitrate	34
Phosphotungstic acid	27

[a] Under reflux condition for 12 h; [b] 7.5 mol-% (relative to used aldehyde); [c] isolated yield.

Table 2. Solvent effect on the yield of **9** under reflux conditions[a].

Solvent	Time (h)	Yield (%)[b]
MeCN	12	76
EtOH	12	61
MeOH	12	55

[a] In the presence of 10.75 mol-% (relative to used aldehyde) of $ZrCl_4$; [b] isolated yield.

In the next step, the amount of the catalyst ($ZrCl_4$) was optimized for the synthesis of compound **9**. According to the data presented in Table 3 the best yield was obtained by using 8.6 mol-% (relative to used aldehyde) of $ZrCl_4$.

The results presented in Table 1 show that among the zirconium salts considered in this study $ZrCl_4$ is the most active catalyst for this conversion. The increased activity of $ZrCl_4$ over other zirconium salts may be due to a structural difference of this compound. Zirconium(IV) chloride adopts a polymeric structure, in which each Zr is octahedrally coordinated [30]. In zirconium(IV) acetylacetonate, Zr^{4+} is surrounded by four acetylacetonate anions. These structural differences of zirconium salts make Zr^{4+} in $ZrCl_4$ a better Lewis acid.

Under optimized reaction conditions, a mixture of an aldehyde (2 mmol), a β-ketoamide (2 mmol) and urea (3 mmol) in the presence of catalytic amounts of zirconium(IV) chloride (0.172 mmol; 8.6 mol-% relative to used aldehyde) was either refluxed in dry acetonitrile (10 mL) or irradiated with microwaves until

Table 3. Optimization of the amount of catalyst for the synthesis of **9** under reflux conditions; solvent: acetonitrile.

$ZrCl_4$ (mol-%)[a]	Time (h)	Yield (%)[b]
2.15	12	51
4.3	12	61
6.45	12	67
8.6	12	76
10.75	12	76

[a] Relative to used aldehyde; [b] isolated yield.

Table 4. Synthesis of 3,4-dihydropyrimidine-5-carboxamides **1** – **20** under reflux conditions or microwave irradiation[a].

			Yield (%)[b]	
Product	R^1	R^2	Δ[c]	MW[d]
1	C_6H_5	C_6H_5	51 (12)	45
2	C_6H_5	$C_6H_5CH_2$	50 (10)	49
3	C_6H_5	*c*-C_6H_{11}	47 (10)	45
4	C_6H_5	*p*-FC_6H_4	47 (10)	47
5	C_6H_5	*o*-ClC_6H_4	51 (10)	50
6	C_6H_5	*p*-ClC_6H_4	48 (10)	46
7	C_6H_5	*p*-BrC_6H_4	46 (10)	44
8	C_6H_5	*p*-$MeOC_6H_4$	66 (10)	54
9	*o*-ClC_6H_4	*o*-ClC_6H_4	76 (8)	75
10	*m*-ClC_6H_4	*o*-ClC_6H_4	71 (12)	65
11	*p*-ClC_6H_4	*o*-ClC_6H_4	74 (8)	70
12	*o*-BrC_6H_4	*o*-ClC_6H_4	80 (6)	73
13	*m*-BrC_6H_4	*o*-ClC_6H_4	79 (6)	72
14	*p*-BrC_6H_4	*o*-ClC_6H_4	80 (6)	76
15	*m*-$NO_2C_6H_4$	*o*-ClC_6H_4	74 (6)	76
16	*p*-$NO_2C_6H_4$	*o*-ClC_6H_4	85 (6)	80
17	*m*-$MeOC_6H_4$	*o*-ClC_6H_4	54 (8)	52
18	*p*-$MeOC_6H_4$	*o*-ClC_6H_4	43 (12)	38
19	*p*-MeC_6H_4	*o*-ClC_6H_4	64 (8)	59
20	$MeCHC_6H_5$	*o*-ClC_6H_4	41 (12)	35

[a] In the presence of 8.6 mol-% (relative to used aldehyde) of $ZrCl_4$; [b] isolated yield; [c] yield (reaction time in h); [d] 10 minutes of irradiation.

Table 5. Structurally relevant ^{1}H NMR chemical shifts (δ values) and CO stretching bands (cm^{-1}) in the IR spectra.

Comp.	R^1	R^2	6-CH_3	1-NH	3-NH	4-CH	NHR^2	CO
1[a]	C_6H_5	C_6H_5	2.04	6.99	8.69	5.40	9.54	1685, 1710
2[b]	C_6H_5	$C_6H_5CH_2$	2.02	7.49	8.10	5.30	8.56	1680, 1710
3	C_6H_5	*c*-C_6H_{11}	1.94	7.39	7.42	5.26	8.48	1670, 1715
4	C_6H_5	*p*-FC_6H_4	2.03	7.61	8.75	5.40	9.64	1670, 1710
5	C_6H_5	*o*-ClC_6H_4	2.16	7.62	8.79	5.36	9.00	1680, 1700
6	C_6H_5	*p*-ClC_6H_4	2.04	7.63	8.79	5.41	9.73	1670, 1705
7	C_6H_5	*p*-BrC_6H_4	2.03	7.63	8.78	5.40	9.69	1675, 1705
8	C_6H_5	*p*-$MeOC_6H_4$	2.04	7.56	8.68	5.40	9.43	1675, 1710
9	*o*-ClC_6H_4	*o*-ClC_6H_4	2.17	7.52	8.89	5.77	9.10	1650, 1705
10	*m*-ClC_6H_4	*o*-ClC_6H_4	2.16	7.70	8.88	5.38	9.18	1645, 1710
11	*p*-ClC_6H_4	*o*-ClC_6H_4	2.16	7.69	8.87	5.38	9.12	1660, 1700
12	*o*-BrC_6H_4	*o*-ClC_6H_4	2.17	7.58	8.90	5.73	9.10	1650, 1705
13	*m*-BrC_6H_4	*o*-ClC_6H_4	2.17	7.73	8.91	5.40	9.19	1655, 1710
14	*p*-BrC_6H_4	*o*-ClC_6H_4	2.15	7.67	8.86	5.35	9.13	1675, 1705
15	*m*-$NO_2C_6H_4$	*o*-ClC_6H_4	2.18	8.18	8.98	5.53	9.28	1660, 1720
16	*p*-$NO_2C_6H_4$	*o*-ClC_6H_4	2.17	8.26	8.96	5.51	9.26	1655, 1705
17	*m*-$MeOC_6H_4$	*o*-ClC_6H_4	2.17	7.67	8.86	5.36	9.04	1650, 1675
18	*p*-$MeOC_6H_4$	*o*-ClC_6H_4	2.15	7.57	8.79	5.30	8.93	1665, 1690
19	*p*-MeC_6H_4	*o*-ClC_6H_4	2.15	7.60	8.80	5.32	8.98	1670, 1700
20	$MeCHC_6H_5$	*o*-ClC_6H_4	2.02	7.49	8.42	4.46	9.10	1670, 1700

[a] The ^{1}H-NMR data were taken from ref. [18]; [b] the ^{1}H-NMR data were taken from ref. [31].

maximum progression of the reactions (Scheme 2). It should be noted that on prolonged refluxing of the reaction mixtures (for compounds except **1**, **10**, **18** and **20**) up to 12 h, the yields of the products did not increase. The results are presented in Table 4.

The results presented in Table 4 indicate that the yield of products depends most on the nature of the aryl group in the aldehyde compounds and not on the nature of the aryl group in the β-ketoamide compounds. On the other hand, by application of microwave irradiation no significant changes in the yields of the products are observed, but as expected the time of reaction is drastically reduced from 6 – 12 h to 10 min.

The products were characterized by their IR, ^{1}H NMR, ^{13}C NMR, MS, and UV data. IR spectra show the characteristic bands for both CO groups. In the ^{1}H NMR spectra singlets appear for three different NH, a singlet for 6-CH_3 and a broad singlet for 4-H. These data are shown in Table 5. The other spectroscopic data are given in the Experimental Section.

Conclusion

In conclusion, we used $ZrCl_4$ as an efficient catalyst for the synthesis of some 3,4-dihydropyrimidine-5-carboxamides. The yields of products depend most on the nature of the aryl or alkyl group of the aldehyde compounds and not on the nature of the aryl or alkyl group in the β-ketoamide compounds.

Experimental Section

Melting points were determined on a Stuart Scientific SMP2 apparatus and are uncorrected. IR spectra were recorded using KBr discs on a Shimadzu IR-435 instrument. ^{1}H NMR spectra were obtained with a Bruker 300 MHz instrument. ^{13}C NMR spectra were recorded with a Bruker 75.48 MHz spectrometer. Mass spectra were obtained on a Platform II Mass Spectrometer from Micromass; EI mode at 70 eV. UV spectra (in ethanol) were taken with a Shimadzu UV-160 spectrometer. Elemental analyses data have been obtained with a Leco 932 CHNS-analyzer. β-Ketoamides used in this work were prepared either by adoption of the reported procedure [32] (reaction of the appropriate amine with methyl acetoacetate in the presence of catalytic amounts of sodium hydroxide in dry toluene at reflux temperature) or by adoption of the reported procedure [33] (reaction of amines with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one in dry toluene at reflux temperature).

General procedure for the synthesis of DHPMs under reflux conditions

A mixture of aldehyde (2.0 mmol), β-ketoamide (2.0 mmol), urea (3.0 mmol), and zirconium(IV) chloride (0.172 mmol; 8.6 mol-% relative to used aldehyde) in dry acetonitrile (10 mL) was refluxed for the times given in Table 4. The mixture was cooled to r. t., the solvent was evaporated under reduced pressure, and then the remaining mixture was filtered. The precipitate was washed with water to remove excess urea and the catalyst, dried, and purified either by recrystallization from ethanol or by chromatography.

General procedure for synthesis of DHPMs under microwave irradiation

A mixture of aldehyde (2.0 mmol), β-ketoamide (2.0 mmol), urea (3.0 mmol), and zirconium(IV) chloride (0.172 mmol; 8.6 mol-% relative to used aldehyde) in dry acetonitrile (2 mL) was irradiated with microwaves (Microwave oven from National and irradiation power at 900 W) for 10 min (one minute relaxation after each one minute irradiation to avoid splashing of solvent; 10 min total irradiation time). The remaining mixture was filtered, washed with water to remove excess urea and the catalyst, dried, and purified either by recrystallization from ethanol or by chromatography.

*6-Methyl-2-(1H)-oxo-4-phenyl-3,4-dihydropyrimidine-5-phenylcarboxamide (**1**)*

Two times recrystallized. M. p.: 243 – 245 °C (lit: 245 – 247 °C) [18]. – IR: ν = 3250 (N-H), 1710 (CONH), 1685 (CO), 1630 cm^{-1}. – ^{13}C NMR (75.48 MHz, [D_6]DMSO): δ = 17.73, 55.42, 104.54, 126.84, 126.99, 127.21, 127.73, 127.91, 128.18, 128.95, 129.81, 135.66, 140.86, 144.41, 152.91, 165.69. – MS (EI, 70 eV): *m/z* (%) = 256 (2), 240 (3), 213 (3), 212 (3), 119 (3), 105 (6), 104 (2), 93 (5), 92 (3), 77 (6). – UV (EtOH): $\lambda_{max}(\log \varepsilon_{max})$ = 282.5 (4.01), 205.5 nm (4.31).

*6-Methyl-2-(1H)-oxo-4-phenyl-3,4-dihydropyrimidine-5-benzylcarboxamide (**2**)*

Two times recrystallized. M. p.: 207 – 209 °C (lit. 210 – 212 °C) [31]. – IR: ν = 3250 (N-H), 1710 (CONH), 1680 (CO), 1615 cm^{-1}. – MS (EI, 70 eV): *m/z* (%) = 187 (4), 107 (5), 106 (9), 105 (12), 104 (26), 91 (100), 77 (95). – UV (EtOH): $\lambda_{max}(\log \varepsilon_{max})$ = 272.5 (3.69), 206.5 nm (4.32).

*6-Methyl-2-(1H)-oxo-4-phenyl-3,4-dihydropyrimidine-5-cyclohexylcarboxamide (**3**)*

Two times recrystallized. M. p.: 171 – 173 °C. – IR: ν = 3300 (N-H), 2910 (C-H str.), 1715 (CONH), 1670 (CO), 1610 cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): δ = 1.03 – 1.20 (m, 5H, cyclohexyl H), 1.50 – 1.59 (m, 5H, cyclohexyl H), 1.94 (s, 3H, CH_3), 3.48 (m, 1H, cyclohexyl C*H*-N), 5.26 (br s, 1H, pyrimidine-4H), 7.20 – 7.33 (m, 5H, C_6H_5), 7.39 (s, 1H, 1-NH), 7.42 (s, 1H, 3-NH), 8.48 (s, 1H, *H*NC_6H_{11}). – ^{13}C NMR (75.48 MHz, [D_6]DMSO): δ = 17.19, 25.20, 25.67, 32.69, 32.80, 48.06, 55.49, 106.01, 126.65, 127.55, 128.70, 136.57, 144.84, 153.30, 165.80. – MS (EI, 70 eV): *m/z* (%) = 313 (4), 187 (8), 126 (4), 105 (10), 104 (6), 99 (12), 98 (2), 83 (26), 77 (100). – UV (EtOH): $\lambda_{max}(\log \varepsilon_{max})$ = 269.5 (3.88), 206.0 nm (4.31). – $C_{18}H_{23}N_3O_2$ (313.4): calcd. C 68.98, H 7.40, N 13.41; found C 68.45, H 7.26, N 12.97.

*6-Methyl-2-(1H)-oxo-4-phenyl-3,4-dihydropyrimidine-5-(4′-fluorophenyl)carboxamide (**4**)*

Two times recrystallized. M. p.: 254 – 256 °C. – IR: ν = 3230 (N-H), 1710 (CONH), 1670 (CO), 1625 cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): δ = 2.03 (s, 3H, CH_3), 5.40 (br s, 1H, pyrimidine-4H), 7.05 – 7.58 (several multiplets, 9H, aromatic H), 7.61 (s, 1H, 1-NH), 8.75 (s, 1H, 3-NH), 9.64 (s, 1H, HNAr). – ^{13}C NMR (75.48 MHz, [D_6]DMSO): δ = 17.50, 55.44, 105.68, 115.37, 115.66, 121.70, 121.80, 126.67, 127.79, 128.95, 136.07, 139.01, 144.76, 153.07, 165.69. – MS (EI, 70 eV): *m/z* (%) = 215 (4), 187 (11), 138 (9), 137 (10), 111 (33), 110 (60), 105 (10), 104 (14), 95 (15), 77 (96), 76 (18). – UV (EtOH): $\lambda_{max}(\log \varepsilon_{max})$ = 282.0 (4.12), 205.0 nm (4.38).

*6-Methyl-2-(1H)-oxo-4-phenyl-3,4-dihydropyrimidine-5-(2′-chlorophenyl)carboxamide (**5**)*

Column chromatography (ethyl acetate). M. p.: 205 – 207 °C. – IR: ν = 3200, 3090 (N-H), 1700 (CONH), 1680 (CO), 1625 cm^{-1}. – ^1H NMR (300 MHz, [D6]DMSO): δ = 2.16 (s, 3H, CH_3), 5.36 (br s, 1H, pyrimidine-4H), 7.13 – 7.48 (several multiplets, 9H, aromatic H), 7.62 (s, 1H, 1-NH), 8.79 (s, 1H, 3-NH), 9.00 (s, 1H, HNAr). – ^{13}C NMR (75.48 MHz, [D6]DMSO): δ = 17.73, 55.42, 104.54, 126.84, 126.99, 127.21, 127.73, 127.91, 128.18, 128.94, 129.81, 135.66, 140.86, 144.41, 152.90, 165.69. – MS (EI, 70 eV): *m/z* (%) = 343 (3), 341 (9), 306 (12), 215 (100), 214 (28), 187 (13), 155 (3), 154 (2), 153 (5), 129 (25), 128 (12), 127 (57), 126 (5), 105 (9), 104 (18), 77 (42), 76 (6). – UV (EtOH): $\lambda_{max}(\log \varepsilon_{max})$ = 288.0 (4.26), 210.0 nm (4.56). – $C_{18}H_{16}ClN_3O_2$ (341.8): calcd. C 63.25, H 4.72, N 12.29; found C 62.78, H 4.74, N 12.10.

*6-Methyl-2-(1H)-oxo-4-phenyl-3,4-dihydropyrimidine-5-(4′-chlorophenyl)carboxamide (**6**)*

Preparative layer chromatography (ethyl acetate). M. p.: 265 – 266 °C. – IR: ν = 3230 (N-H), 1705 (CONH), 1670 (CO), 1625 cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): δ = 2.04 (s, 3H, CH_3), 5.41 (br s, 1H, pyrimidine-4H), 7.23 – 7.55 (several multiplets, 9H, aromatic H), 7.63 (s, 1H, 1-NH), 8.79 (s, 1H, 3-NH), 9.73 (s, 1H, HNAr). – ^{13}C NMR (75.48 MHz, [D_6]DMSO): δ = 17.54, 55.38, 105.57, 115.06, 121.89, 126.66, 127.80, 128.95, 131.76, 139.09, 139.53, 144.74, 153.02, 165.86. – MS (EI, 70 eV): *m/z* (%) = 215 (18), 187 (9), 155 (3), 154 (4), 153 (6), 129 (15), 128 (23), 127 (32), 126 (33), 113 (4), 111 (15), 105 (14), 104 (18), 77 (100), 76 (19). – UV (EtOH): $\lambda_{max}(\log \varepsilon_{max})$ = 279.0 (4.32), 206.0 nm (4.40). – $C_{18}H_{16}ClN_3O_2$ (341.8): calcd. C 63.25, H 4.72, N 12.29; found C 63.11, H 4.75, N 12.11.

*6-Methyl-2-(1H)-oxo-4-phenyl-3,4-dihydropyrimidine-5-(4′-bromophenyl)carboxamide (**7**)*

Two times recrystallized. M. p.: 269 – 270 °C. – IR: ν = 3240 (N-H), 1705 (CONH), 1675 (CO), 1625 cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): δ = 2.03 (s, 3H, CH_3), 5.40 (br s, 1H, pyrimidine-4H), 7.22 – 7.54 (several multiplets, 9H, aromatic H), 7.63 (s, 1H, 1-NH), 8.78 (s, 1H, 3-NH), 9.69 (s, 1H, HNAr). – ^{13}C NMR (75.48 MHz, [D_6]DMSO): δ = 17.54, 55.40, 105.59, 115.09, 121.88, 126.64, 127.80, 128.95, 131.77, 139.07, 139.51, 144.73, 153.01, 165.85. – MS (EI, 70 eV): *m/z* (%) = 215 (10), 199 (7), 197 (4), 187 (5), 173 (10), 172 (16), 171 (9), 170 (9), 105 (11), 104 (21), 77 (89), 76 (30). – UV (EtOH): $\lambda_{max}(\log \varepsilon_{max})$ = 286.0 (4.16), 206.0 nm (4.37). – $C_{18}H_{16}BrN_3O_2$ (386.2): calcd. C 55.97, H 4.18, N 10.88; found C 55.95, H 4.52, N 10.53.

*6-Methyl-2-(1H)-oxo-4-phenyl-3,4-dihydropyrimidine-5-(4′-methoxyphenyl)carboxamide (**8**)*

Preparative layer chromatography (ethyl acetate). M. p.: 241 – 243 °C. – IR: ν = 3250 (N-H), 1710 (CONH), 1675 (CO), 1625 cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): δ = 2.04 (s, 3H, CH_3), 3.69 (s, 3H, OCH_3), 5.40 (br s, 1H, pyrimidine-4H), 6.81 – 7.46 (several multiplets, 9H, aromatic H), 7.56 (s, 1H, 1-NH), 8.68 (s, 1H, 3-NH), 9.43 (s, 1H, HNAr). – ^{13}C NMR (75.48 MHz, [D_6]DMSO): δ = 17.46, 55.54, 55.59, 106.00, 114.10, 121.64, 126.70, 127.75, 128.91, 132.79, 138.30, 144.79, 153.16, 155.63, 165.38. – MS (EI, 70 eV): *m/z* (%) = 337 (3), 215 (4), 149 (10), 123 (32), 122 (77), 105 (18), 77 (100), 76 (34). – UV (EtOH): $\lambda_{max}(\log \varepsilon_{max})$ = 284.4 (4.34), 212.4 nm (4.13). – $C_{19}H_{19}N_3O_3$ (337.4): calcd. C 67.64, H 5.68, N 12.46; found C 67.14, H 5.66, N 12.04.

*6-Methyl-2-(1H)-oxo-4-(2-chlorophenyl)-3,4-dihydropyrimidine-5-(2′-chlorophenyl)carboxamide (**9**)*

One recrystallization. M. p.: 245 – 247 °C. – IR: ν = 3205, 3095 (N-H), 1705 (CONH), 1650 (CO), 1590 cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): δ = 2.17 (s, 3H, CH_3), 5.77 (br s, 1H, pyrimidine-4H), 7.11 – 7.50 (several multiplets, 8H, aromatic H), 7.52 (s, 1H, 1-NH), 8.89 (s, 1H, 3-NH), 9.10 (s, 1H, HNAr). – ^{13}C NMR (75.48 MHz, [D_6]DMSO): δ = 17.63, 53.24, 103.76, 126.82, 126.91, 127.73, 127.97, 128.11, 129.75, 129.82, 129.90, 129.98, 132.33, 135.54, 140.47, 141.00, 152.50, 165.48. – MS (EI, 70 eV): *m/z* (%) = 377 (2), 375 (4), 340 (10), 249 (78), 222 (2), 221 (13), 156 (5), 155 (6), 154 (7), 153 (9), 141 (10), 140 (22), 139 (25), 138 (33), 129 (32), 128 (27), 127 (100), 126 (26), 113 (16), 111 (49), 76 (24). – UV (EtOH): $\lambda_{max}(\log \varepsilon_{max})$ = 289.0 (3.84), 206.0 nm (4.33). – $C_{18}H_{15}Cl_2N_3O_2$ (376.2): calcd. C 57.46, H 4.02, N 11.17; found C 57.22, H 3.99, N 11.17.

*6-Methyl-2-(1H)-oxo-4-(3-chlorophenyl)-3,4-dihydropyrimidine-5-(2′-chlorophenyl)carboxamide (**10**)*

One recrystallization. M. p.: 188 – 190 °C. – IR: ν = 3400, 3300 (N-H), 1710 (CONH), 1645 (CO), 1600 cm^{-1}. –^1H NMR (300 MHz, [D_6]DMSO): δ = 2.16 (s, 3H, CH_3), 5.38 (br s, 1H, pyrimidine-4H), 7.15 – 7.45 (several multiplets, 8H, aromatic H), 7.70 (s, 1H, 1-NH), 8.88 (s, 1H, 3-NH), 9.18 (s, 1H, HNAr). – ^{13}C NMR (75.48 MHz, [D_6]DMSO): δ = 17.80, 54.98, 104.08, 125.64, 126.93, 127.10, 127.64, 127.75, 127.83, 128.69, 129.87, 130.92, 133.54, 135.60, 141.15, 146.88, 152.80, 165.60. – MS (EI, 70 eV): *m/z* (%) = 377 (4), 221 (3), 156 (12), 155 (9), 154 (9), 153 (5), 140 (12), 138 (7), 129 (5), 128 (4), 127 (18), 126 (11), 113 (11), 111 (28), 76 (52). – UV (EtOH): $\lambda_{max}(\log \varepsilon_{max})$ = 285.5 (3.80), 206.5 nm (4.22). – $C_{18}H_{15}Cl_2N_3O_2$ (376.2): calcd. C 57.46, H 4.02, N 11.17; found C 57.53, H 4.20, N 11.18.

*6-Methyl-2-(1H)-oxo-4-(4-chlorophenyl)-3,4-dihydropyrimidine-5-(2′-chlorophenyl)carboxamide (**11**)*

One recrystallization. M. p.: 245 – 247 °C. – IR: ν = 3210 (N-H), 1700 (CONH), 1660 (CO), 1620 cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): δ = 2.16 (s, 3H, CH_3), 5.38 (br s, 1H, pyrimidine-4H), 7.16 – 7.41 (several multiplets, 8H, aromatic H), 7.69 (s, 1H, 1-NH), 8.87 (s, 1H, 3-NH), 9.12 (s, 1H, HNAr). – ^{13}C NMR (75.48 MHz, [D_6]DMSO): δ = 17.76, 54.86, 104.26, 127.00, 127.48, 127.74, 128.48, 128.90, 129.84, 132.43, 135.58, 140.92, 143.39, 152.79, 165.61. – MS (EI, 70 eV): *m/z* (%) = 223 (2), 221 (9), 168 (3), 166 (3), 156 (4), 155 (4), 154 (10), 153 (7), 140 (4), 139 (3), 138 (7), 129 (8), 128 (11), 127 (23), 126 (17), 113 (15), 111 (66), 76 (32). – UV (EtOH): $\lambda_{max}(\log \varepsilon_{max})$ = 275.0 (4.11), 205.0 nm (4.24). – $C_{18}H_{15}Cl_2N_3O_2$ (376.2): calcd. C 57.46, H 4.02, N 11.17; found C 57.33, H 4.12, N 11.15.

*6-Methyl-2-(1H)-oxo-4-(2-bromophenyl)-3,4-dihydropyrimidine-5-(2′-chlorophenyl)carboxamide (**12**)*

One recrystallization. M. p.: 221 – 223 °C. – IR: ν = 3200, 3100 (N-H), 1705 (CONH), 1650 (CO), 1590 cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): δ = 2.17 (s, 3H, CH_3), 5.73 (br s, 1H, pyrimidine-4H), 7.11 – 7.56 (several multiplets, 8H, aromatic H), 7.58 (s, 1H, 1-NH), 8.90 (s, 1H, 3-NH), 9.10 (s, 1H, HNAr). – ^{13}C NMR (75.48 MHz, [D_6]DMSO): δ = 17.63, 55.71, 104.12, 122.78, 126.86, 127.74, 127.90, 128.79, 129.83, 130.11, 133.21, 135.49, 140.22, 142.63, 152.37, 165.48. – MS (EI, 70 eV): *m/z* (%) = 342 (6), 341 (4), 340 (19), 293 (28), 267 (6), 265 (7), 185 (23), 184 (13), 183 (15), 182 (8), 157 (15), 156 (9), 155 (16), 154 (7), 129 (37), 128 (34), 127 (96), 126 (20), 76 (55). – UV (EtOH): $\lambda_{max}(\log \varepsilon_{max})$ = 279.0 (4.27), 209.0 nm (4.53). – $C_{18}H_{15}BrClN_3O_2$ (420.7): calcd. C 51.39, H 3.59, N 9.99; found C 51.11, H 3.60, N 9.72.

*6-Methyl-2-(1H)-oxo-4-(3-bromophenyl)-3,4-dihydropyrimidine-5-(2′-chlorophenyl)carboxamide (**13**)*

One recrystallization. M. p.: 206 – 208 °C. – IR: ν = 3430, 3300 (N-H), 1710 (CONH), 1655 (CO), 1605 cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): δ = 2.17 (s, 3H, CH_3), 5.40 (br s, 1H, pyrimidine-4H), 7.17 – 7.51 (several multiplets, 8H, aromatic H), 7.73 (s, 1H, 1-NH), 8.91 (s, 1H, 3-NH), 9.19 (s, 1H, HNAr). – ^{13}C NMR (75.48 MHz, [D_6]DMSO): δ = 17.81, 54.93, 104.06, 122.22, 125.99, 127.15, 127.71, 127.75, 128.78, 129.81, 129.88, 130.74, 131.24, 135.57, 141.15, 147.10, 152.83, 165.60. – MS (EI, 70 eV): *m/z* (%) = 420 (4), 390 (4), 348 (4), 342 (4), 267 (4), 265 (7), 156 (4), 155 (9), 154 (3), 129 (2), 128 (17), 127 (9), 126 (25), 113 (6), 111 (12), 76 (38). – UV (EtOH): $\lambda_{max}(\log \varepsilon_{max})$ = 286.5 (4.07), 209.5 nm (4.53). – $C_{18}H_{15}BrClN_3O_2$ (420.7): calcd. C 51.39, H 3.59, N 9.99; found C 51.34, H 3.75, N 9.94.

*6-Methyl-2-(1H)-oxo-4-(4-bromophenyl)-3,4-dihydropyrimidine-5-(2′-chlorophenyl)carboxamide (**14**)*

One recrystallization. M. p.: 254 – 256 °C. – IR: ν = 3260 (N-H), 1705 (CONH), 1675 (CO), 1635 cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): δ = 2.15 (s, 3H, CH_3), 5.35 (br s, 1H, pyrimidine-4H), 7.17 – 7.57 (several multiplets, 8H, aromatic H), 7.67 (s, 1H, 1-NH), 8.86 (s, 1H, 3-NH), 9.13 (s, 1H, HNAr). – ^{13}C NMR (75.48 MHz, [D_6]DMSO): δ = 17.74, 54.89, 104.20, 120.95, 127.05, 127.56, 127.76, 128.55, 129.25, 129.85, 131.82, 135.57, 140.88, 143.82, 152.76, 165.60. – MS (EI, 70 eV): *m/z* (%) = 422 (8), 421 (8), 293 (5), 156 (8), 155 (4), 154 (10), 129 (2), 128 (19), 127 (13), 126 (10), 111 (9), 76 (30). – UV (EtOH): $\lambda_{max}(\log \varepsilon_{max})$ = 290.0 (4.08), 210.0 nm (4.49). – $C_{18}H_{15}BrClN_3O_2$ (420.7): calcd. C 51.39, H 3.59, N 9.99; found C 51.09, H 3.74, N 9.87.

*6-Methyl-2-(1H)-oxo-4-(3-nitrophenyl)-3,4-dihydropyrimidine-5-(2′-chlorophenyl)carboxamide (**15**)*

One recrystallization. M. p.: 202 – 204 °C. – IR: ν = 3250 (N-H), 1720 (CONH), 1660 (CO), 1640 cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): δ = 2.18 (s, 3H, CH_3), 5.53 (br s, 1H, pyrimidine-4H), 7.15 – 8.14 (several multiplets, 8H, aromatic H), 8.18 (s, 1H, 1-NH), 8.98 (s, 1H, 3-NH), 9.28 (s, 1H, HNAr). – ^{13}C NMR (75.48 MHz, [D_6]DMSO): δ = 17.84, 54.89, 103.79, 121.78, 122.92, 127.30, 127.76, 127.97, 128.99, 129.88, 130.66, 133.78, 135.49, 141.45, 146.69, 148.24, 152.68, 165.52. – MS (EI, 70 eV): *m/z* (%) = 260 (3), 217 (3), 177 (3), 155 (4), 154 (3), 153 (8), 150 (13), 149 (5), 129 (14), 128 (10), 127 (38), 126 (9), 113 (2), 111 (23), 76 (100). – UV (EtOH): $\lambda_{max}(\log \varepsilon_{max})$ = 266.0 (4.21), 209.5 nm (4.47). – $C_{18}H_{15}ClN_4O_4$ (386.8): calcd. C 55.89, H 3.91, N 14.49; found C 55.76, H 3.90, N 14.45.

*6-Methyl-2-(1H)-oxo-4-(4-nitrophenyl)-3,4-dihydropyrimidine-5-(2′-chlorophenyl)carboxamide (**16**)*

One recrystallization. M. p.: 248 – 250 °C. – IR: ν = 3240, 3090 (N-H), 1705 (CONH), 1655 (CO), 1590 cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): δ = 2.17 (s, 3H, CH_3), 5.51 (br s, 1H, pyrimidine-4H), 7.15 – 8.23 (several multiplets, 8H, aromatic H), 8.26 (s, 1H, 1-NH), 8.96 (s, 1H, 3-NH), 9.26 (s, 1H, HNAr). – ^{13}C NMR (75.48 MHz, [D_6]DMSO): δ = 17.82, 55.06, 103.81, 124.28, 127.21, 127.77, 127.84, 128.25, 128.84, 129.87, 135.51, 141.24, 147.25, 151.78, 152.73, 165.53. – MS (EI, 70 eV): *m/z* (%) = 386 (2), 232 (2), 177 (2), 155 (4), 154 (9), 153 (3), 129 (17), 128 (14), 127 (29), 126 (14), 122 (6), 111 (19), 76 (50). – UV (EtOH): $\lambda_{max}(\log \varepsilon_{max})$ = 272.0 (4.22), 206.0 nm (4.38). – $C_{18}H_{15}ClN_4O_4$ (386.8): calcd. C 55.89, H 3.91, N 14.49; found C 55.42, H 4.16, N 14.42.

*6-Methyl-2-(1H)-oxo-4-(3-methoxyphenyl)-3,4-dihydropyrimidine-5-(2′-chlorophenyl)carboxamide (**17**)*

One recrystallization. M. p.: 240 – 242 °C. – IR: ν = 3200 (N-H), 1675 (CONH), 1650 (CO), 1620 cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): δ = 2.17 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 5.36 (br s, 1H, pyrimidine-4H), 6.83 – 7.51 (several multiplets, 8H, aromatic H), 7.67 (s, 1H, 1-NH), 8.86 (s, 1H, 3-NH), 9.04 (s, 1H, HNAr). – ^{13}C NMR (75.48 MHz, [D_6]DMSO): δ = 17.74, 55.27, 55.45, 104.44, 112.90, 113.03, 119.04, 126.82, 127.12, 127.74, 128.08, 129.83, 130.12, 135.66, 141.01, 145.93, 153.01, 159.82, 165.69. – MS (EI, 70 eV): *m/z* (%) = 371 (2), 336 (2), 245 (100), 244 (43), 218 (2), 217 (12), 162 (79), 156 (4), 155 (18), 154 (7), 153 (53), 135 (22), 134 (15), 129 (28), 128 (15), 127 (86), 126 (13), 113 (3), 111 (18), 107 (12), 76 (15). – UV (EtOH): $\lambda_{max}(\log \varepsilon_{max})$ = 282.0 (3.86), 204.5 nm (4.31). – $C_{19}H_{18}ClN_3O_3$ (371.8): calcd. C 61.38, H 4.88, N 11.30; found C 61.08, H 4.85, N 11.25.

*6-Methyl-2-(1H)-oxo-4-(4-methoxyphenyl)-3,4-dihydropyrimidine-5-(2′-chlorophenyl)carboxamide (**18**)*

Preparative layer chromatography (ethyl acetate). M. p.: 218 – 220 °C. – IR: ν = 3200 (N-H), 1690 (CONH), 1665 (CO), 1625 cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): δ = 2.15 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 5.30 (br s, 1H, pyrimidine-4H), 6.89 – 7.49 (several multiplets, 8H, aromatic H), 7.57 (s, 1H, 1-NH), 8.79 (s, 1H, 3-NH), 8.93 (s, 1H, HNAr). – ^{13}C NMR (75.48 MHz, [D_6]DMSO): δ = 17.72, 54.84, 55.56, 104.60, 114.30, 126.69, 126.88, 127.74, 127.80, 128.31, 129.78, 135.64, 136.44, 140.98, 152.85, 159.16, 165.66. – MS (EI, 70 eV): *m/z* (%) = 371 (3), 336 (5), 245 (54), 244 (6), 217 (9), 162 (100), 155 (2), 153 (5), 135 (7), 134 (10), 129 (8), 128 (4), 127 (24), 126 (4), 111 (5), 107 (5), 76 (4). – UV (EtOH): $\lambda_{max}(\log \varepsilon_{max})$: 283.0 (4.35),

212.0 nm (4.32). – $C_{19}H_{18}ClN_3O_3$ (371.8): calcd. C 61.38, H 4.88, N 11.30; found C 61.20, H 5.14, N 11.09.

*6-Methyl-2-(1H)-oxo-4-(4-methylphenyl)-3,4-dihydropyrimidine-5-(2′-chlorophenyl)carboxamide (**19**)*

Two times recrystallized. M. p.: 205 – 207 °C. – IR: ν = 3220 (N-H), 1700 (CONH), 1670 (CO), 1630 cm^{-1}. – ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 2.15 (s, 3H, pyrimidine-C_6-CH_3), 2.27 (s, 3H, 4-CH_3), 5.32 (br s, 1H, pyrimidine-4H), 7.14 – 7.48 (several multiplets, 8H, aromatic H), 7.60 (s, 1H, 1-NH), 8.80 (s, 1H, 3-NH), 8.98 (s, 1H, HNAr). – ^{13}C NMR (75.48 MHz, [D$_6$]DMSO): δ = 17.72, 21.13, 55.10, 104.61, 126.74, 126.90, 127.02, 127.74, 127.96, 129.46, 129.79, 135.67, 137.06, 140.83, 141.48, 152.91, 165.68. – MS (EI, 70 eV): *m/z* (%) = 355 (4), 320 (6), 229 (100), 228 (15), 202 (2), 201 (12), 156 (3), 155 (4), 154 (3), 153 (8), 129 (17), 128 (10), 127 (46), 126 (5), 119 (13), 118 (13), 113 (2), 111 (9), 91 (48), 76 (3). – UV (EtOH): $\lambda_{max}(\log \varepsilon_{max})$ = 288.5 (4.15), 208.5 nm (4.49). – $C_{19}H_{18}ClN_3O_2$ (355.8): calcd. C 64.13, H 5.10, N 11.81; found C 64.47, H 5.08, N 11.80.

*6-Methyl-2-(1H)-oxo-4-(1-phenylethyl)-3,4-dihydropyrimidine-5-(2′-chlorophenyl)carboxamide (**20**)*

One recrystallization. M. p.: 203 – 204 °C. – IR: ν = 3200 (N-H), 2900 (C-H str.), 1700 (CONH), 1670 (CO), 1590 cm^{-1}. – ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 1.21 (d, ^3J= 7.02, 3H, C*H*$_3$CHPh), 2.02 (s, 3H, CH_3), 2.93(m, 1H, CH_3C*H*Ph), 4.46 (br s, 1H, pyrimidine-4H), 6.96 – 7.46 (several multiplets, 9H, aromatic H), 7.49 (s, 1H, 1-NH), 8.42 (s, 1H, 3-NH), 9.10 (s, 1H, HNAr). – ^{13}C NMR (75.48 MHz, [D$_6$]DMSO): δ = 15.27, 17.43, 46.51, 57.66, 104.03, 126.71, 126.95, 127.67, 127.78, 128.30, 128.62, 128.70, 129.81, 135.75, 140.53, 142.84, 153.76, 166.47. – MS (EI, 70 eV): *m/z* (%) = 137 (10), 129 (4), 128 (3), 127 (11), 126 (3), 111 (4), 110 (9), 105 (100), 104 (17), 77 (55), 76 (4). – UV (EtOH): $\lambda_{max}(\log \varepsilon_{max})$ = 283.5 (4.04), 207.5 nm (4.44). – $C_{20}H_{20}ClN_3O_2$ (369.8): calcd. C 64.95, H 5.45, N 11.36; found C 64.49, H 5.54, N 11.33.

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