Ramin Javahershenas and Jabbar Khalafy*

A new synthesis of pyrrolo[3,2-*d*]pyrimidine derivatives by a one-pot, three-component reaction in the presence of L-proline as an organocatalyst

https://doi.org/10.1515/hc-2017-0187
Received September 23, 2017; accepted November 4, 2017; previously published online January 12, 2018

Abstract: A one-pot, three-component reaction of 4-hydroxycoumarin, arylglyoxals, and 6-aminouracil or 1,3-dimethyl-6-aminouracil in the presence of L-proline as an organocatalyst in acetic acid under reflux conditions provided a series of new pyrrolo[3,2-*d*]pyrimidine derivatives in good yields.

Keywords: 1,3-Dimethyl-6-aminouracil; 4-hydroxycoumarin; 6-aminouracil; arylglyoxals; one-pot; pyrrolo[3,2-*d*]pyrimidines.

Introduction

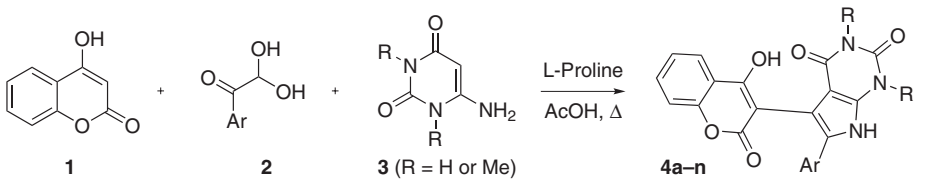
Pyrrolo[3,2-*d*]pyrimidines have many pharmaceutical applications. They are antitumor [1], antimicrobial [2], antibacterial [3], antifolate [4], anticonvulsant [5], antileishmanial [6], anti-inflammatory [7], antiaggressive [8], antiviral [9], anticoagulant [10], antioxidant [11], antifungal [12], antiasthmatic [13] and anti-HIV agents [14]. In continuation of our interests in the preparation of heterocyclic compounds by one-pot, multicomponent reactions [15–20], herein we report the synthesis of coumarinyl-substituted pyrrolo[3,2-*d*]pyrimidine-2,4(3*H*)-dione derivatives **4a–n** (Scheme 1) by a one-pot, three-component reaction of 4-hydroxycoumarin, arylglyoxals and 6-aminouracil or 1,3-dimethyl-6-aminouracil in the presence of L-proline as an organocatalyst.

Results and discussion

Bharti [21] has recently reported that the three-component reaction of 4-hydroxycoumarin, an aldehyde and 1,3-dimethyl-6-aminouracil in the presence of a catalytic amount of L-proline in ethanol under reflux conditions provided 6-amino-5-[(4-hydroxy-2-oxo-2*H*-chromen-3-yl) methyl]-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione. It was of interest to replace the aldehyde with an arylglyoxal in this reaction. Arylglyoxals are efficiently synthesized in the form of hydrates by the oxidation of acetophenones with selenium dioxide in ethanol under reflux conditions [20]. While this work was in progress, Choudhury and coworkers [22] reported that the treatment of 4-hydroxycoumarin (**1**) with an arylglyoxal **2** and 1,3-dimethyl-6-aminouracil (**3**) in AcOH under microwave conditions furnished pyrrolo[2,3-*d*]pyrimidine derivatives **4h**, **4k** and **4m**. In this paper, we report the one-pot, three-component reaction of 4-hydroxycoumarin (**1**), arylglyoxal **2** and 6-aminouracil or 1,3-dimethyl-6-aminouracil (**3**) leading to pyrrolo[2,3-*d*]pyrimidine derivatives **4a–n** efficiently catalyzed by L-proline (Scheme 1).

The reaction of 4-hydroxycoumarin (**1**), phenylglyoxal (**2a**) and 6-aminouracil (**3**) was chosen as the model reaction. In the absence of L-proline, no product was observed at room temperature even after 24 h. Refluxing the reaction mixture in acetic acid without the catalyst for 7 h gave the desired product **4a** in only a 14% yield. The product was fully characterized by its Fourier-transform infrared spectroscopy (FT IR), ^{1}H nuclear magnetic resonance (^{1}H NMR) and ^{13}C NMR spectral data. The use of increasing amounts of L-proline as an organocatalyst gradually improved the yield. Under optimized conditions, the reaction was conducted in acetic acid under reflux for 7 h and furnished product **4a** in a 73% yield. This reaction was attempted in the presence of other catalysts including K_2CO_3 (21% yield), triethylenediamine (41% yield), 4-dimethylaminopyridine (35% yield), pyrrolidine (38% yield), tetra-*n*-butyl ammonium bromide (48% yield), sodium dodecyl sulfate (31% yield), $ZrOCl_2$ (45% yield) and *p*-toluenesulfonic acid (46% yield) using acetic acid as a solvent. As can be seen, the use of L-proline proved to be the best in terms of yield. The model reaction in the presence of L-proline was also conducted in ethanol/water (31% yield), ethanol (35% yield), acetonitrile (32% yield), water (41% yield), dichloromethane (trace amount of **4a**) and tetrahydrofuran (trace amount of **4a**). Thus, the highest yield of **4a** (73%) was obtained from the reaction conducted in acetic acid.

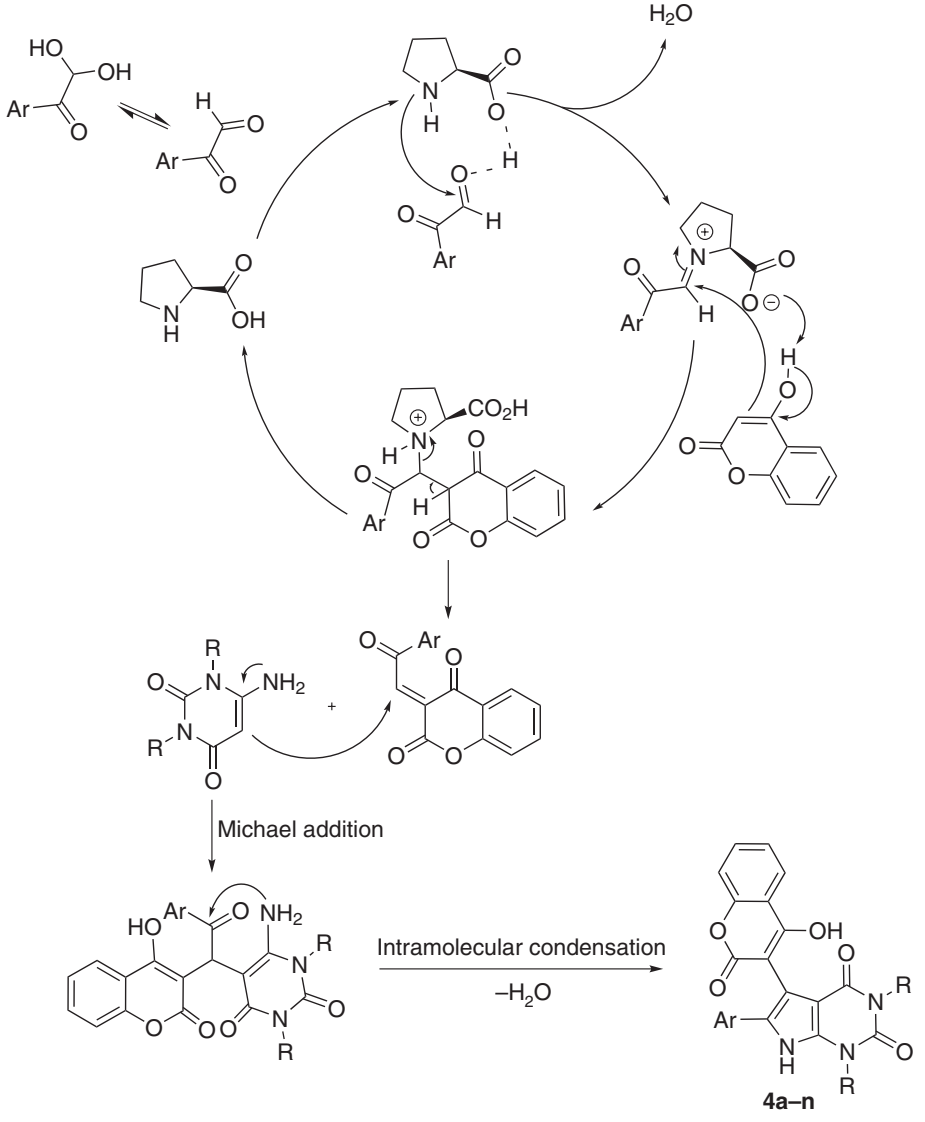
***Corresponding author: Jabbar Khalafy,** Department of Organic Chemistry, Faculty of Chemistry, Urmia University, 5756151818 Urmia, Iran, e-mail: jkhalafi@yahoo.com; j.khalafi@urmia.ac.ir
Ramin Javahershenas: Department of Organic Chemistry, Faculty of Chemistry, Urmia University, 5756151818 Urmia, Iran.
http://orcid.org/0000-0001-5771-7203



1 **2** **3** (R = H or Me) **4a–n**

4a: Ar = Ph; R = H
4b: Ar = 4-MeC_6H_4; R = H
4c: Ar = 4-ClC_6H_4; R = H
4d: Ar = 4-$MeOC_6H_4$; R = H
4e: Ar = 4-$O_2NC_6H_4$; R = H
4f: Ar = 4-FC_6H_4; R = H
4g: Ar = 3,4-$(MeO)_2C_6H_3$; R = H
4h: Ar = Ph; R = Me
4i: Ar = 4-MeC_6H_4; R = Me
4j: Ar = 4-ClC_6H_4; R = Me
4k: Ar = 4-$MeOC_6H_4$; R = Me
4l: Ar = 4-O2NC_6H_4; R = Me
4m: Ar = 4-FC_6H_4; R = Me
4n: Ar = 3,4-$(MeO)_2C_6H_3$; R = Me

Scheme 1 Synthesis of pyrrolo[3,2-*d*]pyrimidine derivatives **4a–n**.



Scheme 2 The proposed mechanism for **4a–n**.

Mechanistically (Scheme 2), the formation of product **4a–n** can be explained in terms of the Knoevenagel condensation of hydroxycoumarin with the aryglyoxal, catalyzed by L-proline, followed by Michael addition of 6-aminouracil or 1,3-dimethyl-6-aminouracil to the Knoevenagel intermediate product and then intramolecular heterocyclization of the Michael product.

Conclusion

Pyrrolo[3,2-*d*]pyrimidine derivatives **4a–n** were synthesized by the one-pot, three-component reaction of 4-hydroxycoumarin, arylglyoxal and 1,3-dimethyl-6-aminouracil or 6-aminouracil using 20 mol% of L-proline as an organocatalyst in acetic acid under reflux.

Experimental

The solvents were distilled and dried according to Perrin and Armarego [23]. The melting points were measured on an Electrothermal 9200 apparatus and are uncorrected. FT-IR spectra were recorded on a Thermo Nicolet (Nexus 670) spectrometer using KBr discs. The ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker DRX-300 Avance spectrometer in DMSO-d_6 with tetramethylsilane (TMS) as the internal reference. Elemental analyses were performed using a Leco Analyzer 932.

Arylglyoxals were obtained in the form of hydrates by the oxidation of acetophenones with selenium dioxide in ethanol under reflux conditions as previously reported [20].

General procedure for synthesis of pyrrolo[3, 2-*d*] pyrimidine derivatives 4a–n

A mixture of 4-hydroxycoumarin (**1**, 1 mmol), arylglyoxal hydrate (**2**, 1 mmol), 6-aminouracil or 1,3-dimethyl-6-aminouracil (**3**, 1 mmol) and L-proline (0.2 mmol) in acetic acid (5 mL) was heated under reflux for 4 h (**4i**), 5 h (**4b** and **4l**), 6 h (**4c**, **4e**, **4h, 4j** and **4k**), 7 h (**4a**, **4d**, **4m** and **4n**) and 8 h (**4f** and **4g**). The reaction was monitored by thin-layer chromatography (TLC) eluting with EtOAc/hexanes (3:1). After the completion of the reaction, the resultant precipitate was filtered, washed with acetic acid and cold water, dried and crystallized from ethanol.

6-(Phenyl)-5-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-1,7-dihydro-2*H*-pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*)-dione (4a) Yield 73%; pale yellow powder; mp > 300°C; IR: ν_{max} 3374, 3203, 3100, 2932, 1707, 1665, 1659, 1496, 1449, 1397, 1267, 1215, 1151, 1022, 893, 813, 762, 688 cm^{-1}; ^{1}H NMR: δ 11.81 (s, 1H, exchanged with D_2O, OH), 11.45 (s, 1H, exchanged with D_2O, NH), 10.96 (s, 1H, exchanged with D_2O, NH), 10.46 (s, 1H, exchanged with D_2O, NH), 7.84 (d, *J* = 7.2 Hz, 1H, Ar), 7.63 (t, *J* = 7.5 Hz, 1H, Ar), 7.50–7.25 (m, 6H, Ar), 7.18 (d, *J* = 6.9 Hz, 1H, Ar); ^{13}C NMR: δ 162.0, 161.8, 159.9, 152.9, 151.5, 140.5, 132.6, 132.19, 129.0, 128.8, 127.2, 126.6, 124.4, 111.7, 116.7, 105.9, 100.1, 99.6. Anal. Calcd for $C_{21}H_{13}N_3O_5$: C, 65.12 H, 3.38 N, 10.85. Found: C, 65.21 H, 3.32 N, 10.90.

6-(4-Methylphenyl)-5-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-1,7-dihydro-2*H*-pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*)-dione (4b) Yield 81%; white powder; mp > 300°C; IR: ν_{max} 3365, 3207, 3080, 1681, 1624, 1504, 1446, 1392, 1168, 1113, 1019, 974, 891, 765 cm^{-1}; ^{1}H NMR: δ 11.73 (s, 1H, exchanged with D_2O, OH), 11.43 (s, 1H, exchanged with D_2O, NH), 10.89 (s, 1H, exchanged with D_2O, NH), 10.43 (s, 1H, exchanged with D_2O, NH), 7.83 (d, *J* = 7.8 Hz, 1H, Ar), 7.63 (t, *J* = 7.2 Hz, 1H, Ar), 7.39 (bd, *J* = 9.0 Hz, 1H, Ar), 7.35 (t, *J* = 7.5 Hz, 1H, Ar), 7.27 (d, *J* = 7.5 Hz, 2H, Ar), 7.09 (d, *J* = 7.5 Hz, 2H, Ar), 2.22 (s, 3H, Me); ^{13}C NMR: δ 163.4, 158.3, 152.9, 152.1, 140.2, 132.7, 132.8, 129.6, 128.9, 128.5, 127.0, 124.3, 124.0, 116.6, 116.5, 106.7, 101.0, 99.2, 21.1. Anal. Calcd for $C_{22}H_{15}N_3O_5$: C, 65.83 H, 3.77 N, 10.47. Found: C, 65.88 H, 3.70 N, 10.35.

6-(4-Chlorophenyl)-5-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-1,7-dihydro-2*H*-pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*)-dione (4c) Yield 78%; white powder; mp > 300°C; IR: ν_{max} 3405, 3271, 2932, 1700, 1684, 1624, 1505, 1448, 1405, 1249, 1175, 1113, 1028, 763 cm^{-1}; ^{1}H NMR: δ 11.84 (s, 1H, exchanged with D_2O, OH), 11.52 (s, 1H, exchanged with D_2O, NH), 10.39 (s, 1H, exchanged with D_2O, NH), 10.21 (s, 1H, exchanged with D_2O, NH), 7.97 (bd, *J* = 8.1 Hz, 3H, Ar), 7.52 (bd, *J* = 8.4 Hz, 3H, Ar), 7.38 (t, *J* = 8.4 Hz, 1H, Ar), 7.37 (t, *J* = 8.7 Hz, 1H, Ar); ^{13}C NMR: δ 162.0, 161.7 158.9, 153.0, 151.5, 140.6, 132.7, 132.2, 129.0, 128.9, 127.2, 126.6, 124.4, 116.7, 116.6, 105.9, 100.1, 99.6. Anal. Calcd for $C_{21}H_{12}ClN_3O_5$: C, 59.80 H, 2.87 N, 9.96. Found: C, 59.71 H, 2.73 N, 10.15.

6-(4-Methoxyphenyl)-5-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-1,7-dihydro-2*H*-pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*)-dione (4d) Yield 80%; pale yellow powder; mp > 300°C; IR ν_{max} 3432, 3347, 3179, 3073, 2951, 1686, 1624, 1560, 1501, 1452, 1377, 1283, 1226, 1119, 1052, 977, 862, 756 cm^{-1}; ^{1}H NMR: δ 11.68 (s, 1H, exchanged with D_2O, OH), 11.42 (s, 1H, exchanged with D_2O, NH), 10.88 (s, 1H, exchanged with D_2O, NH), 10.42 (s, 1H, exchanged with D_2O, NH), 7.84 (d, *J* = 7.8 Hz, 1H, Ar), 7.63 (t, *J* = 7.5 Hz, 1H, Ar), 7.39 (bd, *J* = 9.0 Hz, 1H, Ar), 7.34 (br t, *J* = 9.0 Hz, 1H, Ar), 7.31 (d, *J* = 8.4 Hz, 2H, Ar), 6.87 (d, *J* = 9.0 Hz, 2H, Ar), 3.69 (s, 3H, OMe); ^{13}C NMR: δ 162.1, 161.8, 159.9, 158.7, 153.0, 151.5, 140.2, 132.5, 129.2, 128.0, 124.7, 124.3, 116.6, 114.3, 104.6, 100.1, 99.6, 55.5. Anal. Calcd for $C_{22}H_{15}N_3O_6$: C, 63.31 H, 3.62 N, 10.07. Found: C, 63.23 H, 3.71 N, 10.17.

6-(4-Nitrophenyl)-5-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-1,7-dihydro-2*H*-pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*)-dione (4e) Yield 72%; orange powder; mp > 300°C; IR: ν_{max} 3419, 3312, 3161, 2226, 1701, 1674, 1599, 1522, 1450, 1397, 1341, 1246, 1109, 977, 837, 761, 702, 545 cm^{-1}; ^{1}H NMR: δ 12.15 (s, 1H, exchanged with D_2O, OH), 11.70 (s, 1H, exchanged with D_2O, NH), 10.60 (s, 1H, exchanged with D_2O, NH), 10.37 (s, 1H, exchanged with D_2O, NH), 8.34 (d, *J* = 7.8 Hz, 1H, Ar), 8.13 (t, *J* = 7.5 Hz, 1H, Ar), 7.89 (bd, *J* = 9.0 Hz, 1H, Ar), 7.84 (br t, *J* = 9.0 Hz, 1H, Ar), 7.81 (d, *J* = 8.4 Hz, 2H, Ar), 7.37 (d, *J* = 9.0 Hz, 2H, Ar); ^{13}C-NMR: δ 163.0, 162.1, 161.7, 159.8, 154.0, 153.1, 151.5, 150.3, 150.1, 145.6, 141.6, 140.9, 138.8, 126.8, 126.7, 124.4, 118.8, 116.0, 101.4, 99.0. Anal. Calcd for $C_{21}H_{12}N_4O_7$: C, 58.34 H, 2.80 N, 12.96. Found: C, 58.28 H, 2.88 N, 12.85.

6-(4-Fluorophenyl)-5-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-1,7-dihydro-2*H*-pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*)-dione (4f) Yield 71%; pale yellow powder; mp > 300°C; IR: ν_{max} 3365, 3198, 3050, 1700, 1671, 1613, 1496, 1449, 1407, 1264, 1214, 1121, 1020, 892, 761, 690 cm^{-1}; ^{1}H

NMR: δ 11.82 (s, 1H, exchanged with D_2O, OH), 11.52 (s, 1H, exchanged with D_2O, NH), 10.96 (s, 1H, exchanged with D_2O, NH), 10.47 (s, 1H, exchanged with D_2O, NH), 7.84 (d, *J* = 7.2 Hz, 1H, Ar), 7.64 (t, *J* = 7.8 Hz, 1H, Ar), 7.41 (t, *J* = 7.2 Hz, 2H, Ar), 7.33 (d, *J* = 7.5 Hz, 2H, Ar), 7.15 (t, *J* = 8.7 Hz, 2H, Ar); ^{13}C NMR: δ 163.1, 162.0, 161.9, 159.9, 153.0, 151.6, 140.4, 132.6, 128.7, 128.2, 124.4, 116.6, 116.5, 115.9, 115.6, 105.8, 100.2, 99.3. Anal. Calcd for $C_{21}H_{12}FN_3O_5$: C, 62.23 H, 2.98 N, 10.37. Found: C, 62.31 H, 2.90 N, 10.29.

6-(3,4-Dimethoxyphenyl)-5-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-1,7-dihydro-2*H*-pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*)-dione (4g) Yield 76%; yellow powder; mp > 300°C; IR ν_{max} 3526, 3416, 3200, 3058, 1700, 1681, 1608, 1512, 1445, 1261, 1213, 1126, 1018, 918, 761, 714, 603 cm^{-1}; ^{1}H NMR: δ 11.66 (s, 1H, exchanged with D_2O, OH), 11.45(s, 1H, exchanged with D_2O, NH), 10.94 (s, 1H, exchanged wit D_2O, NH), 10.44 (s, 1H, exchanged with D_2O, NH), 7.84 (d, *J* = 7.8 Hz, 1H, Ar), 7.63 (t, *J* = 7.5 Hz, 1H, Ar), 7.38 (d, *J* = 8.4 Hz, 1H, Ar), 7.35 (t, *J* = 7.2 Hz, 1H, Ar), 7.02 (s, 1H, Ar), 6.91 (t, *J* = 8.4 Hz, 1H, Ar), 6.89 (t, *J* = 8.7 Hz, 1H, Ar), 3.73 (s, 3H, OMe), 3.69 (s, 3H, OMe); ^{13}C NMR: δ 162.1, 161.9, 159.9, 152.9, 151.6, 148.7, 148.2, 140.1, 129.1, 124.8, 124.3, 119.1, 116.6, 112.3, 110.7, 104.9, 100.2, 99.8, 55.9, 55.6. Anal. Calcd for $C_{23}H_{17}N_3O_7$: C, 61.75 H, 3.83 N, 9.39. Found: C, 61.80 H, 3.86 N, 9.31.

6-(Phenyl)-7-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-1,3-dimethyl-1,5-dihydro-2*H*-pyrrolo[3,2-*d*]pyrimidine-2,4(3*H*)-dione (4h) Yield 77%; pale yellow powder; mp > 300°C [22].

6-(4-Methylphenyl)-7-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-1,3-dimethyl-1,5-dihydro-2*H*-pyrrolo[3,2-*d*]pyrimidine-2,4(3*H*)-dione (4i) Yield 86%; pale yellow powder; mp > 300°C; IR: ν_{max} 3427, 3197, 3047, 2949, 1687, 1648, 1552, 1500, 1447, 1387, 1280, 1221, 1150, 978, 895, 833, 760, 688 cm^{-1}; ^{1}H NMR: δ 11.76 (s, 1H, exchanged with D_2O, OH), 11.53 (s, 1H, exchanged with D_2O, 1H of NH), 7.84 (d, *J* = 8.1 Hz, 1H, Ar), 7.64 (t, *J* = 8.7 Hz, 1H, Ar), 7.38 (t, *J* = 8.7 Hz, 2H, Ar), 7.34 (d, *J* = 7.5 Hz, 2H, Ar), 7.15 (d, *J* = 7.8 Hz, 2H, Ar), 3.53 (s, 3H, 3-Me), 3.16 (s, 3H, 1-Me), 2.27 (s, 3H, Me); ^{13}C NMR: δ 163.1, 157.1, 157.0, 153.4, 153.3, 151.6, 151.0, 145.4, 144.0, 141.2, 137.5, 132.6, 128.2, 126.6, 126.5, 124.2, 123.8, 115.9, 100.9, 31.2, 26.8, 21.2. Anal. Calcd for $C_{24}H_{19}N_3O_5$: C, 67.13 H, 4.46 N, 9.79. Found: C, 67.05 H, 4.50 N, 9.84.

6-(4-Chlorophenyl)-7-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-1,3-dimethyl-1,5-dihydro-2*H*-pyrrolo[3,2-*d*]pyrimidine-2,4(3*H*)-dione (4j) Yield 80%; pale yellow powder; mp > 300°C; IR: ν_{max} 3452, 3361, 3188, 2954, 1695, 1649, 1608, 1554, 1449, 1389, 1272, 1237, 1164, 1059, 976, 895, 765, cm^{-1}; ^{1}H NMR: δ 11.84 (s, 1H, exchanged with D_2O, OH), 11.64 (s, 1H, exchanged with D_2O, NH), 7.86 (d, *J* = 7.2 Hz, 1H, Ar), 7.64 (t, *J* = 7.5 Hz, 1H, Ar), 7.55–7.25 (m, 6H, Ar), 3.50 (s, 3H, 3-Me), 3.31 (s, 3H, 1-Me); ^{13}C NMR: δ 161.1, 158.3, 153.0, 151.6, 151.1, 132.7, 132.0, 131.5, 130.8, 128.9, 128.6, 128.5, 128.4, 124.3, 124.1, 116.6, 100.1, 96.3, 31.0, 28.1. Anal. Calcd for $C_{23}H_{16}ClN_3O_5$: C, 61.41 H, 3.59 N, 9.34. Found: C, 61.33 H, 3.45 N, 9.42.

6-(4-Methoxyphenyl)-7-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-1,3-dimethyl-1,5-dihydro-2*H*-pyrrolo[3,2-*d*]pyrimidine-2,4(3*H*)-dione (4k) Yield 84%; pale yellow powder; mp > 300°C (Lit. [22]: yield 93%, white solid, mp 391–393°C).

6-(4-Nitrophenyl)-7-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-1,3-dimethyl-1,5-dihydro-2*H*-pyrrolo[3,2-*d*]pyrimidine-2,4(3*H*)-dione (4l) Yield 75%; orange powder; mp > 300°C; IR: ν_{max} 3427, 3149, 3057, 2944, 2241, 1690, 1678, 1642, 1561, 1484, 1277, 1098, 1021, 975, 844, 742, 628 cm^{-1}; ^{1}H NMR: δ 12.03 (bs, 1H, exchanged with D_2O, OH), 11.73 (s, 1H, exchanged with D_2O, NH), 8.08 (t, *J* = 8.1 Hz, 2H, Ar), 7.91 (t, *J* = 7.8 Hz, 1H, Ar), 7.80–7.50 (m, 4H, Ar), 7.41 (d, *J* = 8.1 Hz, 1H, Ar), 7.36 (t, *J* = 7.8 Hz, 1H, Ar), 3.49 (s, 3H, 3-Me), 3.22 (s, 3H, 1-Me); ^{13}C NMR: δ 162.1, 158.2, 158.0, 153.4, 153.3, 151.6, 151.0, 145.4, 144.9, 141.2, 138.6, 132.6, 127.2, 126.7, 126.4, 124.1, 123.8, 116.6, 110.9, 31.1, 27.8. Anal. Calcd for $C_{23}H_{16}N_4O_7$: C, 60.00 H, 3.50 N, 12.17. Found: C, 59.95 H, 3.57 N, 12.26.

6-(4-Fluorophenyl)-7-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-1,3-dimethyl-1,5-dihydro-2*H*-pyrrolo[3,2-*d*]pyrimidine-2,4(3*H*)-dione (4m) Yield 74%; white powder; mp 272–274°C (Lit. [22]: yield 92%; white solid, mp 268–270°C).

6-(3,4-Dimethoxyphenyl)-7-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-1,3-dimethyl-1,5-dihydro-2*H*-pyrrolo[3,2-*d*]pyrimidine-2,4(3*H*)-dione (4n) Yield 79%; pale yellow powder; mp > 300°C; IR: ν_{max} 3376, 3198, 2980, 1702, 1683, 1619, 1503, 1440, 1219, 1122, 1027, 976, 829, 758, 676 cm^{-1}; ^{1}H NMR: δ 11.73 (s, 1H, exchanged with D_2O, OH), 10.98 (s, 1H, exchanged with D_2O, NH), 7.86 (d, *J* = 7.8 Hz, 1H, Ar), 7.64 (t, *J* = 7.5 Hz, 1H, Ar), 7.41 (d, *J* = 7.5 Hz, 1H, Ar), 7.35 (t, *J* = 7.8 Hz, 1H, Ar), 7.05 (s, 1H, Ar), 7.00 (d, *J* = 8.4 Hz, 1H, Ar), 6.93 (d, *J* = 8.4 Hz, 1H, Ar), 3.71 (s, 3H, MeO), 3.64 (s, 3H, MeO), 3.57 (s, 3H, 3-Me), 3.17 (s, 3H, 1-Me); ^{13}C NMR: δ 162.2, 162.0, 158.4, 153.3, 153.0, 151.1, 148.7, 148.6, 139.9, 132.6, 129.9, 125.0, 124.5, 119.7, 116.5, 112.3, 111.1, 105.7, 100.0, 99.7, 55.9, 55.6, 31.2, 27.8. Anal. Calcd for $C_{25}H_{21}N_3O_7$: C, 63.16 H, 4.45 N, 8.84. Found: C, 63.08 H, 4.54 N, 8.75.

Acknowledgments: We are grateful to Urmia University for the financial support. We also thank Professor R.H. Prager from Flinders University, Australia, for proofreading and language editing of the manuscript.

References

[1] Ryota, M.; Keisuke, A.; Seijiro, M. Asymmetric indoline synthesis via intramolecular Aza-Michael addition mediated by bifunctional organocatalysts. *Org. Lett*. **2013**, *15*, 3658–3661.

[2] Emmadi, N. R.; Atmakur, K.; Bingi, C.; Godumagadda, N. R.; Kumar, C. G.; Nanubolu, J. B. Regioselective synthesis of 3-benzyl substituted pyrimidino chromen-2-ones and evaluation of anti-microbial and anti-biofilm activities. *Bioorg. Med. Chem. Lett*. **2014**, *24*, 485–489.

[3] Paengsri, W.; Lee, V. S.; Chong, W. L.; Wahab, H. A.; Baramee, A. Synthesis, antituberculosis activity and molecular docking studies for novel naphthoquinone derivatives. *Int. J. Biol. Chem*. **2012**, *6*, 69–88.

[4] Rosowsky, A.; Mota, C. E.; Queener, S. F. Synthesis and antifolate activity of 2,4-diamino-5,6,7,8-tetrahydropyrido[4,3-*d*] pyrimidine analogues of trimetrexate and piritrexim. *J. Heterocycl. Chem*. **1995**, *32*, 335–340.

[5] Deyanov, A. B.; Niyazov, R. K.; Nazmetdinov, F. Y.; Syropyatov, B. Y.; Kolla, V. E.; Konshin, M. E. Amides, nitriles of 2-arylamino-5-carboxy(carbethoxy)-6-methylnicotinic acids and 1-aryl-6-carbethoxy-7-methyl-4-oxo-1,4-dihydropyrido[2,3-*d*]pyrimidines – synthesis and biological activity. *Khim.-Farm. Zh*. **1991**, *25*, 26–28.

[6] Satti, N. K.; Suri, K. A.; Sun, O. P.; Kapil, A. Synthesis and antileishmanial activity of some pyrido[1,2-*a*]pyrimidines and phenanthrolines. *Indian J. Chem. Sect. B*. **1993**, *32B*, 978–980.
[7] Kolla, V. E.; Deyanov, A. B.; Nazmetdinov, F. Y.; Kashina, Z. N.; Drovosekova, L. P. Examining the anti-inflammatory and analgesic activity of 2-substituted 1-aryl-6-carboxy(carboethoxy)-7-methyl-4-oxo-1,4-dihydro pyrido[2,3-d] pyrimidines. *Khim.-Farm. Zh*. **1993**, *27*, 29–33.
[8] Saladowska, H.; Bartoszko-Malik, A.; Zawisza, T. Synthesis and properties of new derivatives of ethyl 7-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-5-carboxylate. *Farmaco* **1990**, *45*, 101–110.
[9] Nasr, M. N.; Gineinah, M. M. Pyrido[2,3-*d*]pyrimidines and pyrimido[5′,4′:5,6]pyrido[2,3-*d*]pyrimidines as new antiviral agents: synthesis and biological activity. *Arch. Pharm*. **2002**, *6*, 289–295.
[10] Jung, J. C.; Jung, Y. J.; Park, O. S. Synthetic approaches and biological activities of 4-hydroxycoumarin derivatives. *Molecules* **2009**, *14*, 4790–4803.
[11] Berghot, M. A.; Kandeel, E. M.; Abdel-Rahman, A. H.; Abdel-Motaal, M. Synthesis, antioxidant and cytotoxic activities of novel naphthoquinone derivatives from 2,3-dihydro-2,3-epoxy-1,4- naphthoquinone. *Med. Chem*. **2014**, *4*, 381–388.
[12] Tangmouo, J. G.; Meli, A. L.; Komguem, J.; Kuete, V.; Ngounou, F. N.; Lontsi, D.; Beng, V. P.; Choudhary, M. I.; Sondengam, B. L. Crassiflorone, a new naphthoquinone from Diospyros crassiflora. *Tetrahedron Lett.* **2006**, *47*, 3067–3069.
[13] Siddiqui, I. R.; Shamin, S.; Singh, A.; Srivastava, V.; Yadav, S. Moisture compatible and recyclable indium (III) chloride catalyzed and microwave assisted efficient route to substituted 1*H*-quinolin-2-ones. *Arkivoc* **2010**, 11, 232–241.
[14] Desai, J. T.; Desai, C. K.; Desai, K. R. A convenient, rapid and eco-friendly synthesis of isoxazoline heterocyclic moiety containing bridge at 2°-amine as potential pharmacological agent. *J. Iran. Chem. Soc*. **2008**, *5*, 67–73.
[15] Khalafy, J.; Etivand, N.; Dilmaghani, S.; Ezzati, M.; Poursattar Marjani, A. A convenient and mild synthesis of new 2-aryl-3-hydroxy-6,7-dihydro-1*H*-indol-4(5*H*)-ones via a one-pot, three-component reaction in water. *Tetrahedron Lett*. **2014**, *55*, 3781–3783.
[16] Khalafy, J.; Ezzati, M.; Rimaz, M.; Poursattar Marjani, A.; Yaghoobnejad Asl, H. An efficient and facile regioselective synthesis of new substituted (*E*)-1-(3-aryl-7,8-dihydrocinnoline-5(6*H*)-ylidene)hydrazines and (1*E*,2*E*)-1,2-bis(3-aryl-7,8-dihydrocinnoline-5(6*H*)-ylidene)hydrazines. *J. Iran. Chem. Soc*. **2014**, *11*, 1067–1074.
[17] Poursattar Marjani, A.; Khadafy, J.; Mahmoudi, S. A simple one-pot synthesis of new 9-aroyl-3,4,6,7,9,10-hexahydro-1,8(2*H*,5*H*)-acridinediones. *Arkivoc* **2016**, *iii*, 262–260.
[18] Khalafy, J.; Badparvar, F.; Poursattar Marjani, A. Synthesis of 1-aryl-6,6-dimethyl-2-phenyl-6,7-dihydro-1*H*-indol-4(5*H*)-ones by two steps, in a three-component reaction. *J. Chil. Chem. Soc*. **2016**, *61*, 3112–3115.
[19] Poursattar Marjani, A.; Khalafy, J.; Chitan, M.; Mahmoodi, S. Microwave-assisted synthesis of acridine-1,8(2*H*,5*H*)-diones via a one-pot, three-component reaction. *Iran. J. Chem. Chem. Eng*. **2017**, *36*, 1–6.
[20] Javahershenas, R.; Khalafy, J. A green synthesis of 7-amino-5-(4-aroyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4,5,8-hexahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile derivatives by a one-pot, three component reaction. *J. Heterocycl. Chem*. **2017**, *54*, 3163–3168.
[21] Bharti, R.; Parvin, T. Molecular diversity from the L-proline catalyzed, three-component reactions of 4-hydroxycoumarin, aldehyde, and 3-aminopyrazole or 1,3-dimethyl-6-aminouracil. *Synth. Commun*. **2015**, *45*, 1442–1450.
[22] Mishra, R.; Panday, A. K.; Choudhury, L. H.; Pal, J.; Subramanian, R.; Verma, A. Multicomponent reactions of arylglyoxal, 4-hydroxycoumarin, and cyclic 1,3-c,n-binucleophiles: binucleophile-directed synthesis of fused five- and six-membered *n*-heterocycles. *Eup. J. Org. Chem*. **2017**, *2017*, 2789–2800.
[23] Perrin, D. D.; Armarego, W. L. F. Purification of Laboratory Chemicals; Pergamon Press: Oxford, 1988.