An Efficient Synthesis of *N*-Substituted-3-aryl-3-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)propanamides by Four-Component Reaction in Aqueous Medium

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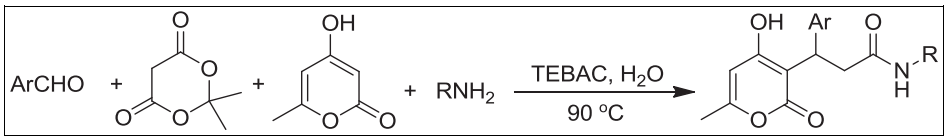

A mild and efficient synthesis of *N*-substituted-3-aryl-3-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)propanamides via four-component reaction of an aldehyde, amine, Meldrum's acid, and 4-hydroxy-6-methyl-2*H*-pyran-2-one in the presence of benzyltriethylammonium chloride (TEBAC) in aqueous medium is described. This method has the advantages of accessible starting materials, good yields, mild reaction conditions, and begin environmentally friendly.

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INTRODUCTION

The amide bond plays an important role in the elaboration and composition of biological and chemical systems [1]. Amides are traditionally synthesized by the reaction of amines with activated carboxyl acid derivatives [2]. And amides can also be synthesized by the Staudinger reaction [3], the Beckmann rearrangement [4], Schmidt reaction [5], aminocarbonylation of alkenes [6], haloarenes [7] and alkynes [8], oxidative amidation of alhydes [9], hydrative amide synthesis with alkynes [10], and the amidation of thio acids with azides [11]. Jia X. S. [12] recently reported Samarium-mediated facile method for the formation of amide bonds by the reaction of acyl chlorides and amines. However, the amides synthesized by most of the methods are traditional, few of them contain heterocyclic substitutional groups. Thus, the synthesis of amides containing heterocyclic substitutional groups is a challenging goal.

Multicomponent reactions (MCRs), in which multiple reactions are combined into the synthetic operation have been used extensively to form carbon—carbon bonds in the synthetic chemistry [13]. Such reactions offer a wide range of possibilities for the efficient construction of highly complex molecules in a single procedural step, thus avoiding the complicated purification operations and allowing savings of both solvents and reagents. In the past decade, there has been tremendous development in three and four-component reactions, and great efforts continue to be made to develop new MCRs [14].

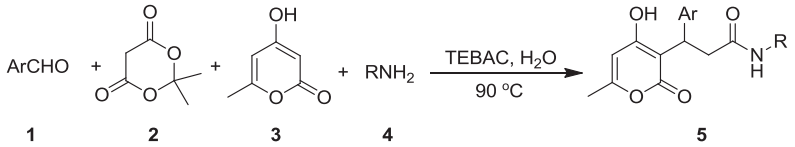
Science Breslow demonstrated hydrophobic efforts could strongly enhance the rate of some organic reactions and rediscovered the use of water as solvent in organic synthesis in 1980s [15], there has been a growing recognition that water has become an attractive medium for many organic reactions, such as Diels–Alder reactions [16], Claisen rearrangement reactions [17], Reformatsky reactions [18], and Pinacol-coupling reactions [19], not only for the advantages concerning the avoidance of expensive drying reactions, catalysts, and solvents, but also for some unique reactivity and selectivity [20]. On the other hand, organic reactions in water without using harmful organic solvents is one of the current focuses today especially in the environmentally conscious society, because water is abundant, nontoxic, and environment-friendly when compared with organic solvents used accordingly.

RESULTS AND DISCUSSION

As a continuation of our interest in green synthesis and our previous work [21] on MCR in aqueous medium, herein we report a green, one-pot, efficient synthesis of novel propanamide derivatives in aqueous medium (Scheme 1).

The choice of an appropriate reaction media is of crucial importance for successful organic synthesis. Initially, the four-component reaction of 4-chlorobenzaldehyde **1a**, Meldrum's acid **2**, 4-hydroxy-6-methyl-2*H*-pyran-2-one **3**, and 4-methylaniline **4a** was investigated to establish the optimization of the reaction conditions; reaction temperature and different solvents were screened in the model reaction. The results were summarized in Table 1. It can been seen from Table 1 that water showed a superior advantage not only in promoting the reaction but also in isolation procedure, and the best yield was achieved (Table 1, entry 2). In this reaction, catalyst benzyltriethylammonium chloride (TEBAC) (*N*-benzyl-*N*,*N*,*N*-triethylammonium) can provide the yield (Table 1, entry 1). Thus, water employed as the reaction media for the following reactions.

Scheme 1



1 2 3 4 5

Table 1

Optimization of solvent in the synthesis of **5a**.

Entry	Solvent	Temperature (°C)	Reaction time (h)	Yield (%)
1	H_2O, TEBAC	90	5	98
2	H_2O	90	7	70
3	CH_3COCH_3	Reflux	10	0
4	C_2H_5OH	Reflux	10	0
5	CH_3CN	Reflux	10	48
6	$CH_3COOC_2H_5$	Reflux	10	29
7	$ClCH_2CH_2Cl$	Reflux	10	43

Under the conditions described earlier (H_2O, TEBAC, 90°C), the scope of these MCRs was examined (Table 2). A range of novel valuable structures of **5** were synthesized in good to excellent yields by simply four-component reaction in aqueous media. The results are summarized in Table 2.

Apart from the mild conditions of the process and its excellent results, the simplicity of product isolation and the possibility to recycle the reaction solution offer a significant advantage. Because TEBAC is soluble in water and the desired product is less soluble in water, the products can be directly separated by cooling to RT, and filtering after the reaction is completed. The remaining reaction solution can be recycled. Studies using **1a**, **2**, **3**, and **4a** as model substrates showed that the recovered reaction solution could be successively recycled in subsequent reaction without any decrease of yield (Table 3).

All the products were characterized by ^{1}H-NMR, IR, and HRMS spectra. The structure of **5e** was further confirmed by X-ray diffraction analysis. The molecular structure of the product **5e** is shown in Figure 1.

Although the mechanism of the reaction has not yet been established, a possible explanation is proposed in Scheme 2.

The reaction might proceed via sequential condensation, addition, cyclization, and elimination. First, a Knoevenagel condensation between aldehydes **1** with Meldrum's acid **2** to afford intermediate **A**. The Michael addition of **A** with 4-hydroxy-6-methyl-2*H*-pyran-2-one **3** would then furnish the intermediate product **B**, which subsequently underwent intramolecular cyclization and then released acetone and carbon dioxide to give intermediate product **C**. The intermediate product **C** then attacked by amine **4** to give the product **5**.

In summary, a series of *N*-substituted-3-aryl-3-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-propanamides were synthesized via four-component reaction of aldehyde, amine, Meldrum's acid, and 4-hydroxy-6-methyl-2*H*-pyran-2-one in the presence of TEBAC in aqueous medium. This protocol has the advantages of accessible starting materials, high yield, mild reaction condensations, and environmentally friendly.

Table 2

Synthesis of compounds **5** in aqueous media.

Entry	Product	Ar	R	Time (h)	Yield (%)
1	**5a**	4-ClC_6H_4	4-$CH_3C_6H_4$	5	98
2	**5b**	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	10	97
3	**5c**	4-$CH_3OC_6H_4$	4-$CH_3C_6H_4$	6	95
4	**5d**	3-ClC_6H_4	4-$CH_3C_6H_4$	10	88
5	**5e**	2-$NO_2C_6H_4$	4-$CH_3C_6H_4$	8	90
6	**5f**	3,4-$OCH_2OC_6H_3$	4-$CH_3C_6H_4$	5	90
7	**5g**	Thiophen-2-yl	4-$CH_3C_6H_4$	11	87
8	**5h**	4-ClC_6H_4	3-ClC_6H_4	8	90
9	**5i**	4-ClC_6H_4	4-FC_6H_4	10	95
10	**5j**	4-ClC_6H_4	4-$NO_2C_6H_4$	14	85
11	**5k**	4-ClC_6H_4	2-ClC_6H_4	15	70
12	**5l**	4-ClC_6H_4	3-Cl-4-$CH_3C_6H_3$	6	98
13	**5m**	4-ClC_6H_4	$C_6H_5CH_2$	4	96

Table 3

Reuse of aqueous medium containing TEBAC in the preparation of **5a**.

Round	1	2	3	4	5	6
Yield (%)	98	98	96	92	95	92

EXPERIMENTAL

Commercial solvents and reagents were used as received. IR spectra were obtained on a Tensor 27 spectrophotometer. ^{1}H-NMR spectra were recorded using Bruker DPX-400 MHz instrument, at 293 K unless otherwise noted, with residue peaks of the solvents DMSO-d_6 ($\delta = 2.50$) used for reference. HRMS were obtained on a microma GCT–TOF instrument. X-ray crystallographic analysis was performed with a Rigaku Mercury diffractometer.

Preparation of propanamides 5; general procedure. A mixture of the aldehyde **1** (2 mmol), Meldrum's acid **2** (2 mmol), 4-hydroxy-6-methyl-2*H*-pyran-2-one **3** (2 mmol), amine **4** (2 mmol), and TEBAC (0.1 g) in water (10 mL) was stirred for 4–20 h at 90°C, then cooled to RT. The crystalline powder formed was collected by filtration, washed with water, and recrystallized from ethanol to give pure **5**.

3-(4-Chlorophenyl)-3-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-*N*-*p*-tolylpropanamide (5a). This compound was obtained as solid with mp 221–222°C. IR (KBr) ν: 3287, 3206, 3064, 1695, 1653, 1602, 1551, 1512, 1489, 403, 1259, 997, 811, 790, 719 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): $\delta = 2.12$ (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 2.92 (dd, $J_1 = 6.8$ Hz, $J_2 = 15.2$ Hz, 1H, CH), 3.33 (dd, $J_1 = 8.8$ Hz, $J_2 = 15.2$ Hz, 1H, CH), 4.76 (t, $J = 7.6$ Hz, 1H, CH), 5.99 (s, 1H, CH), 7.05 (d, $J = 8.4$ Hz, 2H, ArH), 7.29 (d,

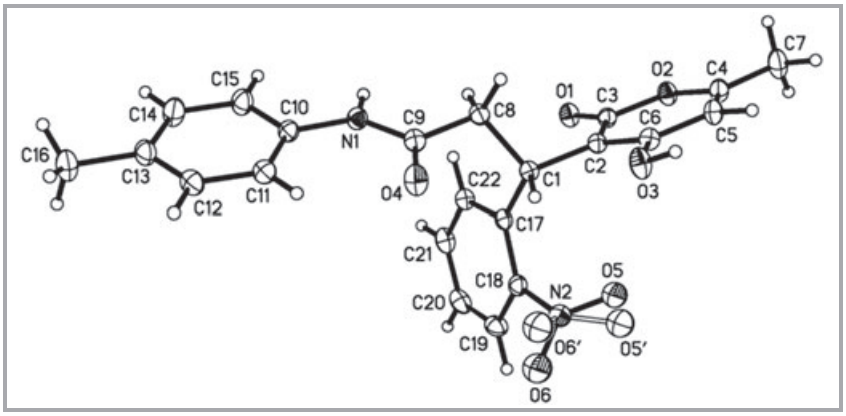
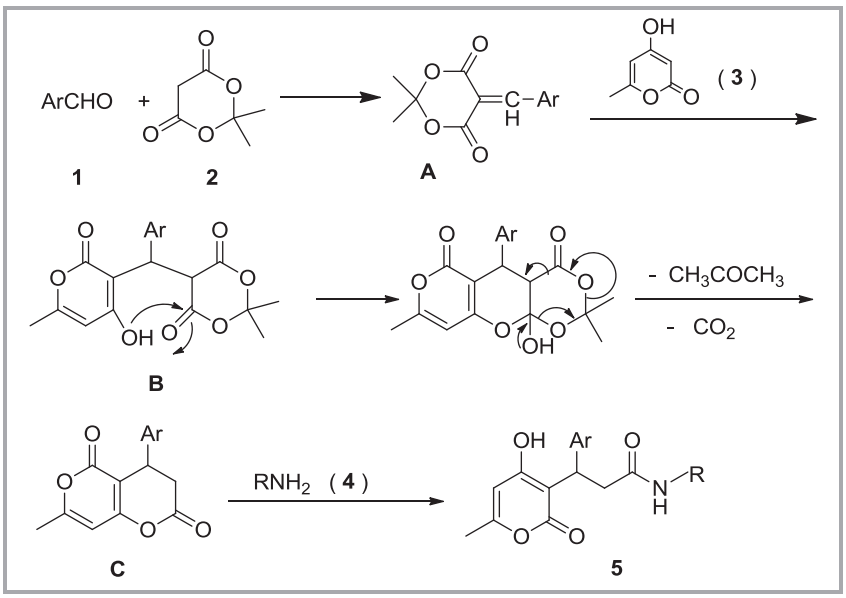


Figure 1. Molecular structure of **5e**.

Scheme 2. Possible mechanism for the formation of product **5**.



J = 8.8 Hz, 2H, ArH), 7.35 (d, J = 8.8 Hz, 2H, ArH), 7.41 (d, J = 8.0 Hz, 2H, ArH), 9.90 (s, 1H, NH), 11.58 (s, 1H, OH). HRMS: *m/z* Calcd for $C_{22}H_{20}^{35}ClNO_4$: 420.0979 (M + Na); found 420.0992.

3-(4-Hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-*N*,3-di(*p*-tolyl) propanamide (5b). This compound was obtained as solid with mp 250–252°C. IR (KBr) ν: 3287, 3194, 3031, 1682, 1638, 1602, 1541, 1514, 1404, 1256, 996, 940, 818, 782 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 2.10 (s, 3H, CH_3), 2.21 (s, 6H, 2 × CH_3), 2.94 (dd, J_1 = 6.8 Hz, J_2 = 15.2 Hz, 1H, CH), 3.30 (dd, J_1 = 8.4 Hz, J_2 = 15.2 Hz, 1H, CH), 4.73 (t, J = 7.6 Hz, 1H, CH), 5.97 (s, 1H, CH), 7.05–7.00 (m, 4H, ArH), 7.24 (d, J = 8.0 Hz, 2H, ArH), 7.42 (d, J = 8.4 Hz, 2H, ArH), 9.87 (s, 1H, NH), 11.57 (s, 1H, OH). HRMS: *m/z* Calcd for $C_{23}H_{23}NO_4$: 378.1705 (M + H); found 378.1725.

3-(4-Hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-3-(4-methoxyphenyl)-*N*-*p*-tolylpropanamide (5c). This compound was obtained as solid with mp 230–232°C. IR (KBr) ν: 3232, 3113, 3071, 1684, 1645, 1606, 1565, 1512, 1456, 1253, 1167, 998, 932, 824, 782, 764 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 2.12 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 2.90 (dd, J_1 = 6.8 Hz, J_2 = 15.2 Hz, 1H, CH), 3.32 (dd, J_1 = 8.8 Hz, J_2 = 15.2 Hz, 1H, CH), 3.69 (s, 3H, CH_3O), 4.76 (t, J = 7.6 Hz, 1H, CH), 5.99 (s, 1H, CH), 6.82 (d, J = 8.8 Hz, 2H, ArH), 7.28 (d, J = 8.4 Hz, 2H, ArH), 7.36 (d, J = 8.4 Hz, 2H, ArH), 7.44 (d, J = 8.8 Hz, 2H, ArH), 9.84 (s, 1H, NH), 11.54 (s, 1H, OH). HRMS: *m/z* Calcd for $C_{23}H_{23}NO_5$: 416.1474 (M + Na); found 416.1467.

3-(3-Chlorophenyl)-3-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-*N*-*p*-tolylpropanamide (5d). This compound was obtained as solid with mp 259–261°C. IR (KBr) ν: 3287, 3155, 3067, 1681, 1638, 1604, 1541, 1515, 1474, 1318, 1255, 1128, 998, 817, 775, 697 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 2.12 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 2.93 (dd, J_1 = 6.8 Hz, J_2 = 15.2 Hz, 1H, CH), 3.35 (dd, J_1 = 8.8 Hz, J_2 = 15.2 Hz, 1H, CH), 4.76 (t, J = 7.6 Hz, 1H, CH), 6.00 (s, 1H, CH), 7.05 (d, J = 8.4 Hz, 2H, ArH), 7.20 (d, J = 7.2 Hz, 1H, ArH), 7.43–7.28 (m, 5H, ArH), 9.92 (s, 1H, NH), 11.64 (s, 1H, OH). HRMS: *m/z* Calcd for $C_{22}H_{20}^{35}ClNO_4$: 420.0979 (M + Na); found 420.0974.

3-(4-Hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-3-(2-nitrophenyl)-*N*-*p*-tolylpropanamide (5e). This compound was obtained as solid with mp 232–234°C. IR (KBr) ν: 3270, 3190, 3039, 1685, 1655, 1602, 1569, 1522, 1448, 1383, 1271, 1251, 1106, 997, 855, 821, 781, 712, 699 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 2.10 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 3.08 (dd, J_1 = 6.8 Hz, J_2 = 15.2 Hz, 1H, CH), 3.30 (dd, J_1 = 8.8 Hz, J_2 = 15.2 Hz, 1H, CH), 5.09 (t, J = 7.6 Hz, 1H, CH), 5.94 (s, 1H, CH), 7.06 (d, J = 8.4 Hz, 2H, ArH), 7.36–7.44 (m, 3H, ArH), 7.60 (t, J = 7.6 Hz, 1H, ArH), 7.70 (d, J = 8.0 Hz, 1H, ArH), 7.81 (d, J = 8.0 Hz, 1H, ArH), 9.91 (s, 1H, NH), 11.64 (s, 1H, OH). HRMS: *m/z* Calcd for $C_{22}H_{20}N_2O_6$: 431.1219 (M + Na); found 431.1212.

Crystal data. $C_{25}H_{27}N_3O_7$; M = 481.50, yellow block crystals, 0.60 × 0.44 × 0.30 mm, triclinic, space group P-1, a = 9.4431(14) Å, b = 10.0026(15) Å, c = 13.382(2) Å, α = 83.674(9)°, β = 80.784(9)°, γ = 77.878(8)°, V = 1216.0(3) Å^3, Z = 2, D_c = 1.315 g cm^{-1}, F (000) = 508, μ(MoKα) = 0.097 mm^{-1}. Intensity data were collected on a diffractometer with graphite monochromated MoKα radiation (λ = 0.71070 Å) using ω scan mode with 3.09° < θ < 25.34°. 4411 unique reflections were measured, and 3574 reflections with $I > 2\sigma(I)$ were used in the refinement. The structure was solved by direct methods and expanded using Fourier techniques. The final cycle of full-matrix least squares technique to R_1 = 0.0723 and wR_2 = 0.1766.

3-(3,4-Methylenedioxyphenyl)-3-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-*N*-*p*-tolylpropanamide (5f). This compound was obtained as solid with mp 228–230°C. IR (KBr) ν: 3297, 3208, 3033, 1680, 1650, 1603, 1543, 1515, 1446, 1252, 1041, 939, 817, 783 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 2.11 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 2.90 (dd, J_1 = 6.8 Hz, J_2 = 15.2 Hz, 1H, CH), 3.28 (dd, J_1 = 8.8 Hz, J_2 = 15.2 Hz, 1H, CH), 4.69 (t, J = 7.6 Hz, 1H, CH), 5.91 (s, 2H, OCH_2O), 5.98 (s, 1H, CH), 6.73–6.80 (m, 2H, ArH), 6.94 (s, 1H, ArH), 7.04 (d, J = 8.0 Hz, 2H, ArH), 7.42 (d, J = 8.0 Hz, 2H, ArH), 9.86 (s, 1H, NH), 11.46 (s, 1H, OH). HRMS: *m/z* Calcd for $C_{23}H_{21}NO_6$: 430.1267 (M + Na); found 430.1271.

3-(4-Hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-3-(thiophen-2-yl)-*N*-*p*-tolylpropanamide (5g). This compound was obtained as solid with mp 263–265°C. IR (KBr) ν: 3287, 3206, 3079, 1684, 1651, 1603, 1541, 1515, 1445, 1128, 997, 851, 818, 783, 697 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 2.12 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 3.00 (dd, J_1 = 6.8 Hz, J_2 = 15.2 Hz, 1H, CH), 3.31 (dd, J_1 = 8.8 Hz, J_2 = 15.2 Hz, 1H, CH), 5.00 (t, J = 7.6 Hz, 1H, CH), 6.00 (s, 1H, CH), 6.89–6.85 (m, 2H, ArH), 7.05 (d, J = 8.4 Hz, 2H, ArH), 7.21 (d, J = 4.4 Hz, 2H, ArH), 7.44 (d, J = 8.4 Hz, 2H, ArH), 9.92 (s, 1H, NH), 11.60 (s, 1H, OH). HRMS: *m/z* Calcd for $C_{20}H_{19}NO_4S$: 392.0933 (M + Na); found 392.0928.

***N*-(3-Chlorophenyl)-3-(4-chlorophenyl)-3-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)propanamide (5h)**. This compound was obtained as solid with mp 272–274°C. IR (KBr) ν: 3276, 3192, 3078, 1682, 1647, 1594, 1541, 1490, 1446, 1221, 1059, 973, 818, 731, 718, 685 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 2.12 (s, 3H, CH_3), 3.00 (dd, J_1 = 6.8 Hz, J_2 = 15.2 Hz, 1H, CH), 3.35 (dd, J_1 = 8.8 Hz, J_2 = 15.2 Hz, 1H, CH), 4.75 (t, J = 7.6 Hz, 1H, CH), 6.00 (s, 1H, CH), 7.05 (d, J = 7.6 Hz, 1H, ArH), 7.28–7.40 (m, 6H, ArH), 7.77 (s, 1H, ArH), 10.21 (s, 1H, NH), 11.65 (s, 1H, OH). HRMS: *m/z* Calcd for $C_{21}H_{17}^{35}Cl_2NO_4$: 440.0433 (M + Na); found 440.0411.

3-(4-Chlorophenyl)-*N*-(4-fluorophenyl)-3-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)propanamide (5i). This compound was obtained as solid with mp 225–227°C. IR (KBr) ν: 3292, 3156, 3090, 1677, 1643, 1616, 1587, 1510, 1445, 1289, 1257, 978, 835, 789, 768, 709 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 2.12 (s, 3H, CH_3), 2.95 (dd, J_1 = 6.8 Hz, J_2 = 15.2 Hz, 1H, CH), 3.32 (dd, J_1 = 8.8 Hz, J_2 = 15.2 Hz, 1H, CH), 4.76 (t, J = 7.6 Hz, 1H, CH), 5.99 (s, 1H, CH), 7.09 (t, J = 8.8 Hz, 2H, ArH), 7.29 (d, J = 8.4 Hz, 2H, ArH), 7.35 (d, J = 8.4 Hz, 2H, ArH), 7.53–7.57 (m, 2H, ArH), 10.05 (s, 1H, NH), 11.55 (s, 1H, OH). HRMS: *m/z* Calcd for $C_{21}H_{17}^{35}ClFNO_4$: 424.0728 (M + Na); found 424.0717.

3-(4-Chlorophenyl)-3-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-*N*-(4-nitrophenyl)propanamide (5j). This compound was obtained as solid with mp 246–247°C. IR (KBr) ν: 3217, 3047, 1684, 1652, 1615, 1584, 1557, 1511, 1446, 1381, 1242, 1091, 977, 858, 778, 733, 712, 689 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 2.12 (s, 3H, CH_3), 3.10 (dd, J_1 = 6.8 Hz, J_2 = 15.2 Hz, 1H, CH), 3.43 (dd, J_1 = 8.8 Hz, J_2 = 15.2 Hz, 1H, CH), 4.76 (t, J = 7.6 Hz, 1H, CH), 6.00 (s, 1H, CH), 7.30 (d, J = 8.4 Hz, 2H, ArH), 7.36 (d, J = 8.4 Hz, 2H, ArH), 7.79 (d, J = 8.8 Hz, 2H, ArH), 8.18 (d, J = 8.8 Hz, 2H, ArH), 10.64 (s, 1H, NH), 11.65 (s, 1H, OH). HRMS: *m/z* Calcd for $C_{21}H_{17}^{35}ClN_2O_6$: 451.0673 (M + Na); found 451.0665.

***N*-(2-Chlorophenyl)-3-(4-chlorophenyl)-3-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)propanamide (5k)**. This compound was obtained as solid with mp 220–222°C. IR (KBr) ν: 3224, 3195, 3038, 1681, 1616, 1586, 1544, 1490, 1475, 1443, 1255, 1061, 996,

859, 812, 778, 731, 705 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 2.13 (s, 3H, CH_3), 3.03 (dd, J_1 = 6.8 Hz, J_2 = 15.2 Hz, 1H, CH), 3.30 (dd, J_1 = 8.8 Hz, J_2 = 15.2 Hz, 1H, CH), 4.74 (t, J = 7.6 Hz, 1H, CH), 6.00 (s, 1H, CH), 7.17 (t, J = 6.8 Hz, 1H, ArH), 7.26–7.31 (m, 3H, ArH), 7.38 (d, J = 8.4 Hz, 2H, ArH), 7.45 (d, J = 6.8 Hz, 1H, ArH), 7.53 (d, J = 7.2 Hz, 1H, ArH), 9.56 (s, 1H, NH), 11.57 (s, 1H, OH). HRMS: *m/z* Calcd for $C_{21}H_{17}^{35}Cl_2NO_4$: 440.0433 (M + Na); found 440.0422.

***N*-(3-Chloro-4-methylphenyl)-3-(4-chlorophenyl)-3-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)propanamide (5l)**. This compound was obtained as solid with mp 238–240°C. IR (KBr) ν: 3293, 3194, 3060, 1677, 1646, 1597, 1538, 1498, 1446, 1254, 1106, 978, 867, 817, 786, 709, 694 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 2.12 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 2.98 (dd, J_1 = 6.8 Hz, J_2 = 15.2 Hz, 1H, CH), 3.33 (dd, J_1 = 8.8 Hz, J_2 = 15.2 Hz, 1H, CH), 4.76 (t, J = 7.6 Hz, 1H, CH), 6.00 (s, 1H, CH), 7.21 (d, J = 8.4 Hz, 1H, ArH), 7.28–7.30 (m, 3H, ArH), 7.35 (d, J = 8.4 Hz, 2H, ArH), 7.75 (s, 1H, ArH), 10.10 (s, 1H, NH), 11.56 (s, 1H, OH). HRMS: *m/z* Calcd for $C_{22}H_{19}^{35}Cl_2NO_4$: 454.0589 (M + Na); 454.0587.

***N*-Benzyl-3-(4-chlorophenyl)-3-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)propanamide (5m)**. This compound was obtained as solid with mp 223–225°C. IR (KBr) ν: 3260, 3101, 3027, 1683, 1646, 1600, 1507, 1559, 1490, 1446, 1318, 1267, 996, 791, 696 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 2.12 (s, 3H, CH_3), 2.80 (dd, J_1 = 6.8 Hz, J_2 = 15.2 Hz, 1H, CH), 3.17 (dd, J_1 = 8.8 Hz, J_2 = 15.2 Hz, 1H, CH), 4.13–4.25 (m, 2H, CH_2), 4.70 (t, J = 8.0 Hz, 1H, CH), 5.99 (s, 1H, CH), 7.00 (d, J = 6.0 Hz, 2H, ArH), 7.18–7.22 (m, 3H, ArH), 7.28 (d, J = 8.8 Hz, 2H, ArH), 7.35 (d, J = 8.4 Hz, 2H, ArH), 8.39 (s, 1H, NH), 11.52 (s, 1H, OH).

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