A highly efficient protocol for the synthesis of new 3-(α-aroylamido)-4-hydroxycoumarin derivatives using $SnCl_2$–SiO_2 nanoparticles under solvent-free conditions

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An efficient and simple protocol for the synthesis of the title compounds is described *via* a one-pot, three-component reaction of 4-hydroxycoumarin, aryl glyoxals and amides, using $SnCl_2$–SiO_2 nanoparticles as a heterogeneous catalyst under solvent-free conditions. The advantages of this synthesis include excellent yields, mild reaction conditions, atom economy, a reusable catalyst and no need for chromatographic separations.

Keywords: solvent-free, $SnCl_2$–SiO_2 nanoparticles, aryl glyoxal, 4-hydroxycoumarin, multi-component reactions

Coumarin and its derivatives are an important class of heterocyclic compounds and are the key core of various natural products.[1,2] The application of coumarin derivatives as bioactive molecules against different kinds of diseases is of great interest for medicinal chemists. Coumarin derivatives have a wide spectrum of biological activities, such as anticancer, anticoagulant, anti-HIV, antimalarial and anti-inflammatory activities, and are usually associated with low toxicity.[3–7] The most significant are 3-substituted-4-hydroxy coumarin derivatives, which have important clinical applications[8,9] (Fig. 1).

A literature survey reveals that tin salts show high Lewis acidity compared with other transition metal salts, in the order $Sn^{2+} >> Zn^{2+} > Pb^{2+} \approx Hg^{2+}$.[10] As Sn^{2+} salts have higher Lewis acidity compared with other metal salts, we selected $SnCl_2$ as a homogeneous catalyst. Furthermore, to improve the efficiency, loading, applicability and recyclability of the catalyst, we chose silica nanoparticles as a partner due to their high surface area, large pore volume and recyclability. Hence, silica nanoparticles may be useful as supports for the immobilisation of Sn^{2+} salts. We immobilised $SnCl_2$ by reaction of the hydroxyl groups on silica (Scheme 1), thus converting a homogeneous $SnCl_2$ catalyst into a heterogeneous catalyst with improved features for the synthesis of 3-(α-aroylamido)-4-hydroxycoumarin derivatives.

Multi-component reactions (MCRs) are important for generating high levels of diversity, as they allow more than two building blocks to be combined in a practical, time-saving, one-pot operation, giving rise to complex structures by simultaneous formation of two or more bonds.

MCRs have received considerable attention because of their wide range of applications in pharmaceutical chemistry for the creation of structural diversity and combinatorial libraries for drug discovery.[11,12]

Recently, we reported the reaction of 4-hydroxycoumarin, aromatic aldehydes and amides in the presence of *p*-toluene sulfonic acid to produce 3-(α-amidobenzyl)-4-hydroxycoumarin derivatives.[13] Khodabakhshi *et al.* have reported a three-component process for the synthesis of aroylamido coumarin derivatives from reaction of aryl glyoxal, benzamide and 4-hydroxycoumarin in the presence of molybdate sulfuric acid, tungstate sulfuric acid, zirconium oxychloride and Fe_3O_4 nanoparticles.[14–17] However, these methods have drawbacks, such as requiring long reaction times,[13,17] acidic conditions,[13-15] column chromatography to purify the products[14–16] and expensive catalysts, as well as catalysts that are not recyclable.[13,14,16] In all of these reports, reactions with aromatic amides were reported. Therefore, there is scope to develop more efficient and convenient methods for the synthesis of new coumarin

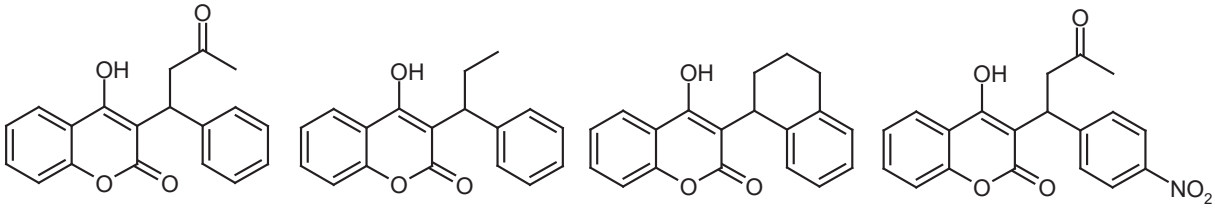
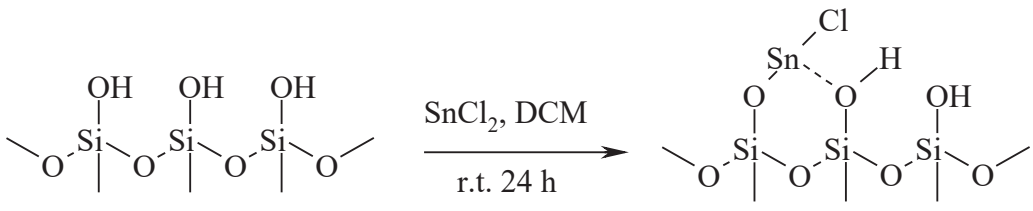


Fig. 1 3-Substituted-4-hydroxy coumarin derivatives.



Scheme 1

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derivatives. To the best of our knowledge, there are no reports on the use of $SnCl_2$–SiO_2 nanoparticles (NPs) in the synthesis of 3-(α-aroylamido)-4-hydroxycoumarin derivatives.

Considering the above reports and in continuation of our studies on one-pot MCRs,[18–20] we here report for the first time a one-pot, three-component reaction of 4-hydroxycoumarin or 4-hydroxy-6-methylpyran-1-one **1**, aryl glyoxals **2** and aliphatic amides **3**, in the presence of $SnCl_2$–SiO_2 NPs as a heterogeneous catalyst for the synthesis of 3-(α-aroylamido)-4-hydroxycoumarin derivatives **4** in solvent-free conditions (Scheme 2).

Aryl glyoxals **2** were prepared by the reaction between their corresponding acetophenone and SeO_2 according to reported procedures.[21] First, to optimise the reaction conditions, the reaction of 4-hydroxycoumarin with *p*-methyl phenyl glyoxal and acetamide was selected as a model. As the formation of bis-aroyl coumarins[22] is possible, we first treated acetamide with *p*-methyl phenyl glyoxal to form the corresponding imine and then added 4-hydroxycoumarin to the mixture. In all cases, the reaction was performed under solvent-free conditions. To find the best and most effective catalyst, we screened the model reaction in the presence of different nanocatalysts, such as CaO, $FeCl_3$, Fe_3O_4, SiO_2, $SnCl_2$ and $SnCl_2$–SiO_2 (Table 1). The results showed that $SnCl_2$–SiO_2 NPs was the most efficient catalyst for the reaction in solvent-free conditions (Table 1, entry 7). Only a trace amount of the product was formed in the absence of catalyst (Table 1, entry 1).

To find the optimum amount of catalyst, we screened the model reaction in the absence and presence of several amounts of $SnCl_2$–SiO_2 NPs. In the absence of the $SnCl_2$–SiO_2 NPs, only a trace amount of the product was formed. In the presence of $SnCl_2$–SiO_2 NPs, it was found that 20 mol% of $SnCl_2$–SiO_2 NPs is optimal to carry out the reaction over a short duration. However, further increase of the molar amount of the catalyst from 20 mol% to 40 mol% did not significantly increase the yield of the product.

Table 1 Preparation of *N*-[1-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxo-2-*p*-tolyl-ethyl]-acetamide (**4a**) using different catalysts[a]

Entry	Catalyst	Catalyst (mol %)	Time (h)	Yield[b] (%)
1	–	–	3	trace
2	MgO	20	2	30
3	Al_2O_3	20	2	35
4	CaO	20	2	40
5	$FeCl_3$	20	2	35
6	SiO_2	20	2	45
7	$SnCl_2$	20	2	50
8	Fe_3O_4	20	2	75
9	$SnCl_2$-SiO_2	20	2	82

[a]Reaction conditions: 4-hydroxy coumarin (1.0 mmol), acetamide (1.1 mmol), p-methyl phenyl glyoxal (1.0 mmol), neat 100°C.
[b]Isolated yield.

To study the scope of the reaction, a series of aryl glyoxals were employed. The results are shown in Table 2. In all cases, the aromatic ring of the aryl glyoxal substituted with either electron-donating or electron-withdrawing groups underwent the reaction smoothly and gave the products in good yields (Table 2).

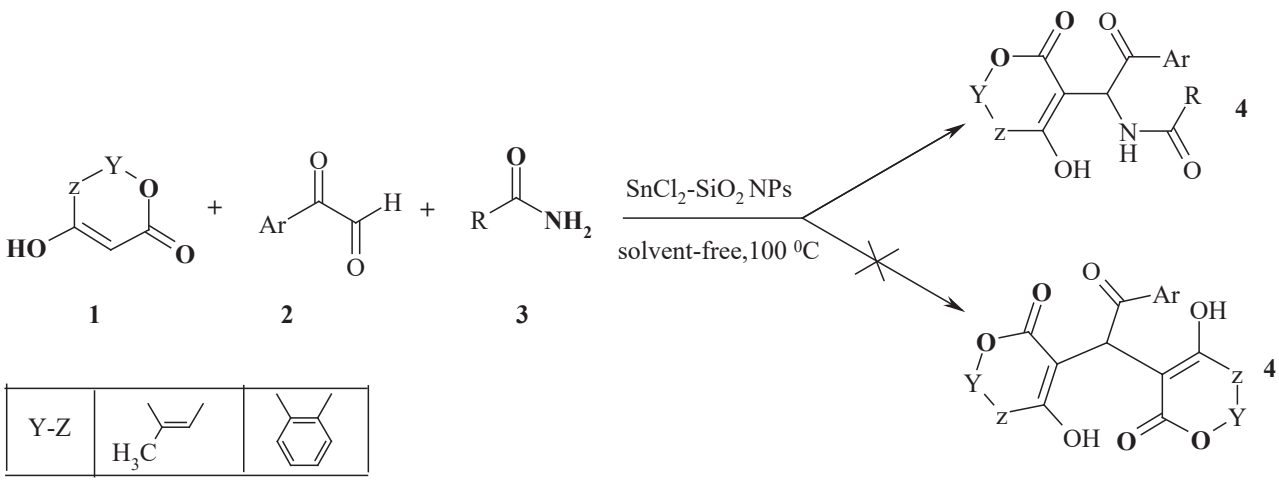
Compounds **4a–i** were new and their structures were deduced by elemental and spectral analysis. The ^{1}H NMR spectrum of compound **4a** exhibited a two-singlet signal at δ = 2.21 and 2.35 ppm for the protons of the methyl groups. The methine and NH protons are coupled and two doublets were observed for them at 6.03 and 8.09 ppm, respectively. When the ^{1}H NMR spectrum was recorded after addition of some D_2O to the $CDCl_3$ solution of **4a**, the doublet related to the NH proton disappeared and the doublet corresponding to the methine proton was converted to a singlet. The proton of the hydroxyl group resonated at 12.78 ppm as a broad singlet. The ^{13}C NMR spectrum of compound **4a** showed 18 distinct signals consistent with the proposed structure.

A possible mechanism for the formation of the products **4a–i** is proposed in Scheme 3. The reaction of aryl glyoxal **2** with amides **3** in the presence of the $SnCl_2$–SiO_2 NPs catalyst is proposed to give the corresponding iminium ion **5**. Next attack of 4-hydroxycoumarin or 4-hydroxy-6-methylpyran-1-one **1** by the iminium ion **5** followed by a 1,3-H shift leads to the final product **4** (Scheme 3).

The reusability of the catalyst was tested in the synthesis of 3-(α-aroylamido)-4-hydroxycoumarin derivatives. The catalyst was recovered after each run, washed with ethanol, dried in an oven at 100 °C for 20 min before use and tested for its activity in the subsequent run. The catalyst was tested for three runs. The catalyst showed very good reusability. It was determined that the catalyst can be recycled for at least two cycles without any change in activity.

Conclusion

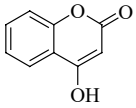
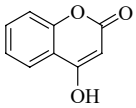
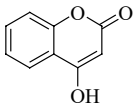
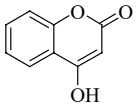
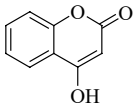
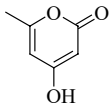
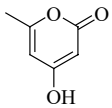
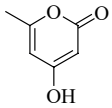
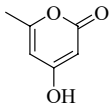
In summary, the reaction between 4-hydroxycoumarin or 4-hydroxy-6-methylpyran-1-one, aryl glyoxals and aliphatic amides in the presence of a catalytic amount of $SnCl_2$–SiO_2 NPs provides a simple one-pot entry for the synthesis of 3-(αaroylamido)-4-hydroxycoumarin derivatives of potential synthetic and pharmaceutical interest. This method has advantages, such as the use of a safe, inexpensive and recyclable catalyst, avoidance of



Scheme 2 Reaction between 4-hydroxycoumarin or 4-hydroxy-6-methylpyran-1-one, aryl glyoxals and aliphatic amides, catalysed by $SnCl_2$–SiO_2 NPs.

organic solvents, high yields of products and short reaction times. Furthermore, all products were obtained through simple filtration with no need for column chromatography, which reduces the waste as well as environmental pollution.

Table 2 Three-component reaction of 4-hydroxycoumarin or 4-hydroxy-6-methylpyran-1-one, aryl glyoxals and amides, catalysed by $SnCl_2$–SiO_2 NPs

Entry	Substrate	Ar	R	Time (min)	Yield (%)	M.p. (°C)
4a		4-CH_3-C_6H_4	CH_3	120	82	202–205
4b		C_6H_5	CH_3	120	78	196–198
4c		C_6H_5	C_2H_5	130	82	200
4d		4-CH_3-C_6H_4	C_2H_5	100	75	198–200
4e		4-Cl-C_6H_4	C_2H_5	100	80	190
4f		4-CH_3-C_6H_4	CH_3	110	76	189
4g		C_6H_5	CH_3	120	82	190–192
4h		4-CH_3-C_6H_4	C_2H_5	120	85	200–202
4i		4-Cl-C_6H_4	CH_3	120	80	201

Experimental

Melting points were determined with an Electrothermal 9100 apparatus. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyser. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionisation potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 Avance spectrometer in solution in $CDCl_3$ using TMS as an internal standard. The chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification.

Preparation of nano silica-supported stannous chloride

Nano silica gel-supported tin (II) chloride was prepared according to the procedure reported in the literature with some modifications.[23,24] In a typical procedure, tin (II) chloride dihydrate (0.28 g) was added to a suspension of silica gel nanoparticles (3.075 g) in dichloromethane (DCM) (25.0 mL). The mixture was stirred at r.t. overnight. Then the solvent was removed under reduced pressure and the residue was heated at 100 °C under vacuum for 5 h to furnish $SnCl_2$–SiO_2 NPs. The prepared $SnCl_2$–SiO_2 NPs were structurally characterised by SEM analysis and the IR spectrum. Figure 2 indicates that the original morphology of the nanoparticles was approximately spherical with the diameter varying between 25 and 60 nm.

Synthesis of 3-(α-aroylamido)-4-hydroxycoumarin derivatives (**4a–i**)*; general procedure*

A mixture of aryl glyoxal (1 mmol), amides (1.1 mmol) and $SnCl_2$–SiO_2 NPs (20 mol%) was stirred and heated at 70 °C for 30 min. Then

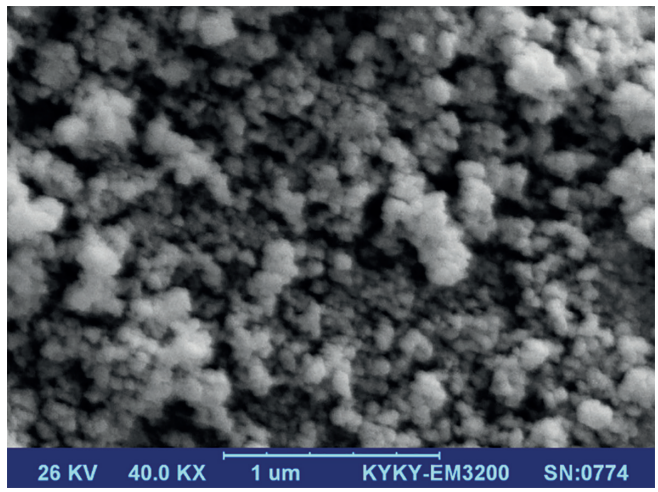
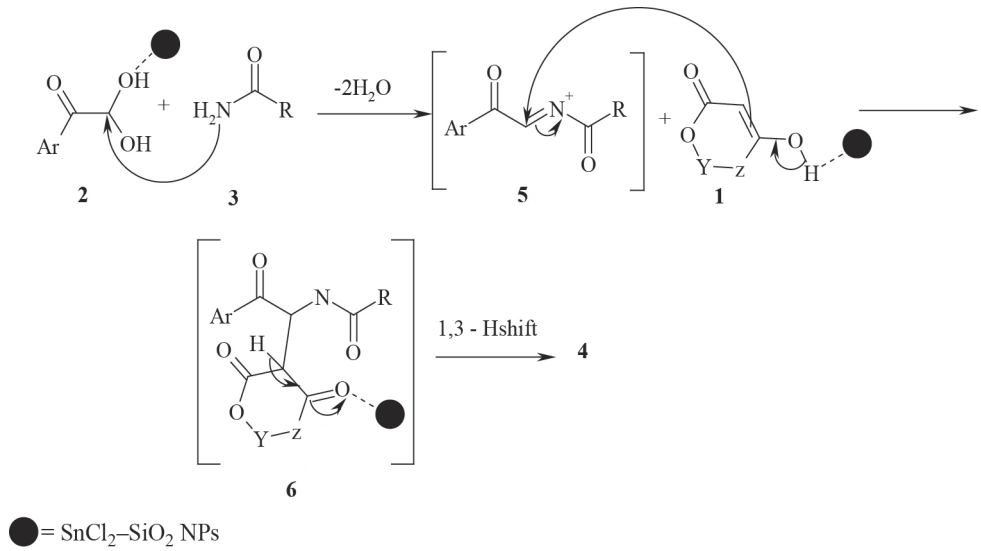


Fig. 2 SEM image of synthesised $SnCl_2$–SiO_2 NPs.



Scheme 3 Suggested pathway for the formation of compounds **4a–i**.

4-hydroxycoumarin or 4-hydroxy-6-methylpyran-1-one (1 mmol) was added to the mixture and the reaction was stirred for the appropriate amount of time (100–130 min) at 100 °C. The reaction progress was monitored by TLC (EtOAc:hexane, 1:2). After reaction completion, the mixture was added to hot EtOH and centrifuged to separate the catalyst. The solvent was evaporated and the products were purified by recrystallisation from EtOH.

N-*[1-(4-Hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxo-2*-p-*tolyl-ethyl]-acetamide* (**4a**): White powder, m.p. 202–205 °C; IR (KBr) (ν_{max}, cm^{-1}): 3309 (N–H), 1690 (C=O); MS (*m/z*, %): 351 (7); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.21 (3 H, s, CH_3), 2.35 (3 H, s, CH_3), 6.03 (1H, d, $^3J_{HH}$ = 6 Hz, C*H*–NH), 7.16–8.01 (8H, m, arom), 8.08 (1H, d, $^3J_{HH}$ = 6 Hz, N*H*), 12.78 (1H, broad, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.70 (*C*H_3), 22.54 (*C*H_3), 51.73 (*C*H–NH), 104.81, 116.54, 116.60, 124.13, 124.64, 128.20, 129.43, 131.49, 132.85, 144.75, 153.27, 161.64 (C arom and olefin), 165.41, 173.44, 192.18 (3*C*=O). Anal. calcd for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.88; N, 3.99; found: C, 68.59; H, 4.75; N, 3.90%.

N-*[1-(4-Hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxo-2-phenyl-ethyl]-acetamide* (**4b**): White powder; m.p. 196–198 °C; IR (KBr) (ν_{max}, cm^{-1}): 3376 (N–H), 1695 (C=O); MS (*m/z*, %): 337 (9); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.21(3H, s, CH_3), 6.08 (1H, d, $^3J_{HH}$ = 6.5 Hz, C*H*–NH), 7.09–7.82 (9H, m, arom), 8.06 (1H, d, $^3J_{HH}$ = 6.5 Hz, NH), 12.82 (1H, broad, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.42 (CH_3), 50.12 (CH), 101.12, 121.54, 125.52, 126.82, 128.41, 128.78, 129.85, 130.81, 133.24, 143.17, 152.11, 161.19 (C arom and olefin), 163.93, 171.15, 187.46 (3*C*=O). Anal. calcd for $C_{19}H_{15}NO_5$: C, 67.65; H, 4.48; N, 4.15; found: C, 67.55; H, 4.32; N, 4.23%.

N-*[1-(4-Hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxo-2-phenyl-ethyl]-propinamide* (**4c**): White powder; m.p. 200 °C; IR (KBr) (ν_{max}, cm^{-1}): 3340 (N–H), 1694 (C=O); MS (*m/z*, %): 351 (6); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 (3H, t, CH_3, $^3J_{HH}$ = 7.5 Hz), 2.46 (2H, q, $^3J_{HH}$ = 7.5 Hz, CH_2), 6.05 (1H, d, $^3J_{HH}$ = 6 Hz, C*H*–NH), 7.12–8.03 (9H arom and OH), 8.16 (1H, d, $^3J_{HH}$ = 6 Hz, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.04 (*C*H_3), 29.82 (*C*H_2), 50.45 (*C*H–NH), 92.62, 117.54, 122.56, 125.57, 126.83, 128.46, 128.66, 128.89, 133.27, 136.81, 152.45, 161.93 (C arom), 162.15, 173.74, 187.45 (3*C*=O). Anal. calcd for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.88; N, 3.99; found: C, 68.45; H, 4.77; N, 3.86%.

N-*[1-(4-Hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxo-2-*p-*tolyl-ethyl]-propionamide* (**4d**): White powder; m.p. 198–200 °C; IR (KBr) (ν_{max}, cm^{-1}): 3376 (N–H), 1695 (C=O); MS (*m/z*, %): 365 (11); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (3H, m, CH_3), 2.26 (3H, s, CH_3), 2.46 (2H, q, $^3J_{HH}$ = 7.2 Hz, CH_2), 6.05 (1H, d, $^3J_{HH}$ = 6.5 Hz, C*H*–NH), 6.99–8.01 (9H arom and OH), 8.22 (1H, d, $^3J_{HH}$ = 6.5 Hz, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.01 (CH_3), 24.35 (CH_3), 29.83 (CH_2), 50.45 (*C*H–NH), 103.22, 115.78, 121.52, 126.81, 128.72, 129.77, 129.47, 133.58, 135.26, 137.58, 150.26, 162.92 (C arom and olefin), 164.33, 173.75 ,187.49 (3*C*=O). Anal. calcd for $C_{21}H_{19}NO_5$: C, 69.03; H, 5.24; N, 3.83; found: C, 69.17; H, 5.32; N, 3.71%.

N-*[2-(4-Chloro-phenyl)-1-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxo-ethyl]-propionamide* (**4e**): White powder; m.p. 190 °C; IR (KBr) (ν_{max}, cm^{-1}): 3351 (N–H), 1694 (C=O); MS (*m/z*, %): 385 (7); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 (3H, t, $^3J_{HH}$ = 7.5 Hz, CH_3), 2.48 (2H, q, $^3J_{HH}$ = 7.5 Hz, CH_2), 6.02 (1H, d, $^3J_{HH}$ = 6 Hz, CH–NH), 7.14–8.11 (9H arom and OH), 8.02 (1H, d, $^3J_{HH}$ = 6.5 Hz, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.51 (CH_3), 28.85 (CH_2), 51.77 (CH–NH) 104.24, 116.53, 124.26, 124.65, 128.70, 129.01, 129.38, 132.57, 132.85, 134.26, 140.02, 153.20 (C arom and olefin), 167.75, 177.24, 191.86 (3*C*=O). Anal. calcd for $C_{20}H_{16}ClNO_5$: C, 62.26; H, 4.18; N, 3.63; found: C, 62.32; H, 4.06; N, 3.51%.

N-*[1-(4-Hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-2-oxo-2-*p-*tolyl-ethyl]-acetamide* (**4f**): White powder; m.p. 189 °C; IR (KBr) (ν_{max}, cm^{-1}): 3287 (N–H), 1690 (C=O); MS (*m/z*, %): 315 (6); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.15 (3H, s, CH_3), 2.21 (3H, s, CH_3), 2.35 (3H, s, CH_3), 5.90 (1H, d, $^3J_{HH}$ = 6.2 Hz, *C*H–NH), 6.06 (1H, s, C*H*=C), 7.13–7.73 (5H arom), 8.02 (1H, d, $^3J_{HH}$ = 6 Hz, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.01(*C*H_3), 23.43 (*C*H_3), 24,33 (*C*H_3), 50.63 (*C*H–NH), 101.05, 128.76, 128.85, 129.45, 129.65, 133.84, 142.85, 162.25 (C arom and olefin), 167.68, 171.12, 187.43 (3*C*=O). Anal. calcd for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43; N, 4.44; found: C, 64.82; H, 5.31; N, 4.54%.

N-*[1-(4-Hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-2-oxo-2-phenyl-ethyl]-acetamide* (**4g**): White powder; m.p. 190–192 °C; IR (KBr) (ν_{max}, cm^{-1}): 3289 (N–H), 1683 (C=O); MS (*m/z*, %): 301 (12); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.05 (3H, s, CH_3), 2.21 (3H, s, CH_3), 5.91 (1H, d, $^3J_{HH}$ = 7 Hz, C*H*–NH), 6.06 (1H, s, C*H*=C), 7.26–7.82 (6H, arom), 8.10 (1H, d, $^3J_{HH}$ = 7 Hz, N*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.63 (*C*H_3), 22.52 (*C*H_3), 51.24 (*C*H–NH), 101.97, 103.07, 128.08, 128.58, 129.50, 132.96, 135.75, 162.04 (C arom and olefin), 170.94, 173.63, 194.19 (3*C*=O). Anal. calcd for $C_{16}H_{15}NO_5$: C, 63.78; H, 5.02; N, 4.65; found: C, 63.69; H, 5.11; N, 4.57%.

N-*[1-(4-Hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-2-oxo-2-*p-*tolyl-ethyl] propionamide* (**4h**): White powder; m.p. 200–202 °C; IR (KBr) (ν_{max}, cm^{-1}): 3290 (N–H), 1692 (C=O); MS (*m/z*, %): 329 (7); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18 (3H, t, $^3J_{HH}$ = 7.5 Hz, CH_3), 2.09 (3H, s, CH_3), 2.19 (3H, s, CH_3), 2.34 (2H, m, CH_2), 5.92 (1H, d, $^3J_{HH}$ = 6 Hz, C*H*–NH), 6.05 (1H, s, CH=C), 7.15–7.72 (5H, arom), 7.95 (1H, broad, N*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.59 (*C*H_3), 19.79 (*C*H_3), 28.98 (*C*H_2), 50.99 (*C*H), 102.13, 103.05, 128.18, 129.09, 129.28, 131.61, 133.10, 144.57, 163.12 (C arom and olefin), 169.41, 176.59, 194.61 (3*C*=O); Anal. calcd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.81; N, 4.25; found: C, 65.52; H, 5.73; N, 4.11%.

N-*[2-(4-Chloro-phenyl)-1-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-2-oxo-ethyl]-acetamide* (**4i**): White powder; m.p. 201 °C; IR (KBr) (ν_{max}, cm^{-1}): 3295 (N–H), 1693 (C=O); MS (*m/z*, %): 335 (11); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.01 (3H, s, CH_3), 2.20 (3H, s, CH_3), 5.90 (1H, d, $^3J_{HH}$ = 6.5 Hz, C*H*–NH), 6.13 (1H, s, C*H*=C), 7.35 (2H, d, $^3J_{HH}$ = 8.7 Hz, arom), 7.75 (2H, d, $^3J_{HH}$ = 8.7 Hz, arom), 7.95 (1H, d, $^3J_{HH}$ = 6.5 Hz, N*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.66 (*C*H_3), 22.50 (*C*H_3), 51.25 (*C*H), 102.14, 103.04, 128.74, 128.96, 129.42, 132.57, 140.03, 163.48 (C arom and olefin), 169.77, 173.46, 192.11 (3*C*=O). Anal. calcd for $C_{16}H_{14}ClNO_5$: C, 57.24; H, 4.20; N, 4.17; found: C, 57.33; H, 4.11; N, 4.23%.

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