

Chromone-3-carboxaldehydes in Passerini Reactions Using TosMIC as the Isonitrile Component

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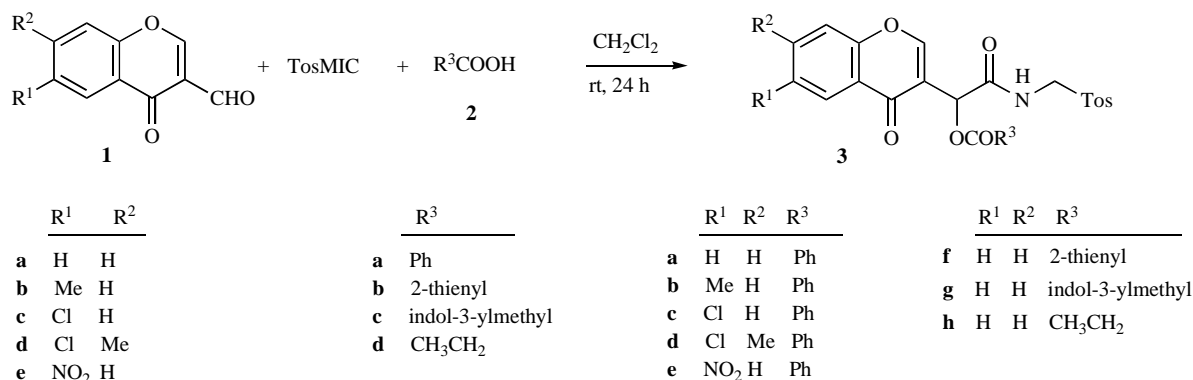
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Abstract: *p*-Toluenesulfonylmethyl isocyanide (TosMIC) is used as the isonitrile component in Passerini reactions with chromone-3-carboxaldehydes to yield chromenyl-amidoesters in good yields.

Keywords: Chromenyl-acetamides, chromone-3-carboxaldehydes, Passerini reaction, three component reaction, TosMIC

Besides forming the basic nucleus of an entire class of natural products, i.e. flavones [1], the chromone moiety forms the important component of pharmacophores of a large number of molecules of medicinal significance [2] including anticancer agents, such as psorospermin and pluramycin A [3,4]. Consequently, considerable attention is being devoted to isolation from natural resources, chemistry and synthesis of chromone derivatives, and evaluation of their biological activity with stress on their potential medicinal applications [2-6]. Chromone-3-carboxaldehyde represents a very reactive system owing to the presence of an unsaturated keto function, a conjugated second carbonyl group at C-3 and of a reactive center at C-2. Therefore, chromone-

isocyanides are very versatile reactions [12] in terms of scaffolds and number of accessible compounds. Amongst these reactions, the Passerini [13] multicomponent reaction occupies an important position. However, the synthetic utility of TosMIC as an isonitrile input in a Passerini reaction remains yet underexploited, although further advantages could derive from the fact that the products, besides being diversely functionalized, also bear an additional methylene group, which can serve as a handle for further manipulation. Only very recently, Krisna *et al.* [14] studied the use of TosMIC as the isonitrile component in Passerini reactions with 2,3-epoxy- and sugar derived aldehydes. TosMIC has most commonly been used [15] in heterocyclic ring construction, in particular



Scheme 1. Reaction of chromone-3-carboxaldehydes **1** with TosMIC in the presence of carboxylic acids **2**.

3-carboxaldehydes can be readily converted into a broad range of heterocyclic systems either by cycloaddition strategies [7,8] or through reaction with several nucleophiles [9,10].

Moreover, the rich and fascinating chemistry that stems from multicomponent reactions (MCRs) provides [11] a powerful tool towards the one-pot synthesis of diverse and complex compounds on the one hand and small and 'drug-like' heterocycles on the other hand. MCRs that involve

of oxazole and pyrrole moieties. Recently, we published the 2-tosyl-4-(2-hydroxybenzoyl) pyrrole synthesis mediated by the reaction between chromone-3-carboxaldehydes with TosMIC [16]. This work motivated us to extrapolate the synthetic utility of TosMIC as an isonitrile moiety in three component reactions involving chromone-3-carboxaldehydes, aiming at the isolation of chromenyl-amidoesters, in view of the diverse biological activity shown by 3-substituted chromone derivatives [17].

When a methylene chloride solution of the chromone-3-carboxaldehydes (**1a–1e**) was allowed to react with equimolar amounts of benzoic acid and TosMIC 2-benzoyloxy-2-(4-oxo-4*H*-chromen-3-yl)-*N*-*p*-tosylmethyl-acetamides (**3a–3e**) were isolated in very good yields 70–85% (Scheme 1, Table

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Table 1. Reactants and Products

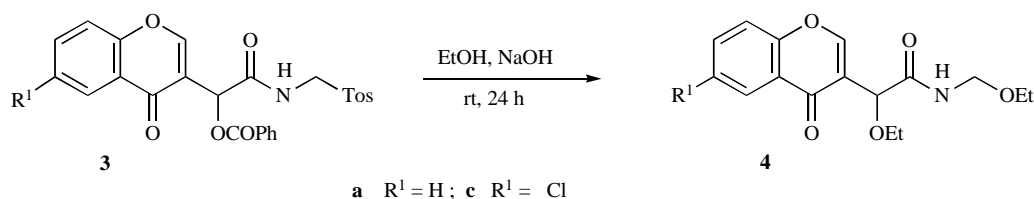
Entry	Chromone	Acid	Prod	Yield %
1	1a	2a	3a	72
2	1b	2a	3b	70
3	1c	2a	3c	85
4	1d	2a	3d	75
5	1e	2a	3e	80
6	1a	2b	3f	32
7	1a	2c	3g	35
8	1a	2d	3h	29

1) [18,19]. The reaction proceeded successfully also with acids containing a heterocyclic ring, such as 2-thiophenyl and 3-indolylacetic acids, though in lower yields. Having established a positive outcome of the Passerini reaction by using an aromatic acid, in order to examine the generality of the reaction, the reaction was repeated with the aliphatic propionic acid. The reaction proceeded uniformly to afford product **3h**, but in comparatively low yield (29%, Table 1).

Next, we also studied some possible transformations of the isolated chromenyl-amido-esters **3**. For this reason **3a** and **3c** were stirred at room temperature in ethanolic sodium hydroxide solution for 24 h, whereupon through a double nucleophilic substitution the chromenyl-acetamides **4a** and **4c** were isolated in 71 % and 74% yield, respectively (Scheme 2) [20].

The assigned molecular structures of all new compounds **3** are based on rigorous spectroscopic analysis including IR, NMR (^1H , ^{13}C , COSY, NOESY, HETCOR and COLOC), MS and elemental analysis data. Regarding the structure of products **3** the assignment of **3b** is described. The elemental analysis and mass spectra unequivocally established the reaction of one molecule of chromone-carboxaldehyde **1b** with one molecule of TosMIC and one molecule of benzoic acid, a fact that was also confirmed from the ^{13}C NMR spectrum, where 23 different signals were observed. Moreover, in the IR spectrum besides the carbonyl absorptions at 1702, 1682 and 1655 cm^{-1} an NH absorption appeared at 3379 cm^{-1} . From the H-H COSY spectrum three distinguishable proton groups were defined corresponding to the three aromatic rings. In the ^1H NMR the presence of the tosyl group was identified from the three proton singlet at δ 2.30 (with the corresponding carbon at 21.6 ppm) and the *p*-substituted phenyl moiety (δ $\text{H}_{2',6''} = 7.60$, δ $\text{H}_{3',5''} = 6.99$, with corresponding carbons resonating at 128.9 and 129.6 ppm, respec-

tively) [19]. The Tos-methyl group protons gave COLOC correlations with the carbon at 129.6 ppm and also with the quaternary carbon at 145.0 ppm, whereas the protons at δ 6.99 correlated with the quaternary carbon at 133.7 ppm. The TosMIC methylene protons, due to restricted rotation of the tosyl group, appeared as two doublet of doublets at δ 4.50 ($J = 14.25, 5.25\text{ Hz}$) and δ 5.00 ($J = 14.25, 8.45\text{ Hz}$) with corresponding carbon at 60.0 ppm, due to additional coupling with the neighboring NH group (δ 7.86). The methylene protons correlated with a carbonyl carbon at 167.4 ppm, being the former isonitrile carbon, so the whole sequence of the TosMIC reactant was identified, as depicted in Fig. (1). Concerning the chromone aromatic moiety, this was identified from the splitting pattern of the aromatic protons, resonating as a doublet at δ 8.06 ($J = 1.3\text{ Hz}$), a multiplet at δ 7.56–7.63, and a doublet at δ 7.44 ($J = 8.4\text{ Hz}$) and their carbons resonating at 125.3, 136.0 and 118.0 ppm, respectively. The chromone methyl group proton singlet appeared at δ 2.51 (with carbon at 21.1 ppm), whereas the 2'-position proton appeared as a doublet at δ 8.10, coupled with the C-2 aliphatic proton by allylic coupling ($J = 0.75\text{ Hz}$) with the corresponding carbon resonating at 155.0 ppm). This proton showed COLOC correlations with the chromone carbonyl carbon at 176.4 ppm and also with the quaternary carbons at 118.7 (C-3') and 154.6 (C-8a') via $^2J_{\text{C-H}}$ and $^3J_{\text{C-H}}$ couplings. With the last carbon at 154.6 ppm is correlated also the 7'-position proton. Moreover, the one proton signal which appeared as a doublet at δ 6.29 ($J = 0.75\text{ Hz}$, C 68.4 ppm) correlated with the three carbonyl carbons at 165.0, 167.4 and 176.4 and also with the C-2' protonated carbon, indicating thus its correspondence to the former formyl proton. Finally, the five phenyl ring protons showed the expected characteristic proton and carbon absorptions, in addition to the carbonyl carbon at 165.0 ppm.

Scheme 2. Reaction of chromonyl amidoester **3a** and **3c** with ethanolic NaOH.

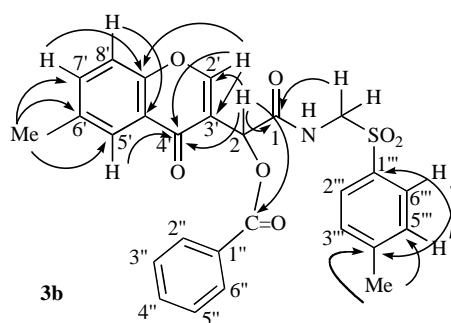


Fig. (1). Diagnostic COLOC correlations between protons and carbons (via $^2J_{C-H}$ and $^3J_{C-H}$), and position numbering in compound **3b**.

In some spectra a characteristic allylic coupling between the C(2)-H and C(2')-H of ~0.6–0.8 Hz is observed. Moreover, in all compounds the NHCH₂ methylene protons show AB pattern with geminal coupling of ~14 Hz in addition to two distinctly defined coupling constants of ~8 Hz and ~5 Hz, due to simultaneous coupling with the NH proton, confirming thus the configuration in molecular model depicted in Fig. (2) (after PM3 calculation).

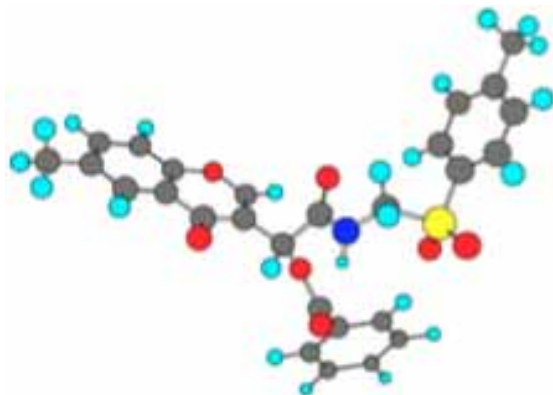


Fig. (2). Molecular model calculated for compound **3b** (PM3).

In conclusion, we have studied a Passerini reaction involving chromones and TosMIC leading to the isolation of unknown chromenyl-amidoesters **3**. The transformation of the isolated chromenyl-amidoesters **3** to chromenyl-acetamides **4** in ethanolic sodium hydroxide solution was also examined. Work is continuing in our laboratory in this area and we will report on further studies in the future.

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- Synthesis of the Passerini adducts 3: General Experimental Procedure.** To a stirred solution of chromone-3-carboxaldehyde (1.16 mmol) in CH₂Cl₂ (4 mL) was added the appropriate acid (1.16 mmol) and TosMIC (1.04 mmol) at room temperature. The reaction mixture was stirred for 12 h. After complete consumption of TosMIC, the solvent was removed to obtain a residue, which was purified by column chromatography, eluting with a 2:1 petroleum ether-ethyl acetate mixture, to afford products **3** in 29–85% yield.
- Data of Compound 3a.** White solid, mp 191–193 °C. IR (nujol) ν_{max} : 3388, 1705, 1700, 1645 cm⁻¹. ¹H NMR: (CDCl₃, 300 MHz) δ : 2.31 (s, 3H, 4'''-CH₃), 4.52 (dd, J = 14.1, 5.4 Hz, 1H, N-CH₂), 4.99 (dd, J = 14.1, 8.2 Hz, 1H, N-CH₂), 6.26 (d, J = 0.75 Hz, 1H, H-2), 7.02 (d, J = 8.0 Hz, 2H, H-3''',5'''), 7.45–7.50 (m, 2H, H-3'',5''), 7.53 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H, H-6'), 7.55 (d, J = 8.5 Hz, 1H, H-8'), 7.62 (tt, J = 7.5, 1.25 Hz, 1H, H-4'), 7.63 (d, J = 8.0 Hz, 2H, H-2'',6'''), 7.75 (br m, 1H, NH), 7.79 (ddd, J = 8.5, 7.0, 1.75 Hz, 1H, H-7'), 8.05–8.08 (m, 2H, H-2'',6''), 8.14 (d, J = 0.75 Hz, 1H, H-2), 8.29 (dd, J = 8.0, 1.7 Hz, 1H, H-5'). ¹³C NMR: (CDCl₃, 75 MHz) 21.6 (4'''-CH₃), 60.0 (N-CH₂), 68.5 (C-2), 118.3 (C-8'), 118.9 (C-3'), 123.8 (4a'), 126.06 (5'), 126.13 (6'), 128.7 (C-3'',5''), 128.9 (C-2'',6'''), 129.7 (C-3''',5'''), 130.0 (C-2'',6''), 133.5 (C-1''), 133.7 (1'''), 133.9 (C-4''), 134.7 (C-7), 145.1 (C-4'''), 155.2 (C-2'), 156.3 (C-8a'), 165.0 (2-CO), 167.3 (C-1), 176.4 (C-4'). MS (LCMS) m/z (%) 514 (100, M⁺ + 23). Anal. Calcd for C₂₆H₂₁NO₅ (491.51): C, 63.53; H, 4.31; N, 2.85%. Found: C, 63.70; H, 4.17, N, 2.71%.
- Data of Compound 3b.** Yield 0.368 g, 70%, white solid, mp 194–196 °C. IR (nujol) ν_{max} : 3379, 1702, 1682, 1655 cm⁻¹. ¹H NMR: (CDCl₃, 300 MHz) δ : 2.30 (s, 3H, 4'''-CH₃), 2.51 (s, 3H, 6'-CH₃), 4.50 (dd, J = 14.25, 5.25 Hz, 1H, N-CH₂), 5.00 (dd, J = 14.25, 8.45 Hz, 1H, N-CH₂), 6.29 (d, J = 0.75 Hz, 1H, H-2), 6.99 (d, J = 8.2 Hz, 2H, H-3''',5'''), 7.44 (d, J = 8.4 Hz, 1H, H-8'), 7.47 (m, 2H, H-3'',5''), 7.56–7.63 (m, 2H, H-7', 4'), 7.60 (d, J = 8.2 Hz, 2H, H-2'',6'''), 7.87 (br dd, J = 8.4, 5.3 Hz, 1H, NH), 8.04–8.07 (m, 2H, H-2'',6''), 8.06 (d, J = 1.3 Hz, 1H, H-5'), 8.10 (d, J = 0.75 Hz, 1H, H-2). ¹³C NMR: (CDCl₃, 75 MHz) 21.1 (6'-CH₃), 21.6 (4'''-CH₃), 60.0 (N-CH₂), 68.4 (C-2), 118.0 (C-8'), 118.7 (C-3'), 123.4 (4a'), 125.3 (5'), 128.6 (C-3'',5''), 128.9 (C-2'',6'''), 129.6 (C-3''',5'''), 129.9 (C-2'',6''), 133.7 (1'''), 133.8 (C-4''), 136.0 (C-7), 136.3 (C-6'), 136.3 (C-1'), 145.0 (C-4'''), 154.6 (C-8a'), 155.0 (C-2'), 165.0 (2-CO), 167.4 (C-1), 176.4 (C-4'). MS (LCMS) m/z (%) 528 (100,

$M^+ + 23$). Anal. Calcd for $C_{27}H_{23}NO_7S$ (505.54): C, 64.15; H, 4.59; N, 2.77%. Found: C, 64.00; H, 4.52; N, 2.65%.

Data of Compound 3c. White solid, mp 223–225 °C. IR (nujol) ν_{max} : 3320, 1707, 1646 cm^{-1} . 1H NMR: ($CDCl_3$, 300 MHz) δ : 2.33 (s, 3H, 4''-CH₃), 4.55 (dd, $J = 14.2$, 5.8 Hz, 1H, N-CH₂), 4.94 (dd, $J = 14.2$, 8.0 Hz, 1H, N-CH₂), 6.25 (d, $J = 0.5$ Hz, 1H, H-2), 7.10 (d, $J = 8.0$ Hz, 2H, H-3''',5'''), 7.43–7.50 (m, 2H, H-3''',5'''), 7.49 (d, $J = 9.0$ Hz, 1H, H-8'), 7.70 (dd, $J = 9.0$, 2.5 Hz, 1H, H-7'), 7.62 (tt, $J = 7.3$, 1.7 Hz, 1H, H-4''), 7.66 (d, $J = 8.0$ Hz, 2H, H-2'',6'''), 7.60–7.70 (br m 1H, NH), 8.04–8.07 (m, 2H, H-2'',6'''), 8.15 (d, $J = 0.5$ Hz, 1H, H-2''), 8.22 (d, $J = 2.5$ Hz, 1H, H-5'). ^{13}C NMR: ($CDCl_3$, 75 MHz) 21.7 (4''-CH₃), 60.1 (N-CH₂), 68.5 (C-2), 119.1 (C-3'), 120.0 (C-8'), 124.7 (4a'), 125.4 (5'), 128.7 (C-3''',5'''), 128.9 (C-2''',6'''), 129.7 (C-3''',5'''), 130.0 (C-2'',6'''), 132.2 (6'), 133.8 (1''), 134.0 (C-4''), 134.9 (C-7'), 135.0 (C-1'), 145.2 (C-4'''), 154.6 (C-8a'), 155.6 (C-2'), 164.9 (2-CO), 167.1 (C-1), 175.2 (C-4'). Anal. Calcd for $C_{26}H_{20}ClNO_7S$ (525.96): C, 59.37; H, 3.83; N, 2.66%. Found: C, 59.51; H, 4.00; N, 2.58%.

Data of Compound 3d. White solid, mp 138–140 °C. IR (nujol) ν_{max} : 3311, 1727, 1669, 1635 cm^{-1} . 1H NMR: ($CDCl_3$, 300 MHz) δ : 2.33 (s, 3H, 4''-CH₃), 2.54 (s, 3H, 7'-CH₃), 4.57 (dd, $J = 14.0$, 6.0 Hz, 1H, N-CH₂), 4.86 (dd, $J = 14.0$, 7.5 Hz, 1H, N-CH₂), 6.37 (s, 1H, H-2), 7.14 (d, $J = 8.1$ Hz, 2H, H-3''',5'''), 7.43–7.48 (m, 2H, H-3''',5'''), 7.47 (s, 1H, H-8'), 7.61 (t, $J = 7.5$ Hz, 1H, H-4''), 7.67 (d, $J = 8.1$ Hz, 2H, H-2''',6'''), 8.03–8.05 (m, 2H, H-2'',6'''), 8.07 (s, 1H, H-5'), 8.14 (s, 1H, H-2'), 9.1 (br m, 1H, NH). ^{13}C NMR: ($CDCl_3$, 75 MHz) 20.1 (7'-CH₃), 20.8 (4''-CH₃), 59.7 (N-CH₂), 67.0 (C-2), 118.2 (C-3'), 119.5 (C-8'), 122.0 (4a'), 124.5 (5'), 127.8 (C-2''',6'''), 128.1 (C-3''',5'''), 128.9 (C-3''',5'''), 129.2 (C-2'',6'''), 131.6 (6'), 132.9 (C-4''), 133.3 (1''), 133.4 (C-1'), 143.0 (C-7'), 144.2 (C-4'''), 153.7 (C-8a'), 155.2 (C-2'), 164.3 (2-CO), 166.9 (C-1), 173.5 (C-4'). MS (LCMS) m/z (%) 562/564 (100, $M^+ + 23$). Anal. Calcd for $C_{27}H_{22}ClNO_7S$ (539.98): C, 60.06; H, 4.11; N, 2.59%. Found: C, 60.20; H, 4.17; N, 2.48%.

Data of Compound 3e. White solid, mp 149–151 °C. IR (nujol) ν_{max} : 3326, 1729, 1668, 1645 cm^{-1} . 1H NMR: ($CDCl_3 + DMSO-d_6$, 300 MHz) δ : 2.37 (s, 3H, 4''-CH₃), 4.62 (dd, $J = 14.2$, 5.5 Hz, 1H, N-CH₂), 4.89 (dd, $J = 14.2$, 8.0 Hz, 1H, N-CH₂), 6.24 (s, 1H, H-2), 7.21 (d, $J = 8.1$ Hz, 2H, H-3''',5'''), 7.47–7.53 (m, 2H, H-3''',5'''), 7.5 (br m, 1H, NH), 7.61–7.65 (m, 1H, H-4''), 7.68 (d, $J = 9.3$ Hz, 1H, H-8'), 7.73 (d, $J = 8.1$ Hz, 2H, H-2''',6'''), 8.04–8.09 (m, 2H, H-2'',6'''), 8.23 (s, 1H, H-2'), 8.57 (dd, $J = 9.3$, 2.8 Hz, 1H, H-7'), 9.10 (d, $J = 2.8$ Hz, 1H, H-5'). ^{13}C NMR: ($CDCl_3 + DMSO-d_6$, 75 MHz) 20.6 (4''-CH₃), 59.7 (N-CH₂), 66.5 (C-2), 119.1 (C-3'), 119.6 (C-8'), 121.3 (5'), 122.9 (4a'), 127.6 (C-2''',6'''), 127.9 (C-3''',5'''), 128.7 (C-3''',5'''), 129.0 (C-2'',6'''), 132.0 (C-1'), 132.8 (C-4''), 132.9 (C-7'), 133.4 (1''), 145.0 (C-4'''), 147.0 (6'), 155.8 (C-2), 158.0 (C-8a'), 164.1 (2-CO), 166.5 (C-1), 173.1 (C-4'). MS (LCMS) m/z (%) 559 (100, $M^+ + 23$). Anal. Calcd for $C_{26}H_{20}N_2O_9S$ (536.51): C, 58.21; H, 3.76; N, 5.22%. Found: C, 58.07; H, 3.67; N, 5.31%.

Data of Compound 3f. White solid, mp 186–188 °C. IR (nujol) ν_{max} : 3379, 1705, 1700, 1645 cm^{-1} . 1H NMR: ($CDCl_3 + DMSO-d_6$, 300 MHz) δ : 2.33 (s, 3H, 4''-CH₃), 4.55 (dd, $J = 14.0$, 5.5 Hz, 1H, N-CH₂), 4.85 (dd, $J = 14.0$, 7.0 Hz, 1H, N-CH₂), 6.35 (s, 1H, H-2), 7.12 (d, $J = 7.5$ Hz, 2H, H-3''',5'''), 7.49–7.79 (m, 6H, H-6',7',8',th-3'',th-4'',th-5''), 7.65 (d, $J = 8.1$ Hz, 2H, H-2''',6'''), 8.07 (s, 1H, H-2'), 8.20 (d, $J = 7.0$ Hz, 1H, H-5'), 9.3 (br m, 1H, NH). ^{13}C NMR: ($CDCl_3 + DMSO-d_6$, 75 MHz) 20.4 (4''-CH₃), 59.3 (N-CH₂), 66.5 (C-2), 117.3 (C-8'), 117.8 (C-3'), 122.6 (4a'), 124.6 (5'), 124.8 (6'), 126.9 (th-C-4''), 127.7 (C-2''',6'''), 128.5 (C-3''',5'''), 131.2 (th-C-2''), 132.6 (C-7'), 133.1 (1''), 133.3 (th-C-3'), 133.5 (th-C-5'), 143.7 (C-4'''), 154.9 (C-2'), 155.0 (C-8a'), 159.5 (2-CO), 166.5 (C-1), 174.0 (C-4'). MS (LCMS) m/z (%) 520 (100, $M^+ + 23$). Anal. Calcd for $C_{24}H_{19}NO_7S_2$ (497.54): C, 57.94; H, 3.85; N, 2.82%. Found: C, 58.02; H, 3.77; N, 2.94%.

Data of Compound 3g. White solid, mp 133–136 °C. IR (nujol) ν_{max} : 3393, 1700, 1646 cm^{-1} . 1H NMR: ($CDCl_3$, 300 MHz) δ : 2.29

(s, 3H, 4''-CH₃), 3.91 (s, 2H, ind-3''-CH₂), 4.37 (dd, $J = 14.1$, 5.5 Hz, 1H, N-CH₂), 4.75 (dd, $J = 14.1$, 8.2 Hz, 1H, N-CH₂), 5.96 (s, 1H, H-2), 6.99 (d, $J = 7.9$ Hz, 2H, H-3''',5'''), 7.15 (ddd, $J = 7.7$, 7.2, 1.1 Hz, 1H, ind-5''), 7.22 (ddd, $J = 8.1$, 7.2, 1.2 Hz, 1H, ind-6''), 7.25 (s, 1H, ind-2''), 7.40 (br d, $J = 8.1$ Hz, 1H, ind-7''), 7.47–7.53 (m, 2H, H-6',8'), 7.52 (d, $J = 7.9$ Hz, 2H, H-2''',6'''), 7.63 (br d, $J = 7.7$ Hz, 1H, ind-4''), 7.86 (s, 1H, H-2'), 7.76 (ddd, $J = 8.5$, 7.2, 1.7 Hz, 1H, H-7'), 8.24 (dd, $J = 8.2$, 1.7 Hz, 1H, H-5'), 8.38 (br s, 1H, NH). ^{13}C NMR: ($CDCl_3$, 75 MHz) 21.6 (4''-CH₃), 31.2 (ind-3''-CH₂), 60.0 (N-CH₂), 68.3 (C-2), 107.3 (ind-C-3''), 111.6 (ind-C-7''), 118.2 (C-8'), 118.7 (ind-C-4''), 118.7 (C-3'), 119.8 (ind-C-6''), 122.4 (ind-C-5''), 123.6 (ind-C-2''), 123.7 (4a'), 125.9 (6'), 126.0 (5'), 126.9 (ind-C-3a''), 128.8 (C-2''',6'''), 129.6 (C-3''',5'''), 133.7 (1''), 134.5 (C-7'), 136.2 (ind-C-7a''), 145.0 (C-4''), 155.8 (C-2'), 156.2 (C-8a'), 167.3 (C-1), 170.2 (2-CO), 176.1 (C-4').

Data of Compound 3h. White solid, mp 156–158 °C. IR (nujol) ν_{max} : 3309, 1745, 1718, 1635 cm^{-1} . 1H NMR: ($CDCl_3$, 300 MHz) δ : 1.16 (t, $J = 7.5$ Hz, 3H, CH₃), 2.33 (s, 3H, 4''-CH₃), 2.42 (dq, $J = 15.5$, 7.5 Hz, 1H, CH₂), 2.51 (dq, $J = 15.5$, 7.5 Hz, 1H, CH₂), 4.46 (dd, $J = 14.1$, 5.1 Hz, 1H, N-CH₂), 5.00 (dd, $J = 14.1$, 8.4 Hz, 1H, N-CH₂), 6.06 (s, 1H, H-2), 7.02 (d, $J = 8.0$ Hz, 2H, H-3''',5'''), 7.50–7.56 (m, 2H, H-6',8'), 7.60 (d, $J = 8.0$ Hz, 2H, H-2''',6'''), 7.76–7.80 (m, 2H, H-7', NH), 8.01 (s, 1H, H-2'), 8.28 (d, $J = 7.8$ Hz, 1H, H-5'). ^{13}C NMR: ($CDCl_3$, 75 MHz) 8.8 (-CH₂-CH₃), 21.6 (4''-CH₃), 27.2 (-CH₂-CH₃), 59.6 (N-CH₂), 67.5 (C-2), 118.2 (C-8'), 118.7 (C-3''), 123.6 (4a'), 126.0 (5'), 126.1 (6'), 128.8 (C-2''',6'''), 129.6 (C-3''',5'''), 133.7 (1''), 134.6 (C-7'), 145.0 (C-4''), 155.2 (C-2'), 156.2 (C-8a'), 167.4 (C-1), 172.8 (2-CO), 176.3 (C-4'). MS (LCMS) m/z (%) 466 (100, $M^+ + 23$). Anal. Calcd for $C_{22}H_{21}NO_7S$ (443.47): C, 59.58; H, 4.77; N, 3.16%. Found: C, 59.70; H, 4.87; N, 3.05%.

[20] **Synthesis of 2-ethoxy-N-(ethoxymethyl)-2-(4-oxo-4H-chromen-3-yl)acetamide 4a.** A solution of NaOH (50 mg) in EtOH, (5 mL) was added to a solution of **3a** (0.5 mmol) in EtOH (1 mL). The mixture was stirred at room temperature for 24 h, the volume was reduced to 1 mL, whereupon the solid, which precipitated, was filtered and washed initially with water and then with cold ethanol, yielding compound **4a** in an essentially pure form. Yield, 71%, white solid; IR (nujol) ν_{max} : 1623 cm^{-1} . 1H NMR: ($CDCl_3$, 300 MHz) δ : 1.18 (t, $J = 7.0$ Hz, 3H, CH₃), 1.30 (t, $J = 7.0$ Hz, 3H, CH₃), 3.56 (dq, $J = 7.0$, 4.5 Hz, 1H, CH₂), 3.58 (dq, $J = 7.0$, 4.5 Hz, 1H, CH₂), 3.63 (dq, $J = 7.0$, 4.5 Hz, 1H, CH₂), 3.65 (dq, $J = 7.0$, 4.5 Hz, 1H, CH₂), 4.716 (dd, $J = 10.3$, 7.0 Hz, 1H, N-CH₂), 4.816 (dd, $J = 10.3$, 7.0 Hz, 1H, N-CH₂), 4.92 (d, $J = 0.75$ Hz, 1H, H-2), 7.43 (ddd, $J = 8.0$, 7.0, 1.0 Hz, 1H, H-6'), 7.47 (dd, $J = 8.5$, 1.0 Hz, 1H, H-8'), 7.69 (ddd, $J = 8.5$, 7.0, 1.75 Hz, 1H, H-7'), 7.75 (br m, 1H, NH), 8.04 (d, $J = 0.75$ Hz, 1H, H-2'), 8.21 (dd, $J = 8.0$, 1.75 Hz, 1H, H-5'). ^{13}C NMR: 15.1 (CH₃), 15.2 (CH₃), 64.1 (CH₂), 66.0 (CH₂), 69.7 (C-2), 74.7 (N-CH₂), 118.2 (C-8'), 121.3 (C-3'), 124.0 (C-4a'), 125.5 (C-5'), 126.0 (C-6'), 134.0 (C-7'), 155.0 (C-2'), 156.3 (C-8a'), 170.8 (C-1), 176.5 (C-4'). MS (LCMS) m/z (%) 328 (100, $M^+ + 23$). Anal. Calcd for $C_{16}H_{19}NO_5$ (305.33): C, 62.94; H, 6.27; N, 4.59%. Found: C, 63.16; H, 6.40; N, 4.38%.

Data of Compound 4c. Yield, 74%, white solid, mp 177–179 °C (CH_2Cl_2 -pet. ether). 1H NMR: ($CDCl_3$, 300 MHz) δ : 1.20 (t, $J = 7.0$ Hz, 3H, CH₃), 1.27 (t, $J = 7.0$ Hz, 3H, CH₃), 3.55 (dq, $J = 7.0$, 4.5 Hz, 1H, CH₂), 3.57 (dq, $J = 7.0$, 4.5 Hz, 1H, CH₂), 3.63 (dq, $J = 7.0$, 4.5 Hz, 1H, CH₂), 3.65 (dq, $J = 7.0$, 4.5 Hz, 1H, CH₂), 4.80 (d, $J = 6.8$ Hz, 2H, N-CH₂), 4.95 (s, 1H, H-2), 7.43 (d, $J = 9.0$ Hz, 1H, H-8'), 7.62 (dd, $J = 9.0$, 2.5 Hz, 1H, H-7'), 7.70 (br m, 1H, NH), 8.02 (s, 1H, H-2'), 8.16 (d, $J = 2.5$ Hz, 1H, H-5'). ^{13}C NMR: 15.1 (CH₃), 15.2 (CH₃), 64.1 (CH₂), 66.2 (CH₂), 69.7 (C-2), 74.6 (N-CH₂), 119.9 (C-8'), 121.4 (C-3'), 124.9 (C-4a'), 125.4 (C-5'), 131.5 (C-6'), 134.3 (C-7'), 154.7 (C-8a'), 155.1 (C-2'), 170.6 (C-1), 175.4 (C-4'). MS (LCMS) m/z (%) 328 (100, $M^+ + 23$). Anal. Calcd for $C_{16}H_{19}ClNO_5$ (339.77): C, 56.56; H, 5.34; N, 4.12%. Found: C, 56.39; H, 5.42; N, 4.18%.