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Supplementary Information

Novel benzofuran-chromone and –coumarine derivatives: synthesis and biological activity in K562 human leukemia cells

Clemens Zwergel[a], Sergio Valente[a, b], Angela Salvato[c], Zhanjie Xu[a], Oualid Talhi[d], Antonello Mai[b], Artur Silva[d], Lucia Altucci[c,e] and Gilbert Kirsch[a*]

[a] *Laboratoire d'Ingenierie Moléculaire et Biochimie Pharmacologique, Institut Jean Barriol, Université de Lorraine, 1 Boulevard Arago, 57070 Metz, France*
[b] *Dipartimento di Chimica e Tecnologie del Farmaco, Sapienza Università di Roma, P.le A. Moro 5, 00185 Roma, Italy*
[c] *Dipartimento di Biochimica, Biofisica e Patologia generale, Seconda Università di Napoli, Vico L. De Crecchio 7, 80138, Napoli, Italy*
[d] *Department of Chemistry, University of Aveiro, QOPNA, 3810-193 Aveiro, Portugal*
[e] *Istituto di genetica e Biofisica IGB Via P. Castellino 1111, 80131 Naples, IT*
Tel: +33387315295 Fax: +33387315801 E-mail: kirsch@univ-lorraine.fr

Synthesis of the starting materials and the reference compound 30:

Synthesis of 7-Methoxy-4(chloromethyl)coumarine

A mixture of 3-methoxyphenol (30 mmol) and ethyl 4-chloroacetoacetate(33 mmol) was added dropwise to concentrated sulphuric acid while the temperature was kept below 10 ºC. The reaction was then allowed to reach RT and stirred for 24 hrs. Quenching the mixture with ice-cold water gave the crude product, which was first filtered and then recrystallized from ethanol.

6) 7-Methoxy-4(chloromethyl)coumarine[1]

mp: 195-197 ; colourless solid; yield: 51%; ^{1}H NMR (250 MHz, $CDCl_3$) d 3.86 (s, 3H, –OCH_3), 4.98 (s, 2H, –CH_2Cl), 6.49 (s, 1H, -C*H*COO-), 6.98–7.04 (m, 2H, aromatic protons) 7.74-7.77 (d, 1H, *J*=7.5 Hz, aromatic proton) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) d 41.33, 55.82, 101.24, 110.79, 112.64, 125.14, 131.03, 149.59, 155.78, 160.74, 163.00

General procedure for the synthesis of 3-formylchromones:

To a stirred solution of corresponding *o*-hydroxy- acetophenone (30mmol) in dimethylformamide (40mL), phosphorous oxychloride (60mmol) was added drop-wise at 0°C over 20-30 mins. The mixture was stirred on ice for further 30 mins and then continued at RT for 3-5 hrs. The mixture was treated with ice-cold water (100 mL). The resulting solid was filtered, washed with plenty of water and purified if necessary by recrystallization from ethanol.

9) 3-Formylchromone[2]

mp: 152-154; yellow solid; yield: 63%; ^{1}H NMR (250 MHz, $CDCl_3$) d 7.48–7.56 (m, 2H, aromatic protons), 7.73–7.79 (m, 1H, aromatic proton), 8.28-8.32 (d, 1H, *J*=10.0 Hz, aromatic proton), 8.55 (s, 1H, -O-C*H*=C-), 10.40 (s, 1H –C*H*O) ppm; ^{13}C NMR (62.5MHz, $CDCl_3$) d 118.64, 120.32, 125.31, 126.13, 126.65, 134.86, 156.22, 160.74, 175.85, 188.53

10)6-Methyl-3-formylchromone[3]

mp: 169-170 ; yield: 20%; ^{1}H NMR (250 MHz, $CDCl_3$) d 2.44 (s,1H; -C*H*$_3$), 744–7.48 (m, 2H, aromatic protons), 7.55(s, 1H, aromatic proton), 8.06 (s, 1H, aromatic proton), 8.52 (s, 1H, -O-C*H*=C-), 10.37 (s, 1H –C*H*O) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) d 21.02, 118.69, 120.17, 124.81, 125.75, 136.14, 137.12, 154.74, 160.29, 173.97, 188.95

11) 6,7-Dimethyl-3-formylchromone[4]

mp: 157-159 ; yield: 14%; ^{1}H NMR (250 MHz, $CDCl_3$) d 2.39 (s,1H; -CH_3), 2.42 (s,1H; -CH_3), 7.44–7.60 (m, 2H, aromatic protons), 7.31 (s, 1H, aromatic proton), 8.03 (s, 1H, aromatic proton), 8.51 (s, 1H, -O-C*H*=C-), 10.39 (s, 1H –C*H*O) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) d 19.41, 20.51, 118.69, 120.17, 123.03, 125.75, 136.14, 145.51, 154.74, 160.29, 175.97, 188.95

12) 7-Chloro-3-formylchromone[5]

mp: 184-186; yield: 41%; ^{1}H NMR (250 MHz, $CDCl_3$) d 7.46–7.50 (d, 2H, *J*=10.0Hz, aromatic protons), 7.57 (s, 1H, aromatic proton), 8.23-8.26 (d, 1H, *J*=7.5 Hz, aromatic proton), 8.52 (s, 1H, -O-C*H*=C-), 10.38 (s, 1H –C*H*O) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) d 118.75, 120.50, 123.02, 123.81, 127.49, 141.06, 156.24, 160.55, 175.14, 188.16

13) 6-Chloro-3-formylchromone[6]

mp: 170-172; yield: 66%; ^{1}H NMR (250 MHz, $CDCl_3$) d 7.50–7.53 (d, 1H, *J*=7.5Hz, aromatic proton), 7.68–7.72 (dd, 1H, *J*=10.0Hz, aromatic proton), 8.25-8.26 (d, 1H, *J*=2.5 Hz, aromatic proton), 8.55 (s, 1H, -O-C*H*=C-), 10.36 (s, 1H –C*H*O) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) d 120.24, 120.31, 125.63, 126.30, 132.84, 135.02, 154.50, 160.68, 174.87, 188.15

14) 6-Fluoro-3-formylchromone[7]

mp: 157-159; yield: 40%; ^{1}H NMR (250 MHz, $CDCl_3$) d 7.44–7.60 (m, 2H, aromatic protons), 7.68–7.72 (dd, 1H, *J*=10.0Hz, aromatic proton), 8.92-8.96 (dd, 1H, *J*=10.0 Hz, aromatic proton), 8.56 (s, 1H, -O-C*H*=C-), 10.38 (s, 1H –C*H*O) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) d 110.05, 120.34, 121.30, 122.05, 125.33, 126.60, 153.88, 160.32, 175.01, 188.20 h

15) 7-Methoxy-3-formylchromone[3,8]

mp: 188-190; yield: 12%; ^{1}H NMR (250 MHz, $CDCl_3$) d 3.92 (s, 3H, –OCH_3), 6.92–6.93 (d, 1H, *J*=2.5Hz, aromatic proton), 7.03–7.08 (dd, 1H, *J*=12.5Hz, aromatic proton), 8.19-8.22 (d, 1H, *J*=7.5Hz, aromatic proton), 8.50 (s, 1H, -O-C*H*=C-), 10.40 (s, 1H –C*H*O) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) d 55.93, 101.35, 115.54, 118.82, 120.16, 127.34, 158.04, 160.24, 164.82, 175.27, 189.02

16) 5-Methoxy-3-formylchromone[9]

mp: 127-129; yield: 36%; ^{1}H NMR (250 MHz, $CDCl_3$) d 4.02 (s, 3H, –OCH_3), 6.89–6.92 (d, 1H, *J*=7.5Hz, aromatic proton), 7.06–7.09 (d, 1H, *J*=7.5Hz, aromatic proton), 7.61-7.64 (m, 1H, aromatic proton), 8.39 (s, 1H, -O-C*H*=C-), 10.34 (s, 1H –C*H*O) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) d 56.57, 107.93, 110.40, 115.53, 121.21, 134.93, 158.07, 158.74, 160.35, 175.83, 189.16

17) 7,8-Dimethoxy-3-formylchormone[3]

mp: 230-232; yield: 32%; ^{1}H NMR (250 MHz, $CDCl_3$) d 3.99 (s, 3H, –OCH_3), 4.02 (s, 3H, –OCH_3), 7.09–7.12 (d, 1H, *J*=7.5Hz, aromatic proton), 8.00-8.04 (d, 1H, *J*=10.0Hz, aromatic proton), 8.52 (s, 1H, -O-C*H*=C-), 10.37 (s, 1H –C*H*O) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) d 56.45, 61.64, 110.94, 119.37, 119.67, 121.38, 137.19, 150.43, 157.55, 160.38, 175.45, 188.68

Compound 18a is commercial and compounds 18b and 19 were prepared according to the literature by Cagniant et al. [10]

Synthesis of (*Z*)-2-(4-methoxybenzylidene)-6-methylbenzofuran-3(2*H*)-one 30

A mixture of the 4- methoxybenzaldehyde (5 mmol) and **18b** (5 mmol) were refluxed in EtOH (5 mL) with 3 drops of glacial acetic acidic and 5 drops of pyrrolidine for 1h. The mixture was allowed to cool down to room temperature and precipitated product **30** was filtered, washed with a small amout of ice-cold ethanol and recrystallized from ethanol[2].

30) (*Z*)-2-(4-methoxybenzylidene)-6-methylbenzofuran-3(2*H*)-one [11]

mp: 114-116; yellow solid; yield: 64%; ^{1}H NMR (250 MHz, $CDCl_3$) d 2.53 (s, 3H, –C*H*$_3$), 3.90 (s, 3H, –OC*H*$_3$), 6.88 (s, 1H, =C*H*COO–), 6.99-7.06 (m, 3H, aromatic protons), 7.16 (s, 1H, =C-C*H*=C), 7.70–7.72 (d, 1H, *J*=5.0 Hz, aromatic proton) ppm, 7.89–7.92 (d, 2H, *J*=7.5 Hz, aromatic protons) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) d 21.62, 55.87, 112.84, 113.65, 114.21, 114.30, 119.47, 123.74, 124.69, 130.53, 132.81, 132.90, 146.92, 150.06, 159.82, 166.17, 182.62 HRMS (ESI) [M+H]+ $C_{17}H_{14}O_3$ calculated: 266.296 found: 266.289.

Elemental Analysis: calculated: C: 76.86%; H: 5.30%; O: 18.02% found: C: 76.78%; H: 5.35% (Elemental analysis and HRMS was done to check the purity of the compound for biological testing)

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