Supporting Information

Deciphering the mechanism of carbonic anhydrase inhibition with coumarins and thiocoumarins [#]

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Reaction of 6-hydroxycoumarin with alkyl halides was done in Schotten-Baumann conditions in the presence of the stoichiometriuc amoount of NaOH in ethanol-water as solvent, at room temperature.[12] Acidification of the reaction mixture and evaporatoion of the solvent afforded the crude products 6-10 which were recrystallized from ethanol or purified by flash chromatography as described below.

^{1}H, spectra were recorded using a Bruker Advance III 300 MHz spectrometer. The chemical shifts are reported in parts per million (ppm) and the coupling constants (*J*) are expressed in Hertz (Hz). Melting points (m.p.) were measured in open capillary tubes, unless otherwise stated, using a Büchi Melting Point B-540 melting point apparatus and are uncorrected. Thin layer chromatography (TLC) was carried out on Merck silica gel 60 F_{254} aluminium backed plates. Elution of the plates was carried out using MeOH/DCM or MeOH/$CHCl_3$ systems. Visualization was achieved with UV light at 254 nm, by dipping into a 0.5 % aqueous potassium permanganate solution, or by exposure to iodine. Flash column chromatography was carried out using silica gel (obtained from Aldrich Chemical Co.) as the adsorbent . The crude product was introduced into the column as a solution in the same elution solvent system, alternatively as a powder obtained by mixing the crude product with the same weight of silica gel in acetone and then removing the solvent *in vacuo* at room temperature, or dissolved into a minimum amount of DCM or carbon tetrachloride. All moisture or air sensitive reactions were carried out in oven-dried glassware under a positive pressure of nitrogen or argon using standard syringe/septa techniques. All the inert gases used (nitrogen and argon) were passed through jacket columns fitted with activated silica gel containing cobalt (II) chloride adsorbed as humidity indicator.

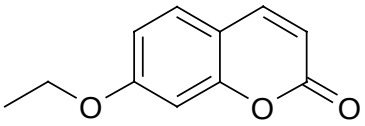
7-ethoxy-2H-chromen-2-one **6**: δ_H (300MHz, DMSO-d_6) 1.37 (3H, t *J*= 13.8, 2'-H_3); 4.15 (2H, q *J*= 13.8, 1'-H_2); 6.30 (1H, d *J*= 9.5, 3-H); 6.95 (1H, dd *J*= 8.4 2.4, 6-H); 6.99 (1H, d *J*= 2, 8-H_2); 7.63 (1H, d, *J*= 8.4, 5-H) 8.00 (1H, d *J*= 9.5, 4-H); *m/z* (ESI+) 191.18 ($[M+H]^+$ 12%), 213.15 ($[M+Na]^+$ 25%), 403.17 ($[2M+Na]^+$ 100%); m.p: 91.8°C.

7-propoxy-2H-chromen-2-one **7**: δ_H (400MHz, DMSO-d_6) 0.99 (3H, t *J*= 14.6, 3'-H_3); 1.73-1.78 (2H, m *J*= 14.6, 2'-H_2); 4.04 (2H, t *J*= 12.8, 1'-H_2); 6.28 (1H, d *J*= 9.4, 3-H); 6.94 (1H, dd *J*= 8.4 2.4, 6-H); 6.97 (1H, d *J*= 2, 8-H); 7.62 (1H, d *J*=8.4, 5-H) 7.99 (1H, d, *J*=9.4, 4-H); *m/z* (ESI+) 205.23 ($[M+H]^+$ 5%), 227.20 ($[M+Na]^+$ 100%), 241.19 (4); m.p: 67.6°C.

7-butoxy-2H-chromen-2-one **8**: δ_H (400MHz, DMSO-d_6) 0.98 (3H, t *J*= 14.8, 4'-H_3); 1.45-1.49 (2H, m *J*= 14.8, 3'-H_2); 1.77-1.72 (2H, m *J*= 12.2, 2'-H_2); 4.11 (2H, t *J*= 12.8, 1'-H_2); 6.31 (1H, d *J*= 9.4, 3-H); 6.98 (1H, dd *J*= 8.4 2.8, 6-H); 7.11 (1H, d *J*= 2.4, 8-H); 7.65 (1H, d *J*= 8.4, 5-H); 8.02 (1H, d, *J*= 9.4, 4-H); *m/z* (ESI+) 219.21 ($[M+H]^+$ 7%), 241.19 ($[M+Na]^+$ 100%), 273.22 (4), 301.26 (12), 441.34 (5), 459.20 (.$[2M+Na]^+$ 47%); m.p: 61.8°C.

7-(benzyloxy)-2H-chromen-2-one **9**: δ_H (400MHz, DMSO-d_6); 5.26 (2H, s, 1'-H_2); 6.33 (1H, d *J*= 9.4, 3-H); 7.07 (1H, dd *J*= 8.6 2.4, 6-H); 7.12 (1H, d *J*= 2.4, 8-H); 7.39-7.53 (5H, m, Ar-H) 7.68 (1H, d, *J*= 8.6, 5-H); 8.03 (1H, d *J*= 9.4, 4-H); *m/z* (ESI+) 205.23 (7), 253.24 ($[M+H]^+$ 70%), 275.22 ($[M+Na]^+$ 92%), 307.12 (5), 493.17 (15), 527.29 (.$[2M+Na]^+$ 55%); m.p: 94.4°C.

7-phenethoxy-2H-chromen-2-one **10**: δ_H (400MHz, DMSO-d_6); 3.11 (2H, t *J*= 13.6, 2'-H_2); 4.35 (2H, t *J*= 13.6, 1'-H_2); 6.32 (1H, d *J*= 9.6, 3-H); 6.98 (1H, dd *J*= 8.6 2.4, 6-H); 7.04 (1H, d *J*= 2.4, 8-H); 7.27-7.39 (5H, m, Ar-H) 7.65 (1H, d, *J*= 8.6, 5-H); 8.02 (1H, d *J*= 9.6, 4-H); *m/z* (ESI+) 267.22 ($[M+H]^+$ 42%), 289.20 ($[M+Na]^+$ 100%), 321.17 (4), 357.07 (4), 393.21 (10), 413.36 (35), 441.47 (5), 507.23 (8), 555.27 (.$[2M+Na]^+$ 55%); m.p: 84.8°C.



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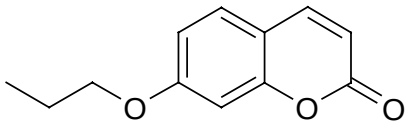

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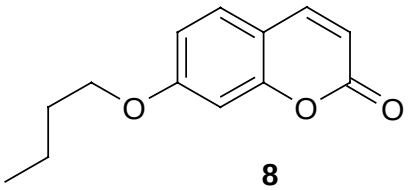

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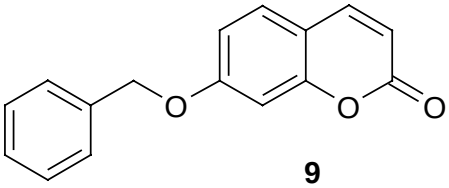

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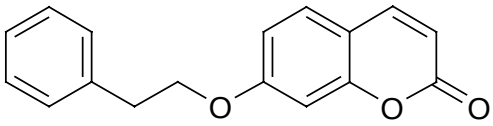

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