Heteroannulation of chromene derivatives. Synthesis of chromeno[4,3-*e*] indazolone, chromeno[4,3-*f*]quinazoline and pyrano[3,2-*c*]chromene derivatives

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Pentane-2,4-dione and 3-ethoxycarbonylcoumarin react in the presence of sodium ethoxide to form 10-acetyl-7,9-dihydroxy-6*H*-benzo[*c*]chromen-6-one (**2**). Compound **2** reacted with aromatic aldehydes and ethyl cyanoacetate to give the chromeno-chromenediones **3** and **4** respectively, with hydrazine hydrate to form the azine **5**, with phenyl hydrazine giving the chromeno-indazole **6**, with primary amines to form the imines **7a–f**, and with thiourea to give the chromeno-quinazoline **8**. Methyl 2-amino-4-(4-methoxyphenyl)-5-oxo-4,5-dihydro-pyrano[3,2-*c*]chromene-3-carboxylate (**9a**) and the corresponding 3-carbonitrile **9b** were prepared, and the reactions of the ester **9a** with phenacyl chloride, furoyl chloride, and hydrazine hydrate were investigated.

Keywords: 1-benzopyrans, fused pyrans, pyrazoles, indazoles, pyrimidines, coumarins, phenols, imines

Chromene derivatives exhibit various biological activities. They act as anticoagulants, photointercalants or enzyme inhibitors,[1,2] antibacterials,[3-5] fungicides,[6] anti-inflammatory[7] and antitumor[8,9] agents, and several studies from the viewpoint of chemical taxonomy[10,11] have been made. A variety of pyrans and condensed pyrans have been prepared using nitriles as starting materials.[12-15] Within this context and also as a contribution to our work on the synthesis of new heterocyclic derivatives of potential biological activity,[16-20] we present here our efforts in the synthesis of several new compounds featuring different heterocyclic rings fused onto the chromene moiety with the aim of obtaining more and better pharmacologically active compounds.

Results and discussion

The reaction of 3-ethoxycarbonylcoumarins with pentane-2,4-dione has previously been claimed to afford 1-acetyl-2-methyl-4a,10b-dihydro-4*H*,5*H*-pyrano[3,4 *c*][1]benzopyran-4,5-dione (**1**) as the major product in a moderate yield.[21] We find that no pyranobenzopyrone derivative could be isolated in such a reaction; instead we have found that the sole product obtained, in good yield, is the benzo[*c*]chromene derivative **2**. [The precise relationship of the compound reported in ref. 21 as having structure **1** to the product reported here as structure **2** is not clarified. We believe that it might be the same compound; the melting-point reported[21] for structure **1** (199 °C) is fairly close to what we find for **2** (192–194 °C). It should be noted that the IR bands reported for the C=O groups of **1** (1680 and 1640 cm^{-1}) are not compatible with that structure.]

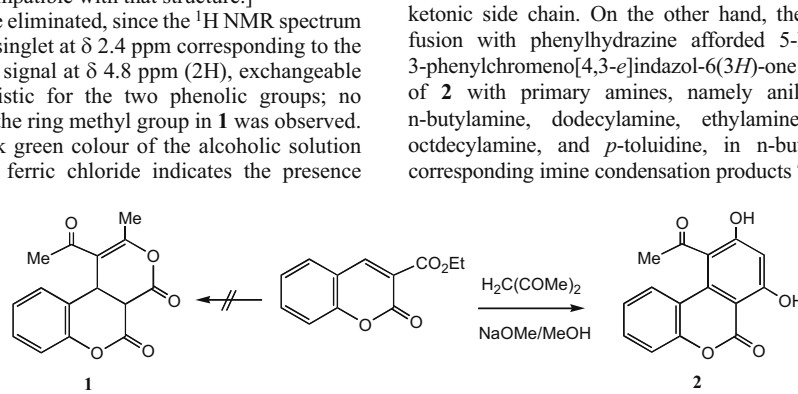
Structure **1** could be eliminated, since the ^1H NMR spectrum revealed a single 3H singlet at δ 2.4 ppm corresponding to the acetyl group, a broad signal at δ 4.8 ppm (2H), exchangeable with D_2O, characteristic for the two phenolic groups; no signal attributable to the ring methyl group in **1** was observed. Furthermore, the dark green colour of the alcoholic solution formed with neutral ferric chloride indicates the presence of phenolic OH groups. The remaining spectroscopic and analytical data lent further support to structure **2** (see Experimental). The reaction proceeded by a simple Michael addition followed by cyclisation and dehydrogenation to give the more stable product **2**.

The reactions of **2** with electrophilic and nucleophilic reagents were also investigated. Thus, treatment of compound **2** with aromatic aldehydes, namely 4-methoxybenzaldehyde, 4-(dimethylamino)benzaldehyde, 4-chlorobenzaldehyde and cinnamaldehyde, in the presence of anhydrous sodium methoxide by fusion at 170 °C or by reflux in n-butanol in the presence of a few drops of piperidine afforded 3-aryl-6-hydroxy-2,3-dihydro-1*H*,7*H*-chromeno[6,5-*c*]chromene-1,7-diones **3a–d**.

The structures of compounds **3** were deduced from their microanalytical and spectral data. The ^1H NMR spectra show the ABX pattern of the CO–CH_2–CH moiety. The magnetic nonequivalence of the protons H_A and H_B of the methylene group adjacent to the carbonyl shows an AB system associated with these protons with a geminal coupling of 11.3 Hz and affords the eight lines of the AB part of an ABX system,[22] on account of its attachment to an asymmetric centre.

Fusing compound **2** with ethyl cyanoacetate in the presence of metallic sodium afforded 6-hydroxy-1-methyl-3,7-dioxo-chromeno[4,3-*f*]chromene-2-carbonitrile (**4**). (Scheme 2)

The reaction of **2** with hydrazine hydrate (80%) yielded the corresponding azine **5** in which hydrazine has condensed with two molecules of **2** through nucleophilic attack at the ketonic side chain. On the other hand, the reaction of **2** by fusion with phenylhydrazine afforded 5-hydroxy-1-methyl-3-phenylchromeno[4,3-*e*]indazol-6(3*H*)-one (**6**). Refluxing of **2** with primary amines, namely aniline, benzylamine, n-butylamine, dodecylamine, ethylamine, hexdecylamine, octdecylamine, and *p*-toluidine, in n-butanol yielded the corresponding imine condensation products **7a–h** (Scheme 2).



1 **2**

Scheme 1

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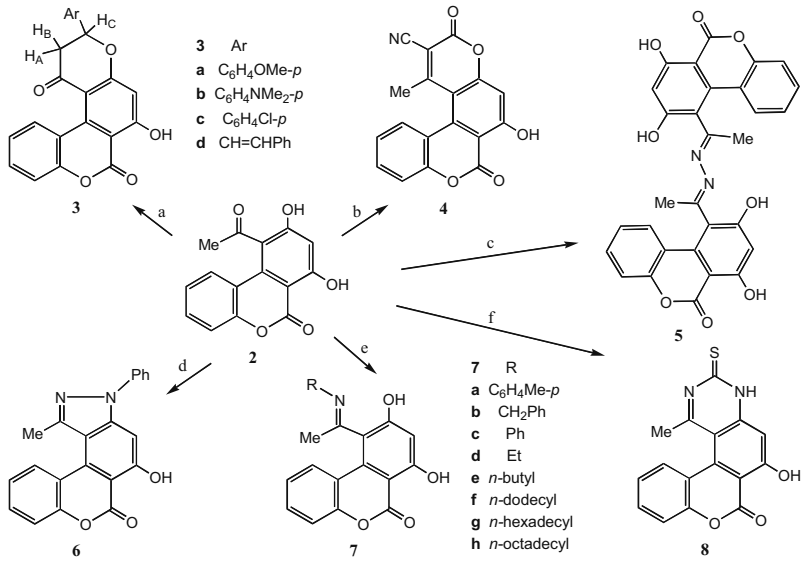


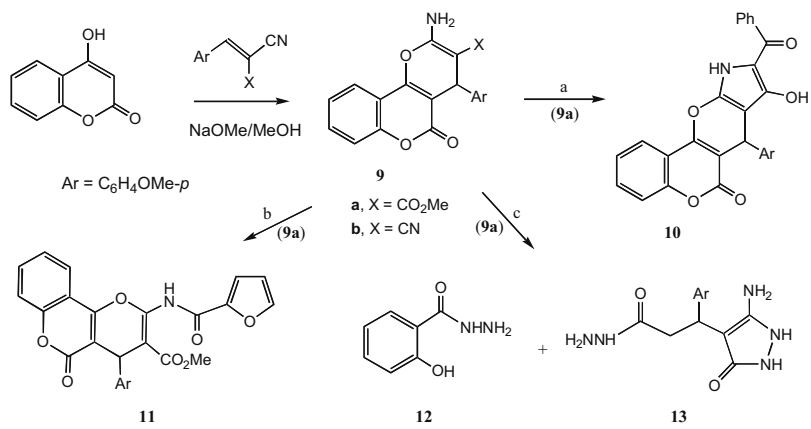
Scheme 2

When compound **2** was reacted with thiourea in boiling acetic acid it yielded 6-hydroxy-1-methyl-3-thioxo-3,4-dihydrochromeno[4,3-*f*]quinazolin-7-one (**8**), as evidenced by the microanalytical and spectroscopic data (see Experimental).

4*H*-Pyrano[3,2-*c*]benzopyrones characterised by a phenanthrene-like structure as found in tetrahydrocannabinol that belongs to the few CNS active compounds without nitogen heteroatoms.[23] Heber[24] has synthesised so-called azocannabinoids from the reaction of 4-amino-7-hydroxycoumarins with α,β-unsaturated carbonyl compounds. In the present work, the reaction of 4-hydroxycoumarin with ethyl-α-cyano-4-methoxycinnamate and α-cyano-4-methoxycinnamonitrile in the presence of anhydrous sodium methoxide in absolute methanol under reflux yielded the corresponding 2-amino-2-carbomethoxy(cyano)-4-(4-methoxyphenyl)-5*H*-pyrano[3,2-*c*]benzopyran-5-ones **9a** and **9b**, respectively (Scheme 3). The formation of compound **9a,b** could be visualised according the simple Michael addition of the carbanion (C_3-coumarinyl) to the β-carbon of the activated nitrile followed by 1,6-*exo*-*dig* cyclisation and transesterification. Structure **9a** gets more chemical evidence through the reaction with phenacyl chloride, furoyl chloride and hydrazine hydrate. Thus, treatment of compound **9a** with phenacyl chloride in refluxing pyridine yielded 9-benzoyl-7,10-dihydro-8-hydroxy-7-(4-methoxyphenyl)-4*H*-[1]benzopyrano[3′,4′:5,6]pyrano[2,3-*b*]pyrrol-6-one (**10**). Similarly, acylation of compound **9a** with furoyl chloride in boiling pyridine afforded methyl-2-furoylamino-4-(4-methoxyphenyl)-5-oxo-5*H*-pyrano[3,2-*c*]benzopyran-3-carboxylate (**11**). Hydrazinolysis of compound **9a** using hydrazine hydrate (80%) afforded a crude solid product (two spots in TLC) which upon purification yielded salicylic acid hydrazide (**12**) and 3-(5-amino-3-oxopyrazolin-4-yl)-3-(4-methoxyphenyl) propanoic acid hydrazide (**13**).

Experimental

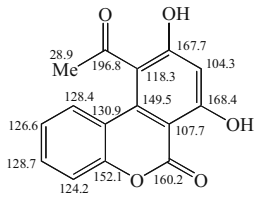
Melting points were taken on a Griffin and George melting point apparatus. IR spectra were recorded on a Pye Unicam SP 1200



Scheme 3

spectrophotometer using the KBr wafer technique. ^{1}H NMR spectra were determined on a Varian Gemini 200 MHz using TMS as internal standard. ^{13}C NMR spectra were measured on a JEOL 75 MHz spectrometer. EI MS were measured on a Shimadzu-GC-MS, QP 1000 EX instrument operating at 70 eV. Elemental analyses were carried out at the Microanalytical Unit, Faculty of Science, Ain Shams University with a Perkin-Elmer Series II CHNS/O elemental analyser. The homogeneity of the synthesised compounds was checked using TLC with aluminium sheets silica gel F_{254} (Merck).

10-Acetyl-7,9-dihydroxy-6H-benzo[c]chromen-6-one (**2**): Ethyl coumarin-3-carboxylate (4.4 g, 0.02 mol), dry sodium ethoxide (1.1 g, 0.02 mole) and pentane-2,4-dione (2.4 ml, 0.024 mole) were stirred together in a flask heated in an oil-bath at 170 °C for 3 h. After cooling, the reaction mixture was treated with cold dilute hydrochloric acid. The solid that separated was filtered off, washed several times with water, dried, and recrystallised from ethanol as orange crystals (67%), m.p. 192–194 °C. IR: ν_{max} 3449 br (OH), 1697 (lactone CO), 1673 cm^{-1} (chelated ketone CO). NMR ($CDCl_3$): δ_H 8.1–7.1 (m, 4H), 6.7 (s, 1H, C8-H), 5.3 (br.s, 2H, 2OH), 2.4 (s, 3H, CH_3); δ_C, see inset structure. EI MS: *m/z* (%) 270 (M^+, 51), 255 (M–CH_3, 100), 227 (M–$COCH_3$, 96), 171 (8.5), 143 (12), 115 (19), 89 (20), 77 (42). Anal. Calcd for $C_{15}H_{10}O_5$ (270.24): C, 66.66; H, 3.72. Found: C, 67.0; H, 3.49%.



^{13}C NMR of compound **2**

3-Aryl-2,3-dihydrochromeno[6,5-c]chromene-1,7-diones (**3a-d**): Compound **2** (2.7 g, 0.01 mol), an aromatic aldehyde (0.01 mol) and piperidine (0.5 ml) were refluxed in n-butanol (50 ml) for 6 h, when no more substrate was detected (TLC). The solid deposited from the hot solution was filtered off, dried and recrystallised to give **3a–d**.

3-(4-Methoxyphenyl) compound (**3a**): Recrystallised from AcOH as yellow crystals (73%), m.p. 230–232 °C. IR: ν_{max} br. 3500 (OH), 1687, 1670 cm^{-1} (CO). NMR (DMSO-d_6): δ_H 7.7–6.5 (m, 9H_{ar}), 5.8 (s, 1H, exchangeable with D_2O), 5.3 (t, H_a, J_{ac} = 5.8 Hz, J_{ab} = 6.4 Hz), 3.9 (s, 3H, OMe), 3.2 (d,d, H_c, J_{cb} = 16.8 Hz, J_{ac} 7.1 Hz), 2.9 (d,d, H_b, J_{bc} = 17.4 Hz, J_{ab} = 5.7 Hz). ^{13}C NMR (DMSO-d_6); δ_C 190.2 (CO), 50.6 (C2), 48.7 (C3), 107.3 (C5), 166.4 (C6) 108.2 [(C6a), 159.3 (CO), 153.3 (C–O), 123.7, 128.3, 126.4, 127.3, 130.7, 148.6 coumarinyl carbons], 164.1 (C4a), 123.7, 127.8, 118.2, 158.3 C_{ar}, 55.4 (MeO). EI MS: *m/z* (%) 388 (M^+, 100), 255 (29), 227 (3.4), 134 (73), 120 (60). Anal. Calcd for $C_{23}H_{16}O_6$ (388.37): C, 71.13; H, 4.15. Found: C, 71.41; H, 4.08%.

3-(4-Dimethylaminophenyl) compound (**3b**): Recrystallised from dioxan as red crystals (65%), m.p. 277–279 °C. IR: ν_{max} 3473 br (OH), 1692, 1678 cm^{-1} (CO). NMR (DMSO-d_6): δ_H 7.9–6.6 (m, 9H_{ar}), 5.9 (s, 1H, OH, exchangeable with D_2O), 5.1 (t, H_a, J_{ac} = 6.1 Hz, J_{ab} = 6.7 Hz), 3.4 (d,d, H_c, J_{bc} = 17.1 Hz, J_{ac} = 6.7 Hz), 3.1 (d,d, H_b, J_{bc} = 17.6 Hz, J_{ab} = 6.2 Hz), 2.85 (s, 6H, NMe_2). EI MS: *m/z* (%) 401 (M^+, 35), 357 (63), 120 (100). Anal. Calcd for $C_{24}H_{19}NO_5$ 401.42): C, 71.81; H, 4.77; N, 3.48. Found: C, 72.01; H, 4.51; N, 3.77%.

3-(4-Chlorophenyl) compound (**3c**): Recrystallised from AcOH as orange crystals (51%), m.p. 280–281 °C. IR: ν_{max} 3472 br (OH), 1687, 1670 cm^{-1} (CO). NMR (DMSO-d_6): δ_H 8.1–7.2 (m, 9H_{ar}), 5.6 (s, 1H, exchangeable with D_2O), 4.99 (t, H_a, J_{ac} = 5.2 Hz, J_{ab} = 7.1 Hz), 3.3 (d,d, H_c, J_{bc} = 15.8 Hz, J_{ac} = 6.44 Hz), 3.0 (d,d, H_b, J_{bc} = 16.8 Hz, J_{ba} = 6.0 Hz). EI MS: *m/z* (%) 394 (M^+, 32.4), 392 (M^+, 100). Anal. Calcd for $C_{22}H_{13}ClO_5$ (392.79): C, 67.27; H, 3.33; Cl, 9.02. Found: C, 67.51; H, 3.50; Cl, 9.20%.

3-*(β-Styryl) compound* (**3d**): Recrystallised from AcOH as orange crystals (60%), m.p. 268–269 °C. IR: ν_{max} 3492 br (OH), 1688, 1669 cm^{-1} (CO). EI MS: *m/z* (%) 384 (M^+, 33), 281 (66), 104 (100), 77 (41). Anal. Calcd for $C_{24}H_{16}O_5$ (384.39): C, 74.99; H, 4.19. Found: C, 75.28; H, 4.37%.

Reaction of **2** *with ethyl cyanoacetate; formation of 6-hydroxy-1-methyl-3,7-dioxo-3H,7H-chromeno[4,3-f]chromene-2-carbonitrile* (**4**)*:* A mixture of the acetyl compound **2** (2.7 g, 0.01 mole) and ethyl cyanoacetate (1.13 g, 0.01 mole) was stirred in the presence of sodium metal (0.5 g, 0.02 mole) in dry xylene on an oil-bath at 180 °C for 3 h. The reaction mixture was cooled and poured into cold dilute hydrochloric acid. The deposited solid was filtered off, washed several times with water, dried and then recrystallised from acetic acid to give **4** as light brown crystals (34%), m.p. 340–342 °C. IR: ν_{max} 3437 br (OH), 2228 (C≡N), 1736 (lactone CO), 1671 cm^{-1} (chelated ketone CO). NMR (DMSO-d_6): δ_H 7.6–6.6 (m, 5H_{ar}), 5.2 (s, 1H, OH), 1.67 (s, 3H, CH_3); δ_C 128.1, 125.9, 127.7, 124.3 (C9–C12), 152.3 (C8a), 131.4 (C12a), 161.1 (C7), 108.6 (C6a), 160.9 (C6), 109.2 (C5), 157.7 (C3), 96.4 (C2), 115.3 (C≡N), 170.1 (C1), 14.4 (CH_3), 118.4, 144.6, 130.9. EI MS: *m/z* (%) 319 (M^+, 84), 291(M-CO, 100), 262 (33), 76 (40). Anal. Calcd for $C_{18}H_9NO_5$ (319.27): C, 67.71; H, 2.84; N, 4.38. Found: C, 68.08; H, 2.60; N, 4.6%.

Reaction of **2** *with hydrazine: formation of azine* **5:** To a solution of **2** (2.7 g, 0.01 mole) in n-butanol, hydrazine hydrate (80%) (0.01 mole) was added with stirring. The mixture was refluxed for 8 h until no more substrate remained (TLC). Evaporation of the excess solvent left a solid product which recrystallised from acetic acid as orange crystals (35%), m.p. 346–348 °C. IR: ν_{max} 3413 br (OH), 1693 (CO), 1634 cm^{-1} (C=N). NMR (DMSO-d_6): δ_H 7.8–6.67 (m, 10H_{ar}), 5.1 (br. s, 4H), 2.1 (s, 6H). EI MS: *m/z* (%) 536 (M^+, 28), 268 (100), 228 (60). Anal. Calcd for $C_{30}H_{20}N_2O_8$ (536.50): C, 67.16; H, 3.75; N, 5.22. Found: C, 66.87; H, 3.52; N, 5.45%.

Reaction of **2** *with phenyl hydrazine; formation of 5-hydroxy-1-methyl-3-phenylchromeno[4,3-e]indazol-6(3H)-one* (**6**)*:* A mixture of compound **2** (2.7 g, 0.01 mole) and phenylhydrazine (1.08 g, 0.01 mole) was heated on an oil-bath at 180 °C for 3 h (TLC). The reaction mixture was then poured into ice-cold hydrochloric acid. The solid obtained was filtered off, washed several times with water, dried and recrystallised from acetic acid to give the chromeno-indazole derivative **6** as yellow crystals (24%), m.p. 265–267 °C. IR: ν_{max} 3422, 1691 (CO), 1640 cm^{-1} (C=N). NMR (DMSO-d_6): δ_H 7.8–6.9 (m, 10H_{ar}), 5.3 (s, 1H), 2.6 (s, 3H). EI MS: *m/z* (%) 342 (M^+, 100), 282 (36), 238 (14), 77 (66). Anal. Calcd for $C_{21}H_{14}N_2O_3$ (342.33): C, 73.68; H, 4.11; N, 8.18. Found: C, 73.72; H, 4.16; N, 8.44%.

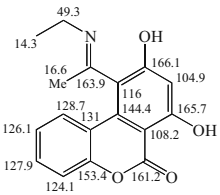
Reaction of **2** with primary amines; formation of 10-[1-(substituted imino)ethyl]-7,9-dihydroxy-6H-benzo[c]chromen-6-one **7a–h:** To a solution of **2** (0.9 g, 0.0033 mole) in n-butanol, a primary amine (p-toluidine, benzylamine, aniline, ethylamine, n-butylamine, dodecylamine, hexdecylamine or octdecylamine) was added and the whole mixture was refluxed for 6 hrs until no more substrate (TLC) was detected. The reaction mixture was poured onto ice-cold hydrochloric acid. The solid deposited was washed several times with water, dried and recrystallised from the indicated solvent to give **7a–h**.

p-Tolylimine **7a**: Yellow crystals (78%) from AcOH, m.p. 214–216 °C. IR: ν_{max} 3462 br. (OH), 1680 (CO), 1640 cm^{-1} (C=N). NMR (DMSO-d_6): δ_H 8–7.2 (m, 8H_{ar}), 6.3 (s, 1H, C_8-H), 4.66 (br.s, 2H, OH exchangeable with D_2O), 2.3 (s, 3H, Ar-Me), 0.9 (s, 3H, Me). EI MS: *m/z* (%) 359 (M^+, 100), 344 (58), 254 (44), 91 (41), 65 (38). Anal. Calcd for $C_{22}H_{17}NO_4$ (359.36): C, 73.53; H, 4.76; N, 3.89. Found: C, 73.74; H, 4.61; N, 3.67%.

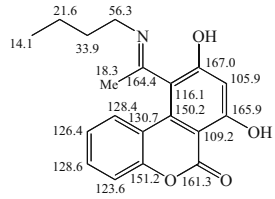
Benzylimine **7b**: pale yellow crystals (71%) from benzene, m.p. 145–146 °C. IR: ν_{max} 3436 br (OH), 1682 (CO), 1632 cm^{-1} (C=N). NMR (DMSO-d_6): δ_H 7.8–7.1 (m, 9H_{ar}), 6.48 (s, 1H, C8-H), 5.0 (br.s, 2H, exchangeable with D_2O), 4.81 (s, 2H, CH_2Ph), 1.2 (s, 3H, Me). EI MS: *m/z* (%) 359 (M^+, 33), 263 (100), 91 (82), 65 (32). Anal. Calcd for $C_{22}H_{17}NO_4$ (359.36): C, 73.53; H, 4.76; N, 3.89. Found: C, 73.74; H, 4.61; N, 3.67%.

Phenylimine **7c**: Recrystallised from toluene as pale yellow crystals (67%), m.p. 150–152 °C. IR: ν_{max} 3426 br (OH), 1676 (CO), 1628 cm^{-1} (C=N). NMR ($CDCl_3$): δ_H 7.7–7.1 (m, 9H_{ar}), 6.4 (s, 1H, C_8–H), 4.7 (br.s, 2H, exchangeable with D_2O), 1.08 (s, 3H, Me). EI MS: *m/z* (%) 345 (M^+, 100). Anal. Calcd for $C_{21}H_{15}NO_4$ (345.33): C, 73.04; H, 4.37; N, 4.05. Found: C, 72.91; H, 4.17; N, 4.20%.

Ethylimine **7d**: Recrystallised from AcOH as pale yellow crystals (61%), m.p. 207–209 °C. IR: ν_{max} 3470 br (OH), 1686 (CO), 1632 cm^{-1} (C=N). NMR (DMSO-d_6): δ_H 7.6–7.1 (m, 4H_{ar}), 6.3 (s, 1H, C_8-H), 3.56 (q, 2H), 1.2 (t, 3H), 0.99 (s, 3H, Me); δ_C, see inset structure. Anal. Calcd for $C_{17}H_{15}NO_4$ (297.29): C, 68.68; H, 5.07; N, 4.71. Found: C, 68.76; H, 5.2; N, 4.52%.



^{13}C NMR of compound **7d**



^{13}C NMR of compounds **7e**

n-Butylimine **7e**: Recrystallised from toluene as pale yellow crystals (56%), m.p. 165–167 °C. IR: ν_{max} br. 3444 (OH), 1688 (CO), 1638 cm^{-1} (C=N). NMR ($CDCl_3$): δ_H 7.8–7.2 (m, 4H$_{ar}$), 6.6 (s, 1H, C_8-H), 5.2 (br. s, 2H, exchangeable with D_2O), 3.6 (t, 2H), 1.7–1.3 (m, 4H), 1.08 (s, 3H, Me), 0.92 (s, 3H, Me); δ_C, see inset structure. EI MS: *m/z* (%) 325 (M^+, 71), 268 (100), 226 (43). Anal. Calcd for $C_{19}H_{19}NO_4$ (325.34): C, 70.14; H, 5.87; N, 4.30. Found: C, 70.32; H, 5.60; N, 4.55%.

n-Dodecylimine **7f**: Recrystallised from benzene as pale yellow crystals (52%), m.p. 142–143 °C. IR: ν_{max} 3462 br (OH), 1682 (CO), 1633 cm^{-1} (C=N). NMR ($CDCl_3$): δ_H 7.6–7.1 (m, 4H$_{ar}$), 6.4 (s, 1H, C_8-H), 5.1 (br.s, 2H, exchangeable with D_2O), 3.6 (t, 2H), 1.66–1.3 (m, 20H), 1.03 (t, 3H), 0.94 (s, 3H, Me). EI MS: *m/z* (%) 437 (M^+, 66), 268 (100). Anal. Calcd for $C_{27}H_{35}NO_4$ (437.53): C, 74.12; H, 8.05; N, 3.20. Found: C, 74.42; H, 7.76; N, 3.0%.

n-Hexadecylimine **7g**: Recrystallised from light petroleum ether as pale yellow crystals (49%), m.p.110–111 °C. IR: ν_{max} 3446 br (OH), 1688 (CO), 1636 cm^{-1} (C=N). NMR ($CDCl_3$): δ_H 7.8–7.2 (m, 4H$_{ar}$), 6.6 (s, 1H, C_8-H), 5.19 (br.s, 2H), 3.56 (t, 2H), 1.69–1.36 (m, 28H), 1.03 (t, 3H), 0.99 (s, 3H, Me). EI MS: *m/z* (%) 493 (M^+, 40), 267 (100). Anal. Calcd for $C_{31}H_{43}NO_4$ (493.63): C, 75.43; H, 8.76; N, 2.83. Found: C, 75.29; H, 8.49; N, 2.61%.

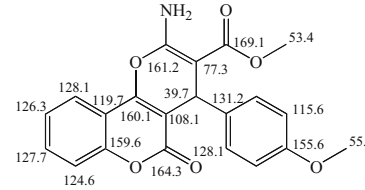
n-Octadecylimine **7h**: Recrystallised from benzene as pale yellow crystals (56%), m.135–137 °C. IR: ν_{max} 3470 br (OH), 1686 (CO), 1636 cm^{-1} (C=N). NMR ($CDCl_3$): δ_H 7.7–7.2 (m, 4H$_{ar}$), 6.48 (s, 1H, C_8-H), 4.98 (br.s, 2H), 3.54 (t, 2H), 1.65–1.3 (m, 32H), 1.1 (t, 3H), 0.97 (s, 3H, Me). EI MS: *m/z* (%) 521 (M^+, 17), 268 (100). Anal. Calcd for $C_{33}H_{47}NO_4$ (521.68): C, 75.97; H, 9.06; N, 2.68. Found: C, 75.77; H, 9.24; N, 2.91%.

6-Hydroxy-1-methyl-3-thioxo-3,4-dihydrochromeno[4,3-f] quinazolin-7-one (**8**): A mixture of **2** (2.7 g, 0.01 mole) and thiourea (1.52 g, 0.02 mole) was dissolved in acetic acid and heated under reflux for 3 h (TLC). The reaction mixture was poured onto cold water and the solid that separated was filtered off, washed with dilute ethanol, dried and recrystallised from dioxan to give **8** as deep yellow crystals (41%), m.p. 183–185 °C. IR: ν_{max} 3492 br (NH, OH), 1691 (CO), 1632 (C=N), 1324 cm^{-1} (C=S). NMR (DMSO-d_6): δ_H 7.3–6.6 (m, 5H$_{ar}$), 5.3 (br.s, 1H), 3.0 (br.s, 1H), 1.5 (s, 3H, Me). EI MS: *m/z* (%) 310 (M^+, 11), 282 (100), 223 (60), 76 (32). Anal. Calcd for $C_{16}H_{10}N_2O_3S$ (310.25): C, 61.94; H, 3.24; N, 9.03; S, 10.32. Found: C, 62.34; H, 2.98; N, 8.82; S, 10.07%.

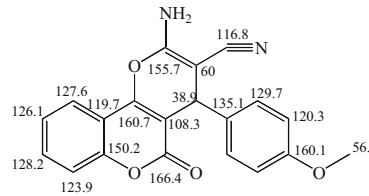
Formation of the pyrano-chromenones **9a** *and* **9b:** A mixture of 4-hydroxycoumarin (1.62 g, 0.01 mole), sodium methoxide (0.5 g sodium in 50 ml absolute methanol) and ethyl-α-cyano-4-methoxycinnamate or α-cyano-4-methoxycinnamonitrile (0.01 mole) was refluxed with stirring for 3 h (TLC). The reaction mixture was poured on cold dilute acetic acid and allowed to stand for 1 h at room temperature. The solid that separated in each case was filtered off, washed with water, dried and recrystallised from the indicated solvent.

Methyl 2-amino-4-(4-methoxyphenyl)-5-oxo-4,5-dihydropyrano [3,2-c]chromene-3-carboxylate (**9a**): Yellow crystals (66%) from benzene, m.p. 165–167 °C. IR: ν_{max} 3422, 3306, 3271 (NH_2), 1695 (CO unsaturated δ-lactone), 1658 cm^{-1} (chelated CO ester). NMR ($CDCl_3$): δ_H 7.4–6.9 (m, 8H$_{ar}$), 4.7 (s, 1H, C_4-H), 4.0 (br.s, 2H, exchangeable with D_2O), 3.85 (s, 3H, OMe), 3.7 (s, 3H, COOMe); δ_C, see inset structure. EI MS: *m/z* (%) 379 (M^+, 38), 320 (35), 272 (99), 249 (69), 240 (100), 145 (27), 121 (64), 117 (52), 89 (64). Anal. Calcd for $C_{21}H_{17}NO_6$ (379.35): C, 66.49; H, 4.51; N, 3.69. Found: C, 66.70; H, 4.21; N, 3.82%.

2-Amino-4-(4-methoxyphenyl)-5-oxo-4,5-dihydropyrano[3,2-c] chromene-3-carbonitrile (**9b**): Yellow crystals (52%) from acetic acid, m.p. 231–233 °C. IR: ν_{max} 3399, 3322, 3171 (NH_2), 2194 (C≡N), 1709 cm^{-1} (CO unsaturated δ-lactone). NMR (DMSO-d_6): δ_H 7.3–6.9 (m, 8H$_{ar}$), 4.7 (s, 1H, C_4-H), 4.0 (br.s, 2H, exchangeable with D_2O), 3.85 (s, 3H, OMe); δ_C, see inset structure. EI MS: *m/z* (%) 346 (M^+, 17), 280 (92), 279 (100), 249 (75), 240 (26), 145 (22), 121 (19), (89 (40), 66 (74). Anal. Calcd for $C_{20}H_{14}N_2O_4$ (346.32): C, 69.36; H, 4.06; N, 8.09. Found: C, 69.52; H, 4.11; N, 8.43%.



^{13}C NMR of compound **9a**



^{13}C NMR of compound **9b**

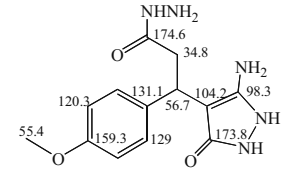
*3-Aryl-2,3-dihydrochromeno[6,5-c]chromene-1,7-dion*If *9-Benzoyl-8-hydroxy-7-(4-methoxyphenyl)-7,10-dihydro-6H-chromeno[3',4':5,6] pyrano[2,3-b]pyrrol-6-one* (**10**)

Phenacyl chloride (1.5 g, 0.01 mole) was added dropwise with stirring to the ester **9a** (3.79 g, 0.01 mole) in pyridine (20 ml) over 1 h and the mixture was then heated under reflux for another 1 h, monitoring the progress of the reaction by TLC. Evaporation of the solvent in vacuo left a semisolid product which was triturated with acetone and the solid which separated was filtered off, dried and recrystallised from dioxan to give compound **10** as yellow crystals (41%), m.p. 324–326 °C. IR: ν_{max} 3425 br (NH, OH), 1727 (CO), 1661 cm^{-1} (chelated ketone CO). NMR (DMSO-d_6): δ_H 8.3–7.2 (m, 14H$_{ar}$ + NH), 6.8 (br.s, 1H), 4.7 (s, 1H, C_4-H), 3.65 (s, 3H, OMe). EI MS: *m/z* (%) 447 (M^+–H_2O, 15.9), 424 (56.0), 317 (100), 92 (13.0). Anal. Calcd for $C_{28}H_{19}NO_6$ (465.44): C, 72.25; H, 4.11; N, 3.01. Found: C, 72.49; H, 4.19; N, 3.0%.

Methyl 2-furoylamino-4-(4-methoxyphenyl)-5-oxo-4,5-dihydro-pyrano[3,2-c]chromene-3-carboxylate (**11**): Furoyl chloride (2 g, 0.015 mol) was added dropwise with stirring to a solution of the ester **9a** (3.79 g, 0.01 mole) in pyridine (20 ml), and the mixture was refluxed for 2 h (TLC). The reaction mixture then poured onto crushed ice containing acetic acid. The solid that separated was filtered off, dried and recrystallised from light petroleum ether (b.p. 80–100 °C) to give **11** as yellow crystals (63%), m.p. 102–104 °C. IR: ν_{max} 3270 (NH), 1730 (CO unsaturated δ-lactone), 1710 (CO ester), 1670 cm^{-1} (CO amide). NMR ($CDCl_3$): δ_H 8.7 (s, 1H, NH), 8.18–6.82 (m, 11H$_{ar}$), 4.8 (s, 1H, C_4-H), 3.91 (s, 3H, OMe). EI MS: *m/z* (%) 473 (M^+, 10), 280 (77), 279 (82), 250 (64), 121(26), 92 (100), 64 (48). Anal. Calcd for $C_{26}H_{19}NO_8$ (473.41): C, 65.96; H, 4.04; N, 2.95. Found: C, 66.10; H, 4.0; N, 3.2%.

Hydrazinolysis of ester **9a**; *formation of* **12** *and* **13:** A solution of **9a** with hydrazine hydrate (80%) in molar ratio 1:3 in absolute ethanol (30 ml) was heated under reflux for 8 h (TLC). Evaporation of the excess solvent left a crude solid product (two spots in TLC) which triturated with diethyl ether. The residue was filtered off, dried and recrystallised from ethanol to give salicylic acid hydrazide **12**. Evaporation of ether left a solid product which recrystallised from acetic acid to give **13**.

3-(5-Amino-3-oxopyrazolin-4-yl)-3(4-methoxyphenyl)propanoyl hydrazide (**13**):Yellowish-white crystals (41%), m.p. 156–158 °C. IR: ν_{max} 3462, 3376, 3290, 3176 (NH_2), 1680 cm^{-1} (CO). NMR ($CDCl_3$): δ_H 8.3 (s, 2H, 2NH, exchangeable with D_2O), 7.1–6.7 (m, 4H$_{ar}$), 4.9



^{13}C NMR of compound **13**

(t, H_a, J_{ac} 5.99 Hz, J_{ab} 6.8 Hz), 3.9 (s, 3H, OMe), 3.3 (d,d, H_c, J_{cb} 16.8 Hz, J_{ac} 7.1 Hz), 3.1 (d,d, H_b, J_{bc} 17.2 Hz, J_{ba} 6.6 Hz), 2.2 (br.s, 5H, exchangeable with D_2O). EI MS: *m/z* (%) 263 (M^+-N_2, 100), 260 (67), 232 (17), 185 (22), 77 (80). Anal. Calcd for $C_{13}H_{17}N_5O_3$ (291.29): C, 53.6; H, 5.87; N, 24.04. Found: C, 53.92; H, 5.41; N, 23.74%.

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