[3,1]Oxazino[5',4':5,6]-, pyrido[3',2':5,6]-, pyrimidino[5',4':5,6]-, and pyrrolo[3',2':5,6]pyrano[3,2-c]chromene derivatives from 9-amino-7-(4-chlorophenyl)-6-oxo-6*H*,7*H*-pyrano[3,2-c]chromene-8-carbonitrile

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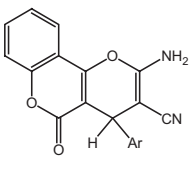
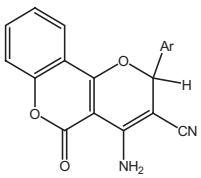
Pyrido[3',2':5,6]-, [3,1]Oxazino[5',4':5,6]-, pyrimidino[5',4':5,6]-, and pyrrolo[3',2':5,6] pyrano[3,2-*c*]chromene derivatives were obtained via the reaction of 9-amino-7-(4-chlorophenyl)-6-oxo-6*H*,7*H*-pyrano[3,2-*c*]chromene-8-carbonitrile ***1*** with diethyl malonate, Schiff's base, acetic acid, phenyl isothiocyanate and chloroacetic acid, respectively. Alkylation, acylation and hydrazinolysis of **1** were also discussed. The IR, ^{1}H NMR, ^{13}C NMR and MS spectra of the synthesised compounds were discussed.

Keywords: pyrido[3',2':5,6]-, [3,1]-oxazino[5',4':5,6]-, pyrimidino[5',4':5,6]-, and pyrrolo[3',2':5,6]pyrano[3,2-c] chromene derivatives

9-Amino-7-(4-chlorophenyl)-6-oxo-6*H*,7*H*-pyrano[3,2-*c*] chromene-8-carbonitrile **1** has been synthesised following the method described[1] by treating 4-chloro-2-cyanocinnamonitrile with 4-hydroxybenzopyran-2-one. Structural proof has been obtained through two components condensation of cinnamonitrile derivative and 4-hydroxy benzopyran-2-one in equimolar proportions under the previous conditions to yield 1:1 adducts for which two isomeric structures **1** and **2** seemed possible. Structure **1** is established for the reaction products based on ^{1}H NMR spectrum which revealed the presence of a signal at δ 4.35 ppm for one proton linked with an sp^3 carbon, signal at a similar position have been observed for 4H-pyran.[2,3]



(1)



(2)

The formation of **1** is assumed to proceed via addition of coumarinyl-C-3 to the activated double bond of cinnamonitrile derivative followed by 1,6-*exo-dig*. cyclisation of Michael adduct.[4-6] Structure **1** get more support through chemical reactions with electrophilic reagents such as furoyl chloride, acetic acid, acetic anhydride, ethyl chloroacetate, chloroacetic acid, phenyl isothiocyanate, Schiff's base, diethyl malonate and nucleophilic reagents such as hydrazine hydrate.

7-(4-Chlorophenyl)-9-furoylamino-6-oxo-6*H*,7*H*-pyrano [3,2-*c*]chromene-8-carbonitrile **3** has been synthesised by treating the compound **1** with furoyl chloride in refluxing pyridine. Treatment of compound **1** with acetic acid afforded 7-(4-chlorophenyl)-10-methyl-6*H*,7*H*,8H-[3,1]oxazino[5',4': 5,6]pyrano[3,2-*c*]chromene-6,8-dione **4**. Similar treatment of compound **1** with acetic anhydride yielded the *N,N*-diacetyl derivative **5**. Alkylation of **1** using ethyl chloroacetate in refluxing pyridine afforded 7-(4-chlorophenyl)-9-ethoxycarbonylmethylamino-6-oxo-6*H*,7*H*-pyrano [3,2-*c*] chromene-3-carbonitrile **6**.

Treatment of **1** with chloroacetic acid in boiling pyridine resulted in the formation of the pyrrolo[2',3':5,6]pyrano [3,2-*c*]chromene derivative **7**. The aminonitrile **1** reacted with phenylisothiocyanate in refluxing pyridine followed by acidification and produced an insoluble red crystalline product which was identified as 7-(4-chlorophenyl)-8-imino-9-phenyl-10-thioxo-8,9,10,11-tetrahydro-6*H*,7*H*-pyrimidino[5',4':5,6] pyrano[3,2-*c*]chromene-6-one **8**.

Schiff's base resulted from the condensation of 4-dimethyl-aminobenzaldehyde with aniline was allowed to conduct with compound **1** in refluxing butan-1-ol and acetic acid yielded the oxazinopyranochromene derivative **9** (Scheme 1). The formation of 9 could be visualised in terms of the route shown in Scheme 2.

The aminonitrile **1** was subjected to further transformation to produce fused heterocyclic system which incorporating pyridine nucleus with pyranobenzopyranone moiety. Thus, the reaction of **1** with diethyl malonate in the presence of sodium ethoxide yielded ethyl 8-amino-7-(4-chlorophenyl)-6,10-dioxo-10,11-dihydro-6*H*,7*H*-pyrido[3',2':5,6]pyrano[3,2-*c*] chromene-9-carboxylate **10**.

The behaviour of **1** towards the action of hydrazine hydrate was also investigated. Thus, when compound **1** was treated with hydrazine hydrate in boiling ethanol, a crystalline product with molecular formula $C_{16}H_{13}N_2O_3Cl$ was formed. The IR spectrum of this product devoid absorption bands for C≡N and C=O of δ-lactone and showed bands corresponding to $\nu_{NH,\ OH}$ (br) and $\nu_{C=N}$ at 3352, 3170 cm^{-1} and 1668 cm^{-1}, respectively. Structure of the pyrazolidinone derivative **11** was deduced for this product on the basis of the following arguments: (1) The correct elemental analysis. (2) The alcoholic solution of **11** shows dark green colour with ferric chloride solution, which indicate the cleavage of the δ-lactone ring and the presence of phenolic –OH group. (3) The mass spectrum shows fragmentation pattern which in accord with the proposed structure (c.f. Experimental). The conversion of the iminocarbonitrile **1** to the compound **11** using hydrazine hydrate could be visualised in terms of the forgoing pathway (Scheme 3).

Experimental

All melting points were taken on Griffin and Geory melting point apparatus and are uncorrected. IR spectra were recorded on Pye Unicam SP 1200 spectrophotometer using KBr wafer technique. ^{1}H NMR and ^{13}C NMR spectra were determined on a Varian Gemini 200 MHz, Brucher Ac-200 MHz using TMS as internal standard (chemical shifts in δ-scale). EI-MS were measured on a Schimadzu-GC-MS instrument operating at 70 eV. Microanalysis measurements were carried out at Ain Shams University labs and satisfactory analytical data (± 0.4) were obtained for all compounds.

9-Amino-7-(4-chlorophenyl)-6-oxo-6H,7H-pyrano[3,2-c]chromene-8-carbonitrile (**1**): A mixture of 4-chloro-2-cyanocinnamonitrile (1.89 g, 10 mmole) and 4-hydroxybenzopyran-2-one (1.62 g, 10 mmole) in absolute ethanol (30 ml) containing triethylamine (0.5 ml) was heated under reflux for 3 h (TLC). The solid product precipitated during reflux was filtered off, washed with hot ethanol, dried and recrystallised from dioxane to give **1** as white crystals, m.p. 268–270°C, yield 55%. IR (KBr): 3379, 3290, 3187 cm^{-1} (NH_2), 2190 cm^{-1} (C≡N), 1713 cm^{-1}

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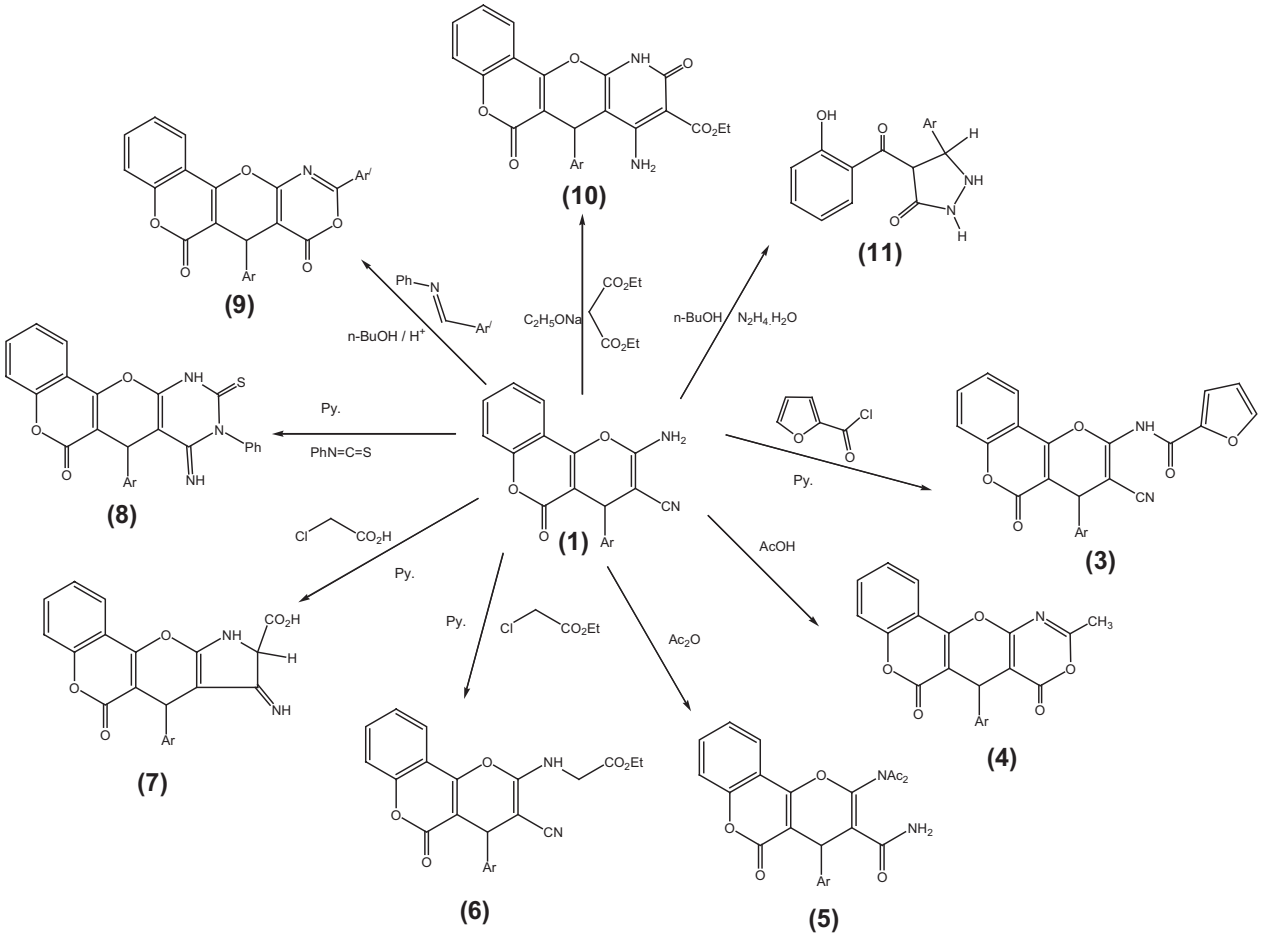
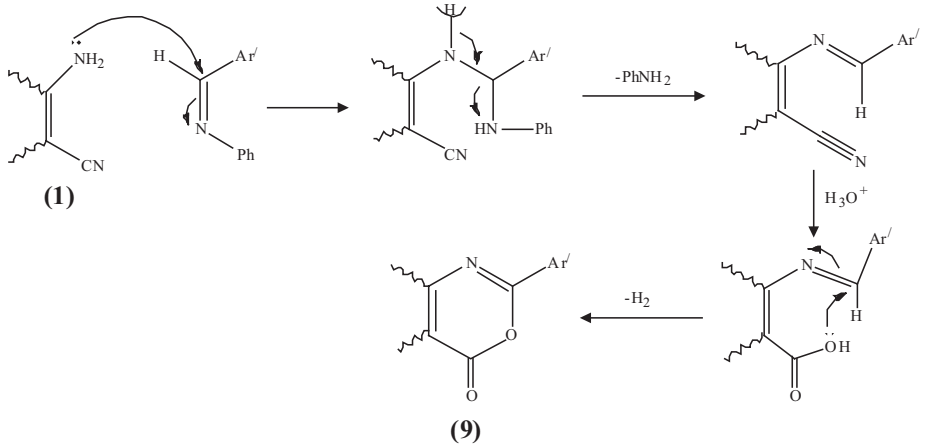


Scheme 1

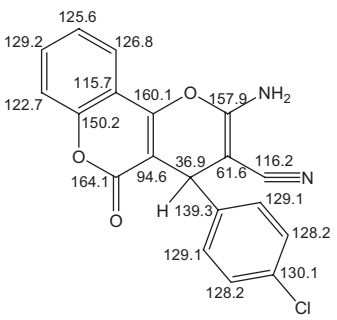


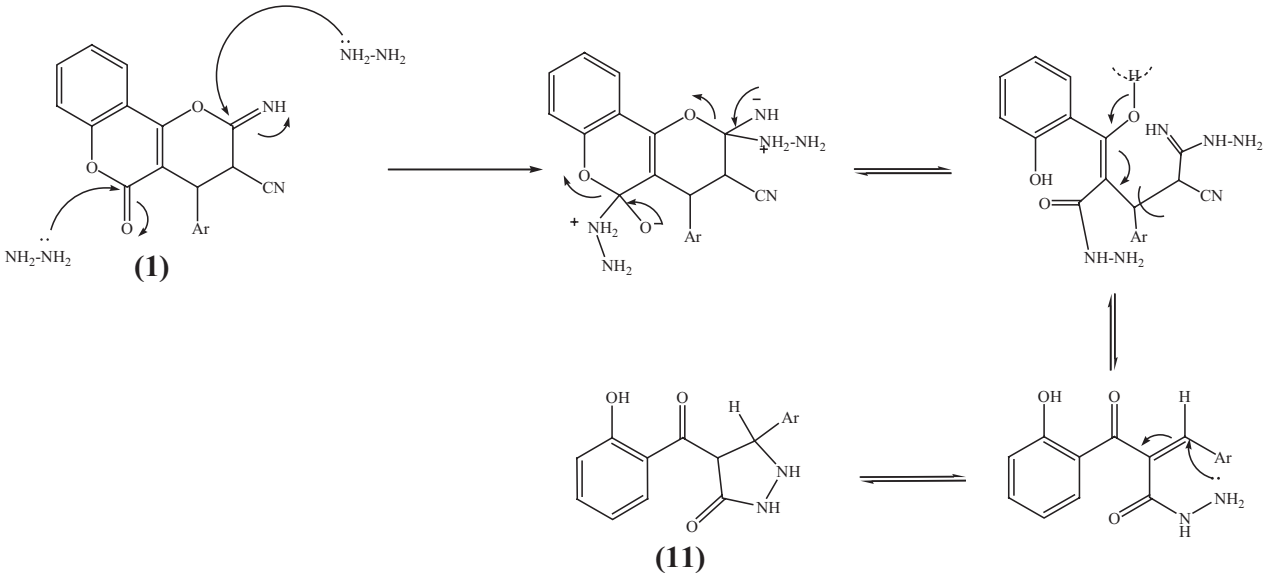
Scheme 2

(C=O), 1645 cm^{-1} (C=N). ^{1}H NMR ($CDCl_3$, δ ppm) 7.9–7.2 (m, 8H), 6.9 (br.s, 2H, exchangeable with D_2O), 4.35 (s, 1H). EI-MS *m/z* (%): 351 (M, 13.9), 347 (100), 239 (25.3), 189 (71.7), 121 (13.4). Anal. Calcd. for $C_{19}H_{11}ClN_2O_3$ (350.76): C, 65.06; H, 3.16; N, 7.98; Cl, 10.10. Found: C, 64.87; H, 3.32; N, 8.21; Cl, 10.11.

Formation of 7-(4-Chlorophenyl)-9-furoylamino-6-oxo-6H,7H-pyrano[3,2-c]chromene-8-carbonitrile **(3):** 2-Furoyl chloride (0.66 ml, 5 mmole) was added dropwise to a solution of pyranobenzopyran-5-one **1** (1.75 g, 5 mmole) in pyridine (20 ml), and the reaction mixture was refluxed for 30 min, left to cool and acidified with cold dilute hydrochloric acid. The crude solid product which deposited was collected by suction, washed several times with water, dried and then recrystallised from benzene as white crystals, m.p. > 300°C, yield 80%. IR (KBr): br. 3389 cm^{-1} (NH, OH), 2197 cm^{-1} (C≡N), 1730 cm^{-1} ($C=O_{\delta\text{-lactone}}$), 1672 cm^{-1} ($C=O_{amide}$). ^{1}H NMR (DMSO-$d_6$, δ ppm)

^{13}C NMR ($CDCl_3$)





Scheme 3

9.1 (br.s, 1H, exchangeable with D_2O), 7.7–6.59 (m, 11H), 4.1 (s, 1H). EI-MS *m/z* (%): 445 (M, 53.6), 350 (12.6), 317 (100), 95 (69.9). Anal. Calcd. for $C_{24}H_{13}ClN_2O_5$ (444.83): C, 64.80; H, 2.94; N, 6.29; Cl, 7.97. Found: C, 64.55; H, 3.21; N, 5.89; Cl, 8.12.

7-(4-Chlorophenyl)-10-methyl-6H,7H,8H-[3,1]-oxazino[5',4':5,6] pyrano[3,2-c] chromene-6,8-dione **(4):** A mixture of **1** (1.75 g, 5 mmole) and acetic acid (20 ml) was refluxed for 3 h until no more substrate was observed by TLC. The solvent was concentrated under vacuum and diluted with water. The precipitate was filtered off, washed several times with water, dried and recrystallised from benzene to give **4** as pale brown crystals, m.p. 158–160°C, yield 68%. IR (KBr): 1770 cm^{-1} ($C{=}O_{oxazinone}$), 1717 cm^{-1} ($C{=}O_{\delta\text{-lactone}}$), 1643 cm^{-1} (C=N). ^1H NMR ($CDCl_3$, δ ppm) 7.7-7.1 (m, $8H_{arom.}$), 5.1 (s, 1H, C_4-H), 2.1 (s, 3H, Me). EI-MS *m/z* (%): 394 (M, 16.9), 358 (12.2), 350 (33.1), 311 (100), 282 (22.7), 95 (66.3). Anal. Calcd. for $C_{21}H_{12}ClNO_5$ (393.78): C, 64.05; H, 3.07; N, 3.55; Cl, 9.00. Found: C, 63.77; H, 3.11; N, 4.0; Cl, 8.88.

7-(4-Chlorophenyl)-9-(N,N-diacetylamino)-6-oxo-6H,7H-pyrano[3,2-c]chromene-8-carboxamide **(5):** A suspension of **1** (1.75 g, 5 mmole) in freshly distilled acetic anhydride (15 ml) was heated under reflux for 3 h. 100 ml of water was added and the residue was basified with Na_2CO_3 and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude residue was crystallised from methanol as colourless crystals, m.p. 316–318°C, yield 31%. IR (KBr): 3432, 3310, 3210 cm^{-1} (NH_2), 1726 cm^{-1} ($C{=}O_{\delta\text{-lactone}}$), 1668 cm^{-1} ($C{=}O_{amide}$). ^1H NMR (DMSO-d_6, δ ppm) 8.2 (br.s, 2H, exchangeable with D_2O), 7.8–7.3 (m, $8H_{arom.}$), 4.6 (s, 1H, C_5-H), 2.38 (s, 6H). EI-MS *m/z* (%): 428 (M-HCN, 25.6), 293 (23.9), 317 (100). Anal. Calcd. for $C_{23}H_{17}ClN_2O_6$ (452.85): C, 61.0; H, 3.78; N, 6.18; Cl, 7.82. Found: C, 60.62; H, 3.76; N, 5.68; Cl, 7.77.

7-(4-Chlorophenyl)-9-ethoxycarbonylmethylamino-6-oxo-6H,7H-pyrano[3,2-c] chromene-3-carbonitrile **(6):**A mixture of **1** (1.75 g, 5 mmole) and ethyl chloroacetate (0.61 ml, 5 mmole) in pyridine (20 ml) was refluxed for 10 h until no more substrate was observed by TLC. After cooling at r.t., the solvent was concentrated under vacuo and the reaction mixture was acidified with cold diluted HCl. The crude solid product that deposited was collected by suction, washed with water, dried and then recrystallised from benzene to give the compound **6** as white crystals, m.p. 144–146°C, yield 36%. IR (KBr): 3316 cm^{-1} (NH), 2198 cm^{-1} (C≡N), 1738 cm^{-1} (C=O), 1718 cm^{-1} ($C{=}O_{ester}$). ^1H NMR ($CDCl_3$, δ ppm) 8.1 (br.s, 1H, exchangeable with D_2O), 7.9–6.9 (m, $8H_{arom.}$), 4.8 (s, 1H), 4.2 (q, 2H), 3.5–3.2 (d,d, 2H), 1.2 (t, 3H). EI-MS *m/z* (%): 437 (M, 37.5), 363 (11.9), 311 (100), 297 (58.3), 239 (41.7), 121 (56.1). Anal. Calcd. for $C_{23}H_{17}ClN_2O_5$ (436.85): C, 63.23; H, 3.92; N, 6.41; Cl, 8.13. Found: C, 63.69; H, 4.2; N, 6.22; Cl, 7.94.

7-(4-Chlorophenyl)-8-imino-6-oxo-8,9-dihydro-6H,7H-pyrrolo [3',2':5,6]pyrano [3,2-c]chromene-9-carboxylic acid **(7):** A mixture of **1** (1.75 g, 5 mmole) and chloroacetic acid (0.47 ml, 5 mmole) in pyridine (20 ml) was refluxed for 6 h (TLC). After cooling at r.t., the reaction mixture was acidified with cold diluted acetic acid. The crude solid product was collected by filtration and dissolved in $NaHCO_3$ solution (10%). The alkaline filtrate then acidified with cold diluted hydrochloric acid. The deposited solid was dried, and recrystallised from benzene to give the compound **7** as light brown crystals, m.p. 150–152°C, yield 20%. IR (KBr):br. 3500–2500 cm^{-1} (NH), 1717 cm^{-1} (C=O), 1705 cm^{-1} ($C{=}O_{acid}$), 1632 cm^{-1} (C=N). ^1H NMR ($CDCl_3$, δ ppm) 12.3 (s, 1H, exchangeable with D_2O), 10.1 (br.s, 1H, exchangeable with D_2O), 7.3–7.1 (m, $8H_{arom.}$), 4.9 (m, 2H), 4.13 (s, 1H). EI-MS *m/z* (%): 326 (54.2), 300 (42.8), 298 (100), 263 (42), 248 (26.9), 178 (24.8). Anal. Calcd. for $C_{21}H_{13}ClN_2O_5$ (408.8): C, 61.70; H, 3.20; N, 6.85; Cl, 8.67. Found: C, 62.08; H, 3.41; N, 7.11; Cl, 9.19.

7-(4-Chlorophenyl)-8-imino-9-phenyl-10-thioxo-8,9,10,11-tetrahydro-6H,7H-pyrimidino[5',4':5,6] pyrano[3,2-c]chromene-6-one **(8):** A mixture of **1** (1.75 g, 5 mmole) and phenyl isothiocyanate (0.6 ml, 5 mmole) in pyridine (15 ml) was refluxed for 6 h until no more substrate (TLC). The solvent was removed under vacuum, and the reaction mixture was diluted with water to give a crude solid which was filtered off, washed several times with water, dried and recrystallised from ethanol to give **8** as dark red crystals, m.p. 223–225°C, yield 33%. IR (KBr): 3389 cm^{-1} (NH), 1719 cm^{-1} (C=O), 1640 cm^{-1} (C=N), 1132 cm^{-1} (C=S). ^1H NMR (DMSO-d_6, δ ppm) 11.12 (s, 1H, exchangeable with D_2O), 7.8–6.27 (m, $13H_{arom.}$), 4.7 (s, 1H), 3.8 (br.s, 1H, exchangeable with D_2O). EI-MS *m/z* (%): 470 (M, 14.7), 315 (25.1), 221 (20.3), 92 (25.9), 77 (100). Anal. Calcd. for $C_{26}H_{16}ClN_3O_3S$ (485.94): C, 64.26; H, 3.31; N, 8.64; Cl, 7.29; S, 6.59. Found: C, 64.71; H, 3.41; N, 8.26; Cl, 7.08; S, 6.61.

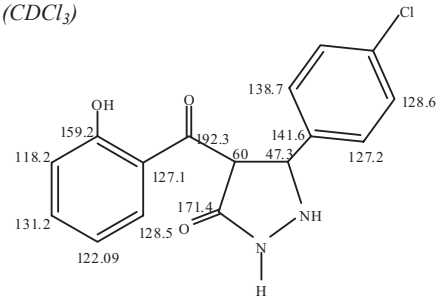
7-(4-Chlorophenyl)-10-[4-(dimethylamino)phenyl]-8,9,10,11-tetrahydro-6H,7H,8H-[3,1]oxazino[5',4':5,6]pyrano[3,2-c]chromene-6,8-dione **(9):** A mixture of **1** (1.75 g, 5 mmole) and 4-dimethyl-aminobenzylidene aniline (1.22 g, 5 mmole) was refluxed in n-butanol (20 ml) for 10 h. The reaction mixture was concentrated, left to cool and the solid deposited was filtered off by suction, washed with light petroleum ether and then recrystallised from benzene to afford **9** as orange crystals, m.p. 210–212°C, yield 30%. IR (KBr): 1792 cm^{-1} (C=O), 1722 cm^{-1} (C=O), 1645 cm^{-1} (C=N). ^1H NMR ($CDCl_3$, δ ppm) 8.1–7.0 (m, $12H_{arom.}$), 4.3 (s, 1H), 2.79 (s, 6H). EI-MS m/z (%): 501 (6.6), 326 (46.8), 300 (27.5), 298 (100), 263 (29.4), 121 (67.3), 92 (40),. Anal. Calcd. for $C_{28}H_{19}ClN_2O_5$ (498.92): C, 67.40; H, 3.83; N, 5.61; Cl, 7.10. Found: C, 68.03; H, 4.1; N, 5.38; Cl, 6.67.

Ethyl-8-amino-7-(4-chlorophenyl)-6,10-dioxo-10,11-dihydro-6H,7H-pyrido[3',2':5,6] pyrano[3,2-c]chromene-9-carboxylate **(10):** To a mixture of diethyl malonate (0.8 ml, 5 mmole) and the iminonitrile **1** (1.75 g, 5 mmole), a solution of sodium ethoxide (0.5 g sodium in 20 ml dry ethanol) was added and the reaction mixture was refluxed for 8 h until no more substrate (TLC).The excess solvent was evaporated *in vacuo* and the remaining semisolid product was acidified in cold dilute acetic acid. The crude solid product was collected by suction, washed with water, dried and then recrystallised from a mixture of light petroleum ether (b.p. 80–100°C)-ethyl acetate to afford **10** as a pale yellow crystals, m.p. 188–190°C, yield 55%.

IR (KBr): br. 3460, 3288, 3113 cm^{-1} (NH, OH), 1710 cm^{-1} ($C=O_{ester}$), 1712 cm^{-1} (C=O), 1670 cm^{-1} ($C=O_{amide}$). ^1H NMR ($CDCl_3$, δ ppm) 9.0 (s, 1H, exchangeable with D_2O), 7.84–7.12 (m, $8H_{arom.}$), 5.13 (s, 1H), 4.78 (br.s, 2H, exchangeable with D_2O), 4.4 (q, 2H), 1.13 (t, 3H). EI-MS *m/z* (%): 437 (M-C_2H_4, 10.1), 402 (14.4), 326 (25.6), 298 (100). Anal. Calcd. for $C_{24}H_{17}ClN_2O_6$ (464.86): C, 62.01; H, 3.68; N, 6.02; Cl, 7.62. Found: C, 61.87; H, 3.90; N, 6.09; Cl, 7.88.

3-(4-Chlorophenyl)-4-(2-hydroxybenzoyl) pyrazolidin-5-one **(11):** To a solution of **1** (1.75 g, 5 mmole) in butan-1-ol (20 ml). hydrazine hydrate (0.96 ml, 30 mmole) was added dropwise with stirring at r.t. for 10 min. The whole mixture was refluxed for 4 h. The solvent was removed by vacuum and the reaction mixture was acidified with cold dilute HCl. The separated solid was collected by suction, dried and recrystallised from light petroleum ether (b.p. 80–100°C) as a pale brown crystals, m.p. 202–204°C, yield 40%. IR (KBr): br. 3352, 3170 cm^{-1} (NH, OH), 1668 cm^{-1} (C=O). ^1H NMR ($CDCl_3$, δ ppm) 10.3 (s, 1H), 8.2 (br.s, 2H), 7.6–6.95 (m, $8H_{arom.}$), 5.16 (m, 1H). EI-MS *m/z* (%): 317 (M, 19.7), 276 (31.3), 166 (70.6), 165 (100), 138 (28.4), 111 (46.4). Anal. Calcd. for $C_{16}H_{13}ClN_2O_3$ (316.74): C, 60.67; H, 4.13; N, 8.84; Cl, 11.19. Found: C, 61.05; H, 4.33; N, 8.49; Cl, 10.77.

^{13}C NMR ($CDCl_3$)



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