Synthesis and spectral study of novel benzopyrone and quinolinone derivatives

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A series of novel benzopyrones and quinolinone derivatives were prepared using the readily obtainable 6-nitro-benzo-2-pyron-3-carboxylate through the reaction with nitrogen nucleophilic reagents such as cyclohexyl amine, *p*-aminoacetophenone, diamines, hydrazine hydrate, thiosemicarbazide, anthranilic acid and carbon nucleophile as malononitrile. The IR, ^{1}H NMR and mass spectra of the new synthesised compounds were discussed.

Keywords: benzopyrones, quinolinone, fused 1,3,4-thiadiazepine derivatives

The coumarin nucleus is widely available from plants and is an important class of oxygen heterocycle.[1–3] The useful medical properties associated with these naturally occurring coumarins have lead to the investigation of several synthetic analogues. A large number of compounds containing coumarin have been investigated because of their anti-inflammatory[4], antibacterial[5], vasorelaxant[6], antihepatitis-C virus agent[7] and antiproliferative activities[8]. In view of this, and as continuation of our effort[9–15] to identify new, potent, selective and less toxic antimicrobial agents, we aimed to synthesise a new coumarin derivative that exhibits high therapeutic activity.

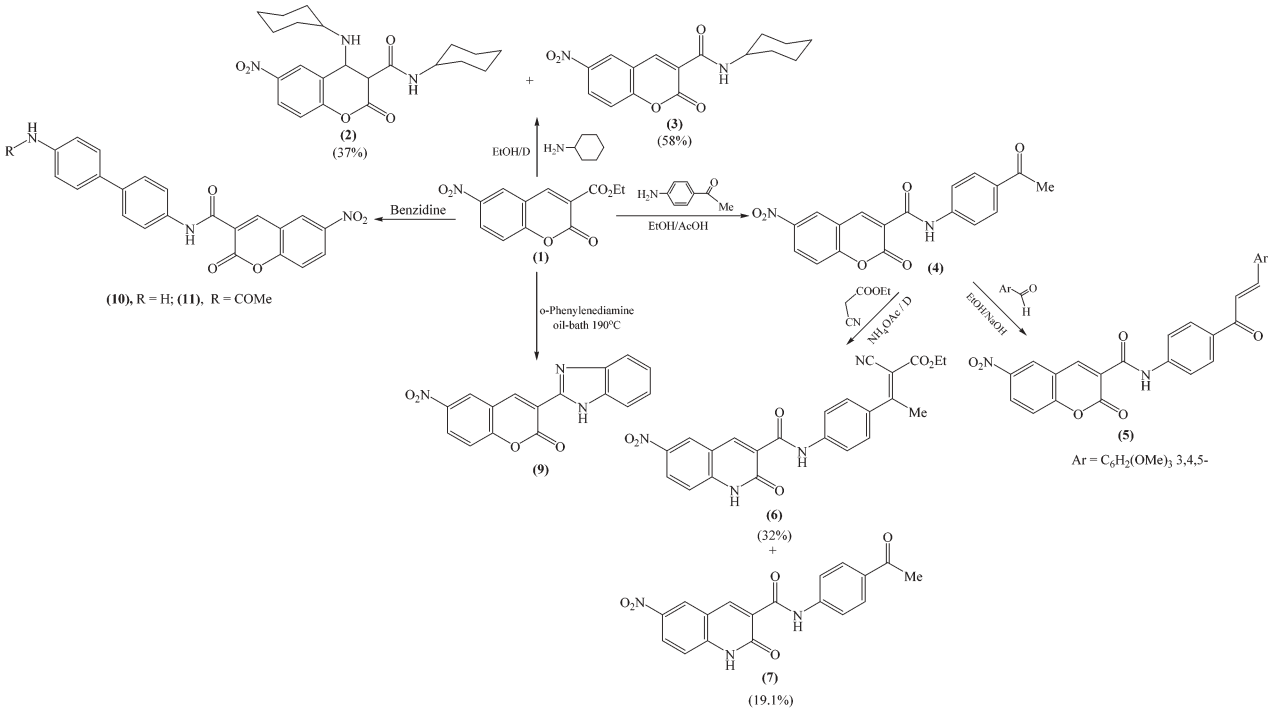
Results and discussion

Nitration of 3-carboethoxy coumarin in HNO_3/AcOH mixture afforded 3-carboethoxy-6-nitrocoumarin **1** as the sole product (one spot in the TLC). The structure of **1** was characterised by its analytical and spectroscopic data (IR, ^{1}H NMR, MS). Thus, the IR spectrum of **1** showed sharp bands at 1736 cm^{-1} ($\nu_{C=O}$ of α,β-unsaturated δ-lactone), 1706 cm^{-1} ($\nu_{C=O}$ of ester group). However, ^{1}H NMR spectrum of **1** in $CDCl_3$ showed the following absorptions from low to high field: δ (ppm) 7.89–7.2 (m, 4H$_{arom.}$ + olefinic C$_4$–H), 4.2 (q, 2H, $\underline{CH_2}CH_3$, J = 6.7 Hz) and 1.2 (t, 3H, $CH_2\underline{CH_3}$, J = 6.7 Hz).

The EI fragmentation pattern of compound **1** is consistent with the proposed structure. The C–O bond cleavage of the molecular ion followed by a rearrangement through the γ-hydrogen shift leads to the loss of the ethylene molecule and to the formation of the ion [M$^{+\cdot}$-28] which loss CO_2 to give the base peak at m/z = 191 (100%).

It has been reported[16] that the reaction of amines with 3-carboethoxy coumarin produced the corresponding 3-coumarin carboxamide without fission of the heterocyclic ring. In the present investigation, we aim to illustrate the effect of a nitro group in 6-position on the reactivity of both α,β-unsaturated δ-lactone and ester groups towards primary amines as nitrogen nucleophiles. Thus, compound **1** reacted with cyclohexyl amine in boiling ethanol and produced a semi-solid which was triturated with ethanol to give soluble and insoluble fractions. The soluble fraction (37%) after evaporation of the solvent and purification was identified as 4-N-cyclohexylamino-6-nitro-3-(N-cyclohexyl) carboxamido coumarin **2** (Scheme 1).

The structure of **2** was substantiated from the analytical and spectroscopic data. Thus, IR spectrum displayed the stretching absorption bands at 3360,3300 cm^{-1} (ν_{NH}), 1758 cm^{-1} ($\nu_{C=O}$ saturated δ-lactone), 1663 cm^{-1} ($\nu_{C=O}$ amide) and at 1600 ($\nu_{C=C}$) which were consistent with the proposed structure. ^{1}H NMR



Scheme 1

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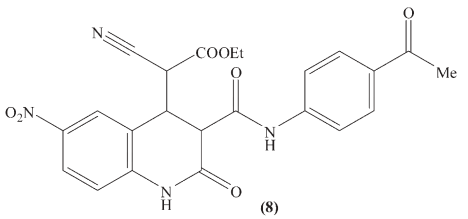
spectrum (DMSO-d_6) exhibited absorptions at δ (ppm) 8.9–8.6 (two s, 2H, exchangeable NH), 7.5 (s, $3H_{arom.}$), 3.0 (d, 1H, C_3–H, J = 4.2 Hz), 2.8 (t, 1H, C_4–H, J = 5.5 Hz) and 2.0–1.2 (br, 22H, two cyclohexyl groups). The mass spectrum of compound **2** displayed the correct molecular ion peak at m/z = 415 as the base peak. The insoluble fraction (58%) was crystallised from dilute acetic acid to produce 6-nitro-3-(N-cyclohexyl) carboxamidobenzo-2-pyrone **3** whose structure was deduced from the following evidence: (i) Correct analytical data. (ii) Its IR spectrum showed the stretching frequency of the NH group at 3210 cm^{-1} besides the C=O absorption bands at 1726 cm^{-1} and 1658 cm^{-1} which are characteristic for α,β-unsaturated δ-lactone and amide, respectively. (iii) The ^{1}H NMR spectrum ($CDCl_3$) showed the signals at δ (ppm) 8.2 (br.s, 1H, exchangeable NH), 7.4–7.2 (br.s, $4H_{arom.}$ + C_4–H) and 2.0–1.2 (m, 11H, C_6H_{11}). (iv) The EI fragmentation pattern of **3** was completely in accord with the proposed structure, which show the correct molecular ion at m/z = 316 together with the base peak at m/z = 146 attributable for the coumarin moiety.

Refluxing compound **1** with 4-aminoacetophenone in boiling ethanol in the presence of acetic acid afforded 6-nitro-3-N-(4-acetylphenyl) carboxamidobenzo-2-pyrone **4** as the sole product (Scheme 1). The assigned structure of **4** was consistent with the study of its IR spectrum which displayed ν_{NH} (br) at 3380 cm^{-1}, $\nu_{C=O}$ (δ-lactone) at 1730 cm^{-1}, $\nu_{C=O}$ (ketone) at 1675 cm^{-1} and $\nu_{C=O}$ (amide) at 1648. Both the mass spectrum and ^{1}H NMR spectrum of **4** ($CDCl_3$) revealed signals which agree with the proposed structure. Formation of **4** had probably occurred through the nucleophilic addition of the amino group to the positively polarised carbonyl of the carboxylate group through the A_{AC}^2 mechanism.

Furthermore, the structure of **4** was substantiated from the following evidence.

First, compound **4** was stirred with 3,4,5-trimethoxybenzaldehyde in the presence of ethanolic sodium hydroxide (10%) to give the corresponding chalcone **5** whose structure was confirmed by the elemental analysis and IR spectrum which exhibited $\nu_{C=O}$ (δ-lactone) at 1738 cm^{-1}, $\nu_{C=O}$ (α,β-unsaturated ketone) at 1676 cm^{-1}, $\nu_{C=O}$ (amide) at 1656 cm^{-1}. Second, compound **4** was fused with ethyl cyanoacetate in the presence of ammonium acetate in an oil bath at 160–170 °C. The resulting semi-solid contained two products (TLC, two spots, R_f = 0.3, R_f = 0.42). This mixture was separated by fractional crystallisations (see exp.) and gave **6** (32%) and **7** (19.1%) (Scheme 1).

The formulation assigned for compound **6** was established by analytical and spectroscopic data. Thus, the IR spectrum of **6** displayed $\nu_{C\equiv N}$ at 2226 cm^{-1}, $\nu_{C=O}$ (ester) at 1708 cm^{-1}, $\nu_{C=O}$ (amide) at 1660, 1654 cm^{-1} with olefinic absorption at 1612 cm^{-1}. There was an indication of hydrogen bonded –OH absorption at 3300–3500 cm^{-1}ponting to an enolisable system (lactam lactim) and laking for the $\nu_{C=O}$ (unsaturated δ-lactone) and $\nu_{C=O}$ of ketone. Furthermore, compound **6** failed to react with phenyl hydrazine, 2,4-dinitrophenyl hydrazine or hydroxylamine hydrochloride indicating the absence of free ketonic group. Thus, Michael adduct **8** was rejected.



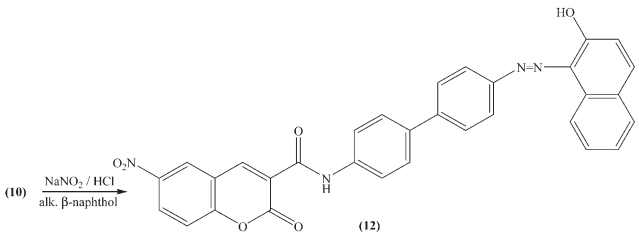
(8)

Moreover, the ^{1}H NMR spectrum of compound **6** displayed signals at δ (ppm) 10.3 and 8.6 as two singlets each integrating for one proton which disappeared using D_2O and two multiplet in range 8.3–7.1 integrates for 8H representing for aromatic protons and olefinic proton at C_4-position. The ethyl protons appeared as quartet for 2H at δ 4.28 ppm and triplet for 3H at δ 1.27 ppm with equal coupling constant (J = 6.7 Hz). Furthermore, a singlet appears at δ 2.4 ppm representing the methyl group. The mass spectrum of **6** was in accord with the assigned structure.

The structure of the 3-substituted quinolin-2(H)-one derivative **7** was inferred from the analytical and spectroscopic data (IR, ^{1}HNMR, MS). ^{1}HNMR (DMSO-d_6) spectrum exhibited two singlets at δ 10.3, 8.9 ppm which disappeared in D_2O representing the two NH together with multiplet integrated for 8H at δ 8.2–7.1 ppm corresponding to aromatic protons with olefinic proton at C4.The methyl protons appeared as singlet integrated for 3H at δ 2.4 ppm. Furthermore, the fragmentation pattern of the mass spectrum displayed the molecular ion peak at m/z = 351 which is the base peak.

The proclivity of compound **1** towards diamines was also investigated. 6-Nitro-3-(benzimidazol-2-yl)benzo-2-pyrone **9** was obtained upon heating compound **1** with *o*-phenylene diamine in an oil-bath at 190 °C (Scheme 1). Structure **9** was established from the analytical and spectroscopic data. The IR spectrum lacked the $\nu_{C=O}$ characteristic for the ester group and exhibited $\nu_{C=O}$ at 1726 cm^{-1} (α,β-unsaturated δ-lactone), $\nu_{C=N}$ at 1632 cm^{-1}, and ν_{NH} at 3345 cm^{-1}. Furthermore, the ^{1}H NMR spectrum ($CDCl_3$) showed a singlet at δ 9.1 ppm for one proton which is characteristic for NH and multiplet for (8H) at δ 7.8–7.2 ppm attributable for aromatic protons and C_4–H. The mass spectrum showed the radical cation peak at m/z = 307 (41.3%) which represent the molecular ion peak upon loss of benzimidazolyl moiety yielded the base peak at m/z = 190 (100%).

Treatment of **1** with benzidine in boiling ethanol furnished 6-nitro-3N-(4′-aminobiphenyl) carboxamidobenzo-2-pyrone **10** as the sole product. The structure **10** was substantiated exclusively from IR, ^{1}HNMR and mass spectral data. IR spectrum of **10** exhibited the stretching frequencies of NH as doublet at 3440, 3370 cm^{-1}, $\nu_{C=O}$ (δ-lactone) at 1730 cm^{-1} and $\nu_{C=O}$ (amide) at 1668 cm^{-1} and the ^{1}HNMR spectrum ($CDCl_3$) of **10** displayed signals at δ (ppm) 9 (s, 1H, NH, exchangeable with D_2O), 7.9–7.1 (m, $12H_{arom.}$ + C_4–H) and broad singlet at δ 4.6 ppm for 2H exchangeable with D_2O corresponding to NH_2 protons. The highest recorded peak at m/z = 399 attributed to the $M^{+\cdot}$-2 peak. The base peak (m/z = 184) represented the benzidine radical cation which is obtained by α-cleavage. Diazotization of **10** and coupling with alkaline β-naphthol gave the red dye **12** which is a good evidence for the presence of a primary aromatic amino group.



(10) **(12)**

Compound **10** upon recrystallisation with acetic acid produced the *N*-acetyl derivative **11** whose the structure was substantiated from the elemental analysis and molecular weight determination, the IR spectrum showed additional $\nu_{C=O}$ at 1670 cm^{-1} which is attributable to the acetamido group and ^{1}HNMR spectrum (DMSO-d_6) of **11** showed a singlet at δ 2.36 attributable for CH_3CO group besides the characteristic signals for aromatic and olefinic protons.

It has been reported that the reaction of coumarins with hydrazine hydrate affects the fission of heterocyclic ring[17]. In the present investigation, the study of behaviour of 3-carboethoxy-6-nitrocoumarin **1** towards hydrazine hydrate has

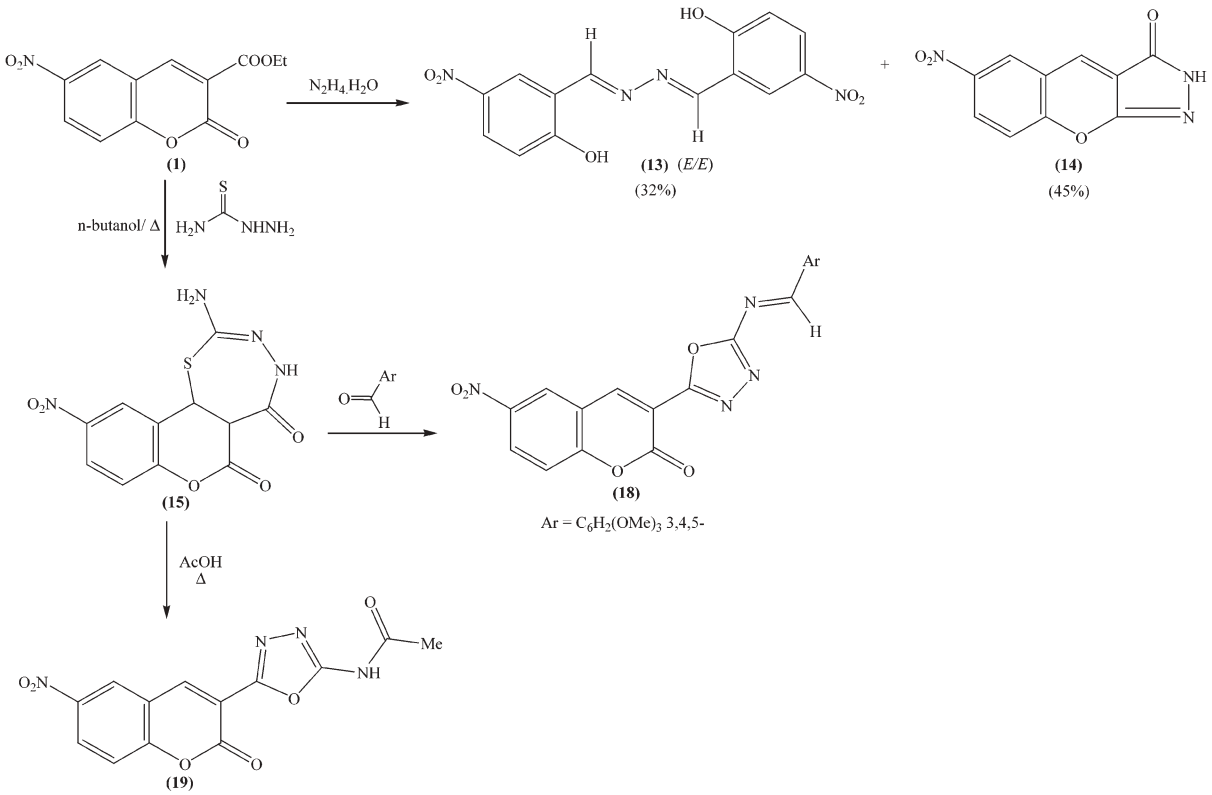
been extended. Compound **1** contains two possible sites for nitrogen nucleophiles. Thus, compound **1** reacted with hydrazine hydrate to give a mixture of two products (two spots in TLC, R_f = 4.15, 3.16).

The azine derivative **13** could be isolated in pure crystalline form by trituration of the crude mixture with benzene (Scheme 2).

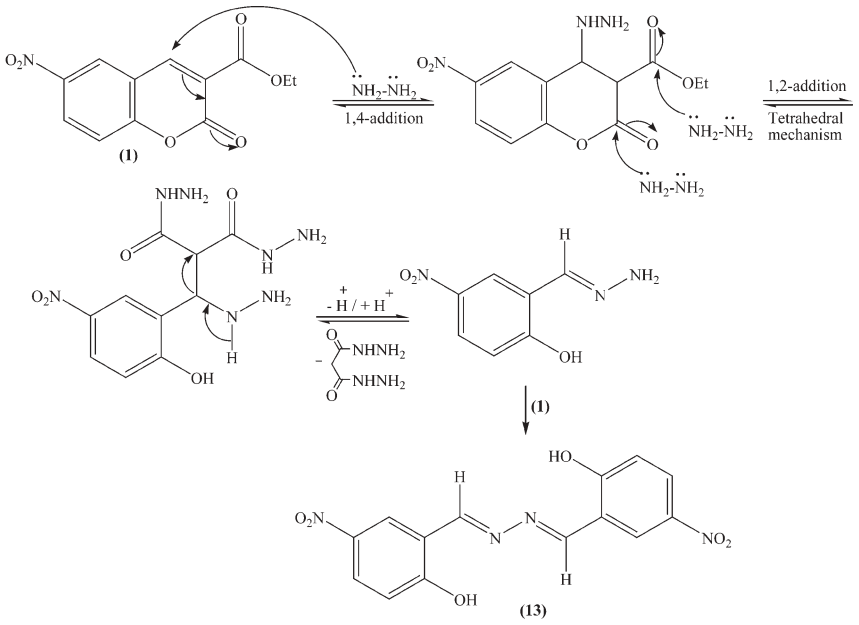
One possible approach to explain the formation of the azine **13** involves the hydrazinolysis of δ-lactone through 1,4-addition followed by ring fission of the heterocyclic ring and also the hydrazinolysis of the ester group (Scheme 3).

Compound **14** (soluble fraction in benzene) was obtained in pure crystalline form after slow evaporation of benzene. The structure **14** was confirmed by microanalytical and spectroscopic data. The formation of **14** could be visualised as in Scheme 4.

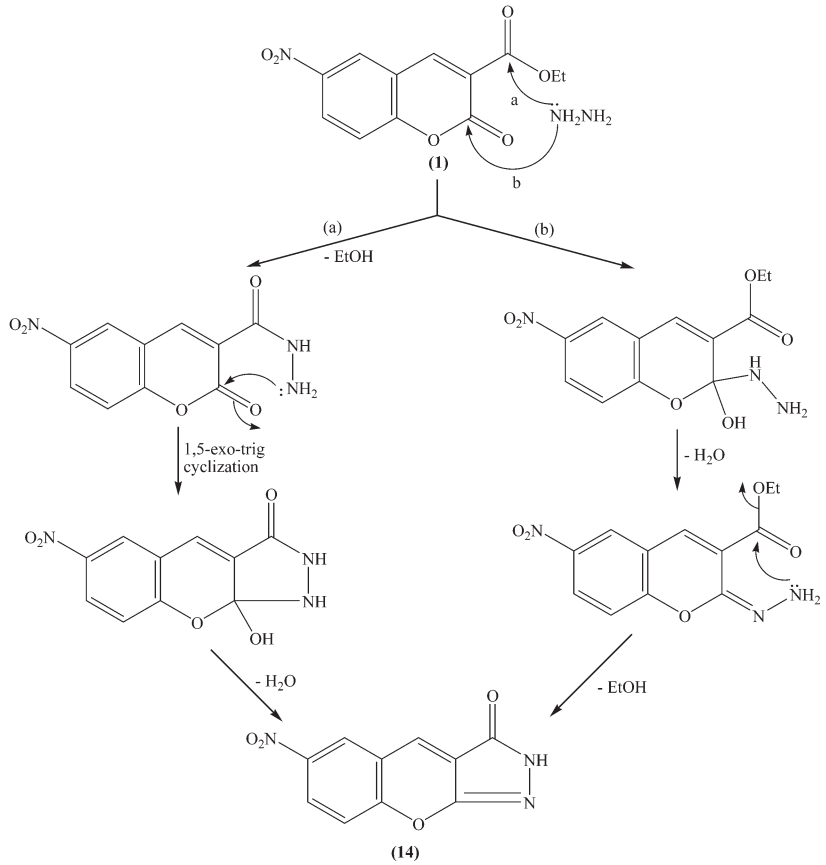
It has been reported[18] that 4-alkyl-3-carboethoxybenzo-2-pyrone undergoes cyclocondensation with thiosemicabazide and yielded 3-[1,2,4-triazol-3-yl]benzo-2-pyrone derivative. This reaction was reinvestigated with compound **1**. Thus, treatment of **1** with thiosemicabazide in refluxing *n*-butanol, resulted in the formation of the product with molecular formula $C_{11}H_8N_4O_5S$ ($M^{+\cdot}$ = 308). This formula indicates the removal of ethanol molecule during the reaction pathway from the two reactants. Three possible structures were assumed for this product **15–17**.



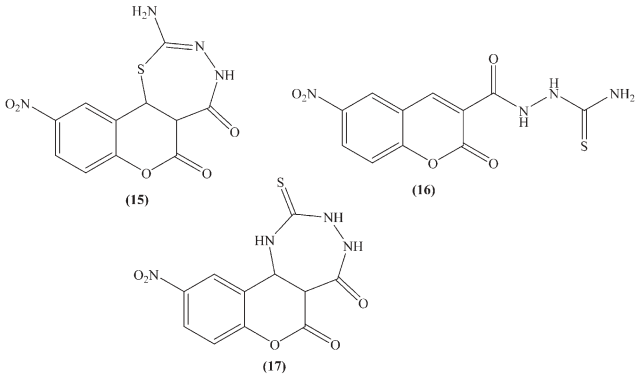
Scheme 2



Scheme 3



Scheme 4



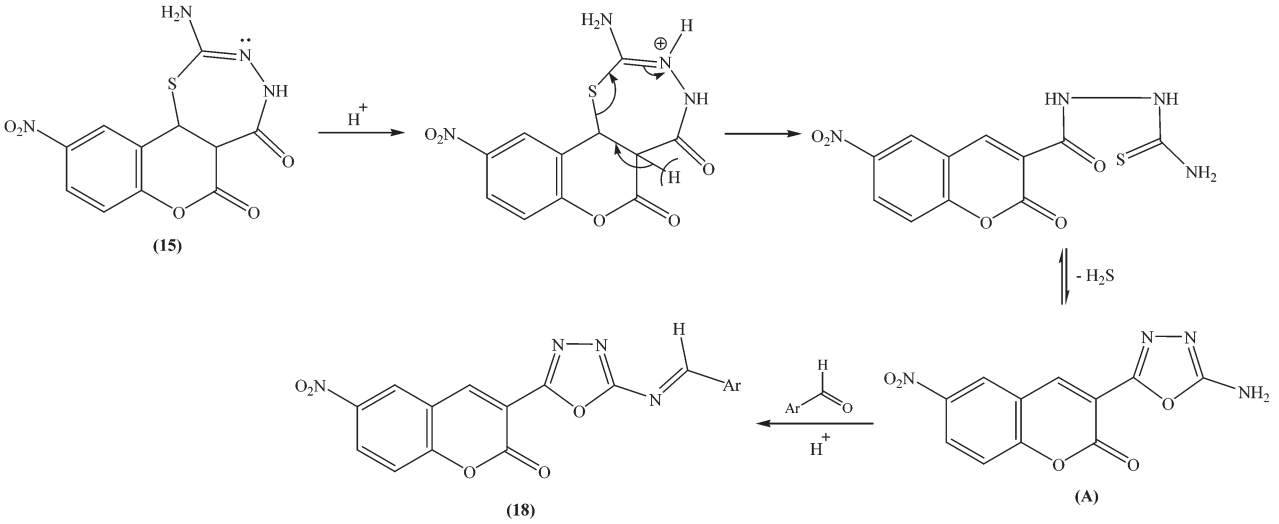
The IR and ^{1}HNMR of the product revealed a pattern completely different from that expected for structures **16** and **17** and can only be intelligibly interpreted in terms of structure **15** since the IR spectrum of the product showed absorption bands corresponding to the amino groups (3390 and 3280 cm^{-1}), NH group (3190 cm^{-1}), saturated δ-lactone (1742 cm^{-1}), cyclic amide (1680 cm^{-1}), 1614 cm^{-1} (C=N) and lacked $\nu_{C=S}$. The ^{1}H NMR spectrum ($CDCl_3$) showed signals characteristic for 3NH protons at δ 9.1, 8.8 as two singlet with ratio (2:1) and multiplet for aromatic protons together with two doublets each integrated for one proton. The EI fragmentation pattern for compound **15** showed peak at *m/z* = 310 ($M^{+\cdot}$+2). Furthermore, compound **15** was condensed with 3,4,5-trimethoxybenzaldehyde in the presence of catalytic amount of dilute acetic acid, H_2S gas was released during the reaction time and the product formed was investigated. This product lacked sulfur in ordinary element test and elemental analysis, N% = 12.64. The IR spectrum exhibited $\nu_{C=O}$ at 1730 cm^{-1}(unsat. δ-lactone) and $\nu_{C=N}$ at 1648 cm^{-1} and its believed that the assigned structure **18** was in accord with the above results (Scheme 3). The highest recorded peak in the mass spectrum of compound **18** at *m/z* = 452 represent the molecular ion peak. The conversion of **15** to **18** could be explained on the basis of acid-catalysed ring opening followed by elimination of H_2S gas to give the 1,3,4-oxadiazole derivative **A** and finally simple condensation reaction (Scheme 5).

Ample evidence for the postulated mechanism is obtained by refluxing compound **15** with acetic acid which afforded the N-acetylamino derivative **19** which is a good support for the formation of intermediate **A**. The IR and ^{1}H NMR were consistent with the assigned structure **19**.

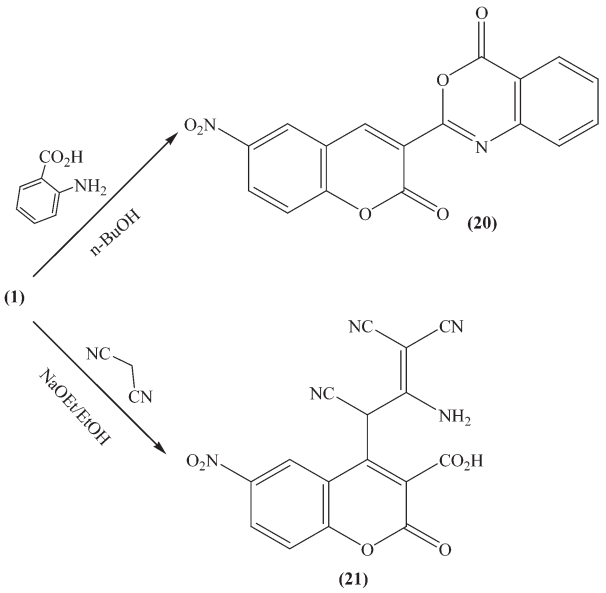
The behaviour of 3-carboxy-6-nitrobenzo-2-pyrone towards anthranilic acid has been further investigated in the present study.[19] The treatment of **1** with anthranilic acid in refluxing *n*-butanol afforded 6-nitro-3-[3,1-benzoxazin-4-oxo-2-yl] benzo-2-pyrone **20** (Scheme 6).

The structure assigned for **20** was consistent with the analytical data. Its IR spectrum displayed well defined absorption bands at 1763 cm^{-1} ($\nu_{C=O}$ of benzoxazinone ring), 1732 cm^{-1} ($\nu_{C=O}$ of δ-lactone). On the other hand, the mass spectrum exhibited peak at *m/z* = 336 (27.9%) attributable for the parent molecular ion.

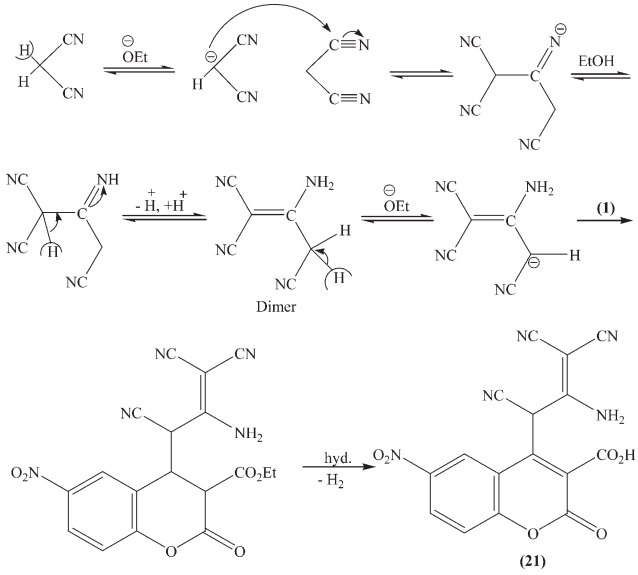
Compound **1** reacted with malononitrile in the presence of NaOEt/EtOH under Michael conditions and yielded **21** as the sole product. Compound **21** was soluble in sodium bicarbonate solution and its IR spectrum displayed broad absorption band at 3460–2960 cm^{-1} ($\nu_{NH2,\ OH}$), $\nu_{C\equiv N}$ at 2226 cm^{-1}, $\nu_{C=O}$ at 1732 cm^{-1} (unsat. δ-lactone), $\nu_{C=O}$ at 1693 cm^{-1} (unsaturated acid), $\nu_{C=C}$ at 1615 cm^{-1}. Moreover, the ^{1}H NMR spectrum showed the absence of signals characteristic for ethyl protons and only deshielded acidic proton appeared at δ 11.4 ppm which indicates the hydrolysis of the ester group during the reaction conditions. The formation of Michael adduct **21** possibly takes place via the formation of malononitrile dimer followed by carbanion 1,4-addition (Scheme 7).



Scheme 5



Scheme 6



Scheme 7

Conclusion

1,3,4-Oxadiazolyl-3,1-benzoxazinyl-, benzimidazolyl-, 1,3,4-thiadiazapine benzopyran-2-one and other novel 3-substituted benzopyran-2-one and quinolone-2-one derivative were prepared using the easily accessible starting material 6-nitro benzopyran-3-carboxylate via the reaction with different amines, diamine, anthranilic acid, hydrazine, thiosemicarbazide and carbon nucleophile. The synthesised compounds were obtained in good yields.

Experimental

Melting points were determined on a Biotius hot-stage microscope and are uncorrected. The IR spectra were recorded on a Pye-Unicam SP 1200 spectrophotometer using the KBr Wafer technique. The ^{1}H NMR spectra were determined on Varian A-60 and Joel NMR EX-270 MHz spectrometers using TMS as an internal standard. The mass spectra were carried out on an MS QP 1000 EX schimdzu spectrometer, Japan EI 70 eV, ionisation chamber 250 °C. Microanalysis was performed by Microanalytical units, Cairo and Ain Shams Universities. The homogeneity of the synthesised products was controlled by TLC.

Ethyl-6-nitrobenzo-2-pyrone-3-carboxylate (**1**): A mixture of 3-carboethoxy benzo-2-pyrone[20–22] (2.17 g, 0.01 mol) and an equal volume of conc. HNO_3 and glacial acetic acid (20 mL) was refluxed for 3h. After cooling, the reaction mixture was quenched by adding crushed ice. The yellow solid product obtained was filtered, washed several times with H_2O, dried and then recrystallised from ethanol to give **1** as yellow crystals, m.p. 160–163 °C (yield 86%). IR (KBr): 1736 cm^{-1} (ν_{CO} α,β-unsaturated δ-lactone), 1706 cm^{-1} (ν_{CO} α,β-unsaturated ester), 1605 cm^{-1} ($\nu_{C=C}$). ^{1}H NMR ($CDCl_3$): δ (ppm) 7.89–7.2 (m, 4H$_{arom.}$ + C_4–H), 4.2 (q, 2H, J = 6.7 Hz), 1.2 (t, 3H, J = 6.7 Hz). MS (*m/z*): 263 ($M^{+\cdot}$, 23.3), 235 (M-C_2H_4, 33.85), 218 (M-OEt, 30.11), 191 (100), 163 (23.76), 144 (22.63), 117 (31.7), 89 (37). Anal. Calcd for $C_{12}H_9NO_6$ (263): C, 54,75; H, 3.42; N, 5.32. Found: C, 54,55; H, 2.98; N, 5.6%.

(**2**) *and* (**3**): A solution of 3-carboethoxy-6-nitro benzo-2-pyrone **1** (2.63 g, 0.01 mol) in absolute ethanol and (50 mL) was treated with cyclohexylamine (2 mL, 0.02 mol) and the mixture was heated under reflux for 3h. After concentration and cooling, the semi-solid product obtained was refluxed with ethanol to give soluble and insoluble fractions. The soluble fraction, after evaporation of the solvent and purification with benzene left **2** as pale yellow crystals, m.p. 120–122 °C (yield 37%). IR (KBr): 3360, 3300 cm^{-1} (ν_{NH}), 1758 cm^{-1} (ν_{CO} saturated δ-lactone), 1663 cm^{-1} ($\nu_{CO\ amide}$). ^{1}H NMR ($CDCl_3$): δ (ppm) 8.9 (s, 1H, NH, exchangeable with D_2O), 8.6 (s, 1H, NH, exchangeable with D_2O), 7.5 (s, 3H$_{arom.}$), 3.0 (d, 1H, C_3-H, J = 4.2 Hz), 2.8 (t, 1H, C_4–H, J = 5.5 Hz), 2.0–1.2 (m, 22H, cyclohexyl protons). MS (*m/z*):

415 (100), 323 (62.6), 295 (16.6), 202 (37.9), 92 (66.2). Anal. Calcd for $C_{22}H_{29}N_3O_5$ (415): C, 63.61; H, 6.98; N, 10.12. Found: C, 63.9; H, 6.73; N, 9.9%. The insoluble fraction was recrystallised from dilute acetic acid to give 6-nitro-3-N-(cyclohexyl)carboxamido benzo-2-pyrone **3** as orange crystals, m.p. 220–222 °C (yield 58%). IR (KBr): 3210 cm^{-1} (ν_{NH}), 1726 cm^{-1} (ν_{CO}), 1658 cm^{-1} (ν_{CO}). ^1H NMR ($CDCl_3$): δ (ppm) 8.2 (s, 1H, NH, exchangeable with D_2O), 7.4–7.2 (br.s, $4H_{arom.}$ + C_4–H), 2.0 (m, 11H, C_6H_{11}). MS (*m/z*): 316 ($M^{+\cdot}$, 22.8), 190 (76.3), 162 (8.6), 146 (100), 117 (76.1), 101 (9.2), 89 (56.2), 77 (10.1). Anal. Calcd for $C_{16}H_{16}N_2O_5$ (316): C, 60.76; H, 5.06; N, 8.86. Found: C, 60.87; H, 5.31; N, 8.77%.

(**4**): A mixture of compound **1** (2.63 g, 0.01 mol) and *p*-aminoacetophenone (1.35 g, 0.01 mol) was dissolved in ethanol (20 mL) and heated under reflux for 2h (TLC). After concentration and cooling, the solid product obtained was triturated with methanol, filtered off, dried and recrystallised from a mixture of benzene–light petroleum ether (60–80 °C) to give **4** as orange crystals, m.p. 160–162 °C (yield 46%). IR (KBr): 3380 cm^{-1} (ν_{NH}), 1730 (ν_{CO} δ-lactone), 1675 cm^{-1} ($\nu_{CO\ ketone}$), 1648 cm^{-1} ($\nu_{CO\ amide}$). ^1H NMR ($CDCl_3$): δ (ppm) 9 (s, 1H, NH, exchangeable with D_2O), 7.9–7.2 (m, $7H_{arom.}$ + C_4–H), 2.4 (s, 3H, MeCO). MS (*m/z*): 352 ($M^{+\cdot}$, 16.8), 190 (56.3), 146 (100), 135 (20.3), 120 (25.1), 117 (53.4), 92 (11.4), 89 (33.1), 77 (6.8). Anal. Calcd for $C_{18}H_{12}N_2O_6$ (352): C, 61.36; H, 3.4; N, 7.95. Found: C, 61.61; H, 3.53; N, 8.0%

(**5**): Compound **4** (3.5 g, 0.01 mol) was dissolved in ethanolic sodium hydroxide solution (20 mL, 10%). A solution of 3,4,5-trimethoxy benzaldehyde (1.96 g, 0.01 mol) in 15 ml ethanol was gradually added while stirring in an ice bath for 1h. The solid that separated was filtered off, washed several times with H_2O, dried and recrystallised from ethanol to give **5** as brick-red crystals, m.p. 85–87 °C (yield 76.7%). IR (KBr): 3271 cm^{-1} (ν_{NH}), 1738 (ν_{CO} δ-lactone), 1676 cm^{-1} ($\nu_{CO\ amide}$), 1656 cm^{-1} (ν_{CO} α,β-unsaturated ketone). ^1H NMR ($CDCl_3$): δ (ppm) 8.7 (s, 1H, NH, exchangeable with D_2O), 7.8–7.3 (m, $8H_{arom.}$ + C_4–H), 6.9 (s, $2H_{arom.}$), 6.6 (d, 2H, *J* = 11.3 Hz), 3.85 (s, 6H, 2OMe), 3.8 (s, 3H, OMe). MS (*m/z*): 530 ($M^{+\cdot}$, 70.3), 337 (100), 221 (22.1), 218 (67.2), 191 (90.3), 146 (46.6). Anal. Calcd for $C_{28}H_{22}N_2O_9$ (530): C, 63.39; H, 4.15; N, 5.28. Found: C, 63.61; H, 3.98; N, 5.08.

(**6**) *and* (**7**): A mixture of compound **4** (0.01 mol), ethylcyanoacetate (0.01 mol) and ammonium acetate (0.3 mol) was stirred in an oil-bath at 160–170 °C for 6h (TLC). The reaction mixture was poured onto water. The brown solid that separated was filtered off, washed several times with H_2O, dried and treated with benzene/drops of methanol to give **6** as light brown crystals, m.p. 270–272 °C (yield 32%). IR (KBr): 3500–3300 cm^{-1} ($\nu_{NH,OH}$), 2226 ($\nu_{C\equiv N}$), 1708 (ν_{CO} ester), 1660 cm^{-1} ($\nu_{CO\ amide}$). ^1H NMR (DMSO-d_6): δ (ppm) 10.3 (s, 1H, NH, exchangeable with D_2O), 8.6 (s, 1H, NH, exchangeable with D_2O), 8.3–7.1 (m, $8H_{arom.}$ + C_4–H), 4.28 (q, 2H, *J* = 6.7 Hz), 2.4 (s, 3H, Me), 1.27 (t, 3H, *J* = 6.7 Hz). MS (*m/z*): 446 ($M^{+\cdot}$, 30.2), 230 (100), 217 (80.2), 202 (36.1), 190 (22.9), 185 (42.3), 158 (16.8), 157 (27.1), 145 (40.4). Anal. Calcd for $C_{23}H_{18}N_4O_6$ (446): C, 61.88; H, 4.03; N, 12.55. Found: C, 62.03; H, 4.11; N, 12.34%. The remaining solid was crystallised from methanol to give **7** as brown crystals, m.p. >300 °C (yield 19.1%). IR (KBr): 3550–3000 cm^{-1} ($\nu_{NH,OH}$), 1695 (ν_{CO} ketone), 1660 cm^{-1} ($\nu_{CO\ amide}$), 1654 (ν_{CO}). ^1H NMR (DMSO-d_6): δ (ppm) 10.3 (s, 1H, NH, exchangeable with D_2O), 8.9 (s, 1H, NH, exchangeable with D_2O), 8.2–7.1 (m, $8H_{arom.}$ + C_4–H), 2.4 (s, 3H, Me). MS (*m/z*): 351 ($M^{+\cdot}$, 100), 217 (42.6), 189 (13.6), 144 (21.9), 135 (77.3), 120 (33.1), 92 (28.3). Anal. Calcd for $C_{18}H_{13}N_3O_5$ (351): C, 61.54; H, 3.7; N, 11.96. Found: C, 61.77; H, 3.75; N, 11.68%.

Reaction of **1** *with diamine*

(A) With o-phenylenediamine gives 6-nitro-3-(benzimidazol-2-yl) benzo-2-pyrone (**9**): A mixture of **1** (0.01 mol) and *o*-phenylenediamine (0.01 mol) was heated in an oil-bath at 170 °C for 12h. The reaction mixture was triturated with dilute methanol, filtered off, and recrystallised from methanol to give **9** as light brown crystals, m.p. 190–195 °C (yield 62%). IR (KBr): 3345 cm^{-1} (ν_{NH}), 1726 (ν_{CO} α,β-unsaturated δ-lactone), 1632 cm^{-1} ($\nu_{C=N}$). ^1H NMR ($CDCl_3$): δ (ppm) 9.1 (s, 1H, NH, exchangeable with D_2O), 7.8–7.2 (m, $8H_{arom.}$ + C_4–H). MS (*m/z*): 307 ($M^{+\cdot}$, 41.3), 190 (100), 163 (11.2), 146 (7.8). Anal. Calcd for $C_{16}H_9N_3O_4$ (307): C, 62.54; H, 2.93; N, 13.68. Found: C, 62.32; H, 2.77; N, 13.61%.

(B) With benzidine gives 6-nitro-3-N-(4-aminobiphenyl)carboxamido benzo-2-pyrone (**10**) *and its N-acetylated derivative* (**11**): A mixture of **1** (2.63 g, 0.01 mol) and benzidine (1.84 g, 0.01 mol) in abs. ethanol (50 mL) was refluxed for 3h (TLC). The reaction mixture was concentrated, cooled and the solid separated was filtered off, dried and recrystallised from benzene to give **10** as red crystals, m.p. 188–190 °C (yield 61%). IR (KBr): 3440, 3370 cm^{-1} (ν_{NH2}), 1730 (ν_{CO}), 1668 cm^{-1} ($\nu_{CO\ amide}$). ^1H NMR ($CDCl_3$): δ (ppm) 9 (s, 1H, NH, exchangeable with D_2O), 7.9–7.1 (m, $12H_{arom.}$ + C_4–H), 4.6 (br.s, 2H, NH_2, exchangeable with D_2O). MS (*m/z*): 399 ($M^{+\cdot}$ - 2, 13.9), 356 (27.3), 234 (16.2), 218 (26.1), 190 (70.2), 184 (100), 146 (30.1), 117 (77.6), 89 (40.0). Anal. Calcd for $C_{22}H_{15}N_3O_5$ (401): C, 65.83; H, 3.74; N, 10.47. Found: C, 65.88; H, 3.67; N, 10.22%. Recrystallisation of **11** with glacial acetic acid deposited a yellow crystals **11**, m.p. 192–194 °C (yield 86%). IR (KBr): 3379, 3197 cm^{-1} (ν_{NH}), 1736 cm^{-1} (ν_{CO}), 1670, 1665 cm^{-1}. ^1H NMR (DMSO-d_6): δ (ppm) 9.6 (s, 1H, NH, exchangeable with D_2O),8.3 (br.s, 1H, NH, exchangeable with D_2O), 7.9–7.3 (m, $12H_{arom.}$ + C_4–H), 2.36 (s, 3H, COMe). MS (*m/z*): 401 (M- CH_2=C=O, 31.2), 234 (22.7), 218 (11.3), 190 (97.3), 184 (100), 146 (52.6), 117 (23.6). Anal. Calcd for $C_{24}H_{17}N_3O_6$ (443): C, 65.01; H, 3.83; N, 9.48. Found: C, 65.32; H, 3.66; N, 9.51%.

Hydrazinolysis of (**1**): (**13**) *and* (**14**): A solution of compound **1** (2.63 g, 0.01 mol) in absolute ethanol (50 mL) was treated with hydrazine hydrate (0.03 mol) and the mixture was heated under reflux for 5h (TLC). The solid separated after concentration was filtered off, washed with dilute HCl, then with water, and finally dried and triturated with benzene. The insoluble fraction was crystallised from benzene to give **13** as pale yellow crystals, m.p. 170–172 °C (yield 41.7%). IR (KBr): 3530–3150 (br.) cm^{-1} (ν_{OH}), 1626 cm^{-1} ($\nu_{C=N}$). MS (*m/z*): 330 ($M^{+\cdot}$, 17.2), 285 (100), 192 (50.0), 165 (37.9), 164 (87.6), 137 (44.2), 120 (21.6), 93 (66.1), 65 (30.2). Anal. Calcd for $C_{14}H_{10}N_4O_6$ (330): C, 50.9; H, 3.03; N, 16.96. Found: C, 51.81; H, 3.29; N, 16.66%. Evaporation of benzene left a crude product which recrystallised from light petroleum ether (b.p. 80–100 °C) to give **14** as pale yellow crystals, m.p. 106–108 °C (yield 23%). IR (KBr): 3262 cm^{-1} (ν_{NH}), 1663 cm^{-1} ($\nu_{C=O}$),1622 cm^{-1} ($\nu_{C=N}$). MS (*m/z*): 230 ($M^{+\cdot}$-1, 21.9), 203(M-N_2, 16.7), 188 (100), 186 (50.4), 139 (30.1), 93 (70.2), 65 (66.1). Anal. Calcd for $C_{10}H_5N_3O_4$ (231): C, 51.94; H, 2.16; N, 18.18. Found: C, 52.07; H, 2.41; N, 18.33%.

(Z)-2-Amino-10-nitro-4H-chromeno[3,4-f][1,3,4]thiadiazepine-5,6(5aH,11bH)-dione (**15**): A mixture of **1** (0.01 mol), thiosemicarbazide (0.01 mol) and *n*-butanol (30 mL) was stirred in an oil-bath at 180 °C for 6h. The solid which separated after trituration with ethanol was filtered off, washed with cold ethanol, and recrystallised from ethanol to give **15** as pale yellow crystals, m.p. 135–140 °C (yield 45%). IR (KBr): 3390, 3280 cm^{-1} (ν_{NH2}), 3190 (ν_{NH}), 1742 ($\nu_{CO\ sat.\delta\ lactone}$), 1680 cm^{-1} ($\nu_{CO\ amide}$). ^1H NMR ($CDCl_3$): δ (ppm) 9.1 (br.s, 2H, NH_2, exchangeable with D_2O), 8.8 (s, 1H, NH, exchangeable with D_2O), 7.8 (m, $3H_{arom.}$), 3.1 (d, 1H, C_6-H, *J* = 4.8 Hz), 2.8 (d, 1H, C_7-H, *J* = 3.3 Hz). MS (*m/z*): 310 (M + 2, 17.6), 269 (19.6), 235 (30.2), 191 (70.7), 146 (100), 102 (33.6). Anal. Calcd for $C_{11}H_8N_4O_5S$ (308): C, 42.85; H, 2.59; N, 18.18. Found: C, 42.56; H, 2.7; N, 17.76%.

3-(5-(3,4,5-Trimethoxy benzylideneamino)-1,3,4-oxadiazol-2-yl)-6-nitro-2H-chromen-2-one (**18**): Compound **15** (0.01 mol) was dissolved in acetic acid (20 mL). 3,4,5-trimethoxybenzaldehyde (0.01 mol) in acetic acid (10 mL) was gradually added while stirring for 30 min. The reaction mixture was refluxed for 2h. H_2S gas was released during the reaction time. The reaction mixture was diluted with water, and the solid separated was filtered off and crystallised from methanol to give **18** as orange crystals, m.p. 125–127 °C (yield 51%). IR (KBr): 1730 cm^{-1} ($\nu_{CO\ unsat.\delta\ lactone}$), 1648 cm^{-1} ($\nu_{C=N}$). ^1H NMR ($CDCl_3$): δ (ppm) 9.1 (s, 1H, N=CH), 8.3–7.4 (m, $4H_{arom}$+C_4-H), 6.9 (s, $2H_{arom}$), 3.87 (s, 6H, OMe), 3.8 (s, 3H, OMe). MS (*m/z*): 452 ($M^{+\cdot}$, 100), 259 (M-ArCN, 44.2), 191 (27.9), 146 (50.1). Anal. Calcd for $C_{21}H_{16}N_4O_8$ (452): C, 55.75; H, 3.53; N, 12.38. Found: C, 55.67; H, 3.43; N, 12.64%.

N-(5-(6-Nitro-2-oxo-2H-chromen-3-yl)-1,3,4-oxadiazol-2-yl)acetamide (**19**): A solution of compound **15** (0.5 g, mol) in glacial acetic acid (20 mL) was refluxed for 3h. After cooling, the reaction mixture was diluted with water. The deposited solid was filtered off, dried and recrystallised from dioxane to give **19** as yellow crystals, m.p. 166–168 °C (yield 47.5%). IR (KBr): 3212 cm^{-1} (ν_{NH}), 1734 cm^{-1} (ν_{CO}), 1679 cm^{-1} (ν_{CO}). ^1H NMR (DMSO-d_6): δ (ppm) 9.6 (s, 1H, NH, exchangeable with D_2O), 7.7–7.4 (m, $4H_{arom}$+C_4-H), 2.1 (s, 3H, MeCO). MS (*m/z*): 316 ($M^{+\cdot}$, 100), 274 (82.6), 191 (26.6), 188 (43.3), 92 (63.4). Anal. Calcd for $C_{13}H_8N_4O_6$ (316): C, 49.36; H, 2.53; N, 17.72. Found: C, 49.71; H, 2.6; N, 17.53%.

3-(3,1-Benzoxazin-4-oxo-2-yl)benzo-2-pyrone (**20**): A solution of 3-carboethoxy-6-nitro benzo-2-pyrone **1** (0.01 mol) in *n*-butanol

(20 mL) was treated with anthranilic acid (0.01 mol) then refluxed for 8h. The solid that separated after cooling was collected, washed several times with water, dried and crystallised from benzene to give **20** as yellow crystals, m.p. 153–155 °C (yield 63%). IR (KBr): 1763 cm^{-1} ($\nu_{CObenzoxazinone}$), 1732 cm^{-1} ($\nu_{CO\ unsat.\delta\ lactone}$). MS (*m/z*): 336 ($M^+$, 27.9), 190 (33.1), 146 (100), 118 (20.1). Anal. Calcd for $C_{17}H_8N_2O_6$ (336): C, 60.71; H, 2.38; N, 8.33. Found: C, 61.06; H, 2.51; N, 8.0%.

Michael adduct (**21**): The carboethoxy benzo-2-pyrone **1** (0.01 mol) was dissolved in a minimum amount of absolute ethanol and treated with an alcoholic solution of sodium ethoxide (0.01 mol). The malononitrile (0.01 mol) was then added and the mixture was kept overnight then refluxed on water-bath for 6h. The cold mixture was acidified with dilute acetic acid, and the deposited solid was filtered off and crystallised from methanol to give **21** as pale yellow crystals, m.p. 170–173 °C (yield 36.3%). IR (KBr): br. 3460–2960 cm^{-1} ($\nu_{NH2,OH}$), 2226 ($\nu_{C\equiv N}$), 1732 cm^{-1} ($\nu_{CO\ unsat.\delta\ lactone}$), 1693 cm^{-1} ($\nu_{CO\ unsat.\ acid}$). ^{1}H NMR ($CDCl_3$): δ (ppm) 11.4 (s, 1H, COOH, exchangeable with D_2O), 7.7 (m, $3H_{arom}$), 5.1 (br.s, 2H, NH_2, exchangeable with D_2O), 4.1 (s, 1H). MS (*m/z*): 365 ($M^{+\cdot}$, 11.3), 235 (72.3), 190 (100), 146 (40.2), 118 (16.3), 71 (52.7). Anal. Calcd for $C_{16}H_7N_5O_6$ (365): C, 52.6; H, 1.91; N, 19.17. Found: C, 52.43; H, 2.13; N, 18.77%.

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