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Ring opening and ring closure reactions of chromone-3-carboxylic acid: unexpected routes to synthesize functionalized benzoxocinones and heteroannulated pyranochromenes

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Abstract: Unexpected routes to synthesize functionalized benzoxocinones and heteroannulated pyranochromenes were achieved via transformations of the γ-pyrone ring in chromone-3-carboxylic acid throughout its reactions with some acyclic and cyclic carbon nucleophiles. A key part of the reaction mechanisms is discussed. Structures of the new synthesized products were established on the basis of elemental analysis and spectral data (IR, MS, and ^{1}H and ^{13}C NMR).

Key words: Chromone-3-carboxylic acid, benzoxocinone, pyranochromenes, ring expansion, carbon nucleophiles

1. Introduction

Chromone compounds are known to exhibit a broad spectrum of biological properties such as anticancer,[1,2] antimicrobial,[3,4] antiviral,[5] and antitobacco mosaic virus[6] activities. They are versatile molecules because their chemical reactivity towards nucleophiles provides a useful route for preparation of a variety of heterocyclic systems.[7,8] The use of chromone compounds to synthesize heterocyclic systems via ring opening and ring closure sequences with appropriate nucleophiles is well known.[9–17] There are only a few publications using chromone-3-carboxylic acids or their esters in nucleophilic reactions, where nitrogen nucleophiles attack the γ-pyrone ring at C$-$2 position with concomitant ring opening and recyclization at C$-$4 or the carboxylic group, leading to the formation of various nitrogen heterocycles.[18–21] However, only the reaction of chromone-3-carboxylic acid (**1**) with carbon nucleophiles, namely malononitrile and cyanoacetamide, has been studied.[22] In continuation of our studies on the chemistry of 3-substituted chromones,[23–30] the present work reports unexpected and convenient routes to synthesize functionalized benzoxocinones and annulated pyranochromenes via reaction of chromone-3-carboxylic acid (**1**) with a variety of acyclic and cyclic carbon nucleophiles.

2. Results and discussion

In previous research,[22] we found that the γ-pyrone ring in chromone-3-carboxylic acid (**1**) was expanded to an oxocinone ring under the reaction with malononitrile to produce 2-amino-3-cyano-6*H*-benzoxocin-6-one (**2**) as depicted in Figure 1. The work was extended in the present research to study the effect of other acyclic and cyclic carbon nucleophiles on chromone-3-carboxylic acid (**1**) to confirm the ring expansion phenomenon.

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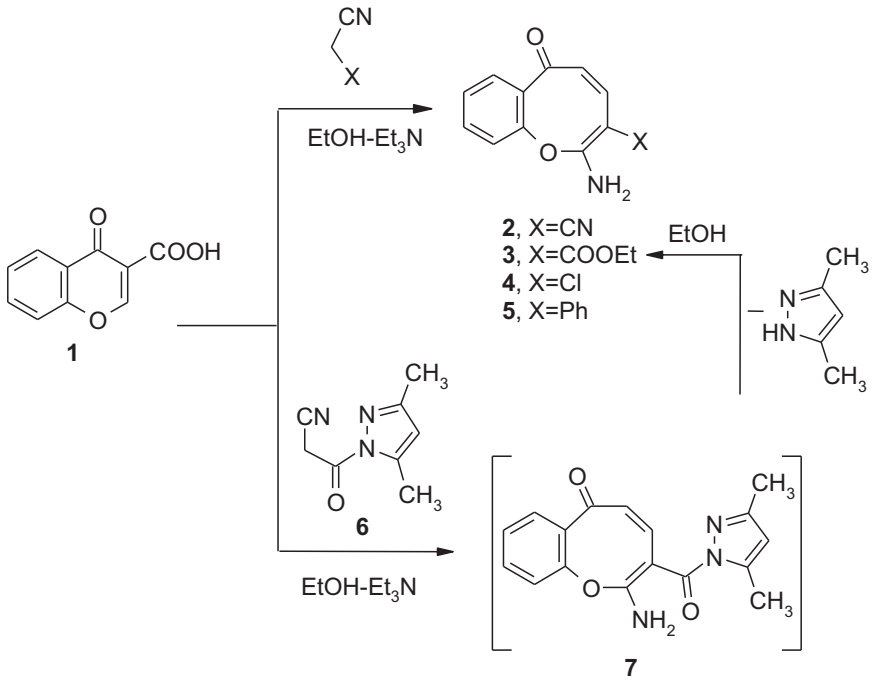

Figure 1. Formation of benzoxocin-6-ones **2**–**5**.

Reaction of carboxylic acid **1** with some acyclic active methylene compounds, namely ethyl cyanoacetate, chloroacetonitrile, and benzyl cyanide, in absolute ethanol containing a few drops of triethylamine as a basic catalyst led to the expansion of the γ-pyrone ring in chromone-3-carboxylic acid (**1**), affording 2-amino-3-substituted-6*H*-benzoxocin-6-ones **3**–**5**, respectively (Figure 1). Compound **3** was also obtained authentically from the reaction of carboxylic acid **1** with 3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-3-oxopropanenitrile (**6**) under the same reaction conditions to give the nonisolable intermediate **7**, which was hydrolyzed in situ by ethanol, giving the ethyl ester **3** (Figure 1).[25] We envisioned that this transformation occurred by way of Michael addition, ring opening, decarboxylation, and intramolecular cyclization. In this pathway, the electron-deficient chromone behaves as an acceptor in Michael addition of nucleophilic active methylene to generate intermediate **A**. This process is followed by chromone ring opening to form intermediate **B**, which underwent decarboxylation to give intermediate **C1.** The latter intermediate **C1** underwent an intramolecular cyclization at the internal nitrile to afford the target compounds (route a) (Figure 2).[31] The route b to produce iminopyran derivative **8** was excluded on the basis of the spectral data (Figure 2).

The structures of compounds **3**–**5** were deduced from their elemental analysis and spectral data (see Experimental section). For example, the UV spectrum of compound **3** showed three electronic transition bands at λ_{max} 271, 346, and 450 nm corresponding to $\pi - \pi^*$ and $n - \pi^*$ transitions and the extended conjugation between the electron donating amino group at position 2 and the electron withdrawing carbonyl group at position 6. The IR spectrum of ethyl ester **3** showed characteristic absorption bands at 3339 (br, NH_2), 1679 ($C{=}O_{ester}$), and 1629 ($C{=}O_{oxocinone}$) cm^{-1}. Furthermore, its ^1H NMR spectrum displayed triplet and quartet signals at δ 0.92 (CH_3) and 4.01 (CH_2) ppm, respectively, assignable to the ethoxy protons. In addition, there were two exchangeable signals with D_2O at δ 8.51 and 8.64 ppm assigned to the amino protons. The H–4 and H–5 protons of the oxocinone ring appeared as doublets at δ 5.16 and 4.72 ppm, respectively, with the same coupling constant (J = 12.0 Hz), which confirmed that these protons are in trans configuration.

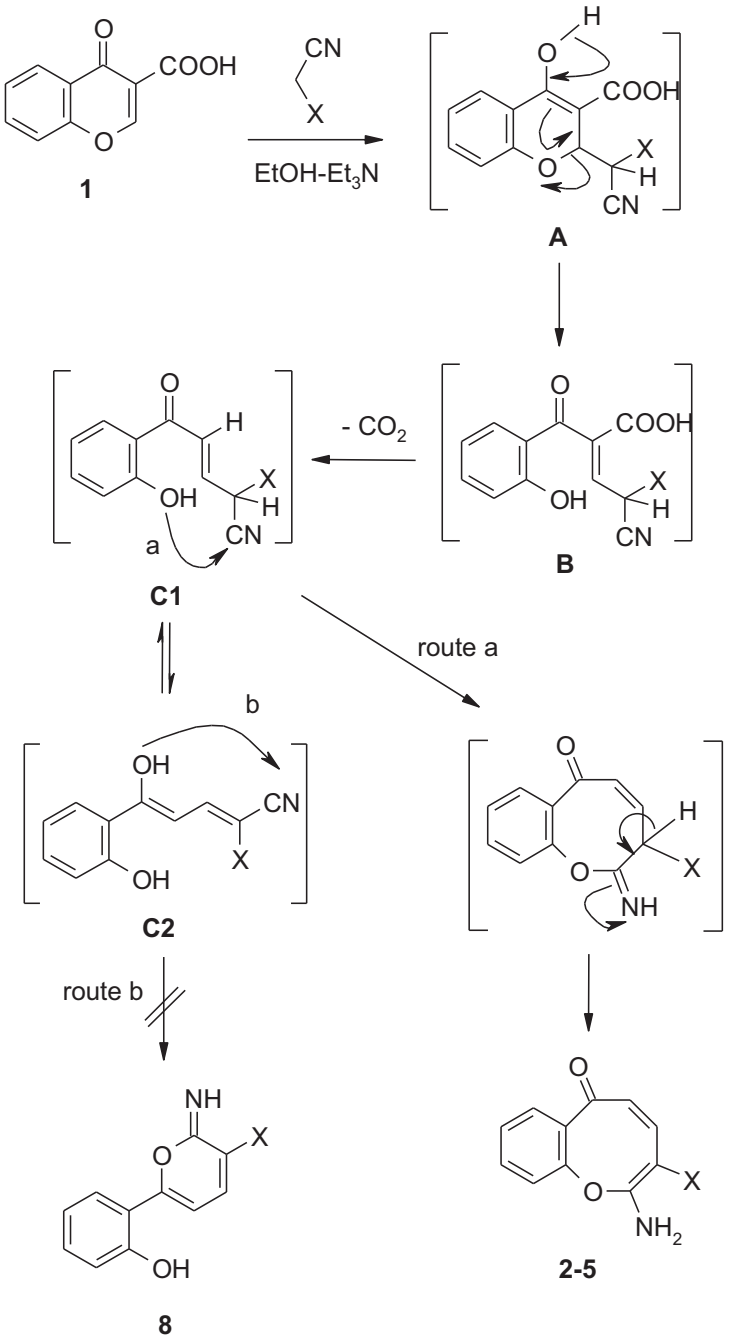

Figure 2. The proposed mechanism for the formation of benzoxocin-6-ones **2**–**5**.

On the other hand, when compound **4** was allowed to react with sodium cyanide in ethanol, compound **2** was obtained (Figure 3).[22,32] The ^{13}C NMR spectrum of compound **2** exhibited three characteristic signals at δ 102.3, 109.1, and 137.4 ppm corresponding to C–5, C≡N, and C–4, respectively. Moreover, treatment of ethyl ester **3** with equivalent amounts of piperidine and morpholine in boiling ethanol yielded 2-amino-3-(piperidin/morpholin-1-ylcarbonyl)-6*H*-1-benzoxocin-6-ones **9** and **10**, respectively (Figure 3). Compounds **9** and **10** were also obtained authentically from the direct reaction of carboxylic acid **1** with ethyl cyanoacetate in

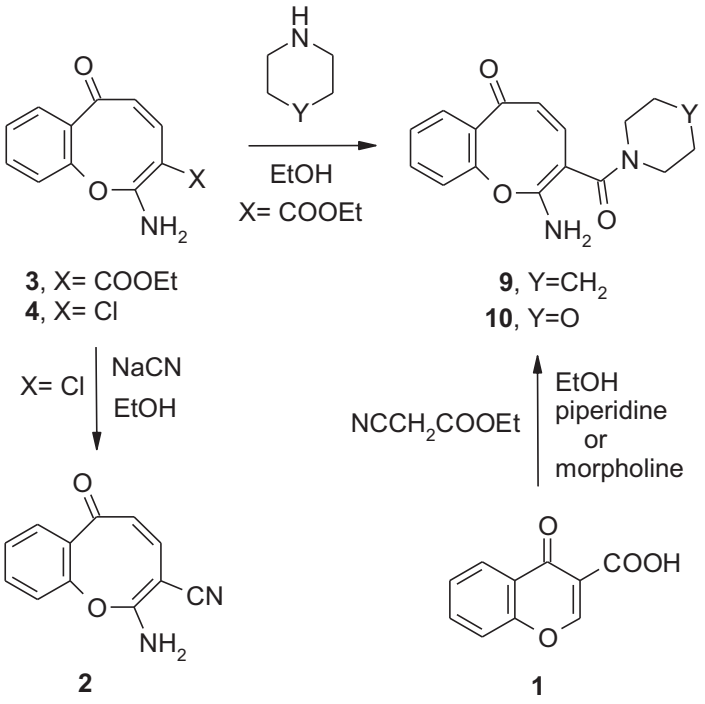

Figure 3. Formation of benzoxocin-6-ones **2**, **9**, and **10**.

absolute ethanol containing a few drops of piperidine and morpholine, respectively (Figure 3). The postulated mechanism for the formation of carboxamides **9** and **10** from compound **1** occurred via the formation of ethyl ester **3**, which was not isolated when piperidine or morpholine were used as catalysts but underwent rapid nucleophilic substitution for the ethoxy group by the nucleophiles used under the reaction condition. Structures of compounds **9** and **10** were deduced from their elemental analysis and spectral data (see Experimental section).

The present study was extended to investigate the chemical behavior of chromone-3-carboxylic acid (**1**) towards some acyclic carbon nucleophiles containing an active methylene group between two carbonyl groups. Therefore, boiling carboxylic acid **1** with acetylacetone and ethyl acetoacetate in absolute ethanol containing a few drops of triethylamine afforded the corresponding 2-methyl-3-substituted-6*H*-1-benzoxocin-6-ones **11** and **12**, respectively (Figure 4). The reaction proceeds via the previously suggested reaction mechanism described in Figure 2. The IR spectra of compounds **11** and **12** showed characteristic absorption bands at 1696/1672 (C=O) and 1637/1641 ($C{=}O_{oxocinone}$) cm^{-1}, respectively. In addition, the ^{1}H NMR spectrum of compound **11** showed two characteristic doublets, with the same coupling constant ($J = 12.2$ Hz), at δ 5.56 and 4.84 ppm, attributed to H–4 and H–5 protons, respectively. The same protons were observed at δ 7.94 and 6.89 ppm ($J = 14.0$ Hz) in compound **12**. Furthermore, the ^{13}C NMR spectrum of compound **11** exhibited four characteristic signals at δ 118.7, 139.0, 188.5, and 198.2 ppm corresponding to C–5, C–4, $C{=}O_{oxocinone}$, and $C{=}O_{acetyl}$, respectively.

Interestingly, it was found that chromone-3-carboxylic acid (**1**) showed unexpected behavior towards diethyl malonate compared to the previous acylic active methylene compounds. Thus, contrary to our expectation, refluxing an equimolar amount of carboxylic acid **1** with diethyl malonate in absolute ethanol containing a few drops of triethylamine produced 2-(2-hydroxyphenyl)-4*H*,5*H*-pyrano[2,3-*b*] chromen-5-one (**13**) (Figure 5). The expected benzoxocinone derivative **14** was excluded due to the absence of ethoxycarbonyl, H–4, and

H–5 protons in its ^{1}H NMR spectrum (Figure 5). The product **13** was formed via nucleophilic attack of diethyl malonate anion at the C–2 position of carboxylic acid **1**, followed by decarboxylation and abstraction of protons by triethylamine to give the intermediate **A1** or **A2**. Michael addition of the intermediate **A2** on another molecule of carboxylic acid **1**, followed by ring opening furnished the intermediate **C**, which underwent decar-

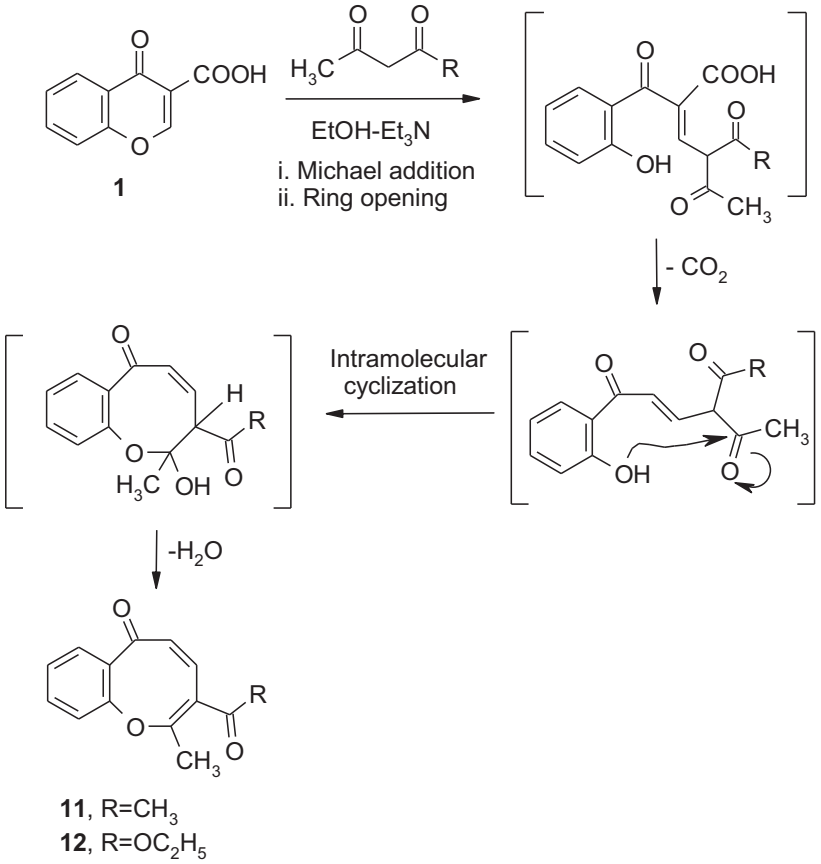

Figure 4. Formation of benzoxocin-6-ones **11** and **12**.

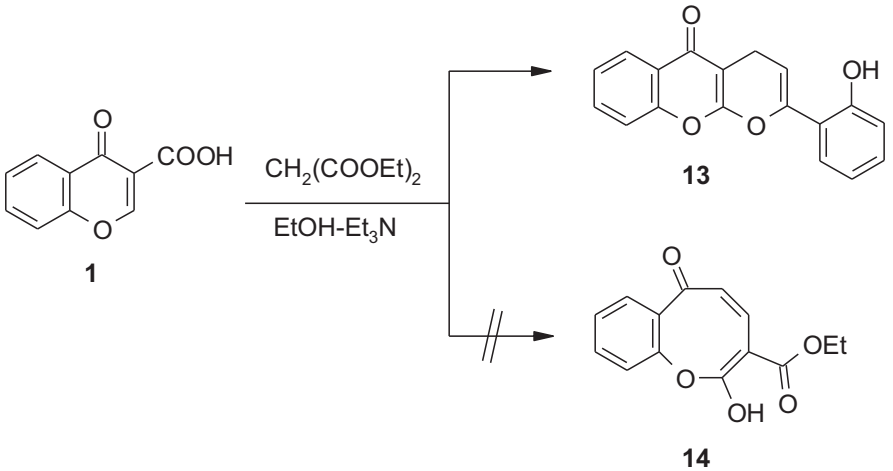

Figure 5. Formation of 2-(2-hydroxyphenyl)-4*H*,5*H*-pyrano[2,3-*b*]chromen-5-one (**13**).

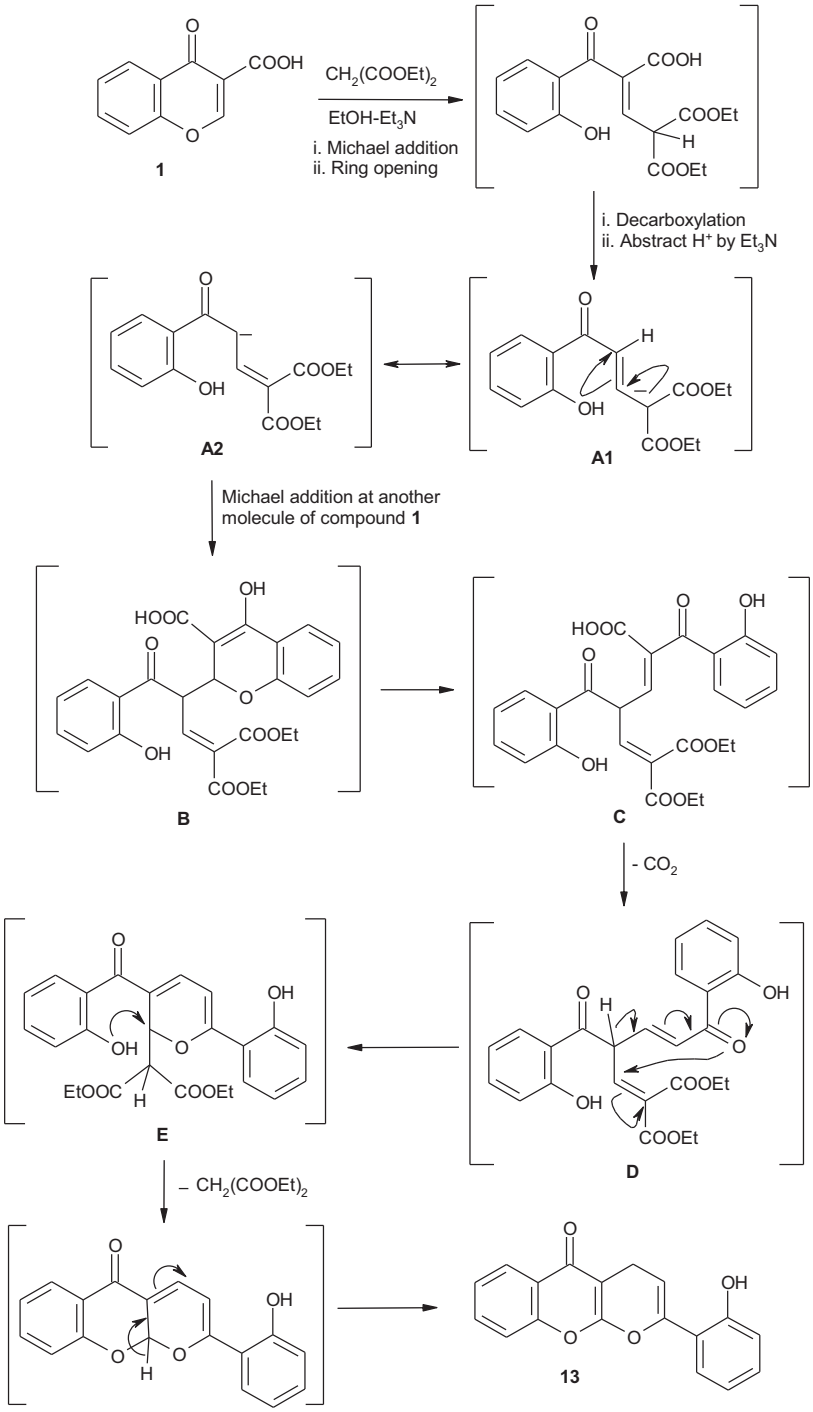

Figure 6. The proposed mechanism for the formation of compound **13**.

boxylation to give the intermediate **D**. Intramolecular nucleophilic cyclizations with loss of a diethyl malonate molecule took place for the latter intermediate **D** to produce the target compound **13** (Figure 6). The ^{1}H NMR spectrum of compound **13** showed doublet and triplet signals at δ 3.90 and 4.79 ppm assigned to CH_2 and H–3 protons of the pyran ring, respectively, while the phenolic OH proton appeared at δ 11.60 ppm as a broad

D_2O-exchangeable signal. Moreover, its ^{13}C NMR spectrum exhibited three characteristic signals at δ 28.9, 94.0, and 175.8 ppm corresponding to CH_2, C–3, and C=O, respectively. The mass spectrum of compound **13** showed a molecular ion peak at m/z 292, which is consistent with its molecular formula ($C_{18}H_{12}O_4$) and supported the proposed structure.

In most of the previously mentioned reactions, the γ-pyrone ring in chromone-3-carboxylic acid (**1**) was expanded to an oxocinone ring upon its reaction with acyclic active methylene compounds to produce 6*H*-benzoxocin-6-one derivatives. This encouraged us to study the chemical behavior of chromone-3-carboxylic acid (**1**) towards some cyclic active methylene compounds.

Thus, treatment of chromone-3-carboxylic acid (**1**) with dimedone produced 2-(2-hydroxyphenyl)-7,7-dimethyl-6,7-dihydrochromen-5-one (**15**) and not the ring expanded product 2,2-dimethyl-2*H*-dibenzo[*b*, *g*]oxocine-4,7(1*H*,3*H*)-dione (**16**) as depicted in Figure 7. The structure of compound **15** was elucidated from its elemental analysis and spectral data. The IR spectrum of compound **15** showed a broad absorption band at 3100 cm^{-1} attributed to the phenolic OH group. Its ^1H NMR spectrum showed a distinguished singlet at δ 7.34 ppm due

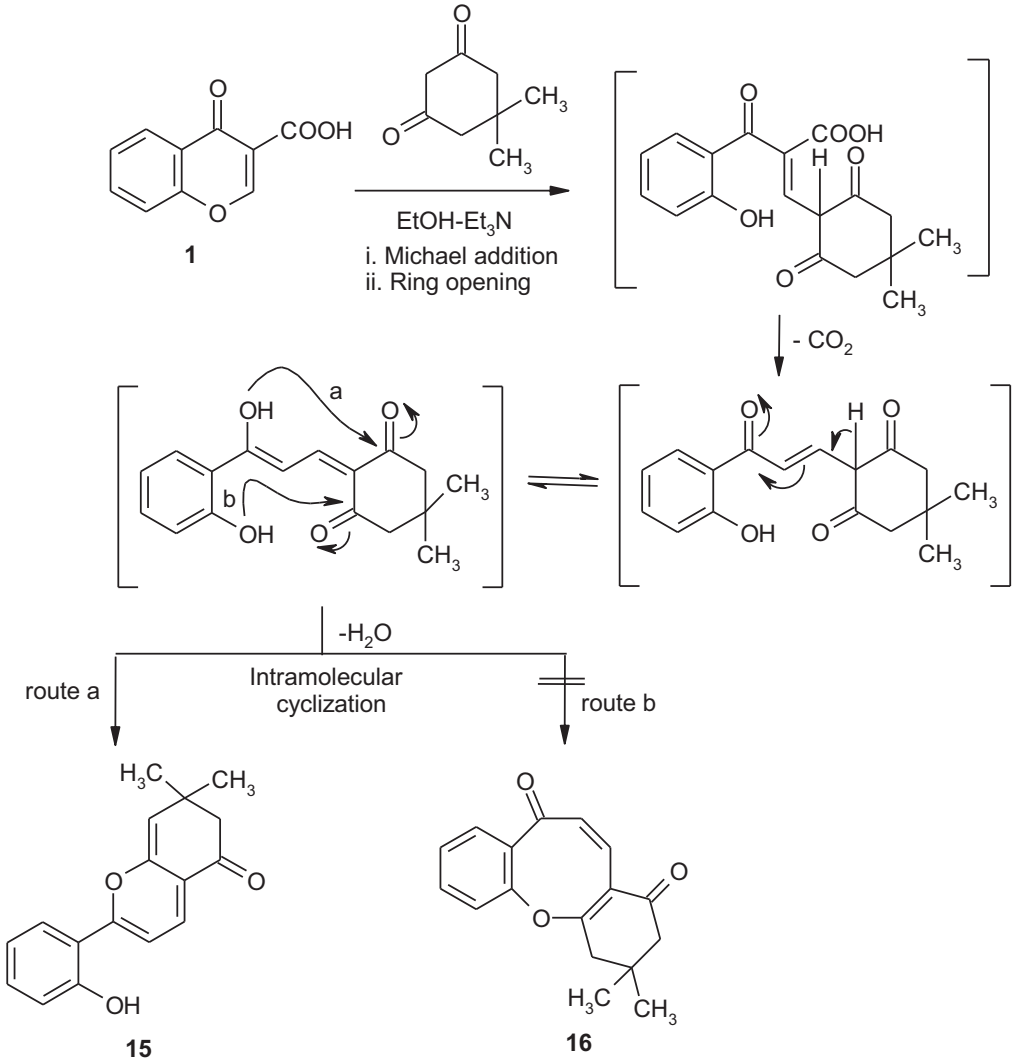

Figure 7. Formation of compound **15.**

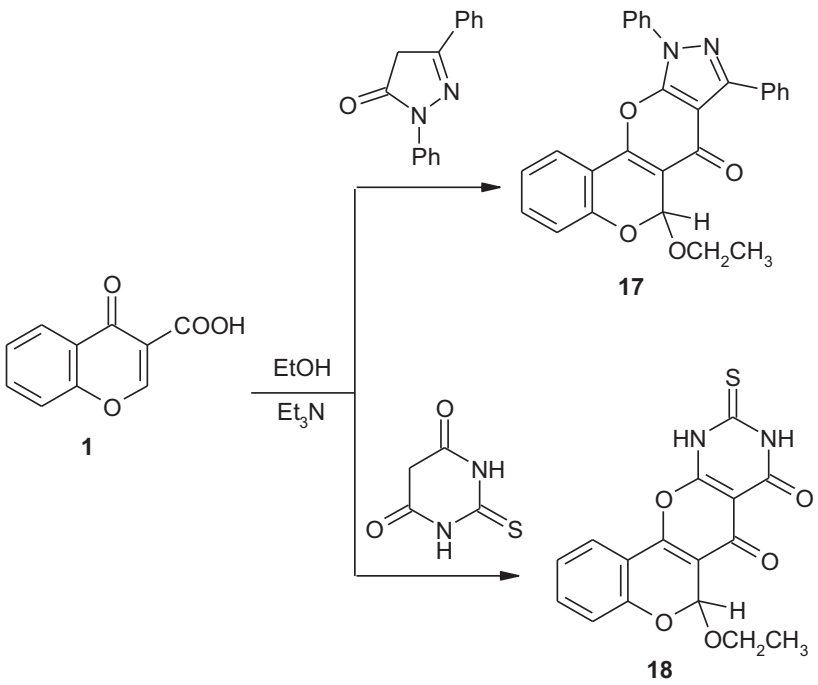

Figure 8. Formation of the chromenopyranopyrazole **17** and chromenopyranopyrimidine **18**.

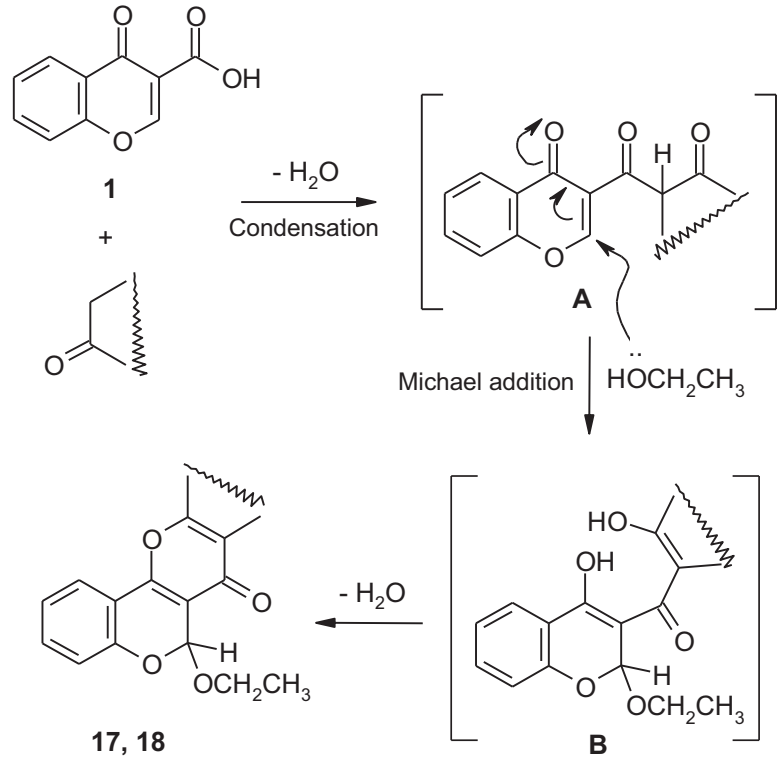

Figure 9. The proposed mechanism for the formation of compounds **17** and **18**.

to H–8 protons and two doublets at δ 8.02 and 8.07 ppm (J =8.2 Hz) attributed to H–3 and H–4 protons of the pyran ring. Furthermore, the mass spectrum of compound **15** showed a molecular ion peak at m/z 268, which agreed well with the proposed structure and the base peak at m/z 93 due to phenolic cation. The formation of compound **15** may proceed via the same reaction mechanism but the enolic OH (route a) and not phenolic OH (route b) attacked the C=O function with loss of one molecule of water (Figure 7).

Finally, the reaction between chromone-3-carboxylic acid (**1**) and some heterocycles containing active methylene group was studied. Surprisingly, heating an ethanolic solution of the carboxylic acid **1** with 1,3-diphenyl-1$H-$pyrazol-5(4H)-one and thiobarbituric acid under reflux for 2 h produced the novel unexpected products identified as 1,3-diphenyl-5-ethoxy-5H-chromeno[3‘,4‘:5,6]pyrano[2,3-c]pyrazol-4 (1H)-one (**17**) and 6-ethoxy-2-thioxo-2H,6H-chromeno[3‘,4‘:5,6]pyrano[2,3-d]pyrimidine-4,5-(1H,3H)-dione (**18**), respectively, in moderate yields (Figure 8). The microanalyses and mass spectral data of the isolated products are consistent with the assigned structures **17** and **18**. The ^{1}H NMR spectra of these products exhibited broad singlets at δ 5.44 and 6.90 ppm due to the protons H–2 of chromene rings, respectively. In addition, the signals at δ 1.14, 1.16 (CH_3) and 3.04, 3.63 (CH_2) ppm were assigned to their ethoxy groups. The ^{13}C NMR spectra of structures **17** and **18** exhibited characteristic signals for the carbonyl groups of γ-pyrone rings at δ175.4 and 175.9 ppm, respectively, while the carbon atoms of C–2 in chromene rings appeared at δ 99.8 and 93.7 ppm, respectively. In addition, their ethoxy carbon atoms were displayed at δ26.0, 24.6 (CH_3) and 45.7, 45.8 (CH_2) ppm, respectively.

The formation of compounds **17** and **18** probably involves condensation of carboxylic acid **1** with the cyclic active methylene compounds, yielding the intermediate **A**. The next step is an intramolecular nucleophilic attack of ethanol at the C–2 position of the reactive γ-pyrone ring, yielding intermediate **B**, which underwent cyclodehydration to form the target products **17** and **18** (Figure 9).[33]

3. Experimental

3.1. General

Melting points are uncorrected and were recorded in open capillary tubes on a Stuart SMP3 melting point apparatus. UV absorption spectra were recorded on a Jasco model (V-550) UV spectrophotometer. Infrared spectra were recorded on a FT-IR Bruker Vector 22 spectrophotometer using the KBr wafer technique. The ^{1}H NMR spectra (chemical shift in δ) were measured on a Gemini spectrometer (200 MHz) and Mercury-300BB (300 MHz) using DMSO-d_6 as solvent and TMS as an internal standard. The ^{13}C NMR spectra (chemical shift in δ) were measured on a Mercury-300BB (75 MHz) and a Bruker spectrometer (100 MHz) using DMSO-d_6 as solvent. Mass spectra recorded on a Gas Chromatographic GCMSqp 1000 ex Shimadzu instrument at 70 eV. The purity of the synthesized compounds was checked by thin layer chromatography (TLC). Elemental analyses were performed on a PerkinElmer 2400II at the Chemical War Department, Ministry of Defense, Cairo, Egypt. Chromone-3-carboxylic acid (**1**),[34] 3-(3,5-dimethyl-1H-pyrazol-1-yl)-3-oxopropanenitrile (**6**),[35] and 1,3-diphenyl-1$H-$pyrazol-5(4H)-one[36] were prepared according to the literature.

3.2. General procedure for the synthesis of 2-amino-3-substituted-6H-1-benzoxocin-6-ones 3–5

A mixture of chromone-3-carboxylic acid (**1**) (0.95 g, 5 mmol) and acyclic active methylene compounds, namely ethyl cyanoacetate, chloroacetonitrile, benzyl cyanide, and 3-(3,5-dimethyl-1H-pyrazol-1-yl)-3-oxopropanenitrile (**6**) (5 mmol), in absolute ethanol (20 mL) containing a few drops of triethylamine was heated under reflux for

4 h. The solvent was concentrated to half its volume under vacuum. The formed solids were filtered and recrystallized from ethanol to give compounds **3**–**5**.

3.2.1. Ethyl 2-amino-6-oxo-6H-1-benzoxocine-3-carboxylate (3)

Beige crystals, yield (0.58 g, 45%), mp 163–164 °C. UV-Vis (ethanol): λ_{max} (ε) = 271 (4.30), 346 (2.84), 450 nm (1.19). IR (KBr, cm^{-1}): 3339 (br, NH_2), 3069 (C–H_{arom}), 2924, 2875 (C–H_{aliph}), 1679 (C=O_{ester}), 1629 (C=$O_{oxocinone}$), 1602 (C=C). ^{1}H NMR (200 MHz, DMSO-d_6): δ 0.92 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 4.01 (q, 2H, J= 7.2 Hz, OCH_2CH_3), 4.72 (d, 1H, J = 12.0 Hz, H–5), 5.16 (d, 1H, J = 12.0 Hz, H–4), 7.47 (t, 1H, J = 7.2 Hz, H–8), 7.61 (d, 1H, J = 7.2 Hz, H–10), 7.77 (t, 1H, J = 7.2 Hz, H–9), 8.03 (d, 1H, J = 7.2 Hz, H–7), 8.51 (s, 1H, NH_2 exchangeable with D_2O), 8.64 (s, 1H, NH_2 exchangeable with D_2O). MS (m/z, %): 259 (M^+, 5%), 192 (100), 178 (43), 162 (17), 93 (13), 77 (22), 69 (30). Anal. Calcd. for $C_{14}H_{13}NO_4$ (259.26): C, 64.86; H, 5.05; N, 5.40%; Found C, 64.62; H, 4.86; N, 5.31%.

3.2.2. 2-Amino-3-chloro-6H-1-benzoxocin-6-one (4)

White crystals, yield (0.65 g, 59%), mp 154–155 °C. IR (KBr, cm^{-1}): 3409, 3302 (NH_2), 3061 (C–H_{arom}), 1626 (C=$O_{oxocinone}$), 760 (C–Cl). ^{1}H NMR (200 MHz, DMSO-d_6): δ 6.51 (d, 1H, J= 10.0 Hz, H–5), 7.31 (d, 1H, J = 7.8 Hz, H–10), 7.42 (t, 1H, J= 7.5 Hz, H–8), 7.57 (t, 1H, J= 7.2 Hz, H–9), 7.91 (d, 1H, J= 7.8 Hz, H–7), 8.56 (br, 2H, NH_2 exchangeable with D_2O), 8.99 (d, 1H, J = 10.0 Hz, H–4). Anal. Calcd. for $C_{11}H_8ClNO_2$ (221.64): C, 59.61; H, 3.64; N, 6.32%; Found C, 59.33; H, 3.40; N, 6.15%.

3.2.3. 2-Amino-3-phenyl-6H-1-benzoxocin-6-one (5)

White crystals, yield (0.61 g, 46%), mp 143–145 °C. IR (KBr, cm^{-1}): 3251 (br, NH_2), 3023 (C–H_{arom}), 1632 (C=$O_{oxocinone}$), 1598 (C=C). ^{1}H NMR (200 MHz, DMSO-d_6): δ 6.10 (d, 1H, J= 12.0 Hz, H–5), 6.75 (d, 1H, J= 12.0 Hz, H–4), 7.08–8.13 (m, 9H, Ar–H), 9.82 (brs, 2H, NH_2 exchangeable with D_2O). MS (m/z, %): 263 (M^+, 40), 207 (27), 196 (40), 119 (33), 97 (20), 77 (60), 51 (100). Anal. Calcd. for $C_{17}H_{13}NO_2$ (263.30): C, 77.55; H, 4.98; N, 5.32%; Found C, 77.23; H, 4.61; N, 5.04%.

3.3. 2-Amino-3-cyano-6H-1-benzoxocin-6-one (2)

A mixture of compound **4** (0.66 g, 3 mmol) and sodium cyanide (0.15 g, 3 mmol) in ethanol (20 mL) was heated under reflux for 4 h. The solid formed during heating was filtered and recrystallized from DMF/H_2O to give compound **2** as orange-red crystals. Yield: (0.43 g, 41%), mp 276-277 °C (Lit.[22] mp 277–278 °C). IR (KBr, cm^{-1}): 3403, 3120 (NH_2), 2201 (C≡N), 1652 (C=$O_{oxocinone}$), 1599 (C=C). ^{13}C NMR (75 MHz, DMSO-d_6): δ 63.7 (C–3), 102.3 (C–5), 109.1 (C≡N), 118.2 (C–10), 119.0 (C–6a), 123.0 (C–8), 125.9 (C–7), 131.9 (C–9), 137.4 (C–4), 146.6 (C–10a), 148.8 (C–2), 163.4 (C=O). Anal. Calcd. for $C_{12}H_8N_2O_2$ (212.21): C, 67.92; H, 3.80; N, 13.20%; Found C, 67.69; H, 3.75; N, 12.96%.

3.4. General procedure for the synthesis of 2-amino-3-(piperidin/morpholin-1-yl carbonyl)-6*H*-1-benzoxocin-6-ones 9 and 10

Method A: a mixture of carboxylic acid **1** (0.95 g, 5 mmol) and ethyl cyanoacetate (0.57 g, 5 mmol) in absolute ethanol (20 mL) containing a few drops of piperidine and/or morpholine was heated under reflux for 2 h. The orange crystals yielded during heating were filtered and recrystallized from ethanol.

Method B: a mixture of ethyl ester **3** (0.52 g, 2 mmol) and piperidine and/or morpholine (2 mmol) in absolute ethanol (15 mL) was heated under reflux for 2 h. The orange crystals yielded during heating were filtered and recrystallized from ethanol.

3.4.1. 2-Amino-3-(piperidin-1-ylcarbonyl)-6H-1-benzoxocin-6-one (9)

Yields: (method A) (0.31 g, 38%), (method B) (0.70 g, 49%), mp 213–214 °C. UV-Vis (ethanol): λ_{max} (ε) = 291 (4.01), 345 (4.37), 414 nm (3.23). IR (KBr, cm^{-1}): 3371, 3270 (NH_2), 3057 (C–H_{arom}), 2866, 2824 (C–H_{aliph}), 1693 (C=O_{amide}), 1646 (C=$O_{oxocinone}$), 1611 (C=C). ^{1}H NMR (200 MHz, DMSO-d_6): δ 0.92–1.60 (m, 6H, 3CH_2), 3.81–4.18 (m, 4H, 2 CH_2), 6.68 (d, 1H, J = 13.6 Hz, H–5), 6.93–7.32 (m, 3H, Ar–H), 7.61 (d, 1H, J = 13.6 Hz, H–4), 7.91 (br, 1H, H–7), 9.76 (br, 2H, NH_2 exchangeable with D_2O). ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.9 (CH_2), 23.0 (CH_2), 42.3 (CH_2N), 102.7 (C–3), 110.5 (C–5), 127.0 (C–10), 129.6 (C–6a), 130.3 (C–8), 130.6 (C–7), 131.7 (C–9), 143.5 (C–4), 156.8 (C–10a), 163.4 (C–2), 167.7 (C=$O_{oxocinone}$), 168.5 (C=O_{amide}). MS (m/z, %): 298 (M^+, 13%), 214 (55), 157 (37), 131 (35), 115 (22), 84 (100), 77 (15), 65 (31). Anal. Calcd. for $C_{17}H_{18}N_2O_3$ (298.34): C, 68.44; H, 6.08; N, 9.39%; Found C, 68.13; H, 5.87; N, 9.24%.

3.4.2. 2-Amino-3-(morpholin-1-ylcarbonyl)-6H-1-benzoxocin-6-one (10)

Yields: (method A) (0.55 g, 37%), (method B) (0.78 g, 53%), mp 235–236 °C. IR (KBr, cm^{-1}): 3361, 3276 (NH_2), 3098 (C–H_{arom}), 2854 (C–H_{aliph}), 1698 (C=O_{amide}), 1635 (C=$O_{oxocinone}$), 1594 (C=C). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.83 (t, 4H, J = 6.9 Hz, NCH_2), 4.16 (t, 4H, J = 7.2 Hz, OCH_2), 6.00 (d, 1H, J = 13.2 Hz, H–5), 6.89–7.32 (m, 3H, Ar–H), 7.60 (d, 1H, J = 13.5 Hz, H–4), 7.88 (br, 2H, NH_2 exchangeable with D_2O), 8.02 (d, 1H, J = 8.1 Hz, H–7). Anal. Calcd. for $C_{16}H_{16}N_2O_4$ (300.32): C, 63.99; H, 5.37; N, 9.33%; Found C, 63.63; H, 5.13; N, 9.12%.

3.5. General procedure for the synthesis of 2-methyl-3-substituted-6*H*-1-benzoxocin-6-ones 11 and 12

A mixture of carboxylic acid **1** (0.95 g, 5 mmol) and acetylacetone (0.5 g, 5 mmol) or ethyl acetoacetate (0.65 g, 5 mmol) in absolute ethanol (20 mL) containing a few drops of triethylamine was heated under reflux for 4 h. Two thirds of the solvent was evaporated under vacuum to give pale yellow crystals, which were filtered and recrystallized from ethanol to give compounds **11** and **12**, respectively.

3.5.1. 3-Acetyl-2-methyl-6H-1-benzoxocin-6-one (11)

Yield (0.56 g, 0.49%), mp 219–220 °C. IR (KBr, cm^{-1}): 3074 (C–H_{arom}), 2964, 2934 (C–H_{aliph}), 1696 (C=O_{acetyl}), 1637 (C=$O_{oxocinone}$), 1610 (C=C). ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.26 (s, 3H, CH_3), 3.39 (s, 3H, $COCH_3$), 4.84 (d, 1H, J = 12.2 Hz, H–5), 5.56 (d, 1H, J = 12.2 Hz, H–4), 7.51 (t, 1H, J = 8.0 Hz, H–8), 7.65 (d, 1H, J= 8.4 Hz, H–10), 7.82 (t, 1H, J = 8.4 Hz, H–9), 8.05 (d, 1H, J = 8.0 Hz, H–7). ^{13}C NMR (75 MHz, DMSO-d_6): δ 18.2 (CH_3), 26.5 (CH_3), 118.7 (C–3), 127.8 (C–5), 128.1 (C–10), 128.5 (C–6a), 128.8 (C–8), 129.7 (C–7), 138.0 (C–9), 139.0 (C–4), 153.2 (C–2), 156.0 (C–10a), 188.5 (C=$O_{oxocinone}$), 198.2 (C=O_{acetyl}). MS (m/z, %): 228 (M^+, 1%), 210 (17), 148 (11), 134 (41), 91 (40), 77 (9), 65 (100), 51 (7%). Anal. Calcd. for $C_{14}H_{12}O_3$ (228.25): C, 73.67; H, 5.30%; Found C, 73.32; H, 5.09%.

3.5.2. Ethyl 2-methyl-6-oxo-6H-1-benzoxocine-3-carboxylate (12)

Yield (0.52 g, 38%), mp 189–190 °C. IR (KBr, cm^{-1}): 3069 (C–H_{arom}), 2979, 2856 (C–H_{aliph}), 1672 (C=O_{ester}), 1641 (C=$O_{oxocinone}$), 1607 (C=C). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.17 (t, 3H, J= 7.2 Hz, OCH_2CH_3), 2.56 (s, 3H, CH_3), 3.10 (q, 2H, J= 7.2 Hz, OCH_2CH_3), 6.89 (d, 1H, J = 14.0 Hz, H–5), 7.41 (t, 2H, H–8 and H–10), 7.82 (d, 1H, J = 7.5 Hz, H–9), 7.94 (d, 1H, J = 14.0 Hz, H–4), 8.15 (d, 1H, J = 8.0 Hz, H–7). Anal. Calcd. for $C_{15}H_{14}O_4$ (258.28): C, 69.76; H, 5.46%; Found C, 69.52; H, 5.13%.

3.6. 2-(2-Hydroxyphenyl)-4*H*,5H-pyrano[2,3-*b*]chromen-5-one (13)

A mixture of carboxylic acid **1** (0.95 g, 5 mmol) and diethyl malonate (0.80 g, 5 mmol) in absolute ethanol (20 mL) containing a few drops of triethylamine was heated under reflux for 2 h. The white crystals precipitated during heating were filtered and recrystallized from DMF/EtOH to give compound **13**. Yield (0.54 g, 37%), mp > 300 °C. IR (KBr, cm^{-1}): 3423 (br, OH), 3071 (C–H_{arom}), 2911 (C–H_{aliph}), 1632 (C=$O_{\gamma-pyrone}$). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.90 (d, 2H, J = 7.2 Hz, CH_2), 4.79 (t, 1H, J= 7.2 Hz, H–3), 6.95 (t, 1H, J = 8.1 Hz, Ar–H) 7.47–7.63 (m, 2H, Ar–H), 7.61 (t, 1H, Ar–H), 7.78 (t, 1H, Ar–H), 7.97–8.17 (m, 2H, Ar–H), 8.41 (d, 1H, H–6), 11.60 (brs, 1H, OH exchangeable with D_2O). ^{13}C NMR (75 MHz, DMSO-d_6): δ 28.9 (C–4), 86.7 (C–3), 94.0 (C–4a), 111.1 (C–1_{phenol}), 118.2 (C–9), 122.8 (C–3_{phenol}), 123.2 (C–5a), 124.9 (C–5_{phenol}), 125.2 (C–7), 129.0 (C–6_{phenol}), 130.6 (C–4_{phenol}), 133.9 (C–6), 135.9 (C–8), 144.8 (C–2), 154.9 (C–9a), 155.5 (C–2_{phenol}), 158.5 (C–10a), 175.8 (C=$O_{\gamma-pyrone}$). MS (m/z, %): 292 (M^+, 20), 275 (8), 258 (19), 205 (14), 156 (12), 129 (17), 91 (24), 77 (100), 65 (32). Anal. Calcd. for $C_{18}H_{12}O_4$ (292.29): C, 73.97; H, 4.14%; Found C, 73.72; H, 4.05%.

3.7. General procedure for the synthesis of compounds 15–18

A mixture of carboxylic acid **1** (0.95 g, 5 mmol) and cyclic active methylene compounds, namely dimedone (0.7 g, 5 mmol), 1,3-diphenyl-1*H*-pyrazol-5(4*H*)-one (1.18 g, 5 mmol), and thiobarbituric acid (0.72 g, 5 mmol), in absolute ethanol (20 mL) containing a few drops of triethylamine was heated reflux for 4 h. The solids formed after cooling were filtered and recrystallized from ethanol to give the target products.

3.7.1. 2-(2-Hydroxyphenyl)-7,7-dimethyl-6,7-dihydrochromen-5-one (15)

White crystals, yield (0.51 g, 38%), mp 180–181 °C. IR (KBr, cm^{-1}): 3100 (br, OH), 2958, 2886 (C–H_{aliph}), 1648 (C=O_{pyrone}). ^{1}H NMR (200 MHz, DMSO-d_6): 0.99 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 2.29 (s, 2H, CH_2), 6.96–7.02 (m, 2H, Ar–H), 7.34 (s, 1H, H–8), 7.56 (d, 1H, J =6.2 Hz, Ar–H), 7.83 (d, 1H, J =8.2 Hz, Ar–H), 8.02 (d, 1H, J = 8.2 Hz, H–3), 8.07 (d, 1H, J = 8.2 Hz, H–4), 12.01 (brs, 1H, OH exchangeable with D_2O). MS (m/z, %): 268 (M^+, 27), 185 (17), 121 (20), 93 (100), 67 (13), 64 (33). Anal. Calc. for $C_{17}H_{16}O_3$ (268.32): C; 76.10, H; 6.01%. Found C; 75.78, H; 5.85%.

3.7.2. 1,3-Diphenyl-5-ethoxy-5H-chromeno[3‘,4‘:5,6]pyrano[2,3-c]pyrazol-4(1H)-one (17)

Orange yellow crystals, yield (1.34 g, 61%), mp 200–201 °C. IR (KBr, cm^{-1}): 3037 (C–H_{arom}), 2940, 2806 (C–H_{aliph}), 1636 (C=$O_{\gamma-pyrone}$), 1596 (C=N), 1064 (C–O–C). ^{1}H NMR (400 MHz, DMSO-d_6): 1.14 (t, 3H, J =7.2 Hz, OCH_2CH_3), 3.04 (q, 2H, J =7.2 Hz, OCH_2CH_3), 5.44 (s, 1H, H–5), 7.12–7.37 (m, 10H, Ar–H),

7.46–8.03 (m, 3H, Ar–H), 8.54 (s, 1H, H–10). ^{13}C NMR (100 MHz, DMSO-d_6): 26.0 (CH_3), 45.7 (CH_2), 99.8 (C–5), 118.3 (C–3a), 119.7 (C–4a), 123.5–140.3 (17 aromatic carbon atoms), 149.0 (C–3), 154.2 (C–6a), 155.8 (C–10b), 158.3 (C–11a), 175.4 ($C{=}O_{\gamma-\text{pyrone}}$). MS (m/z, %): 392 (M–$OCH_2CH_2$, 27%), 363 (13), 335 (10), 139 (54), 77 (100), 65 (10), 51 (45). Anal. Calc. for $C_{27}H_{20}N_2O_4$ (436.45): C, 74.30; H, 4.62; N, 6.42%. Found: C, 73.98; H, 4.51; N, 6.22%.

3.7.3. 6-Ethoxy-2-thioxo-2H,6H-chromeno[3‘,4‘:5,6]pyrano[2,3-d]pyrimidine-4,5-(1H,3H)-dione (18)

Orange crystals, yield (1.15 g, 67%), mp 231–232 °C. IR (KBr, cm^{-1}): 3112 (br, NH), 2994, 2885 ($C{-}H_{\text{aliph}}$), 1681 ($C{=}O_{\text{pyrimidinone}}$), 1635 ($C{=}O_{\gamma-\text{pyrone}}$), 1180 (C=S), 1016 (C–O–C). ^{1}H NMR (200 MHz, DMSO-d_6): 1.16 (t, 3H, J =7.2 Hz, $OCH_2\,\mathit{CH}_3$), 3.07–3.13 (m, 2H, $O\mathit{CH}_2CH_3$), 5.78 (s, 1H, H–6), 7.43 (t, 1H, J =7.4 Hz, H–10), 7.56 (d, 1H, J =8.4 Hz, H–8), 7.71–7.75 (m, 1H, H–9), 8.00 (d, 1H, J =7.6 Hz, H–11), 8.83 (br, 1H, NH exchangeable with D_2O), 11.53 (s, 1H, NH exchangeable with D_2O). ^{13}C NMR (100 MHz, DMSO-d_6): 24.6 (CH_3), 45.8 (CH_2), 93.7 (C–6), 118.1 (C–4a), 121.1 (C–5a), 123.2 (C–8), 123.4 (11a), 124.9 (C–10), 125.0 (C–11), 133.5 (C–9), 153.2 (C–7a), 155.6 (C–11b), 162.4 (C–12a), 172.7 ($C{=}O_{\text{pyrimidinone}}$), 175.9 ($C{=}O_{\gamma-\text{pyrone}}$), 205.2 (C=S). MS (m/z, %): 300 (M–OCH_2CH_2, 62%), 272 (56), 230 (15), 202 (89), 170 (29), 142 (50), 120 (35), 92 (77), 77 (36), 65 (26), 51 (41), 50 (100). Anal. Calc. for $C_{16}H_{12}N_2O_5S$ (344.34): C, 55.81; H, 3.51; N, 8.14; S, 9.31%. Found: C, 55.53; H, 3.32; N, 7.88; S, 9.09%.

4. Conclusion

The present work reports a convenient method for the synthesis of functionalized benzoxocinones and annulated pyranochromenes from the reaction of chromone-3-carboxylic acid with some acyclic and cyclic methylene nucleophiles. The method depends on cleavage of the O–C bond in the γ-pyrone ring or condensation of the carboxylic group with acyclic and cyclic active methylene compounds, followed by further heterocyclization, leading to the target products in one pot.

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