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CHEMICAL REACTIVITY OF 1*H*-BENZIMIDAZOL-2-YL-ACETONITRILE AND DIMEDONE TOWARD SIMPLE CONDENSATES DERIVED FROM 3-FORMYLCHROMONE

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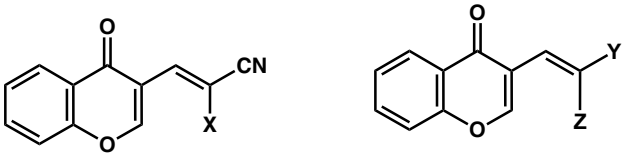
Abstract – The chemical reactivity of 1*H*-benzimidazol-2-ylacetonitrile and dimedone was investigated towards some simple condensates (**1a-d** and **2a-c**) obtained from condensation reaction of 3-formylchromone with some active methylene compounds. Mainly, the used nucleophiles undergo nucleophilic addition at the olefinic carbon with concomitant cycloaddition or cyclocondensation. Chromonylacrylonitrile **1a** reacted with 1*H*-benzimidazol-2-ylacetonitrile through γ-pyrone ring opening followed by cyclocondensation giving pyrido[1,2-*a*]benzimidazole derivative **5**. The simple condensates **2b** and **2c** showed similar behavior towards 1*H*-benzimidazol-2-ylacetonitrile and dimedone leading to the same products which are identical with those obtained from 3-formylchromone with the same reagents. Structures of the new synthesized products were established based on elemental analysis and spectral data.

INTRODUCTION

Chromone derivatives are characterized by their variable biological and pharmacological applications which are anti-cancer,[1] anti-HIV,[2] anti-bacterial,[3] antimicrobial,[4] antifungal,[5] insecticidal,[6] antibiotic,[7] anti-inflammatory,[8] anti-malaria,[9] and treatment of Alzheimer's disease.[10] Chromones are recently utilized in opto-electronic applications.[11] The presence of electron-withdrawing group at position 3 of chromone moiety alters its chemical behavior towards nucleophilic reagents leading to a diversity of heterocyclic oxygen-containing systems.[12] 3-Substituted chromones have variable electron deficient centers and represent active substrates toward nucleophilic reagents producing numerous heterocyclic compounds.[13] In our previous work,[14] the chemical transformations of the simple condensation products derived from

3-formylchromone (**1a-d**) (Figure 1) was studied towards some nitrogen nucleophiles namely benzylamine and *p*-toluidine giving either 2-iminopyranes or pyrano[3,2-*c*]chromenes. Also, reaction of compounds **1b** and **1d** was investigated towards some bi-nitrogen nucleophiles appearing different behavior depending on the solvent used.[15] Moreover, reaction of compounds **1b** and **1d** with cyanoacetamide and cyanoacetohydrazide afforded chromone linked pyridine derivatives at position 3.[16] In some cases the presence of alkyl substituent at the benzene ring of 3-substituted chromones alter the reactivity towards certain nucleophiles.[17] Based on the above knowledge, the present work aims to study the chemical reactivity of the simple condensates **1a-d** and **2a-c** (Figure 1) towards some carbon nucleophiles namely 1*H*-benzimidazol-2-ylacetonitrile (**3**) and dimedone (**4**).



1a; X = H
1b; X = CN
1c; X = $CONH_2$
1d; X = CO_2Et

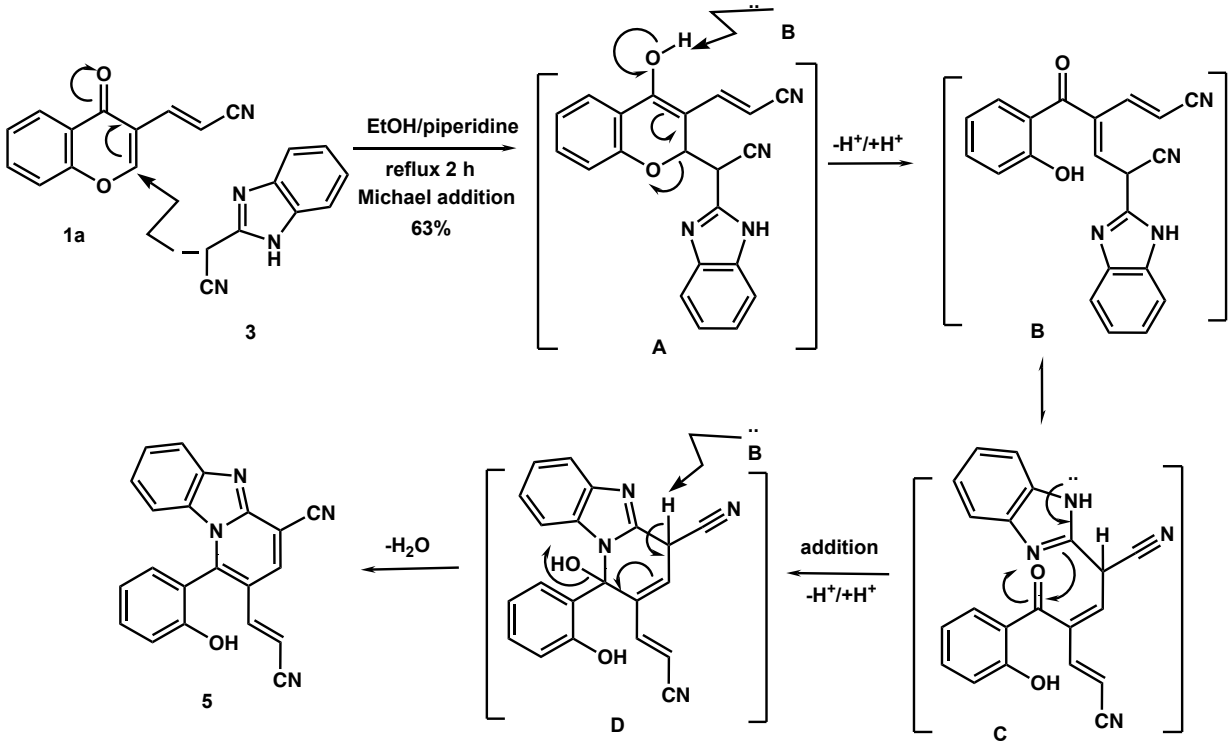
2a; Y = CO_2Et, Z= CO_2Et
2b; Y = COMe, Z= CO_2Et
2c; Y = COMe, Z= COMe

Figure 1. Chemical structures of substituted chromones

RESULTS AND DISCUSSION

The simple condensation products **1a-d** and **2a-c** (Figure 1) may be useful in the synthesis of various heterocyclic systems due to the availability of diverse electron deficient sites. The present work aims to study the chemical behavior of the simple condensates **1a-d** and **2a-c** towards 1*H*-benzimidazol-2-ylacetonitrile (**3**) and dimedone (**4**) as carbon nucleophiles. Thus, treatment of *trans* *β*-(chromon-3-yl)acrylonitrile (**1a**)[18] with 1*H*-benzimidazol-2-ylacetonitrile (**3**), in absolute ethanol containing few drops of piperidine, afforded a canary yellow crystals identified as 2-[(*E*)-2-cyanoethenyl]-1-(2-hydroxyphenyl)pyrido[1,2-*a*]benzimidazole-4-carbonitrile (**5**).[19] Formation of compound **5** proceeds *via* Michael addition of 1*H*-benzimidazol-2-ylacetonitrile at the C-2 position of the chromone moiety (intermediate **A**) followed by retro-Michael with γ-pyrone ring opening (intermediate **B**) with consequent free rotation giving intermediate **C**. The later intermediate underwent cycloaddition (intermediate **D**) with subsequent dehydration as depicted in Scheme 1. The spectral data confirms that, the C-2 position in compound **1a** is the more electron deficient center by the effect of electron withdrawing carbonyl group and the acrylonitrile function at position 3, therefore C-2 position is rapidly attacked by the nucleophile used. The ^{1}H NMR spectrum of compound **5** revealed the presence of two characteristic doublets at δ 6.62 and 6.99 ppm (*J*=16.8 Hz), attributed to the two olefinic protons; confirming *trans* configuration of the two olefinic protons around the exocyclic double bond. Also, the spectrum showed singlet at δ 8.87

ppm attributed to the H-$4_{pyridine}$. The IR spectrum showed characteristic absorption bands at 2249 and 2217 cm^{-1} assigned to the two nitrile functions. In the ^{13}C NMR of compound **5**, the specific signals assignable to the two C≡N function appeared at δ 116.2 and 116.8 ppm. Further, the mass spectrum of compound **5** recorded the parent ion peak, as the base peak, at *m/z* 336, which is coincident with its formula weight (336.36) and supports the identity of the structure.

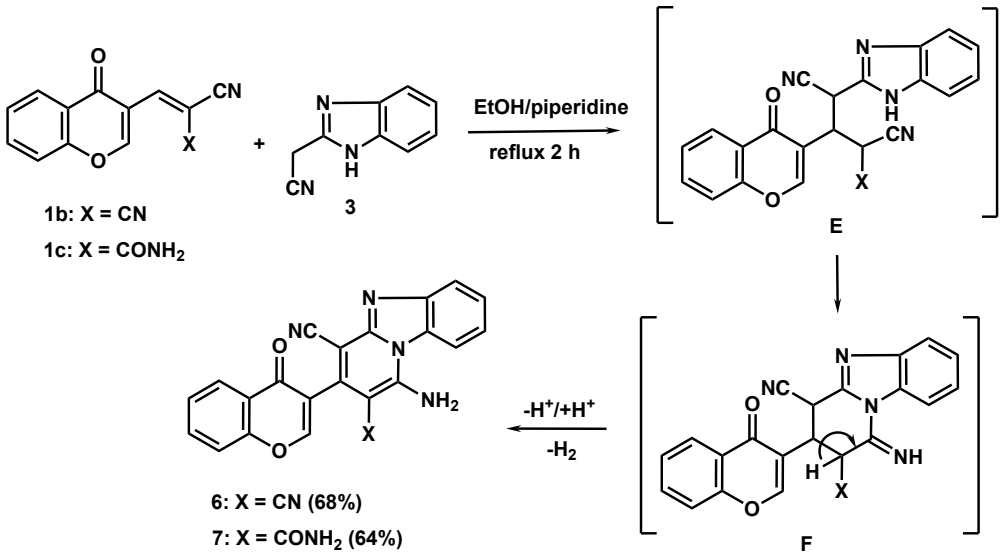


Scheme 1. Reaction of acrylonitrile derivative **1a** with 1*H*-bezimidazol-2-ylacetonitrile (**3**)

Reaction of [(chromon-3-yl)methylidene]propanedinitrile (**1b**)[20] with 1*H*-benzimidazol-2-ylacetonitrile (**3**) in absolute ethanol containing few drops of piperidine, afforded pale yellow crystals identified as 1-amino-3-(chromon-3-yl)pyrido[1,2-*a*]benzimidazole-2,4-dicarbonitrile (**6**) (Scheme 2).[21] Formation of compound **6** proceeds *via* nucleophilic addition of 1*H*-benzimidazol-2-ylacetonitrile (**3**) at the exocyclic double bond (intermediate **E**) followed by cycloaddition of $NH_{benzimidazole}$ onto the nitrile function (intermediate **F**) with concomitant proton transfer and dehydrogenation. In this mechanism, the reaction initially proceeds through nucleophilic attack at the exocyclic vinyl bond which may activated by the two electron withdrawing nitrile functions. The IR and ^1H NMR spectra confirm the presence of chromone moiety intact. The IR spectrum showed characteristic absorption bands at 2207, 2193 (2C≡N) and 1667 cm^{-1} ($C{=}O_{\gamma\text{-pyrone}}$). The ^1H NMR spectrum of compound **6** showed characteristic singlet attributed to the H-$2_{chromone}$ at δ 8.73 ppm. The ^{13}C NMR spectrum displayed downfield signal due to the C=O function at δ 176.7 ppm. The mass spectrum of compound **6** showed the molecular ion peak, as the base peak, at *m/z* 377, which is coincident with the molecular formula ($C_{22}H_{11}N_5O_2$) and confirms the structure.

Under the same mechanism, reaction of 2-cyano-3-(chromon-3-yl)prop-2-enamide (**1c**)[22] with 1*H*-

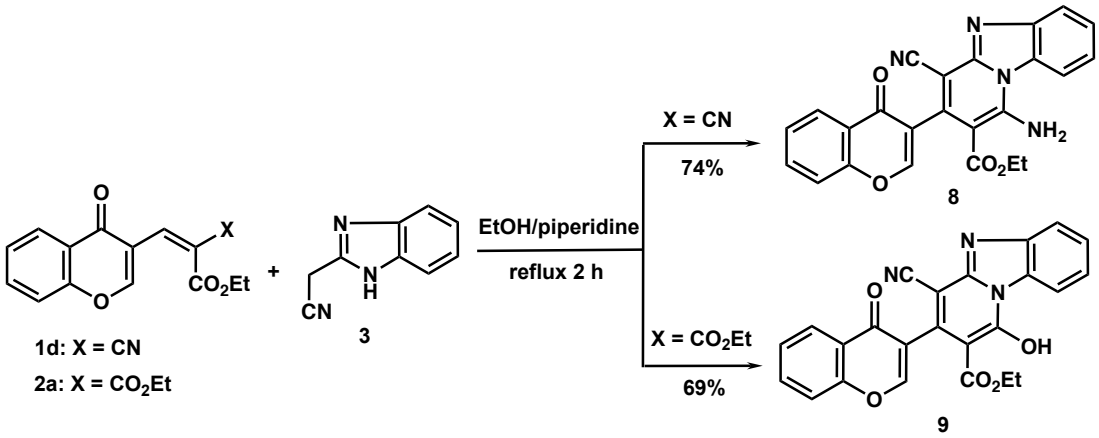
benzimidazol-2-ylacetonitrile (**3**) gave 1-amino-4-cyano-3-(chromon-3-yl)pyrido[1,2-*a*]benzimidazole-2-carboxamide (**7**) (Scheme 2). Its ^{1}H NMR spectrum showed characteristic singlet attributed to the H-2$_{chromone}$ at δ 8.39 ppm, in addition to two exchangeable signals at δ 9.81 (NH_2) and 10.47 ppm (NH_2). Characteristic absorption bands appeared in the IR spectrum of compound **7** at 3419, 3385, 3286, 3207 ($2NH_2$), 2228 (C≡N), 1677 (C=O$_{amide}$) and 1647 cm^{-1} (C=O$_{\gamma\text{-pyrone}}$).



Scheme 2. Synthesis of pyrido[1,2-*a*]benzimidazole derivatives **6** and **7**

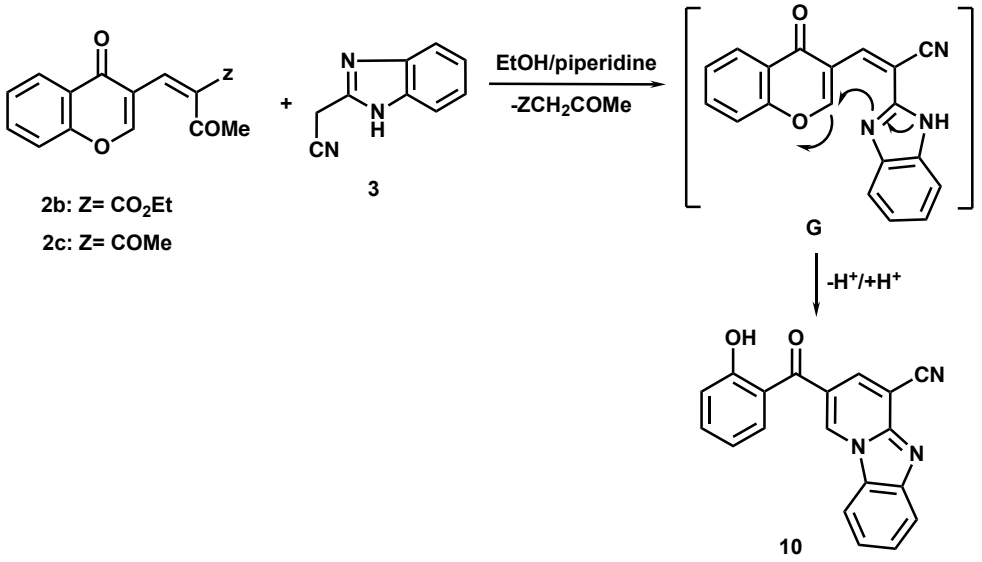
Similarly, treatment of ethyl 2-cyano-3-(chromon-3-yl)prop-2-enoate (**1d**)[22] with 1*H*-benzimidazol-2-ylacetonitrile (**3**), under the same reaction conditions, afforded ethyl 1-amino-3-(chromon-3-yl)pyrido[1,2-*a*]benzimidazole-2-carboxylate (**8**) (Scheme 3). Its IR spectrum exhibited characteristic absorption bands at 3361, 3254 (NH_2), 2237 (C≡N), 1707 (C=O$_{ester}$) and 1648 cm^{-1} (C=O$_{\gamma\text{-pyrone}}$). Its ^{1}H NMR spectrum showed characteristic singlet attributed to the H-2$_{chromone}$ at δ 8.98 ppm, in addition the spectrum of compound **8** showed triplet and quartet signals at δ 1.19 and 4.11 ppm assigned to the ethoxycarbonyl protons. Further, the mass spectrum of compound **8** showed the molecular ion peak at *m/z* 424, which is coincident with the formula weight (424.42) and supports the identity of the structure.

On the other hand, treatment of diethyl [(chromon-3-yl)methylidene]propanedioate (**2a**)[23] with 1*H*-benzimidazol-2-ylacetonitrile (**3**) gave ethyl 4-cyano-1-hydroxy-3-(chromon-3-yl)pyrido[1,2-*a*]-benzimidazole-2-carboxylate (**9**) (Scheme 3). The reaction proceeds *via* nucleophilic addition at the exocyclic double bond followed by cyclocondensation with elimination of ethanol molecule with concomitant dehydrogenation. The IR spectrum of compound **9** showed characteristic absorption bands at 2212 (C≡N), 1696 (C=O$_{ester}$) and 1646 cm^{-1} (C=O$_{\gamma\text{-pyrone}}$). Its ^{1}H NMR spectrum showed characteristic singlet assigned to the H-2$_{chromone}$ at δ 8.63 ppm. Further, the mass spectrum displayed the molecular ion peak at *m/z* 425, which is coincident with the formula weight (425.40) and supports the identity of the structure.



Scheme 3. Synthesis of pyrido[1,2-*a*]benzimidazole derivatives **8** and **9**

Interestingly, reaction of ethyl 3-oxo-2-[(chromon-3-yl)methylidene]butanoate (**2b**)[24] and 3-[(chromon-3-yl)methylidene]pentane-2,4-dione (**2c**)[25] with 1*H*-benzimidazol-2-ylacetonitrile (**3**), in boiling ethanol containing piperidine, produced *via* intermediate **G** the product; 2-[(2-hydroxybenzoyl]pyrido[1,2-*a*]benzimidazole-4-carbonitrile (**10**) which identical with that obtained previously from reaction of 3-formylchromone and 1*H*-benzimidazol-2-ylacetonitrile (Scheme 4).[26] In these reactions, 1*H*-benzimidazol-2-ylacetonitrile (**3**) reacted with compounds **2b** and **2c** *via* nucleophilic attack at the exocyclic double bond (which activated by the two electron withdrawing groups) with concomitant elimination of ethyl acetoacetate or pentane-2,4-dione (intermediate **G**) followed by nucleophilic attack of $NH_{benzimidazole}$ at C-2 position with γ-pyrone ring opening.

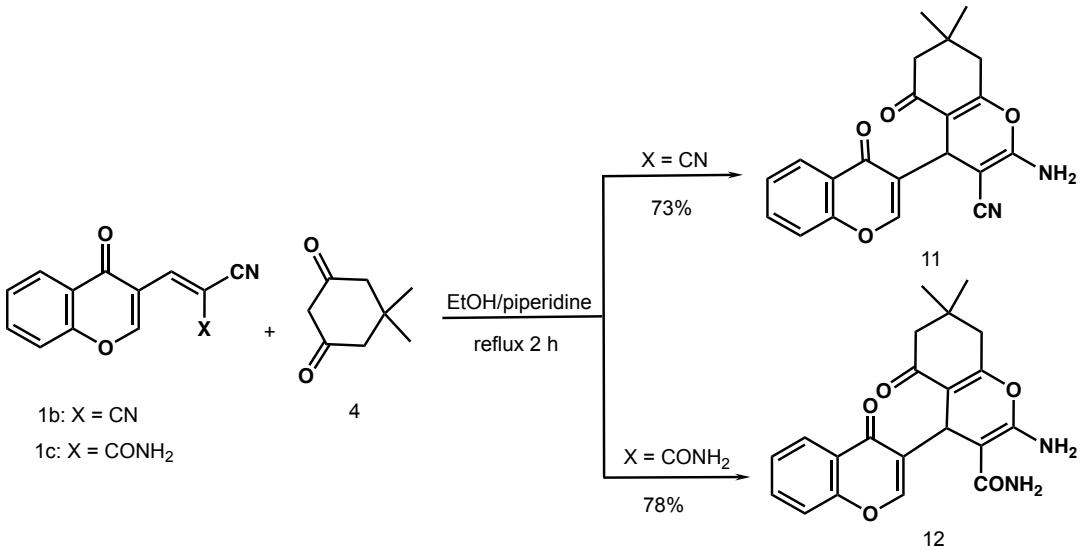


Scheme 4. Reaction of compounds **2b** and **2c** with 1*H*-bezimidazol-2-ylacetonitrile

Next, the chemical reactivity of the simple condensates **1b-d** and **2a-c** was studied towards 5,5-dimethyl-1,3-cyclohexanedione (dimedone) (**4**). Thus, treatment of compound **1b** with dimedone, in absolute

ethanol containing few drops of piperidine, afforded chromene-3-carbonitrile derivative **11** (Scheme 5). The IR spectrum of compound **11** showed characteristic absorption bands at 3477, 3331 (NH_2), 2216 (C≡N), 1689 ($C=O_{chromene}$) and 1653 cm^{-1} ($C=O_{\gamma\text{-pyrone}}$). Its ^1H NMR spectrum revealed characteristic singlet signals at δ 4.13 and 8.35 ppm attributed to H-$4_{chromene}$ and H-$2_{chromone}$, respectively, in addition to an exchangeable signal at δ 6.96 ppm assigned to NH_2 protons. The ^{13}C NMR spectrum showed two downfield signals at δ 176.3 ($C=O_{\gamma\text{-pyrone}}$) and 194.9 ppm ($C=O_{chromene}$).

Similarly, reaction of compound **1c** with dimedone (**4**) gave chromene-3-carboxamide derivative **12** (Scheme 5). The ^1H NMR spectrum of compound **12** showed singlet signals attributed to H-4_{pyran} (δ 4.25) and H-$2_{chromone}$ (δ 8.42), in addition two exchangeable signals assignable to $2NH_2$ observed at δ 7.16 and 9.58 ppm. Structure **12** was further confirmed from the mass spectrum which recorded the molecular ion peak, as the base peak, at *m/z* 380 which agrees well with the suggested molecular formula ($C_{21}H_{20}N_2O_5$).

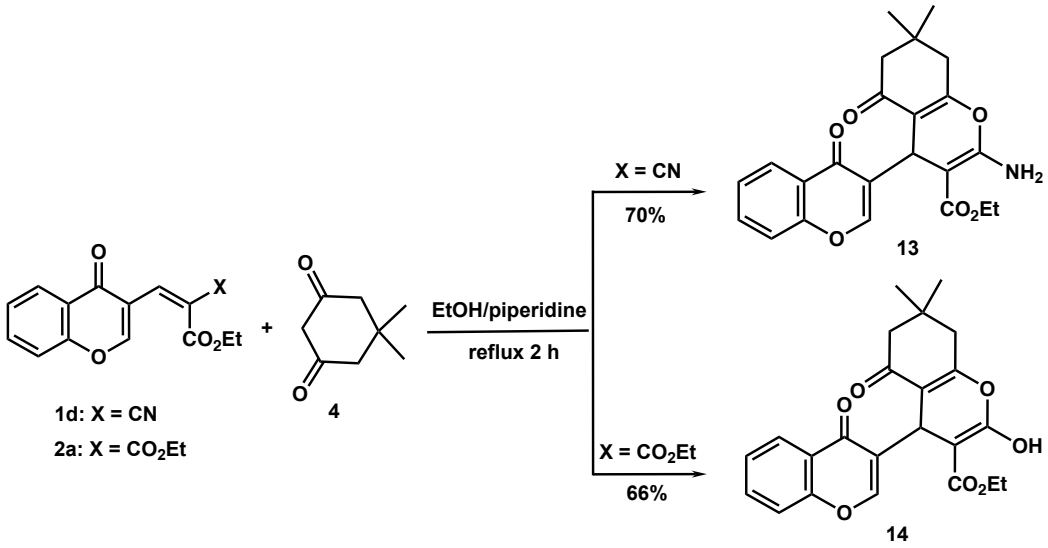


Scheme 5. Reaction of substituted chromones **1b**, **c** with dimedone (**4**)

Also, reaction of compound **1d** with dimedone (**4**), under the previous reaction conditions, produced 2-aminochromene-3-carboxylate derivative **13** (Scheme 6). Its IR spectrum showed characteristic absorption bands at 3382, 3277 (NH_2), 1699 ($C=O_{ester}$), 1682 ($C=O_{chromene}$) and 1647 cm^{-1} ($C=O_{\gamma\text{-pyrone}}$). The ^1H NMR spectrum of compound **13** showed triplet and quartet signals at δ 1.12 and 3.99 ppm assigned to the ethoxycarbonyl protons, in addition to typical signals at δ 4.26 and 8.43 ppm attributed to H-4_{pyran} and H-$2_{chromone}$, respectively. The ethoxycarbonyl group showed specific signals in the ^{13}C NMR spectrum at δ 15.8 (CH_3), 60.5 (OCH_2) and 193.9 (C=O). The mass spectrum of compound **13** recorded the molecular ion peak at *m/z* 409 which agrees well with the formula weight ($C_{23}H_{23}NO_6$) and confirms the structure.

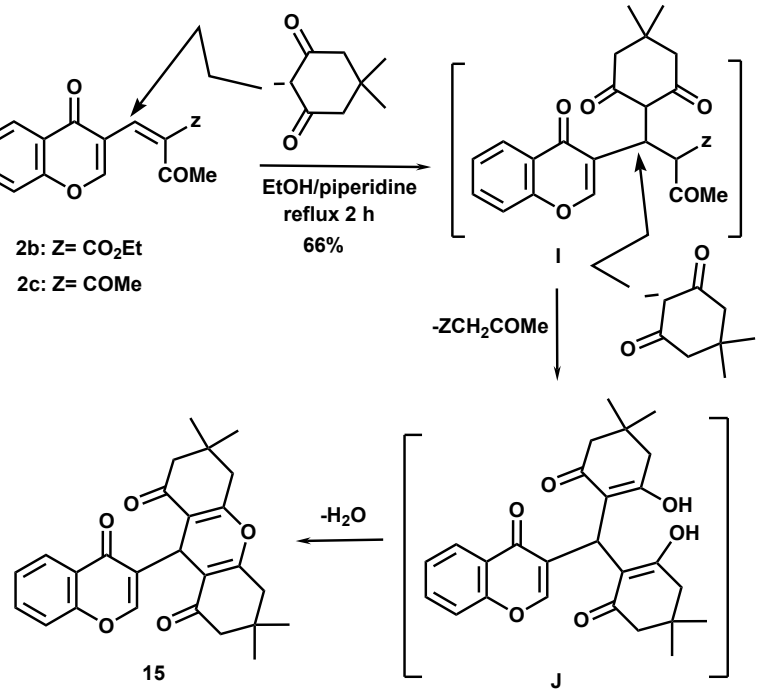
Moreover, reaction of compound **2a** with dimedone, in absolute ethanol containing piperidine, produced 2-hydroxychromene-3-carboxylate derivative **14** (Scheme 6). Its IR spectrum showed characteristic absorption bands at 3428 (OH), 1708 ($C=O_{ester}$), 1685 ($C=O_{chromene}$) and 1654 cm^{-1} ($C=O_{\gamma\text{-pyrone}}$). The ^1H

NMR spectrum displayed distinctive singlets at δ 4.23 (H-4_{pyran}), 8.39 (H-$2_{chromone}$) and 10.58 (OH exchangeable with D_2O). The mass spectrum verified the structure **14** and recorded the parent ion peak at *m/z* 410, which agrees well with the formula weight and confirms the structure.



Scheme 6. Reaction of substituted chromones **1d** and **2a** with dimedone (**4**)

Herein again, reaction of compounds **2b** and **2c** with dimedone (**4**) gave xanthene derivative **15** which identical with that previously obtained from the reaction of 3-formylchromone with dimedone (Scheme 7).[25] In these reactions, two molecules of dimedone underdo nucleophilic attack at the exocyclic olefinic carbon (intermediate **I**) with elimination of ethyl acetoacetate and pentane-2,4-dione (intermediate **J**) followed by cyclodehydration producing compound **15**. The ^{1}H NMR spectrum of compound **15** showed characteristic singlet signals at δ 4.25 and 8.27 ppm attributed to H-$9_{xanthene}$ and H-$2_{chromone}$, respectively.



Scheme 7. Reaction of compounds **2b** and **2c** with dimedone (**4**)

CONCLUSIONS

In conclusion, the chemical transformation of the simple condensation products (**1a-d** and **2a-c**) derived from 3-formylchromone was inspected towards two selected nucleophiles namely 1*H*-benzimidazol-2-ylacetonitrile (**3**) and dimedone (**4**). Compound **1a** reacted with 1*H*-benzimidazol-2-ylacetonitrile through nucleophilic attack at C-2 position followed by cyclocondensation. Compounds **1b-d** and **2a** reacted with 1*H*-benzimidazol-2-ylacetonitrile and dimedone through nucleophilic addition at the olefinic double bond followed by cyclocondensation giving a diversity of chromones bearing heterocyclic systems at 3 position. Compounds **2b**,**c** behave as 3-fromylchromone upon their reaction with the two selected nucleophiles.

EXPERIMENTAL

Melting points were determined on a digital Stuart SMP3 apparatus. Infrared spectra were measured on FTIR Nicolet IS10 spectrophotometer (cm^{-1}), using KBr disks. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured on Mercury-300BB, using DMSO-d_6 as a solvent and TMS (δ) as the internal standard. Mass spectra were obtained using GC-2010 Shimadzu Gas chromatography instrument mass spectrometer (70 eV). Elemental microanalyses were performed on a Perkin–Elmer CHN-2400 analyzer. The purity of the synthesized compounds was tested using TLC.

2-[(*E*)-2-Cyanoethenyl]-1-(2-hydroxyphenyl)pyrido[1,2-*a*]benzimidazole-4-carbonitrile (5). A mixture of chromone derivative **1a** (0.40 g, 2 mmol) and 1*H*-benzimidazol-2-ylacetonitrile (0.31 g, 2 mmol) in absolute EtOH (20 mL) containing piperidine was heated under refluxed for 2 h. The canary yellow crystals obtained during heating were filtered and recrystallized from DMF, yield (0.42 g, 63%), mp> 320 °C. IR (KBr, cm^{-1}): 3429 (OH), 3061 ($CH_{arom.}$), 2249, 2217 (2C≡N), 1622 (C=N), 1605 (C=C). ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 6.30 (d, *J*=7.8 Hz, 1H, Ar-H), 6.62 (d, 1H, *J*=16.8 Hz, olefinic proton), 6.99 (d, 1H, *J*=16.8 Hz, olefinic proton), 7.12-7.22 (m, 3H, Ar-H), 7.42 (d, 1H, *J*=7.5 Hz, Ar-H), 7.49 (t, 1H, *J*=7.8 Hz, Ar-H), 7.69 (t, *J*=7.8 Hz, 1H, Ar-H), 7.93 (d, 1H, *J*=7.5 Hz, Ar-H), 8.87 (s, 1H, H-$4_{pyridine}$), 10.22 (bs, 1H, OH exchangeable with D_2O). ^{13}C NMR (DMSO-d_6, δ, 75 MHz): 85.7, 104.1, 116.2, 116.8, 119.2, 121.3, 123.8, 124.6, 125.2, 126.4, 127.1, 127.6, 129.4, 131.2, 132.7, 134.8, 136.3, 141.3, 144.5, 149.4, 153.9. Mass spectrum (*m/z*, %): 336 (M, 100), 319 (12), 292 (8), 267 (9), 93 (5), 77 (10), 64 (12). Anal. Calcd for $C_{21}H_{12}N_4O$ (336.35): C, 74.99; H, 3.60; N, 16.66%. Found: C, 74.74; H, 3.42; N, 16.50%.

1-Amino-3-(chromon-3-yl)pyrido[1,2-*a*]benzimidazole-2,4-dicarbonitrile (6). A mixture of chromone derivative **1b** (0.44 g, 2 mmol) and 1*H*-benzimidazol-2-ylacetonitrile (0.31 g, 2 mmol) in absolute EtOH (20 mL) containing piperidine was heated under refluxed for 2 h. The pale yellow crystals obtained after cooling were filtered and recrystallized from DMF/H_2O, yield (0.51 g, 68%), mp> 320 °C. IR (KBr,

cm^{-1}): 3322, 3250 (NH_2), 3064 ($CH_{arom.}$), 2207, 2193 (2C≡N), 1667 ($C=O_{\gamma\text{-pyrone}}$), 1633 (C=N), 1590 (C=C). ^{1}H NMR (DMSO-*d*$_6$, δ, 300 MHz): 7.19 (d, 1H, *J*=7.2 Hz, Ar-H), 7.38-7.63 (m, 4H, Ar-H), 7.69 (d, 1H, *J*=7.8 Hz, Ar-H), 7.77 (t, 1H, *J*=7.2 Hz, Ar-H), 8.08 (d, 1H, *J*=7.8 Hz, Ar-H), 8.73 (s, 1H, H-$2_{chromone}$), 10.42 (bs, 2H, NH_2 exchangeable with D_2O). ^{13}C NMR (DMSO-*d*$_6$, δ, 75 MHz): 79.6, 83.4, 116.7, 117.1, 119.8, 121.6, 122.8, 123.1, 124.7, 126.0, 126.8, 127.3, 128.9, 130.6, 133.2, 135.2, 137.1, 143.5, 145.2, 150.6, 152.4, 176.7. Mass spectrum (*m/z*, %): 377 (M, 100), 361 (35), 326 (48), 368 (32), 257 (50), 194 (47), 184 (41), 169 (36), 146 (39), 119 (27), 92 (54), and 64 (15). Anal. Calcd for $C_{22}H_{11}N_5O_2$ (377.37): C, 70.02; H, 2.94; N, 18.56%. Found: C, 69.79; H, 2.65; N, 18.28%.

1-Amino-4-cyano-3-(chromon-3-yl)pyrido[1,2-*a*]benzimidazole-2-carboxamide (7). A mixture of chromone derivative **1c** (0.48 g, 2 mmol) and 1*H*-benzimidazol-2-ylacetonitrile (0.31 g, 2 mmol) in absolute EtOH (20 mL) containing piperidine was heated under refluxed for 2 h. The yellow crystals obtained during heating were filtered and recrystallized from AcOH, yield (0.51 g, 64%), mp> 320 °C. IR (KBr, cm^{-1}): 3419, 3385, 3286, 3207 ($2NH_2$), 2228 (C≡N), 1677 ($C=O_{amide}$), 1647 ($C=O_{\gamma\text{-pyrone}}$), 1628 (C=N), 1601 (C=C). ^{1}H NMR (DMSO-*d*$_6$, δ, 300 MHz): 6.95-7.06 (m, 2H, Ar-H), 7.23-7.36 (m, 3H, Ar-H), 7.48–7.69 (m, 2H, Ar-H), 7.96 (d, 1H, *J*=7.2 Hz, Ar-H), 8.39 (s, 1H, H-$2_{chromone}$), 9.81 (bs, 2H, NH_2 exchangeable with D_2O), 10.47 (bs, 2H, NH_2 exchangeable with D_2O), ^{13}C NMR (DMSO-*d*$_6$, δ, 75 MHz): 86.2, 110.6, 116.3, 119.5, 121.0, 122.5, 123.2, 124.4, 126.2, 127.3, 127.8, 128.7, 130.3, 133.4, 134.9, 136.8, 143.0, 145.8, 151.2, 152.8, 169.2, 175.3. Mass spectrum (*m/z*, %): 395 (M, 42), 367 (32), 324 (27), 299 (16), 273 (52), 145 (19), 120 (100), 105 (63), 92 (24), 77 (48), 64 (21). Anal. Calcd for $C_{22}H_{13}N_5O_3$ (395.38): C, 66.83; H, 3.31; N, 17.71%. Found C, 66.74; H, 3.16; N, 17.44%.

Ethyl 1-amino-3-(chromon-3-yl)pyrido[1,2-*a*]benzimidazole-2-carboxylate (8). A mixture of chromone derivative **1d** (0.52 g, 2 mmol) and 1*H*-benzimidazol-2-ylacetonitrile (0.31 g, 2 mmol) in absolute EtOH (20 mL) containing piperidine was heated under refluxed for 2 h. The pale yellow crystals obtained after cooling were filtered and recrystallized from EtOH, yield (0.63 g, 74%), mp 280-281 °C. IR (KBr, cm^{-1}): 3361, 3254 (NH_2), 3071 ($CH_{arom.}$), 2986 ($CH_{aliph.}$), 2237 (C≡N), 1707 ($C=O_{ester}$), 1648 ($C=O_{\gamma\text{-pyrone}}$), 1610 (C=N), 1586 (C=C). ^{1}H NMR (DMSO-*d*$_6$, δ, 300 MHz): 1.19 (t, 3H, *J*=7.2 Hz, CH_3), 4.11 (q, 2H, *J*=7.2 Hz, CH_2), 6.84 (d, 1H, *J*=7.5 Hz, Ar-H), 7.04 (d, 1H, *J*=8.1 Hz, Ar-H), 7.10-7.27 (m, 2H, Ar-H), 7.42 (d, 1H, *J*=7.5 Hz, Ar-H), 7.51 (t, *J*=7.8 Hz, 1H, Ar-H), 7.63 (t, *J*=7.8 Hz, 1H, Ar-H), 7.93 (d, *J*=8.1 Hz, 1H, Ar-H), 8.98 (s, 1H, H-$2_{chromone}$), 10.17 (bs, 1H, OH exchangeable with D_2O). ^{13}C NMR (DMSO-*d*$_6$, δ, 75 MHz): 16.2, 61.5, 84.9, 113.2, 116.7, 120.3, 121.8, 123.0, 123.8, 124.7, 126.6, 127.5, 128.2, 128.9, 130.8, 133.2, 134.7, 136.2, 143.7, 146.0, 150.6, 152.1, 166.5, 175.6. Mass spectrum (*m/z*, %): 424 (M, 61), 379 (100), 351 (25), 326 (17), 283 (32), 207 (12), 195 (100), 120 (7), 105 (81), 93 (45), 77 (39), 64 (16). Anal. Calcd for $C_{24}H_{16}N_4O_4$ (424.42): C, 67.92; H, 3.80; N, 13.20%. Found: C, 67.79; H, 3.59; N, 13.01%.

Ethyl 4-cyano-1-hydroxy-3-(chromon-3-yl)pyrido[1,2-*a*]benzimidazole-2-carboxylate (9). A mixture of chromone derivative **2a** (0.64 g, 2 mmol) and 1*H*-benzimidazol-2-ylacetonitrile (0.31 g, 2 mmol) in absolute EtOH (20 mL) containing piperidine was heated under refluxed for 2 h. The yellow crystals obtained after cooling were filtered and recrystallized from DMF/H_2O, yield (0.59 g, 69%), mp> 320 °C. IR (KBr, cm^{-1}): 3269 (OH), 3012 ($CH_{arom.}$), 2212 (C≡N), 1696 ($C=O_{ester}$), 1646 ($C=O_{\gamma\text{-pyrone}}$), 1616 (C=N), 1591 (C=C). ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 1.26 (t, 3H, *J*=6.9 Hz, Me), 4.28 (q, 2H, *J*=6.9 Hz, CH_2), 7.45-7.62 (m, 4H, Ar-H), 7.80-7.95 (m, 3H, Ar-H), 8.17 (d, 1H, *J*=7.2 Hz, Ar-H), 8.63 (s, 1H, H-$2_{chromone}$). ^{13}C NMR (DMSO-d_6, δ, 75 MHz): 16.7, 60.5, 86.3, 112.8, 116.5, 120.6, 121.7, 123.6, 123.9, 124.6, 126.9, 127.7, 128.5, 129.7, 131.1, 133.7, 135.4, 137.0, 142.9, 146.2, 150.6, 155.9, 162.6, 166.1, 175.2. Mass spectrum (*m/z*, %): 425 (M, 46), 397 (22), 352 (68), 336 (20), 195 (100), 120 (17), 105 (23), 93 (10), 77 (15), 64 (6). Anal. Calcd for $C_{25}H_{17}N_3O_4$ (425.40): C, 67.76; H, 3.55; N, 9.88%. Found C, 67.60; H, 3.36; N, 9.62%.

2-[(2-Hydroxybenzoyl]pyrido[1,2-*a*]benzimidazole-4-carbonitrile (10). A mixture of chromone derivative **2b** or **2c** (2 mmol) and 1*H*-benzimidazol-2-ylacetonitrile (0.31 g, 2 mmol) in absolute EtOH (20 mL) containing piperidine was heated under refluxed for 2 h. The pale yellow crystals obtained during heating were filtered and recrystallized from DMF/EtOH, yield (0.34 g, 54%), mp 252-253 °C (lit. 250-252 °C).[26] IR (KBr, cm^{-1}): 3064 (br, OH), 3020 ($CH_{arom.}$), 2234 (C≡N), 1646 (C=O), 1627 (C=N), 1600 (C=C). ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 6.99-7.06 (m, 2H, Ar-H), 7.48-7.58 (m, 3H, Ar-H), 7.65 (t, *J*=7.5 Hz, 1H, Ar-H), 7.96 (d, *J*=7.8 Hz, 1H, Ar-H), 8.44 (s, 1H, H-$2_{pyridine}$), 8.55 (d, *J*=7.8 Hz, 1H, Ar-H), 9.79 (s, 1H, H-4 $_{pyridine}$), 10.44 (bs, 1H, OH exchangeable with D_2O). Anal. Calcd for $C_{19}H_{11}N_3O_2$ (313.32): C, 72.84; H, 3.54; N, 13.41%. Found C, 72.56; H, 3.41; N, 13.16%.

2-Amino-7,7-dimethyl-5-oxo-4-(chromon-3-yl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (11). A mixture of chromone derivative **1b** (0.44 g, 2 mmol) and dimedone (0.28 g, 2 mmol) in absolute EtOH (20 mL) containing piperidine was heated under refluxed for 2 h. The pale yellow crystals obtained after cooling were filtered and recrystallized from 2-butanol, yield (0.53 g, 73%), mp 265-266 °C. IR (KBr, cm^{-1}): 3477, 3385 (NH_2), 3067 ($CH_{arom.}$), 2957, 2939, 2874 ($CH_{aliph.}$), 2216 (C≡N), 1689 ($C=O_{chromene}$), 1653 ($C=O_{\gamma\text{-pyrone}}$), 1612 (C=C). ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 0.92 (s, 3H, Me), 1.03 (s, 3H, Me), 2.09 (s, 2H, CH_2), 2.23 (s, 2H, CH_2), 4.13 (s, 1H, H-4_{pyran}), 6.96 (s, 2H, NH_2 exchangeable with D_2O), 7.46 (t, 1H, *J*=7.2 Hz, H-$6_{chromone}$), 7.61 (d, 1H, *J*=7.2 Hz, H-$8_{chromone}$), 7.76 (t, 1H, *J*=7.2 Hz, H-$7_{chromone}$), 8.01 (d, 1H, *J*=7.2 Hz, H-$5_{chromone}$), 8.35 (s, 1H, H-$2_{chromone}$). ^{13}C NMR (DMSO-d_6, δ, 75 MHz): 22.7 (C-4_{pyran}), 26.9 ($2CH_3$), 29.4 (CMe_2), 42.5 (CH_2), 51.1 (CH_2), 68.8 (C-3 $_{pyran}$), 105.7, 114.2 (C-$3_{chromone}$), 116.4 (C≡N), 119.7, 123.8, 125.3, 127.2, 131.6, 145.5, 151.2, 153.4, 157.2, 176.3, 194.9. Mass spectrum (*m/z*, %): 362 (M, 35), 306 (100), 264 (19), 248 (15), 248 (34), 220 (61), 145 (9), 120 (72), 105 (26), 92 (18), 77 (22), 64 (9). Anal. Calcd for $C_{21}H_{18}N_2O_4$ (362.39): C, 69.60; H, 5.01; N, 7.73%. Found: C, 69.41;

H, 4.86; N, 7.65%.

2-Amino-7,7-dimethyl-5-oxo-4-(chromon-3-yl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxamide (12). A mixture of chromone derivative **1c** (0.48 g, 2 mmol) and dimedone (0.28 g, 2 mmol) in absolute EtOH (20 mL) containing piperidine was heated under refluxed for 2 h. The yellow crystals obtained during heating were filtered and recrystallized from AcOH, yield (0.59 g, 78%), mp 280-281 °C. IR (KBr, cm^{-1}): 3409, 3364, 3319, 3244 ($2NH_2$), 3043 ($CH_{arom.}$), 1687 ($C=O_{chromene}$), 1671 ($C=O_{amide}$), 1649 ($C=O_{\gamma\text{-pyrone}}$), 1605 (C=C). ^{1}H NMR (DMSO-*d*$_6$, δ, 300 MHz): 0.96 (s, 3H, Me), 1.05 (s, 3H, Me), 2.02 (s, 2H, CH_2), 2.28 (s, 2H, CH_2), 4.25 (s, 1H, H-4_{pyran}), 7.16 (bs, 2H, NH_2 exchangeable with D_2O), 7.39 (t, 1H, *J*=7.5 Hz, H-$6_{chromone}$), 7.56 (d, 1H, *J*=8.4 Hz, H-$8_{chromone}$), 7.68 (t, 1H, *J*=7.8 Hz, H-$7_{chromone}$), 7.99 (d, *J*=7.5 Hz, 1H, H-$5_{chromone}$), 8.42 (s, 1H, H-$2_{chromone}$), 9.58 (bs, 2H, NH_2 exchangeable with D_2O). ^{13}C NMR (DMSO-*d*$_6$, δ, 75 MHz): 21.4 (C-4_{pyran}), 26.4 ($2CH_3$), 29.5 (*C*Me_2), 42.7 (CH_2), 49.7 (CH_2), 73.5 (C-3_{pyran}), 106.1, 114.5 (C-$3_{chromone}$), 120.4, 124.7, 126.0, 127.6, 130.9, 146.7, 150.4, 153.1, 156.8, 167.3, 176.7, 194.6. Mass spectrum (*m/z*, %): 380 (M, 100), 337 (27), 309 (15), 281 (27), 211 (8), 160 (45), 145 (16), 105 (10), 93 (13), 77 (54), 64 (18). Anal. Calcd for $C_{21}H_{20}N_2O_5$ (380.40): C, 66.31; H, 5.30; N, 7.36%. Found: C, 66.09; H, 5.13; N, 7.30%.

Ethyl 2-amino-7,7-dimethyl-5-oxo-4-(chromon-3-yl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (13). A mixture of chromone derivative **1d** (0.44 g, 2 mmol) and dimedone (0.28 g, 2 mmol) in absolute EtOH (20 mL) containing piperidine was heated under refluxed for 2 h. The white crystals obtained after cooling were filtered and recrystallized from propanol, yield (0.57 g, 70%), mp 224-225 °C. IR (KBr, cm^{-1}): 3382, 3277 (NH_2), 3064 ($CH_{arom.}$), 2961, 2901, 2871 ($CH_{aliph.}$), 1699 ($C=O_{ester}$), 1682 ($C=O_{chromene}$), 1647 ($C=O_{\gamma\text{-pyrone}}$), 1600 (C=C). ^{1}H NMR (DMSO-*d*$_6$, δ, 300 MHz): 0.89 (s, 3H, Me), 1.03 (s, 3H, Me), 1.12 (t, 3H, *J*=6.9 Hz, Me), 2.06 (s, 2H, CH_2), 2.24 (s, 2H, CH_2), 3.99 (q, 2H, *J*=6.9 Hz, CH_2), 4.26 (s, 1H, H-4_{pyran}), 7.42 (t, 1H, *J*=7.2 Hz, H-$6_{chromone}$), 7.59 (d, 1H, *J*=7.5 Hz, H-$8_{chromone}$), 7.67 (s, 2H, NH_2 exchangeable with D_2O), 7.73 (t, 1H, *J*=7.5 Hz, H-$7_{chromone}$), 7.98 (d, 1H, *J*=7.2 Hz, H-$5_{chromone}$), 8.43 (s, 1H, H-$2_{chromone}$). ^{13}C NMR (DMSO-*d*$_6$, δ, 75 MHz): 15.8 (CH_3), 22.2 (C-4_{pyran}), 26.8 ($2CH_3$), 29.2 (*C*Me_2), 42.4 (CH_2), 49.3 (CH_2), 60.5 (OCH_2), 74.1 (C-3_{pyran}), 105.6, 114.3 (C-$3_{chromone}$), 120.7, 124.5, 126.3, 127.2, 131.0, 146.4, 150.9, 153.6, 157.4, 171.3, 175.8, 193.9. Mass spectrum (*m/z*, %): 408 (M, 68), 382 (33), 337 (19), 267 (31), 239 (20), 160 (28), 146 (7), 121 (61), 93 (35), 77 (20), 64 (16). Anal. Calcd for $C_{23}H_{23}NO_6$ (409.44): C, 67.47; H, 5.66; N, 3.42%. Found: C, 67.21; H, 5.61; N, 3.19%.

Ethyl 2-hydroxy-7,7-dimethyl-5-oxo-4-(chromon-3-yl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (14). A mixture of chromone derivative **2a** (0.64 g, 2 mmol) and dimedone (0.28 g, 2 mmol) in absolute EtOH (20 mL) containing piperidine was heated under refluxed for 2 h. The white crystals obtained after cooling were filtered and recrystallized from AcOH/H_2O, yield (0.51 g, 66%), mp 209-210 °C. IR (KBr, cm^{-1}): 3428 (OH), 3039 ($CH_{arom.}$), 2985, 2925, 2893 ($CH_{aliph.}$), 1708 ($C=O_{ester}$),

1685 ($C=O_{chromene}$), 1654 ($C=O_{\gamma\text{-pyrone}}$), 1603 (C=C). ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 0.90 (s, 3H, Me), 1.04 (s, 3H, Me), 1.20 (t, 3H, *J*=6.9 Hz, Me), 2.03 (s, 2H, CH_2), 2.21 (s, 2H, CH_2), 4.02 (q, 2H, *J*=6.9 Hz, CH_2), 4.23 (s, 1H, H-4_{pyran}), 7.46 (t, 1H, *J*=7.2 Hz, H-$6_{chromone}$), 7.57 (d, 1H, *J*=7.2 Hz, H-$8_{chromone}$), 7.82 (t, 1H, *J*=7.2 Hz, H-$7_{chromone}$), 8.09 (d, 1H, *J*=7.5 Hz, H-$5_{chromone}$), 8.39 (s, 1H, H-$2_{chromone}$), 10.58 (s, 1H, OH exchangeable with D_2O). ^{13}C NMR (DMSO-d_6, δ, 75 MHz): 15.3 (CH_3), 22.4 (C-4_{pyran}), 26.9 ($2CH_3$), 29.1 (CMe_2), 42.1 (CH_2), 49.2 (CH_2), 61.2 (OCH_2), 75.0 (C-3_{pyran}), 105.3, 115.7 (C-$3_{chromone}$), 120.3, 123.8, 125.6, 127.7, 130.8, 145.9, 150.5, 153.0, 156.8, 159.1, 165.3, 175.5. Mass spectrum (*m/z*, %): 410 (M, 16), 382 (19), 354 (22), 325 (46), 282 (18), 249 (21), 233 (9), 219 (26), 183 (28), 145 (18), 116 (22), 93 (24), 77 (100) and 64 (11). Anal. Calcd for $C_{23}H_{22}O_7$ (410.43): C, 67.31; H, 5.40%. Found: C, 67.23; H, 5.38%.

3,4,6,7-Tetrahydro-3,3,6,6-tetramethyl-9-(chromon-3-yl)-2*H*-xanthene-1,8(5*H*,9*H*)-1,8-dione (15). A mixture of chromone derivative **2b** or **2c** (2 mmol) and dimedone (0.28 g, 2 mmol) in absolute EtOH (20 mL) containing piperidine was heated under refluxed for 2 h. The white crystals obtained during heating were filtered and recrystallized from AcOH (0.52 g, 62%), mp 289-290 °C ((lit. mp 287-288 °C).[27] IR (KBr, cm^{-1}): 3066 ($CH_{arom.}$), 2952, 2876 ($CH_{aliph.}$), 1664 ($C=O_{xanthene}$), 1636 ($C=O_{\gamma\text{-pyrone}}$), 1570 (C=C). ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 0.73 (s, 6H, 2Me), 0.82 (s, 6H, 2Me), 2.13 (s, 4H, $2CH_2$), 2.38 (s, 4H, $2CH_2$), 4.55 (s 1H, H-4_{pyran}), 7.13-7.67 (m, 3H, Ar-H), 7.97 (d, 1H, *J*=8.1 Hz, H-$5_{chromone}$), 8.35 (s, 1H, H-$2_{chromone}$), Anal. Calcd for $C_{26}H_{26}O_5$ (418.49): C, 74.62; H, 6.26%. Found: C, 74.55; H, 6.21%.

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