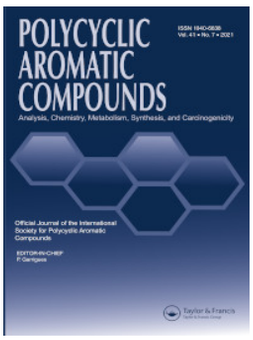

Polycyclic Aromatic Compounds

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The Chemical Behavior of (2*E*)-3-(4,9-Dimethoxy-5-Oxo-5*H*-Furo[3,2-*g*] Chromen-6-yl)Acrylonitrile Towards Some Carbon Nucleophiles

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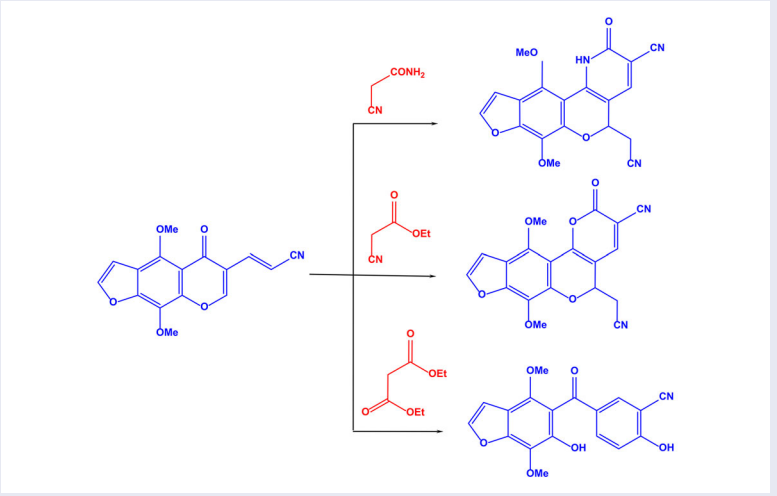
ABSTRACT

Some novel substituted benzofurans and annulated furochromenes were obtained through the treatment of the novel (2*E*)-3-(4,9-dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromen-6-yl)acrylonitrile (2) by some active carbon nucleophiles such as active methylene ketones and methylene nitriles. Thus, the reaction of acrylonitrile **2** with acetylacetone, ethyl acetoacetate, diethylmalonate, and acetoacetanilide in ethanol containing piperidine produced efficiently the corresponding polyfunctionalized benzonitrile derivatives **3**–**5** and furochromeno-pyridine **6**, respectively. Also, treatment of acrylonitrile **2** with some methylene nitriles such as malononitrile, ethyl cyanoacetate, and malononitrile dimer afforded the annulated furochromene derivatives **7**–**9**. Furthermore, the pyrido[1,2-*a*] benzimidazole system **10** was furnished *via* reaction of acrylonitrile **2** with 2-(1 *H*-benzimidazol-2-yl)acetonitrile. These reactions took place through *Michael* addition, retro-*Michael*, and γ-pyrone ring opening followed by different types of recyclization. The chemical structures of the novel products were established on the basis of their spectral data and elemental analysis.



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Benzofuran; benzonitrile; carbon nucleophiles; 6-formylkhellin; furo[32-g] chromen-6-ylacrylonitrile; recyclization

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Introduction

"Khella" is a widespread flowering plant native to Europe, Asia, and North Africa.[1] The khella seeds have many therapeutic properties in traditional medicine for respiratory conditions including bronchitis, asthma, and cough.[2–4] The seeds of this plant contain a furochromone khellin as a major constituent, which is a vasodialator and antispasmodic agent.[5] Also, Khellin was found to be effective in reducing plasma amylase and lipase levels, reduced cerulean-induced oxidative stress.[6] Other pharmacological activities of khellin and its derivatives are known such as melanin inhibition,[7] anti-inflammatory,[8] antimicrobial,[9] anti-HIV,[10] anticancer,[11,12] and cancer chemopreventive activity.[13,14] Considering the above facts and our research program on the chemistry of 6-formylkhellin and chromone compounds towards a diversity of nucleophilic reagents,[15,16] we herein report the construction of some novel substituted benzofurans and annulated furochromenes which are not reported in literature by using Sci-finder website. The methodology depended on the treatment of the novel (2*E*)-3-(4,9-dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromen-6-yl)acrylonitrile (**2**) with a variety of carbon nucleophilic reagents.

Experimental

Melting points were determined on a digital Stuart SMP3 apparatus. Infrared spectra were measured on Fourier transform infrared 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 dimethyl sulfoxide (DMSO)-d_6 as a solvent and tetramethylsilane (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 Perkin-Elmer 2400II at the Chemical War department, Ministry of Defense, Egypt. The purity of the synthesized compounds was checked by thin layer chromatography and elemental microanalysis. 6-Formylkhellin (4,9-dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromene-6-carboxaldehyde) (**1**) was prepared according to the published method in the literature.[17]

Synthesis of (2E)-3-(4,9-dimethoxy-5-oxo-5H-furo[3,2-g]chromen-6-yl)acrylonitrile (2)

A mixture of 6-formylkhellin **1** (2.74 g, 10 mmol) and cyanoacetic acid (0.85 g, 10 mmol) in pyridine (20 mL) was heated under reflux for 1 h. After cooling, the formed yellow crystals were filtered off and crystallized from ethanol (EtOH) to give compound **2** as yellow crystals in 78% yield (2.31 g), mp 234–235 °C. IR (KBr, cm^{-1}): 3125 (CH_{furan}), 3052 (CH_{arom}), 2945, 2923 (CH_{aliph}), 2219 (C≡N), 1647 ($C{=}O_{pyrone}$), 1604 (C=C). ^{1}H-NMR (DMSO-d_6, δ): 3.84 (s, 3 H, OCH_3), 3.98 (s, 3 H, OCH_3), 6.95 (d, 1 H, $J = 16.8$ Hz, $H_{olefinic}$), 7.20 (d, 1 H, $J = 1.8$ Hz, H–3_{furan}), 7.37 (d, 1 H, $J = 16.8$ Hz, $H_{olefinic}$), 7.82 (d, 1 H, $J = 1.8$ Hz, H–2_{furan}), 8.66 (s, 1 H, H–7). ^{13}C-NMR (DMSO-d_6, δ): 57.8 (OCH_3), 58.4 (OCH_3), 98.3, 105.4, 112.1, 113.2, 116.5 (C≡N), 118.9, 123.7, 144.2, 148.4, 150.2, 151.6, 154.5, 156.3, 175.2 ($C{=}O_{pyrone}$). MS (*m/z*, I %): 297 (M^+, 63%), 238 (54), 220 (100), 190 (18), 159 (9), 133 (66), 77 (41), 65 (12). Anal. Calcd. for $C_{16}H_{11}NO_5$ (297.27); C, 64.65%; H, 3.73%; N, 4.71%. Found: C, 64.50%; H, 3.65%; N, 4.48%.

Synthesis of 3-acetyl-5-[(6-hydroxy-4,7-dimethoxy-1-benzofuran-5-yl)carbonyl]-2-methylbenzonitrile (3)

A mixture of compound **2** (0.60 g, 2 mmol) and acetylacetone (0.20 g, 2 mmol) in absolute EtOH (20 mL) containing piperidine (0.1 mL) was heated under reflux for 2 h. The isolated yellow crystals during heating were filtered off, air dried, and crystallized from EtOH to give compound **3** as yellow crystals in 58% yield (0.44 g), mp 289–290 °C. IR (KBr, cm^{-1}): 3438 (OH),

3120 (CH_{furan}), 3036 (CH_{arom}), 2944, 2920 (CH_{aliph}), 2231 (C≡N), 1698 ($C{=}O_{acetyl}$), 1638 ($C{=}O_{benzoyl}$), 1601 (C=C). ^{1}H-NMR (DMSO-d_6, δ): 2.39 (s, 3 H, CH_3), 2.44 (s, 3 H, CH_3), 3.86 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 7.23 (d, 1 H, $J = 2.4$ Hz, H–3_{furan}), 7.36 (s, 1 H, Ar–H), 7.88 (d, 1 H, $J = 2.4$ Hz, H–2_{furan}), 8.04 (s, 1 H, Ar–H), 10.36 (br, 1 H, OH exchangeable with D_2O). ^{13}C-NMR (DMSO-d_6, δ): 16.8 (CH_3), 27.3 (CH_3), 59.1 (OCH_3), 61.4 (OCH_3), 105.1, 107.3, 111.5, 113.2, 116.3 (C≡N), 122.9, 129.2, 133.6, 135.7, 136.1, 138.7, 144.5, 146.8, 152.0, 160.2 (C–OH), 193.7 ($C{=}O_{benzoyl}$), 196.2 ($C{=}O_{acetyl}$). MS (*m/z*, I %): 379 (M^+, 23%), 349 (100), 333 (52), 302 (13), 276 (34), 144 (18), 101 (50), 77 (12), 64 (9). Anal. Calcd. for $C_{21}H_{17}NO_6$ (379.37); C, 66.49%; H, 4.52%; N, 3.69%. Found: C, 66.14%; H, 4.31%; N, 3.32%.

Synthesis of 5-[(6-hydroxy-4,7-dimethoxy-1-benzofuran-5-yl)carbonyl]-2-methyl-benzonitrile (4)

A mixture of compound **2** (0.60 g, 2 mmol) and ethyl acetoacetate (0.26 g, 2 mmol) in absolute EtOH (20 mL) containing piperidine (0.1 mL) was heated under reflux for 2 h. The deposited yellow crystals after cooling were filtered off, air dried, and crystallized from methanol (MeOH) to give compound **4** as yellow crystals in 70% yield (0.47 g), mp 211–212 °C. IR (KBr, cm^{-1}): 3438 (OH), 3129 (CH_{furan}), 3044 (CH_{arom}), 2956, 2923 (CH_{aliph}), 2226 (C≡N), 1638 ($C{=}O_{benzoyl}$), 1599 (C=C). ^{1}H-NMR (DMSO-d_6, δ): 2.43 (s, 3 H, CH_3), 3.88 (s, 3 H, OCH_3), 3.97 (s, 3 H, OCH_3), 7.15 (d, 1 H, $J = 2.1$ Hz, H–3_{furan}), 7.34 (d, 1 H, $J = 8.1$ Hz, Ar–H), 7.49 (d, 1 H, $J = 8.1$ Hz, Ar–H), 7.76 (s, 1 H, Ar–H), 7.90 (d, 1 H, $J = 2.1$ Hz, H–2_{furan}), 10.08 (br, 1 H, OH exchangeable with D_2O). ^{13}C-NMR (DMSO-d_6, δ): 18.7 (CH_3), 57.9 (OCH_3), 58.6 (OCH_3), 102.8, 109.5, 113.3, 116.2 (C≡N), 121.7, 127.0, 131.3, 132.9, 135.0, 139.5, 144.1, 146.0, 147.6, 151.3, 160.6 (C–OH), 194.0 ($C{=}O_{benzoyl}$). MS (*m/z*, I %): 337 (M^+, 100%), 307 (74), 281 (13), 266 (9), 221 (41), 159 (11), 116 (30), 102 (19), 77 (54), 64 (7). Anal. Calcd for $C_{19}H_{15}NO_5$ (337.34); C, 67.65%; H, 4.48%; N, 4.15%. Found: C, 67.35%; H, 4.21%; N, 3.90%.

Synthesis of 2-hydroxy-5-[(6-hydroxy-4,7-dimethoxy-1-benzofuran-5-yl)carbonyl] benzonitrile (5)

A mixture of compound **2** (0.60 g, 2 mmol) and diethyl malonate (0.32 g, 2 mmol) in absolute EtOH (20 mL) containing piperidine (0.1 mL) was heated under reflux for 2 h. The deposited yellow crystals during heating were filtered off, air dried and crystallized from EtOH to give compound **5** as pale yellow crystals in 55% yield (0.37 g), mp 260–261 °C. IR (KBr, cm^{-1}): 3424 (OH), 3141 (CH_{furan}), 3039 (CH_{arom}), 2943, 2918 (CH_{aliph}), 2235 (C≡N), 1634 ($C{=}O_{benzoyl}$), 1602 (C=C). ^{1}H-NMR (DMSO-d_6, δ): 3.88 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 6.86 (d, 1 H, $J = 7.8$ Hz, Ar–H), 7.13 (s, 1 H, Ar–H), 7.14 (d, 1 H, $J = 2.1$ Hz, H–3_{furan}), 7.31 (d, 1 H, $J = 7.8$ Hz, Ar–H), 7.90 (d, 1 H, $J = 2.1$ Hz, H–2_{furan}), 10.18 (br, 1 H, OH exchangeable with D_2O), 10.81 (br, 1 H, OH exchangeable with D_2O). ^{13}C-NMR (DMSO-d_6, δ): 58.3 (OCH_3), 59.8 (OCH_3), 103.5, 106.2, 108.6, 111.4, 116.1 (C≡N), 121.4, 129.1, 131.8, 133.6, 143.7, 146.2, 149.8, 160.4 (C–OH), 162.1 (C–OH), 193.5 ($C{=}O_{benzoyl}$). MS (*m/z*, I %): 339 (M^+, 100%), 323 (21), 293 (9), 191 (28), 161 (7), 135 (36), 118 (63), 91 (12), 77 (22). Anal. Calcd. for $C_{18}H_{13}NO_6$ (339.31); C, 63.72%; H, 3.86%; N, 4.13%. Found: C, 63.62%; H, 3.65%; N, 4.01%.

Synthesis of 3-acetyl-5-cyanomethyl-7,11-dimethoxy-2-oxo-1-phenyl-1,5-dihydro-2H-furo[3′,2′:6,7]chromeno[4,3-b]pyridine (6)

A mixture of compound **2** (0.60 g, 3 mmol) and acetoacetanilide (0.17 g, 2 mmol) in absolute EtOH (20 mL) containing piperidine (0.1 mL) was heated under reflux for 2 h. The deposited

yellow crystals during heating were filtered off, air dried, and crystallized from dimethylformamide (DMF)/EtOH to give compound **6** as yellow crystals in 59% yield (0.54 g), mp 299–300 °C. IR (KBr, cm^{-1}): 3126 (CH_{furan}), 3029 (CH_{arom}), 2967, 2925 (CH_{aliph}), 2253 (C≡N), 1682 ($C{=}O_{acetyl}$), 1656 ($C{=}O_{pyridone}$), 1593 (C=C). ^{1}H-NMR (DMSO-d_6, δ): 2.46 (s, 3 H, CH_3), 3.09 (d, 2 H, $J = 6.9$ Hz, CH_2CN), 3.83 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 5.60 (t, 1 H, $J = 6.9$ Hz, H–5), 7.18 (d, 1 H, $J = 2.1$ Hz, H–3_{furan}), 7.36-7.58 (m, 5 H, Ar–H), 7.82 (d, 1 H, $J = 2.1$ Hz, H–2_{furan}), 8.37 (s, 1 H, H–$4_{pyridine}$). ^{13}C-NMR (DMSO-d_6, δ): 22.8 (CH_2), 28.1 (CH_3), 55.3 (MeO), 56.2 (MeO), 75.2 (CH), 101.5, 104.9, 109.3, 111.0, 117.2 (C≡N), 127.8, 128.3, 128.6, 131.7, 133.7, 134.6, 138.3, 138.9, 143.2, 145.4, 145.6, 147.0, 162.8 (C=O), 184.2 ($C{=}O_{acetyl}$). MS (*m/z*, I %): 456 (M^+, 6%), 416 (M^+–CH_2CN, 100), 309 (16), 265 (25), 237 (42), 159 (14), 133 (20), 77 (30), 64 (13). Anal. Calcd. for $C_{26}H_{20}N_2O_6$ (456.46); C, 68.42%; H, 4.42%; N, 6.14%. Found: C, 68.11%; H, 4.32%; N, 5.98%.

Synthesis of 5-cyanomethyl-7,11-dimethoxy-2-oxo-2H,5H-furo[3′,2′:6,7]chromeno [4,3-b]pyridine-3-carbonitrile (7)

A mixture of compound **2** (0.60 g, 2 mmol) and malononitrile (0.13 g, 2 mmol) or cyanoacetamide (0.17 g, 2 mmol) in absolute EtOH (15 mL) containing piperidine (0.1 mL) was heated under reflux for 2 h. The deposited yellow crystals during heating were filtered off, air dried, and crystallized from MeOH to give compound **7** as yellow crystals in 67–70% yield (0.49–0.51 g), mp > 300 °C. IR (KBr, cm^{-1}): 3239 (NH), 3117 (CH_{furan}), 3061 (CH_{arom}), 2957, 2921 (CH_{aliph}), 2255, 2222 (2 C≡N), 1653 ($C{=}O_{pyridone}$), 1581 (C=C). ^{1}H-NMR (DMSO-d_6, δ): 3.21 (d, 2 H, $J = 6.9$ Hz, CH_2CN), 3.87 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 5.52 (t, 1 H, $J = 6.9$ Hz, H–5), 7.23 (d, 1 H, $J = 2.1$ Hz, H–3_{furan}), 7.86 (d, 1 H, $J = 2.1$ Hz, H–2_{furan}), 8.24 (s, 1 H, H–4), 12.52 (br, 1 H, NH exchangeable with D_2O). ^{13}C-NMR (DMSO-d_6, δ): 23.1 (CH_2), 58.6 (OCH_3), 60.9 (OCH_3), 71.8 (C–5), 100.3, 104.7, 108.4, 113.1, 115.9 (C≡N), 116.8 (C≡N), 120.9, 125.2, 134.3, 139.6, 142.5, 147.8, 148.1, 160.2, 164.3 (C=O). MS (*m/z*, I %): 363 (M^+, 16%), 323 (M^+–CH_2CN; 100), 293 (39), 267 (12), 239 (22), 208 (37), 104 (7), 77 (39), 64 (11). Anal. Calcd. for $C_{19}H_{13}N_3O_5$ (363.32); C, 62.81%; H, 3.61%; N, 11.57%. Found: C, 62.65%; H, 3.40%; N, 11.33%.

Synthesis of 5-cyanomethyl-7,11-dimethoxy-2-oxo-2H,5H-furo[3,2-g]pyrano[3,2-c] chromene-3-carbonitrile (8)

A mixture of compound **2** (0.60 g, 2 mmol) and ethyl cyanoacetate (0.15 g, 2 mmol) in absolute EtOH (15 mL) containing piperidine (0.1 mL) was heated under reflux for 2 h. The deposited yellow crystals after cooling were filtered off, air dried, and crystallized from EtOH to give compound **8** as yellow crystals in 64% yield (0.47 g), mp 218–219 °C. IR (KBr, cm^{-1}): 3111 (CH_{furan}), 3041 (CH_{arom}), 2950, 2928 (CH_{aliph}), 2251, 2224 (2 C≡N), 1742 (C=O), 1575 (C=C). ^{1}H-NMR (DMSO-d_6, δ): 3.24 (d, 2 H, $J = 6.3$ Hz, CH_2CN), 3.84 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 5.50 (t, 1 H, $J = 6.3$ Hz, H–5), 7.28 (d, 1 H, $J = 2.1$ Hz, H–3_{furan}), 7.88 (d, 1 H, $J = 2.1$ Hz, H–2_{furan}), 8.17 (s, 1 H, H–4). ^{13}C-NMR (DMSO-d_6, δ): 23.6 (CH_2), 58.7 (OCH_3), 60.4 (OCH_3), 71.4 (C–5), 97.4, 102.8, 109.5, 112.4, 116.2 (C≡N), 116.8 (C≡N), 122.9, 128.7, 136.6, 142.7, 145.2, 147.1, 162.3, 164.7 (C=O). MS (*m/z*, I %): 364 (M^+, 13%), 324 (M^+–CH_2CN; 100), 290 (21), 262 (46), 232 (14), 190 (17), 159 (32), 132 (62 77 (10), 64 (26). Anal. Calcd. for $C_{19}H_{12}N_2O_6$ (364.31); C, 62.64%; H, 3.32%; N, 7.69%. Found: C, 62.44%; H, 3.15%; N, 7.55%.

Synthesis of {3-cyano-5-(cyanomethyl)-7,11-dimethoxy-1,5-dihydro-2H-furo[3′,2′:6,7] chromeno[4,3-b]pyridin-2-ylidene}propanedinitrile (9)

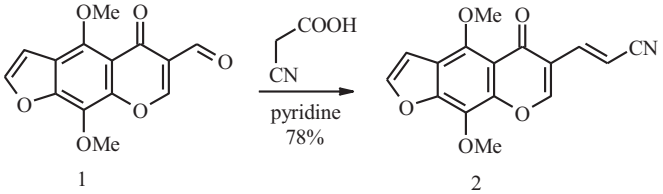
A mixture of compound **2** (0.60 g, 2 mmol) and 2-aminoprop-1-ene-1,1,3-tricarbonitrile (0.14 g, 2 mmol) in absolute EtOH (15 mL) containing piperidine (0.1 mL) was heated under reflux for 2 h. The deposited orange crystals during heating were filtered off, air dried, and crystallized from EtOH to give compound **9** as yellow crystals in 63% yield (0.52 g), mp 241–242 °C. IR (KBr, cm^{-1}): 3262 (NH), 3119 (CH_{furan}), 3029 (CH_{arom}), 2959, 2931 (CH_{aliph}), 2256, 2203, 2197 (4 C≡N), 1602 (C=C). ^{1}H-NMR (DMSO-d_6, δ): 3.27 (d, 2 H, J = 6.6 Hz, CH_2CN), 3.80 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 5.43 (t, 1 H, J = 6.6 Hz, H–5), 7.19 (d, 1 H, J = 2.1 Hz, H–3_{furan}), 7.83 (d, 1 H, J = 2.1 Hz, H–2_{furan}), 8.04 (s, 1 H, H–4), 12.36 (br, 1 H, NH exchangeable with D_2O). ^{13}C-NMR (DMSO-d_6, δ): 22.9 (CH_2), 44.8, 59.6 (OCH_3), 61.7 (OCH_3), 71.1 (C–5), 99.3, 103.2, 106.7, 109.2, 112.4, 115.4 (C≡N), 116.2 (C≡N), 116.4 (C≡N), 116.7 (C≡N), 122.3, 128.1, 137.4, 145.1, 147.4, 152.0, 153.8, 160.5. MS (*m/z*, I %): 411 (M^+, 12%), 371 (M^+–CH_2CN; 100), 341 (32), 311 (62), 235 (39), 205 (8), 77 (26), 64 (35). Anal. Calcd. for $C_{22}H_{13}N_5O_4$ (411.37); C, 64.23%; H, 3.19%; N, 17.02%. Found: C, 64.06%; H, 3.00%; N, 16.75%.

Synthesis of 2-[(E)-2-cyanoethenyl]-1-(6-hydroxy-4,7-dimethoxy-1-benzofuran-5-yl) pyrido[1,2-a]benzimidazole-4-carbonitrile (10)

A mixture of compound **2** (0.60 g, 2 mmol) and 1 *H*-benzimidazol-2-ylacetonitrile (0.32 g, 2 mmol) in absolute EtOH (20 mL) containing piperidine (0.1 mL) was heated under reflux for 15 min. The isolated yellow crystals during heating were filtered off, air dried, and crystallized from DMF to give compound **10** as canary yellow crystals in 62% yield (0.54 g), mp > 300 °C. IR (KBr, cm^{-1}): 3440 (OH), 3124 (CH_{furan}), 3045 (CH_{arom}), 2944, 2915 (CH_{aliph}), 2246, 2216 (2 C≡N), 1618 (C=N), 1589 (C=C). ^{1}H-NMR (DMSO-d_6, δ): 3.82 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 6.36 (d, 1 H, J = 8.1 Hz, Ar–H), 6.64 (d, 1 H, J = 16.4 Hz, $H_{olefinic}$), 7.03 (d, 1 H, J = 16.4 Hz, $H_{olefinic}$), 7.20 (d, 1 H, J = 2.4 Hz, H–3_{furan}), 7.31–7.54 (m, 3 H, Ar–H), 7.86 (d, 1 H, J = 2.4 Hz, H–2_{furan}), 8.56 (s, 1 H, H–3), 10.26 (br, 1 H, OH exchangeable with D_2O). ^{13}C-NMR (DMSO-d_6, δ): 55.6 (OCH_3), 58.8 (OCH_3), 105.2, 105.7, 106.3, 108.9, 111.1, 112.0, 116.3, 116.9, 120.6, 122.9, 123.4, 123.8, 130.6, 134.8, 137.5, 140.9, 143.5, 145.3, 145.9, 146.2, 147.8, 151.9, 161.3. MS (*m/z*, I %): 436 (M^+, 100%), 405 (72), 376 (45), 360 (9), 244 (15), 192 (30), 77 (26), 64 (27). Anal. Calcd. for $C_{25}H_{16}N_4O_4$ (436.42); C, 68.80%; H, 3.70%; N, 12.84%. Found: C, 68.52%; H, 3.46%; N, 12.70%.

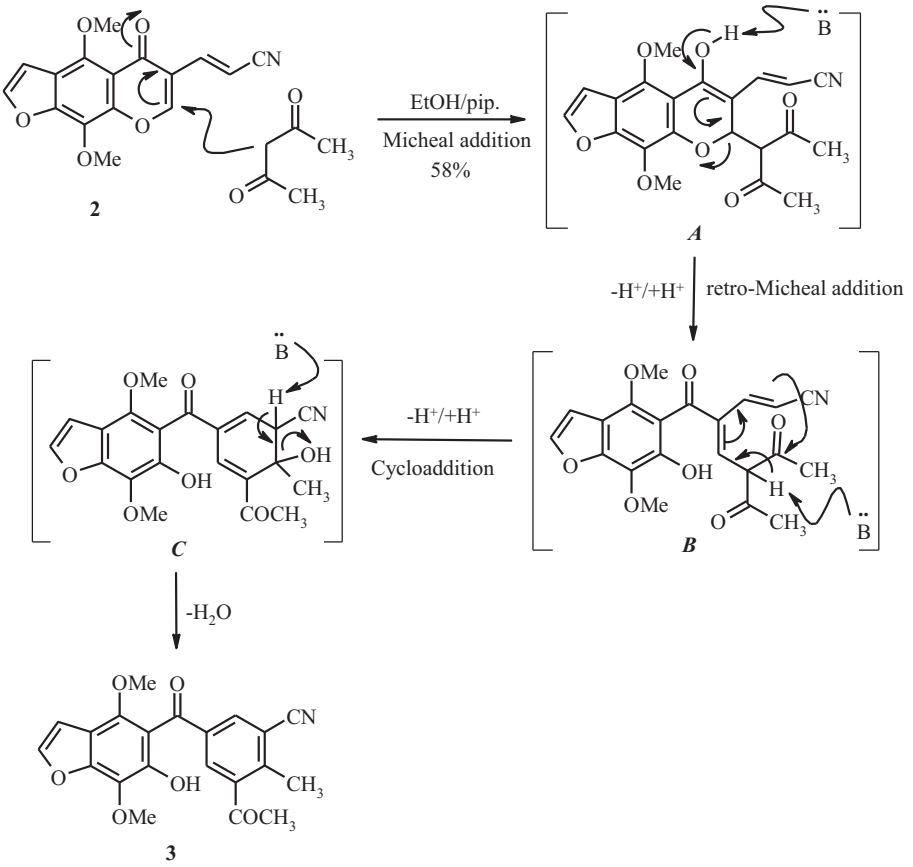
Results and discussion

The novel starting material (2*E*)-3-(4,9-dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromen-6-yl)acrylonitrile (**2**) was prepared *via* condensation of 6-formylkhellin (4,9-dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromene-6-carboxaldehyde) (**1**)[17] with cyanoacetic acid in boiling pyridine (Scheme 1).[18] The IR spectrum of compound **2** displayed the characteristic absorption bands for C≡N and $C{=}O_{pyrone}$



1 2

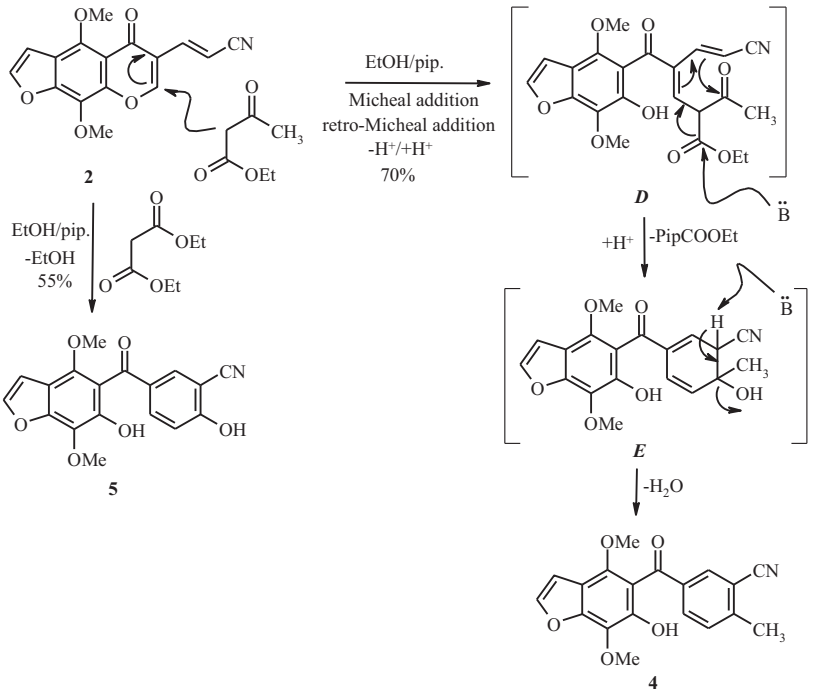
Scheme 1. Formation of 3-(furo[3,2-*g*]chromon-6-yl)acrylonitrile **2**.



Scheme 2. Reaction of acrylonitrile **2** with acetylacetone.

at 2219 and 1647 cm^{-1}, respectively. Its ^{1}H-NMR spectrum exhibited two characteristic doublets at δ 6.95 and 7.37 ppm with high coupling constant ($J = 16.8$ Hz) assigned to the vinyl protons, indicating *trans* configuration around the double bond.[19] Also, there were two doublets appeared at δ 7.20 and 7.82 ppm, which were assigned to H–3_{furan} and H–2_{furan}, respectively.[20] The mass spectrum of compound **2** revealed its molecular ion peak at *m/z* 297 and its base peak at *m/z* 220.

The precursor material **2** has several electron-deficient centers which may be of interest in *domino* reactions with active methylene ketones and nitriles.[21] Thus, treatment of the acrylonitrile derivative **2** with acetylacetone in boiling EtOH in the presence of a catalytic amount of piperidine gave 3-acetyl-5-[(6-hydroxy-4,7-dimethoxy-1-benzofuran-5-yl) carbonyl]-2-methylbenzonitrile (**3**) (Scheme 2). The reaction took place through a *tandem* process involving *Michael* addition at the C–2 position forming the intermediate **A** that underwent pyrone ring opening to give the intermediate **B**. The latter intermediate was cyclized through the exocyclic diene group generating intermediate **C**. Removal of water molecule from the intermediate **C** afforded the isolated product **3** (Scheme 2).[22] The IR spectrum of compound **3** exhibited characteristic absorption bands at 2231 (C≡N), 1698 (C=O_{acetyl}), and 1638 cm^{-1} (C=$O_{benzoyl}$).[23] Its ^{1}H-NMR spectrum showed specific signals attributed to two methyl groups at δ 2.39 and 2.44 ppm, two aromatic singlets at δ 7.36 and 8.04 ppm. In addition, two doublets were observed at δ 7.23 and 7.88 ppm ($J = 2.4$ Hz) assigned to the furan ring protons. Furthermore, its ^{13}C-NMR spectrum revealed some specific signals at δ

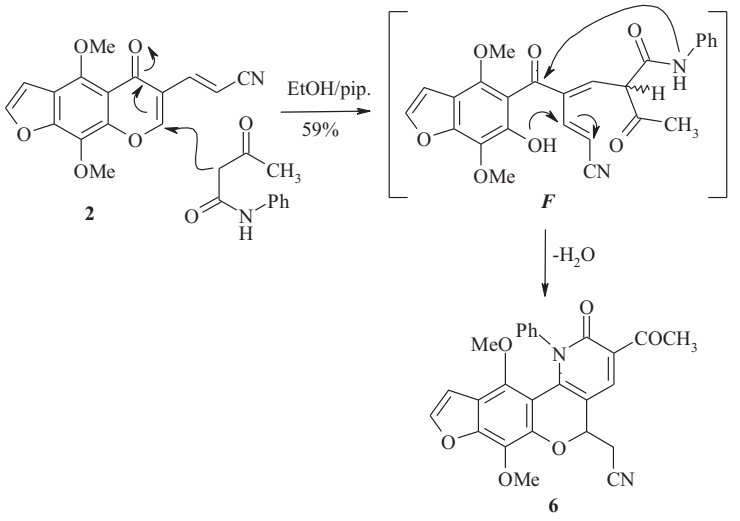


Scheme 3. Formation of benzonitrile derivatives **4** and **5**.

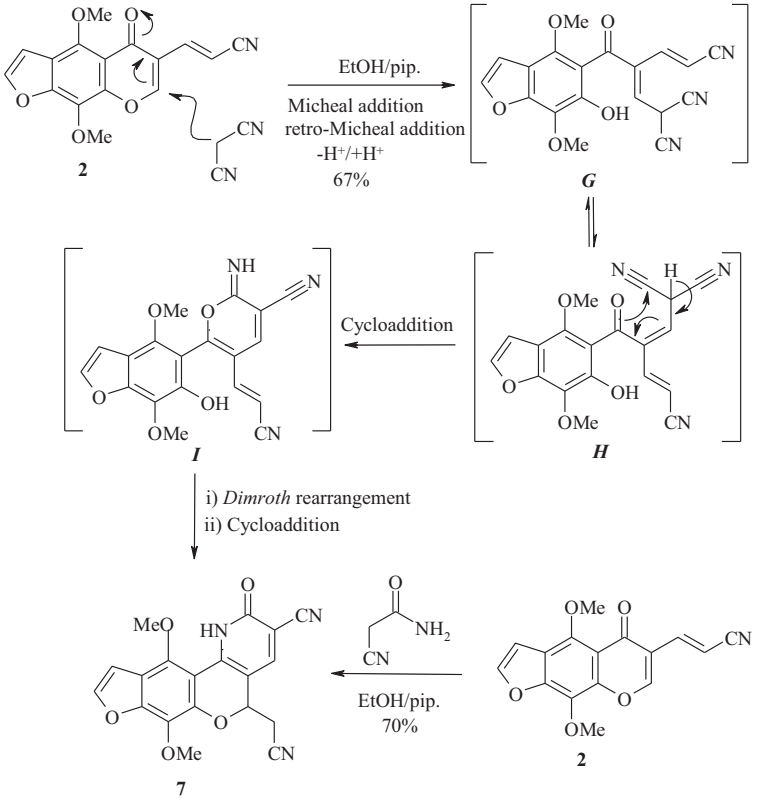
116.3 (C≡N), 160.2 (C–OH), 193.7 ($C{=}O_{benzoyl}$), and 196.2 ($C{=}O_{acetyl}$). The mass spectrum of compound **3** recorded its molecular ion peak at *m/z* 379, which confirmed the proposed structure.

Similarly, reaction of compound **2** with ethyl acetoacetate and diethyl malonate under the same previous basic reaction conditions yielded 5-[(6-hydroxy-4,7-dimethoxy-1-benzofuran-5-yl)carbonyl]-2-methylbenzonitrile (**4**) and 2-hydroxy-5-[(6-hydroxy-4,7-dimethoxy-1-benzofuran-5-yl)carbonyl]benzonitrile (**5**), respectively (Scheme 3). These reactions occurred as similar to formation of compound **3** (Scheme 3). The chemical structure of products **4** and **5** was established from their mass spectra, which revealed their molecular ion peaks as the base peaks at *m/z* 337 and 339, respectively. The ^{1}H-NMR spectrum of compound **4** showed the expected aromatic signals, besides the characteristic methyl protons at δ 2.43 ppm as well as a D_2O-exchangeable signal at δ 10.08 ppm due to the OH proton. Also, the ^{1}H-NMR spectrum of compound **5** showed the specific two OH protons at δ 10.18 and 10.81 ppm.[24] Moreover, their ^{13}C-NMR spectra displayed the characteristic carbon atoms of benzoyl groups at 194 and 193.5 ppm, respectively.[25]

On contrary to the above behavior, reaction of acrylonitrile **2** with acetoacetanilide in boiling EtOH containing a catalytic amount of piperidine afforded 3-acetyl-5-cyanomethyl-7,11-dimethoxy-2-oxo-1-phenyl-1,5-dihydro-2*H*-furo[3′,2′:6,7] chromeno[4,3-*b*]pyridine (**6**) (Scheme 4). The reaction was occurred *through* the non-isolable intermediate **F**, which underwent cyclocondensation then cycloaddition of the phenolic OH group onto the *olefinic* bond (Scheme 4).[26] The ^{1}H-NMR spectrum of the product **6** displayed characteristic doublet and triplet signals at δ 3.09 and 5.60 ppm assigned to CH_2CN and H–5, respectively. In addition, two characteristic singlets were observed at δ 2.46 and 8.37 ppm that attributed to CH_3 and $H{-}4_{pyridine}$, respectively. Moreover, its ^{13}C-NMR displayed the specific carbon atoms CH_2, $CH_{3acetyl}$, and C–5 at δ 22.8, 28.1, and 75.2 ppm, respectively.[27] The molecular ion peak of compound **6** was displayed at *m/z* 456 in its mass spectrum. Furthermore, its base peak was recorded at *m/z* 411 assigned to the molecular ion after loss of a CH_2CN fragment.

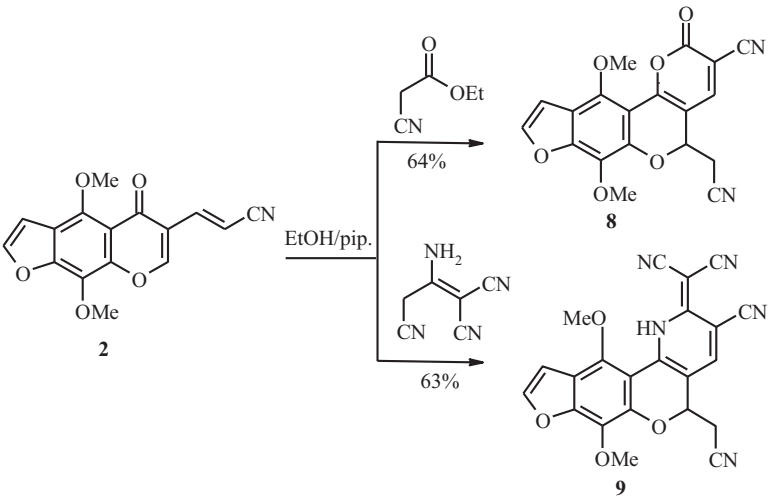


Scheme 4. Reaction of acrylonitrile **2** with acetoacetanilide

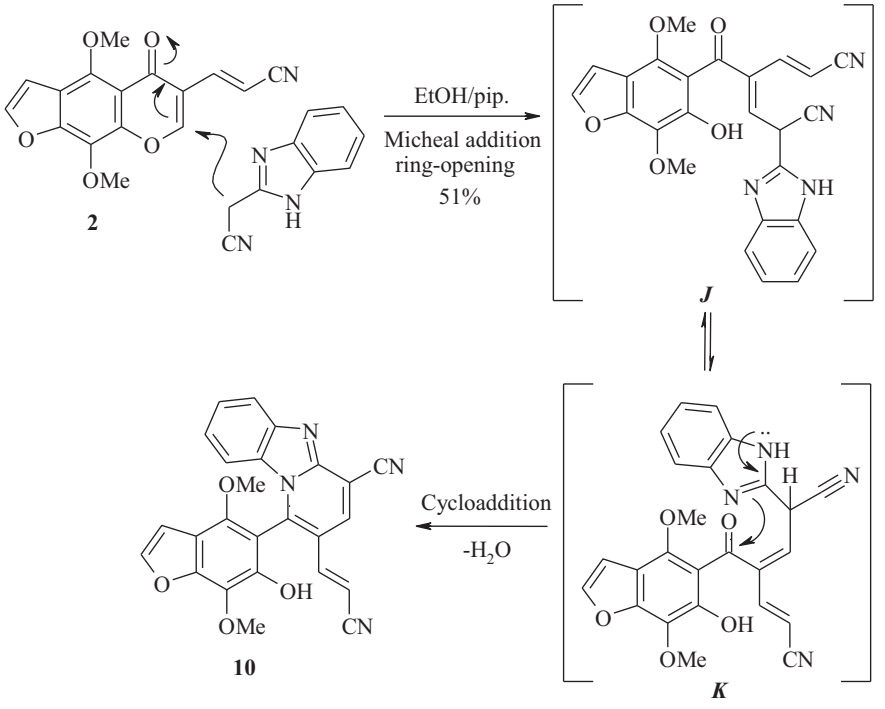


Scheme 5. Reaction of acrylonitrile **1** with malononitrile and cyanoacetamide.

Next, the chemical reactivity of compound **2** toward some active methylene nitriles was studied. Thus, addition of malononitrile to ethanolic solution of compound **2** containing a catalytic amount of piperidine led to the formation of 5-cyanomethyl-7,11-dimethoxy-2-oxo-2*H*,5*H*-furo[3-′,2′:6,7]chromeno[4,3-*b*]pyridine-3-carbonitrile (**7**) (Scheme 5).[17] The reaction took place *via*



Scheme 6. Reaction of acrylonitrile **2** with ethyl cyanoacetate and malononitrile dimer.



Scheme 7. Formation of pyrido[1,2-*a*]benzimidazole derivative **10**.

Michael addition of malononitrile at the C–2 position of the pyrone ring (the more electron deficient center) followed by pyrone ring opening producing the intermediate **G**. The free rotation around the single bond afforded the nonisolable intermediate **H** which underwent another nucleophilic addition at the cyano group forming the intermediate **I**. *Dimroth* rearrangement of the latter intermediate followed by addition of the hydroxyl group on the olefinic bond isolated the final product **7** (Scheme 5). Under the same basic reaction conditions, the product **7** was also obtained

by the reaction of acrylonitrile **2** with cyanoacetamide. The absorption bands 3239 (NH), 2255, 2222 (2 C≡N), and 1653 ($C{=}O_{pyridone}$) cm^{-1} was recorded in the IR spectrum of compound **7**, which supported the suggested structure. Also, its ^{1}H-NMR spectrum exhibited characteristic doublet and triplet signals at δ 3.21 and 5.52 ppm corresponding to CH_2CN and H–5 protons, respectively. A singlet at δ 8.24 ppm was attributed to H–4 proton of pyridine ring while other two doublets ($J = 2.1$ Hz) were observed at δ 7.23 and 7.86 ppm due to $H{-}3_{furan}$ and $H{-}2_{furan}$, respectively. Its ^{13}C-NMR spectrum recorded the characteristic carbon atoms of CH_2 and C–5 at δ 23.1 and 71.8 ppm, respectively. Furthermore, the mass spectrum of compound **7** displayed its molecular ion peak at *m/z* 363 and its base peak at *m/z* 323 which was assigned to the molecular ion after loss of a CH_2CN fragment.

Similar to the latter behavior, treatment of the acrylonitrile **2** with ethyl cyanoacetate and 2-aminoprop-1-ene-1,1,3-tricarbonitrile (malononitrile dimer) afforded the corresponding systems furo[3,2-*g*]pyrano[3,2-*c*]chromene **8** and furo[3′,2′:6,7]chromeno [4,3-*b*]pyridine **9**, respectively, in moderate yields (Scheme 6). The ^{1}H-NMR spectra of systems **8** and **9** showed specific doublet and triplet signals due to CH_2CN and H–5 at δ 3.24/3.27 and 5.50/5.43 ppm, respectively. Moreover, the carbon atoms of CH_2 and C–5 were displayed at δ 23.6/22.9 and 71.4/70.1 ppm in their ^{13}C-NMR spectra.

Finally, refluxing of compound **2** with 2-(1 *H*-benzimidazol-2-yl)acetonitrile in EtOH catalyzed by piperidine furnished the pyrido[1,2-*a*]benzimidazole system **10** that linked to the benzofuran moiety in one molecular frame (Scheme 7). The reaction proceeded according to the suggested mechanism that depicted in Scheme 7. The final product **10** was formed without addition of the OH group onto the olefinic bond. Compound **10** gave a red color with ferric chloride solution which confirmed the presence of free phenolic OH group. The ^{1}H-NMR spectrum of the product **10** exhibited two specific doublets with the same coupling constant ($J = 16.4$ Hz) at δ 6.64 and 7.03 ppm that indicated to the presence of two *olefinic* protons in an *E*-configuration.[28] This confirmed that there was no any addition of the hydroxyl group onto the olefinic bond. Its ^{13}C-NMR spectrum also displayed the carbon atoms of the *olefinic* bond at δ 106.3 and 146.2 ppm. Further support for the structure of compound **10** was derived from its mass spectrum which recorded the molecular ion peak at *m/z* 436 (100%).

Conclusions

The novel (2*E*)-3-(4,9-dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromen-6-yl)acrylonitrile (**2**) was efficiently synthesized. Its chemical behavior toward some examples of methylene ketones and methylene nitriles afforded some novel substituted benzofurans and annulated furochromenes. These reactions involved several steps, starting through *Michael* addition at C-2 position of the γ–pyrone ring then ring opening followed by recyclization through the highly polarized exocyclic π-bond or condensation with the carbonyl group.

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References

1. S. Osama, M. El. Sherei, D. A. Al-Mahdy, M. Bishr, and O. Salama, "Effect of Salicylic Acid Foliar Spraying on Growth Parameters, γ-Pyrones, Phenolic Content and Radical Scavenging Activity of Drought Stressed *Ammi Visnaga* L. plant," *Industrial Crops and Products* 134 (2019): 1–10.
2. A. A. Abu-Hashem, and M. El-Shazly, "Synthesis, Reactions and Biological Activities of Furochromones," *European Journal of Medicinal Chemistry* 90 (2015): 633–65.

3. S. I. Khater, S. A. Kandil, and H. Hussien, "Preparation of Radioiodinated Khellin for the Urinary Tract Imaging," *Journal of Radioanalytical and Nuclear Chemistry* 295, no. 3 (2013): 1939–44.
4. R. Al-Ramahi, N. Jaradat, A. Zaid, F. F. Vincieri, and M. Asmaa, "Medicinal Herbs and Methodologies for Their Pharmaceutical Compounding in the West Bank/Palestine," *Complementary Therapies in Clinical Practice* 20, no. 4 (2014): 280–4.
5. H. K. Sellami, A. Napolitano, M. Masullo, S. Smiti, S. Piacente, and C. Pizza, "Influence of Growing Conditions on Metabolite Profile of *Ammi Visnaga* Umbels with Special Reference to Bioactive Furanochromones and Pyranocoumarins," *Phytochemistry* 95 (2013): 197–206.
6. L. P. Pasari, A. Khurana, P. Anchi, M. A. Saifi, S. Annaldas, and C. Godugu, "Visnagin Attenuates Acute Pancreatitis via Nrf2/NFκB Pathway and Abrogates Associated Multiple Organ Dysfunction," *Biomedicine and Pharmacotherapy* 112 (2019): 108629. doi: 10.1016/j.biopha.2019.108629.
7. A. Ashour, S. El-Sharkawy, M. Amer, F. A. Bar, R. Kondo, and K. Shimizu, "Melanin Biosynthesis Inhibitory Activity of Compounds Isolated from Unused Parts of *Ammi Visnaga*," *Journal of Cosmetics, Dermatological Sciences and Applications* 3, no. 3 (2013): 40–3.[Mismatch.
8. A. A. Abu-Hashem, and M. M. Youssef, "Synthesis of New Visnagen and Khellin Furochromone Pyrimidine Derivatives and Their anti-Inflammatory and Analgesic Activity," *Molecules* 16, no. 3 (2011): 1956–72.
9. R. M. S. Al-Hadhrami, R. M. S. Al Muniri, and M. A. Hossain, "Evaluation of Antimicrobial and Cytotoxic Activities of Polar Solvent Extracts from Leaves of *Ammi Majus* Used by the Omanis," *Pacific Science Review A: Natural Science and Engineering* 18 (2016): 62–5.
10. A. E. Amr, M. M. Abdalla, S. A. Essaouy, M. M. H. Areef, M. H. Elgamal, T. A. Nassear, A. E. Haschich, and M. A. Al-Omar, "Synthesis of Some Substituted 5H-Furo [3,2-g]Chromene and Benzofuran Sulfonate Derivatives as Potent anti-HIV Agents," *Russian Journal of General Chemistry* 87, no. 7 (2017): 1591–600.
11. A. S. S. H. Elgazwy, M. M. Edrees, and N. S. M. Ismail, "Molecular Modeling Study Bioactive Natural Product of Khellin Analogues as a Novel Potential Pharmacophore of EGFR Inhibitors," *Journal of Enzyme Inhibition and Medicinal Chemistry* 28, no. 6 (2013): 1171–81.
12. A. A. Abu-Hashem, and M. El-Shazly, "Synthesis of New Quinoxaline, Pyrimidine, and Pyrazole Furochromone Derivatives as Cytotoxic Agents," *Monatshefte Für Chemie - Chemical Monthly* 148, no. 10 (2017): 1853–63.
13. P. Joshi, V. R. Sonawane, I. S. Williams, G. J. P. McCann, L. Gatchie, R. Sharma, N. Satti, B. Chaudhuri, and S. B. Bharate, "Identification of Karanjin Isolated from the Indian Beech Tree as a Potent CYP1 Enzyme Inhibitor with Cellular Efficacy via Screening of a Natural Product Repository," *MedChemComm* 9, no. 2 (2018): 371–82.
14. I. F. Zaeid, A. M. Nasef, N. M. Fawzy, A. M. Soliman, and M. M. E-Baroudy, "A Novel Multi-Component Reaction of Indoles and Formyl Furochromone Was Described for the Synthesis of Indoles Derivatives with Expected Antitumor Activity," *International Journal of Pharmaceutical Sciences Review and Research* 30 (2015): 306–14.
15. N. M. El-Gohary, M. A. Ibrahim, E. R. El-Sawy, and N. A. Abdel-Fatah, "Chemical Reactivity of 4,9-Dimethoxy-5-Oxo-5H-Furo[3,2-g]Chromene-6-Carboxaldehyde toward Some Nucleophilic Reagents," *Journal of Heterocyclic Chemistry* 54, no. 2 (2017): 1467–78.
16. T. E. Ali, M. A. Assiri, I. S. Yahia, and H. Y. Zahran, "Unusual Behavior of 3-(Dimethylamino)-1-(2-Hydroxyphenyl)Prop-2-en-1-One towards Some Phosphorus Reagents: synthesis of Novel Diethyl 2-Phosphonochromone, Diethyl 3-Phosphono-Pyrone and 1,3,2-Oxathiaphosphinines," *Synthetic Communications* 49, no. 4 (2019): 550–7.
17. M. A. Ibrahim, A. S. Badran, N. M. El-Gohary, and S. H. Hashiem, "Studies on the Chemical Reactions of Some 3-Substituted-6,8-Dimethylchromones with Nucleophilic Reagents," *Journal of Heterocyclic Chemistry* 55, no. 10 (2018): 2315–24.
18. M. A. Ibrahim, and N. M. El-Gohary, "Domino Reactions Between 3-(6-Methylchromonyl) Acrylonitrile and Nucleophilic Reagents," *Tetrahedron* 74, no. 4 (2018): 512–8.
19. M. S. Alam, and D. U. Lee, "Quantum-Chemical Studies to Approach the Antioxidant Mechanism of Nonphenolic Hydrazone Schiff Base Analogs: synthesis, Molecular Structure, Hirschfield and Density Functional Theory Analyses," *Bulletin of the Korean Chemical Society* 36 (2015): 682–91.
20. Z. Ke, G. C. Tsui, X-Sh Peng, and Y.-Y. Yeung, "Five-Membered Ring Systems: furans and Benzofurans," *Progress in Heterocyclic Chemistry* 30 (2018): 169–95.
21. A. S. Plaskon, O. O. Grygorenko, and S. V. Ryabukhin, "Recyclizations of 3-Formylchromones with Binucleophiles," *Tetrahedron* 68, no. 13 (2012): 2743–57.
22. T. E. Ali, M. A. Assiri, N. M. Hassanin, I. S. Yahia, and M. S. A. Hussien, "A Convenient Synthetic Route of Diethyl (4-Oxo-Chromeno[2,3-d]Pyrimidin-2(5)-yl)Phosphonates," *Journal of Heterocyclic Chemistry* 56, no. 5 (2019): 1684–6.

23. Baji vali Shaik, Mohan Seelam, Ramana Tamminana, and Prasad Rao Kammela, "Copper Promoted C-S and C-N Cross-Coupling Reactions: The Synthesis of 2-(N-Aryolamino)Benzothiazoles and 2-(N-Aryolamino)Benzimidazoles," *Tetrahedron* 75, no. 29 (2019): 3865–74.
24. Magdy A. Ibrahim, and Youssef A. Alnamer, "Ring Opening and Recyclization Reactions of 3-Nitrochromone with Some Nucleophilic Reagents," *Journal of Heterocyclic Chemistry* 56, no. 9 (2019): 2341–6.
25. A. M. Abdel Hamid, "Addition–Cyclization Reactions of Furan-2-Carbonyl Isothiocyanate with Nitrogen Nucleophiles as a Synthetic Route to Novel Azines and Azoles of Potential Biological Activity," *Journal of the Iranian Chemical Society* 16, no. 9 (2019): 1853–61.
26. V. Y. Sosnovskikh, "Fluorinated Pyrones, Chromones and Coumarins," *Fluorine in Heterocyclic Chemistry* 2 (2014): 211–90.
27. W. S. Shehab, M. G. Assy, H. Y. Moustafa, M. H. Abdellattif, and H. M. A. Rahman, "Pyrimidines as Block Units in Heterocycles: novel Synthesis of Pyrimidines and Condensed Pyrimidine Derivatives," *Journal of the Iranian Chemical Society* 16, no. 11 (2019): 2451–61.
28. A. M. Farag, K. M. Dawood, H. A. Abdel-Aziz, N. A. Hamdy, and I. M. I. Fakhr, "Synthesis of Some New Azole, Pyrimidine, Pyran, and Benzo/Naphtho[*b*]Furan Derivatives Incorporating Thiazolo[3,2-*a*]Benzimidazole Moiety," *Journal of Heterocyclic Chemistry* 48, no. 2 (2011): 355–60.