Synthesis and reactions of 8-allylchromone-3-carboxaldehyde

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Abstract
8-Allylchromone derivatives **5-7**, **10** and **11** were prepared starting from 8-allylchromone-3-carboxaldehyde **4**. Basic rearrangement of oxime **8** and/or carbonitrile **9** gave 8-allyl-2-aminochromone-3-carboxaldehyde **12**. Chromeno[2,3-*b*] pyridines **14-20** were prepared *via* the reaction of **12** with malononitrile, cyanoacetamide, ethyl cyanoacetate, phenylthioacetonitrile, ethyl acetoacetate, ethyl benzoylacetate and barbituric acid. Structures of the new products have been deduced from elemental analysis and spectral data (IR, ^{1}H NMR and mass spectra).

Keywords: Synthesis, chromone, chromeno[2,3-*b*]pyridine, Friedländer

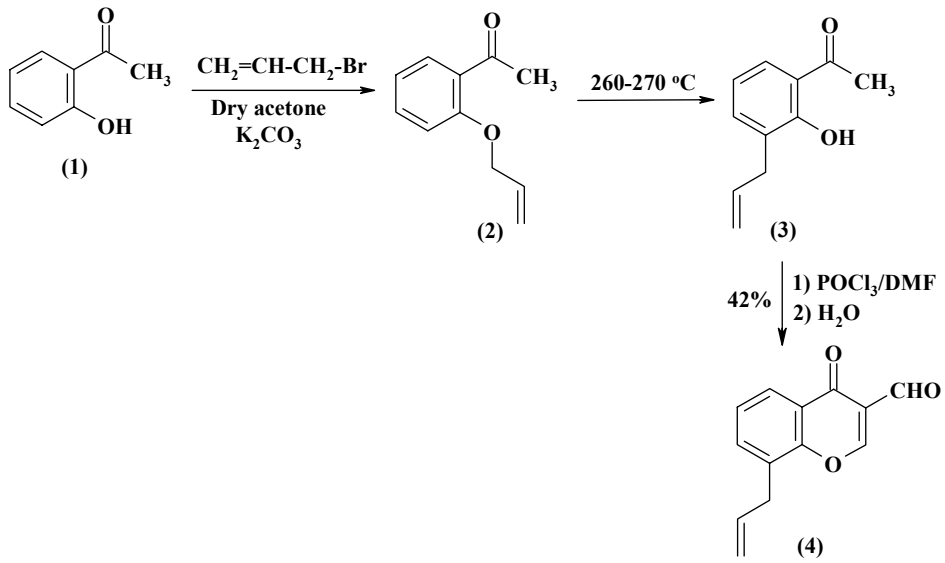
Introduction

Chromone derivatives drew much attention because of their activity against the human immunodeficiency virus (HIV-1)[1-3] and their broad anti-inflammatory,[4] antitumor,[5] antibacterial,[6] antimicrobial,[7] antifungal,[8,9] antibiotic,[10] and insecticidal activities.[11] Chromones bearing an allyl group at position 8 have a special medicinal importance; 8-allyl-2-styrylchromones were used as inhibitors for the growth of tumors.[12] Also, the 8-allyl derivatives were used as a precursor for the synthesis of the 8-acetic acid derivatives which exhibit anticancer properties.[13-15] Heteroannulated chromones showed significant biological activity including pharmacological,[16] anti-inflammatory and antiplatelet activities.[17]

Results and Discussion

In the course of the present work, some new chromone derivatives bearing the allyl group at position 8 have been synthesized starting from 8-allylchromone-3-carboxaldehyde **4**. The synthetic route of compound **4** is depicted in Scheme 1. Standard procedures were used to convert 2-hydroxyacetophenone **1** to its allyl ether derivative **2** which under *Claisen*

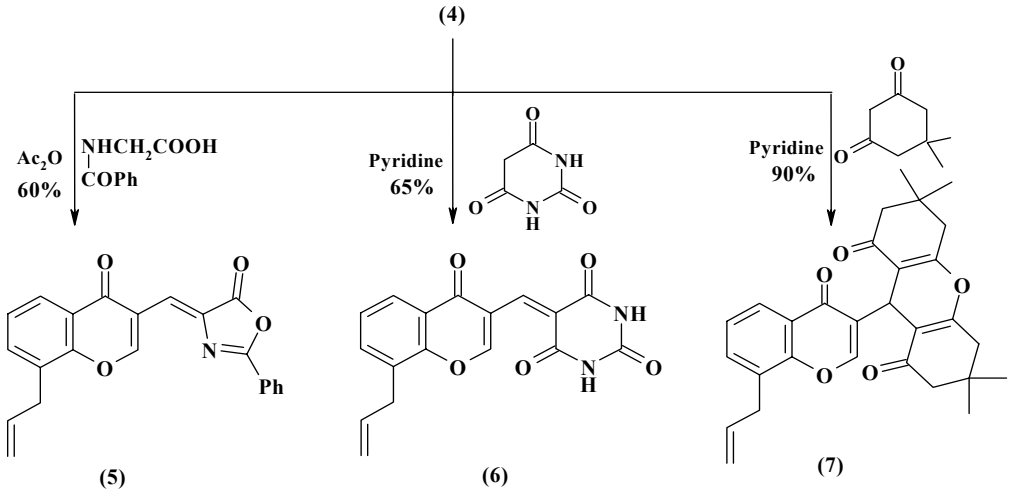
rearrangement gave 3-allyl-2-hydroxyacetophenone **3**.[14] Formylation of **3** by Vilsmeier reagent (DMF/$POCl_3$) afforded the target compound **4**. The structure of compound **4** was confirmed based on correct elemental analysis and spectral data. Its IR spectrum showed two characteristic absorption bands at 1700 ($C=O_{aldehyde}$) and 1647 ($C=O_{\gamma\text{-pyrone}}$) cm^{-1}. The ^1H NMR spectrum showed characteristic signals of the allyl segment at δ 3.62, 5.06 and 6.05 ppm, in addition to two singlet at δ 8.93 and 10.12 ppm attributed to H-2 and the aldehydic proton, respectively.



Scheme 1. Synthetic route to 8-allylchromone-3-carboxaldehyde **4**.

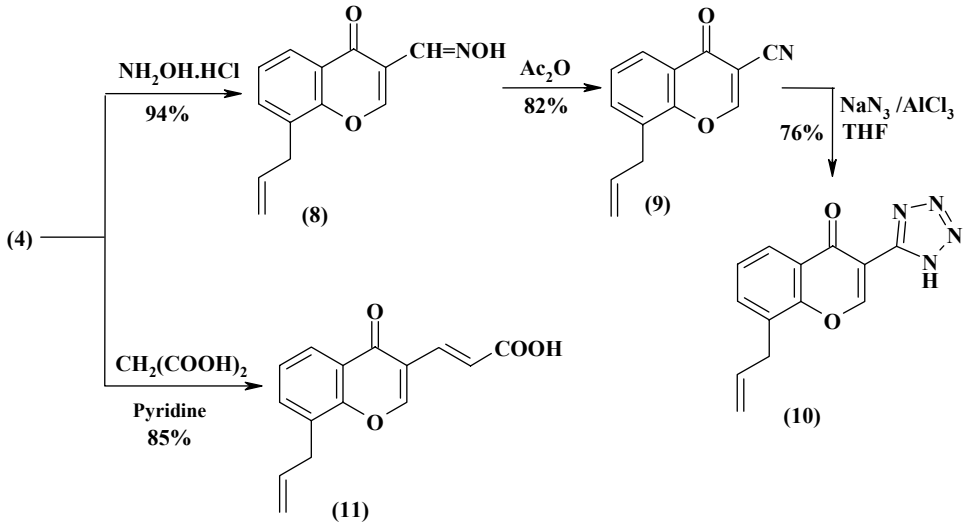
Condensation of 8-allylchromone-3-carboxaldehyde **4** with hippuric acid in boiling acetic anhydride containing freshly fused sodium acetate gave the oxazolone derivative **5** (Scheme 2).[18] The IR spectrum of **5** showed two characteristic absorption bands at 1803 ($C=O_{oxazolone}$) and 1657 ($C=O_{\gamma\text{–pyrone}}$) cm^{-1}. Its ^1H-NMR spectrum exhibited two characteristic singlet signals at δ 8.21 and 9.75 ppm assigned to the H-2 and olefinic proton, respectively.

Also, condensation of **4** with barbituric acid in dry pyridine gave 5-(8-allylchromon-3-ylmethylene)-1,3-dihydropyrimidine-2,4,6-trione **6** (Scheme 2). Its ^1H NMR spectrum showed two singlet signals at δ 8.44 and 9.77 assigned to H-2 and the olefinic proton, respectively, in addition to two exchangeable signals at δ 11.37 and 11.47 ppm attributed to 2NH protons. On the other hand, treatment of carboxaldehyde **4** with dimedone in dry pyridine gave 3,3,6,6-tetramethyl–9-(8-allylchromon-3-yl)-1,2,3,4,5,6,7,8-octahydroxanthene-1,8-dione **7** (Scheme 2). When compound **4** was allowed to react with hydroxylamine hydrochloride in boiling ethanol, the oxime **8** was easily obtained. Dehydration of the latter compound by acetic anhydride afforded the corresponding carbonitrile **9** (Scheme 3).



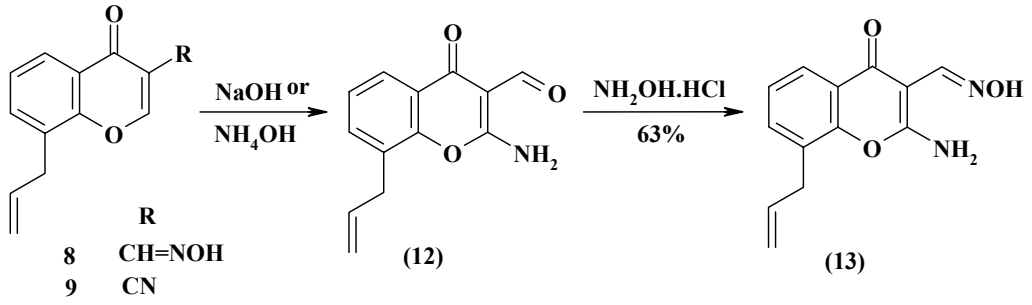
Scheme 2. Formation of 3-substituted-8-allylchromones **5**-**7**.

It has been reported that chromone derivatives bearing an acidic groups at position 3 displayed antiallergic activities.[19,20] Thus, in the present work some analogous compounds containing the allyl moiety at position 8 were prepared. Reaction of the carbonitrile **9** with sodium azide in the presence of aluminum chloride in tetrahydrofuran afforded 8-allyl-3-(1H-tetrazol-5-yl)chromone **10**.[21] Also, *trans* 3-(8-allylchromon-3-yl)acrylic acid **11** was prepared *via* the reaction of 8-allylchromone-3-carboxaldehyde **4** with malonic acid in dry pyridine (Scheme 3). The IR spectrum of compound **10** exhibited characteristic absorption bands at 3192 ($NH_{tetrazole}$) and 1644 ($C=O_{\gamma-pyrone}$) cm^{-1}, while compound **11** displayed bands at 3200-2500 (OH), 1701 ($C=O_{carboxy}$) and 1652 ($C=O_{\gamma-pyrone}$) cm^{-1}.



Scheme 3. Formation of 3-substituted-8-allylchromones **8**-**11**.

On the other hand, the action of 0.05M sodium hydroxide solution or concentrated ammonium hydroxide solution on 8-allylchromone-3-carboxaldehyde-oxime **8** or 8-allylchromone-3-carbonitrile **9** results in opening of the γ-pyrone ring followed by recyclization to give 8-allyl-2-aminochromone-3-carboxaldehyde **12** (Scheme 4).[22] Using ammonium hydroxide solution gave a superior yield and pure product. The IR spectrum of **12** showed characteristic absorption bands at 3304, 3175 (NH_2), 1665 ($C=O_{aldehyde}$) and 1635 ($C=O_{\gamma\text{-pyrone}}$) cm^{-1}; its ^1H NMR spectrum showed signals at δ 9.62 and 10.13 ppm assigned to NH_2 and CHO protons, respectively. The structure was further confirmed from its mass spectrum, which exhibited the molecular ion peak at m/e 229 and the base peak at m/e 201. Treatment of **12** with hydroxylamine hydrochloride in ethanol yielded 8-allyl-2-aminochromone-3-carboxaldehyde-oxime **13**.



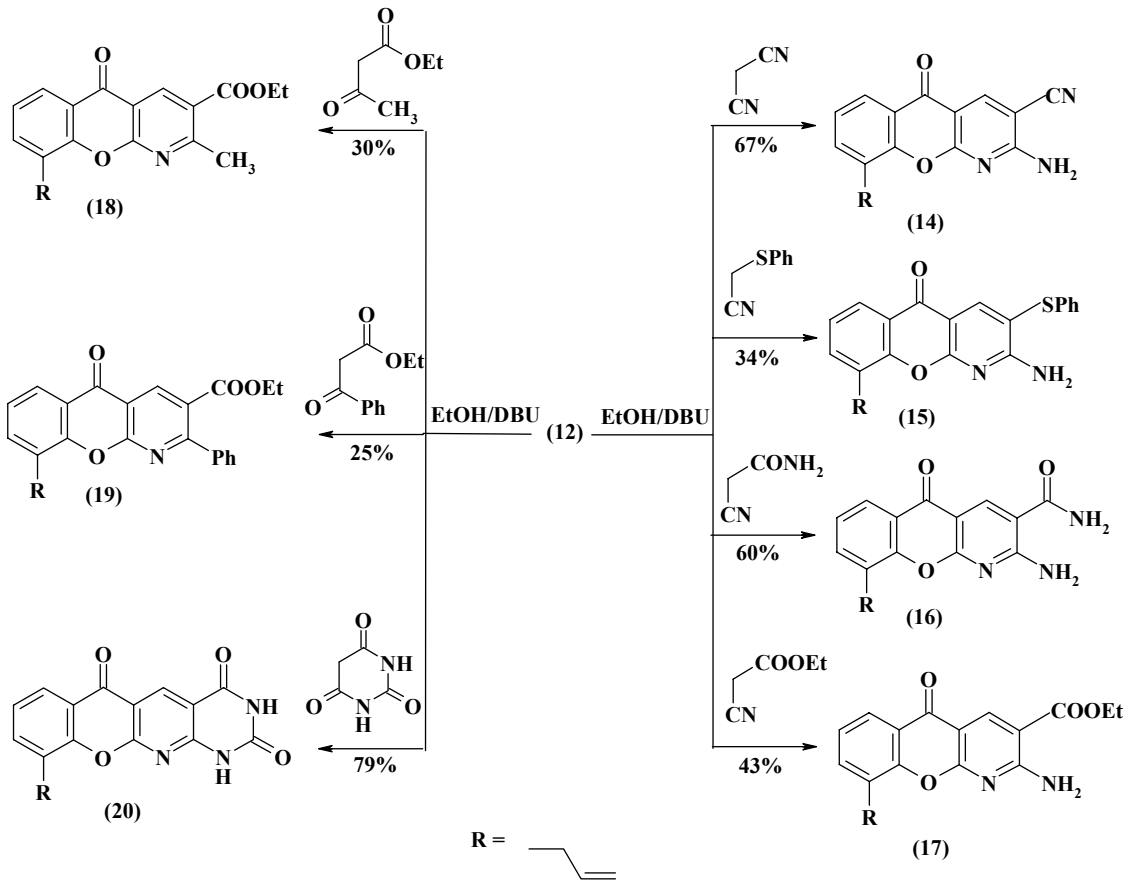
Scheme 4. Synthesis of aminoaldehyde **12** and its corresponding oxime **13**.

In continuation to our interest to prepare chromeno[2,3-*b*]pyridines,[23,24] some new chromeno[2,3-*b*]pyridines **14-20** were prepared successfully from the reaction of 8-allyl-2-aminochromone-3-carboxaldehyde **12** with active methylene compounds in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a basic catalyst. Reaction of **12** with active methylene compounds containing a cyano group adjacent to a methylene group ($-CH_2CN$) namely: malononitrile, cyanoacetamide, ethyl cyanoacetate and phenylthioacetonitrile in absolute ethanol containing few drops of DBU afforded 9-allyl-2-amino-5-oxo-5*H*-chromeno[2,3-*b*]pyridines **14-17**, respectively, through condensation followed by cyclo-addition reactions (Scheme 5). Structures of compounds **14-17** were inferred from their correct elemental analysis and spectral data. The IR spectra of compounds **14-17** displayed characteristic absorption bands in the range 3458- 3173 and 1667-1653 cm^{-1} due to the stretching frequencies of NH_2 groups and C=O of the γ–pyrone systems, respectively. The ^1H NMR spectra of **14-17** showed characteristic singlet signals in the range δ 8.81-8.36 ppm due to H-4 protons, the amino protons were observed in the range δ 8.49-7.53 ppm. Also, the spectrum of **16** showed characteristic triplet and quartet signals at δ 1.38 and 4.36 ppm, respectively, assigned to the ethoxy protons.

On the other hand, Friedländer condensation of *o*-aminoaldehyde **12** with active methylene compounds containing the $-COCH_2CO-$ moiety were studied to construct some new chromeno[2,3-*b*]pyridines **18-20**. Thus, treatment of **12** with ethyl acetoacetate and ethyl

benzoylacetate in ethanol containing DBU gave heteroannulated chromones, ethyl 9-allyl-2-methyl-5-oxo-5*H*-chromeno[2,3-*b*]pyridine-3-carboxylate **18** and its corresponding 2-phenyl analog **19**, respectively (Scheme 5). IR spectra of compounds **18** and **19** showed characteristic absorption bands at 1728/1712 and 1673/1668 cm^{-1} for ($C=O_{ester}$) and ($C=O_{\gamma-pyrone}$), respectively. The ^1H NMR spectrum of **18** showed triplet and quartet signals at δ 1.40 and 4.39 ppm, respectively, in addition to characteristic singlet signals at δ 2.82 and 8.88 ppm due to the CH_3 protons in position 2 and H-4, respectively.

Also, Friedländer condensation of **12** with barbituric acid in the presence of DBU furnished 10-allylchromeno[2',3':2,3]pyrido[6,5-*d*]pyrimidine-2,4,6-trione **20**. The IR spectrum of **20** showed absorption bands at 3198 (NH), 1739, 1676 ($2C=O_{cyclic\ amide}$) and 1650 ($C=O_{\gamma-pyrone}$) cm^{-1}. The ^1H NMR spectrum revealed two exchangeable signals at δ 11.79 and 12.20 ppm assigned to 2NH, in addition to a singlet signal at δ 8.85 ppm attributed to H-5.



Scheme 5. Formation of heteroannulated chromones **14-20.**

Experimental Section

General. All melting points are uncorrected and were recorded in open capillary tubes on a Gallenkamp 595–MFB melting point apparatus. The IR spectra were recorded on an FTIR Bruker Vector 22 spectrophotometer using KBr wafer technique. ^{1}H NMR spectra were measured on a Varian Gemini spectrophotometer 200 MHz using DMSO- d_6 as solvent and TMS (δ ppm) as an internal standard. Mass spectra were obtained using a GCMS qp 1000 ex Schimadzu instrument (70 eV). Elemental microanalyses were performed at the Cairo University Microanalytical Center.

8-Allylchromone-3-carboxaldehyde 4. Phosphoryl chloride (14 mL, 153 mmol) was added drop wise to a pre-cooled DMF (37.5 mL, 500 mmol) and the mixture was stirred at room temperature for 30 min. Then 3-allyl-2-hydroxyacetophenone (7 mL, 39.8 mmol) was added drop wise with continuous stirring. The mixture was stirred at room temperature for 2h, left overnight and poured into crushed ice (50 g). The solid obtained was filtered, dried in air and crystallized from petroleum ether (60-80) to give **4** as yellow crystals, yield 3.5 g (42%), m.p. 73-74 ^{o}C. IR (KBr, cm^{-1}): 1700 (C=O$_{aldehyde}$), 1647 (C=O$_{\gamma\text{-pyrone}}$) and 1607 (C=C) cm^{-1}. ^{1}H NMR (DMSO-d_6, δ): 3.62 (2H, d, J = 6.4 Hz, H-1'), 5.06 (2H, m, H-3'), 6.05 (1H, m, H-2'), 7.50 (1H, t, J = 7.4 Hz, H-6), 7.73 (1H, dd, J = 7.6 and 1.2 Hz, H-7), 8.02 (1H, dd, J = 7.9 and 1.8 Hz, H-5), 8.93 (1H, s, H-2), 10.12 (1H, s, CHO). Anal. Calcd. for $C_{13}H_{10}O_3$ (214.22): C, 72.89; H, 4.71. Found C, 72.90; H, 4.80.

4-(8-Allylchromon-3-ylmethylene)-2-phenyl-4*H*-oxazol-5-one 5. To a mixture of hippuric acid (0.358 g, 2 mmol) and freshly fused sodium acetate (0.4 g) in Ac_2O (20 mL), compound **4** (0.428 g, 2 mmol) was added. The reaction mixture was heated at reflux for 30 min. The solid deposited after cooling was filtered and recrystallized from ethanol to give **5** as yellow crystals, yield 0.43 g (60%), m.p. 177-178 ^{o}C. IR (KBr, cm^{-1}): 1803 (C=O$_{oxazolone}$), 1657 (C=O$_{\gamma\text{-pyrone}}$), 1611 and 1568 (C=N and C=C) cm^{-1}. ^{1}H NMR (DMSO-d_6, δ): 3.67 (2H, d, J = 6.2 Hz, H-1''), 5.18 (2H, m, H-3''), 6.20 (1H, m, H-2''), 7.37-8.17 (8H, m, Ar-H), 8.21 (1H, s, H-2') and 9.75 (1H, s, CH=C). Anal. Calcd. for $C_{22}H_{15}NO_4$ (357.37): C, 73.94; H, 4.23; N, 3.92. Found C, 74.01; H, 3.97; N, 3.91.

5-(8-Allylchromon-3-ylmethylene)-1,3-dihydropyrimidine-2,4,6-trione 6. To a solution of **4** (0.428 g, 2 mmol) in dry pyridine (5 mL), a solution of barbituric acid (0.3 g, 2.5 mmol) in dry pyridine (5 mL) was added. The reaction mixture was heated on a water bath for 1 h. The mixture was cooled and the solid deposited after acidification with dil. HCl was filtered and crystallized from aqueous dioxane to give **6** as yellow crystals, yield 0.42 g (65%), m.p. 186-187 ^{o}C. IR (KBr, cm^{-1}): 3199 (2NH), 1747, 1704 (C=O$_{cyclic\ amide}$), 1673 (C=O$_{\gamma\text{-pyrone}}$) and 1589 (C=C) cm^{-1}. ^{1}H NMR (DMSO-d_6, δ): 3.66 (2H, d, J = 6.4 Hz, H-1''), 5.16 (2H, m, H-3''), 6.08 (1H, m, H-2''), 7.56 (1H, t, J = 7.6 Hz, H-6'), 7.75 (1H, dd, J = 7.4 and 1.6 Hz, H-7'), 8.05 (1H, dd, J = 7.8 and 1.7 Hz, H-5'), 8.44 (1H, s, H-2'), 9.77 (1H, s, CH=C), 11.37 and 11.47 (2H, each s, 2NH

exchangeable with D_2O). Anal. Calcd. for $C_{17}H_{12}N_2O_5$ (324.30): C, 62.96; H, 3.73; N, 8.64. Found C, 62.95; H, 3.85; N, 8.63.

3,3,6,6-Tetramethyl-9-(8-allylchromon-3-yl)-1,2,3,4,5,6,7,8-octahydroxanthene-1,8-dione 7. To a solution of **4** (0.428 g, 2 mmol) in dry pyridine (5 mL), dimedone (0.8 g, 5.7 mmol) was added and stirred at room temperature for 1h, then the mixture was acidified with 6N HCl. The solid deposited was filtered and crystallized from aqueous dioxane to give **7** as white crystals, yield 0.8 g (90%), m.p. 200-201 ^oC. IR (KBr, cm^{-1}): 1662 ($C=O_{xanthene}$), 1632 ($C=O_{\gamma\text{-pyrone}}$) and 1579 (C=C) cm^{-1}. ^1H NMR (DMSO-d_6, δ): 0.87 (6H, s, $2CH_3$), 1.02 (6H, s, $2CH_3$), 2.01-2.61 (8H, m, 4 CH_2), 3.57 (2H, d, J = 5.5 Hz, H-1''), 4.34 (1H, s, pyran H), 5.16 (2H, m, H-3''), 5.98 (1H, m, H-2''), 7.33 (1H, m, H-6'), 7.59 (1H, d, J = 7.2 Hz, H-7'), 7.87 (1H, d, J = 7.8 Hz, H-5') and 8.35 (1H, s, H-2'). Anal. Calcd. for $C_{29}H_{30}O_5$ (458.56): C, 75.96; H, 6.59. Found C, 75.62; H, 6.44.

8-Allylchromone-3-carboxaldehyde-oxime 8. A mixture of **4** (2.14 g, 10 mmol) in ethanol (15 mL) and hydroxylamine hydrochloride (0.77 g, 11 mmol) was heated at reflux for 15 min. The solid obtained after cooling was filtered and recrystallized from ethanol to give **8** as white crystals, yield 2.15 g (94%), m.p. 163-164 ^oC. IR (KBr, cm^{-1}): 3267 (OH), 1636 ($C=O_{\gamma\text{-pyrone}}$) 1613 and 1574 (C=N and C=C) cm^{-1}. ^1H NMR (DMSO-d_6, δ): 3.65 (2H, d, J = 6.2 Hz, H-1`), 5.14 (2H, m, H-3'), 6.00 (1H, m, H-2'), 7.44 (1H, m, H-6), 7.70 (1H, d, J = 7.0, H-7), 8.00 (1H, dd, J = 8.8 and 1.8 Hz, H-5), 8.09 (1H, s, CH=N), 8.72 (1H, s, H-2), 11.44 (1H, s, OH_{oxime}). Anal. Calcd. for $C_{13}H_{11}NO_3$ (229.24): C, 68.11; H, 4.84; N, 6.11. Found C, 67.95; H, 4.90; N, 6.14.

8-Allylchromone-3-carbonitrile 9. A mixture of **8** (0.45 g, 2 mmol) and Ac_2O (2 mL) was heated at reflux for 4 h. The reaction mixture was cooled and poured into crushed ice (30 g); the solid obtained was filtered and recrystallized from benzene/petroleum ether (40-60) to give **9** as yellow crystals, yield 0.34 g (82%), m.p. 97-98 ^oC. IR (KBr, cm^{-1}): 2239 (C≡N), 1658 ($C=O_{\gamma\text{-pyrone}}$) and 1616 (C=C) cm^{-1}. ^1H NMR (DMSO-d_6, δ): 3.65 (2H, d, J = 6.0 Hz, H-1'), 5.07 (2H, m, H-3'), 6.00 (1H, m, H-2'), 7.55 (1H, t, J = 7.8 Hz, H-6), 7.80 (1H, d, J = 7.4 Hz, H-7), 8.01 (1H, d, J = 7.8 Hz, H-5), 9.28 (1H, s, H-2). Anal. Calcd. for $C_{13}H_9NO_2$ (211.22): C, 73.92; H, 4.29; N, 6.63. Found C, 73.26; H, 4.04; N, 6.84.

8-Allyl-3-(1*H*-tetrazol-5-yl)chromone 10. To THF (8 ml) pre-cooled in an ice-bath were added pulverized anhydrous $AlCl_3$ (0.585 g, 4.4 mmol), sodium azide (0.572 g, 8.8 mmol) and compound **9** (0.422 g, 2 mmol). The ice-bath was removed and the mixture was stirred under reflux for 10 h, then left to cool and acidified with 15% HCl (5 mL). The solid obtained was filtered and crystallized from aqueous dioxane to give **10** as white crystals, yield 0.38 g (76%), m.p. 267-268 ^oC. IR (KBr, cm^{-1}): 3192 (NH), 1644 ($C=O_{\gamma\text{-pyrone}}$) and 1582 (C=C) cm^{-1}. ^1H NMR (DMSO-d_6, δ): 3.68 (2H, d, J = 6.4 Hz, H-1'), 5.11 (2H, m, H-3'), 6.10 (1H, m, H-2'), 7.54 (1H, m, H-6), 7.61 (1H, d, J = 7.3 Hz, H-7), 8.09 (1H, d, J = 7.9 Hz, H-5), 9.31 (1H, s, H-2), 16.58 (1H, s, NH exchangeable with D_2O). Anal. Calcd. for $C_{13}H_{10}N_4O_2$ (254.25): C, 61.41; H, 3.96 ; N, 22.04. Found C, 61.70; H, 3.90; N, 21.86.

3-(8-Allylchromon-3-yl)acrylic acid 11. To a solution of **4** (0.32 g, 15 mmol) in dry pyridine (5 mL), malonic acid (0.26 g, 25 mmol) was added. The reaction mixture was heated on a water bath for 2 h. The solid deposited after acidification with dil. HCl was filtered and crystallized from acetic acid to give **11** as yellow crystals, yield 0.32 g (85%), m.p. 195-196 °C. IR (KBr, cm^{-1}): 3200-2500 (OH), 1701 ($C=O_{carboxy}$), 1652 ($C=O_{\gamma\text{-pyrone}}$) and 1614 (C=C) cm^{-1}. ^1H NMR (DMSO-d_6, δ): 3.50 (2H, d, J = 6.4 Hz, H-1''), 5.09 (2H, m, H-3''), 6.02 (1H, m, H-2''), 7.13 (1H, d, J = 15.8 Hz, olefinic proton), 7.43 (2H, m, H-6'+ olefinic H), 7.67 (1H, d, J = 7.0 Hz, H-7'), 8.20 (1H, d, J = 6.5 Hz, H-5'), 8.88 (1H, s, H-2') and 12.41 (1H, s, COOH exchangeable with D_2O). Anal. Calcd. for $C_{15}H_{12}O_4$ (256.26): C, 70.31; H, 4.72. Found C, 70.46; H, 4.58.

8-Allyl-2-aminochromone-3-carboxaldehyde 12

a) Using NaOH. A mixture of **8** (2.29 g, 10 mmol) or **9** (2.11, 10 mmol) and 0.05M sodium hydroxide solution (15 mL) was stirred at 70 °C for 2 h. Water was added (50 mL) and the solid obtained was filtered and recrystallized from ethanol to give **12** as yellow crystals, yield (70%), m.p. 225-226 °C.

b) Using NH_4OH. A mixture of **8** (2.29 g, 10 mmol) or **9** (2.11, 10 mmol) and concentrated NH_4OH solution (10 mL) was stirred at room temperature until the solid dissolved and then was diluted with water (10 mL). The product obtained was filtered and recrystallized from ethanol to give **12** as yellow crystals, yield (90%), m.p. 225-226 °C. IR (KBr, cm^{-1}): 3304, 3175 (NH_2), 1665 ($C=O_{aldehyde}$), 1635 ($C=O_{\gamma\text{-pyrone}}$) and 1602 (C=C) cm^{-1}. ^1H NMR (DMSO-d_6, δ): 3.62 (2H, d, J = 6.5 Hz, H-1'), 5.21 (2H, m, H-3'), 6.00 (1H, m, H-2'), 7.42 (1H, m, H-6), 7.62 (1H, d, J = 7.3 Hz, H-7), 7.94 (1H, dd, J = 7.6 and 1.7 Hz, H-5), 9.62 (2H, s, NH_2), 10.13 (1H, s, CHO). *M/e* (relative intensity): 229 (M^+, 16), 230 (M^+ +1, 4), 201 (100), 200 (38), 188 (2), 172 (4), 131 (58), 116 (13), 103 (21), 77 (45), 76 (10), 68 (34). Anal. Calcd. for $C_{13}H_{11}NO_3$ (229.24): C, 68.11; H, 4.84; N, 6.11. Found C, 68.23; H, 4.69; N, 6.18.

8-Allyl-2-aminochromone-3-carboxaldehyde-oxime 13. To a solution of **12** (0.458 g, 2 mmol) in ethanol (5 mL), hydroxylamine hydrochloride (0.154 g, 2.2 mmol) was added. The reaction mixture was heated at reflux on a water bath for 15 min. The solid obtained was filtered and recrystallized from ethanol to give **13** as white crystals, yield 0.3 g (63%), m.p. 231-232 °C. IR (KBr, cm^{-1}): 3355, 3214 (NH_2 and OH), 1644 ($C=O_{\gamma\text{-pyrone}}$), 1604 and 1544 (C=N and C=C) cm^{-1}. ^1H NMR (DMSO-d_6, δ): 3.61 (2H, d, J = 6.7 Hz, H-1'), 5.14 (2H, m, H-3'), 6.12 (1H, m, H-2'), 7.30 (1H, t, J = 7.5 Hz, H-6), 7.51 (1H, d, J = 7.8, H-7), 7.85 (1H, dd, J = 7.8 and 1.58 Hz, H-5), 8.44 (1H, s, CH=N), 8.90 (2H, br, NH_2), 10.77 (1H, s, OH_{oxime}). Anal. Calcd. for $C_{13}H_{12}N_2O_3$ (244.25): C, 63.93; H,4.95; N,11.47. Found C, 63.82; H, 5.03; N, 11.31.

9-Allyl-2-amino-5-oxo-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile 14. To a solution of **12** (0.458 g, 2 mmol) in absolute ethanol (25 mL) and DBU (0.4 mL), malononitrile (0.56 g, 2 mmol) was added. The reaction mixture was heated at reflux for 30 min. The solid obtained during heating was filtered and recrystallized from aqueous DMF to give **14** as yellow crystals, yield 0.37 g (67%), m.p. 263-264 °C. IR (KBr, cm^{-1}): 3458, 3348 (NH_2), 2221 (C≡N), 1662 ($C=O_{\gamma\text{-pyrone}}$), 1602 and 1541 (C=N and C=C) cm^{-1}. ^1H NMR (DMSO-d_6, δ): 3.60 (2H, d, J = 5.6 Hz, H-1'), 5.07 (2H, m, H-3'), 6.04 (1H, m, H-2'), 7.37 (1H, t, J = 7.6 Hz, H-7), 7.62 (1H, d, J =

7.0 Hz, H-8), 7.92 (1H, d, *J* = 7.6 Hz, H-6), 8.13 (2H, br, NH_2) and 8.54 (1H, s, H-4). *M/e* (relative intensity): 277 (M^+, 91), 278 (M^++1, 10), 250 (9), 222 (7), 162 (51), 140 (5), 133 (12), 117 (5), 105 (9), 89 (14), 77 (18), 65 (14). Anal. Calcd. for $C_{16}H_{11}N_3O_3$ (277.28): C, 69.31; H, 4.00; N,15.15. Found C, 69.61; H, 4.02; N, 15.02.

9-Allyl-2-amino-3-phenylthio-chromeno[2,3-*b*]pyridin-5-one 15. A mixture of **12** (0.229 g, 1 mmol), DBU (0.4 mL) and phenylthioacetonitrile (0.15 mL, 1 mmol) was heated at reflux in absolute ethanol (20 mL) for 3h. The solid obtained after cooling was filtered and recrystallized from ethanol to give **15** as a pale yellow crystals, yield 0.24 g (34%), m.p. 234-235 ^oC. IR (KBr, cm^{-1}): 3456, 3266 (NH_2), 1660 ($C=O_{\gamma\text{-pyrone}}$) 1625 and 1579 (C=N and C=C) cm^{-1}. ^1H NMR (DMSO-d_6, δ): 3.67 (2H, d, *J* = 6.3 Hz, H-1'), 5.10 (2H, m, H-3'), 6.10 (1H, m, H-2'), 7.25-8.02 (8H, m, Ar-H), 7.98 (2H, br, NH_2) and 8.36 (1H, s, H-4). Anal. Calcd. for $C_{21}H_{16}N_2O_2S$ (360.44): C, 69.98; H, 4.47; N,7.77; S, 8.88. Found C, 70.34; H, 4.43; N, 7.90; S, 8.88.

9-Allyl-2-amino-5-oxo-5*H*-chromeno[2,3-*b*]pyridine-3-carboxamide 16. A mixture of **12** (0.229 g, 1 mmol), DBU (0.4 mL) and cyanoacetamide (0.84 g, 1 mmol) was heated at reflux in absolute ethanol (20 mL) for 30 min. The solid obtained during heating was filtered and recrystallized from aqueous DMF to give **16** as yellow crystals, yield 0.177 g (60%), m.p. above 300 ^oC. IR (KBr, cm^{-1}): 3389, 3228, 3173 ($2NH_2$), 1653 ($C=O_{amide}$), 1624 ($C=O_{\gamma\text{-pyrone}}$) 1604 and 1545 (C=N and C=C) cm^{-1}. ^1H NMR (DMSO-d_6, δ): 3.64 (2H, d, *J* = 5.2 Hz, H-1'), 5.08 (2H, m, H-3'), 6.05 (1H, m, H-2'), 7.39 (1H, t, *J* = 7.6 Hz, H-7), 7.53 (2H, br, NH_2), 7.67 (1H, d, *J* = 7.02 Hz, H-8), 8.02 (1H, d, *J* = 7.32 Hz, H-6), 8.41 (2H, br, $CONH_2$) and 8.81 (1H, s, H-4). *M/e* (relative intensity): 295 (M^+, 100), 296 (M^+ +1, 18), 278 (10), 250 (23), 223 (5), 163 (8), 133 (12), 115 (17), 94 (14), 77 (12), 67 (14). Anal. Calcd. for $C_{16}H_{13}N_3O_3$ (295.30): C, 65.08; H, 4.44; N,14.23. Found C, 64.68; H, 4.56; N, 13.83.

Ethyl 9-allyl-2-amino-5-oxo-5*H*-chromeno[2,3-*b*]pyridine-3-carboxylate 17. To a solution of **12** (0.458 g, 2 mmol) in absolute ethanol (20 mL) and DBU (0.4 mL), ethyl cyanoacetate (0.226 g, 2 mmol) was added. The reaction mixture was heated at reflux for 30 min, then left to cool at room temperature. The solid obtained was filtered and recrystallized from ethanol to give **17** as white crystals, yield 0.28 g (43%), m.p. 239-240 ^oC. IR (KBr, cm^{-1}): 3407, 3272 (NH_2), 1697($C=O_{ester}$), 1667 ($C=O_{\gamma\text{-pyrone}}$) 1626 and 1593 (C=N and C=C) cm^{-1}. ^1H NMR (DMSO-d_6, δ): 1.38 (3H, t, *J* = 7.1 Hz, $OCH_2\mathit{CH_3}$), 3.64 (2H, d, *J* = 6.9 Hz, H-1'), 4.38 (2H, q, *J* = 7.2 Hz, $O\mathit{CH_2}CH_3$), 5.09 (2H, m, H-3'), 6.12 (1H, m, H-2'), 7.41 (1H, t, *J* = 7.6 Hz, H-7), 7.68 (1H, d, *J* = 7.2 Hz, H-8), 8.01 (1H, dd, *J* = 7.2 and 1.9 Hz, H-6), 8.10 and 8.49 (2H, each s, 2NH exchangeable with D_2O), 8.81 (1H, s, H-4). *M/e* (relative intensity): 324 (M^+, 52), 325 (M^+ +1, 10), 277 (8), 250 (12), 178 (24), 152 (10), 128 (25), 99 (33), 97 (81), 77 (10), 69 (100), 55 (78). Anal. Calcd for $C_{18}H_{16}N_2O_4$ (324.34): C, 66.66; H, 4.97; N, 8.64. Found C, 66.65; H, 4.84; N, 8.62.

Ethyl 9-allyl-2-methyl-5-oxo-5*H*-chromeno[2,3-*b*]pyridine-3-carboxylate 18. A mixture of **12** (0.29 g, 1.2 mmol), DBU (0.4 mL) and ethyl acetoacetate (0.17 mL, 1.3 mmol) was heated at reflux in absolute ethanol (20 mL) for 6 h. The solid so formed after cooling was filtered and recrystallized from ethanol to give **18** as white crystals, yield 0.12 g (30%), m.p. 128-129 ^oC. IR

(KBr, cm^{-1}): 1728 ($C=O_{ester}$), 1673 ($C=O_{\gamma\text{-pyrone}}$) 1599 and 1552 (C=N and C=C) cm^{-1}. ^1H NMR (DMSO-d_6, δ): 1.40 (3H, t, J = 7.2 Hz, OCH_2CH_3), 2.82 (3H, s, CH_3), 3.72 (2H, d, J = 6.1 Hz, H-1'), 4.39 (2H, q, J = 7.3 Hz, OCH_2CH_3), 5.18 (2H, m, H-3'), 6.11 (1H, m, H-2'), 7.48 (1H, t, J = 7.94 Hz, H-7), 7.79 (1H, d, J = 7.1 Hz, H-8), 8.06 (1H, d, J = 7.8 Hz, H-6) and 8.88 (1H, s, H-4). Anal. Calcd. for $C_{19}H_{17}NO_4$ (323.35): C, 70.58; H, 5.30; N, 4.33. Found C, 70.88; H, 4.93; N, 4.37.

Ethyl 9-allyl-2-phenyl-5-oxo-5*H*-chromono[2,3-*b*]pyridine-3-carboxylate 19. A mixture of **12** (0.229 g, 1 mmol), DBU (0.4 ml) and ethyl benzoylacetate (0.2 mL, 1mmol) was heated at reflux in absolute ethanol (20 mL) for 6 h. The reaction mixture was cooled and the solvent was concentrated. The solid obtained was filtered and recrystallized from ethanol to give **19** as yellow crystals, yield 0.08 g (25%), m.p. 145-146 ^oC. IR (KBr, cm^{-1}): 1712 ($C=O_{ester}$), 1668 ($C=O_{\gamma\text{-pyrone}}$), 1594 and 1546 (C=N and C=C) cm^{-1}. ^1H NMR (DMSO-d_6, δ): 1.37 (3H, t, J = 7.4 Hz, OCH_2CH_3), 3.70 (2H, d, J = 6.1 Hz, H-1'), 4.21 (2H, q, J = 7.3 Hz, OCH_2CH_3), 5.25 (2H, m, H-3'), 6.18 (1H, m, H-2'), 7.36-8.12 (7H, m, Ar-H), 8.06 (1H, d, J = 7.6 Hz, H-6) and 8.76 (1H, s, H-4). Anal. Calcd. for $C_{24}H_{19}NO_4$ (385.42): C, 74.79; H, 4.97; N, 3.63. Found C, 74.70; H, 4.92; N, 3.59.

10-Allylchromeno[2',3':2,3]pyrido[6,5-*d*]pyrimidine-2,4,6-trione 20. A mixture of **12** (0.229 g, 1 mmol), barbituric acid (0.128 g, 1 mmol) and DBU (0.5 mL) was heated at reflux in absolute ethanol (20 mL) for 30 min. The solid obtained was filtered, dried in air and recrystallized from aqueous DMF to give **20** as white crystals, yield 0.13g (79%), m.p. above 300^oC. IR (KBr, cm^{-1}): 3198 (NH), 1739, 1676 ($2C=O_{cyclic\ amide}$), 1650 ($C=O_{\gamma\text{-pyrone}}$), 1616 and 1580 (C=N and C=C) cm^{-1}. ^1H NMR (DMSO-d_6, δ): 3.68 (2H, d, J = 5.6 Hz, H-1'), 5.11 (2H, m, H-3'), 6.12 (1H, m, H-2'), 7.48 (1H, m, H-8), 7.76 (1H, d, J = 7.3 Hz, H-9), 8.05 (1H, d, J = 7.2 Hz, H-7), 8.85 (1H, s, H-5), 11.79 and 12.20 (2H, each s, 2NH exchangeable with D_2O). Anal. Calcd. for $C_{17}H_{11}N_3O_4$ (321.29): C, 63.55; H, 3.45; N, 13.08. Found C, 63.28; H, 3.95; N, 13.10.

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