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# SYNTHETIC APPROACHES FOR CONSTRUCTION OF NOVEL 3-HETEROARYLCHROMENO[2,3-*b*]PYRIDINES AND ANNULATED CHROMENOPYRIDOPYRAZOLOPYRIMIDINES

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**Abstract** – Hydrazinolysis of ethyl 2,5-dioxo-1,5-dihydro-2*H*-chromeno[2,3-*b*]-pyridine-3-carboxylate (**2**) afforded chromeno[2,3-*b*]pyridine-3-carbohydrazide **3** which utilized as a precursor for building a diversity of heterocyclic compounds at position 3. Condensation of carbohydrazide **3** with 3-formylchromone produced the condensation product **4**, while addition of carbohydrazide **3** to phenyl isothiocyanate gave hydrazinecarbothioamide derivative **5** which upon cyclization afforded 3-thiadiazolylchromeno[2,3-*b*]pyridine-2,5(1*H*)-dione **6**. Condensation of carbohydrazide **3** with some monoelectrophilic reagents namely ethyl chloroformate, carbon disulfide, acetyl chloride and benzoyl chloride and chromone-3-carboxylic acid gave a variety of novel 3-oxadiazolylchromeno-[2,3-*b*]pyridines **7-10** and **12**. Treatment of carbohydrazide **3** with a variety of 1,3-bielectrophiles such as acetylacetone, ethyl acetoacetate and diethyl malonate yielded 3-(pyrazolyl)carbonylchromeno[2,3-*b*]pyridines **13-15**. Finally, reaction of carbohydrazide **3** with ethyl cyanoacetate and (ethoxymethylene)malononitrile afforded heteroannulated chromeno[2``,3``:6`,5`]pyrido[2`,3`-*d*]pyrazolo[1,5-*a*]-pyrimidines **17** and **18**. Structures of the synthesized products were confirmed based on their analytical and spectral data.

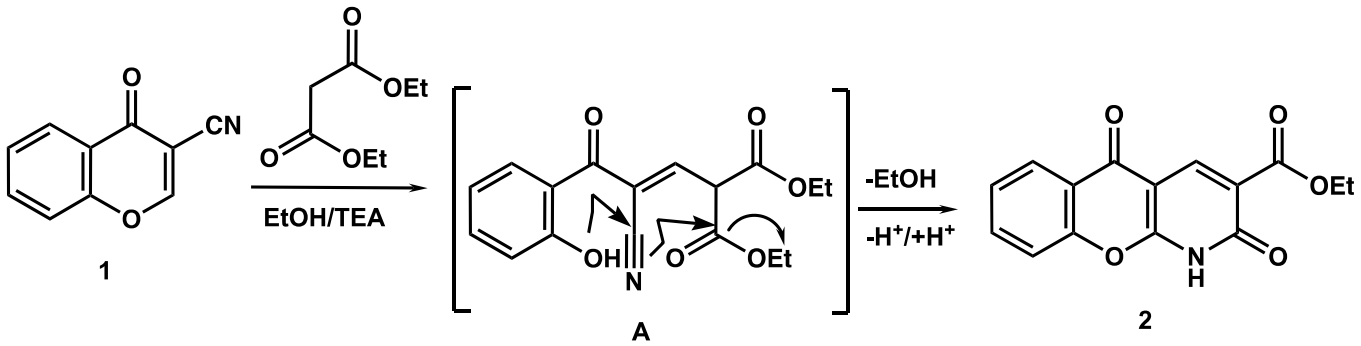
## INTRODUCTION

Chromones are commonly distributed in nature and have low toxicity,[1] as well as a wide variety of biological and pharmacological activities including anti-inflammatory,[2] anti-HIV,[3] anti-cancer,[4] anti-bacterial,[5] anti-malaria,[6] anti-cancer,[7] and Alzheimer's disease.[8] Chromone derivatives have recently

been used in a number of opto-electronic applications.[9] The introduction of electron-withdrawing group at position 3 of chromone moiety changes the reactivity of the γ-pyrone ring against nucleophilic reagents and opens up a wide synthetic spectrum of these essential heterocyclic oxygen-containing systems.[10] 3-Substituted chromones are active substrates and easily attacked at C-2 position by nucleophilic reagents and are used as useful synthetic intermediates in the construction of several heterocyclic compounds.[11] Chromone-3-carbonitrile are essential source for building of chromeno[2,3-*b*]pyridines through their reactions with active methylene compounds.[12] The present work aimed to utilize ethyl 2,5-dioxo-1,5-dihydro-2*H*-chromeno[2,3-*b*]pyridine-3-carboxylate (**2**)[13] for construction of some novel chromeno[2,3-*b*]pyridines bearing variable heterocyclic systems at position 3.

## RESULTS AND DISCUSSION

Reaction of chromone-3-carbonitrile (**1**) with diethyl malonate in boiling ethanol containing few drops of triethylamine (TEA), afforded ethyl 2,5-dioxo-1,5-dihydro-2*H*-chromeno[2,3-*b*]pyridine-3-carboxylate (**2**) *via* γ-pyrone ring opening (intermediate **A**) followed by recyclization as depicted in Scheme 1.[13]



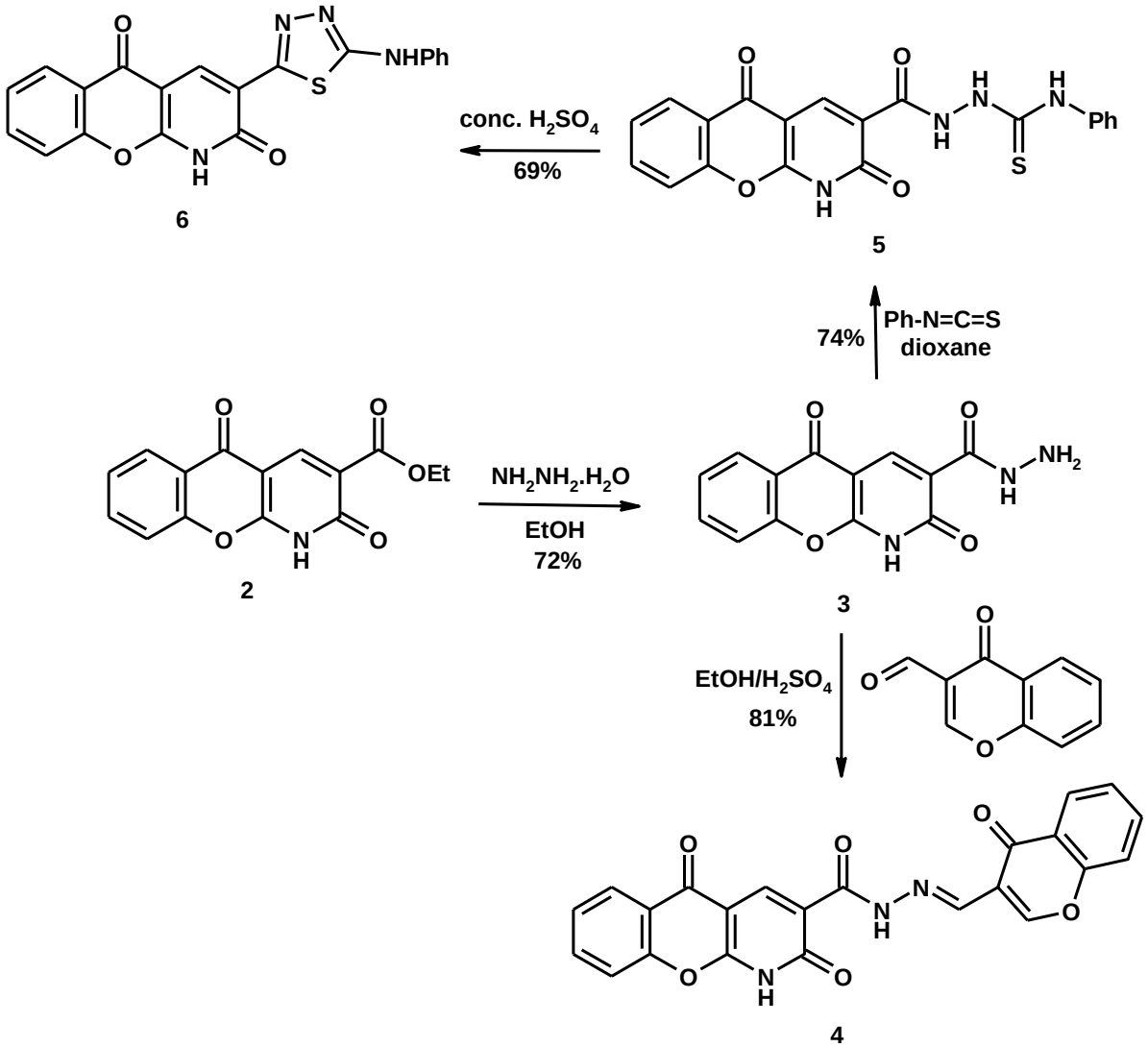

**Scheme 1.** Synthesis of chromeno[2,3-*b*]pyridine-3-carboxylate **2**

Hydrazinolysis of ethyl ester **2** with hydrazine hydrate in boiling ethanol gave chromeno[2,3-*b*]pyridine-3-carbohydrazide derivative **3** (Scheme 2). The mass spectrum of compound **3** recorded the molecular ion peak at *m/z* 271 corresponding to the suggested molecular formula $C_{13}H_9N_3O_4$. Its $^1$H NMR spectrum revealed typical singlet attributed to H-$4_{pyridine}$ at δ 8.68.

Simple condensation of carbohydrazide **3** with 3-formylchromone[14] in boiling ethanol containing concentrated sulfuric acid as a catalyst furnished the condensation product **4** (Scheme 2). The $^1$H NMR spectrum of compound **4** showed three specific singlet at δ 8.56 (CH=N), 8.62 (H-$4_{pyridine}$) and 8.83 (H-$2_{chromone}$). The molecular formula was confirmed from the mass spectrum which recorded the molecular ion peak at *m/z* 427 which agrees well with the formula weight (427.37).

Addition of carbohydrazide **3** into phenyl isothiocyanate in dry dioxane afforded hydrazinecarbothioamide derivative **5**. Cyclization of compound **5** in concentrated sulfuric acid under stirring conditions afforded 3-thiadiazolylchromeno[2,3-*b*]pyridine **6** (Scheme 2). The IR spectrum of

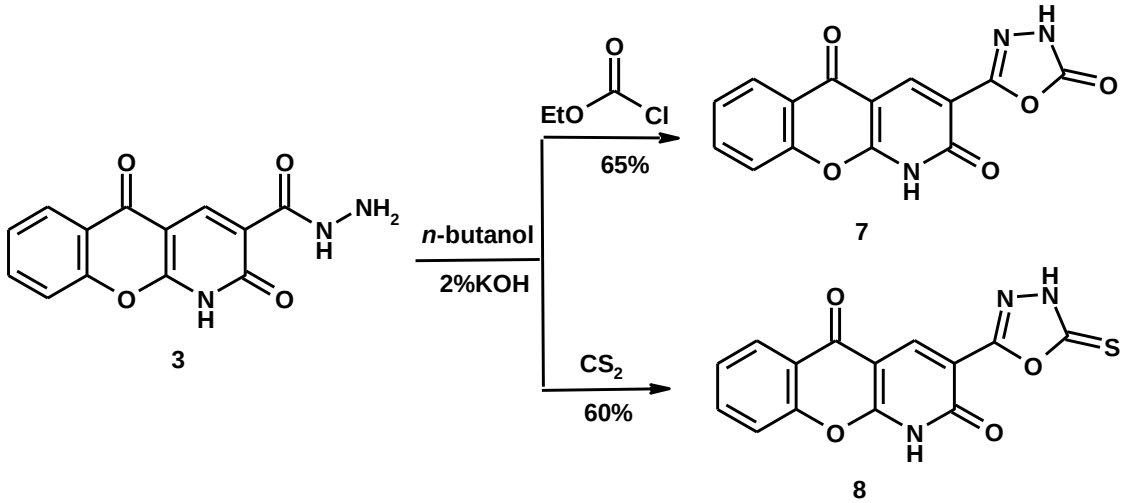
compound **5** recorded specific absorption bands at 1686 ($C=O_{pyridone}$), 1668 ($C=O_{hydrazide}$), 1647 ($C=O_{\gamma\text{-pyrone}}$) and 1214 $cm^{-1}$ (C=S). Its $^1H$ NMR spectrum appeared four $D_2O$ exchangeable signals attributable to four NH protons at δ 8.91, 9.22, 9.48 and 10.54, in addition to a specific singlet at δ 8.63 attributed to $H\text{-}4_{pyridine}$. The $^{13}C$ NMR spectrum of compound **5** showed downfield signals at δ 162.3, 167.5, 175.7 and 184.2 attributed to (C-2 as C=O), (C=O as hydrazide), (C5 as C=O) and (C=S), respectively. The mass spectrum of compound **6** showed the parent ion peak at *m/z* 388 which in coincident with the proposed molecular formula ($C_{20}H_{12}N_4O_3S$). The specific singlet of $H\text{-}4_{pyridine}$ appeared in the $^1H$ NMR spectrum of compound **6** at δ 8.72.




**Scheme 2.** Formation of carbohydrazide **3** and its condensation and addition reactions

Next, carbohydrazide **3** was allowed to react with some monoelectrophilic reagents aiming to construct a variety of novel oxadiazolylchromeno[2,3-*b*]pyridines. Thus, condensation of carbohydrazide **3** with ethyl chloroformate and carbon disulfide in boiling butanol containing potassium hydroxide solution (2%) gave oxadiazolylchromeno[2,3-*b*]pyridines **7** and **8**, respectively (Scheme 3). The molecular ion peaks

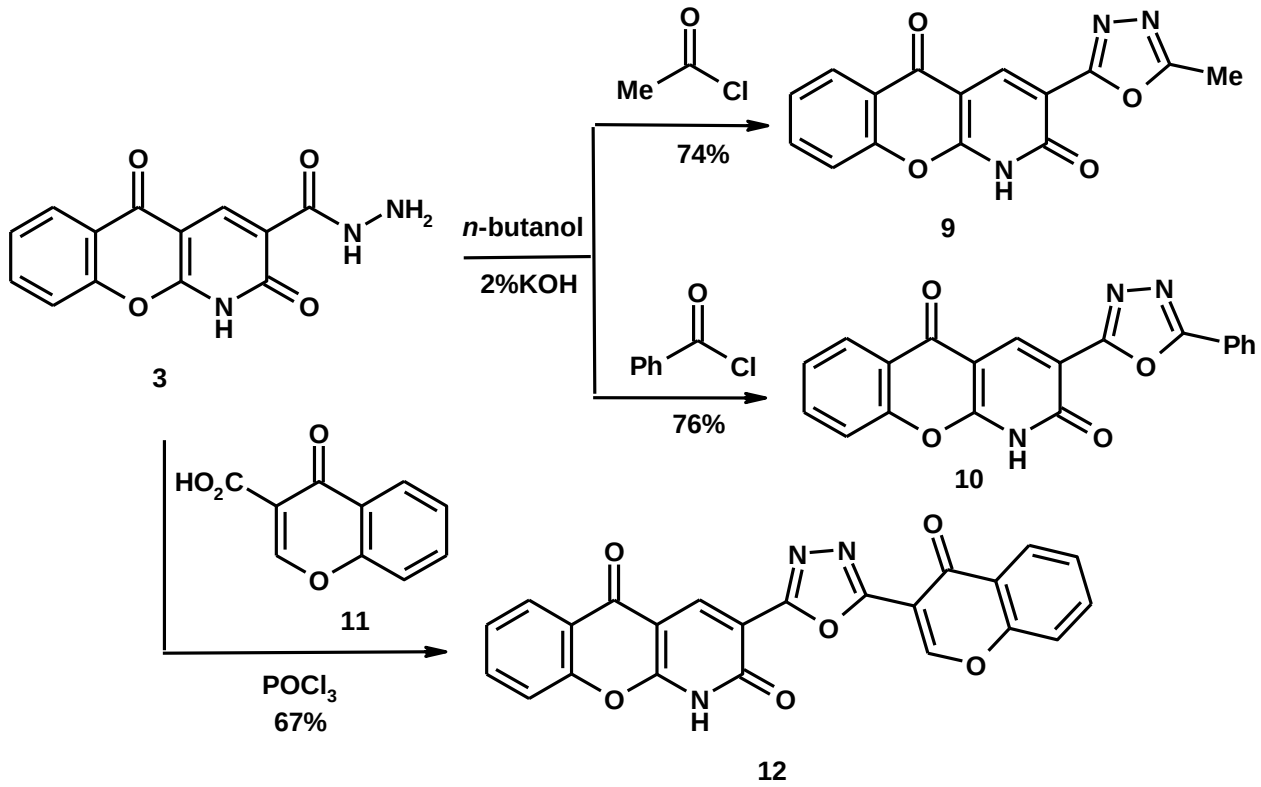
appeared in the mass spectrum of compounds **7** and **8** at *m/z* 297 and 313 that agree well with the suggested formula weights $C_{14}H_7N_3O_5$ and $C_{14}H_7N_3O_4S$, respectively. The $^1$H NMR spectra of compounds **7** and **8** showed typical singlet attributed to H-$4_{pyridine}$ at δ 8.80 and 8.75.




**Scheme 3.** Formation of oxadiazolylchromeno[2,3-*b*]pyridines **7** and **8**

Under the previous reaction conditions, treatment of carbohydrazide **3** with acetyl chloride and benzoyl chloride afforded oxadiazole derivatives **9** and **10**, respectively (Scheme 4). The molecular formula weights of compounds **9** and **10** were recorded in the mass spectra, as the base peaks, at *m/z* 295 and 357. The IR spectra of compounds **9** and **10** recorded characteristic absorption bands at 1682/1693 (C=$O_{pyridone}$), 1649/1653 (C=$O_{\gamma\text{-pyrone}}$) and 1610/1604 cm$^{-1}$ (C=N). The $^1$H NMR spectra of compounds **9** and **10** displayed definite singlet attributable to H-$4_{pyridine}$ at δ 8.85 and 8.79. The spectrum of compound **9** revealed singlet signal due to the methyl protons at δ 2.28. The $^{13}$C NMR spectrum of compound **9** revealed typical signal due to the methyl carbon at δ 15.3.

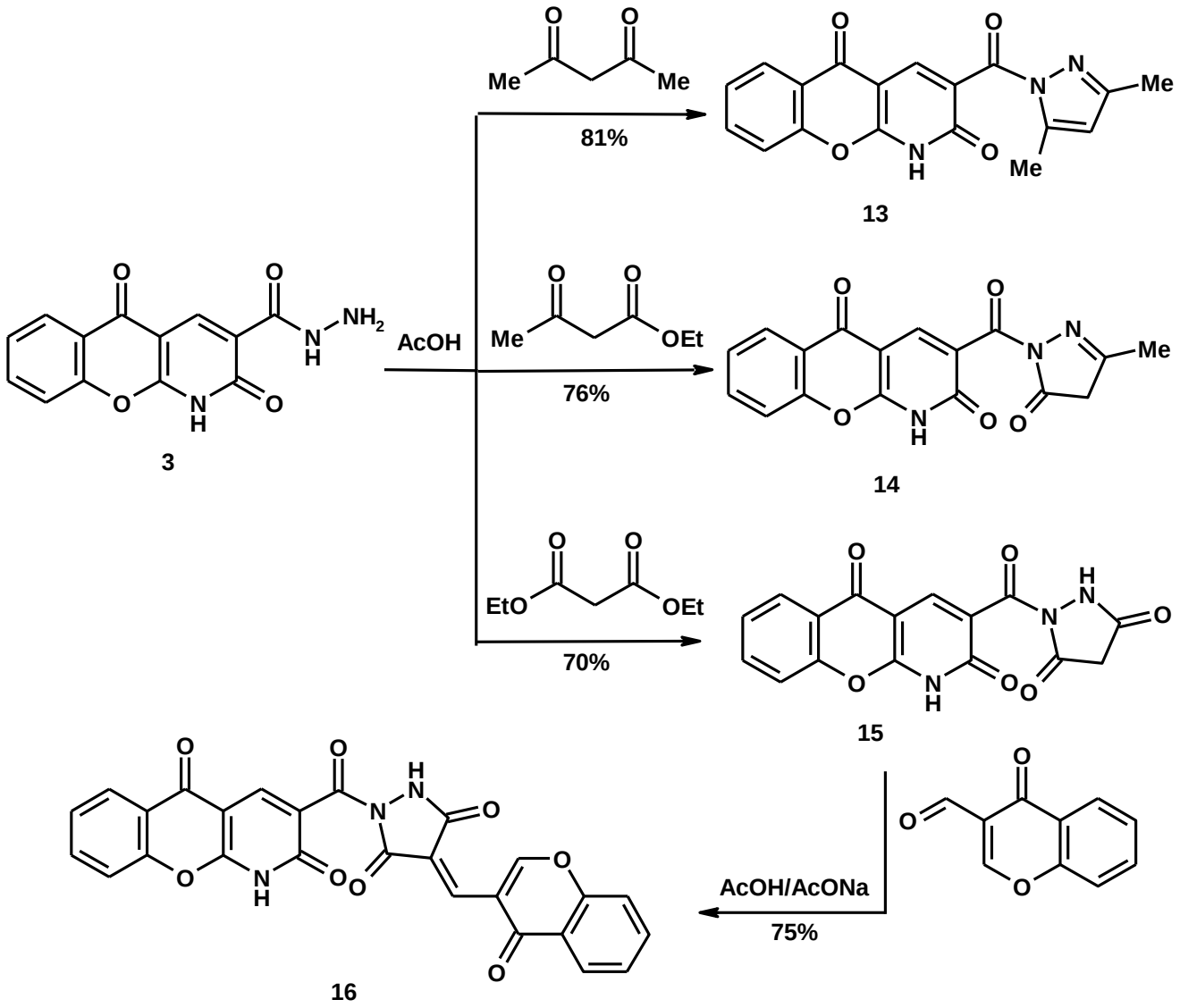
Further, boiling carbohydrazide **3** with chromone-3-carboxylic acid (**11**)[15] in phosphorus oxychloride afforded the novel oxadiazole **12** bearing chromone and chromeno[2,3-*b*]pyridine in the same molecular frame (Scheme 4). Two characteristic singlet appeared in the $^1$H NMR spectrum of compound **12** at δ 8.73 (H-$4_{pyridine}$) and 8.90 (H-$2_{chromone}$). In addition, the pyridine NH proton observed as $D_2O$ exchangeable signal at δ 10.09. The mass spectrum confirms the molecular weight of compound **12** and showed the parent ion peak at *m/z* 425.




**Scheme 4.** Formation of oxadiazolylchromeno[2,3-*b*]pyridines **9**, **10** and **12**

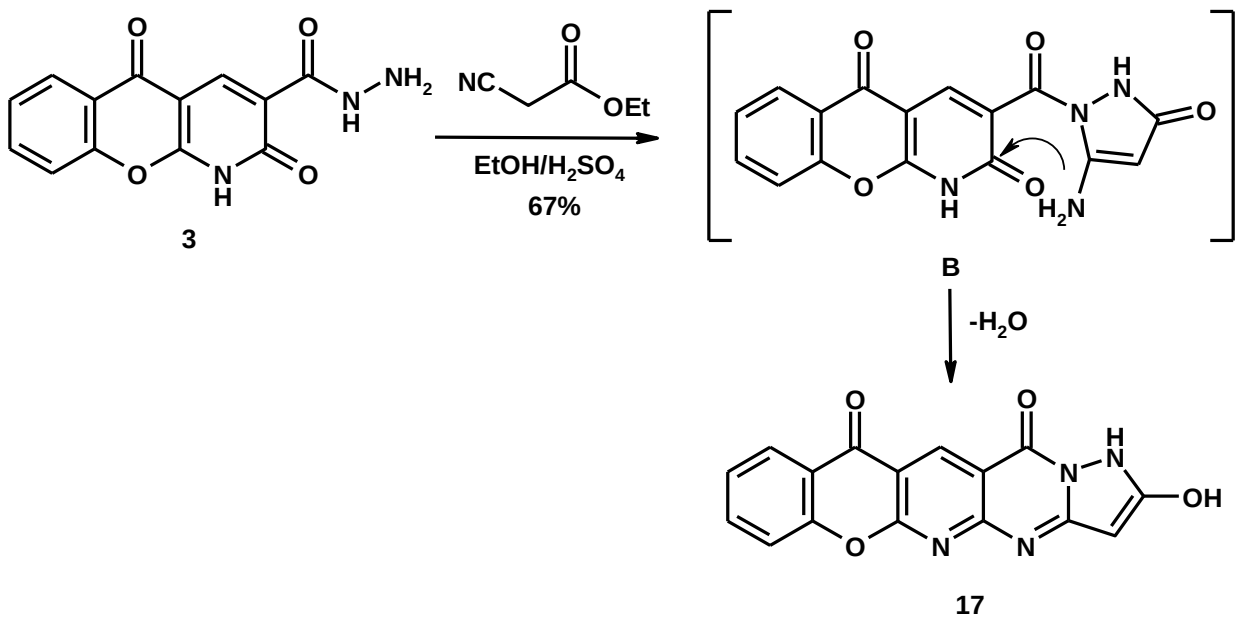
On the other hand, carbohydrazide **3** was allowed to reacted with a variety of 1,3-bielectrophiles. Therefore, reaction of carbohydrazide **3** with acetylacetone, ethyl acetoacetate and diethyl malonate in boiling acetic acid afforded the novel 3-(pyrazolyl)carbonylchromeno[2,3-*b*]pyridines **13-15**, respectively (Scheme 5). Structures of compounds **13-15** were confirmed from their mass spectra which recorded the molecular ion peaks at *m/z* 335, 337 and 339 that agree well with the proposed molecular formula weights 335.31, 337.29 and 339.26, respectively. In the $^{1}$H NMR spectra of compounds **13-15**, the H-4$_{pyridine}$ appeared as specific singlet at δ 8.82, 8.77 and 8.79, respectively. The active methylene protons in compounds **14** and **15** appeared as characteristic singlet at δ 3.06 and 3.38, respectively.

The active methylene group in compound **15** condensed with the formyl function in 3-formylchromone giving the condensation product **16** (Scheme 5). The $^{1}$H NMR spectrum of compound **16** showed three typical singlets attributed to CH$_{olefinic}$, H-4$_{pyridine}$ and H-2$_{chromone}$ at δ 8.39, 8.71 and 8.89. Its mass spectrum showed the molecular ion peak at *m/z* 495 and confirms the proposed structure.



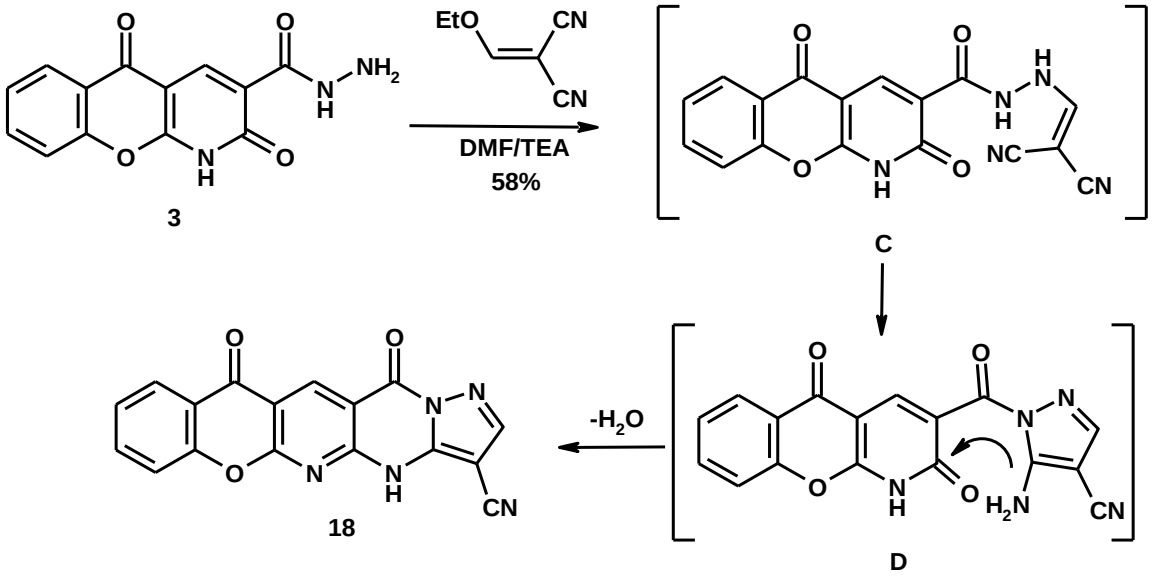

**Scheme 5.** Synthesis of 3-(pyrazolyl)carbonylchromeno[2,3-*b*]pyridines **13**-**16**

After that, condensation of carbohydrazide **3** with ethyl cyanoacetate, in boiling ethanol containing sulfuric acid, afforded chromeno[2``, 3``:6`,5`]pyrido[2`,3`-*d*]pyrazolo[1,5-*a*]pyrimidine **17**. The reaction occurs through the formation of 5-aminopyrazole intermediate **B** followed by cyclocondensation as illustrated in Scheme 6. The molecular weight of compound **17** was recorded in the mass spectrum at *m/z* 320 which agrees well with its molecular formula $C_{16}H_8N_4O_4$. The IR spectrum showed two typical absorption bands due to $C{=}O_{pyrimidinone}$ and $C{=}O_{\gamma\text{-pyrone}}$ at 1674 and 1657 $cm^{-1}$. Two charateristic singlet appeared in the $^1H$ NMR spectrum of compound **17** at δ 6.78 ($H\text{-}4_{pyrazole}$) and 8.74 ($H\text{-}4_{pyridine}$).




**Scheme 6.** Formation of chromeno[2``, 3``: 6`,5`]pyrido[2`,3`-*d*]pyrazolo[1,5-*a*]pyrimidine **17**

Finally, carbohydrazide **3** reacted with (ethoxymethylene)malononitrile in boiling DMF containing TEA giving the novel annulated chromeno[2``, 3``: 6`,5`]pyrido[2`,3`-*d*]pyrazolo[1,5-*a*]pyrimidine **18**, *via* intermediates **C** and **D** (Scheme 7). The IR spectra of compound **18** showed characteristic absorption bands at 2231 (C≡N), 1671 ($C=O_{pyrimidinone}$) and 1652 $cm^{-1}$ ($C=O_{\gamma\text{-pyrone}}$). The $^{1}H$ NMR spectra showed specific singlet signals at δ 8.56 ($H\text{-}3_{pyrazole}$) and 8.82 ($H\text{-}4_{pyridine}$). The mass spectrum of compound **18** recorded the moleculat ion peak, as the base peak, at *m/z* 329 and confirms the structure. The two-carbonyl carbons appeared in the $^{13}C$ NMR spectrum at downfield region at δ 165.2 and 178.8.




**Scheme 7.** Formation of chromeno[2``, 3``: 6`,5`]pyrido [2`,3`-*d*]pyrazolo[1,5-*a*]pyrimidine **18**

## CONCLUSIONS

The novel 2,5-dioxo-1,5-dihydro-2*H*-chromeno[2,3-*b*]pyridine-3-carbohydrazide (**3**) was synthesized from the reaction of ethyl 2,5-dioxo-1,5-dihydro-2*H*-chromeno[2,3-*b*]pyridine-3-carboxylate (**2**) with hydrazine hydrate. Carbohydrazide **3** used as a starting material to create a diversity of heterocyclic compounds. The condensation product **4** was formed by condensation of carbohydrazide **3** with 3-formylchromone, adding carbohydrazide **3** to phenylisothiocyanate gave hydrazinecarbothioamide derivative **5** which upon cyclization in conc. $H_2SO_4$ provided 3-thiadiazolylchromeno[2,3-*b*]pyridine-2,5(1*H*)-dione **6**. Carbohydrazide **3** reacted with several monoelectrophilic reagents namely ethyl chloroformate, carbon disulfide, acetyl chloride benzoyl chloride, and chromone-3-carboxylic acid giving a variety of novel 3-oxadiazolylchromeno[2,3-*b*]pyridines, **7**-**10** and **12**. Novel 3-(pyrazolyl)carbonyl-chromeno[2,3-*b*]pyridines **13**-**15** were obtained from treatment of carbohydrazide **3** with some 1,3-bielectrophils such as acetylacetone, ethyl acetoacetate and diethyl malonate. Heteroannulated chromenopyridopyrazolopyrimidines **17** and **18** were synthesized from condensation reaction of carbohydrazide **3** with ethyl cyanoacetate and (ethoxymethylene)malononitrile.

## 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. Ethyl 2,5-dioxo-1,5-dihydro-2*H*-chromeno[2,3-*b*]pyridine-3-carboxylate (**2**) was prepared according to literature.[13]

**2,5-Dioxo-1,5-dihydro-2*H*-chromeno[2,3-*b*]pyridine-3-carbohydrazide (3).** To a hot solution of ethyl ester **2** (0.57 g, 2 mmol) in absolute EtOH (15 mL), hydrazine hydrate (0.15 mL, 3 mmol) was added. The reaction mixture was heated under reflux for 2 h. The pale yellow crystals obtained after cooling were filtered and recrystallized from *2*-propanol, mp > 300 ºC, yield (0.39 g, 72%). IR (KBr, $cm^{-1}$): 3365, 3324, 3270 ($NH_2$, NH), 3045 ($CH_{arom.}$), 1681 ($C{=}O_{pyridone}$), 1674 ($C{=}O_{hydrazide}$), 1648 ($C{=}O_{\gamma\text{-}pyrone}$), 1589 (C=C). $^1$H NMR (DMSO-$d_6$, δ, 300 MHz): 6.38 (br, 2H, $NH_2$ exchangeable with $D_2O$), 7.31 (t, 1H, *J*=6.9 Hz, H-7), 7.53 (d, 1H, *J*=6.9 Hz, H-9), 7.81 (t, 1H, *J*=6.9 Hz, H-8), 8.12 (d, 1H, *J*=6.9 Hz, H-6), 8.68 (s, 1H, $H\text{-}4_{pyridine}$), 9.23 (br, 1H, NH exchangeable with $D_2O$). $^{13}$C NMR (DMSO-$d_6$, δ, 75 MHz): 92.8 (C4a), 118.4 (C-9), 122.6 (C5a), 124.1 (C7), 128.3 (C8), 131.5 (C3), 134.7 (C-6), 148.3 (C-4), 151.2 (C9a),

158.1 (C10a), 162.6 (C-2 as C=O), 167.9 (C=O as hydrazide), 175.4 (C5 as C=O). Mass spectrum (*m/z*, %): 271 ($M^+$, 14), 240 (36), 212 (27), 197 (8), 120 (100), 105 (75), 93 (26), 77 (17) and 64 (33). Anal. Calcd for $C_{13}H_9N_3O_4$ (271.23): C, 57.57; H, 3.34; N, 15.49%. Found: C, 57.24; H, 3.28; N, 15.37%.

**2,5-Dioxo-*N*'-[(chromon-3-yl)methylidene]-1,5-dihydro-2*H*-chromeno[2,3-*b*]pyridine-3-carbohydrazide (4).** To a hot solution of carbohydrazide **3** (0.54 g, 2 mmol) in absolute EtOH (20 mL), 3-formylchromone (0.35 g, 2 mmol), in absolute EtOH (10 mL) containing conc. $H_2SO_4$ (0.1 mL) was added. The reaction mixture was heated under reflux for 10 min. The white crystals obtained during heating were filtered and recrystallized from DMF/$H_2O$, mp 288-289 ºC, yield (0.70 g, 81%). IR (KBr, $cm^{-1}$): 3346 (2NH), 3038 ($CH_{arom.}$), 1683 ($C=O_{pyridone}$), 1670 ($C=O_{hydrazide}$), 1657, 1651 (2C=O $_{\gamma\text{-pyrone}}$), 1606 (C=N), 1578 (C=C). $^1$H NMR (DMSO-*d*$_6$, δ, 300 MHz): 7.21-7.27 (m, 2H, Ar-H), 7.34-7.38 (m, 2H, Ar-H), 7.75-7.78 (m, 2H, Ar-H), 7.98 (d, 1H, *J*=7.2 Hz, Ar-H), 8.09 (d, 1H, *J*=7.8 Hz, Ar-H), 8.56 (s, 1H, CH=N), 8.62 (s, 1H, H-$4_{pyridine}$), 8.83 (s, 1H, H-$2_{chromone}$), 9.51 (br, 1H, NH exchangeable with $D_2O$). Mass spectrum (*m/z*, %): 427 ($M^+$, 8), 255 (100), 212 (20), 171 (43), 145 (12), 121 (45), 93 (17), 77 (31) and 65 (12). Anal. Calcd for $C_{23}H_{13}N_3O_6$ (427.37): C, 64.64; H, 3.07; N, 9.83%. Found: C, 64.35; H, 3.02; N, 9.69%.

**2-[(2,5-Dioxo-1,5-dihydro-2*H*-chromeno[2,3-*b*]pyridin-3-yl)carbonyl]-*N*-phenylhydrazinecarbothioamide (5).** To a hot solution of carbohydrazide **3** (0.54 g, 2 mmol) in dioxane (30 mL), phenyl isothiocyanate (0.27 g, 24 mL, 2 mmol) in dioxane (10 mL) was added dropwise with continuous stirring for 30 min. The white crystals separated were filtered and recrystallized from xylene, mp 275-276 ºC, yield (0.61 g, 74%). IR (KBr, $cm^{-1}$): 3402, 3359, 3312, 3261 (4NH), 3072 ($CH_{arom.}$), 1686 (C=O $_{pyridone}$), 1668 ($C=O_{hydrazide}$), 1647 ($C=O_{\gamma\text{-pyrone}}$), 1580 (C=C), 1214 (C=S). $^1$H NMR (DMSO-*d*$_6$, δ, 300 MHz): 7.18-7.35 (m, 5H, Ph-H), 7.39 (t, 1H, *J*=6.6 Hz, H-7), 7.58 (d, 1H, *J*=6.9 Hz, H-9), 7.83 (t, 1H, *J*=6.9 Hz, H-8), 8.10 (d, 1H, *J*=6.6 Hz, H-6), 8.63 (s, 1H, H-$4_{pyridine}$), 8.91 (br, 1H, NH exchangeable with $D_2O$), 9.22 (br, 1H, NH exchangeable with $D_2O$), 9.48 (br, 1H, NH exchangeable with $D_2O$), 10.54 (br, 1H, NH exchangeable with $D_2O$). $^{13}$C NMR (DMSO-*d*$_6$, δ, 75 MHz): 92.5 (C4a), 118.0 (C-9), 122.5 (C5a), 124.3 (C7), 125.2 (C4-Ph), 127.1 (C2, C6-Ph), 128.8 (C8), 129.4 (C3, C5-Ph), 130.7 (C3), 134.1 (C6), 136.9 (C1-Ph), 148.5 (C-4), 151.4 (C9a), 158.8 (C10a), 162.3 (C-2 as C=O), 167.5 (C=O as hydrazide), 175.7 (C5 as C=O), 184.2 (C=S). Mass spectrum (*m/z*, %): 406 ($M^+$, 10), 314 (7), 255 (100), 240 (39), 212 (18), 184 (9), 120 (65), 105 (35), 92 (18), 77 (42) and 64 (11). Anal. Calcd for $C_{20}H_{14}N_4O_4S$ (406.41): C, 59.11; H, 3.47; N, 13.79; S, 7.89%. Found: C, 58.90; H, 3.21; N, 13.47; S, 7.62%.

**3-[5-(Phenylamino)-1,3,4-thiadiazol-2-yl]-2*H*-chromeno[2,3-*b*]pyridine-2,5(1*H*)-dione (6).** Compound **5** (0.82 g, 2 mmol) was stirred in conc. $H_2SO_4$ (10 mL) at room temperature for 1 h. The mixture was poured onto crushed ice (50 mL) with continuous stirring for 15 min. The pale brown solid separated was filtered and crystallized from AcOH, mp > 300 ºC, yield (0.54 g, 69%). IR (KBr, $cm^{-1}$):

3358, 3227 (2NH), 3055 ($CH_{arom.}$), 1679 ($C=O_{pyridone}$), 1651 ($C=O_{\gamma\text{-pyrone}}$), 1610 (C=N), 1584 (C=C). $^1$H NMR (DMSO-*d*$_6$, δ, 300 MHz): 6.98-7.28 (m, 6H, Ph-H and H-7), 7.55 (d, 1H, *J*=7.2 Hz, H-9), 7.77 (t, 1H, *J*=7.2 Hz, H-8), 8.08 (d, 1H, *J*=7.2 Hz, H-6), 8.72 (s, 1H, H-$4_{pyridine}$), 9.38 (br, 1H, NH exchangeable with $D_2O$), 9.94 (br, 1H, NH exchangeable with $D_2O$). $^{13}$C NMR (DMSO-*d*$_6$, δ, 75 MHz): 93.1 (C4a), 118.3 (C-9), 122.4 (C5a), 124.8 (C7), 125.1 (C4-Ph), 126.8 (C2, C6-Ph), 128.6 (C8), 129.9 (C3, C5-Ph), 130.5 (C3), 134.5 (C6), 136.6 (C1-Ph), 148.0 (C-4), 151.5 (C9a), 153.7 (C-$3_{thiadiazole}$), 155.6 (C-$5_{thiadiazole}$), 158.5 (C10a), 162.8 (C-2 as C=O), 175.4 (C5 as C=O). Mass spectrum (*m/z*, %): 388 ($M^+$, 100), 360 (79), 268 (23), 164 (14), 121 (45), 105 (22), 93 (16), 77 (32) and 64 (7). Anal. Calcd for $C_{20}H_{12}N_4O_3S$ (388.40): C, 61.85; H, 3.11; N, 14.43; S, 8.25%. Found: C, 61.54; H, 3.02; N, 14.25; S, 8.13%.

**3-(5-Oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2*H*-chromeno[2,3-*b*]pyridine-2,5(1*H*)-dione (7).** A mixture of carbohydrazide **3** (0.54 g, 2 mmol) and ethyl chloroformate (0.22 g, 0.2 mL, 2 mmol), in *n*-butanol (20 mL) containing KOH (2%, 10 mL), was heated under reflux for 30 min. After cooling the reaction mixture was poured onto crushed ice and neutralized with conc. HCl. The pale yellow solid so formed was filtered and crystallized from toluene as pale yellow crystals, mp 261-262 ºC, yield (0.39 g, 65%). IR (KBr, $cm^{-1}$): 3338, 3294 (2NH), 3067 ($CH_{arom.}$), 1742 (OC=O), 1682 ($C=O_{pyridone}$), 1653 ($C=O_{\gamma\text{-pyrone}}$), 1603 (C=N), 1573 (C=C). $^1$H NMR (DMSO-*d*$_6$, δ, 300 MHz): 7.28 (t, 1H, *J*=7.2 Hz, H-7), 7.49 (d, 1H, *J*=6.9 Hz, H-9), 7.80 (t, 1H, *J*=7.2 Hz, H-8), 8.11 (d, 1H, *J*=6.9 Hz, H-6), 8.80 (s, 1H, H-$4_{pyridine}$), 10.19 (br, 1H, NH exchangeable with $D_2O$), 10.62 (br, 1H, NH exchangeable with $D_2O$). $^{13}$C NMR (DMSO-*d*$_6$, δ, 75 MHz): 92.3 (C4a), 118.6 (C9), 122.4 (C5a), 123.9 (C7), 128.7 (C8), 130.3 (C3), 134.6 (C6), 148.9 (C4), 151.1 (C9a), 153.6 ($C5_{oxadiazole}$), 158.5 (C10a), 162.0 (C2 as C=O), 166.9 ($C2_{oxadiazole}$), 175.8 (C5 as C=O). Mass spectrum (*m/z*, %): 297 ($M^+$, 25), 238 (37), 210 (54), 182 (13), 145 (19), 120 (100), 105 (35), 93 (11), 77 (43) and 65 (9). Anal. Calcd for $C_{14}H_7N_3O_5$ (297.22): C, 56.57; H, 2.37; N, 14.14%. Found: C, 56.25; H, 2.10; N, 13.84%.

**3-(5-Thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2*H*-chromeno[2,3-*b*]pyridine-2,5(1*H*)-dione (8).** A mixture of carbohydrazide **3** (0.54 g, 2 mmol) and carbon disulfide (0.24 g, 0.18 mL, 3 mmol), in *n*-butanol (20 mL) containing KOH (2%, 10 mL), was heated under reflux for 30 min. After cooling the reaction mixture was poured onto crushed ice and neutralized with conc. HCl. The dark yellow solid so formed was filtered and crystallized from dioxane as yellow crystals, mp 296-297 ºC, yield (0.37 g, 60%). IR (KBr, $cm^{-1}$): 3352, 3304 (2NH), 3058 ($CH_{arom.}$), 1689 ($C=O_{pyridone}$), 1645 ($C=O_{\gamma\text{-pyrone}}$), 1601 (C=N), 1578 (C=C), 1236 (C=S). $^1$H NMR (DMSO-*d*$_6$, δ, 300 MHz): 7.22 (t, 1H, *J*=6.6 Hz, H-7), 7.48 (d, 1H, *J*=6.6 Hz, H-9), 7.82 (t, 1H, *J*=6.6 Hz, H-8), 8.06 (d, 1H, *J*=6.6 Hz, H-6), 8.75 (s, 1H, H-$4_{pyridine}$), 10.36 (br, 1H, NH exchangeable with $D_2O$), 10.71 (br, 1H, NH exchangeable with $D_2O$). $^{13}$C NMR (DMSO-*d*$_6$, δ, 75 MHz): 92.1 (C4a), 118.8 (C-9), 122.2 (C5a), 124.2 (C7), 128.5 (C8), 130.0 (C3), 134.7 (C6), 148.3 (C4), 151.4 (C9a), 153.9 ($C5_{oxadiazole}$), 158.4 (C10a), 162.2 (C-2 as C=O), 175.6 (C5 as C=O), 188.7

($C2_{oxadiazole}$ as C=S). Mass spectrum (*m/z*, %): 313 ($M^+$, 28), 285 (19), 252 (40), 120 (100), 105 (24), 93 (24), 77 (16) and 64 (8). Anal. Calcd for $C_{14}H_7N_3O_4S$ (313.29): C, 53.67; H, 2.25; N, 13.41; S, 10.23%. Found: C, 53.40; H, 2.09; N, 13.18; S, 10.11%.

**3-(5-Methyl-1,3,4-oxadiazol-2-yl)-2*H*-chromeno[2,3-*b*]pyridine-2,5(1*H*)-dione (9).** A mixture of carbohydrazide **3** (0.54 g, 2 mmol) and acetyl chloride (0.16 g, 0.15 mL, 2 mmol), in *n*-butanol (20 mL) containing KOH (2%, 10 mL), was heated under reflux for 30 min. After cooling the reaction mixture was poured onto crushed ice and neutralized with conc. HCl. The pale yellow solid so formed was filtered and crystallized from AcOH/$H_2O$ as pale yellow crystals, mp 255-256 ºC, yield (0.44 g, 74%). IR (KBr, $cm^{-1}$): 3408 (NH), 3066 ($CH_{arom.}$), 2923, 2884 ($CH_{aliph.}$), 1682 ($C=O_{pyridone}$), 1649 ($C=O_{\gamma\text{-pyrone}}$), 1610 (C=N), 1591 (C=C). $^1$H NMR (DMSO-$d_6$, δ, 300 MHz): 2.28 (s, 3H, $CH_3$), 7.27 (t, 1H, *J*=6.6 Hz, H-7), 7.52 (d, 1H, *J*=6.9 Hz, H-9), 7.81 (t, 1H, *J*=6.6 Hz, H-8), 8.09 (d, 1H, *J*=6.9 Hz, H-6), 8.85 (s, 1H, H-$4_{pyridine}$), 10.25 (br, 1H, NH exchangeable with $D_2O$). $^{13}$C NMR (DMSO-$d_6$, δ, 75 MHz): 15.3 ($CH_3$), 92.0 (C4a), 117.8 (C-9), 122.0 (C5a), 124.3 (C7), 128.9 (C8), 131.1 (C3), 134.4 (C6), 148.2 (C-4), 151.6 (C9a), 153.6 ($C5_{oxadiazole}$), 154.2 ($C2_{oxadiazole}$), 158.3 (C10a), 162.1 (C-2 as C=O), 175.7 (C5 as C=O). Mass spectrum (*m/z*, %): 295 ($M^+$, 100), 267 (65), 226 (21), 184 (15), 159 (12), 120 (72), 105 (33), 77 (46) and 64 (15). Anal. Calcd for $C_{15}H_9N_3O_4$ (295.25): C, 61.02; H, 3.07; N, 14.23%. Found: C, 60.84; H, 2.84; N, 14.07%.

**3-(5-Phenyl-1,3,4-oxadiazol-2-yl)-2*H*-chromeno[2,3-*b*]pyridine-2,5(1*H*)-dione (10).** A mixture of carbohydrazide **3** (0.54 g, 2 mmol) and benzoyl chloride (0.28 g, 0.24 mL, 2 mmol), in *n*-butanol (20 mL) containing KOH (2%, 10 mL), was heated under reflux for 30 min. After cooling the reaction mixture was poured onto crushed ice and neutralized with conc. HCl. The white solid separated was filtered and crystallized from AcOH as white crystals, mp > 300 ºC, yield (0.54 g, 76%). IR (KBr, $cm^{-1}$): 3375 (NH), 3059 ($CH_{arom.}$), 1673 ($C=O_{pyridone}$), 1653 ($C=O_{\gamma\text{-pyrone}}$), 1604 (C=N), 1596 (C=C). $^1$H NMR (DMSO-$d_6$, δ, 300 MHz): 6.98-7.28 (m, 6H, Ph-H and H-7), 7.52 (d, 1H, *J*=6.9 Hz, H-9), 7.81 (t, 1H, *J*=6.6 Hz, H-8), 8.09 (d, 1H, *J*=6.9 Hz, H-6), 8.79 (s, 1H, H-$4_{pyridine}$), 10.25 (br, 1H, NH exchangeable with $D_2O$). $^{13}$C NMR (DMSO-$d_6$, δ, 75 MHz): 92.4 (C4a), 118.1 (C-9), 122.3 (C5a), 124.2 (C7), 125.8 (C1-Ph), 127.3 (C2, C6-Ph), 128.5 (C8), 129.1 (C4-Ph), 129.9 (C3, C5-Ph), 131.6 (C3), 135.0 (C6), 148.8 (C-4), 151.2 (C9a), 153.7 ($C5_{oxadiazole}$), 155.3 ($C2_{oxadiazole}$), 158.7 (C10a), 162.5 (C-2 as C=O), 175.6 (C5 as C=O). Mass spectrum (*m/z*, %): 357 ($M^+$, 100), 329 (81), 252 (51), 220 (57), 121 (46), 105 (13), 77 (21) and 64 (11). Anal. Calcd for $C_{20}H_{11}N_3O_4$ (357.32): C, 67.23; H, 3.10; N, 11.76%. Found: C, 67.14; H, 3.02; N, 11.61%.

**3-[5-(Chromon-3-yl)-1,3,4-oxadiazol-2-yl]-2*H*-chromeno[2,3-*b*]pyridine-2,5(1*H*)-dione (12).** A mixture of carbohydrazide **3** (0.54 g, 2 mmol) and chromone-3-carboxylic acid (**11**) (0.38 g, 2 mmol), in phosphorous oxychloride (15 mL) was heated under reflux for 1 h. After cooling the reaction mixture was

poured onto crushed ice and left overnight. The white solid separated was filtered and crystallized from AcOH as white crystals, mp 271-272 ºC, yield (0.57 g, 67%). IR (KBr, $cm^{-1}$): 3386 (NH), 3039 ($CH_{arom.}$), 1684 ($C=O_{pyridone}$), 1658, 1654 ($2C=O_{\gamma\text{-pyrone}}$), 1582 (C=C). $^1$H NMR (DMSO-*d*$_6$, δ, 300 MHz): 7.19-7.42 (m, 4H, Ar-H), 7.50-7.57 (m, 2H, Ar-H), 7.99-8.06 (m, 2H, Ar-H), 8.73 (s, 1H, $H\text{-}4_{pyridine}$), 8.90 (s, 1H, $H\text{-}2_{chromone}$), 10.09 (br, 1H, NH exchangeable with $D_2O$). Mass spectrum (*m/z*, %): 425 ($M^+$, 34), 369 (100), 252 (46), 145 (28), 120 (83), 105 (9), 93 (28), 77 (13) and 64 (7). Anal. Calcd for $C_{23}H_{11}N_3O_6$ (425.35): C, 64.95; H, 2.61; N, 9.88%. Found: C, 64.66; H, 2.38; N, 9.54%.

**3-[(3,5-Dimethyl-1*H*-pyrazol-1-yl)carbonyl]-2*H*-chromeno[2,3-*b*]pyridine-2,5(1*H*)-dione (13).** A mixture of carbohydrazide **3** (0.54 g, 2 mmol) and acetylacetone (0.20 g, 0.20 mL, 2 mmol), in acetic acid (20 mL) was heated under reflux for 30 min. The white crystals separated after cooling were filtered and crystallized from toluene, mp 243-244 ºC, yield (0.54 g, 81%). IR (KBr, $cm^{-1}$): 3409 (NH), 3047 ($CH_{arom.}$), 2924, 2875 ($CH_{aliph.}$), 1687 ($C=O_{pyridone}$), 1674 ($C=O_{amide}$), 1646 ($C=O_{\gamma\text{-pyrone}}$), 1608 (C=N), 1577 (C=C). $^1$H NMR (DMSO-*d*$_6$, δ, 300 MHz): 2.08 (s, 3H, $CH_3$), 2.12 (s, 3H, $CH_3$), 7.20 (t, 1H, *J*=7.5 Hz, H-7), 7.33 (s, 1H, $H\text{-}4_{pyrazole}$), 7.59 (d, 1H, *J*=7.5 Hz, H-9), 7.84 (t, 1H, *J*=7.2 Hz, H-8), 8.06 (d, 1H, *J*=7.2 Hz, H-6), 8.82 (s, 1H, $H\text{-}4_{pyridine}$), 10.43 (br, 1H, NH exchangeable with $D_2O$). $^{13}$C NMR (DMSO-*d*$_6$, δ, 75 MHz): 14.3 ($CH_3$), 16.8 ($CH_3$), 92.6 (C4a), 107.2 ($C4_{pyrazole}$), 119.1 (C-9), 123.3 (C5a), 124.9 (C7), 128.1 (C8), 130.8 (C3), 134.5 (C-6), 141.5 ($C5_{pyrazole}$), 143.2 ($C3_{pyrazole}$), 148.5 (C-4), 151.6 (C9a), 157.8 (C10a), 162.7 (C-2 as C=O), 172.9 ($C=O_{ketone}$), 175.6 (C5 as C=O). Mass spectrum (*m/z*, %): 335 ($M^+$, 29), 240 (100), 212 (42), 120 (32), 105 (13), 92 (8), 77 (19) and 64 (12). Anal. Calcd for $C_{18}H_{13}N_3O_6$ (335.31): C, 64.47; H, 3.91; N, 12.53%. Found: C, 64.35; H, 3.77; N, 12.38%.

**3-[(3-Methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl)carbonyl]-2*H*-chromeno[2,3-*b*]pyridine-2,5(1*H*)-dione (14).** A mixture of carbohydrazide **3** (0.54 g, 2 mmol) and ethyl acetoacetate (0.26 g, 0.26 mL, 2 mmol), in acetic acid (20 mL) was heated under reflux for 30 min. The white crystals separated after cooling were filtered and crystallized from dioxane, mp 257-258 ºC, yield (0.51 g, 75%). IR (KBr, $cm^{-1}$): 3396 (NH), 3052 ($CH_{arom.}$), 2962, 2934, 2874 ($CH_{aliph.}$), 1688 ($C=O_{pyridone}$), 1677 (C=O), 1654 ($C=O_{\gamma\text{-pyrone}}$), 1602 (C=N), 1572 (C=C). $^1$H NMR (DMSO-*d*$_6$, δ, 300 MHz): 2.10 (s, 3H, $CH_3$), 3.06 (s, 2H, $CH_2$), 7.25 (t, 1H, *J*=7.2 Hz, H-7), 7.54 (d, 1H, *J*=7.2 Hz, H-9), 7.82 (t, 1H, *J*=7.2 Hz, H-8), 8.04 (d, 1H, *J*=7.2 Hz, H-6), 8.77 (s, 1H, $H\text{-}4_{pyridine}$), 10.31 (br, 1H, NH exchangeable with $D_2O$). $^{13}$C NMR (DMSO-*d*$_6$, δ, 75 MHz): 15.9 ($CH_3$), 38.4 ($CH_2$ as $C4_{pyrazole}$), 92.4 (C4a), 118.7 (C-9), 122.5 (C5a), 124.4 (C7), 128.6 (C8), 130.1 (C3), 134.7 (C-6), 142.6 ($C3_{pyrazole}$), 148.3 (C-4), 151.8 (C9a), 158.2 (C10a), 162.8 (C-2 as C=O), 165.3 ($C5_{pyrazole}$ as C=O), 173.1 ($C=O_{ketone}$), 175.9 (C5 as C=O). Mass spectrum (*m/z*, %): 337 ($M^+$, 34), 240 (100), 225 (7), 192 (9), 164 (18), 120 (52), 105 (27), 93 (16), 77 (42) and 64 (34). Anal. Calcd for $C_{17}H_{11}N_3O_5$ (337.29): C, 60.54; H, 3.29; N, 12.46%. Found: C, 60.35; H, 3.11; N, 12.28%.

**3-[(3,5-Dioxopyrazolidin-1-yl)carbonyl]-2*H*-chromeno[2,3-*b*]pyridine-2,5(1*H*)-dione (15).** A mixture of carbohydrazide **3** (0.54 g, 2 mmol) and diethyl malonate (0.28 g, 0.28 mL, 2 mmol), in acetic acid (20 mL) was heated under reflux for 30 min. The white crystals separated after cooling were filtered and crystallized from dioxane, mp > 300 ºC, yield (0.48 g, 70%). IR (KBr, $cm^{-1}$): 3419, 3384 (2NH), 3042 ($CH_{arom.}$), 2951, 2922 ($CH_{aliph.}$), 1690 ($C=O_{pyridone}$), 1681, 1673 (3C=O), 1658 ($C=O_{\gamma\text{-pyrone}}$), 1612 (C=N), 1581 (C=C). $^1$H NMR (DMSO-$d_6$, δ, 300 MHz): 3.38 (s, 2H, $CH_2$), 7.23 (t, 1H, *J*=7.5 Hz, H-7), 7.50 (d, 1H, *J*=7.5 Hz, H-9), 7.83 (t, 1H, *J*=7.2 Hz, H-8), 8.08 (d, 1H, *J*=7.5 Hz, H-6), 8.79 (s, 1H, H-$4_{pyridine}$), 10.54 (br, 1H, NH exchangeable with $D_2O$), 11.21 (br, 1H, NH exchangeable with $D_2O$). $^{13}$C NMR (DMSO-$d_6$, δ, 75 MHz): 43.4 ($CH_2$), 93.2 (C4a), 118.1 (C-9), 121.9 (C5a), 124.3 (C7), 127.8 (C8), 131.9 (C3), 135.0 (C-6), 147.8 (C-4), 151.5 (C9a), 157.7 (C10a), 162.1 (C-2 as C=O), 164.3 (C-$3_{pyrazole}$ as C=O), 165.9 (C-$5_{pyrazole}$ as C=O), 167.3 (C=O as hydrazide), 175.9 (C5 as C=O). Mass spectrum (*m/z*, %): 339 ($M^+$, 16), 240 (100), 212 (15), 184 (7), 120 (77), 105 (19), 93 (25), 77 (56) and 65 (7). Anal. Calcd for $C_{16}H_9N_3O_6$ (339.26): C, 56.64; H, 2.67; N, 12.39%. Found: C, 56.50; H, 2.46; N, 12.25%.

**3-({3,5-Dioxo-4-[(4-oxo-4*H*-chromen-3-yl)methylidene]pyrazolidin-1-yl}carbonyl)-2*H*-chromeno[2,3-*b*]pyridine-2,5(1*H*)-dione (16).** A mixture of compound **15** (0.37 g, 1 mmol) and 3-formylchromone (0.17 g, 1 mmol), in acetic acid (15 mL) containing freshly fused sodium acetate (0.2 g) was heated under reflux for 2 h. The pale yellow crystals obtained during heating were filtered and crystallized from xylene, mp > 300 ºC, yield (0.37 g, 75%). IR (KBr, $cm^{-1}$): 3406, 3368 (2NH), 3028 ($CH_{arom.}$), 1692 ($C=O_{pyridone}$), 1684, 1671 (3C=O), 1652, 1646 ($2C=O_{\gamma\text{-pyrone}}$), 1592 (C=C). $^1$H NMR (DMSO-$d_6$, δ, 300 MHz): 7.19 (t, 1H, *J*=6.9 Hz, Ar-H), 7.24 (t, 1H, *J*=6.9 Hz, Ar-H), 7.53-7.56 (m, 2H, Ar-H), 7.78 (t, 1H, *J*=6.6 Hz, Ar-H), 7.85 (t, 1H, *J*=6.9 Hz, Ar-H), 8.09- 8.11 (m, 2H, Ar-H), 8.39 (s, 1H, $CH_{olefinic}$), 8.71 (s, 1H, H-$4_{pyridine}$), 8.89 (s, 1H, H-$2_{chromone}$), 10.37 (br, 1H, NH exchangeable with $D_2O$), 11.49 (br, 1H, NH exchangeable with $D_2O$). Mass spectrum (*m/z*, %): 495 ($M^+$, 35), 255 (50), 240 (69), 212 (15), 145 (26), 120 (100), 105 (41), 93 (22), 77 (17) and 64 (12). Anal. Calcd for $C_{26}H_{13}N_3O_8$ (495.40): C, 63.04; H, 2.64; N, 8.48%. Found: C, 62.95; H, 2.36; N, 8.29%.

**2-Hydroxy-1*H*-chromeno[2``,3``:6`,5`]pyrido[2`,3`-*d*]pyrazolo[1,5-*a*]pyrimidine-11,13(11*H*,13*H*)-dione (17).** A mixture of carbohydrazide **3** (0.54 g, 2 mmol) and ethyl cyanoacetate (0.23 g, 0.22 mL, 2 mmol), in acetic acid (20 mL) was heated under reflux for 30 min. The pale yellow crystals separated during heating were filtered and crystallized from DMF/$H_2O$, mp > 300 ºC, yield (0.43 g, 67%). IR (KBr, $cm^{-1}$): 3426 (OH), 3375 (NH), 3039 ($CH_{arom.}$), 1674 ($C=O_{pyrimidinone}$), 1657 ($C=O_{\gamma\text{-pyrone}}$), 1611 (C=N), 1585 (C=C). $^1$H NMR (DMSO-$d_6$, δ, 300 MHz): 6.78 (s, 1H, H-$4_{pyrazole}$), 7.21 (t, 1H, *J*=6.6 Hz, H-9), 7.46 (d, 1H, *J*=6.9 Hz, H-7), 7.79 (t, 1H, *J*=6.9 Hz, H-8), 8.05 (d, 1H, *J*=6.6 Hz, H-10), 8.74 (s, 1H, H-$4_{pyridine}$), 11.21 (br, 1H, NH exchangeable with $D_2O$), 12.89 (br, 1H, NH exchangeable with $D_2O$). $^{13}$C NMR (DMSO-$d_6$, δ, 75 MHz): 74.2 (C2), 107.4 (C12a), 112.1 (C11a), 115.8 (C-10a), 120.5 (C7), 123.9 (C9),

126.8 (C8), 130.6 (C10), 146.1 (C12), 151.3 (C6a), 154.7 (C4a), 158.4 (C5a), 161.3 (C3a), 165.5 (C-13 as C=O), 179.4 (C-11 as C=O), 189.2 (C-2 as C-OH). Mass spectrum (*m/z*, %): 320 ($M^+$, 72), 292 (100), 264 (62), 248 (43), 222 (8), 167 (19), 120 (65), 105 (30), 93 (13) and 77 (10). Anal. Calcd for $C_{16}H_8N_4O_4$ (320.26): C, 60.00; H, 2.52; N, 17.49%. Found: C, 59.69; H, 2.30; N, 17.18%.

**3-Cyano-4*H*-chromeno[2``,3``:6`,5`]pyrido[2`,3`-*d*]pyrazolo[1,5-*a*]pyrimidine-11,13(11*H*,13*H*)-dione (18).** A mixture of carbohydrazide **3** (0.54 g, 2 mmol) and (ethoxymethylene)malononitrile (0.25 g, 2 mmol), in DMF (15 mL) containing TEA (0.1 mL) was heated under reflux for 2 h. The yellow crystals separated during heating were filtered and crystallized from DMF, mp > 300 ºC, yield (0.38 g, 58%). IR (KBr, $cm^{-1}$): 3298 (NH), 3053 ($CH_{arom.}$), 2231 (C≡N), 1671 ($C=O_{pyrimidinone}$), 1652 ($C=O_{\gamma\text{-pyrone}}$), 1613 (C=N), 1576 (C=C). $^1$H NMR (DMSO-$d_6$, δ, 300 MHz): 7.29 (t, 1H, *J*=6.9 Hz, H-9), 7.53 (d, 1H, *J*=6.9 Hz, H-7), 7.86 (t, 1H, *J*=6.9 Hz, H-8), 8.13 (d, 1H, *J*=6.9 Hz, H-10), 8.56 (s, 1H, $H\text{-}3_{pyrazole}$), 8.82 (s, 1H, $H\text{-}4_{pyridine}$), 11.02 (br, 1H, NH exchangeable with $D_2O$). $^{13}$C NMR (DMSO-$d_6$, δ, 75 MHz): 81.8 (C3), 107.9 (C12a), 112.3 (C11a), 115.4 (C-10a), 116.7 (C≡N), 120.2 (C7), 124.2 (C9), 127.1 (C8), 130.8 (C10), 141.9 (C2), 146.4 (C12), 151.0 (C6a), 154.2 (C4a), 158.6 (C5a), 161.6 (C3a), 165.2 (C-13 as C=O), 178.8 (C-11 as C=O). Mass spectrum (*m/z*, %): 329 ($M^+$, 100), 301 (81), 273 (48), 246 (12), 220 (25), 121 (48), 105 (16), 93 (23), 77 (28) and 64 (19). Anal. Calcd for $C_{17}H_7N_5O_3$ (329.27): C, 62.01; H, 2.14; N, 21.27%. Found: C, 61.85; H, 2.02; N, 21.13%.

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