Studies on the Chemical Reactions of Some 3-Substituted-6,8-dimethylchromones with Nucleophilic Reagents

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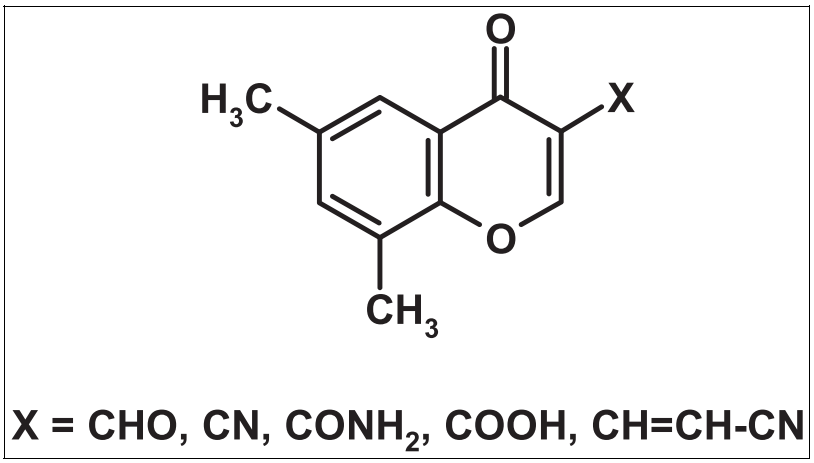

A variety of 3-substituted-6,8-dimethylchromones have been synthesized and characterized. The chemical reactivity of 3-substituted-6,8-dimethylchromones was studied towards some nucleophiles, namely, *S*-benzyldithiocarbazate, *o*-phenylenediamine, and cyanoacetamide, and a diversity of products were efficiently synthesized. Reactions of 3-substituted-6,8-dimethylchromones (except 3-formyl-6,8-dimethylchromone), with nucleophilic reagents, usually proceed through nucleophilic attack at C-2 position followed by different types of heterocyclization depending on the functional group present at C-3 position. Structures of the newly synthesized products have been established based on elemental analysis and spectral data.

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INTRODUCTION

Substituted chromones represent one of the major classes of naturally occurring compounds [1,2]. Chromones have shown diverse biological activities including antimicrobial [3], anti-inflammatory [4], antioxidant [5,6], anticancer [7,8], antitumor [9,10], neuroprotective [11], and human immunodeficiency virus inhibitory [12]. Quantum chemical studies, density functional theory calculations, electronic absorption spectra, and optical properties of some chromone derivatives were studied [13–16]. 3-Substituted chromones possess an activated endocyclic olefinic bond, three electrophilic centers (C-2, C-4 as C=O, and the carbon atom of the functional group present at C-3 of the γ-pyrone ring). C-2 is more electrophilic than the other carbon atoms. The chemistry of 3-substituted chromones is more varied, and their chemical behavior depends widely on the type of the functional group present at C-3 position [17–20]. Chromones bearing electron-withdrawing substituents in the 3-position react with 1,2-dinucleophiles and 1,3-dinucleophiles delivering the corresponding five-membered and six-membered heterocycles. This domino-transformation usually involves initial nucleophilic addition on the 2-position of the chromone skeleton with subsequent γ-pyrone ring opening followed by the formation of new heterocyclic systems. These types of transformations are facilitated by the electron-withdrawing group present at the 3-position [21–24].

RESULTS AND DISCUSSION

The present work aimed to synthesize a variety of 3-substituted-6,8-dimethylchromones and study their chemical behavior towards selected nucleophiles, namely, *S*-benzyldithiocarbazate, *o*-phenylenediamine, and cyanoacetamide.

6,8-Dimethylchromone-3-carboxaldehyde (**1**) [25] and 6,8-dimethylchromone-3-carbonitrile (**2**) [26] were prepared as previously reported. Herein, treating carboxaldehyde **1** with *N*-bromosuccinimide (NBS) in carbon tetrachloride under irradiation using 200-W

tungsten lamp followed by quenching with water afforded 6,8-dimethylchromone-3-carboxylic acid (**3**) (Scheme 1). Quenching the reaction medium in the previous reaction with aqueous ammonia, instead of water, produced 6,8-dimethylchromone-3-carboxamide (**4**) in moderate yield (Scheme 1) [27].

Condensation reaction of carboxaldehyde **1** with cyanoacetic acid in boiling pyridine furnished *E*-chromonylacrylonitrile derivative **5**, via condensation followed by decarboxylation under the reaction conditions (Scheme 1). The IR spectrum of compound **5** revealed characteristic absorption bands at $\bar{\nu}$ 2216 and 1637 cm^{-1} attributable to (C≡N) and ($C{=}O_{\gamma\text{-pyrone}}$), respectively. The ^{1}H-NMR spectrum of compound **5** showed two characteristic doublets at δ 6.93 and 7.33 with high coupling constant (J = 16.4 Hz) assigned to vinyl protons, indicating *trans* configuration around the double bond. Further, the mass spectrum of compound **5** revealed the molecular ion peak at *m/z* 225 and confirms the structure.

Next, stirring carbonitrile **2** with 2*M* sodium hydroxide solution at 70°C for 2 h gave 2-amino-6,8-dimethylchromone-3-carboxaldehyde (**6**), throughout ring opening following by ring closure (Scheme 1) [28].

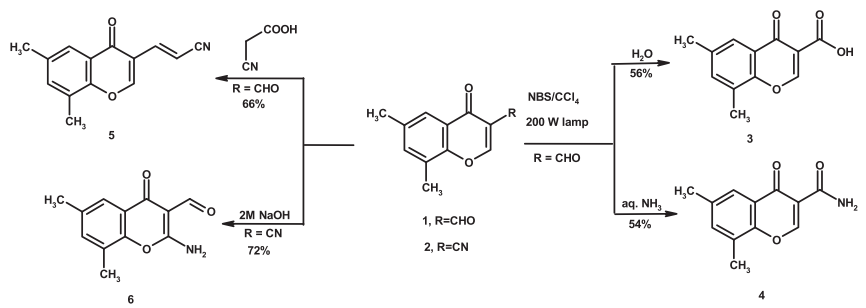
Condensation of carboxaldehyde **1** with *S*-benzyldithiocarbazate in ethanol under stirring afforded the corresponding hydrazone **7** (Scheme 2). Repeating the reaction in boiling ethanol in the presence of piperidine yielded piperidinylcarbonothioylpyrazole derivative **8**, throughout nucleophilic substitution of SCH_2Ph group with piperidinyl group (intermediate **A**) with concomitant γ-pyrone ring opening (Scheme 2). Similarly, using morpholine, instead of piperidine, in the previous reaction yielded morpholinylcarbonothioylpyrazole derivative **9**, via intermediate **B** (Scheme 2). Compounds **8** and **9** give red color with $FeCl_3$ solution, indicating the presence of free phenolic OH group. ^{1}H-NMR spectra of compounds **8** and **9** showed the absence of phenyl protons indicating elimination of SCH_2Ph group during the reaction. The ^{13}C-NMR spectrum of compound **9** showed specific signals assignable to N $(CH_2)_2$, O $(CH_2)_2$, C=O, and C=S at δ 52.2, 65.6, 176.8, and 191.1, respectively. Also, the mass spectra of compounds **8** and **9** showed their molecular ion peaks, at *m/z* 343 and 345, which agree well with the assigned molecular formulas and confirm the suggested structures.

Then, heating carboxaldehyde **1** with *o*-phenylenediamine in 95% ethanol for 1 min produced orange crystals in high yield. Inspection of the spectral data confirms the formation of addition product **10**, throughout addition of amino group into the formyl group (1,2-addition) with addition of water molecule at C2–C3 double bond (1,2-addition) during the reaction (Scheme 3). The mass spectrum of compound **10** showed the molecular ion peak, as the base peak, at *m/z* 328, which agrees well with the proposed structure.

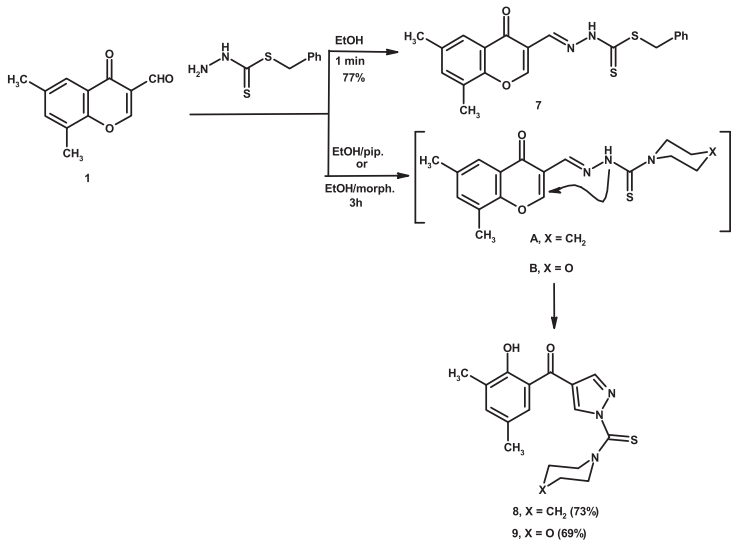
Repeating the previous reaction under reflux for 2 h furnished the annulated benzochromenodiazepine derivative **11** as pale yellow crystals, via the formation of compound **10** followed by elimination of two molecules of water with subsequent dehydrogenation (Scheme 3) [29,30]. In this reaction, the orange crystals formed after 1 min was dissolved under reflux, indicating the formation of compound **11** throughout compound **10** (as isolable intermediate). The ^{1}H-NMR spectrum of compound **11** showed characteristic singlets at δ 7.58 (H-2), 7.86 (H-4), and 9.34 ($H\text{-}6_{diazepine}$), in addition to D_2O-exchangeable signal attributable to NH proton at δ 11.93. Structure of compound **11** was deduced from its mass spectrum, which showed the molecular ion peak at *m/z* 290, as the base peak, and supports the assigned structure.

Treatment of carboxaldehyde **1** with cyanoacetamide in boiling ethanol containing few drops of piperidine produced pyridine-3-carbonitrile derivative **12** in good yield (Scheme 3). Compound **12** gave red color with $FeCl_3$ solution, indicating the presence of phenolic OH group and confirms the γ-pyrone ring opening. Mass spectrum of compound **12** revealed the molecular ion peak at *m/z* 268, which is in agreement with the assigned molecular formula ($C_{15}H_{12}N_2O_3$). Its IR spectrum showed characteristic absorption bands at $\bar{\nu}$ 3208 (OH), 3137 (NH), 2238 (C≡N), and 1694 cm^{-1} ($C{=}O_{pyridone}$). The ^{1}H-NMR spectrum of compound **12** showed

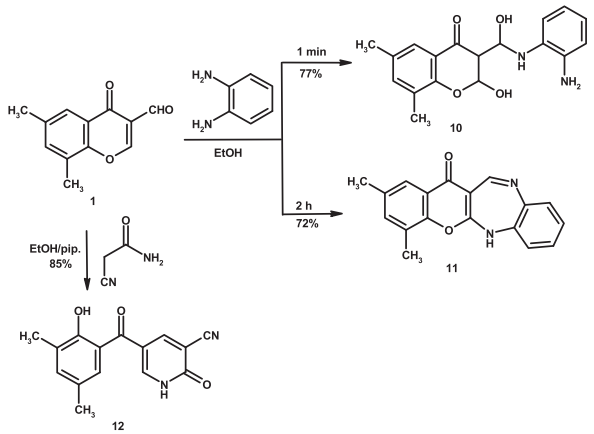
Scheme 1. Synthesis of 3-substituted-6,8-dimethylchromones.



Scheme 2. Reaction of carboxaldehyde **1** with and *S*-benzyldithiocarbazate.



Scheme 3. Reaction of carboxaldehyde **1** with *o*-phenylenediamine and cyanoacetamide.



characteristic singlets at δ 8.15 and 8.29 attributed to H-$4_{pyridine}$ and H-$6_{pyridine}$, respectively, in addition to D_2O-exchangeable signal at δ 10.30 attributable to NH and OH protons.

Next, the chemical behavior of 6,8-dimethylchromone-3-carbonitrile (**2**) was studied towards *S*-benzyldithiocarbazate under different reaction conditions. Treatment of carbonitrile **2** with *S*-benzyldithiocarbazate in boiling ethanol furnished pyrazole derivative **13**, via γ-pyrone ring opening (intermediate **C**) followed by addition into the nitrile function (intermediate **D**) as shown in Scheme 4. Carrying out the latter reaction in benzene as a solvent containing triethylamine furnished hydrazone derivative **14**, via (intermediates **C** and **E**) (Scheme 5). The ^{1}H-NMR spectrum of compound **13** showed specific singlet at δ 8.08 attributed to H-$3_{pyrazole}$, while ^{1}H-NMR spectrum of compound **14** showed specific singlet at δ 8.36 attributed to azomethine proton. The ^{13}C-NMR spectrum of compound **14** revealed characteristic signals δ 37.7, 91.9, 173.8, and 196.7 attributable to CH_2, C-$3_{chromone}$, C=O, and C=S, respectively.

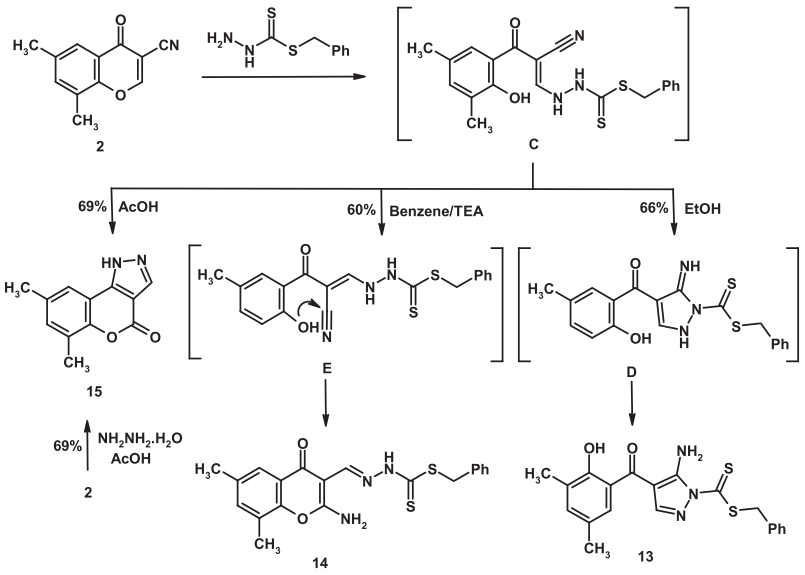
Interestingly, boiling carbonitrile **2** with *S*-benzyldithiocarbazate in acetic acid afforded chromeno[4,3-*c*]pyrazol-4(1*H*)-one derivative **15**, which was obtained authentically from the reaction of carbonitrile **2** with hydrazine hydrate in boiling acetic acid (Scheme 4). IR spectrum displayed characteristic absorption bands at $\bar{\nu}$ 1710 (C=$O_{\alpha\text{-pyrone}}$) and 1602 cm^{-1} (C=N). ^{1}H-NMR spectrum consists of three singlet signals attributed to H-7, H-9, and H-$3_{pyrazole}$ at δ 6.78, 7.38, and 8.44, respectively. The mass spectrum of compound **15** recorded the molecular ion peak at *m*/*z* 214, as the base peak, corresponding to the formula weight (214.22) and confirms the suggested structure.

Reaction of carbonitrile **2** with *o*-phenylenediamine in boiling dimethylformamide (DMF) afforded benzochromenodiazepine derivative **11** (co-identical mp, mmp, and spectral data with that prepared from the reaction of aldehyde **1** with the same reagent) (Scheme 5) [31].

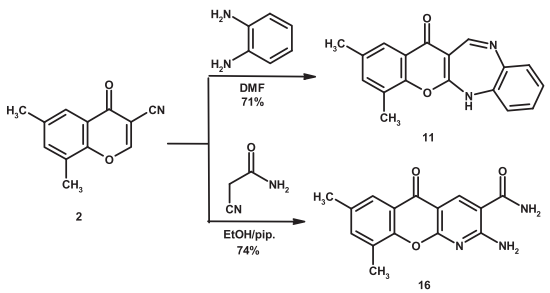
After that, reaction of carbonitrile **2** with cyanoacetamide in boiling ethanol containing few drops of piperidine gave chromeno[2,3-*b*] pyridine **16** in good yield (Scheme 5). The mass spectrum presented the molecular ion peak at *m*/*z* 283 (100%) as the base peak, corresponding to the molecular formula ($C_{15}H_{13}N_3O_3$). ^{1}H-NMR spectrum of compound **16** showed characteristic singlet at δ 8.84 assigned to H-$4_{pyridine}$.

Next, the chemical transformations of 6,8-dimethylchromone-3-carboxamide (**4**) were studied towards the previous nucleophilic reagents. Treating

Scheme 4. Reaction of carbonitrile **2** with *S*-benzyldithiocarbazate. TEA, triethylamine.



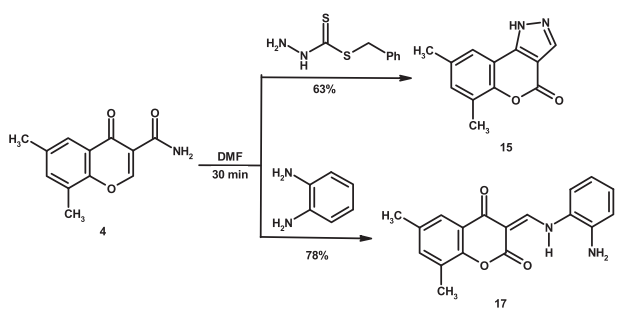
Scheme 5. Reaction of carbonitrile **2** with *o*-phenylenediamine and cyanoacetamide. DMF, dimethylformamide.



carboxamide **4** with *S*-benzyldithiocarbazate in DMF under reflux afforded chromenopyrazole derivative **15** (Scheme 6) (co-identical spectral data with that from the reaction of carbonitrile **2** with the same reagent in acetic acid).

Boiling carboxamide **4** with *o*-phenylenedimine in refluxing DMF afforded the chromane-2,4-dione derivative **17**, as *Z* isomer (Scheme 6). The ^{1}H-NMR spectrum of compound **17** showed characteristic doublet (J = 15.2 Hz) exchanged to singlet in D_2O, at δ 7.57, which was assigned to the exocyclic vinyl proton, in addition to D_2O-exchangeable doublet assigned to the NH proton at δ 13.45. The structure of compound **17** was further deduced from its mass spectrum, which revealed the molecular ion peak at *m*/*z* 308 and the base peak at *m*/*z* 307 assigned to M^+ after loss of hydrogen as a radical.

Scheme 6. Conversion of carboxamide **4** into coumarines **15** and **17**. DMF, dimethylformamide.

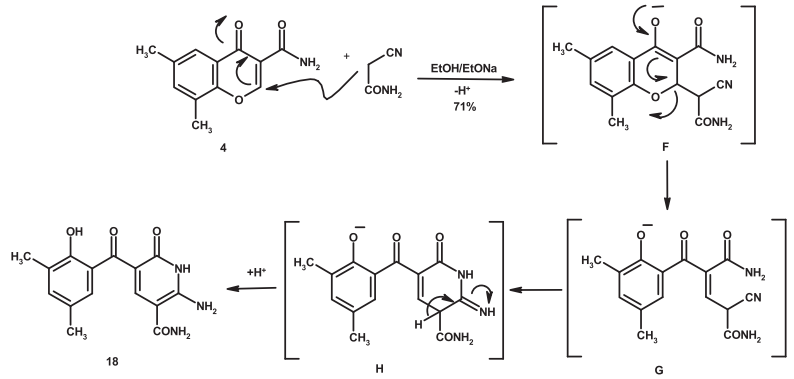


Moreover, treatment of carboxamide **4** with cyanoacetamide in sodium ethoxide under reflux produced the pyridine derivative **18**. The reaction proceeds via deprotonation of cyanoacetamide followed by nucleophilic attack at C-2 position (intermediate **F**) and γ-pyrone ring opening (intermediate **G**) with concomitant cycloaddition (intermediate **H**) and proton transfer as depicted in Scheme 7.

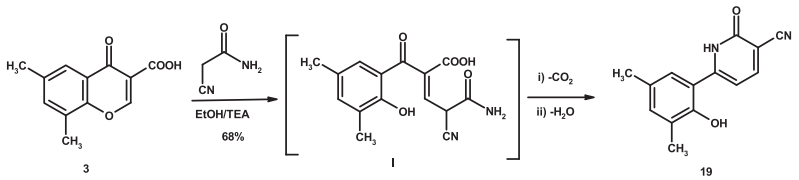
In the current study, the chemical transformation of carboxylic acid **3** and acrylonitrile **5** was concised towards cyanoacetamide. Therefore, treatment of carboxylic acid **3** with cyanoacetamide in ethanol containing few drops of triethylamine as a catalyst afforded 6-(2-hydroxy-3,5-dimethylphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (**19**) (Scheme 8). The mass spectrum revealed the molecular ion peak at *m*/*z* 240, which is consistent with the proposed molecular formula $C_{14}H_{12}N_2O_2$.

Finally, treatment of (2*E*)-3-(6,8-dimethylchromon-3-yl) acrylonitrile (**5**) with cyanoacetamide in boiling ethanol containing few drops of piperidine afforded 5-(cyanomethyl)-7,9-dimethyl-2-oxo-1,5-dihydro-2*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (**20**), via a non-isolable intermediates **J** and **K**, as described in Scheme 9. Structure of compound **20**

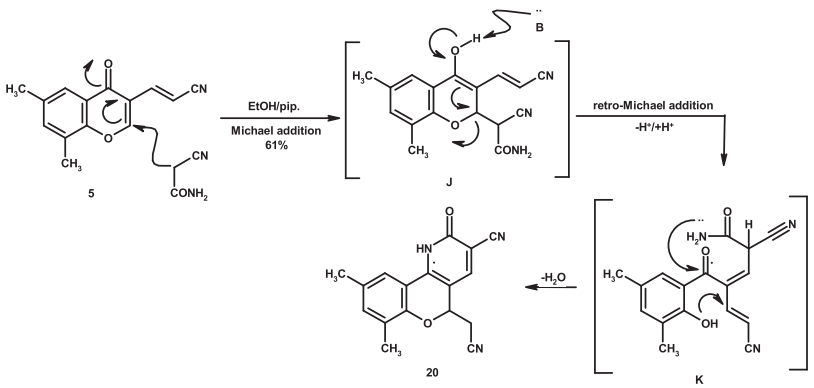
Scheme 7. Reaction of carboxamide **4** with cyanoacetamide.



Scheme 8. Reaction of carboxylic acid **3** with cyanoacetamide. TEA, triethylamine.



Scheme 9. Reaction of acrylonitrile **5** with cyanoacetamide.



was deduced from its mass spectrum, which revealed the molecular ion peak at *m/z* 291 and the base peak at *m/z* 251, and assigned to the molecular ion after loss of CH_2CN moiety. The ^{1}H-NMR spectrum showed characteristic doublet and triplet at δ 2.99 and 5.45 attributable to (CH_2CN) and (H-5), respectively, and supports the identity of the assigned structure.

CONCLUSION

A variety of 3-substituted-6,8-dimethylchromones were efficiently synthesized and found as a good precursors for the synthesis of different heterocyclic systems. 3-Substituted 6,8-dimethylchromones possess three electron deficient centers: C-2, C-4, and carbon atom of the functional group present at position 3. In all reactions of 3-substituted-6,8-dimethylchromones (except 3-formyl-6,8-dimethylchromone), with nucleophilic reagent, it was found that the nucleophile usually attack the chromone ring at C-2 position followed by different types of heterocyclization depending on the functional group present at C-3 position. In case of 3-formyl-6,8-dimethylchromone, the nucleophiles reacted with the aldehyde function with subsequent γ-pyrone ring opening leading to a diversity of nitrogen heterocyclic systems.

EXPERIMENTAL

General. Melting points were determined on a digital Stuart SMP3 apparatus (Büchi, Flawil, Switzerland). Infrared spectra were measured on PerkinElmer 293 spectrophotometer (cm^{-1}) (Thermo Fisher Scientific, Waltham, MA), using KBr disks. ^{1}H-NMR spectra were measured on Mercury-300BB/400BB (300 and 400 MHz) (Bruker, Rheinstetten, Germany), using DMSO-d_6 as a solvent and tetramethylsilane (δ) as the internal standard. ^{13}C-NMR spectra were measured on Mercury400BB (75 and 100 MHz), using DMSO-d_6 as a solvent and tetramethylsilane (δ) as the internal standard. Mass spectra were obtained using GC-2010 Shimadzu gas chromatography instrument mass spectrometer (70 eV) (Manchester, England). Elemental microanalyses were performed on a PerkinElmer CHN-2400 analyzer (Leco, St. Joseph, MI).

6,8-Dimethylchromone-3-carboxylic acid (3). A mixture of carboxaldehyde **1** (2.02 g, 10 mmol) and NBS (2.14 g, 12 mmol) in carbon tetrachloride (50 mL) was stirred under illumination from 200-W tungsten lamp for 40 min. The solvent was evaporated under vacuum, and the residue was cooled in an ice bath followed by addition of distilled water (10 mL) with continuous stirring. The solid obtained was filtered, washed with water, then diethyl ether, and crystallized from acetic acid to give compound **3** as white crystals, mp 210–211°C, yield 1.23 g (56%). IR (KBr, cm^{-1}): 3100 (br, OH), 3056 (CH_{arom}), 2925, 2887 ($CH_{aliph.}$), 1763 ($C{=}O_{carboxylic\ acid}$), 1651 ($C{=}O_{\gamma\text{-pyrone}}$), 1624 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6): 2.38 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 7.59 (s, 1H, H-7), 7.74 (s, 1H, H-5), 9.10 (s, 1H, H-2), 13.29 (bs, 1H, COOH, exchangeable with D_2O). ^{13}C-NMR (75 MHz, DMSO-d_6): 15.6 (CH_3), 19.9 (CH_3), 107.3, 115.7, 121.6, 123.4, 129.6, 133.0, 150.7, 156.2, 171.5 (C-4 as C=O), 188.2 ($C{=}O_{acid}$). Mass spectrum, *m/z* (I_r %): 218 (3), 217 (16), 199 (100), 174 (7), 149 (15), 120 (19), 91 (27), 77 (18), 65 (18). *Anal*. Calcd for $C_{12}H_{10}O_4$ (218.21): C, 66.05; H, 4.62%. Found: C, 65.70; H, 4.50%.

6,8-Dimethylchromone-3-carboxamide (4). A mixture of carboxaldehyde **1** (2.02 g, 10 mmol) and NBS (2.14 g, 12 mmol) in carbon tetrachloride (50 mL) was stirred under illumination from 200-W tungsten lamp for 40 min. The solvent was evaporated under vacuum, and the residue was cooled in an ice bath followed by addition of ammonia (5 mL) with continuous stirring. The reaction mixture was neutralized with 10% acetic acid. The solid obtained was filtered, washed with water, and crystallized from DMF/H_2O to give compound **4** as white crystals, mp 268–269°C, yield 1.18 g (54%), mp 268–269°C. IR (KBr, cm^{-1}): 3336, 3143 (NH_2), 3082 (CH_{arom}), 2922, 2880 ($CH_{aliph.}$), 1684 ($C{=}O_{amide}$), 1647 ($C{=}O_{\gamma\text{-pyrone}}$), 1601 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6): 2.22 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 7.55 (s, 1H, H-7), 7.77 (s, 1H, H-5), 8.56 (s, 2H, NH_2 exchangeable with D_2O), 8.99 (s, 1H, H-2). Mass spectrum, *m/z* (I_r %): 217 (100), 201 (38), 174 (42), 148 (12), 120 (12), 91 (37), 77 (18), 65 (21). *Anal*. Calcd for $C_{12}H_{11}NO_3$ (217.22): C, 66.35; H, 5.10; N, 6.45%. Found: C, 66.25; H, 5.00; N, 6.29%.

(2E)-3-(6,8-Dimethylchromon-3-yl)acrylonitrile (5). A mixture of carboxaldehyde **1** (2.02 g, 10 mmol) and cyanoacetic acid (0.85 g, 10 mmol) in pyridine (10 mL) was heated under reflux for 1 h. The pale yellow crystals obtained after cooling were filtered and crystallized from MeOH to give compound **5** as white crystals, yield 1.48 g (66%), mp 221–222°C. IR (KBr, cm^{-1}): 3105 ($CH_{olefinic}$), 3079 ($CH_{arom.}$), 2935, 2920 ($CH_{aliph.}$), 2216 (C≡N), 1637 ($C{=}O_{\gamma\text{-pyrone}}$), 1615 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6): 2.36 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 6.93 (d, 1H, J = 16.4 Hz, $H_{olefinic}$), 7.33 (d, 1H, J = 16.4 Hz, $H_{olefinic}$), 7.49 (s, 1H, H-7), 7.68 (s, 1H, H-5), 8.72 (s, 1H, H-2). ^{13}C-NMR (75 MHz, DMSO-d_6): 15.5 (CH_3), 20.1 (CH_3), 91.5, 116.8, 121.0, 124.2, 126.9, 128.7, 130.2, 133.4, 137.0, 153.2, 155.4, 175.2 (C=O). Mass spectrum, *m/z* (I_r %): 225 (51), 199 (38), 171 (32), 148 (100), 120 (22), 77 (45), 65 (13). *Anal*. Calcd for $C_{14}H_{11}NO_2$ (225.24): C, 74.65; H, 4.92; N, 6.22%. Found: C, 74.60; H, 4.70; N, 6.00%.

2-Amino-6,8-dimethylchromene-3-carboxaldehyde (6). A mixture of carbonitrile **2** (1.99 g, 10 mmol) and 2*M* sodium hydroxide solution (20 mL) was stirred at 70°C for 2 h. Water was added (40 mL), and the solid obtained was filtered and crystallized from AcOH to give compound **6** as yellow crystals, yield 1.44 (72%), mp 255–256°C. IR (KBr, cm^{-1}): 3258 (br, NH_2), 3074 ($CH_{arom.}$), 2998, 2918, 2885 ($CH_{aliph.}$), 2756 ($C{-}H_{aldehyde}$), 1675 ($C{=}O_{aldehyde}$), 1636 ($C{=}O_{\gamma\text{-pyrone}}$), 1602 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6): 2.33 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 7.38 (s, 1H, H-7), 7.61 (s, 1H, H-5), 9.45 (s, H, NH exchangeable with D_2O), 9.51 (s, H, NH, exchangeable with D_2O), 10.04 (s, 1H, CHO). ^{13}C-NMR (75 MHz, DMSO-d_6): 14.6 (CH_3), 20.1 (CH_3), 94.7 (C-3), 122.3, 126.1, 128.3, 129.9, 132.7, 135.0, 135.9, 153.1, 168.4, 174.6 (CH=O), 189.1 (CH=O). Mass spectrum, *m/z* (I_r %): 217 (100), 189 (26), 174 (17), 148 (66), 121 (36), 91 (14), 77 (46), 64 (11). *Anal*. Calcd for $C_{12}H_{11}NO_3$ (217.22): C, 66.35; H, 5.10; N, 6.45%. Found: C, 66.14; H, 4.80; N, 6.24%.

Benzyl 2-[(6,8-dimethylchromon-3-yl)methylidene] hydrazinecarbodithioate (7). To a hot solution of carboxaldehyde **1** (0.61 g, 3 mmol) in absolute ethanol (15 mL), *S*-benzyldithiocarbazate (0.58 g, 3 mmol) in absolute ethanol (10 mL) was added with continuous stirring, and the reaction mixture was heated under reflux for 1 min. The white crystals obtained during heating were filtered off and crystallized from DMF/EtOH to

give compound **7** as white crystals, mp 230–231°C, yield 0.89 g (77%). IR (KBr, cm^{-1}): 3165 (NH), 3036 ($CH_{arom.}$), 2997, 2920, 2890 ($CH_{aliph.}$), 1634 ($C{=}O_{\gamma\text{-pyrone}}$), 1605 (C=N), 1577 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6): 2.18 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 4.61 (s, 2H, CH_2), 7.25–7.47 (m, 5H, Ar–H), 7.51 (s, 1H, H-7), 7.69 (s, 1H, H-5), 8.43 (s, 1H, CH=N), 9.06 (s, 1H, H-2), 11.39 (s, 1H, NH, exchangeable with D_2O). Mass spectrum, *m/z* (I_r %): 382 (21), 216 (7), 200 (11), 148 (7), 120 (6), 105 (6), 91 (100), 77 (13), 65 (20). *Anal*. Calcd for $C_{20}H_{18}N_2O_2S_2$ (382.49): C, 62.80; H, 4.74; N, 7.32; S, 16.77%. Found: C, 62.75; H, 4.55; N, 7.10; S, 16.49%.

4-(2-Hydroxy-3,5-dimethylbenzoyl)-1-(piperidin-1-ylcarbonothioyl)-1H-pyrazole (8). To a hot solution of carboxaldehyde **1** (0.61 g, 3 mmol) in absolute ethanol (15 mL), *S*-benzyldithiocarbazate (0.58 g, 3 mmol) in absolute ethanol (10 mL) containing piperidine (0.1 mL) was added with continuous stirring. The solid formed after 1 min was dissolved after 20 min. The reaction mixture was refluxed for another 2 h. The yellow crystals obtained after cooling were filtered off and crystallized from EtOH to give compound **8** as pale yellow crystals, mp 157–158°C, yield 0.75 g (73%). IR (KBr, cm^{-1}): 3400 (OH), 3080 ($CH_{arom.}$), 2949, 2860 ($CH_{aliph.}$), 1635 ($C{=}O_{benzoyl}$), 1589 (C=N), 1547 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6): 1.67 (t, 6H, $3CH_2$), 2.18 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 3.59 (s, 4H, $2NCH_2$), 7.29 (s, 1H, Ar–H), 7.53 (s, 1H, Ar–H), 8.25 (s, 1H, $H_{pyrazole}$), 8.81 (s, 1H, $H_{pyrazole}$), 11.68 (bs, 1H, OH, exchangeable with D_2O). ^{13}C-NMR (75 MHz, DMSO-d_6): 15.3 (CH_3), 19.6 (CH_3), 25.1 (CH_2), 29.4 (CH_2), 52.0 (NCH_2), 119.2, 122.5, 125.8, 127.3, 128.1, 136.8, 136.9, 142.7, 157.4, 177.2 (C=O), 190.9 (C=S). Mass spectrum, *m/z* (I_r %): 343 (23), 248 (5), 231 (25), 202 (17), 148 (6), 128 (100), 112 (10), 91 (13), 84 (30), 77 (8), 69 (77), 65 (5). *Anal*. Calcd for $C_{18}H_{21}N_3O_2S$ (343.44): C, 62.95; H, 6.16; N, 12.23; S, 9.34%. Found: C, 62.71; H, 6.10; N, 12.11; S, 9.05%.

4-(2-Hydroxy-3,5-dimethylbenzoyl)-1-(morpholin-4-ylcarbonothioyl)-1H-pyrazole (9). To a hot solution of carboxaldehyde **1** (0.61 g, 3 mmol) in absolute ethanol (15 mL), *S*-benzyldithiocarbazate (0.58 g, 3 mmol) in absolute ethanol (10 mL) containing morpholine (0.1 mL) was added with continuous stirring. The solid formed after 1 min was dissolved after 20 min. The reaction mixture was refluxed for another 2 h. The yellow crystals obtained after cooling were filtered off and crystallized from EtOH to give compound **9** as pale yellow crystals, mp 189–190°C, yield 0.71 g (69%). IR (KBr, cm^{-1}): 3090 ($CH_{arom.}$), 2972, 2921, 2855 ($CH_{aliph.}$), 1647 ($C{=}O_{benzoyl}$), 1624 (C=N), 1588 (C=C).^{1}H-NMR (400 MHz, DMSO-d_6): 2.18 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 3.71 (s, 4H, 2 NCH_2), 4.18 (s, 4H, 2 OCH_2), 7.30 (s, 1H, Ar–H), 7.48 (s, 1H, Ar–H), 8.27 (s, 1H, H-$3_{pyrazole}$), 8.82 (s, 1H, H-$5_{pyrazole}$), 11.65 (bs, 1H, OH, exchangeable with D_2O). ^{13}C-NMR (75 MHz, DMSO-d_6): 15.1 (CH_3), 19.8 (CH_3), 52.2 (NCH_2), 65.6 (OCH_2), 119.5, 122.4, 126.1, 127.5, 128.3, 137.0, 137.3, 142.2, 157.0, 176.8 (C=O), 191.1 (C=S). Mass spectrum, *m/z* (I_r %): 345 (26), 250 (4), 231 (30), 202 (7), 148 (10), 130 (70), 120 (8), 86 (100), 77 (12), 65 (7). *Anal*. Calcd for $C_{17}H_{19}N_3O_3S$ (345.42): C, 59.11; H, 5.54; N, 12.17; S, 9.28%. Found: C, 58.80; H, 5.44; N, 11.80; S, 9.15%.

3-{[(2-Aminophenyl)amino](hydroxy)methyl}-2-hydroxy-6,8-dimethyl-2,3-dihydro-4H-chromen-4-one (10). To a hot solution of carboxaldehyde **1** (0.61 g, 3 mmol) in 95% ethanol (20 mL), *o*-phenylenediamine (0.33 g, 3 mmol) was added and stirred for 1 min. The resulting orange crystals were filtered off and crystallized from EtOH to give compound **10** as orange crystals, mp 205°C, yield 0.78 g (79%). IR (KBr, cm^{-1}): 3446 (br, NH_2, NH, OH), 2922, 2860 ($CH_{aliph.}$), 1638 ($C{=}O_{\gamma\text{-pyrone}}$), 1597 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6): 2.13 (s, 3H, CH_3), 2.19–2.22 (m, 1H, NC*H*O), 2.35 (t, 1H, H-3), 2.43 (s, 3H, CH_3), 5.52 (bs, 2H, NH_2 exchangeable with D_2O), 6.56 (s, 1H, H-2), 6.84–6.95 (m, 2H, Ar–H), 7.14–7.19 (m, 1H, Ar–H), 7.40 (s, 1H, H-7), 7.45 (d, 1H, Ar–H), 7.57 (s, 1H, H-5), 7.64 (bs, 1H, OH exchangeable with D_2O), 9.33 (bs, 1H, NH exchangeable with D_2O), 9.67 (d, 1H, OH exchangeable with D_2O). ^{13}C-NMR (75 MHz, DMSO-d_6): 14.0 (CH_3), 20.1 (CH_3), 60.9, 61.6, 71.3, 117.1, 118.2, 120.7, 124.6, 126.0, 131.4, 133.3, 133.7, 136.5, 140.1, 150.5, 151.4, 164.9. Mass spectrum, *m/z* (I_r %): 328 (100), 291 (71), 283 (15), 263 (16), 247 (8), 200 (16), 159 (6), 119 (25), 105 (16), 91 (64), 77 (52), 65 (74). *Anal*. Calcd for $C_{18}H_{20}N_2O_4$ (328.36): C, 65.84; H, 6.14; N, 8.53%. Found: C, 65.55; H, 6.02; N, 8.26%.

1,3-Dimethyl-12H-benzo[b]chromeno[2,3-e][1,4]diazepin-5-one (11).

Method A. A mixture of carboxaldehyde **1** (0.61 g, 3 mmol) and *o*-phenylenediamine (0.33 g, 3 mmol) in 95% ethanol (20 mL) was heated under reflux for 2 h. After cooling, the resulting yellow solid was filtered off and crystallized from DMF/EtOH to give compound **11** as white crystals, mp 283–284°C, yield 0.63 g (77%).

Method B. A mixture of carbonitrile **2** (0.60 g, 3 mmol) and *o*-phenylenediamine (0.33 g, 3 mmol) in DMF (10 mL) was heated under reflux for 2 h. After cooling, the reaction mixture was poured onto ice (~30 g), and the resulting solid was filtered off and crystallized from DMF/EtOH to give compound **11** as white crystals, mp 283–284°C, yield 0.56 g (71%). IR (KBr, cm^{-1}): 3220 (NH), 3087 ($CH_{arom.}$), 2970, 2937 ($CH_{aliph.}$), 1646 ($C{=}O_{\gamma\text{-pyrone}}$), 1624 (C=N), 1601 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6): 2.43 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 7.17 (d, 2H, J = 6.4 Hz, Ar–H), 7.58 (s, 1H, H-2), 7.65 (d, 2H, J = 6.4 Hz, Ar–H), 7.86

(s, 1H, H-4), 9.34 (s, 1H, $H_{diazepine}$), 11.93 (bs, 1H, NH exchangeable with D_2O). ^{13}C-NMR (75 MHz, DMSO-d_6): 17.0 (CH_3), 20.7 (CH_3), 113.7, 118.8, 121.1, 125.6, 130.5, 135.2, 137.6, 138.7, 145.7, 149.2, 153.6, 159.7, 164.5, 168.9, 176.6, 199.1. Mass spectrum, *m/z* (I_r %): 290 (100), 261 (4), 233 (12), 145 (6), 120 (4), 105 (4), 91 (12), 77 (4), 65 (5). *Anal*. Calcd for $C_{18}H_{14}N_2O_2$ (290.32): C, 74.47; H, 4.86; N, 9.65%. Found: C, 74.20; H, 4.50; N, 9.45%.

5-(2-Hydroxy-3,5-dimethylbenzoyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (12). A mixture of carboxaldehyde **1** (0.61 g, 3 mmol) and cyanoacetamide (0.26 g, 3 mmol) in absolute ethanol (20 mL) containing piperidine (0.1 mL) was heated under reflux for 30 min. The yellow crystals obtained during heating were filtered off and crystallized from DMF/EtOH to give compound **12** as yellow crystals, mp 288–289°C, yield 0.68 g (85%). IR (KBr, cm^{-1}): 3208 (OH), 3137 (NH), 3072 ($CH_{arom.}$), 2935, 2875 ($CH_{aliph.}$), 2238 (C≡N), 1694 ($C{=}O_{pyridone}$), 1674 ($C{=}O_{benzoyl}$), 1623 (C=N), 1592 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6): 2.17 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 7.12 (s, 1H, Ar–H), 7.20 (s, 1H, Ar–H), 8.15 (s, 1H, H-$4_{pyridine}$), 8.29 (s, 1H, H-$6_{pyridine}$), 10.30 (bs, 2H, NH, OH, exchangeable with D_2O). Mass spectrum, *m/z* (I_r %): 268 (43), 148 (63), 120 (100), 91 (56), 77 (31), 65 (17). *Anal*. Calcd for $C_{15}H_{12}N_2O_3$ (268.27): C, 67.16; H, 4.51; N, 10.44%. Found: C, 66.80; H, 4.30; N, 10.21%.

Benzyl 5-amino-4-(2-hydroxy-3,5-dimethylbenzoyl)-1H-pyrazole-1-carbodithioate (13). A mixture of carbonitrile **2** (0.60 g, 3 mmol) and *S*-benzyldithiocarbazate (0.58 g, 3 mmol) in absolute ethanol (15 mL) was heated under reflux for 2 h. The pale yellow crystals deposited after cooling were filtered off and crystallized from EtOH to give compound **13** as pale yellow crystals, mp 241–242°C, yield 0.79 g (66%). IR (KBr, cm^{-1}): 3371 (OH), 3261, 3170 (NH_2), 3040 ($CH_{arom.}$), 2912, 2890 ($CH_{aliph.}$), 1635 (C=O), 1603 (C=N), 1533 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6): 2.15 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 4.46 (s, 2H, CH_2), 7.17 (s, 1H, Ar–H), 7.27–7.51 (m, 5H, Ar–H), 7.69 (s, 1H, Ar–H), 8.08 (s, 1H, H-$3_{pyrazole}$), 8.99 (bs, 2H, NH_2 exchangeable with D_2O), 10.92 (bs, 1H, OH exchangeable with D_2O). Mass spectrum, *m/z* (I_r %): 397 (59), 321 (6), 258 (11), 217 (8), 173 (11), 149 (13), 120 (6), 91 (100), 77 (11), 65 (14). *Anal*. Calcd for $C_{20}H_{19}N_3O_2S_2$ (397.51): C, 60.43; H, 4.82; N, 10.57; S, 16.13%. Found: C, 60.20; H, 4.60; N, 10.35; S, 16.00%.

Benzyl 2-[(2-amino-6,8-dimethylchromon-3-yl)methylidene] hydrazine-carbodithioate (14). A mixture of carbonitrile **2** (0.60 g, 3 mmol) and *S*-benzyldithiocarbazate (0.58 g, 3 mmol) in dry benzene (30 mL) containing triethylamine (0.1 mL) was heated under reflux for 4 h. The solid deposited after cooling was filtered off and crystallized from DMF/EtOH to give compound **14** as yellow crystals, mp 250–251°C, yield 0.71 g (60%). IR (KBr, cm^{-1}): 3403, 3210, 3143 (NH_2, NH), 2979, 2955, 2920 ($CH_{aliph.}$), 1631 (C=O), 1606 (C=N), 1571 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6): 2.32 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 4.46 (s, 2H, CH_2), 7.23–7.47 (m, 5H, Ar–H), 7.58 (s, 1H, H-7), 7.69 (s, 1H, H-5), 8.36 (s, 1H, CH=N), 8.63 (bs, 1H, NH exchangeable with D_2O), 9.39 (bs, H, NH exchangeable with D_2O), 13.33 (s, 1H, NH exchangeable with D_2O). ^{13}C-NMR (75 MHz, DMSO-d_6): 14.8 (CH_3), 20.4 (CH_3), 37.7 (CH_2), 91.9 (C-3), 117.3, 120.9, 123.0, 125.4, 127.5, 128.6, 135.2, 136.7, 139.7, 144.7, 154.4, 162.5, 173.8 (C=O), 196.7 (C=S). Mass spectrum, *m/z* (I_r %): 397 (32), 320 (19), 215 (65), 171 (9), 148 (33), 121 (15), 91 (100), 77 (49), 64 (8). *Anal*. Calcd for $C_{20}H_{19}N_3O_2S_2$ (397.51): C, 60.43; H, 4.82; N, 10.57; S, 16.13%. Found: C, 60.20; H, 4.45; N, 10.30; S, 15.85%.

6,8-Dimethylchromeno[4,3-c]pyrazol-4(1H)-one (15).

Method A. A mixture of carbonitrile **3** (0.60 g, 3 mmol) and *S*-benzyldithiocarbazate (0.58 g, 3 mmol) in acetic acid (15 mL) was heated under reflux for 2 h. After cooling, the reaction mixture was poured onto crushed ice (~25 g). The solid deposited was filtered off and crystallized from EtOH to give compound **15** as white crystals, mp 233–234°C, yield 0.39 g (61%).

Method B. A mixture of carbonitrile **2** (0.60 g, 3 mmol) and hydrazine hydrate (0.15 g, 3 mmol) in acetic acid (15 mL) was heated under reflux for 2 h. After cooling, the reaction mixture was poured onto crushed ice. The white solid so formed was filtered off and crystallized from EtOH to give compound **15** as white crystals, mp 233–234°C, yield 0.44 g (69%).

Method C. A mixture of carboxamide **4** (0.65 g, 3 mmol) and *S*-benzyldithiocarbazate in DMF (15 mL) was heated under reflux for 2 h. After cooling, the reaction mixture was poured onto crushed ice. The yellow solid so formed was filtered off and crystallized from ethanol to give compound **15** as white crystals, mp 233–234°C, yield 0.40 g (63%). IR (KBr, cm^{-1}): 3401 (NH), 3009 ($CH_{arom.}$), 2940, 2885, 2825 ($CH_{aliph.}$), 1710 ($C{=}O_{\alpha\text{-pyrone}}$), 1602 (C=N), 1538 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6): 2.01 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 6.78 (s, 1H, H-7), 7.38 (s, 1H, H-9), 8.44 (s, 1H, H-$3_{pyrazole}$). ^{13}C-NMR (75 MHz, DMSO-d_6): 14.7 (CH_3), 20.4 (CH_3), 113.5, 121.7, 126.7, 128.7, 130.0, 132.3, 137.6, 150.1, 155.5, 156.4. Mass spectrum, *m/z* (I_r %): 214 (100), 199 (40), 185 (6), 130 (10), 115 (8), 107 (12), 92 (13), 77 (13), 65 (11). *Anal*. Calcd for $C_{12}H_{10}N_2O_2$ (214.22): C, 67.28; H, 4.71; N, 13.08%. Found: C, 67.00; H, 4.50; N, 12.80%.

2-Amino-7,9-dimethyl-5-oxo-5H-chromeno[2,3-b]pyridine-3-carboxamide (16). To a solution of carbonitrile **2** (0.60 g, 3 mmol) in absolute ethanol (15 mL), cyanoacetamide

(0.26 g, 3 mmol) in absolute ethanol (10 mL) and piperidine (0.1 mL) was added. The reaction mixture was refluxed for 30 min. The yellow crystals obtained during heating were filtered and recrystallized from DMF/H_2O to give compound **16** as yellow crystals, yield mp > 300°C, yield 0.63 g (74%). IR (KBr, cm^{-1}): 3368, 3225, 3185 ($2NH_2$), 2941 ($CH_{aliph.}$), 1665 ($C{=}O_{amide}$), 1655 ($C{=}O_{\gamma\text{-}pyrone}$), 1612 (C=N), 1542 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6): 2.28 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 7.21 (s, 1H, H-8), 7.96 (s, 1H, H-6), 8.84 (s, 1H, H-4), 11.87 (bs, 4H, $2NH_2$ exchangeable with D_2O). ^{13}C-NMR (75 MHz, DMSO-d_6): 14.2 (CH_3), 20.4 (CH_3), 103.4, 107.9, 118.5, 126.7, 128.4, 129.8, 133.4, 146.3, 151.6, 154.5, 159.2, 166.8, 179.1 (C=O). Mass spectrum, *m/z* (I_r %): 283 (100), 266 (47), 238 (24), 209 (3), 91 (11), 77 (7), 65 (8). *Anal*. Calcd for $C_{15}H_{13}N_3O_3$ (283.28): C, 63.60; H, 4.63; N, 14.83%. Found: C, 63.35; H, 4.40; N, 14.60%.

(3*Z*)-3-{[(2-Aminophenyl)amino]methylidene}-6,8-dimethyl-2*H*-chromane-2,4(3*H*)-dione (17). A mixture of carboxamide **4** (0.65 g, 3 mmol) and *o*-phenylenediamine (0.33 g, 3 mmol) in DMF (15 mL) was heated under reflux for 2 h. The pale yellow crystals obtained after cooling were filtered off and recrystallized from DMF to give compound **17** as yellow crystals, mp 231–232°C, yield 0.72 g (78%). IR (KBr, cm^{-1}): 3387, 3337, 3149 (NH_2, NH), 3081 ($CH_{arom.}$), 2920, 2890 ($CH_{aliph.}$), 1718 ($C{=}O_{\alpha\text{-}pyrone}$), 1684 (C=O), 1601 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6): 2.39 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 5.24 (bs, 2H, NH_2 exchangeable with D_2O), 6.75 (t, 1H, *J* = 6.8 Hz, Ar–H), 6.91 (d, 1H, *J* = 7.2 Hz, Ar–H), 7.08 (t, 1H, *J* = 7.2 Hz, Ar–H), 7.38 (s, 1H, H–7), 7.46 (d, 1H, *J* = 6.8 Hz, Ar–H), 7.57 (d, 1H, *J* = 15.2 Hz, $H_{olefinic}$), 7.79 (s, 1H, H-5), 13.45 (d, 1H, *J* = 12.4 Hz, NH exchangeable with D_2O). Mass spectrum, *m/z* (I_r %): 308 (69), 307 (100), 290 (13), 263 (11), 159 (14), 149 (13), 119 (79), 105 (12), 91 (52), 77 (41), 65 (63). *Anal*. Calcd for $C_{18}H_{16}N_2O_3$ (308.34): C, 70.12; H, 5.23; N, 9.09%. Found: C, 69.80; H, 5.10; N, 8.70%.

2-Amino-5-(2-hydroxy-3,5-dimethylbenzoyl]-6-oxo-1,6-dihydropyridine-3-carboxamide (18). A mixture of carboxamide **4** (0.65 g, 3 mmol) and cyanoacetamide (0.25 g, 3 mmol) in sodium ethoxide (prepared by dissolving 0.2 g sodium in 20 mL absolute ethanol) was heated under reflux for 2 h. After cooling, the reaction mixture was poured onto crushed ice and neutralized with concentrated HCl. The solid so formed was filtered off and recrystallized from DMF/EtOH to give compound **18** as white crystals, mp > 300°C, yield 0.65 g (71%). IR (KBr, cm^{-1}): 3373, 3249, 3161 ($2NH_2$, NH, OH), 1683 ($C{=}O_{pyridone}$), 1648 ($C{=}O_{amide}$), 1619 ($C{=}O_{benzoyl}$), 1566 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6, δ): 2.37 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 7.49 (s, 1H, Ar–H), 7.73 (s, 1H, Ar–H), 8.11 (s, 1H, NH exchangeable with D_2O), 8.13 (s, 1H, NH exchangeable with D_2O), 8.36 (bs, 2H, NH_2 exchangeable with D_2O), 8.65 (bs, H, NH exchangeable with D_2O), 8.78 (s, 1H, H-$4_{pyridine}$). Mass spectrum, *m/z* (I_r %): 301 (59), 285 (41), 271 (80), 257 (61), 241 (47), 228 (22), 149 (100), 121 (49), 77 (14), 66 (55). *Anal*. Calcd for $C_{15}H_{15}N_3O_4$ (301.29): C, 59.79; H, 5.02; N, 13.95%. Found: C, 59.50; H, 4.80; N, 13.60%.

6-(2-Hydroxy-3,5-dimethylphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (19). A mixture of carboxylic acid **3** (0.65 g, 3 mmol) and cyanoacetamide (0.25 g, 3 mmol) in ethanol (15 mL) containing few drops of triethylamine was refluxed on water bath for 30 min. The solid obtained after cooling was filtered and crystallized from DMF to give compound **19** as pale yellow crystals, mp > 300°C, yield 0.49 g (68%). IR (KBr, cm^{-1}): 3302 (OH), 3216 (NH), 3077 ($CH_{arom.}$), 2237 (C≡N), 1652 (C=O), 1620 (C=C). ^{1}H-NMR (300 MHz, DMSO-d_6, δ): 2.40 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 7.26 (d, 1H, *J* = 9.0 Hz, Ar–H), 7.46 (d, 1H, *J* = 8.4 Hz, Ar–H), 7.94 (s, 1H, Ar–H), 8.22 (s, 1H, Ar–H), 9.46 (s, H, NH exchangeable with D_2O). ^{13}C-NMR (100 MHz, DMSO-d_6): 17.3 (CH_3), 20.7 (CH_3), 92.5 (C-3), 117.1 (C≡N), 121.3, 125.4, 135.1, 147, 150.9, 151.5, 164.5, 166.4, 171.8, 174.2. Mass spectrum, *m/z* (I_r %): 240 (46), 222 (18), 194 (12), 147 (15), 120 (100), 92 (39), 80 (85), 65 (45). *Anal*. Calcd for $C_{14}H_{12}N_2O_2$ (240.26): C, 69.99; H, 5.03; N, 11.66%. Found: C, 69.70; H, 5.00; N, 11.40%.

5-(Cyanomethyl)-7,9-dimethyl-2-oxo-1,5-dihydro-2H-chromeno[4,3-b]pyridine-3-carbonitrile (20). A mixture of acrylonitrile **5** (0.66 g, 3 mmol) and cyanoacetamide (0.26 g, 3 mmol) in absolute ethanol (20 mL) containing piperidine (0.1 mL) was heated under reflux for 2 h. The yellow crystals deposited during heating were filtered off, and crystallized from EtOH to give compound **20** as yellow crystals, yield 0.53 g (61%), mp > 300°C. IR (KBr, cm^{-1}): 3420 (NH), 2950, 2862 ($CH_{aliph.}$), 2235 (C≡N), 2200 (C≡N), 1652 (C=O), 1617 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6): 2.16 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.99 (d, 2H, *J* = 5.6 Hz, CH_2CN), 5.45 (t, 1H, *J* = 6.4 Hz, H-5), 7.04 (s, 1H, H-8), 7.59 (s, 1H, H-10), 7.64 (s, 1H, H-$4_{pyridine}$). ^{13}C-NMR (DMSO-d_6, δ): 15.7 (CH_3), 20.4 (CH_3), 23.1 (CH_2), 71.3 (C-5), 110.4, 116.6 (C≡N), 117.5 (C≡N), 118.4, 123.1, 125.0, 132.3, 132.9, 135.7, 136.8, 143.9, 151.4, 162.3 (C-2). Mass spectrum, *m/z* (I_r %): 291 (8), 251 (100), 223 (6), 179 (3), 104 (7), 98 (9), 85 (13), 77 (8), 71 (24), 65 (7). *Anal*. Calcd for $C_{17}H_{13}N_3O_2$ (291.30): C, 70.09; H, 4.50; N, 14.42%. Found: C, 69.80; H, 4.30; N, 14.10%.

REFERENCES AND NOTES

[1] Gaspar, A.; Matos, M. J.; Garrido, J.; Uriarte, E.; Borges, F. Chem Rev 2014, 114, 4960.

[2] Wang, G.; Chen, M.; Wang, J.; Peng, Y.; Li, L.; Xie, Z.-Z.; Deng, B.; Chen, S.; Li, W. Bioorg Med Chem Lett 2017, 27, 2957.

[3] Ibrahim, M. A.; Ali, T. E. J Braz Chem Soc 2010, 21, 1007.
[4] Kumar, V.; Gupta, M.; Gandhi, S. G.; Bharate, S. S.; Kumar, A.; Vishwakarma, R. A.; Bharate, S. B. Tetrahedron Lett 2017, 58, 3974.
[5] Kavitha, P.; Saritha, M.; Reddy, K. L. Spectrochim Acta A 2013, 102, 159.
[6] Demetgül, C.; Beyazit, N. Carbohydr Polym 2018, 181, 812.
[7] Jayashree, B. S.; Gurushyam, S.; Pai, A. Asian J Pharmaceut Sci 2016, 11, 185.
[8] Kumara, P. M.; Srimany, A.; Ravikanth, G.; Shaanker, R. U.; Pradeep, T. Phytochemistry 2015, 116, 104.
[9] Huang, W.; Ding, Y.; Miao, Y.; Liu, M.-Z.; Li, Y.; Yang, G.-F. Eur J Med Chem 2009, 44, 3687.
[10] Huang, W.; Liu, M.-Z.; Li, Y.; Tan, Y.; Yang, G.-F. Bioorg Med Chem 2007, 15, 5191.
[11] Larget, R.; Lockhart, B.; Renard, P.; Largeron, M. Bioorg Med Chem Lett 2000, 10, 835.
[12] Groweiss, A.; Cardellins, J. H.; Boyd, M. R. J Nat Prod 2000, 63, 1537.
[13] Farag, A. A. M.; Roushdy, N.; Abdel Halim, S.; El-Gohary, N. M.; Ibrahim, M. A.; Said, S. Spectrochim Acta A 2018, 191, 478.
[14] Ibrahim, M. A.; Abdel Halim, S.; Roushdy, N.; Farag, A. A. M.; El-Gohary, N. M. Opt Mater 2017, 73, 290.
[15] Ibrahim, M. A.; Farag, A. A. M.; Roushdy, N.; El-Gohary, N. M. J Mol Str 2016, 1105, 370.
[16] Ibrahim, M. A.; Farag, A. A. M.; Roushdy, N.; El-Gohary, N. M. Opt Mater 2016, 51, 70.
[17] Iaroshenko, V. O.; Mkrtchyan, S.; Gevorgyan, A.; Grigoryan, T.; Villinger, A.; Langer, P. RSC Adv 2015, 5, 28717.
[18] Iaroshenko, V. O.; Mkrtchyan, S.; Gevorgyan, A.; Miliutina, M.; Villinger, A.; Volochnyuk, D.; Sosnovskikh, V. Y.; Langer, P. Org Biomol Chem 2012, 10, 890.
[19] Sosnovskikh, V. Y.; Moshkin, V. S.; Kodess, M. I. Tetrahedron Lett 2008, 49, 6856.
[20] Ibrahim, M. A.; El-Gohary, N. M.; Said, S. Heterocycles 2015, 91, 1863.
[21] Sosnovskikh, V. Y.; Khalymbadzha, I. A.; Irgashev, R. A.; Slepukhin, P. A. Tetrahedron 2008, 64, 10172.
[22] Sosnovskikh, V. Y.; Irgashev, R. A.; Kodess, M. I. Tetrahedron 2008, 64, 2997.
[23] Ibrahim, M. A.; El-Gohary, N. M. Heterocycles 2014, 89, 413.
[24] Ibrahim, M. A.; Ali, T. E. Turk J Chem 2015, 39, 412.
[25] Nohara, A.; Umetani, T.; Sanno, Y. Tetrahedron 1974, 30, 3551.
[26] Nohara, A.; Kuriki, H.; Saijo, T.; Sugihara, H.; Kanno, M.; Sanno, Y. J Med Chem 1977, 20, 141.
[27] Nohara, A.; Umetani, T.; Ukawa, K.; Sanno, Y. Chem Pharm Bull 1974, 22, 2959.
[28] Ibrahim, S. S.; Allimony, H. A.; Abdel-Halim, A. M.; Ibrahim, M. A. Arkivoc 2009, xiv, 28.
[29] Fitton, A. O.; Houghton, P. G.; Suschitzky, H. Synthesis 1979, 1979, 337.
[30] Ibrahim, M. A.; Ali, T. E.; El-Kazak, A. M.; Mohamed, A. M. J Heterocyclic Chem 2015, 52, 815.
[31] Sosnovskikh, V. Y.; Moshkin, V. S.; Kodess, M. I. Tetrahedron Lett 2009, 50, 6515.