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STUDIES ON THE CHEMICAL BEHAVIOR OF THE NOVEL 6,8-DIBROMO-7-HYDROXYCHROMONE-3-CARBOXALDEHYDE TOWARDS SOME CARBON NUCLEOPHILIC REAGENTS

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Abstract – A novel 6,8-dibromo-7-hydroxychromone-3-carboxaldehyde (**4**) was prepared by the Vilsemier-Haack formylation of 3,5-dibromo-2,4-dihydroxyacetophenone (**3**). The chemical reactivity of carboxaldehyde **4** was studied towards some carbon nucleophiles as cyclic and acyclic active methylene nucleophiles and also 1,3-*C,N*- and 1,3-*C,C*-binucleophiles as a route to achieve ring transformation to produce a variety of heterocyclic systems. Structures of the newly synthesized products have been deduced on the basis of elemental analysis and spectral data.

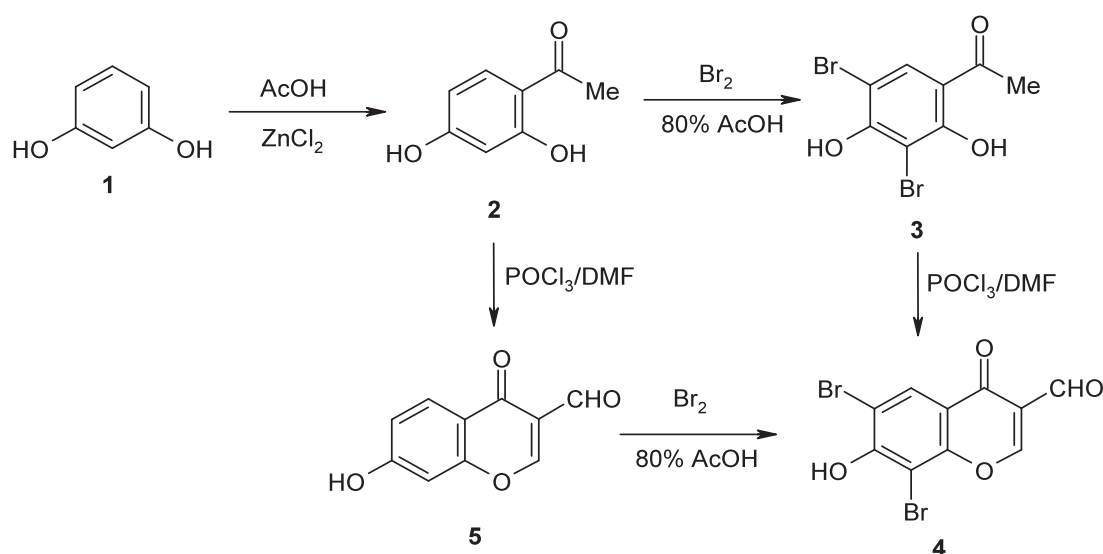
INTRODUCTION

3-Formylchromone has been used as precursor to prepare a diversity of heterocyclic systems,¹⁻⁵ owing to the presence of an α,β -unsaturated keto-function, a conjugated formyl group at C-3 and in particular due to the active center at C-2. The C-2 position is very reactive towards *Michael* addition of nucleophiles with opening of the γ -pyrone ring followed by a new cyclization.⁶⁻⁹ Numerous bromine-containing heterocycles exhibit strong biological activity due to their ability to inhibit specific enzymes, good solubility in lipids, and easy penetration through cell membranes.¹⁰⁻¹² Furthermore, nitrogen-containing heterocycles have well-known biological properties in medicinal and pharmaceutical fields.¹³⁻¹⁵ These observations directed our attention to synthesis the novel 6,8-dibromo-7-hydroxychromone-3-carboxaldehyde (**4**), as starting compound, to react with some carbon nucleophiles such as cyclic and acyclic active methylene nucleophiles and also 1,3-*C,N*- and 1,3-*C,C*-binucleophiles as a route to obtain a novel nitrogen heterocyclic systems such as chromonyloxazolone, chromonylthiazolidinone,

chromonylxanthene, pyrano[3,2-*c*]chromene, pyrano[3,2-*c*]quinoline, pyridylpyridine, pyrido[1,2-*a*]-benzimidazole, pyrido[3,2-*d*]pyrimidine and quinazolinone which would be expected to have biological activities.

RESULTS AND DISCUSSION

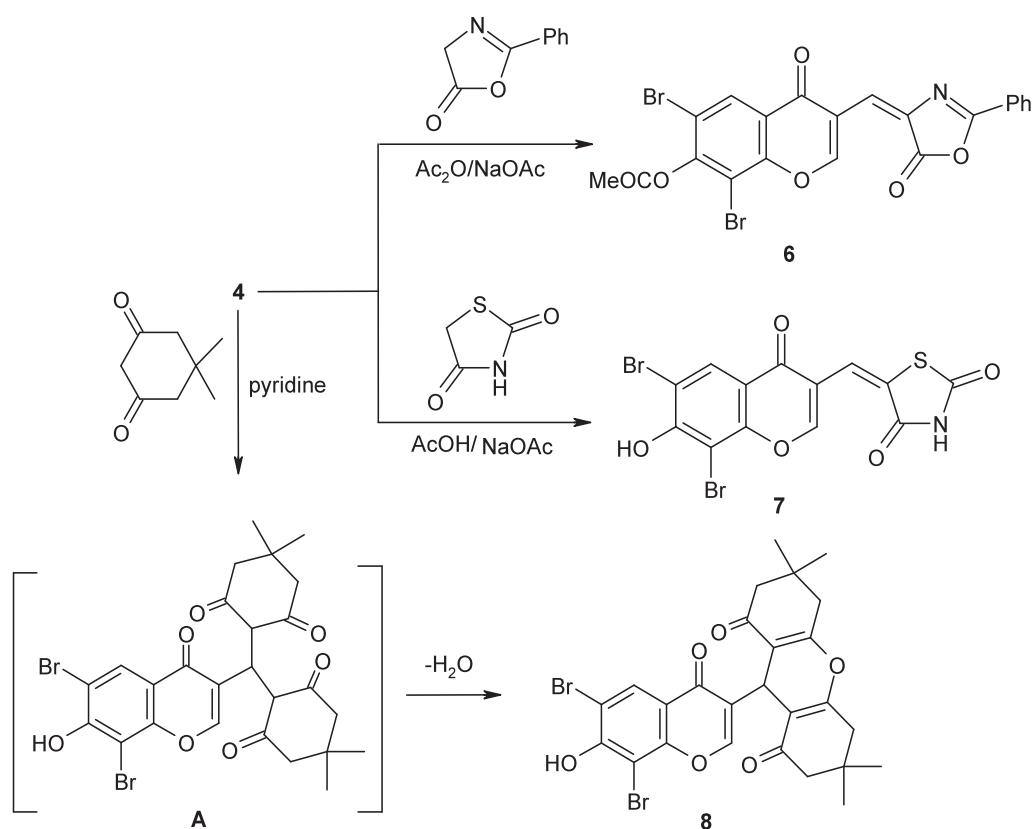
Acetylation of resorcinol (**1**) with glacial acetic acid in the presence of freshly fused zinc chloride, using the standard procedure,¹⁶ gave 2,4-dihydroxyacetophenone (**2**) which upon bromination using bromine in 80% acetic acid afforded 3,5-dibromo-2,4-dihydroxyacetophenone (**3**).¹⁷ Applying Vilsemier-Haack formylation on the latter compound produced the novel 6,8-dibromo-7-hydroxychromone-3-carboxaldehyde (**4**).¹⁸ Compound **4** was also obtained *via* Vilsemier-Haack formylation of 2,4-dihydroxyacetophenone (**2**) to produce 7-hydroxychromone-3-carboxaldehyde (**5**)¹⁹ which upon bromination afforded the target compound **4** (Scheme 1). Structure of carboxaldehyde **4** was deduced from its correct elemental analysis and spectral data. Its IR spectrum showed two characteristic absorption bands at 1685 and 1667 cm^{-1} attributed to $\text{C}=\text{O}_{\text{formyl}}$ and $\text{C}=\text{O}_{\gamma\text{-pyrone}}$, respectively. Its $^1\text{H-NMR}$ spectrum consists of three singlets at δ 8.16, 8.89 and 10.07 ppm due to $\text{H-5}_{\text{chromone}}$, $\text{H-2}_{\text{chromone}}$ and CHO protons, respectively. $^{13}\text{C-NMR}$ spectrum of compound **4** showed two characteristic downfield signals at δ 172.8 and 187.9 ppm attributed to the C-4 (as $\text{C}=\text{O}$) and the aldehydic carbons, respectively. Also, the mass spectrum of compound **4** showed the molecular ion peak at m/z 346, and the base peak at m/z 320. In addition, the relative intensities of M^+ , $\text{M}+2$ and $\text{M}+4$ are in the ratio 1:2:1 as expected for compounds contains two bromine atoms.



Scheme 1

Chromone bearing heterocyclic systems at position 3 recorded variable biological activities.²⁰ Thus, a variety of heterocyclic systems linked to chromone moiety at position 3 were synthesized *via* reaction of 6,8-dibromo-7-hydroxychromone-3-carboxaldehyde (**4**) with some cyclic active methylene nucleophiles. Thus, condensation of carboxaldehyde **4** with hippuric acid in boiling acetic anhydride containing freshly fused sodium acetate gave 6,8-dibromo-3-[(5-oxo-2-phenyl-1,3-oxazol-4-ylidene)methyl]chromon-7-yl acetate (**6**) (Scheme 2). The IR spectrum of compound **6** showed characteristic absorption bands at 1782 ($\text{C}=\text{O}_{\text{oxazolone}}$), 1718 ($\text{C}=\text{O}_{\text{acetyl}}$), 1654 ($\text{C}=\text{O}_{\gamma\text{-pyrone}}$) and 1610 cm^{-1} ($\text{C}=\text{N}$). Its $^1\text{H-NMR}$ spectrum exhibited characteristic singlets at δ 2.11 ($\text{CH}_3_{\text{acetyl}}$), 6.43 (exocyclic $\text{CH}=\text{C}$), 7.89 ($\text{H-5}_{\text{chromone}}$) and 8.32 ($\text{H-2}_{\text{chromone}}$) ppm.

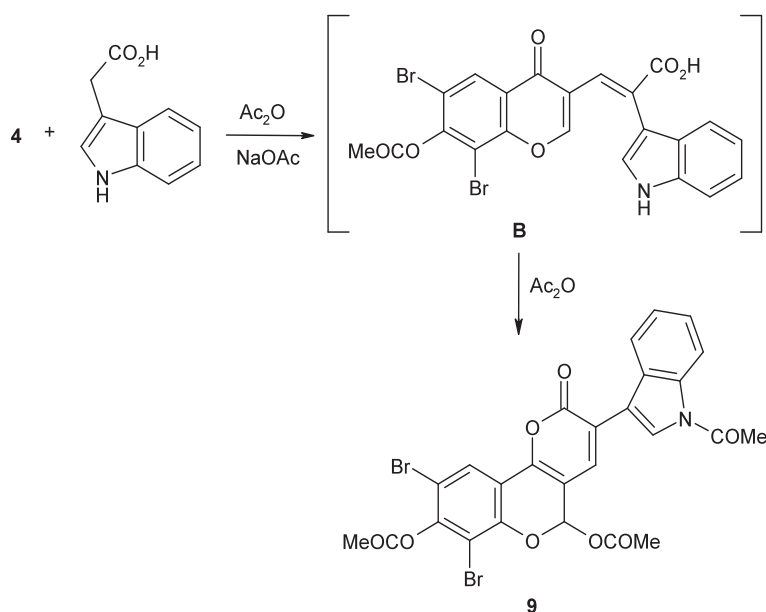
Also, Knoevenagel condensation of aldehyde **4** with thiazolidine-2,4-dione in glacial acetic acid containing freshly fused sodium acetate afforded the target compound, 6,8-dibromo-3-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]chromone (**7**) (Scheme 2). Its $^1\text{H-NMR}$ spectrum showed three singlets at δ 7.64, 8.18 and 8.88 ppm attributed to exocyclic methine proton, $\text{H-5}_{\text{chromone}}$ and $\text{H-2}_{\text{chromone}}$, respectively, in addition to the NH proton which observed as a broad signal exchangeable with D_2O at δ 12.50 ppm. Also, its mass spectrum showed the molecular ion peak at m/z 445 and the base peak at m/z 376.



Scheme 2

Interestingly, dimedone showed different behavior, than the previous cyclic active methylene compounds. Thus, carboxaldehyde **4** reacted with two molecules of dimedone in dry pyridine to produce 9-(6,8-dibromo-7-hydroxychromon-3-yl)-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8-octahydroxanthene-1,8-dione (**8**) (Scheme 2).²¹ The ¹H-NMR spectrum showed characteristic singlets at δ 4.32, 8.03 and 8.38 ppm attributed to H-9_{xanthene}, H-5_{chromone} and H-2_{chromone}, respectively. Its ¹³C-NMR spectrum showed upfield signals assigned to the methyl carbons at δ 25.9 and 26.2 ppm. The mass spectrum of compound **8** showed the molecular ion peak at m/z 590 which agrees well with the molecular formula (C₂₆H₂₄Br₂O₆).

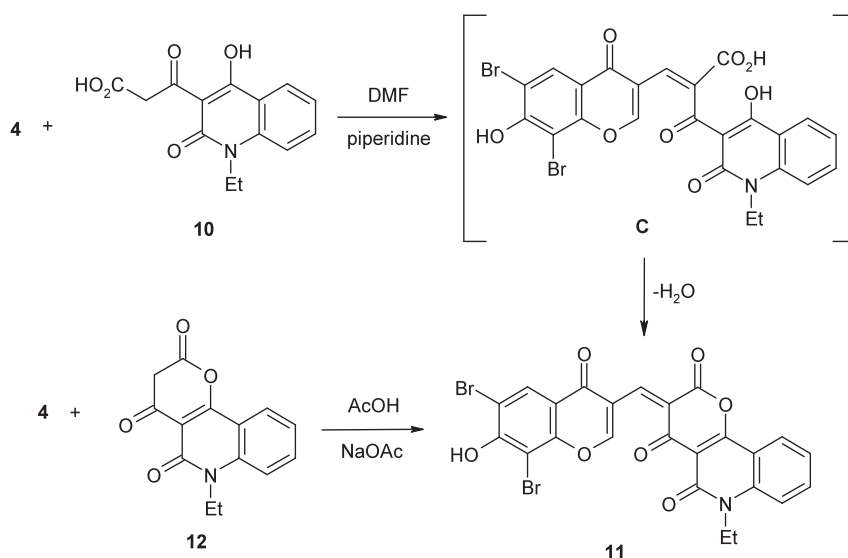
Reaction of carboxaldehyde **1** with some acyclic active methylene nucleophiles was studied. Thus, condensation of carboxaldehyde **4** with indole-3-acetic acid in boiling acetic anhydride containing freshly fused sodium acetate gave 3-(1-acetyl-1*H*-indol-3-yl)-7,9-dibromo-2-oxo-2*H*,5*H*-pyrano[3,2-*c*]chromene-5,8-diyl diacetate **9** (Scheme 3).²² The IR spectrum of compound **9** showed characteristic absorption bands at 1780 (C=O _{α -lactone}), 1736, 1719, 1645 (3 C=O_{acetyl}) cm⁻¹. Its ¹H-NMR spectrum showed three characteristic singlets at δ 1.91, 2.05 and 2.73 ppm attributed to protons of three methyl groups, in addition to three characteristic singlet signals at δ 6.40 (H-5 as OCHO), 7.70 (H-10), 8.26 (H-2_{indole}) and 8.44 (H-4).



Scheme 3

Similarly, reaction of carboxaldehyde **4** with β -ketoacid **10**,²³ in boiling DMF containing few drops of piperidine, furnished directly the cyclized product, 3-[(6,8-dibromo-7-hydroxychromon-3-yl)methylidene]-6-ethyl-6*H*-pyrano[3,2-*c*]quinoline-2,4,5-(3*H*,5*H*) trione (**11**), in one step reaction. Under these reaction conditions, the Knoevenagel condensation intermediate **C** was not isolated but underwent intramolecular nucleophilic lactonization to form the cyclized product directly **11** (Scheme 4). The latter

compound **11** was also obtained from the reaction of the pyrano[3,2-*c*]quinoline derivative **12**²⁴ with carboxaldehyde **4** in glacial acetic acid containing freshly fused sodium acetate.²⁵ The ¹H-NMR spectrum of **11** showed three characteristic singlets at δ 8.29 (H-5_{chromone}), 8.39 (exocyclic CH=C) and 9.15 ppm (H-2_{chromone}).

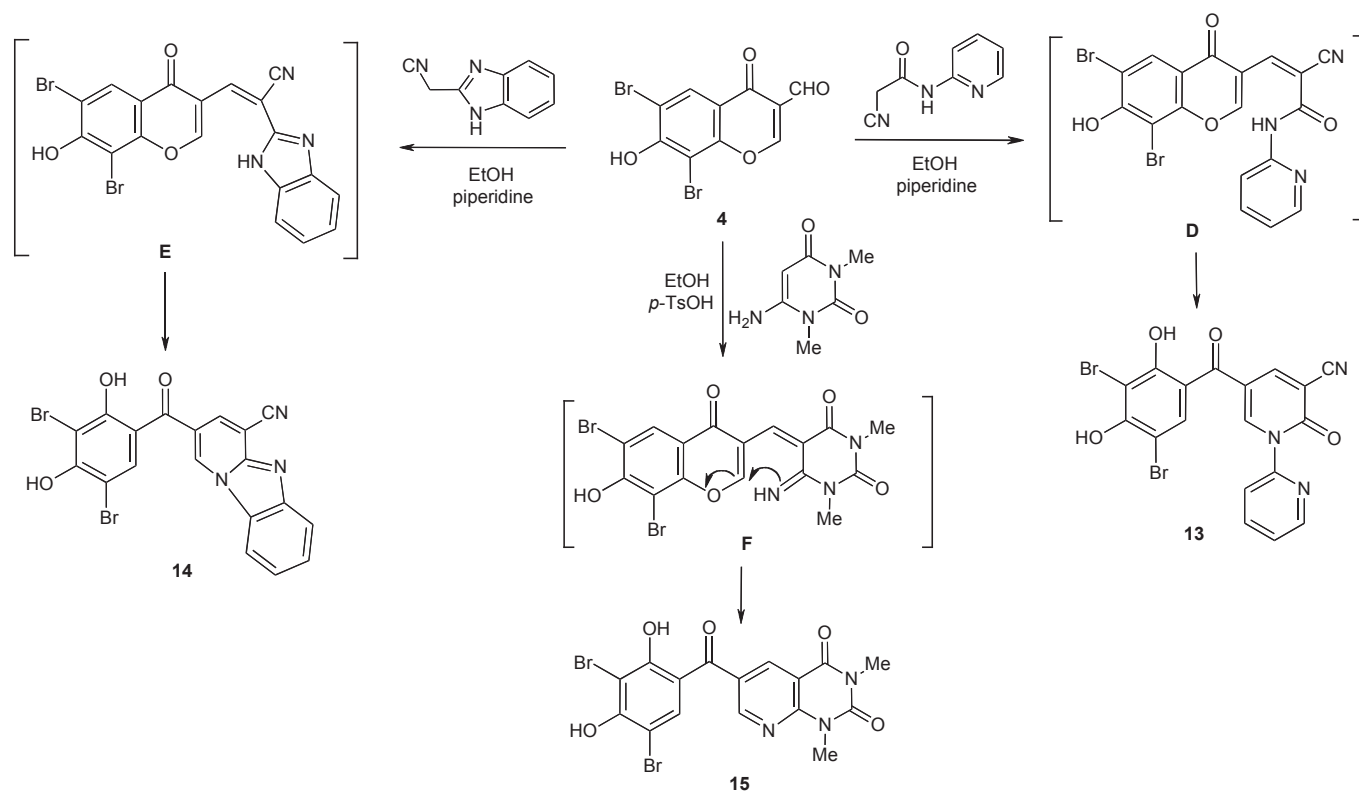


Scheme 4

Next, we studied the reaction of carboxaldehyde **4** with some 1,3-*C,N*-binucleophiles which produced some biheterocyclic systems *via* γ -pyrone ring opening followed by ring closure. Thus, condensation of carboxaldehyde **4** with 2-cyano-*N*-(pyridin-2-yl)acetamide and 1*H*-benzimidazol-2-ylacetonitrile, in boiling EtOH containing few drops of piperidine, afforded 5-(3,5-dibromo-2,4-dihydroxybenzoyl)-2-oxo-2*H*-1-(pyridin-2-yl)pyridine-3-carbonitrile (**13**)²⁶ and 2-(3,5-dibromo-2,4-dihydroxybenzoyl)pyrido[1,2-*a*] benzimidazole-4-carbonitrile (**14**), respectively (Scheme 5).²⁷ The reaction proceeds *via* condensation followed by nucleophilic attack at C-2 position with γ -pyrone ring opening. Their IR spectra showed characteristic absorption bands at 2209, 2240 (C \equiv N) and 1637, 1630 (C=O_{benzoyl}) cm⁻¹, respectively. The ¹H-NMR spectra of compounds **13** and **14** showed two characteristic singlets for each one at δ 8.02, 8.63 and 7.97, 8.07 ppm, respectively, attributed to protons of pyridine rings. Moreover, the mass spectrum of compound **14** showed the molecular ion peak at *m/z* 485 which agrees well with the molecular formula (C₁₉H₉Br₂N₃O₃).

Similarly, condensation of carboxaldehyde **4** with 6-amino-5*H*-1,3-dimethylpyrimidine-2,4-(1*H*,3*H*)-dione gave the pyrido[3,2-*d*]pyrimidine derivative **15**, through condensation of the formyl group with the active methylene group, to give the intermediate **F**, which underwent γ -pyrone ring opening by the imine nitrogen as shown in Scheme 5.²⁸ The ¹H-NMR spectrum recorded characteristic singlet signals at δ 3.30 (CH₃), 3.67 (CH₃), 7.63 (H-6_{resorcinol}), 8.53 (H-8), 8.99 (H-6) ppm. Also, its ¹³C-NMR spectrum showed

characteristic signals attributed to the two methyl carbons at δ 28.2 and 29.5 ppm. The mass spectrum of compound **15** showed the molecular ion peak at m/e 483 which agrees well with the molecular formula ($C_{16}H_{11}Br_2N_3O_5$) and supports the identity of the structure.



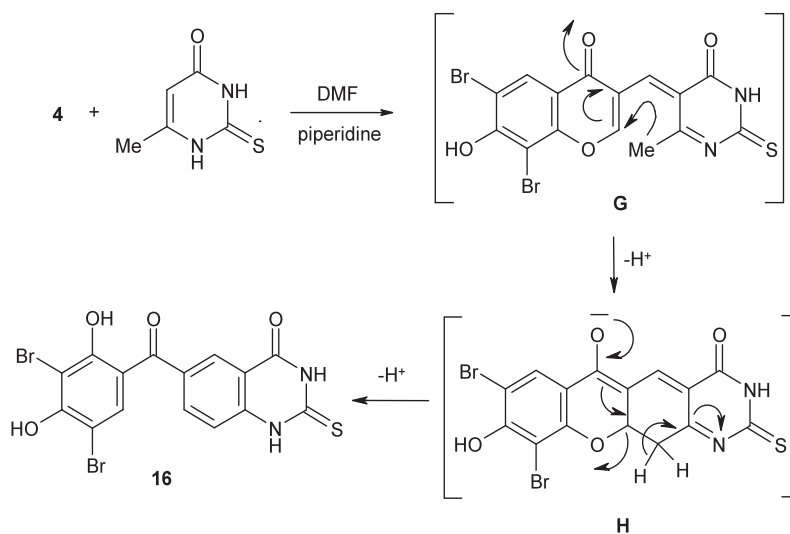
Scheme 5

Finally, treatment of carboxaldehyde **4** with 1,3-*C,C*-binucleophile namely 6-methyl-2-thioxo-2,3-dihydropyrimidin-4(1H)-one, in boiling DMF containing few drops of piperidine, produced 6-(3,5-dibromo-2,4-dihydroxybenzoyl)-2-thioxo-1,3-dihydroquinazolin-4-one (**16**) as shown in Scheme 6. Its 1H -NMR spectrum showed two characteristic singlets at δ 7.95 and 8.14 ppm attributed to H-6_{resorcinol} and H-5_{quinazoline}, respectively, while the H-7 and H-8 of quinazoline moiety appeared as doublets at 8.07 and 7.05 ppm, respectively. The mass spectrum of compound **16** showed the molecular ion peak at m/z 472 which agrees well with the suggested structure.

CONCLUSIONS

The novel 6,8-dibromo-7-hydroxychromone-3-carboxaldehyde (**4**) was efficiently synthesized and utilized to react with some carbon nucleophiles such as cyclic and cyclic active methylene nucleophiles and also 1,3-*C,N*- and 1,3-*C,C*-binucleophiles as a route to obtain a novel nitrogen heterocyclic systems including chromonyloxazolone, chromonylthiazolidinone, chromonylxanthene, pyrano[3,2-*c*]chromene, pyrano[3,2-*c*]quinoline, pyridylpyridine, pyrido[1,2-*a*]benzimidazole, pyrido[3,2-*d*]pyrimidine and

quinazolinone.



Scheme 6

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. ^1H NMR (300MHz) and ^{13}C NMR (75 MHz) spectra were measured on Mercury-300BB, using $\text{DMSO}-d_6$ 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 at the Chemical War department, Ministry of Defense, Egypt.

3,5-Dibromo-2,4-dihydroxyacetophenone (3)

To a solution of 2,4-dihydroxyacetophenone (**2**) (15.2 g, 0.1 mol) in acetic acid (80%, 20 mL), bromine (32 g, 10.4 mL, 0.2 mol) in acetic acid (10 mL) was added dropwise with continuous stirring for 15 min. The pale red crystals obtained were filtered off and recrystallized from benzene to give compound **3** as white crystals, yield (14.4 g, 46%), mp 173-174 °C (lit. 172-173 °C).¹⁷ IR (KBr, cm^{-1}): 3399 (br, OH), 1624 ($\text{C}=\text{O}_{\text{hydrogen bonded}}$), 1559 ($\text{C}=\text{C}$).

6,8-Dibromo-7-hydroxychromone-3-carboxaldehyde (4).

Method A: Phosphoryl chloride (3 mL) was added dropwise with continuous stirring to a pre-cooled DMF (10 mL) and the mixture was further stirred at room temperature for 30 min. Then 3,5-dibromo-2,4-dihydroxyacetophenone (**3**) (0.93 g, 3 mmol) in DMF (10 mL) was added dropwise with continuous stirring. The reaction mixture was stirred at room temperature for 2 h, left overnight and poured onto crushed ice (50 g). The obtained solid was filtered off, air dried and crystallized from EtOH to give

compound **4** as pale yellow crystals, yield (0.80 g, 77%), mp 250-251 °C.

Method B: A mixture of 7-hydroxychromone-3-carboxaldehyde (**5**) (0.57 g, 3 mmol) and bromine (0.96 g, 0.32 mL, 6 mmol) in acetic acid (80%, 5 mL) was stirred at room temperature for 1 h. The obtained solid was filtered off and crystallized from EtOH to give compound **4** as pale yellow crystals, yield (0.61 g, 59%), mp 250-251 °C. IR (KBr, cm^{-1}): 3235 (OH), 3058 (CH_{arom}), 1685 ($\text{C}=\text{O}_{\text{formyl}}$), 1667 ($\text{C}=\text{O}_{\gamma\text{-pyrone}}$), 1599 ($\text{C}=\text{C}$). $^1\text{H-NMR}$ ($\text{DMSO-}d_6$): 8.16 (s, 1H, H-5_{chromone}), 8.89 (s, 1H, H-2_{chromone}), 10.07 (s, 1H, CHO). $^{13}\text{C-NMR}$ ($\text{DMSO-}d_6$): 100.4 (C-8), 110.8 (C-6), 118.9 (C-3), 119.7 (C-4a), 127.6 (C-5), 153.1 (C-8a), 156.9 (C-7), 163.2 (C-2), 172.8 (C=O), 187.9 (CHO). MS (m/z , I%): 350 (M+4, 2), 348 (M+2, 5), 346 (M^+ , 2), 322 (52), 320 (100), 318 (50), 296 (8), 294 (16), 292 (8), 280 (3), 278 (7), 276 (3), 215 (2), 213 (2), 199 (3), 197 (3), 187 (3), 185 (4), 175 (2), 173 (2), 159 (2), 157 (2), 133 (3), 119 (2), 91 (2). Anal. Calcd for $\text{C}_{10}\text{H}_4\text{Br}_2\text{O}_4$ (347.94): C, 34.52; H, 1.16%. Found: C, 34.17; H, 1.16%.

6,8-Dibromo-3-[(5-oxo-2-phenyl-1,3-oxazol-4-ylidene)methyl]chromon-7-yl acetate (6).

A solution of hippuric acid (0.18 g, 1 mmol) in acetic anhydride (10 mL) containing freshly fused sodium acetate (0.1 g) was heated under reflux for 1 h. The carboxaldehyde **4** (0.35 g, 1 mmol) was added to the reaction mixture and further heated for 4 h. After cooling, the reaction mixture was poured onto crushed ice. The obtained solid was filtered off and crystallized from acetic acid to give compound **6** as yellow crystals, yield (0.31 g, 58%), mp > 300 °C. IR (KBr, cm^{-1}): 3063 (CH_{arom}), 1782 ($\text{C}=\text{O}_{\text{oxazolone}}$), 1718 ($\text{C}=\text{O}_{\text{acetyl}}$), 1654 ($\text{C}=\text{O}_{\gamma\text{-pyrone}}$), 1610 ($\text{C}=\text{N}$), 1590 ($\text{C}=\text{C}$). $^1\text{H-NMR}$ ($\text{DMSO-}d_6$): 2.11 (s, 3H, $\text{CH}_3_{\text{acetyl}}$), 6.43 (s, 1H, exocyclic $\text{CH}=\text{C}$), 7.49-7.67 (m, 4H, Ar-H), 7.89 (s, 1H, H-5_{chromone}), 7.96 (d, 1H, $J=7.2$ Hz, Ar-H), 8.32 (s, 1H, H-2_{chromone}). Anal. Calcd for $\text{C}_{21}\text{H}_{11}\text{Br}_2\text{NO}_6$ (533.13); C, 47.31; H, 2.08; N, 2.63%. Found: C, 47.15; H, 2.01; N, 2.45%.

6,8-Dibromo-3-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]chromone (7).

A mixture of carboxaldehyde **4** (0.35 g, 1 mmol) and thiazolidinedione (0.12 g, 1 mmol), in glacial acetic acid (20 mL) containing freshly fused sodium acetate (0.1 g), was heated under reflux for 1 h. The yellow crystals obtained after cooling were filtered off and crystallized from acetic acid to give compound **7** as yellow crystals, yield (0.34 g, 76%), mp > 300 °C. IR (KBr, cm^{-1}): 3455 (OH), 3197 (NH), 3058 (CH_{arom}), 1733 ($\text{C}=\text{O}_{\text{thiazolidine}}$), 1685 ($\text{C}=\text{O}_{\text{thiazolidine}}$), 1664 ($\text{C}=\text{O}_{\gamma\text{-pyrone}}$), 1598 ($\text{C}=\text{C}$). $^1\text{H-NMR}$ ($\text{DMSO-}d_6$): 7.64 (s, 1H, exocyclic $\text{CH}=\text{C}$), 8.18 (s, 1H, H-5_{chromone}), 8.88 (s, 1H, H-2_{chromone}), 12.50 (brs, 1H, NH exchangeable with D_2O). MS (m/z , I%): 449 (M+4, 25), 447 (M+2, 45), 445 (M^+ , 23), 404 (35), 376 (100), 359 (9), 279 (6), 85 (21). Anal. Calcd for $\text{C}_{13}\text{H}_5\text{Br}_2\text{NO}_5\text{S}$ (447.06); C, 34.93; H, 1.13; N, 3.13; S, 7.17%. Found: C, 34.39; H, 1.15; N, 3.17; S, 7.07%.

9-(6,8-Dibromo-7-hydroxychromon-3-yl)-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8-octahydroanthene-1,8-dione (8).

A mixture of carboxaldehyde **4** (0.35 g, 1 mmol) and dimedone (0.28 g, 2 mmol) in dry pyridine (10 mL)

was heated under reflux for 2 h. The obtained solid after acidification with diluted hydrochloric acid, was filtered off and crystallized from acetic acid to give compound **8** as white crystals, yield (0.38 g, 64%), mp > 300 °C. IR (KBr, cm⁻¹): 3219 (OH), 3087 (CH_{arom}), 2959, 2936, 2871 (CH_{aliph}), 1710, 1670 (2C=O_{xanthene}), 1660 (C=O_{γ-pyrone}), 1616 (C=C). ¹H-NMR (DMSO-*d*₆): 0.87 (s, 6H, 2 CH₃), 1.02 (s, 6H, 2 CH₃), 1.91 (s, 2H, CH₂), 2.02 (s, 2H, CH₂), 2.08 (s, 2H, CH₂), 2.24 (s, 2H, CH₂), 4.32 (s, 1H, H-9_{xanthene}), 8.03 (s, 1H, H-5_{chromone}), 8.38 (s, 1H, H-2_{chromone}), 11.20 (s, 1H, OH exchangeable with D₂O). ¹³C-NMR (DMSO-*d*₆): 25.9 (2CH₃), 26.2 (2CH₃), 28.7 (2CH₂), 29.4 (C-9_{xanthene}), 31.7 (2CMe₂), 50.1 (2CH₂), 99.7, 109.7, 110.2, 118.5, 122.1, 127.3, 152.6, 155.6, 155.7, 164.6, 173.2, 196.1. MS (*m/z*, I%): 594 (M+4, 13), 592 (M+2, 23), 590 (M⁺, 12), 508 (43), 319 (5), 294 (3), 291 (4), 266 (11), 257 (24), 251 (8), 238 (8), 236 (8), 217 (18), 201 (9), 171 (13), 157 (12), 111 (85), 109 (71), 95 (86), 91 (37), 64 (100). Anal. Calcd for C₂₆H₂₄Br₂O₆ (592.29); C, 52.73; H, 4.08%. Found: C, 52.68; H, 4.05%.

3-(1-Acetyl-1*H*-indol-3-yl)-7,9-dibromo-2-oxo-2*H*,5*H*-pyrano[3,2-*c*]chromene-5,8-diyl diacetate (**9**)

A mixture of carboxaldehyde **4** (0.35 g, 1 mmol) and indole-3-acetic acid (0.18 g, 1 mmol), in acetic anhydride (5 mL) containing freshly fused sodium acetate (0.1 g), was heated under reflux for 3 h. After cooling, the reaction mixture was poured onto crushed ice. The obtained solid was filtered off and crystallized from acetic acid to give compound **9** as yellow crystals, yield (0.32 g, 51%), mp > 300 °C. IR (KBr, cm⁻¹): 3071 (CH_{arom}), 1780 (C=O_{α-lactone}), 1736 (C=O_{acetyl}), 1719 (C=O_{acetyl}), 1645 (C=O_{acetyl}), 1602 (C=C). ¹H-NMR (DMSO-*d*₆): 1.91 (s, 3H, CH₃), 2.05 (s, 3H, CH₃), 2.73 (s, 3H, CH₃), 6.40 (s, 1H, H-5 as OCHO), 7.39-7.44 (m, 3H, Ar-H), 7.70 (s, 1H, H-10), 8.04 (d, 1H, *J*= 6.9 Hz, Ar-H), 8.26 (s, 1H, H-2_{indole}), 8.44 (s, 1H, H-4). MS (*m/z*, I%): 614 (M-CH₃, 6), 569 (7), 544 (5), 524 (8), 396 (20), 321 (33), 294 (46), 278 (10), 264 (32), 185 (53), 171 (53), 121 (90), 113 (10), 91 (11), 65 (20), 57 (100). Anal. Calcd for C₂₆H₁₇Br₂NO₈ (631.24); C, 49.47; H, 2.71; N, 2.22%. Found: C, 49.63; H, 2.77; N, 2.39%.

3-[(6,8-Dibromo-7-hydroxychromon-3-yl)methylene]-6-ethyl-6*H*-pyrano[3,2-*c*]quinoline-2,4,5-(3*H*,5*H*)-trione (**11**)

Method A: A mixture of carboxaldehyde **4** (0.35 g, 1 mmol) and 3-(1-ethyl-4-hydroxy-2-oxo-(1*H*)-quinolin-3-yl)-3-oxopropanoic acid (**10**) (0.275 g, 1 mmol), in DMF (5 mL) containing few drops of piperidine, was heated under reflux for 2 h. After cooling, the reaction mixture was poured onto crushed ice. The obtained solid was filtered off and crystallized from DMF/H₂O to give compound **11** as yellow crystals, yield (0.38 g, 65%), mp > 300 °C.

Method B: A mixture of carboxaldehyde **4** (0.35 g, 1 mmol) and 4-hydroxypyrano[3,2-*c*]quinolin-2(1*H*)one (**12**) (0.257 g, 1 mmol), in glacial acetic acid (10 mL) containing freshly fused sodium acetate (0.1 g), was heated under reflux for 2 h. After cooling, the reaction mixture was poured onto ice. The obtained solid was filtered off and crystallized from DMF/H₂O to give compound **11** as yellow crystals, yield (0.41 g, 70%), mp > 300 °C. IR (KBr, cm⁻¹): 3040 (CH_{arom}), 2974 (CH_{aliph}), 1731 (O-C=O), 1670

(C=O_{quinoline} and C=O_{chromone}), 1623 (C=O), 1571 (C=C). ¹H-NMR (DMSO-*d*₆): 1.27 (t, 3H, *J*= 6.9 Hz, CH₃), 4.38 (q, 2H, *J*= 6.9 Hz, CH₂), 7.54 (t, 1H, Ar-H), 7.72-7.92 (m, 2H, Ar-H), 8.15 (d, 1H, *J*= 7.8 Hz, Ar-H), 8.29 (s, 1H, H-5_{chromone}), 8.39 (s, 1H, exocyclic CH), 9.15 (s, 1H, H-2_{chromone}), 13.85 (brs, 1H, OH exchangeable with D₂O). Anal. Calcd for C₂₄H₁₃Br₂NO₇ (587.18); C, 49.09; H, 2.23; N, 2.39%. Found: C, 49.51; H, 2.43; N, 2.61%.

5-(3,5-Dibromo-2,4-dihydroxybenzoyl)-2-oxo-2*H*-1-(pyridin-2-yl)pyridine-3-carbonitrile (13).

A mixture of carboxaldehyde **4** (0.35 g, 1 mmol) and 2-cyano-*N*-(pyridin-2-yl)acetamide (0.16 g, 1 mmol) in absolute EtOH (20 mL) containing few drops of piperidine was heated under reflux for 2 h. The obtained solid after cooling was filtered off and crystallized from EtOH to give compound **13** as pale yellow crystals, yield (0.26 g, 53%), mp > 300 °C. IR (KBr, cm⁻¹): 3292, 3172 (2 OH), 3072 (CH_{arom}), 2209 (C≡N), 1682 (C=O_{pyridone}), 1637 (C=O_{benzoyl}), 1621 (C=N), 1595 (C=C). ¹H-NMR (DMSO-*d*₆): 6.77-6.90 (m, 1H, Ar-H), 7.29 (d, 1H, Ar-H), 7.64 (s, 1H, H-6_{resorcinol}), 7.79-7.91 (m, 1H, Ar-H), 8.02 (s, 1H, H-4_{pyridone}), 8.50 (d, 1H, Ar-H), 8.63 (s, 1H, H-6_{pyridone}). Anal. Calcd for C₁₈H₉Br₂N₃O₄ (491.09); C, 44.02; H, 1.85; N, 8.56%. Found: C, 44.40; H, 2.26; N, 8.69%.

2-(3,5-Dibromo-2,4-dihydroxybenzoyl)pyrido[1,2-*a*]benzimidazole-4-carbonitrile (14).

A mixture of carboxaldehyde **4** (0.35 g, 1 mmol) and benzimidazol-2-ylacetonitrile (0.16 g, 1 mmol) in absolute EtOH (20 mL) containing few drops of piperidine was heated under reflux for 2 h. The obtained solid after cooling was filtered off and crystallized from DMF/EtOH to give compound **14** as yellow crystals, yield (0.30 g, 62%), mp > 300 °C. IR (KBr, cm⁻¹): 3417 (2 OH), 3073 (CH_{arom}), 2240 (C≡N), 1630 (C=O_{benzoyl}), 1617 (C=N), 1605 (C=C). ¹H-NMR (DMSO-*d*₆): 6.25-6.94 (m, 4H, Ar-H), 7.88 (s, 1H, H-6_{resorcinol}), 7.97 (s, 1H, H-3_{pyridine}), 8.07 (s, 1H, H-1_{pyridine}), 10.27 (s, 1H, OH exchangeable with D₂O), 11.88 (s, 1H, OH exchangeable with D₂O). MS (*m/z*, I%): 489 (M+4, 16), 487 (M+2, 35), 485 (M⁺, 14), 407 (11), 295 (12), 216 (4), 193 (91), 192 (36), 188 (7), 157 (7), 165 (30), 102 (38), 90 (36), 77 (50), 64 (100). Anal. Calcd for C₁₉H₉Br₂N₃O₃ (487.11); C, 46.85; H, 1.86; N, 8.63%. Found: C, 46.67; H, 1.92; N, 8.68%.

6-(3,5-Dibromo-2,4-dihydroxybenzoyl)-1,3-dimethylpyrido[3,2-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (15).

A mixture of carboxaldehyde **4** (0.35 g, 1 mmol) and 6-amino-5*H*-1,3-dimethylpyrimidine-2,4-(1*H*,3*H*)-dione (0.15 g, 1 mmol) in absolute EtOH containing *p*-toluenesulphonic acid (0.05 g) was heated under reflux for 3 h. The obtained solid after cooling was filtered off and crystallized from EtOH to give compound **15** as white crystals, yield (0.28 g, 58%), mp 291-292 °C. IR (KBr, cm⁻¹): 3343 (2 OH), 3066 (CH_{arom}), 2949, 2890 (CH_{aliph}), 1717 (2 C=O), 1656 (C=O_{benzoyl}), 1607 (C=N), 1601 (C=C). ¹H-NMR (DMSO-*d*₆): 3.30 (s, 3H, CH₃), 3.67 (s, 3H, CH₃), 7.63 (s, 1H, H-6_{resorcinol}), 8.53 (s, 1H, H-8), 8.99 (s, 1H, H-6), 11.98 (brs, 1H, OH exchangeable with D₂O). ¹³C-NMR (DMSO-*d*₆): 28.2 (CH₃), 29.5 (CH₃), 101.0

(C-2_{resorcinol}), 101.4 (C-6_{resorcinol}), 109.7, 115.7, 127.9, 134.4, 137.3, 150.8, 152.4, 154.1, 157.3, 158.2 (C=O), 160.4 (C=O), 193.4 (C=O). MS (*m/z*, I%): 487 (M+4, 11), 485 (M+2, 64), 483 (M⁺, 8), 469 (21), 310 (100), 295 (41), 294 (14), 278 (98), 267 (79), 251 (19), 237 (26), 157 (36), 121 (35), 94 (21), 77 (6), 64 (26). Anal. Calcd for C₁₆H₁₁Br₂N₃O₅ (485.09); C, 39.62; H, 2.29; N, 8.66%. Found: C, 39.47; H, 2.15; N, 8.38%.

6-(3,5-Dibromo-2,4-dihydroxybenzoyl)-2-thioxo-1,3-dihydroquinazolin-4-one (16).

A mixture of carboxaldehyde **4** (0.35 g, 1 mmol) and 6-methyl-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one (0.14 g, 1 mmol) in DMF (10 mL) containing few drops of piperidine was heated under reflux for 2 h. The obtained solid after cooling was filtered off and crystallized from DMF to give compound **16** as yellow crystals, yield (0.26 g, 55%), mp > 300 °C. IR (KBr, cm⁻¹): 3067 (brs, 2 NH and 2 OH), 1690 (C=O_{amide}), 1609 (C=O_{benzoyl}), 1557 (C=C), 1259 (C=S). ¹H-NMR (DMSO-*d*₆): 6.25 (brs, 1H, NH exchangeable with D₂O), 7.05 (d, 1H, H-8), 7.95 (s, 1H, H-6_{resorcinol}), 8.07 (d, 1H, H-7), 8.14 (s, 1H, H-5_{quinazoline}), 11.80 (brs, NH exchangeable with D₂O). MS (*m/z*, I%): 472 (M+2, 78), 453 (56), 426 (47), 248 (64), 178 (49), 149 (74), 105 (49), 91 (50), 77 (55), 64 (74), 57 (100). Anal. Calcd for C₁₅H₈Br₂N₂O₄S (472.11); C, 38.16; H, 1.71; N, 5.93; S, 6.79%. Found: C, 38.02; H, 1.62; N, 5.91; S, 6.58%.

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