4-AMINO-3-FORMYLCOUMARIN AS BUILDING BLOCK FOR CONSTRUCTION OF NOVEL HETEROANNULATED COUMARINS: SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL EVALUATION

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**Abstract** – The chemical reactivity of 4-amino-3-formylcoumarin (1) was examined towards a diversity of carbon nucleophilic reagents as well as isomeric cyclohexanediones. A variety of heterocyclic compounds namely chromeno[4,3-\(b\)]pyrazolo[4,3-\(e\)]pyridines, chromeno[4,3-\(b\)]benzo[1,6]naphthyridine, chromeno-[4,3-b]quinoline and bis[1]chromenophenanthrolines were efficiently synthesized. Chromeno[4,3-\(b\)]quinoline 6 upon Vilsmeier-Haack formylation afforded the novel \(\beta\)-chloroenaldehyde 10 which used as a key intermediate for buliding a diversity of polyfused systems containing coumarin moiety. Antimicrobial evaluation of the tested compounds showed excellent efficiency especially compounds 2-5, 12 and 14. On the basis of spectral and analytical analysis, the structures of the new products were determined.

**INTRODUCTION**

Coumarins as oxygen heterocyclic compounds are distributed in plants and occur especially in the roots, leaves, fruits and seeds.\(^1\) Substituted coumarins play an important role for inhibition of several cancer cells.\(^2\) The medicinal uses of coumarins and their pharmacological characteristics are controlled by the substitution patterns in their nucleus.\(^3\) Coumarins offer an intriguing framework for creating novel anti-inflammatory therapeutics.\(^4\) Coumarins have a variety biological applications including antibacterial,\(^5\) antifungal,\(^6\) antimicrobial,\(^7\) antiviral,\(^8\) anti-HIV,\(^9\) anti-influenza,\(^10\) antimalarial,\(^11\) antioxidant,\(^12\) antiproliferative,\(^13\) antileishmanial,\(^14\) antiasthmatic,\(^15\) antidepressant,\(^16\) anticoagulant,\(^17\) and
antiplatelet. Coumarin derivatives were examined for their photophysical, photochemical, photoluminescence, fluorescence and optical properties. Density Functional Theory (DFT) were utilized to identify the optical, structural, vibrational and electronic properties of some coumarin derivatives. Condensation reactions with 4-aminocoumarin-3-carboxaldehyde (1) are well known for the synthesis of annulated coumarins. The current work aims to utilize 4-aminocoumarin-3-carboxaldehyde (1) as synthetic intermediate for construction of some new polyfused systems containing chromeno[4,3- b]pyridines.

RESULTS AND DISCUSSION

In the present work, the chemical reactivity of 4-amino-3-formylcoumarin (1) was investigated towards a diversity of cyclic methylene nucleophiles. Thus, Friedländer condensation of compound 1 with pyrazolidine-3,5-dione and 5-amino-2,4-dihydro-3H-pyrazol-3-one, in ethanol containing 1,8-diaza-bicyclo[5.4.0]undec-7-ene (DBU), gave the corresponding chromeno[4,3-b]pyrazolo[4,3-e]pyridines 2 and 3, respectively (Scheme 1). Typical singlet attributed to H-4_pyridine appeared in the 1H NMR spectra at δ 8.61 and 8.72 of compounds 2 and 3, respectively. The molecular ion peaks in their mass spectra were observed at m/z 253 and 252, respectively.

![Scheme 1. Reactions of compound 1 with pyrazolone derivatives](image)

Under similar reaction conditions, treatment of compound 1 with 5-amino-3-methyl-1H-pyrazole as cyclic enamine and 4-hydroxy-1-methylquinolin-2(1H)-one as cyclic enol produced chromeno[4,3-b]pyrazolo[4,3-e]pyridine 4 and chromeno[4,3-b]benzo[1,6]naphthyridine 5, respectively (Scheme 2). These angular penta-annulated compounds were well characterized using the mass spectra which presented the parent ion peaks, as the base peaks, at m/z 251 and 328. Their 1H NMR spectra displayed the methyl and H-4_pyridine as distinctive singlet signals at δ 2.28/3.48 and 8.66/8.82, respectively.
Next, the chemical reactivity of compound 1 was examined towards isomeric cyclohexanediones. Consequently, treating compound 1 with 1,3-cyclohexanedione in molar ratio 1:1 led to 3,4-dihydrochromeno[4,3-b]quinoline-1,11(2H)-dione (6) (Scheme 3). Repeating the reaction in molar ratio 2:1 afforded the novel bis[1]chromeno[4,3-b:4`,3`-J][1,7]phenanthroline-6,16-dione (7) (Scheme 3). The parent ion peaks of compounds 6 and 7 were seen in the mass spectra at $m/z$ 265 and 418, which closely match the suggested formula weights of 265.26 and 418.41, respectively. The $^1$H NMR spectrum of compound 6 exhibited three triplet signals assignable to three methylene (3CH$_2$) groups at $\delta$ 1.72, 2.38 and 3.09, the signal attributed to H-4pyridine observed at $\delta$ 8.79. The IR spectrum of compound 6 showed distinctive absorption bands at 1724 (OC=O), 1687 (C=O) and 1608 cm$^{-1}$ (C=N). While, the IR spectrum of compound 7 displayed typical absorption bands at 1732 (OC=O) and 1622 cm$^{-1}$ (C=N).

**Scheme 2.** Formation of polyfused coumarins 4 and 5

**Scheme 3.** Reaction of compound 1 with 1,3-cyclohexanedione
On the other hand, reaction of 4-amino-3-formylcoumarin (1) with 1,2-cyclohexanedione produced \( \text{bis}[1]\text{chromeno}[4,3-b:3',4'-J][1,10]\text{phenanthroline-6,11-dione} \) (8) (Scheme 4). \(^{24}\) Specific absorption bands at 1726 (OC=O) and 1618 cm\(^{-1}\) (C=N) were seen in its IR spectrum. The mass spectrum presented the molecular ion peak (base peak) at \( m/z \) 418 that approves the suggested molecular formula \((C_{26}H_{14}N_2O_4)\).

Likewise, treating compound 1 with 1,4-cyclohexanedione, in EtOH/DBU, gave \( \text{bis}[1]\text{chromeno-[4,3-b:3',4'-h][4,7]}\text{phenanthroline-6,9-dione} \) (9) (Scheme 4). The mass spectrum exhibited the molecular ion peak, as the base peak, at \( m/z \) 418 \((C_{26}H_{14}N_2O_4)\).

![Scheme 4. Formation of \( \text{bis}[1]\text{chromenophenanthrolines} \) 8 and 9](image.png)

Compound 6 has an active methylene ketone moiety, which motivates us to apply Vilsmeier-Haack reaction on this substrate.\(^{25}\) Thus, the novel 1-chloro-11-oxo-3,4-dihydro-11\(H\)-chromeno[3,4-\(b\)]quinoline-2-carboxaldehyde (10) was produced by formylation of compound 6 utilizing Vilsmeier-Haack reagent (POCl\(_3\)/DMF) (Scheme 5). In the IR spectrum, characteristic absorption bands were seen at 1718 (C=O\(_{\alpha\text{-pyrrole}}\)) and 1707 cm\(^{-1}\) (C=O\(_{\text{aldehyde}}\)). Its \(^1\)H NMR spectrum presented definite singlet signals at \( \delta \) 10.36 attributable to the aldehyde proton, as well as distinguish singlet at \( \delta \) 9.04 assignable to H-4\(_{\text{pyridine}}\). The higher \( \delta \) value of this proton may attribute to the mesomeric effect of C=N and CH=O functions that increase the deshielding of H-4\(_{\text{pyridine}}\). A strong evidence of structure 10 was seen in the mass spectrum, which displayed the molecular ion peak (M\(^{+}/M+2\)) at \( m/z \) 311/313 in relative abundance (59/20\%), confirming the existence of one chlorine atom.
Scheme 5. Formation of 1-chlorochromeno[3,4-b]quinoline-2-carboxaldehyde 10

After that, the behavior of β-chloroenaldehyde 10 was examined towards some bineucleophilic reagents. Thus, treating compound 10 with hydroxylamine hydrochloride, hydrazine hydrate and phenylhydrazine, in boiling DMF containing TEA, yielded the novel angular chromeno[3,4-b]isoxazolo[5,4-f]quinoline 11 and chromeno[3,4-b]pyrazolo[3,4-f]quinolines 12, 13, respectively (Scheme 6).26 The 1H NMR spectra for each compound presented two characteristic singlet signals at δ 8.38/8.78 (H-3isoxazole/H-4pyridine), 8.42/8.80 (H-3pyrazole/H-4pyridine) and 8.43/8.74 (H-3pyrazole/H-4pyridine), respectively. The mass spectra of compounds 11-13 verified the suggested structures and displayed the parent ion peaks at m/z 290.27 (C_{17}H_{10}N_{2}O_{3}), 289.29 (C_{17}H_{11}N_{3}O_{2}) and 365.38 (C_{23}H_{15}N_{3}O_{2}), respectively.

Scheme 6. Condensation of compound 10 with hydroxylamine hydrochloride, hydrazine hydrate and phenylhydrazine
Then, the behavior of β-chloroenaldehyde 10 was studied towards some 1,3-N,N-binucleophiles such as guanidine hydrochloride and acetamidine hydrochloride, generating the novel chromeno[3′,4′:5,6]pyrido[2,3-h]quinazolines 14 and 15, respectively (Scheme 7). In the 1H NMR spectra of compounds 14 and 15, the two singlet signals assignable to H-4pyrimidine and H-4pyridine appeared at δ 8.42/8.39 and 8.79/8.78, respectively. The molecular formulas C_{18}H_{12}N_{4}O_{2} and C_{19}H_{13}N_{3}O_{2} for compounds 14 and 15 were also established from their mass spectra that presented the parent ion peaks at 316.31 and 315.33, respectively.

Scheme 7. Condensation of compound 10 with guanidine and acetamidine

In order to create diazepines annulated chromeno[3,4-b]quinoline, β-chloroenaldehyde 10 was reacted with a variety of 1,4-N,N-binucleophiles. Thus, the novel chromeno[3,4-b][1,4]diazepino[2,3-f]quinoline 16 and chromeno[3,4-b][1,4]benzdiazepino[2,3-f]quinoline 17 were produced from condensation of compound 10 with ethylenediamine and o-phenylenediamine, respectively (Scheme 8). Structures 16 and 17 were established based on their mass spectra which recorded the molecular ion peaks at m/z 317 and 365 which match well with the postulated formula weights 317.34 (C_{19}H_{15}N_{3}O_{2}) and 365.38 (C_{23}H_{15}N_{3}O_{2}), respectively. Specific singlets corresponding to the diazepine ring protons were visible in the 1H NMR spectra of compounds 16 and 17 at δ 8.32 and 8.63, respectively. 13C NMR spectrum of compound 16 displayed characteristic signal due to 4CH_{2} carbons at δ 24.0, 28.1, 36.8 and 38.1.
Scheme 8. Formation of chromeno[3,4-\textit{b}][1,4]diazepino[2,3-\textit{f}]quinoline 16 and chromeno[3,4-\textit{b}][1,4]benzodiazepino[2,3-\textit{f}]quinoline 17

ANTIMICROBIAL EVALUATION

Gram-negative bacteria like \textit{Staphylococcus aureus}, \textit{Bacillus subtilis}, and Gram-positive bacteria like \textit{Salmonella typhimurium}, \textit{Escherichia coli}, in addition to yeast like \textit{Candida albicans}, and fungus like \textit{Asperigillus fumigatus} were used to inspect the antimicrobial activity of the prepared compounds. The conventional disc agar diffusion method was applied to measure the antimicrobial activity. The inhibitory zones and the disc diameter (6 mm) were measured and recorded in Table 1. The information about antimicrobial activity shown in Table 1 was discussed as follows: The synthesized compounds demonstrated variable activity on the development of the chosen microorganisms, and the activity varies between moderate and high activities except compounds 7-9. The latter compounds showed no inhibition action against the selected microorganism and this may attribute the multi-fused heterocyclic rings and therefore insoluble under the experimental conditions. The annulated systems; chromeno[4,3-\textit{b}]pyrazolo-[4,3-\textit{e}]pyridines 2-4 showed excellent inhibition action towards the two types of Gram-negative bacteria, yeast and fungus strains. These compounds also displayed good activity towards \textit{S. aureus} as Gram-positive bacteria especially at high concentration. Chromeno[4,3-\textit{b}]benzo[1,6]naphthyridine 5 showed high inhibition efficiency towards the two kinds of Gram-positive activity as well as \textit{E. coli} as Gram-negative bacteria and \textit{C. albicans} as yeast. Chromeno[3,4-\textit{b}]pyrazolo[3,4-\textit{f}]quinoline 12 presented high efficiency towards Gram-negative bacteria, yeast and fungus due to the annulation of pyrazole ring with chromenoquinoline moiety, in addition to the existence of mobile hydrogen of the pyrazole ring.
Chromeno[3',4`:5,6]pyrido[2,3-h]quinazolines 14 and 15 appeared significant activity against Gram-positive bacteria, also compound 14 appeared high activity towards Gram-negative bacteria which may attribute to the presence of electron donating amino group linked to pyrimidine nucleus.

### Table 1. Antimicrobial inhibition zones of the synthesized compounds at 500 and 1000 μg/mL by disc diffusion assay

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>Gram- negative bacteria</th>
<th>Gram- positive bacteria</th>
<th>Yeasts and Fungi</th>
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<tr>
<td></td>
<td><strong>S. typhimurium</strong></td>
<td><strong>E. coli</strong></td>
<td><strong>S. aureus</strong></td>
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<tr>
<td>2</td>
<td>24 H 18 H 30 H 21 H</td>
<td>26 H 17 I 17 I 13 I</td>
<td>24 H 18 H 26 H 19 H</td>
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<tr>
<td>3</td>
<td>31 H 23 H 29 H 20 H</td>
<td>27 H 16 I 16 I 13 I</td>
<td>30 H 21 H 28 H 20 H</td>
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<tr>
<td>4</td>
<td>28 H 21 H 27 H 20 H</td>
<td>24 H 14 I 14 I 10 I</td>
<td>26 H 19 H 25 H 20 H</td>
</tr>
<tr>
<td>5</td>
<td>18 I 14 I 28 H 21 H</td>
<td>28 H 21 H 26 H 19 H</td>
<td>28 H 22 H 17 I 13 I</td>
</tr>
<tr>
<td>6</td>
<td>15 I 10 I 17 I 13 I</td>
<td>21 I 16 I 27 H 20 H</td>
<td>16 I 13 I 14 I 11 I</td>
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<td>7</td>
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<td>20 I 13 I 16 I 9 I</td>
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<td>14 I 10 I 13 I 10 I</td>
<td>17 I 12 I 14 I 10 I</td>
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<tr>
<td>S</td>
<td>35 26 35 25</td>
<td>36 28 38 27</td>
<td>35 28 37 26</td>
</tr>
</tbody>
</table>

* Considered from 3 values.
I = Intermediate activity, H = High activity, S: Standard drug

S: Cephalothin for Gram-negative bacteria, Chloramphenicol for Gram-positive bacteria, and cycloheximide for yeast and fungi.
CONCLUSION

In conclusion, 4-amino-3-formylcoumarin (1) was utilized as a key precursor for building of polyfused coumarins. Friedländer reaction of compound 1 with some cyclic nucleophiles namely pyrazolidine-3,5-dione, 5-amino-2,4-dihydro-3H-pyrazol-3-one, 5-amino-3-methyl-1H-pyrazole and 4-hydroxy-1-methylquinolin-2(1H)-one produced chromeno[4,3-b]pyrazolo[4,3-e]pyridines (2, 3), chromeno[4,3-b]pyrazolo[4,3-e]pyridine 4 and chromeno[4,3-b]benzo[1,6]naphthyridine 5, respectively. Compound 1 reacted with 1,3-cyclohexanedione in 1:1 and 2:1 molar ratios giving chromeno[4,3-b]quinoline 6 and bis[1]chromenophenanthroline 7. Condensation of compound 1 with 1,2-cyclohexanedione and 1,4-cyclohexanedione yield the 2:1 condensation products (bis[1]chromenophenanthrolines) 8 and 9. Applying Vilsmeier-Haack formylation on chromeno[4,3-b]quinolininedione 6 gave cyclic β-chloroenaldehyde derivative 10 which upon condensation with hydroxylamine, hydrazine hydrate and phenylhydrazine afforded chromeno[3,4-b]isoxazolo[5,4-f]quinoline 11 and chromeno[3,4-b]pyrazolo[3,4-f]quinolines 12, 13. Treatment of β-chloroenaldehyde 10 with guanidine and acetamidine furnished chromeno[3′,4′:5,6]pyrido[2,3-h]quinazolines 14 and 15, respectively. Finally, condensation of β-chloroenaldehyde 10 with ethylenediamine and o-phenylenediamine gave chromeno[3,4-b][1,4]-diazepino[2,3-f]quinoline 16 and chromeno[3,4-b][1,4]benzodiazepino[2,3-f]quinoline 17, respectively.

EXPERIMENTAL

General. 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 (300 MHz) and 13C NMR (75 MHz) spectra were measured on Mercury-300BB, using DMSO-d₆ as a solvent and TMS (δ, ppm) 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. 4-Amino-3-formylcoumarin (1) was prepared according to the published method.

Biological method. The test for the antimicrobial activity was performed on medium potato dextrose agar (PDA) which contained infusion of 200 g potatoes, 6 g dextrose and 15 g agar. Uniform size filter paper disks (6 mm diameter, 3 disks per compound) were impregnated by equal volume (10 µL) from the concentrations of 500 and 1000 µg/mL dissolved compounds in dimethylformamide (DMF) and carefully placed on inoculated agar surface. After incubation for 36 h at 27 °C in the case of bacteria and for 48 h at 24 °C in the case of fungi. The obtained results were recorded for each tested compound as average diameter of inhibition zones of the bacteria and fungus around the disks in mm at the concentrations 500 and 1000 µg/mL. The Standard drug used are; Chloramphenicol in the case of Gram-positive bacteria, Cephalothinin in the case of Gram-negative bacteria and cycloheximide in the case of yeast and fungi.
1,2-Dihydrochromeno[4,3-b]pyrazolo[4,3-e]pyridine-3,5-dione (2). A mixture of 4-amino-3-formyl-coumarin (1) (0.57 g, 3 mmol) and pyrazolidine-3,5-dione (0.30 g, 3 mmol), in absolute EtOH (20 mL) containing DBU (0.1 mL), was heated at reflux for 2 h. The pale-yellow crystals obtained during heating were filtered and crystallized from DMF, mp > 300 °C, yield (0.55 g, 72%). IR (KBr, cm⁻¹): 3396, 3275 (2NH), 3032 (CH arom.), 1729 (OC=O), 1673 (C=O), 1613 (C=N), 1571 (C=C). ¹H NMR (DMSO-d₆, δ): 7.48-7.53 (m, 2H, Ar-H), 7.80 (t, 1H, J=7.8 Hz, Ar-H), 8.02 (d, 1H, J=7.8 Hz, Ar-H), 8.61 (s, 1H, H-4pyridine), 10.26 (s, 1H, NH exchangeable with D₂O), 12.09 (s, 1H, NH exchangeable with D₂O). ¹³C NMR (DMSO-d₆, δ): 108.3, 112.9, 122.6, 124.3, 126.0, 128.7, 130.4, 144.2, 147.3, 150.6, 156.3, 162.9, 168.7. Mass spectrum, m/z (I, %): 253 (42), 238 (100), 210 (42), 182 (25), 141 (19), 120 (51), 92 (39), 77 (38), 64 (14). Anal. Calcd for C₁₃H₁₅N₃O₃ (253.21): C, 61.66; H, 2.79; N, 16.59%. Found: C, 61.38; H, 2.71; N, 16.48%.

3-Aminochromeno[4,3-b]pyrazolo[4,3-e]pyridin-5(1H)-one (3). A mixture of 4-amino-3-formyl-coumarin (1) (0.57 g, 3 mmol) and 5-amino-2,4-dihydro-3H-pyrazol-3-one (0.30 g, 3 mmol), in absolute EtOH (20 mL) containing DBU (0.1 mL), was heated at reflux for 2 h. The pale-yellow crystals obtained during heating were filtered and crystallized from iso-butanol, mp > 300 °C, yield (0.54 g, 78%). IR (KBr, cm⁻¹): 3368, 3315, 3247 (NH₂, NH), 3032 (CH arom.), 1734 (OC=O), 1605 (C=N), 1573 (C=C). ¹H NMR (DMSO-d₆, δ): 7.32-7.39 (m, 2H, Ar-H), 7.76 (t, 1H, J=8.1 Hz, Ar-H), 7.98 (d, 1H, J=7.8 Hz, Ar-H), 8.36 (bs, 2H, NH₂ exchangeable with D₂O), 8.72 (s, 1H, H-4pyridine). ¹³C NMR (DMSO-d₆, δ): 102.3, 115.4, 122.7, 124.9, 126.7, 128.3, 130.9, 143.9, 146.8, 148.6, 150.6, 154.3, 163.2. Mass spectrum, m/z (I, %): 252 (100), 224 (47), 182 (22), 142 (16), 120 (42), 93 (31), 77 (34), 64 (14). Anal. Calcd for C₁₃H₁₃N₃O (252.23): C, 61.90; H, 3.20; N, 22.21%. Found: C, 61.75; H, 3.12; N, 22.06%.

3-Methylchromeno[4,3-b]pyrazolo[4,3-e]pyridin-5(1H)-one (4). A mixture of 4-amino-3-formyl-coumarin (1) (0.57 g, 3 mmol) and 5-amino-3-methyl-1H-pyrazole (0.20 g, 3 mmol), in absolute EtOH (20 mL) containing DBU (0.1 mL), was heated at reflux for 2 h. The pale-yellow crystals obtained during heating were filtered and crystallized from DMF/H₂O, mp > 300 °C, yield (0.49 g, 65%). IR (KBr, cm⁻¹): 3268 (NH), 3039 (CH arom.), 2972, 2936 (CH aliph.), 1718 (OC=O), 1606 (C=N), 1590 (C=C). ¹H NMR (DMSO-d₆, δ): 2.28 (s, 3H, CH₃), 7.46-7.52 (m, 2H, Ar-H), 7.76 (t, 1H, J=7.8 Hz, Ar-H), 8.04 (d, 1H, J=7.8 Hz, Ar-H), 8.66 (s, 1H, H-4pyridine). ¹³C NMR (DMSO-d₆, δ): 16.3, 112.6, 114.7, 121.8, 124.6, 126.3, 128.2, 129.4, 139.3, 144.6, 147.3, 150.2, 153.9, 163.4. Mass spectrum, m/z (I, %): 251 (100), 223 (28), 208 (23), 182 (17), 172 (13), 120 (27), 92 (63), 77 (40), 64 (23). Anal. Calcd for C₁₃H₁₀N₃O₂ (251.24): C, 66.93; H, 3.61; N, 16.73%. Found: C, 66.76; H, 3.48; N, 16.58%.

5-Methylchromeno[4,3-b]benzo[1,6]naphthyridine-6,8(6H, 8H)-dione (5). A mixture of 4-amino-3-
formylcoumarin (1) (0.57 g, 3 mmol) and 4-hydroxy-1-methylquinolin-2(1H)-one (0.53 g, 3 mmol), in absolute EtOH (20 mL) containing DBU (0.1 mL), was heated at reflux for 2 h. The pale-yellow crystals obtained during heating were filtered and crystallized from DMF, mp > 300 °C, yield (0.64 g, 65%). IR (KBr, cm\(^{-1}\)): 3053 (CH\(_{\text{arom.}}\)), 2951, 2912 (CH\(_{\text{aliph.}}\)), 1717 (OC=O), 1615 (C=N), 1602 (C=C). \(^1\)H NMR (DMSO-\(d_6\), \(\delta\)): 3.48 (s, 3H, CH\(_3\)), 7.24-7.56 (m, 6H, Ar-H), 7.74 (t, 1H, \(J=7.2\) Hz, Ar-H), 7.97 (d, 1H, \(J=7.2\) Hz, Ar-H), 8.82 (s, 1H, H-4\(_{\text{pyridine}}\)). Mass spectrum, \(m/z\) (I %): 328 (100), 300 (61), 272 (34), 257 (75), 229 (15), 138 (10), 120 (27), 92 (21), 77 (25), 64 (13). Anal. Calcd for C\(_{20}\)H\(_{12}\)N\(_2\)O\(_3\) (328.32): C, 73.16; H, 3.68; N, 8.53%. Found: C, 72.93; H, 3.56; N, 8.37%.

3,4-Dihydrochromeno[4,3-b]quinoline-1,11(2H)-dione (6). A mixture of 4-amino-3-formylcoumarin (1) (0.57 g, 3 mmol) and cyclohexane-1,3-dione (0.34 g, 3 mmol), in absolute EtOH (20 mL) containing DBU (0.1 mL), was heated at reflux for 2 h. The white crystals obtained after cooling were filtered and crystallized from EtOH to give compound 5 as white crystals, mp 253-254 °C, yield (0.54 g, 68%). IR (KBr, \(\text{cm}^{-1}\)): 3021 (CH\(_{\text{arom.}}\)), 2942, 2917 (CH\(_2\)), 2844 (CH\(_3\)), 1732 (OC=O), 1622 (C=N), 1589 (C=C). \(^1\)H NMR (DMSO-\(d_6\), \(\delta\)): 1.72 (t, 2H, \(J=6.9\) Hz, CH\(_2\)), 2.38 (t, 2H, \(J=6.6\) Hz, CH\(_2\)), 3.09 (t, 2H, \(J=6.6\) Hz, CH\(_2\)), 7.39-7.53 (m, 2H, Ar-H), 7.68 (t, 1H, \(J=7.8\) Hz, Ar-H), 7.95 (d, 1H, \(J=7.6\) Hz, Ar-H), 8.79 (s, 1H, H-4\(_{\text{pyridine}}\)). Mass spectrum, \(m/z\) (I %): 265 (53), 237 (100), 209 (41), 167 (12), 120 (32), 92 (33), 77 (20), 64 (13). Anal. Calcd for C\(_{16}\)H\(_{11}\)NO\(_3\) (265.26): C, 72.45; H, 4.18; N, 5.28%. Found: C, 72.38; H, 4.07; N, 5.16%.

8,9-Dihydro-6H,16H-bis[1]chromeno[4,3-b:4',3'-J][1,7]phenanthroline-6,16-dione (7). A mixture of 4-amino-3-formylcoumarin (1) (0.57 g, 3 mmol) and cyclohexane-1,3-dione (0.17 g, 1.5 mmol), in absolute EtOH (20 mL) containing DBU (0.1 mL), was heated at reflux for 2 h. The yellow crystals obtained during heating were filtered off and crystallized from DMF, mp > 300 °C, yield (0.36 g, 55%). IR (KBr, \(\text{cm}^{-1}\)): 3037 (CH\(_{\text{arom.}}\)), 1728 (OC=O), 1622 (C=N), 1589 (C=C). \(^1\)H NMR (DMSO-\(d_6\), \(\delta\)): 2.16 (s, 4H, 2CH\(_2\)), 7.41-7.56 (m, 4H, 4 Ar-H), 7.68-7.71 (m, 2H, 2Ar-H), 7.96-8.01 (m, 2H, 2Ar-H), 8.69 (s, 2H, 2H-4\(_{\text{pyridine}}\)). Mass spectrum, \(m/z\) (I %): 418 (100), 120 (10), 92 (7), 77 (8), 64 (5). Anal. Calcd for C\(_{26}\)H\(_{14}\)N\(_2\)O\(_4\) (418.41): C, 74.64; H, 3.37; N, 6.70%. Found: C, 74.48; H, 3.19; N, 6.53%.

8,9-Dihydro-6H,11H-bis[1]chromeno[4,3-b:3',4'-J][1,10]phenanthroline-6,11-dione (8). A mixture of 4-amino-3-formylcoumarin (1) (0.57 g, 3 mmol) and cyclohexane-1,2-dione (0.17 g, 1.5 mmol), in absolute EtOH (20 mL) containing DBU (0.1 mL), was heated at reflux for 2 h. The pale-yellow crystals obtained during heating were filtered off and crystallized from DMF, mp > 300 °C, yield (0.36 g, 55%). IR (KBr, \(\text{cm}^{-1}\)): 3051 (CH\(_{\text{arom.}}\)), 1726 (OC=O), 1618 (C=N), 1596 (C=C). \(^1\)H NMR (DMSO-\(d_6\), \(\delta\)): 2.19 (s, 4H, 2CH\(_2\)), 7.40-7.53 (m, 4H, Ar-H), 7.63-7.69 (m, 2H, Ar-H), 7.91-7.95 (m, 2H, Ar-H), 8.72 (s, 2H, H-4\(_{\text{pyridine}}\)). Mass spectrum, \(m/z\) (I %): 418 (100), 362 (10), 120 (13), 92 (9), 77 (10), 64 (6). Anal. Calcd for C\(_{26}\)H\(_{14}\)N\(_2\)O\(_4\) (418.41): C, 74.64; H, 3.37; N, 6.70%. Found: C, 74.53; H, 3.28; N, 6.46%.
8,9-Dihydro-6H,9H-bis[1]chromeno[4,3-b:3',4'-h][4,7]phenanthroline-6,9-dione (9). A mixture of 4-amino-3-formylcoumarin (1) (0.57 g, 3 mmol) and cyclohexane-1,4-dione (0.17 g, 1.5 mmol), in absolute EtOH (20 mL) containing DBU (0.1 mL), was heated at reflux for 2 h. The pale-yellow crystals obtained during heating were filtered off and crystallized from DMF, mp > 300 °C, yield (0.37 g, 57%). IR (KBr, cm⁻¹): 3043 (CH₂arom.), 1723 (OC=O), 1620 (C=N), 1602 (C=C). ¹H NMR (DMSO-d₆, δ): 2.15 (s, 4H, 2CH₂), 7.38-7.49 (m, 4H, Ar-H), 7.65-7.72 (m, 2H, Ar-H), 7.98-8.06 (m, 2H, Ar-H), 8.67 (s, 2H, H-4pyridine). Mass spectrum, m/z (I, %): 418 (100), 362 (13), 142 (6), 120 (11), 77 (8), 64 (4). Anal. Calcd for C₂₆H₁₄N₂O₄ (418.41): C, 74.64; H, 3.37; N, 6.70%. Found: C, 74.49; H, 3.21; N, 6.58%.

1-Chloro-11-oxo-3,4-dihydro-11H-chromeno[3,4-b]quinoline-2-carboxaldehyde (10). To a cold DMF (30 mL), phosphoryl chloride (10 mL) was added drop-wise with stirring at room temperature for 30 min. After that, a solution of compound 6 (2.65 g, 10 mmol) in DMF (15 mL) was added dropwise with continuous stirring. After completion of addition, the reaction mixture was left at room temperature to 2 h, then poured onto crushed ice (ca. 40 g). The yellow solid isolated was filtered and crystallized from acetone as yellow crystals, mp 296-297 °C, yield (0.41 g, 66%). IR (KBr, cm⁻¹): 3062 (CH₂arom.), 1718 (C=O₂pyrone), 1707 (C=Oaldheyde), 1605 (C=N), 1597 (C=C). ¹H NMR (300 MHz, DMSO-d₆, δ): 2.07 (t, 2H, J= 6.0 Hz, CH₂), 2.19 (t, 2H, J= 6.6 Hz, CH₂), 7.21-7.38 (m, 2H, Ar-H), 7.62 (t, 1H, J=7.5 Hz, Ar-H), 7.85 (d, 1H, J=7.5 Hz, Ar-H), 9.04 (s, 1H, H-4pyridine), 10.36 (s, 1H, CHO). ¹³C NMR (75 MHz, DMSO-d₆, δ): 23.7 (CH₂), 26.4 (CH₂), 115.1, 120.4, 122.8, 124.6, 125.9, 127.9, 129.4, 131.2, 138.5, 141.3, 144.8, 148.2, 151.4, 173.7 (C=O₂pyrone), 184.2 (CH=O). Mass spectrum, m/z (I, %): 311/313 (59/20), 283/285 (100/33), 248 (36), 224 (18), 146 (13), 120 (38), 105 (13), 93 (30), 77 (22), 64 (11). Anal. Calcd for C₁₇H₁₀ClNO₃ (311.72): C, 65.50; H, 3.23; N, 4.49%. Found: C, 65.39; H, 3.21; N, 4.28%.

4,5-Dihydro-12H-chromeno[3,4-b]isoxazolo[5,4-f]quinolin-12-one (11). To a solution of compound 10 (0.62 g, 2 mmol) in DMF (10 mL) containing TEA (0.1 mL), hydroxylamine hydrochloride (0.14 g, 2 mmol) in distilled water (5 mL) was added and the reaction mixture was heated under reflux for 2 h. The yellow crystals deposited during heating were filtered and crystallized from AcOH, mp >300 °C, yield (0.37 g, 64%). IR (KBr, cm⁻¹): 3028 (CH₂arom.), 1713 (C=O₂pyrone), 1607 (C=N), 1578 (C=C). ¹H NMR (300 MHz, DMSO-d₆, δ): 2.05 (t, 2H, J=6.0 Hz, CH₂), 2.23 (t, 2H, J=6.0 Hz, CH₂), 7.23 (t, 1H, J=7.2 Hz, Ar-H), 7.51 (d, 1H, J=7.2 Hz, Ar-H), 7.72 (t, 1H, J=7.2 Hz, Ar-H), 7.96 (d, 1H, J=7.2 Hz, Ar-H), 8.38 (s, 1H, H-3isoxazole), 8.78 (s, 1H, H-4pyridine). ¹³C NMR (75 MHz, DMSO-d₆, δ): 23.4 (CH₂), 26.2 (CH₂), 114.7, 120.1, 121.9, 123.5, 125.7, 127.2, 128.8, 130.7, 137.6, 143.9, 146.3, 149.5, 150.6, 153.0, 174.1 (C=O₂pyrone). Mass spectrum, m/z (I, %): 290 (76), 264 (35), 236 (38), 220 (19), 145 (13), 120 (100), 93 (43), 77 (35), 65 (14). Anal. Calcd for C₁₇H₁₀N₂O₃ (290.27): C, 70.34; H, 3.47; N, 9.65%. Found: C, 70.18; H, 3.44; N, 9.48%.

4,5-Dihydro-1H-chromeno[3,4-b]pyrazolo[3,4-f]quinolin-12-one (12). A mixture of compound 10...
(0.62 g, 2 mmol) and hydrazine hydrate (0.1 g, 0.1 mL, 2 mmol) in DMF (10 mL) containing TEA (0.1 mL) was heated under reflux for 2 h. The pale-yellow crystals obtained after cooling were filtered and crystallized from DMF/H2O, mp > 300 °C, yield (0.44 g, 76%). IR (KBr, cm⁻¹): 3286 (NH), 3043 (CHarom.), 1721 (C=Oα-pyrene), 1610 (C=N), 1584 (C=C). ¹H NMR (300 MHz, DMSO-d6, δ): 2.06 (t, 2H, J= 6.0 Hz, CH2), 2.25 (t, 2H, J= 6.0 Hz, CH2), 7.31-7.54 (m, 2H, Ar-H), 7.79 (t, 1H, J=7.5 Hz, Ar-H), 8.11 (d, 1H, J=7.5 Hz, Ar-H), 8.42 (s, 1H, H-3-pyrazole), 8.80 (s, 1H, H-4-pyridine). ¹³C NMR (75 MHz, DMSO-d6, δ): 23.9 (CH2), 27.1 (CH2), 115.3, 119.8, 122.4, 124.6, 126.2, 128.3, 129.5, 130.8, 138.4, 144.7, 147.8, 149.5, 151.7, 153.3, 173.6 (C=Oα-pyrene). Mass spectrum, m/z (I, %): 289 (100), 261 (55), 234 (41), 195 (35), 146 (22), 120 (61), 93 (30), 77 (24), 64 (12). Anal. Calcd for C17H11N3O2 (289.29): C, 70.58; H, 3.83; N, 14.53%. Found: C, 70.55; H, 3.74; N, 14.33%.

4,5-Dihydro-1-phenyl-12H-chromeno[3,4-b]pyrazolo[3,4-f]quinolin-12-one (13). A mixture of compound 10 (0.62 g, 2 mmol) and phenylhydrazine (0.22 mL, 2 mmol) in DMF (10 mL) containing TEA (0.1 mL) was heated under reflux for 2 h. The dark-yellow crystals obtained during heating were filtered and crystallized from DMF, mp > 300 °C, yield (0.51 g, 70%). IR (KBr, cm⁻¹): 3071 (CHarom.), 1709 (C=Oα-pyrene), 1614 (C=N), 1592 (C=C). ¹H NMR (300 MHz, DMSO-d6, δ): 3.07 (t, 2H, J= 6.0 Hz, CH2), 2.19 (t, 2H, J=6.0 Hz, CH2), 7.06-7.46 (m, 7H, Ar-H), 7.69 (t, 1H, J=6.9 Hz, Ar-H), 7.95 (d, 1H, J=6.9 Hz, Ar-H), 8.43 (s, 1H, H-3-pyrazole), 8.74 (s, 1H, H-4-pyridine). Mass spectrum, m/z (I, %): 365 (100), 337 (64), 310 (48), 233 (28), 195 (17), 120 (31), 93 (53), 77 (69), 64 (17). Anal. Calcd for C23H15N3O2 (365.38): C, 75.60; H, 4.14; N, 11.50%. Found: C, 75.31; H, 4.03; N, 11.22%.

2-Amino-5,6-dihydro-13H-chromeno[3',4':5,6]pyrido[2,3-h]quinazolin-13-one (14). A mixture of compound 10 (0.62 g, 2 mmol) and guanidine hydrochloride (0.20 g, 2 mmol) in DMF (10 mL) containing TEA (0.1 mL) was heated under reflux for 2 h. The yellow crystals obtained after cooling were filtered and crystallized from DMF/H2O, mp > 300 °C, yield (0.44 g, 76%). IR (KBr, cm⁻¹): 3385, 3263 (NH2), 3034 (CHarom.), 1719 (C=Oα-pyrene), 1614 (C=N), 1582 (C=C). ¹H NMR (300 MHz, DMSO-d6, δ): 2.04 (t, 2H, J=6.0 Hz, CH2), 2.23 (t, 2H, J=6.0 Hz, CH2), 6.83 (bs, 2H, NH2 exchangeable with D2O), 7.35-7.46 (m, 2H, 2Ar-H), 7.65 (t, 1H, J=7.8 Hz, Ar-H), 8.09 (d, 1H, J= 7.8 Hz, Ar-H), 8.42 (s, 1H, H-4-pyrimidine), 8.79 (s, 1H, H-4-pyridine). ¹³C NMR (75 MHz, DMSO-d6, δ): 23.8 (CH2), 26.2 (CH2), 114.5, 119.8, 121.9, 123.2, 124.6, 126.7, 128.2, 130.3, 138.2, 144.7, 147.3, 149.4, 150.8, 152.1, 155.8, 173.2 (C=Oα-pyrene). Mass spectrum, m/z (I, %): 316 (100), 288 (63), 246 (29), 220 (30), 146 (11), 120 (33), 105 (21), 77 (13), 64 (10). Anal. Calcd for C18H12N4O2 (316.31): C, 68.35; H, 3.82; N, 17.71%. Found: C, 68.14; H, 3.65; N, 17.57%.

2-Methyl-5,6-dihydro-13H-chromeno[3',4':5,6]pyrido[2,3-h]quinazolin-13-one (15). A mixture of compound 10 (0.62 g, 2 mmol) and acetamidine hydrochloride (0.19 g, 2 mmol) in DMF (10 mL) containing TEA (0.1 mL) was heated under reflux for 2 h. The yellow crystals obtained after cooling were
filtered and crystallized from n-butanol, mp > 300 °C, yield (0.42 g, 67%). IR (KBr, cm⁻¹): 3068 (CH₉arom.), 2967, 2934 (CH₃), 1724 (C=O₉pyrone), 1616 (C=N), 1589 (C=C). ¹H NMR (300 MHz, DMSO-d₆, δ): 2.04 (t, 2H, J=6.6 Hz, CH₂), 2.24 (t, 2H, J=6.6 Hz, CH₂), 2.39 (s, 3H, CH₃), 7.26 (t, 1H, J=7.2 Hz, Ar-H), 7.51 (d, 1H, J=7.5 Hz, Ar-H), 7.76 (t, 1H, J=7.2 Hz, Ar-H), 8.02 (d, 1H, J=7.5 Hz, Ar-H), 8.39 (s, 1H, H-4(pyridine)), 8.78 (s, 1H, H-4(pyridine)). ¹³C NMR (75 MHz, DMSO-d₆, δ): 19.3 (CH₃), 24.1 (CH₂), 26.7 (CH₂), 115.3, 120.3, 122.7, 124.1, 125.3, 127.6, 129.1, 131.0, 138.9, 144.3, 147.5, 149.7, 150.5, 152.5, 155.4, 173.8 (C=O₉pyrone). Mass spectrum, m/z (I, %): 315 (100), 300 (32), 272 (39), 245 (46), 220 (32), 145 (16), 120 (27), 92 (23), 77 (30), 65 (8). Anal. Calcd for C₁₉H₁₃N₃O₂ (315.33): C, 72.37; H, 4.16; N, 13.24%. Found: C, 72.14; H, 4.13; N, 13.25%.

2,3,6,7-Tetrahydro-1H-chromeno[3,4-b][1,4]diazepino[2,3-f]quinolin-14(14H)-one (16). A mixture of compound 10 (0.62 g, 2 mmol) and ethylenediamine (0.12 g, 2 mmol) in DMF (10 mL) containing TEA (0.1 mL) was heated under reflux for 2 h. The yellow crystals deposited after cooling were filtered and crystallized from AcOH/H₂O, mp > 300 °C, yield (0.45 g, 71%). IR (KBr, cm⁻¹): 3336 (NH), 3026 (CH₉arom.), 2954, 2921 (CH₉aliph.), 1724 (C=O₉pyrone), 1608 (C=N), 1581 (C=C). ¹H NMR (300 MHz, DMSO-d₆, δ): 1.98 (t, 2H, J=6.0 Hz, CH₂), 2.22 (t, 2H, J=6.0 Hz, CH₂), 2.85 (s, 4H, 2CH₂), 6.54 (bs, 1H, NH exchangeable with D₂O), 7.23 (t, 1H, J=7.5 Hz, Ar-H), 7.48 (d, 1H, J=7.5 Hz, Ar-H), 7.86 (t, 1H, J=7.2 Hz, Ar-H), 8.03 (d, 1H, J=7.2 Hz, Ar-H), 8.32 (s, 1H, H-4(diazepine), 8.57 (s, 1H, H-4(pyridine)). ¹³C NMR (75 MHz, DMSO-d₆, δ): 24.0 (CH₂), 28.1 (CH₂), 36.8 (CH₂), 38.1 (CH₂), 114.6, 119.3, 122.5, 124.1, 125.4, 127.8, 129.5, 131.2, 139.2, 142.9, 146.5, 148.3, 151.1, 152.6, 174.8 (C=O₉pyrone). Mass spectrum, m/z (I, %): 317 (51), 289 (26), 246 (18), 221 (30), 145 (11), 120 (30), 105 (17), 93 (100), 77 (20), 64 (10). Anal. Calcd for C₁₉H₁₅N₃O₂ (317.34): C, 72.16; H, 4.76; N, 13.24%. Found: C, 71.88; H, 4.47; N, 13.21%.

7,8-Dihydro17H-chromeno[3,4-b][1,4]benzodiazepino[2,3-f]quinolin-15(15H)-one (17). A mixture of compound 10 (0.62 g, 2 mmol) and o-phenylenediamine (0.22 g, 2 mmol) in DMF (10 mL) containing TEA (0.1 mL) was heated under reflux for 2 h. The dark-yellow crystals obtained after cooling were filtered and crystallized from AcOH, mp > 300 °C, yield (0.40 g, 64%). IR (KBr, cm⁻¹): 3357 (NH), 3019 (CH₉arom.), 1716 (C=O₉pyrone), 1612 (C=N), 1586 (C=C). ¹H NMR (300 MHz, DMSO-d₆, δ): 2.07 (t, 2H, J= 6.3 Hz, CH₂), 2.21 (t, 2H, J=6.3 Hz, CH₂), 7.08-7.30 (m, 5H, Ar-H), 7.52 (t, 1H, J=7.2 Hz, Ar-H), 7.63 (t, 1H, J=7.5 Hz, Ar-H), 7.96 (d, 1H, J=7.5 Hz, Ar-H), 8.36 (s, 1H, H-4(diazepine), 8.63 (s, 1H, H-4(pyridine)), 10.96 (bs, 1H, NH exchangeable with D₂O). Mass spectrum, m/z (I, %): 365 (100), 337 (53), 310 (36), 221 (25), 146 (18), 120 (42), 92 (13), 77 (20), 64 (9). Anal. Calcd for C₂₃H₁₅N₅O₂ (365.38): C, 75.60; H, 4.14; N, 11.50%. Found: 75.42; H, 3.95; N, 11.31%.
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