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

Najla A. Alshaye^a and Magdy A. Ibrahim^{b*}

^aDepartment of Chemistry, College of Science, Princess Nourah bint Abdulrahman University, P.O. Box 84428, Riyadh 11671, Saudi Arabia: naalshaye@pdnu.edu.sa

^bDepartment of Chemistry, Faculty of Education, Ain Shams University, Roxy, Heliopolis 11757, Cairo, Egypt

*E-mail: magdy_ahmed1977@yahoo.com

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 β -chloroaldehyde **10** which used as a key intermediate for buliding a diversity of polyfused systems conatining 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.

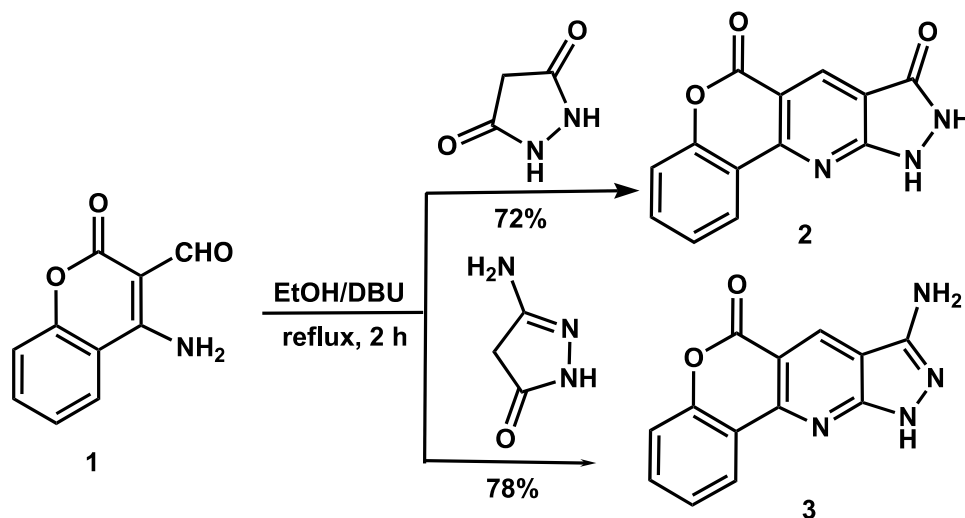
INTRODUCTION

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.¹⁸ Coumarin derivatives were examined for their photophysical, photochemical, photoluminescence, fluorescence and optical properties.¹⁹ Density Functional Theory (DFT) were utilized to identify the optical, structural, vibrational and electronic properties of some coumarin derivatives.²⁰ Condensation reactions with 4-aminocoumarin-3-carboxaldehyde (**1**) are well known for the synthesis of annulated coumarins.²¹ 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.

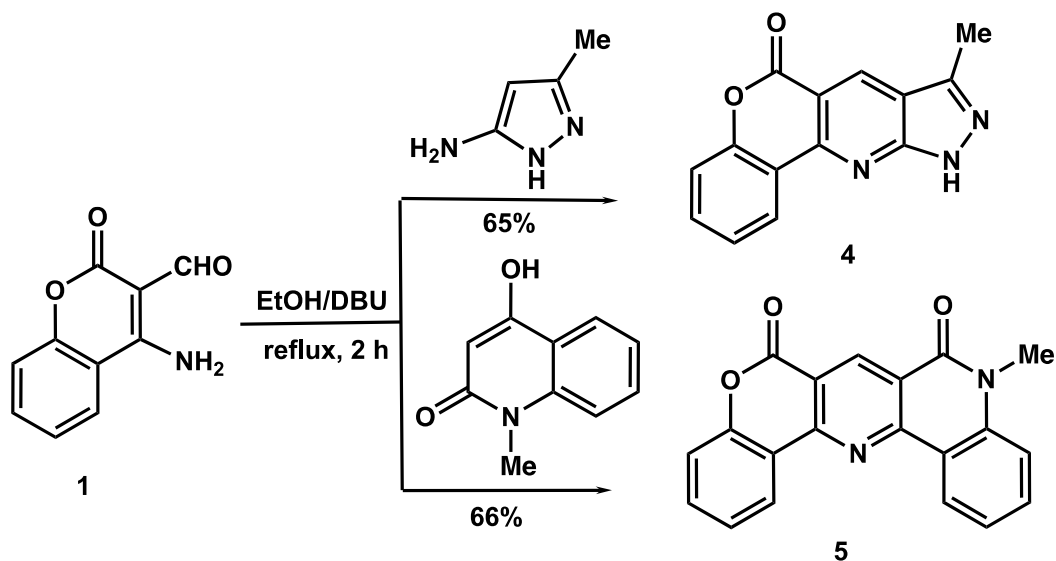
RESULTS AND DISCUSSION

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-3*H*-pyrazol-3-one, in ethanol containing 1,8-diazabicyclo[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).²² 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.



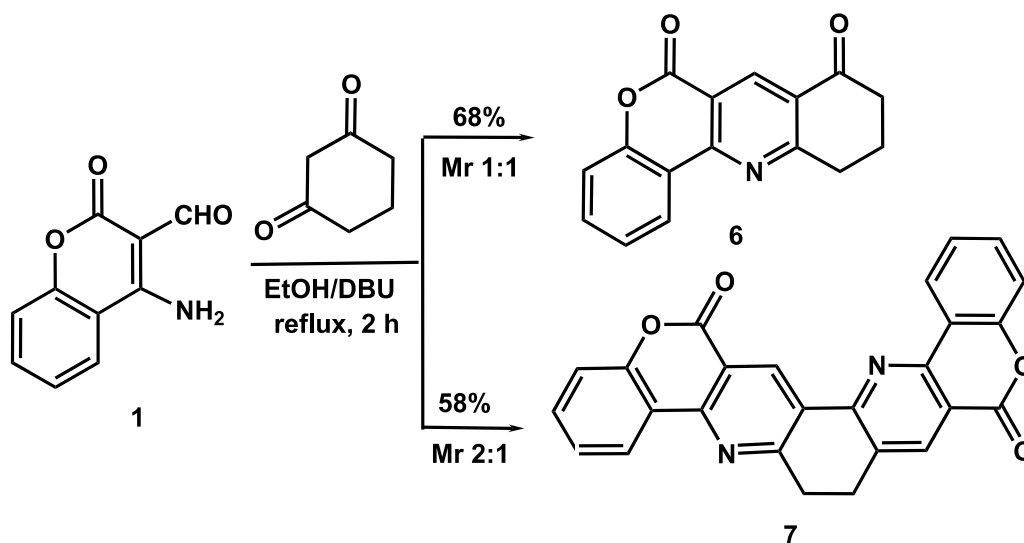
Scheme 1. Reactions of compound **1** with pyrazolone derivatives

Under similar reaction conditions, treatment of compound **1** with 5-amino-3-methyl-1*H*-pyrazole as cyclic enamine and 4-hydroxy-1-methylquinolin-2(1*H*)-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).²³ 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.



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

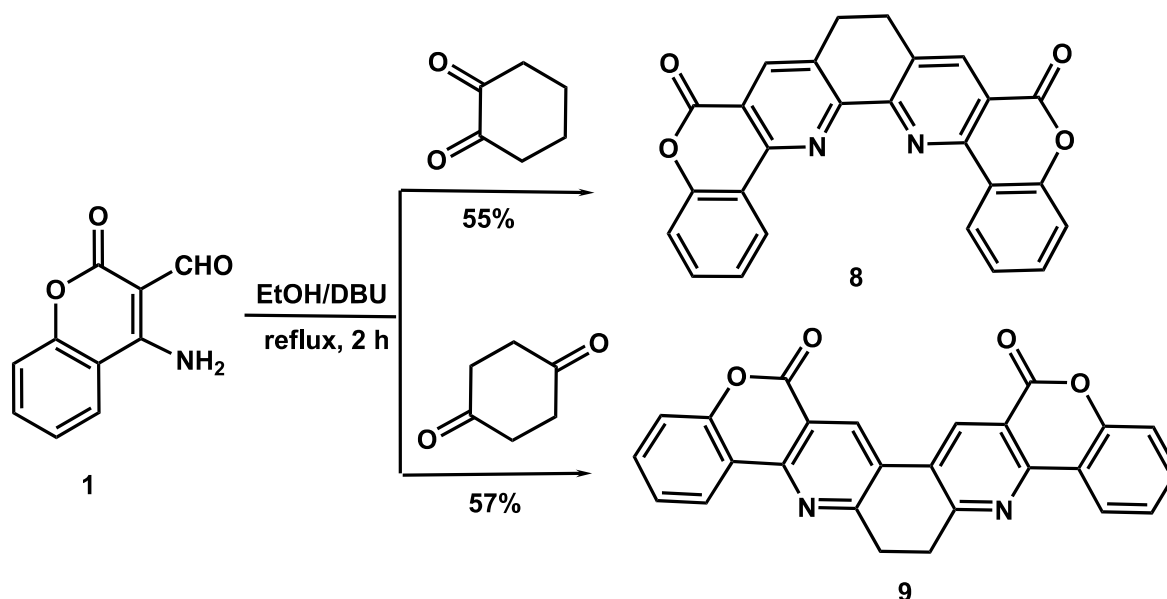
Next, the chemical reactivity of compound **1** was examined towards isomeric cyclohexanediones. Consequently, treating compound **1** with 1,3-cyclohexanedione in molar ratio 1:1 led to 3,4-dihydrochromeno[4,3-*b*]quinoline-1,11(2*H*)-dione (**6**) (Scheme 3).²⁴ Repeating the reaction in molar ratio 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 ^1H NMR spectrum of compound **6** exhibited three triplet signals assignable to three methylene (3CH_2) groups at δ 1.72, 2.38 and 3.09, the signal attributed to H-4_{pyridine} observed at δ 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 3. Reaction of compound **1** with 1,3-cyclohexanedione

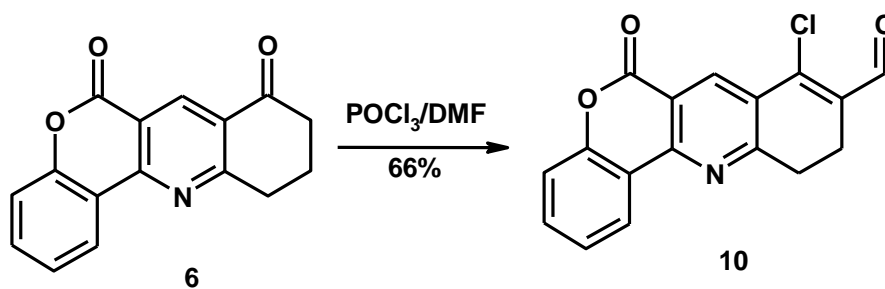
On the other hand, reaction of 4-amino-3-formylcoumarin (**1**) with 1,2-cyclohexanedione produced *bis*[1]chromeno[4,3-*b*:3',4'-*J*][1,10]phenanthroline-6,11-dione (**8**) (Scheme 4).²⁴ Specific absorption bands at 1726 (OC=O) and 1618 cm^{-1} (C=N) were seen in its IR spectrum. The mass spectrum presented the molecular ion peak (base peak) at m/z 418 that approves the suggested molecular formula ($\text{C}_{26}\text{H}_{14}\text{N}_2\text{O}_4$).

Likewise, treating compound **1** with 1,4-cyclohexanedione, in EtOH/DBU, gave *bis*[1]chromeno[4,3-*b*:3',4'-*h*][4,7]phenanthroline-6,9-dione (**9**) (Scheme 4). The mass spectrum exhibited the molecular ion peak, as the base peak, at m/z 418 ($\text{C}_{26}\text{H}_{14}\text{N}_2\text{O}_4$).



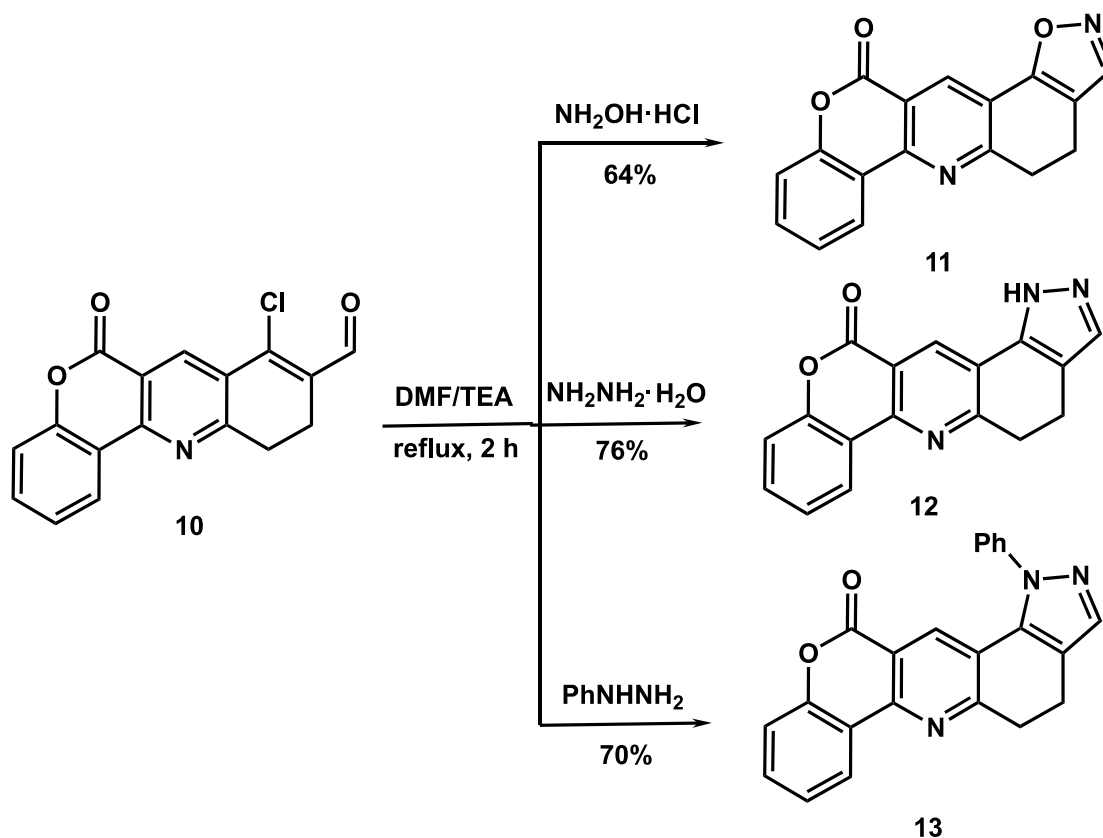
Scheme 4. Formation of *bis*[1]chromenophenanthrolines **8** and **9**

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 ($\text{C}=\text{O}_{\alpha\text{-pyrone}}$) and 1707 cm^{-1} ($\text{C}=\text{O}_{\text{aldehyde}}$). Its ^1H NMR spectrum presented definite singlet signals at δ 10.36 attributable to the aldehyde proton, as well as distinguish singlet at δ 9.04 assignable to H-4_{pyridine}. The higher δ value of this proton may attribute to the mesomeric effect of C=N and CH=O functions that increase the deshielding of H-4_{pyridine}. A strong evidence of structure **10** was seen in the mass spectrum, which displayed the molecular ion peak ($\text{M}^+/\text{M}+2$) at m/z 311/313 in relative abundance (59/20%), confirming the existence of one chlorine atom.



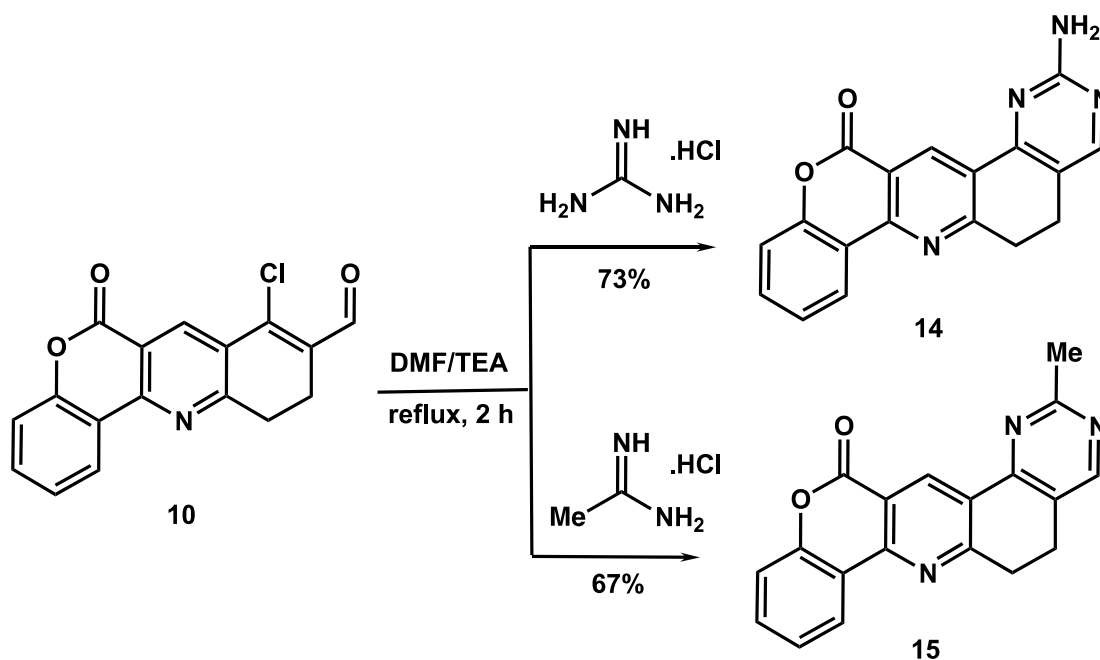
Scheme 5. Formation of 1-chlorochromeno[3,4-*b*]quinoline-2-carboxaldehyde **10**

After that, the behavior of β -chloroenaldehyde **10** was examined towards some binucleophilic 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-3_{isoxazole}/H-4_{pyridine}), 8.42/8.80 (H-3_{pyrazole}/H-4_{pyridine}) and 8.43/8.74 (H-3_{pyrazole}/H-4_{pyridine}), respectively. The mass spectra of compounds **11-13** verified the suggested structures and displayed the parent ion peaks at m/z 290.27 ($\text{C}_{17}\text{H}_{10}\text{N}_2\text{O}_3$), 289.29 ($\text{C}_{17}\text{H}_{11}\text{N}_3\text{O}_2$) and 365.38 ($\text{C}_{23}\text{H}_{15}\text{N}_3\text{O}_2$), respectively.



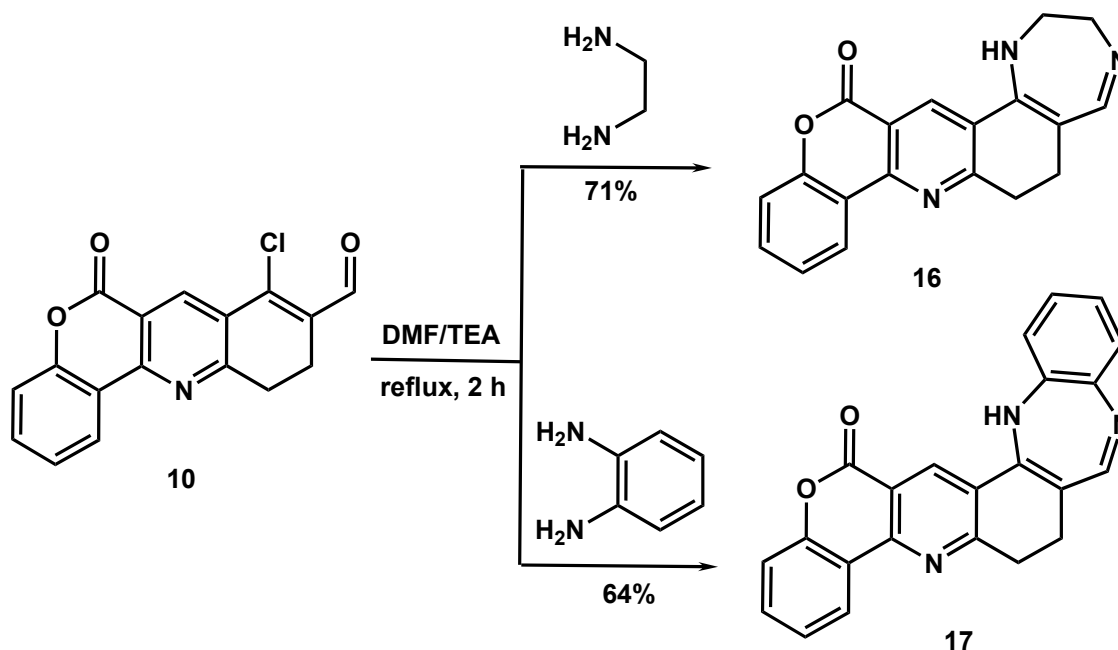
Scheme 6. Condensation of compound **10** with hydroxylamine hydrochloride, hydrazine hydrate and phenylhydrazine

Then, the behavior of β -chloroaldehyde **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-4_{pyrimidine} and H-4_{pyridine} appeared at δ 8.42/8.39 and 8.79/8.78, respectively. The molecular formulas $\text{C}_{18}\text{H}_{12}\text{N}_4\text{O}_2$ and $\text{C}_{19}\text{H}_{13}\text{N}_3\text{O}_2$ 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 -chloroaldehyde **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]benzodiazepino[2,3-*f*]quinoline **17** were produced from condensation of compound **10** with ethylenediamine and *o*-phenylenediamine, respectively (Scheme 8).²⁷ 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 ($\text{C}_{19}\text{H}_{15}\text{N}_3\text{O}_2$) and 365.38 ($\text{C}_{23}\text{H}_{15}\text{N}_3\text{O}_2$), 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. ^{13}C 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-*b*][1,4]diazepino[2,3-*f*]quinoline **16** and chromeno[3,4-*b*][1,4]benzodiazepino[2,3-*f*]quinoline **17**

ANTIMICROBIAL EVALUATION

Gram-negative bacteria like *Staphylococcus aureus*, *Bacillus subtilis*, and Gram-positive bacteria like *Salmonella typhimurium*, *Escherichia coli*, in addition to yeast like *Candida albicans*, and fungus like *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.²⁸ 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-*b*]pyrazolo[4,3-*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 *S. aureus* as Gram-positive bacteria especially at high concentration. Chromeno[4,3-*b*]benzo[1,6]naphthyridine **5** showed high initiation efficiency towards the two kinds of Gram-positive activity as well as *E. coli* as Gram-negative bacteria and *C. albicans* as yeast. Chromeno[3,4-*b*]pyrazolo[3,4-*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

Mean* of zone diameter (mm)												
Compd. No.	Gram- negative bacteria				Gram- positive bacteria				Yeasts and Fungi			
	<i>S. typhimurium</i>		<i>E. coli</i>		<i>S. aureus</i>		<i>B. subtilis</i>		<i>C. albicans</i>		<i>A. fumigatus</i>	
	1000 µg/mL	500 µg/mL	1000 µg/mL	500 µg/mL	1000 µg/mL	500 µg/mL	1000 µg/mL	500 µg/mL	1000 µg/mL	500 µg/mL	1000 µg/mL	500 µg/mL
2	24 H	18 H	30 H	21 H	26 H	17 I	17 I	13 I	24 H	18 H	26 H	19 H
3	31 H	23 H	29 H	20 H	27 H	16 I	16 I	13 I	30 H	21 H	28 H	20 H
4	28 H	21 H	27 H	20 H	24 H	14 I	14 I	10 I	26 H	19 H	25 H	20 H
5	18 I	14 I	28 H	21 H	28 H	21 H	26 H	19 H	28 H	22 H	17 I	13 I
6	15 I	10 I	17 I	13 I	21 I	16 I	27 H	20 H	16 I	13 I	14 I	11 I
7	----	----	----	----	----	----	----	----	----	----	----	----
8	----	----	----	----	----	----	----	----	----	----	----	----
9	----	----	----	----	----	----	----	----	----	----	----	----
10	17 I	12 I	16 I	12 I	18 I	14 I	15 I	11 I	14 I	11 I	16 I	12 I
11	17 I	13 I	13 I	10 I	14 I	10 I	16 I	11 I	15 I	12 I	12 I	9 I
12	28 H	20 H	25 H	18 H	21 I	17 I	19 I	15 I	25 H	18 H	29 H	21 H
13	14 I	11 I	12 I	9 I	15 I	10 I	13 I	11 I	14 I	11 I	26 H	18 H
14	29 H	22 H	26 H	19 H	26 H	18 H	28 H	20 H	15 I	11 I	17 I	12 I
15	19 I	15 I	16 I	13 I	24 H	19 H	26 H	20 H	13 I	9 I	16 I	12 I
16	18 I	13 I	12 I	9 I	20 I	13 I	16 I	9 I	15 I	12 I	13 I	9 I
17	14 I	10 I	13 I	10 I	17 I	12 I	14 I	10 I	17 I	13 I	16 I	13 I
S	35	26	35	25	36	28	38	27	35	28	37	26

* Considered from 3 values.

I = Intermediate activity, H = High activity, S: Standard drug

S: Cephalothinin 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-3*H*-pyrazol-3-one, 5-amino-3-methyl-1*H*-pyrazole and 4-hydroxy-1-methylquinolin-2(1*H*)-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*]quinolinedione **6** gave cyclic β -chloroaldehyde 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 -chloroaldehyde **10** with guanidine and acetamidine furnished chromeno[3',4':5,6]pyrido[2,3-*h*]quinazolines **14** and **15**, respectively. Finally, condensation of β -chloroaldehyde **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 ^{13}C NMR (75 MHz) spectra were measured on Mercury-300BB, using $\text{DMSO-}d_6$ 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.²⁹

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 $\mu\text{g}/\text{mL}$ dissolved compounds in dimethylformamide (DMF) and carefully placed on inoculated agar surface. After incubation for 36 h at 27 $^\circ\text{C}$ in the case of bacteria and for 48 h at 24 $^\circ\text{C}$ 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 $\mu\text{g}/\text{mL}$.²⁸ 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-formylcoumarin (**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_{pyrazolone}), 1613 (C=N), 1571 (C=C). ¹H NMR (DMSO-*d*₆, 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-4_{pyridine}), 10.26 (s, 1H, NH exchangeable with D₂O), 12.09 (s, 1H, NH exchangeable with D₂O). ¹³C NMR (DMSO-*d*₆, 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*_r %): 253 (42), 238 (100), 210 (42), 182 (25), 141 (19), 120 (51), 92 (39), 77 (38), 64 (14). Anal. Calcd for C₁₃H₇N₃O₃ (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(1*H*)-one (3). A mixture of 4-amino-3-formylcoumarin (**1**) (0.57 g, 3 mmol) and 5-amino-2,4-dihydro-3*H*-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-*d*₆, 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-4_{pyridine}), 11.16 (bs, 1H, NH exchangeable with D₂O). ¹³C NMR (DMSO-*d*₆, 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*_r %): 252 (100), 224 (47), 182 (22), 142 (16), 120 (42), 93 (31), 77 (34), 64 (14). Anal. Calcd for C₁₃H₈N₄O₂ (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(1*H*)-one (4). A mixture of 4-amino-3-formylcoumarin (**1**) (0.57 g, 3 mmol) and 5-amino-3-methyl-1*H*-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-*d*₆, 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-4_{pyridine}), 9.93 (bs, 1H, NH exchangeable with D₂O). ¹³C NMR (DMSO-*d*₆, 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*_r %): 251 (100), 223 (28), 208 (23), 182 (17), 172 (13), 120 (27), 92 (63), 77 (40), 64 (23). Anal. Calcd for C₁₄H₉N₃O₂ (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(6*H*, 8*H*)-dione (5). A mixture of 4-amino-3-

formylcoumarin (**1**) (0.57 g, 3 mmol) and 4-hydroxy-1-methylquinolin-2(1*H*)-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_{arom.}), 2951, 2912 (CH_{aliph.}), 1717 (OC=O), 1615 (C=N), 1602 (C=C). ¹H NMR (DMSO-*d*₆, δ): 3.48 (s, 3H, CH₃), 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_{pyridine}). Mass spectrum, *m/z* (*I_r* %): 328 (100), 300 (61), 272 (34), 257 (75), 229 (15), 138 (10), 120 (27), 92 (21), 77 (25), 64 (13). Anal. Calcd for C₂₀H₁₂N₂O₃ (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(2*H*)-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, cm⁻¹): 3021 (CH_{arom.}), 2942, 2917 (CH_{aliph.}), 1724 (OC=O), 1687 (C=O), 1608 (C=N), 1583 (C=C). ¹H NMR (DMSO-*d*₆, δ): 1.72 (t, 2H, *J*=6.9 Hz, CH₂), 2.38 (t, 2H, *J*=6.6 Hz, CH₂), 3.09 (t, 2H, *J*=6.6 Hz, CH₂), 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_{pyridine}). Mass spectrum, *m/z* (*I_r* %): 265 (53), 237 (100), 209 (41), 167 (12), 120 (32), 92 (33), 77 (20), 64 (13). Anal. Calcd for C₁₆H₁₁NO₃ (265.26): C, 72.45; H, 4.18; N, 5.28%. Found: C, 72.38; H, 4.07; N, 5.16%.

8,9-Dihydro-6*H*,16*H*-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 (0.38 g, 58%). IR (KBr, cm⁻¹): 3037 (CH_{arom.}), 1732 (OC=O), 1622 (C=N), 1589 (C=C). ¹H NMR (DMSO-*d*₆, δ): 2.16 (s, 4H, 2CH₂), 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_{pyridine}). Mass spectrum, *m/z* (*I_r* %): 418 (100), 120 (10), 92 (7), 77 (8), 64 (5). Anal. Calcd for C₂₆H₁₄N₂O₄ (418.41): C, 74.64; H, 3.37; N, 6.70%. Found: C, 74.48; H, 3.19; N, 6.53%.

8,9-Dihydro-6*H*,11*H*-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, cm⁻¹): 3051 (CH_{arom.}), 1726 (OC=O), 1618 (C=N), 1596 (C=C). ¹H NMR (DMSO-*d*₆, δ): 2.19 (s, 4H, 2CH₂), 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_{pyridine}). Mass spectrum, *m/z* (*I_r* %): 418 (100), 362 (10), 120 (13), 92 (9), 77 (10), 64 (6). Anal. Calcd for C₂₆H₁₄N₂O₄ (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 (CH_{arom.}), 1723 (OC=O), 1620 (C=N), 1602 (C=C). ¹H NMR (DMSO-*d*₆, 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-4_{pyridine}). Mass spectrum, *m/z* (*I*_r %): 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 (CH_{arom.}), 1718 (C=O_{α-pyrone}), 1707 (C=O_{aldehyde}), 1605 (C=N), 1597 (C=C). ¹H NMR (300 MHz, DMSO-*d*₆, 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-4_{pyridine}), 10.36 (s, 1H, CHO). ¹³C NMR (75 MHz, DMSO-*d*₆, 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=O_{α-pyrone}), 184.2 (CH=O). Mass spectrum, *m/z* (*I*_r %): 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 (CH_{arom.}), 1713 (C=O_{α-pyrone}), 1607 (C=N), 1578 (C=C). ¹H NMR (300 MHz, DMSO-*d*₆, 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-3_{isoxazole}), 8.78 (s, 1H, H-4_{pyridine}). ¹³C NMR (75 MHz, DMSO-*d*₆, 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=O_{α-pyrone}). Mass spectrum, *m/z* (*I*_r %): 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 (CH_{arom.}), 1721 (C=O_{α-pyrone}), 1610 (C=N), 1584 (C=C). ¹H NMR (300 MHz, DMSO-*d*₆, 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-*d*₆, 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=O_{α-pyrone}). Mass spectrum, *m/z* (*I*_r %): 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-12*H*-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 (CH_{arom.}), 1709 (C=O_{α-pyrone}), 1614 (C=N), 1592 (C=C). ¹H NMR (300 MHz, DMSO-*d*₆, δ): 2.01 (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*_r %): 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-13*H*-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 during heating were filtered and crystallized from AcOH/H₂O, mp > 300 °C, yield (0.46 g, 73%). IR (KBr, cm⁻¹): 3385, 3263 (NH₂), 3034 (CH_{arom.}), 1719 (C=O_{α-pyrone}), 1614 (C=N), 1582 (C=C). ¹H NMR (300 MHz, DMSO-*d*₆, 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-*d*₆, 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=O_{α-pyrone}). Mass spectrum, *m/z* (*I*_r %): 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-13*H*-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 (CH_{arom.}), 2967, 2934 (CH₃), 1724 (C=O_{α-pyrone}), 1616 (C=N), 1589 (C=C). ¹H NMR (300 MHz, DMSO-*d*₆, 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_{pyrimidine}), 8.78 (s, 1H, H-4_{pyridine}). ¹³C NMR (75 MHz, DMSO-*d*₆, 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=O_{α-pyrone}). Mass spectrum, *m/z* (*I*_r %): 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, 13.33%. Found: C, 72.14; H, 4.13; N, 13.25%.

2,3,6,7-Tetrahydro-1*H*-chromeno[3,4-*b*][1,4]diazepino[2,3-*f*]quinolin-14(14*H*)-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 (CH_{arom.}), 2954, 2921 (CH_{aliph.}), 1724 (C=O_{α-pyrone}), 1608 (C=N), 1581 (C=C). ¹H NMR (300 MHz, DMSO-*d*₆, 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-*d*₆, 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=O_{α-pyrone}). Mass spectrum, *m/z* (*I*_r %): 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, 71.91; H, 4.76; N, 13.24%. Found: C, 71.88; H, 4.47; N, 13.21%.

7,8-Dihydro-17*H*-chromeno[3,4-*b*][1,4]benzodiazepino[2,3-*f*]quinolin-15(15*H*)-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 (CH_{arom.}), 1716 (C=O_{α-pyrone}), 1612 (C=N), 1586 (C=C). ¹H NMR (300 MHz, DMSO-*d*₆, 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*_r %): 365 (100), 337 (53), 310 (36), 221 (25), 146 (18), 120 (42), 92 (13), 77 (20), 64 (9). Anal. Calcd for C₂₃H₁₅N₃O₂ (365.38): C, 75.60; H, 4.14; N, 11.50%. Found: 75.42; H, 3.95; N, 11.31%.

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