SYNTHETIC APPROACHES FOR CONSTRUCTION OF NOVEL ANGULAR HETEROCYCLIC SYSTEMS CONTAINING CHROMENO-[2,3-b]QUINOLINE

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INTRODUCTION
Chromones are well known biologically active agents including anticancer,1 anti-HIV,2 antiproliferative,3
neuroprotective, antibiotic, antioxidant, antimalarial, antibacterial, antimicrobial, and anti-inflammatory, as well as acetylcholinesterase and α-glucosidase inhibitors. For a variety of chromone derivatives, optical, electronic, fluorescence, photophysical and photoelectrical experiments, besides DFT simulations and molecular docking studies were investigated. β-Chloroenaldehyde on variable heterocyclic rings represent an electron deficient substrates and widely utilized as building block for creation of some novel heterocyclic rings through reactions with different binucleophilic reagents. In our previous work, 1-chloro-9-methyl-11-oxo-3,4-dihydro-11H-chromeno[2,3-b]quinoline-2-carboxaldehyde (1) was synthesized and its reactivity was investigated towards some primary amines, as well as hydrazine hydrate and hydroxylamine. The current work aimed to inspect the reactivity of compound 1 with a diversity of 1,2- and 1,3- as well as 1,4-binucleophiles to create a variety of novel angular heterocyclic compounds including chromeno[2,3-b]quinoline moiety and estimate their antimicrobial efficiency.

RESULTS AND DISCUSSION

Cyclic β-chloroenaldehyde 1 was recently synthesized and may serve as active substrate for building angular annulated chromeno[2,3-b]quinoline due to the presence of aldehyde and chloro groups in the beta position to each other. The reactivity of the aldehyde group towards nucleophilic reagents is better than the chloro function as previously reported. Firstly, the chemical reactivity of cyclic β-chloroenaldehyde 1 was tested towards a variety of 1,2-binucleophilic reagents. So, reacting compound 1 with phenylhydrazine, in DMF containing triethylamine (TEA) under reflux, afforded the novel chromeno[2,3-b]pyrazolo[3,4-f]quinoline (Scheme 1). This reaction occurs through condensation between the aldehyde and amino groups with concomitant loss of HCl molecule. The aldehyde function that was seen in the IR spectrum of compound 1 at 1704 cm⁻¹ has vanished, in the IR spectrum of compound 2. The mass spectra of compound 2 proved the postulated structure and demonstrated the parent ion peak at m/z 379, that matches with its exact mass 379.13. The ¹H NMR spectrum appeared three specific singlets at their typical chemical shift (δ 7.92, 8.62 and 8.85 ppm) assignable to H-11, H-4pyridine and H-3pyrazole.

Similarly, boiling β-chloroenaldehyde 1 with 7-chloro-4-hydrazinylquinoline and 3-hydrazinyl-5,6-diphenyl-1,2,4-triazine in DMF containing TEA, afforded 1-quinolinyl/triazinylchromeno[2,3-b]-pyrazolo[3,4-f]quinolines 5 and 6, respectively (Scheme 1). Their ¹H NMR spectra appeared H-3pyrazole at δ 8.56 and 8.49. Also, their mass spectra exhibited their parent ion peaks at m/z 464 and 534 that coincident with the suggested molecular formula C_{27}H_{17}ClN_{4}O_{2} and C_{33}H_{22}N_{6}O_{2}, respectively.
Scheme 1. Reactions of β-chloroenaldehyde 1 with some hydrazines

Then, the behavior of β-chloroenaldehyde 1 was studied towards some 1,3-N,N-binucleophiles. Therefore, condensation of compound 1 with guanidine, cyanoguanidine and thiourea, in DMF containing TEA under reflux, yielded chromeno[2',3':6,5]pyrido[2,3-h]quinazolines 7-9, respectively (Scheme 2). The identities of the structures 7-9 were determined from the mass spectra which presented their molecular ion peaks at m/z 330, 355 and 347, respectively. The H-4_pyrimidine were observed as singlet signals in the 1H NMR spectra of compounds 7-9 at δ 8.69, 8.48, and 8.59 ppm, respectively.

Scheme 2. Reactions of β-chloroenaldehyde 1 with some 1,3-N,N-binucleophiles

Next, reaction of 1,3-C,N-binucleophiles with β-chloroenaldehyde 1 was also investigated. Thus, reacting compound 1 with cyanoacetamide, N-benzylcyanoacetamide and 1H-benzimidazol-2-ylacetonitrile
afforded chromeno[2,3-\(J\)]phenanthroline-3-carbonitriles 10, 11 and benzoimidazo[1,2-\(a\)]chromeno[2,3-\(J\)]phenanthroline 12 (Scheme 3).\(^\text{18}\) The IR spectra of compounds 10-12 demonstrated typical absorption bands attributable to the nitrile functions at \(\tilde{\nu} \) 2224, 2222 and 2225 cm\(^{-1}\), in addition the IR spectra of compounds 10 and 11 showed specific absorption bands due to C=Opyridone at \(\tilde{\nu} \) 1682 and 1678 cm\(^{-1}\), respectively. The \(^1\)H NMR spectra of compounds 10-12 presented typical singlet signals assignable to 2H-4\(_\text{pyridine}\), for each compound at \(\delta \) (8.65, 8.87), (8.72, 8.86) and (8.61, 8.77), respectively.

![Scheme 3. Formation of chromeno[2,3-\(J\)]phenanthroline derivatives 10-12](image)

Compound 1 was further reacted with some cyclic 1,3-\(C\),\(N\)-binucleophiles namely 5-amino-2,4-dihydro-3\(H\)-pyrazol-3-one and 5-amino-3-methyl-1\(H\)-pyrazole producing the angular chromeno[2,3-\(J\)]pyrazolo[3,4-\(b\)]phenanthrolines 13 and 14, respectively (Scheme 4).\(^\text{19}\) Their molecular ion peaks appeared in the mass spectra at \(m/z \) 370 and 368, as the base peaks, indicating the high stability of the synthesized compounds. Their \(^1\)H NMR spectra displayed two typical singlets in each compound for the pyridine ring protons at \(\delta \) (8.58, 8.71) and (8.48, 8.67), for compounds 13 and 14, respectively.

![Scheme 4. Formation of chromeno[2,3-\(J\)]pyrazolo[3,4-\(b\)]phenanthrolines 13 and 14](image)
Moreover, the chemical behavior of β-chloroenaldehyde \(1\) was studied towards a diversity of 1,4-binucleophiles aiming to construct some novel seven membered rings annulated chromeno[2,3-\(b\)]quinoline. Thus, condensation of compound \(1\) with ethylenediamine and \(o\)-phenylenediamine, in boiling DMF containing TEA, gave the novel chromeno[2,3-\(b\)][1,4]diazepino[2,3-f]quinoline \(15\) and chromeno[2,3-\(b\)][1,4]benzdiazepino[2,3-f]quinoline \(16\), respectively (Scheme 5). Structures of compounds \(15\) and \(16\) were established based on their mass spectra which recorded the molecular ion peaks at \(m/z\) 331 and 379 which match well with the postulated exact mass 331.13 and 379.13, respectively. Specific singlets corresponding to the diazepine ring proton were visible in the \(^1\)H NMR spectra of compounds \(15\) and \(16\) at \(\delta\) 8.21 and 8.27, respectively.

**Scheme 5.** Reactions of β-chloroenaldehyde \(1\) with ethylenediamine and \(o\)-phenylenediamine

Furthermore, reactions of \(o\)-aminophenol and \(o\)-aminothiophenol with β-chloroenaldehyde \(1\), in DMF/TEA under reflux, resulted in chromeno[2,3-\(b\)][1,4]benzoxazepino[2,3-f]quinoline \(17\) and chromeno[2,3-\(b\)][1,4]benzothiazepino[2,3-f]quinoline \(18\), respectively (Scheme 6). Structures \(17\) and \(18\) were validated by the mass spectra which displayed the molecular ion peaks at \(m/z\) 380 and 396, that matched with the suggested formula weights of 380.39 and 396.46, respectively. The oxazepine and thiazepine ring protons appeared in the \(^1\)H NMR spectra as typical singlet at \(\delta\) 8.43 and 8.39 ppm, respectively.

**Scheme 6.** Condensation of β-chloroenaldehyde \(1\) with \(o\)-aminophenol and \(o\)-aminothiophenol
ANTIMICROBIAL EVALUATION

The traditional disc agar diffusion method was used to test the antimicrobial activity of the prepared compounds against Gram-positive bacteria (Staphylococcus aureus, Bacillus subtilis), Gram-negative bacteria (Escherichia coli, Salmonella typhimurium), yeast (Candida albicans), and fungus (Asperigillus fumigatus). The inhibitory zones and the disc diameter (6 mm) were measured and recorded in Table 1. Following was the explanation for the antimicrobial activity data in Table 1: The starting β-chloroenaldehyde 1 displayed low inhibitory action towards Gram-positive bacteria and moderate activity against Gram-negative bacteria as well as yeast and fungus. Building heterocyclic rings on the starting β-chloroenaldehyde 1 by reactions with binucleophilic reagents appeared distinguished change in the inhibitory action towards the tested microorganisms. Formation of pyrazole rings annulated chromeno[2,3-b]quinoline moiety increased the antimicrobial activity towards Gram-negative bacetria and yeast in case phenylpyrazole derivative 2, while hydrazinlypyrazole 5 and triazinylpyrazole 6 recorded excellent inhibitory effect towards all kinds of microorganisms and this may be assignable to the presence of quinoline and triazine nuclei. It was observed that the activity in case of triazine derivative 6 is better than quinoline derivative 5. Further, annulation of pyrimidine moieties with chromeno[2,3-b]quinoline moiety 7-9 presented notable activity against Gram-negative bacteria in case of compounds 7 and 8, while excellent inhibition action in case of compound 9 and this may be due to the presence of thioxopyrimidine derivative. On the other hand, compounds 13 and 14 displayed diverse inhibition action and recorded high activity towards Gram-positive bacteria and fungus strain. This may attribute to the existence of pyrazolopyridine moieties annulated chromeno[2,3-b]quinoline, the inhibitory effect of compound 13 is better than compound 14 and this may be due to the presence of electron rich hydroxyl group.

CONCLUSION

Cyclic β-chloroenaldehyde 1 represent an active substrate for building a novel series of angular heteroaannulated systems containing chromeno[2,3-b]quinoline moiety; through condensation reactions with binucleophilic reagents. The angular chromeno[2,3-b]pyrazolo[3,4-f]quinolines 2,5 and 6 were synthesized from reaction of β-chloroenaldehyde 1 with some hydrazine derivatives. Also, chromeno[2’,3’:6,5]pyrido[2,3-h]quinazolines 7-9 were efficiently obtained from condensation reactions of compound 1 with guanidines and thiourea. Further, the novel chromeno[2,3-J]phenanthrolines 10, 11 and benzoimidazo[1,2-a]chromeno[2,3-J]phenanthrolne 12 were synthesized by reaction of compound 1 with cyanoacetamide, N-benzylcyanoacetamide and 1H-benimidazol-2-ylacetonitrile. Chromeno[2,3-J]pyrazolo[3,4-b]phenanthrolines 13 and 14 were obtained from reaction of compound 1 with 5-amino-2,4-dihydro-3H-pyrazol-3-one and 5-amino-3-methyl-1H-pyrazole. Chromeno[2,3-b][1,4]-
diazepino[2,3-f]quinoline 15, chromeno[2,3-b][1,4]benzodiazepino[2,3-f]quinoline 16, chromeno[2,3-b]-[1,4]benzoxazepino[2,3-f]quinoline 17 and and chromeno[2,3-b][1,4]benzothiazepino[2,3-f]quinoline 18 were also synthesized by reaction of compound 1 with ethylenediamine, o-phenylenediamine, o-aminophenol and o-aminothiophenol, respectively. The in vitro examination of the synthesized compounds for their antimicrobial activity revealed variable inhibition action ranging between moderate and high activity. Mainly, the excellent activity towards the tested bacteria, yeast and fungus was observed for compounds containing pyrazoles and pyrimidines nuclei annulated chromeno[2,3-b]quinoline moiety, while the excellent activity towards Gram-positive bacteria and fungus was recorded for compounds containing pyrazolepyridine fused chromeno[2,3-b]quinoline moiety.

Table 1. In vitro antimicrobial activities of the synthesized compounds at 500 and 1000 µg/mL by disc diffusion assay

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* Calculated from 3 values.

L = Low activity, I = Intermediate activity, H = High activity, S: Standard drug
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. \(^1\)H NMR (300 MHz) and \(^{13}\)C NMR (75 MHz) spectra were measured on Mercury-300BB, using DMSO-\(d_6\) as a solvent and TMS (\(\delta\), 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.

Starting Materials. 1-Chloro-9-methyl-11-oxo-3,4-dihydro-11H-chromeno[2,3-b]quinoline-2-carboxaldehyde (1) was prepared according to literature method.\(^\text{15}\) All other chemicals used are commercially available.

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.\(^\text{21}\) 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.

4,5-Dihydro-10-methyl-1-phenyl-12H-chromeno[2,3-b]pyrazolo[3,4-f]quinolin-12-one (2).

A mixture of \(\beta\)-chloroenaldehyde 1 (0.65 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 (0.49 g, 64%). IR (KBr, cm\(^{-1}\)): 3059 (CH\(_{\text{arom.}}\)), 2942, 2901 (CH\(_{\text{aliph.}}\)), 1656 (C=O\(_{\gamma\text{-pyrone}}\)), 1615 (C=N), 1586 (C=C). \(^1\)H NMR (300 MHz, DMSO-\(d_6\), δ): 2.09 (t, 2H, \(J= 6.6 \text{ Hz, CH}_2\)), 2.21 (t, 2H, \(J= 6.6 \text{ Hz, CH}_2\)), 2.36 (s, 3H, CH\(_3\)), 6.89-7.16 (m, 5H, Ph-H), 7.42 (d, 1H, \(J= 7.8 \text{ Hz, H-8}\)), 7.72 (d, 1H, \(J= 7.8 \text{ Hz, H-9}\)), 7.92 (s, 1H, H-11), 8.62 (s, 1H, H-3\(_{\text{pyrazole}}\)), 8.85 (s, 1H, H-4\(_{\text{pyridine}}\)). \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\), δ): 21.2 (CH\(_3\)), 23.7 (CH\(_2\)), 28.4 (CH\(_2\)), 112.7, 119.1, 120.6, 122.9, 125.1, 125.9, 126.6, 127.3, 128.2, 129.4, 130.6, 133.7, 138.5, 147.9, 150.1, 154.7, 158.1, 162.5, 176.8 (C=O\(_{\gamma\text{-pyrone}}\)). Mass spectrum, \(m/z\) (I(%)): 379 (65), 302 (14), 274 (30), 248 (9), 149 (7), 135 (54), 120 (23), 77 (100), 64 (21). Anal. Calcd for C\(_{24}\)H\(_{17}\)N\(_3\)O\(_2\) (379.41): C, 75.97; H, 4.52; N, 11.08%. Found: C, 75.71; H, 4.33; N, 10.86%.

4,5-Dihydro-10-methyl-1-(7-chloroquinolinyl)-12H-chromeno[2,3-b]pyrazolo[3,4-f]quinolin-12-one (5).

A mixture of compound 1 (0.65 g, 2 mmol) and 7-chloro-4-hydrazinylquinoline (3) (0.38 g, 2 mmol) in DMF (10 mL) containing TEA (0.1 mL) was heated under reflux for 2 h. The orange crystals obtained
during heating were filtered and crystallized from DMF, mp > 300 °C, yield (0.58 g, 63%). IR (KBr, cm⁻¹): 3075 (CH₆), 2932, 2896 (CH₆), 1660 (C=O), 1618 (C=N), 1595 (C=C). ¹H NMR (300 MHz, DMSO-δ₆, δ): 2.03 (t, 2H, J = 6.6 Hz, CH₂), 2.24 (t, 2H, J = 6.6 Hz, CH₂), 2.42 (s, 3H, CH₃), 7.36-7.54 (m, 3H, Ar-H), 7.69 (s, 1H, H-8), 7.78-7.92 (m, 2H, Ar-H), 8.06 (s, 1H, H-11), 8.32 (d, 1H, J = 8.1 Hz, H-2), 8.56 (s, 1H, H-3), 8.81 (s, 1H, H-4). Anal. Calcd for C₁₉H₁₂N₂O₂ (439.40): C, 74.09; H, 4.37; N, 16.80%. Found: C, 73.87; H, 4.02; N, 16.47%.

4,5-Dihydro-10-methyl-1-(5,6-diphenyl-1,2,4-triazin-3-yl)-12H-chromeno[2,3-b]pyrazolo[3,4-f]-quinolin-12-one (6). A mixture of compound 1 (0.65 g, 2 mmol) and 3-hydrazinyl-5,6-diphenyl-1,2,4-triazine (4) (0.58 g, 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 AcOH, mp > 300 °C, yield (0.73 g, 68%). IR (KBr, cm⁻¹): 3038 (CH₆), 2967, 2922 (CH₆), 1658 (C=O), 1612 (C=N), 1579 (C=C). ¹H NMR (300 MHz, DMSO-δ₆, δ): 1.95 (t, 2H, J = 6.3 Hz, CH₂), 2.22 (t, 2H, J = 6.3 Hz, CH₂), 2.43 (s, 3H, CH₃), 6.85-7.10 (m, 10H, Ar-H), 7.58 (d, 1H, J = 7.5 Hz, H-8), 7.83 (d, 1H, J = 7.5 Hz, H-9), 8.02 (s, 1H, H-11), 8.49 (s, 1H, H-3), 8.84 (s, 1H, H-4). Mass spectrum, m/z (I,%): 534 (16), 478 (21), 300 (23), 246 (20), 208 (9), 178 (100), 157 (6), 135 (72), 120 (43), 77 (37), 64 (11). Anal. Calcd for C₃₂H₂₅N₆O₂ (534.57): C, 74.14; H, 4.15; N, 15.72%. Found: C, 73.87; H, 4.02; N, 15.47%.

2-Amino-5,6-dihydro-11-methyl-1H,13H-chromeno[2’,3’:6,5]pyrido[2,3-h]quinazolin-13-one (7). A mixture of compound 1 (0.65 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 (0.47 g, 72%). IR (KBr, cm⁻¹): 3395, 3280 (NH₂), 3059 (CH₆), 2975, 2928 (CH₆), 1643 (C=O), 1610 (C=N), 1586 (C=C). ¹H NMR (300 MHz, DMSO-δ₆, δ): 2.00 (t, 2H, J = 6.1 Hz, CH₂), 2.17 (t, 2H, J = 6.1 Hz, CH₂), 2.33 (s, 3H, CH₃), 6.74 (bs, 2H, NH₂ exchangeable with D₂O), 7.46 (d, 1H, J = 8.4 Hz, H-9), 7.83 (d, 1H, J = 8.4 Hz, H-10), 8.03 (s, 1H, H-12), 8.69 (s, 1H, H-4), 8.92 (s, 1H, H-4). ¹³C NMR (75 MHz, DMSO-δ₆, δ): 21.5 (CH₃), 24.2 (CH₂), 28.1 (CH₂), 113.8, 118.6, 120.3, 122.7, 124.6, 126.1, 128.4, 130.9, 139.2, 148.2, 150.6, 155.1, 157.8, 160.3, 163.1, 176.1 (C=O). Mass spectrum, m/z (I,%): 330 (100), 288 (54), 260 (32), 235 (13), 149 (6), 135 (41), 120 (15), 77 (25), 64 (13). Anal. Calcd for C₁₉H₁₄N₄O₂ (330.34): C, 69.08; H, 4.27; N, 16.96%. Found: C, 68.91; H, 4.13; N, 16.80%.

5,6-Dihydro-11-methyl-13-oxo-13H-chromeno[2’,3’:6,5]pyrido[2,3-h]quinazolin-2(1H)-ylidene-cyanamide (8). A mixture of compound 1 (0.65 g, 2 mmol) and cyanoguanidine (0.16 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 AcOH, mp > 300 °C, yield (0.43 g, 61%). IR (KBr, cm⁻¹): 3342 (NH), 3045 (CH_arom.), 2968, 2922 (CH_aliph.), 2226 (C≡N), 1648 (C=O_pyridone), 1614 (C=N), 1581 (C=C). ¹H NMR (300 MHz, DMSO_d6, δ): 2.04 (t, 2H, J = 6.3 Hz, CH2), 2.18 (t, 2H, J = 6.3 Hz, CH2), 2.32 (s, 3H, CH3), 7.53 (d, 1H, J = 7.8 Hz, H-9), 7.87 (d, 1H, J = 7.8 Hz, H-10), 8.00 (s, 1H, H-12), 8.48 (s, 1H, H-4_pyrimidine), 8.85 (s, 1H, H-4_pyridine), 9.35 (bs, 1H, NH exchangeable with D2O). ¹³C NMR (75 MHz, DMSO-d6, δ): 20.9 (CH3), 23.6 (CH2), 27.4 (CH2), 112.5, 116.3 (C≡N), 118.9, 121.1, 123.4, 124.9, 126.3, 128.0, 130.7, 137.8, 144.8, 148.3, 150.2, 154.6, 156.5, 162.2, 176.7 (C=O_pyrynone). Mass spectrum, m/z (I,%): 355 (97), 327 (62), 248 (5), 135 (36), 120 (21), 77 (17), 64 (9). Anal. Calcd for C20H13N3O2 (355.35): C, 67.60; H, 3.69; N, 19.71%. Found: C, 67.32; H, 3.43; N, 19.46%.


A mixture of compound 1 (0.65 g, 2 mmol) and thiourea (0.16 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 dioxane, mp > 300 °C, yield (0.56 g, 64%). IR (KBr, cm⁻¹): 3313 (NH), 3028 (CH_arom.), 2974, 2941 (CH_aliph.), 1654 (C=O_pyridone), 1617 (C=N), 1586 (C=C). ¹H NMR (300 MHz, DMSO-d6, δ): 1.99 (t, 2H, J = 6.3 Hz, CH2), 2.13 (t, 2H, J = 6.3 Hz, CH2), 2.35 (s, 3H, CH3), 7.47 (d, 1H, J = 7.5 Hz, H-9), 7.79 (d, 1H, J = 7.5 Hz, H-10), 7.92 (s, 1H, H-12), 8.59 (s, 1H, H-4_pyrimidine), 8.82 (s, 1H, H-4_pyrdine), 9.86 (bs, 1H, NH exchangeable with D2O). Mass spectrum, m/z (I,%): 347 (31), 314 (25), 286 (36), 260 (24), 151 (6), 135 (100), 120 (56), 77 (38), 64 (17). Anal. Calcd for C19H13N3O2S (347.39): C, 65.69; H, 3.77; N, 12.10; S, 9.23%. Found: C, 65.48; H, 3.53; N, 12.02; S, 9.12%.

2,13-Dioxo-11-methyl-1,2,5,6-tetrahydro-13H-chromeno[2,3-j]phenanthroline-3-carbonitrile (10).

A mixture of compound 1 (0.65 g, 2 mmol) and cyanoacetamide (0.17 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 DMF/H2O, mp > 300 °C, yield (0.56 g, 79%). IR (KBr, cm⁻¹): 3376 (NH), 3068 (CH_arom.), 2986, 2936 (CH_aliph.), 2224 (C≡N), 1678 (C=O_pyridone), 1653 (C=O_pyrynone), 1617 (C=N), 1581 (C=C). ¹H NMR (300 MHz, DMSO-d6, δ): 1.96 (t, 2H, J = 6.3 Hz, CH2), 2.18 (t, 2H, J = 6.3 Hz, CH2), 2.38 (s, 3H, CH3), 7.45 (d, 1H, J = 8.4 Hz, H-9), 7.78 (d, 1H, J = 8.4 Hz, H-10), 8.06 (s, 1H, H-12), 8.65 (s, 1H, H-4_pyrimidine), 8.87 (s, 1H, H-4_pyridine), 11.85 (bs, 1H, NH exchangeable with D2O). ¹³C NMR (75 MHz, DMSO-d6, δ): 21.8 (CH3), 24.3 (CH2), 28.0 (CH2), 98.3 (C-3_pyridone), 112.5, 116.7 (C≡N), 118.2, 120.6, 122.4, 123.6, 125.1, 126.3, 128.7, 131.2, 137.6, 141.5, 149.4, 154.3, 157.7, 171.5 (C=O_pyridone), 176.7 (C=O_pyrynone). Mass spectrum, m/z (I,%): 355 (100), 327 (74), 299 (29), 248 (14), 209 (21), 157 (10), 135 (32), 120 (54), 77 (28), 64 (9). Anal. Calcd for C21H13N5O3 (355.35): C, 70.98; H, 3.69; N, 11.83%. Found: C, 70.75; H, 3.53; N, 11.62%.
1-Benzyl-2,13-dioxo-11-methyl-5,6-dihydro-2H,13H-chromeno[2,3-J]phenanthroline-3-carbonitrile (11). A mixture of compound 1 (0.65 g, 2 mmol) and N-benzylecyanoacetamide (0.35 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 t-butanol, mp > 300 °C, yield (0.59 g, 66%). IR (KBr, cm⁻¹): 3072 (CH₃aliph.), 2965, 2925 (CH₃aliph.), 2222 (C=O). 1653 (C=O₄-pyrene), 1614 (C=O), 1577 (C=C). ¹H NMR (300 MHz, DMSO-d₆, δ): 2.06 (t, 2H, J= 6.0 Hz, CH₂), 2.19 (t, 2H, J= 6.0 Hz, CH₂), 2.31 (s, 3H, CH₃), 3.42 (s, 2H, NCH₂), 6.76 (t, 1H, J= 6.9 Hz, Ar-H), 6.95 (t, 1H, J= 6.9 Hz, Ar-H), 7.06-7.25 (m, 3H, Ar-H), 7.43 (d, 1H, J= 7.8 Hz, H-9), 7.76 (d, 1H, J= 7.8 Hz, H-10), 8.01 (s, 1H, H-12), 8.72 (s, 1H, H-4pyridine), 8.86 (s, 1H, H-4pyridine). Mass spectrum, m/z (I,%): 445 (31), 417 (16), 326 (13), 298 (7), 283 (10), 232 (12), 208 (14), 134 (68), 120 (42), 91 (100), 77 (36), 64 (17). Anal. Calcd for C₂₉H₁₉N₅O₃ (445.47): C, 75.49; H, 4.30; N, 9.43%. Found: C, 75.16; H, 4.15; N, 9.20%.

8.9-Dihydro-14-methyl-16-oxo-16H-benzoimidazo[1,2-a]chromeno[2,3-J]phenanthroline-6-carbonitrile (12). A mixture of compound 1 (0.65 g, 2 mmol) and 1H-benzimidazol-2-ylacetonitrile (0.31 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 DMF/ EtOH, mp > 300 °C, yield (0.61 g, 71%). IR (KBr, cm⁻¹): 3044 (CH₃aliph.), 2953, 2916 (CH₃aliph.), 2222 (C=O), 1650 (C=O₄-pyrene), 1620 (C=N), 1597 (C=C). ¹H NMR (300 MHz, DMSO-d₆, δ): 2.06 (t, 2H, J= 6.0 Hz, CH₂), 2.19 (t, 2H, J= 6.0 Hz, CH₂), 2.36 (s, 3H, CH₃), 6.94 (t, 1H, J= 7.2 Hz, H-9), 7.12-7.28 (m, 3H, Ar-H), 7.47 (d, 1H, J= 7.5 Hz, H-12), 7.83 (d, 1H, J= 7.5 Hz, H-13), 8.04 (s, 1H, H-15), 8.61 (s, 1H, H-4pyridine), 8.77 (s, 1H, H-4pyridine). Mass spectrum, m/z (I,%): 428 (100), 400 (62), 324 (12), 273 (9), 157 (9), 134 (51), 120 (46), 77 (24), 64 (9). Anal. Calcd for C₂₇H₁₆N₄O₂ (428.44): C, 75.69; H, 3.76; N, 13.08%. Found: C, 75.38; H, 3.51; N, 12.79%.

5,6-Dihydro-3-hydroxy-11-methyl-1H-chromeno[2,3-J]pyrazolo[3,4-b]phenanthroline-13(13H)-one (13). A mixture of compound 1 (0.65 g, 2 mmol) and 5-amino-2,4-dihydro-3H-pyrazol-3-one (0.19 g, 2 mmol) in DMF (10 mL) containing TEA (0.1 mL) was heated under reflux for 2 h. The pale brown crystals obtained during heating were filtered and crystallized from DMF, mp > 300 °C, yield (0.53 g, 72%). IR (KBr, cm⁻¹): 3402 (OH), 3335 (NH), 3058 (CH₃aliph.), 2974, 2938 (CH₃aliph.), 1653 (C=O₄-pyrene), 1612 (C=N), 1583 (C=C). ¹H NMR (300 MHz, DMSO-d₆, δ): 2.00 (t, 2H, J= 6.3 Hz, CH₂), 2.19 (t, 2H, J= 6.3 Hz, CH₂), 2.32 (s, 3H, CH₃), 7.57 (d, 1H, J= 8.4 Hz, H-9), 7.78 (d, 1H, J= 8.4 Hz, H-10), 7.98 (s, 1H, H-12), 8.58 (s, 1H, H-4pyridine), 8.71 (s, 1H, H-4pyridine), 9.56 (bs, 1H, NH exchangeable with D₂O), 11.26 (bs, 1H, NH exchangeable with D₂O). Mass spectrum, m/z (I,%): 370 (100), 342 (43), 299 (50), 285 (21), 230 (36), 181 (13), 135 (68), 121 (26), 77 (17), 64 (5). Anal. Calcd for C₂₁H₁₄N₄O₃ (370.36): C, 68.10; H, 3.81; N, 15.13%. Found: C, 67.85; H, 3.74; N, 15.02%.

5,6-Dihydro-3,11-dimethyl-1H-chromeno[2,3-J]pyrazolo[3,4-b]phenanthroline-13(13H)-one (14).
A mixture of compound 1 (0.65 g, 2 mmol) and 5-amino-3-methyl-1H-pyrazole (0.19 g, 2 mmol) in DMF (10 mL) containing TEA (0.1 mL) was heated under reflux for 2 h. The pale brown crystals obtained after cooling were filtered and crystallized from DMF/H₂O, mp > 300 °C, yield (0.52 g, 70%). IR (KBr, cm⁻¹): 3319 (NH), 3029 (CH₃), 2961 (CH₂), 1661 (C=O₇-pyron), 1618 (C≡N), 1593 (C=O). ¹H NMR (300 MHz, DMSO-d₆, δ): 2.03 (t, 2H, J= 6.6 Hz, CH₂), 2.14 (t, 2H, J= 6.6 Hz, CH₂), 2.33 (s, 3H, CH₃), 2.64 (s, 3H, CH₃), 7.57 (d, 1H, J= 8.4 Hz, H-9), 7.78 (d, 1H, J= 8.4 Hz, H-10), 7.98 (s, 1H, H-12), 8.48 (s, 1H, H-4pyridine), 8.67 (s, 1H, H-4pyridine), 9.86 (bs, 1H, NH exchangeable with D₂O). Mass spectrum, m/z (I, %): 368 (100), 327 (63), 299 (71), 285 (32), 244 (20), 135 (42), 120 (33), 77 (13), 64 (7). Anal. Calcd for C₂₂H₁₅N₂O₂ (368.39): C, 72.49; H, 5.17; N, 12.68%. Found: C, 72.28; H, 5.10; N, 12.32%.

12-Methyl-2,3,6,7-tetrahydro-1H-chromeno[2,3-b][1,4]diazepino[2,3-f]quinolin-14(14H)-one (15).

A mixture of compound 1 (0.65 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 pale yellow crystals obtained after cooling were filtered and crystallized from t-butanol, mp > 300 °C, yield (0.46 g, 69%). IR (KBr, cm⁻¹): 3368 (NH), 3083 (CH₃), 2942, 2915 (CH₂), 1649 (C=O₇-pyron), 1610 (C≡N), 1574 (C≡C). ¹H NMR (300 MHz, DMSO-d₆, δ): 2.05 (t, 2H, J= 6.6 Hz, CH₂), 2.15 (t, 2H, J= 6.6 Hz, CH₂), 2.38 (s, 3H, CH₃), 2.85 (s, 2H, 2CH₂), 6.13 (bs, 1H, NH exchangeable with D₂O), 7.52 (d, 1H, J= 7.5 Hz, H-10), 7.86 (d, 1H, J= 8.1 Hz, H-11), 8.06 (s, 1H, H-13), 8.21 (s, 1H, H-4diazepine), 8.68 (s, 1H, H-4pyridine). ¹³C NMR (75 MHz, DMSO-d₆, δ): 20.7 (CH₃), 23.5 (CH₂), 27.6 (CH₂), 44.7 (CH₂), 45.9, 110.4, 119.1, 120.6, 122.5, 124.9, 126.7, 128.3, 131.5, 137.4, 146.7, 147.3, 153.8, 156.4, 161.6, 176.3 (C=O₇-pyron). Mass spectrum, m/z (I, %): 331 (21), 304 (13), 276 (100), 248 (46), 233 (9), 209 (16), 181 (8), 157 (17), 135 (36), 120 (42), 77 (23), 64 (13). Anal. Calcd for C₂₀H₁₇N₂O₂ (331.37): C, 72.49; H, 5.17; N, 12.68%. Found: C, 72.28; H, 5.10; N, 12.32%.


A mixture of compound 1 (0.65 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 yellow crystals obtained during heating were filtered and crystallized from DMF, mp > 300 °C, yield (0.49 g, 65%). IR (KBr, cm⁻¹): 3385 (NH), 3055 (CH₃), 2965, 2929 (CH₂), 1652 (C=O₇-pyron), 1618 (C≡N), 1579 (C≡C). ¹H NMR (300 MHz, DMSO-d₆, δ): 1.98 (t, 2H, J= 6.1 Hz, CH₂), 2.18 (t, 2H, J= 6.1 Hz, CH₂), 2.40 (s, 3H, CH₃), 7.16-7.32 (m, 4H, Ar-H), 7.49 (d, 1H, J= 8.1 Hz, H-11), 7.79 (d, 1H, J= 8.1 Hz, H-12), 8.09 (s, 1H, H-14), 8.27 (s, 1H, H-4diazepine), 8.76 (s, 1H, H-4pyridine), 9.37 (bs, 1H, NH exchangeable with D₂O). Mass spectrum, m/z (I, %): 379 (63), 351 (48), 324 (52), 233 (17), 181 (6), 135 (23), 120 (52), 91 (18), 77 (14), 64 (7). Anal. Calcd for C₂₀H₁₇N₂O₂ (379.41): C, 75.97; H, 4.52; N, 11.08%. Found: C, 75.74; H, 4.32; N, 10.89%.


A mixture of compound 1 (0.65 g, 2 mmol) and o-aminophenol (0.22 g, 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 t-butanol, mp 290-291 °C, yield (0.44 g, 58%). IR (KBr, cm⁻¹): 3056 (CH_arom.), 2936, 2901 (CH_aliph.), 1654 (C=Oγ-pyrone), 1613 (C=N), 1589 (C=C). ¹H NMR (300 MHz, DMSO-d₆, δ): 2.02 (t, 2H, J= 6.9 Hz, CH₂), 2.21 (t, 2H, J= 6.9 Hz, CH₂), 2.36 (s, 3H, CH₃), 7.29-7.40 (m, 4H, Ar-H), 7.51 (d, 1H, J= 7.5 Hz, H-11), 7.81 (d, 1H, J= 7.5 Hz, H-12), 8.08 (s, 1H, H-14), 8.43 (s, 1H, H-4oxazepine), 8.82 (s, 1H, H-4pyridine). Mass spectrum, m/z (I,%): 380 (14), 353 (26), 277 (21), 249 (15), 209 (13), 135 (100), 120 (38), 92 (32), 77 (36), 64 (10). Anal. Calcd for C₂₄H₁₆N₂O₃ (380.39): C, 75.78; H, 4.24; N, 7.36%. Found: C, 75.62; H, 4.10; N, 7.15%.


A mixture of compound 1 (0.65 g, 2 mmol) and o-aminothiophenol (0.25 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, mp > 300 °C yield (0.47 g, 59%). IR (KBr, cm⁻¹): 3023 (CH_arom.), 2946, 2909 (CH_aliph.), 1652 (C=Oγ-pyrone), 1615 (C=N), 1584 (C=C). ¹H NMR (300 MHz, DMSO-d₆, δ): 2.04 (t, 2H, J= 6.3 Hz, CH₂), 2.23 (t, 2H, J= 6.3 Hz, CH₂), 2.38 (s, 3H, CH₃), 7.38-7.56 (m, 5H, Ar-H and H-11), 7.78 (d, 1H, J= 8.1 Hz, H-12), 8.01 (s, 1H, H-14), 8.39 (s, 1H, H-4thiazepine), 8.87 (s, 1H, H-4pyridine). Mass spectrum, m/z (I,%): 396 (11), 368 (19), 341 (14), 234 (10), 181 (8), 135 (100), 120 (64), 106 (13), 77 (28), 64 (21). Anal. Calcd for C₂₄H₁₆N₂O₂S (396.46): C, 72.71; H, 4.07; N, 7.07; S, 8.09%. Found: C, 72.55; H, 4.01; N, 6.87; S, 8.05%.

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