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Regioselective synthesis of 9,10-dihydro-6*H*-chromeno[4,3-*d*]imidazo-[1,2-*a*]pyridin-6-one derivatives†

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A method for regioselective synthesis of 9,10-dihydro-6*H*-chromeno[4,3-*d*]imidazo[1,2-*a*]pyridin-6-one derivatives has been developed. The reaction was readily performed by reacting inexpensive materials, 4-chloro-3-formylcoumarin and HKAs, in EtOH catalyzed by Et_3N. This protocol has many advantages including convenient operation, short reaction times, green solvent, and simple purification by washing the crude products with 95% EtOH, defined as GAP (Group-Assistant-Purification) chemistry. The library of 9,10-dihydro-6*H*-chromeno[4,3-*d*]imidazo[1,2-*a*]pyridin-6-one derivatives has been constructed with excellent yields.

Introduction

Modern chemistry has been inseparably linked with green chemistry.[1] With the increasing prevalence of green chemistry, alternative technologies that use GAP chemistry, performed without the use of traditional purification by chromatography or recrystallization, is of interest in organic synthesis.[2] The use of GAP chemistry synthesis has increased rapidly in recent years.[3] We are pleased to find that this concept can be extended to other reactions, as shown in this paper.

Coumarin is among the most important heterocyclic systems, present as a structural framework in a large number of bioactive natural products.[4] Derivatives have also been found that antitumor,[5] antioxidant[6] or anti-inflammatory[7] properties and act as non-peptidic HIV protease inhibitors,[8] topoisomerase II Inhibitors,[9] tyrosine kinase inhibitors,[10] diuretics and analgesics,[11] and so on.[12] Heterocycles fused at the 3,4-position of coumarin have also drawn special attention[13] (Fig 1). For example, Costa and co-workers reported the synthesis of 2*H*-chromeno[3,4-*c*]pyridin-5-one derivatives in unsatisfactory yields.

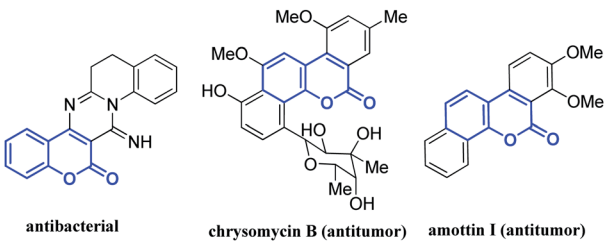
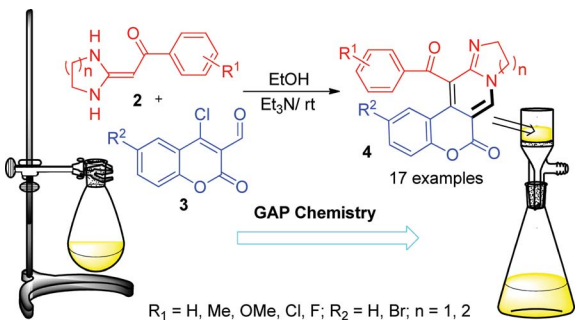


Fig. 1 Coumarin derivatives with biological activities.

However, some of the active compounds can be used as adenosine receptors in the submicromolar range.[14]

In the past several years, our group has demonstrated that HKAs are an emerging, more reactive class of functionalized synthons[15] through which a variety of biologically active heterocyclic[16] and fused heterocyclic compounds can be obtained using easier and more efficient methodologies.[17,18]



Scheme 1 This work: Synthesis of 9,10-dihydro-6*H*-chromeno[4,3-*d*]-imidazo[1,2-*a*]pyridin-6-one derivatives.

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One concern of our group is green chemistry synthesis of diverse libraries of compounds under mild reaction conditions. The green synthesis can usually avoid tedious workup and purifications. Based on these, in this paper we report the method for a one-pot synthesis of 9,10-dihydro-6*H*-chromeno-[4,3-*d*]imidazo[1,2-*a*]pyridin-6-one derivatives (Scheme 1).

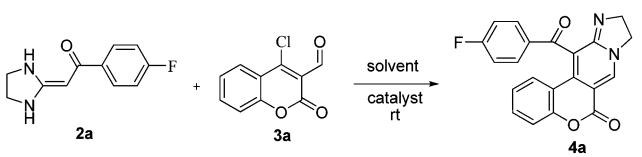
Results and discussion

A initial attempt was made to react HKA **2a** with 4-chloro-3-formylcoumarin **3a** using Et_3N as the catalyst and acetone as the solvent at ambient temperature. After 10 min, an orange solid was obtained in about 73% yield after separation by filtration (Table 1, entry 1). To establish the optimal reaction conditions, we screened other solvents by still using Et_3N as the catalyst at ambient temperature (Table 1, entries 2–4). As a result, we found that EtOH afforded the highest yield (Table 1, entry 4). Subsequently, we screened different catalysts such as HOAc (Table 1, entry 6), Na_2CO_3 (Table 1, entry 5). Among the catalysts, Et_3N showed the highest efficiency (Table 1, entries 5–7).

Having demonstrated the viability of this cascade strategy, different kinds of HKAs and 3-formylcoumarins were used as substrates to synthesize the target compound library under optimized condition. As shown in Table 2, most of the substrates afforded products in good yields (80–96%). 4-chloro-3-formylcoumarin **3a** was used as the standard substrate initially. Entries 1–6 in Table 2 demonstrate that the reaction tolerated significant functionalization of five-member HKAs; substrates with electron-donating groups (such as Me and OMe) on the phenyl ring of the HKAs gave better yields than substrates without substituents or electron-withdrawing groups (such as F and Cl). The yields of substrates of six-member HKAs were similar to those with five-member HKAs (Table 2, entries 12–17).

Changing the hydrogen to a bromo group at the 6-position of 4-chloro-3-formylcoumarin resulted in products with relatively high yields (Table 2, entries 7–11).

Table 1 Optimization of reaction conditions[a]

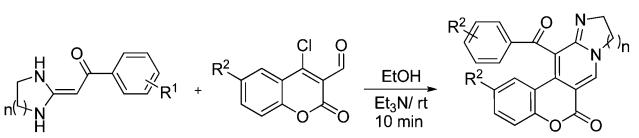


2a 3a 4a

Entry	Solvent	Catalyst	t (°C)	Time (min)	Yield[b] (%)
1	Acetone	Et_3N	r.t.	10	73
2	H_2O	Et_3N	r.t.	10	30
3	MeOH	Et_3N	r.t.	10	65
4	EtOH	Et_3N	r.t.	10	80
5	EtOH	Na_2CO_3	r.t.	10	37
6	EtOH	AcOH	r.t.	10	43
7	EtOH	—	r.t.	10	24

[a] *Reagents and conditions*: HKA **2a** (0.5 mmol), 4-chloro-3-formylcoumarin **3a** (0.5 mmol), catalyst (10 mmol%), solvent (5.0 mL). [b] Isolated yield based on HKA **2a**.

Table 2 Preparation of 9,10-dihydro-6*H*-chromeno[4,3-*d*]imidazo-[1,2-*a*]pyridin-6-one derivatives[a]



2 3 4

Entry	R^1	R^2	n	4	Yield[b] (%)
1	*p*-F (**2a**)	H (**3a**)	1	**4a**	80
2	*p*-Cl (**2b**)	H (**3a**)	1	**4b**	83
3	*o*-Cl (**2c**)	H (**3a**)	1	**4c**	87
4	H (**2d**)	H (**3a**)	1	**4d**	91
5	*p*-Me (**2e**)	H (**3a**)	1	**4e**	93
6	*p*-OMe (**2f**)	H (**3a**)	1	**4f**	95
7	*p*-F (**2a**)	Br (**3b**)	1	**4g**	88
8	*p*-Cl (**2b**)	Br (**3b**)	1	**4h**	90
9	H (**2d**)	Br (**3b**)	1	**4i**	94
10	*p*-Me (**2e**)	Br (**3b**)	1	**4j**	95
11	*p*-OMe (**2f**)	Br (**3b**)	1	**4k**	96
12	*p*-F (**2g**)	H (**3a**)	2	**4l**	84
13	*p*-Cl (**2h**)	H (**3a**)	2	**4m**	88
14	H (**2i**)	H (**3a**)	2	**4n**	91
15	*p*-Me (**2j**)	H (**3a**)	2	**4o**	92
16	*p*-OMe (**2k**)	H (**3a**)	2	**4p**	94
17	*o*-Cl (**2l**)	Br (**3b**)	2	**4q**	90

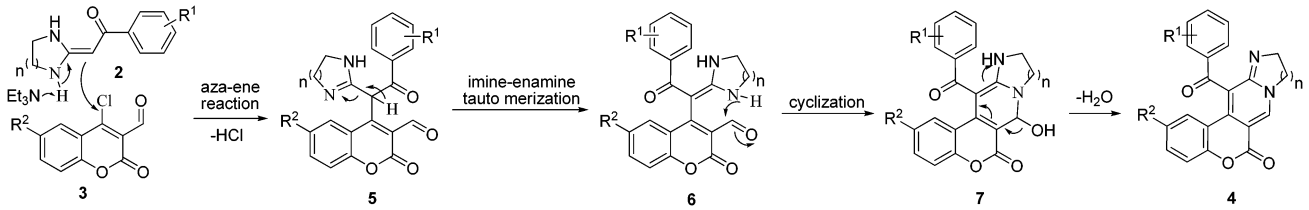
[a] *Reagents and conditions*: HKA **2** (0.5 mmol), 4-chloro-3-formylcoumarin **3** (0.5 mmol), catalyst (10 mmol%), solvent (5.0 mL). [b] Isolated yield based on HKA **2**.

A proposed mechanism for the synthesis of 9,10-dihydro-6*H*-chromeno[4,3-*d*]imidazo[1,2-*a*]pyridin-6-one derivatives **4** is shown in Scheme 2. Being the strong electron-withdrawing keto-carbonyl groups at the α-position of the HKA and the electron-donating diamino groups of HKA. HKA reacted with 4-chloro-3-formylcoumarin **3** *via* addition of an azaene,[19] internal elimination of HCl to afford **5** catalyzed by Et_3N. The intermediate **5** is followed by imine–enamine tautomerization[20] and to yield product **6**. Subsequently, intramolecular attack of the NH group at the aldehyde group occurs *via* a cyclization reaction to form **7**. Finally, H_2O was removed from **7** to give 9,10- dihydro-6*H*-chromeno[4,3-*d*]imidazo[1,2-*a*]pyridin-6-onederivative **4**.

To verify the structure of the 9,10-dihydro-6*H*-chromeno[4,3-*d*]imidazo[1,2-*a*]pyridin-6-one derivatives, **4d** was selected as a representative compound and characterized by X-ray crystallography as shown in Fig. 2.

Conclusions

In conclusion, we have developed a novel, efficient and one-step method for the regioselective synthesis of 9,10-dihydro-6*H*-chromeno[4,3-*d*]imidazo[1,2-*a*]pyridin-6-ones between HKAs and 4-chloro-3-formylcoumarin under simple and mild reaction conditions. The advantages of this method include "Green process" technology – mild reaction conditions, short-time, excellent yields and simple operation.



Scheme 2 Proposed mechanism for synthesis of 9,10-dihydro-6*H*-chromeno[4,3-*d*]imidazo[1,2-*a*]pyridin-6-one derivatives **4**.

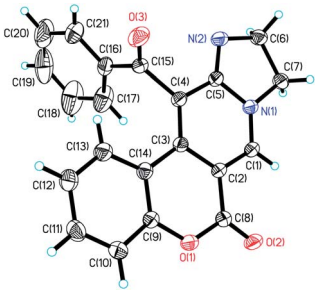


Fig. 2 ORTEP diagram of **4d**; ellipsoids are drawn at the 30% probability level.

Experimental section

All compounds were fully characterized by spectroscopic data. The NMR spectra were recorded on a Bruker DRX500 (^{1}H: 500 MHz, ^{13}C: 125 MHz). Chemical shifts (δ) are expressed in ppm and J values are given in Hz. Deuterated $CDCl_3$ and DMSO-d_6 were used as solvent. IR spectra were recorded on a FT-IR Thermo Nicolet Avatar 360 using a KBr pellet. The reactions were monitored by thin layer chromatography (TLC) using silica gel GF254. The melting points were determined on a XT-4A melting point apparatus and are uncorrected. HRMs were performed on an Agilent LC/Msd TOF instrument. All chemicals and solvents were used as received without further purification unless otherwise stated. Compounds **2** were prepared according to the literature.[21] Materials **3** were synthesized according with the literature.[22]

General procedure

HKA derivatives **2** (0.5 mmol), 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde derivatives **3** (0.5 mmol) and ethanol (5 mL) were placed into a 10 mL round-bottom flask and the mixture was stirred at room temperature for 10 minutes. Upon completion, as monitored by TLC, trimethylamine (10 mmol%) was added and the mixture was stirred at room temperature for 5 minutes. Then the reaction mixture was cooled to room temperature and filtered to give the pure crude product, which was further washed with 95% EtOH to give pure product **4** with a yield of 82–96%. The products were further identified by FTIR, NMR and HRMS, and were found to be in good agreement with the assigned structures. (see ESI†).

12-(4-Fluorobenzoyl)-9,10-dihydro-6*H*-chromeno[4,3-*d*]imidazo[1,2-*a*]pyridin-6-one (4a). Orange solid; mp 291–294 °C; IR (KBr): 1719, 1669, 1622, 1511, 1327, 1273, 1224, 1147, 1086, 1004, 751 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.10–4.12 (m, 2H, NCH_2), 4.25–4.29 (m, 2H, NCH_2), 6.97–7.00 (m, 1H, ArH), 7.20–7.24 (m, 3H, ArH), 7.41–7.46 (m, 2H, ArH), 8.15–8.18 (m, 2H, ArH), 8.50 (s, 1H, CH); ^{13}C NMR (125 MHz, DMSO-d_6 + $CDCl_3$): δ = 49.1, 53.5, 98.8, 115.6, 116.6, 116.8, 118.4, 124.5, 126.9, 132.4, 132.4, 132.4, 132.6, 134.9, 145.9, 152.4, 155.0, 159.3, 165.2, 167.2, 194.1; HRMS (TOF ES$^+$): m/z calcd for $C_{21}H_{13}FN_2O_3$ [(M + H)$^+$], 361.0983; found, 361.0989.

12-(4-Chlorobenzoyl)-9,10-dihydro-6*H*-chromeno[4,3-*d*]imidazo[1,2-*a*]pyridin-6-one (4b). Orange solid; mp 301–304 °C; IR (KBr): 1719, 1674, 1622, 1523, 1454, 1274, 1213, 1094, 1000, 743 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.10–4.12 (m, 2H, NCH_2), 4.24–4.28 (m, 2H, NCH_2), 6.98–7.00 (m, 1H, ArH), 7.23–7.25 (m, 1H, ArH), 7.42–7.45 (m, 2H, ArH), 7.52–7.53 (m, 2H, ArH), 8.07–8.09 (m, 2H, ArH), 8.50 (s, 1H, CH); ^{13}C NMR (125 MHz, DMSO-d_6 + $CDCl_3$): δ = 49.2, 53.5, 98.8, 115.4, 115.6, 118.5, 124.6, 126.9, 129.8, 131.2, 132.8, 134.5, 140.0, 146.0, 152.5, 155.0, 159.2, 194.5; HRMS (TOF ES$^+$): m/z calcd for $C_{21}H_{13}ClN_2O_3$ [(M + H)$^+$], 377.0687; found, 377.0689.

12-(2-Chlorobenzoyl)-9,10-dihydro-6*H*-chromeno[4,3-*d*]imidazo[1,2-*a*]pyridin-6-one (4c). Yellow solid; mp 256–258 °C; IR (KBr): 1695, 1592, 1504, 1422, 1375, 1282, 1196, 1046, 755 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6 + $CDCl_3$): δ = 4.03–4.07 (m, 2H, CH_2), 4.84–4.88 (m, 2H, CH_2), 7.13–7.16 (m, 1H, ArH), 7.26–7.29 (m, 1H, ArH), 7.35 (d, J = 8.15 Hz, 1H, ArH), 7.48 (d, J = 8.05 Hz, 1H, ArH), 7.54–7.62 (m, 2H, ArH), 7.79 (d, J = 7.75 Hz, 1H, ArH), 8.17 (s, 1H, CH); ^{13}C NMR (125 MHz, DMSO-d_6 + $CDCl_3$): δ = 44.7, 51.5, 97.8, 112.1, 114.2, 118.7, 124.6, 127.8, 128.9, 132.1, 133.9, 134.2, 135.4, 135.6, 146.2, 153.1, 155.1, 157.6, 162.7, 194.5; HRMS (TOF ES$^+$): m/z calcd for $C_{21}H_{13}ClN_2O_3$ [(M + H)$^+$], 377.0687; found, 377.0681.

12-Benzoyl-9,10-dihydro-6*H*-chromeno[4,3-*d*]imidazo[1,2-*a*]-pyridin-6-one (4d). Orange solid; mp 272–275 °C; IR (KBr): 1719, 1669, 1617, 1521, 1450, 1327, 1273, 1216, 1145, 1104, 743 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.77–3.79 (m, 2H, NCH_2), 4.17–4.21 (m, 2H, NCH_2), 7.00–7.02 (m, 1H, ArH), 7.23–7.25 (m, 1H, ArH), 7.28–7.29 (m, 1H, ArH), 7.43–7.45 (m, 1H, ArH), 7.54–7.57 (m, 2H, ArH), 7.68–7.69 (m, 1H, ArH), 8.02 (d, J = 7.80 Hz, 2H, ArH), 8.68 (s, 1H, CH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 49.1, 53.4, 98.6, 115.6, 116.0, 118.6, 124.6, 126.9, 129.5, 129.5, 129.7, 129.7, 132.8, 134.7, 134.9, 135.7, 146.0, 152.4, 155.0, 159.4, 195.8; HRMS (TOF ES$^+$): m/z calcd for $C_{21}H_{14}N_2O_3$ [(M + H)$^+$], 343.1077; found, 343.1080.

12-(4-Methylbenzoyl)-9,10-dihydro-6*H*-chromeno[4,3-*d*]imidazo[1,2-*a*]pyridin-6-one (4e). Orange solid; mp 271–274 °C; IR (KBr): 1724, 1664, 1618, 1519, 1450, 1323, 1271, 1222, 1139,

1094, 755 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 2.37 (s, 3H, CH_3), 3.76–3.78 (m, 2H, CH_2), 4.17–4.21 (m, 2H, CH_2), 6.99–7.02 (m, 1H, ArH), 7.23 (d, J = 8.10 Hz, 1H, ArH), 7.31 (d, J = 8.20 Hz, 1H, ArH), 7.35 (d, J = 7.80 Hz, 2H, ArH), 7.42–7.45 (m, 1H, ArH), 7.90 (d, J = 7.85 Hz, 2H, ArH), 8.66 (s, 1H, CH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.7, 49.1, 53.4, 98.6, 115.7, 116.2, 118.5, 124.6, 126.9, 129.6, 129.6, 130.3, 130.3, 132.8, 133.4, 134.4, 145.7, 145.9, 152.4, 155.0, 159.4, 195.2; HRMS (TOF ES^+): m/z calcd for $C_{22}H_{16}N_2O_3$ [$(M + H)^+$], 357.1234; found, 357.1233.

12-(4-Methoxybenzoyl)-9,10-dihydro-6*H*-chromeno[4,3-*d*]-imidazo[1,2-*a*]pyridin-6-one (4f). Orange solid; mp 224–227 °C; IR (KBr): 1724, 1618, 1519, 1458, 1323, 1268, 1155, 1012, 763 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 3.76–3.80 (m, 2H, CH_2), 3.85 (s, 3H, OCH_3), 4.19–4.20 (m, 2H, CH_2), 7.01–7.07 (m, 3H, ArH), 7.24 (d, J = 8.45 Hz, 1H, ArH), 7.36 (d, J = 8.25 Hz, 1H, ArH), 7.43–7.46 (m, 1H, ArH), 7.98 (d, J = 7.00 Hz, 2H, ArH), 8.68 (s, 1H, CH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 49.1, 53.4, 56.0, 98.6, 115.0, 115.0, 115.8, 116.5, 118.5, 124.6, 127.0, 128.9, 131.9, 131.9, 132.7, 134.2, 145.8, 152.4, 155.0, 159.4, 164.6, 194.0; HRMS (TOF ES^+): m/z calcd for $C_{22}H_{16}N_2O_4$ [$(M + H)^+$], 373.1183; found, 373.1189.

2-Bromo-12-(4-fluorobenzoyl)-9,10-dihydro-6*H*-chromeno [4,3-*d*]imidazo[1,2-*a*]pyridin-6-one (4g). Orange solid; mp 296–299 °C; IR (KBr): 1721, 1669, 1623, 1513, 1327, 1224, 1145, 959, 829 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6 + $CDCl_3$): δ = 3.79–3.83 (m, 2H, CH_2), 4.19–4.23 (m, 2H, CH_2), 7.19 (d, J = 8.70 Hz, 2H, ArH), 7.35–7.39 (m, 3H, ArH), 7.59 (d, J = 8.60 Hz, 1H, ArH), 8.10–8.13 (m, 2H, ArH), 8.67 (s, 1H, CH); ^{13}C NMR (125 MHz, DMSO-d_6 + $CDCl_3$): δ = 49.2, 53.6, 98.2, 116.1, 116.9, 117.1, 117.6, 120.8, 129.1, 132.4, 132.5, 132.5, 133.5, 135.2, 146.3, 151.6, 154.8, 158.8, 165.5, 167.7, 194.1; HRMS (TOF ES^+): m/z calcd for $C_{21}H_{12}BrFN_2O_3$ [$(M + H)^+$], 439.0088; found, 439.0090.

2-Bromo-12-(4-chlorobenzoyl)-9,10-dihydro-6*H*-chromeno [4,3-*d*]imidazo[1,2-*a*]pyridin-6-one (4h). Orange solid; mp 302–305 °C; IR (KBr): 1714, 1669, 1622, 1523, 1458, 1331, 1272, 1213, 1094, 963, 653 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 3.79–3.81 (m, 2H, CH_2), 4.20–4.22 (m, 2H, CH_2), 7.23 (d, J = 8.80 Hz, 1H, ArH), 7.35–7.36 (m, 1H, ArH), 7.54–7.56 (m, 1H, ArH), 7.63–7.66 (m, 3H, ArH), 8.05 (d, J = 8.40 Hz, 1H, ArH), 8.71 (s, 1H, CH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 49.2, 53.5, 98.4, 115.8, 116.0, 120.9, 128.5, 129.0, 130.1, 130.1, 130.4, 131.3, 131.3, 134.3, 135.3, 140.2, 146.4, 151.7, 154.8, 158.8, 194.6; HRMS (TOF ES^+): m/z calcd for $C_{21}H_{12}BrClN_2O_3$ [$(M + H)^+$], 454.9793; found, 454.9795.

12-Benzoyl-2-bromo-9,10-dihydro-6*H*-chromeno[4,3-*d*]imidazo[1,2-*a*]pyridin-6-one (4i). Orange solid; mp 302.5–305 °C; IR (KBr): 1719, 1667, 1618, 1521, 1450, 1326, 1269, 1217, 1109, 963, 751 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 3.79–3.81 (m, 2H, CH_2), 4.19–4.21 (m, 2H, CH_2), 7.19–7.20 (m, 1H, ArH), 7.42 (s, 1H, ArH), 7.57–7.59 (m, 3H, ArH), 7.71–7.73 (m, 1H, ArH), 8.03–8.04 (m, 2H, ArH), 8.67 (s, 1H, CH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 49.2, 53.6, 98.2, 116.0, 116.6, 117.7, 120.8, 129.2, 129.4, 129.4, 129.8, 129.8, 133.4, 135.2, 135.2, 135.6, 146.3, 151.7, 154.8, 158.9, 195.6; HRMS (TOF ES^+): m/z calcd for $C_{21}H_{13}BrN_2O_3$ [$(M + H)^+$], 421.0182; found, 421.0186.

2-Bromo-12-(4-methylbenzoyl)-9,10-dihydro-6*H*-chromeno [4,3-*d*]imidazo[1,2-*a*]pyridin-6-one (4j). Orange solid; mp 308–311 °C; IR (KBr): 1719, 1663, 1618, 1515, 1475, 1417, 1335, 1271, 1216, 1111, 967 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 2.40 (s, 3H, CH_3), 3.78–3.80 (m, 2H, CH_2), 4.18–4.22 (m, 2H, CH_2), 7.21 (d, J = 8.75 Hz, 1H, ArH), 7.38 (d, J = 7.60 Hz, 2H, ArH), 7.43 (s, 1H, ArH), 7.62 (d, J = 8.70 Hz, 1H, ArH), 7.92 (d, J = 7.45 Hz, 2H, ArH), 8.68 (s, 1H, CH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.7, 49.2, 53.5, 98.1, 116.0, 116.9, 117.7, 120.8, 129.2, 129.5, 129.5, 130.4, 130.4, 133.1, 133.2, 135.1, 146.0, 146.2, 151.6, 154.8, 158.9, 195.1; HRMS (TOF ES^+): m/z calcd for $C_{22}H_{15}BrN_2O_3$ [$(M + H)^+$], 435.0339; found, 435.0335.

2-Bromo-12-(4-methoxybenzoyl)-9,10-dihydro-6*H*-chrom-eno-[4,3-*d*]imidazo[1,2-*a*]pyridin-6-one (4k). Orange solid; mp 295–298 °C; IR (KBr): 1719, 1659, 1618, 1514, 1460, 1405, 1325, 1267, 1219, 1155, 1129, 1033, 955, 829 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 3.81–3.83 (m, 2H, CH_2), 3.85 (s, 3H, OCH_3), 4.19–4.21 (m, 2H, CH_2), 7.08 (d, J = 7.65 Hz, 2H, ArH), 7.18 (d, J = 8.40 Hz, 1H, ArH), 7.48 (s, 1H, ArH), 7.59 (d, J = 8.00 Hz, 1H, ArH), 8.00 (d, J = 7.60 Hz, 2H, ArH), 8.66 (s, 1H, CH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 49.2, 53.6, 56.1, 98.1, 115.1, 115.1, 116.0, 117.1, 117.8, 120.7, 128.7, 129.3, 131.9, 131.9, 132.9, 135.0, 146.0, 151.6, 154.9, 158.9, 164.8, 193.7; HRMS (TOF ES^+): m/z calcd for $C_{22}H_{15}BrN_2O_4$ [$(M + H)^+$], 451.0288; found, 451.0285.

10,11-Dihydro-13-(4-fluorobenzoyl)-12-azachromeno[4,3-*b*]-quinolizin-6(9*H*)-one (4l). Yellow solid; mp 284–287 °C; IR (KBr): 3422, 1720, 1677, 1617, 1550, 1485, 1301, 1232, 1149, 1099, 751 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 1.81–1.83 (m, 2H, CH_2), 3.23 (m, 2H, CH_2), 4.08–4.10 (m, 2H, CH_2), 6.96–6.97 (m, 1H, ArH), 7.17 (d, J = 7.70 Hz, 1H, ArH), 7.26–7.28 (m, 3H, ArH), 7.37–7.38 (m, 1H, ArH), 8.04–8.06 (m, 2H, ArH), 8.35 (s, 1H, CH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 19.8, 44.4, 50.5, 98.4, 115.5, 116.6, 116.5, 118.4, 123.4, 124.5, 126.8, 130.7, 132.0, 132.0, 132.2, 133.2, 147.8, 148.3, 152.3, 159.5, 164.8–166.8(d, J = 251.30 Hz), 195.3; HRMS (TOF ES^+): m/z calcd for $C_{22}H_{15}FN_2O_3$ [$(M + H)^+$], 375.1139; found, 375.1147.

10,11-Dihydro-13-(4-chlorobenzoyl)-12-azachromeno[4,3-*b*]-quinolizin-6(9*H*)-one (4m). Yellow solid; mp 293–296 °C; IR (KBr): 3419, 1720, 1677, 1617, 1535, 1450, 1303, 1229, 1155, 1097, 747 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 1.81–1.83 (m, 2H, CH_2), 3.25–3.27 (m, 2H, CH_2), 4.08–4.10 (m, 2H, CH_2), 7.00–7.02 (m, 1H, ArH), 7.22 (d, J = 7.20 Hz, 1H, ArH), 7.26–7.27 (d, J = 7.00 Hz, 1H, ArH), 7.42–7.44 (m, 1H, ArH), 7.58 (d, J = 6.80 Hz, 2H, ArH), 8.00 (d, J = 6.75 Hz, 2H, ArH), 8.35 (s, 1H, CH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 19.8, 44.4, 50.5, 98.3, 115.5, 118.6, 123.1, 124.7, 126.7, 129.7, 129.7, 130.8, 130.8, 130.8, 132.4, 135.3, 139.2, 147.8, 148.4, 152.3, 159.5, 195.8; HRMS (TOF ES^+): m/z calcd for $C_{22}H_{15}ClN_2O_3$ [$(M + H)^+$], 391.0844; found, 391.0847.

10,11-Dihydro-13-benzoyl-12-azachromeno[4,3-*b*]quinoliz-in-6(9*H*)-one (4n). Yellow solid; mp 261–264 °C; IR (KBr): 3436, 1695, 1593, 1501, 1374, 1279, 1184, 1052, 743 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 1.78–1.79 (m, 2H, CH_2), 3.27–3.29 (m, 1H, CH_2), 4.07–4.13 (m, 3H, CH_2), 6.95–6.97 (m, 1H, ArH), 7.19–7.20 (d, J = 8.25 Hz, 1H, ArH), 7.28 (d, J = 8.05 Hz, 1H, ArH), 7.38–7.40 (m, 1H, ArH), 7.49–7.52 (m, 2H, ArH), 7.62–7.64 (m, 1H, ArH), 7.98 (d, J = 7.65 Hz, 2H, ArH), 8.35 (s, 1H, CH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 19.8, 44.4, 50.4, 98.2, 115.6, 118.5, 123.7, 124.6, 126.8, 129.2, 129.2, 129.6, 129.6, 130.5, 132.3, 134.3, 136.5, 147.8, 148.3, 152.2, 159.6, 196.9; HRMS (TOF ES^+): m/z calcd for $C_{22}H_{16}N_2O_3$ [$(M + H)^+$], 357.1234; found, 357.1243.

10,11-Dihydro-13-(4-methylbenzoyl)-12-azachromeno[4,3-*b*]-quinolizin-6(9*H*)-one (4o). Yellow solid; mp 279–282 °C; IR (KBr): 1720, 1677, 1535, 1450, 1303, 1229, 1155, 1097, 747 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): $\delta = 1.82$–1.84 (m, 2H, CH_2), 2.37 (s, 3H, CH_3), 3.32–3.34 (m, 1H, CH_2), 4.08–4.10 (m, 3H, CH_2), 6.92–6.95 (m, 1H, ArH), 7.17 (d, $J = 8.20$ Hz, 1H, ArH), 7.28–7.33 (m, 3H, ArH), 7.36–7.39 (m, 1H, ArH), 7.87 (d, $J = 7.95$ Hz, 2H, ArH), 8.32 (s, 1H, CH); ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 19.8$, 21.6, 44.4, 50.5, 98.3, 115.6, 118.4, 124.0, 124.4, 127.0, 129.1, 129.1, 130.0, 130.0, 130.3, 132.1, 134.1, 144.7, 147.8, 148.1, 152.2, 159.6, 196.3; HRMS (TOF ES$^+$): m/z calcd for $C_{23}H_{18}N_2O_3$ [$(M + H)^+$], 371.1390; found, 371.1389.

10,11-Dihydro-13-(4-methoxybenzoyl)-12-azachromeno[4,3-*b*]quinolizin-6(9*H*)-one (4p). Yellow solid; mp 259–262 °C; IR (KBr): 1723, 1663, 1613, 1455, 1312, 1243, 1157, 1098, 1029, 747 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): $\delta = 1.79$–1.80 (m, 2H, CH_2), 3.19–3.22 (m, 2H, CH_2), 3.82 (s, 3H, OCH_3), 4.07–4.09 (m, 2H, CH_2), 6.96–7.03 (m, 3H, ArH), 7.20 (d, $J = 8.10$ Hz, 1H, ArH), 7.35 (d, $J = 8.20$ Hz, 1H, ArH), 7.38–7.41 (m, 1H, ArH), 7.94 (d, $J = 8.30$ Hz, 1H, ArH), 8.34 (s, 1H, CH); ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 19.8$, 44.4, 50.5, 55.9, 98.1, 114.8, 114.8, 115.7, 118.5, 124.1, 124.6, 129.6, 129.6, 130.0, 131.4, 131.4, 132.2, 147.7, 148.2, 152.2, 159.6, 164.1, 195.2; HRMS (TOF ES$^+$): m/z calcd for $C_{23}H_{18}N_2O_4$ [$(M + H)^+$], 387.1339; found, 387.1340.

10,11-Dihydro-2-bromo-13-(4-chlorobenzoyl)-12-azachro-meno-[4,3-*b*]quinolizin-6(9*H*)-one (4q). Yellow solid; mp 305–308 °C; IR (KBr): 1711, 1677, 1616, 1450, 1303, 1198, 1149, 1119, 1004, 820 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): $\delta = 1.80$–1.82 (m, 2H, CH_2), 3.21–3.23 (m, 2H, CH_2), 4.08–4.10 (m, 2H, CH_2), 7.21 (d, $J = 8.20$ Hz, 1H, ArH), 7.35 (s, 1H, ArH), 7.61–7.63 (m, 3H, ArH), 8.02 (d, $J = 7.05$ Hz, 2H, ArH), 8.37 (s, 1H, CH); ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 19.7$, 44.4, 50.5, 97.8, 116.1, 117.5, 120.9, 123.7, 128.9, 129.6, 129.9, 129.9, 130.8, 130.8, 134.8, 135.0, 139.5, 147.7, 148.7, 151.5, 159.1, 195.7; HRMS (TOF ES$^+$): m/z calcd for $C_{22}H_{14}BrClN_2O_3$ [$(M + H)^+$], 468.9949; found, 468.9950.

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