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New synthetic strategy for Friedlander condensation of 4-amino-2-oxo-2*H*-chromene-3-carbaldehyde by heterogeneous catalysis

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Abstract

Chromenopyridines are an important class of compound because of their diverse biological activities. In the present work, we have developed convenient route for the synthesis of chromeno[4,3-*b*] pyridine derivatives (**3a–e**, **5a–e**, and **7a–d**) by Friedlander condensation of 4-amino-2-oxo-2*H*-chromene-3-carbaldehyde with various active methylene compounds. We have used mixed metal oxide catalyst such as nanomaterial Zinc titanate. The reaction was carried out for various solvent systems, also we have altered the concentration of the catalyst. The 2-propanol/water solvent system and 5 mol% catalyst concentration are best as far as yield and rate of reaction are concerned. The structures of the synthesized compounds were confirmed by ^{1}H NMR, ^{13}C NMR, mass spectra, and elemental analysis.

1 | INTRODUCTION

Construction of ring structure toward annulation of various heterocycles from *ortho*-amino aldehyde entity is quite fascinating owing to the two different ways of ring formations namely linear and angular. This construction way predominates direct and regiospecific introduction of functional groups and/or substituents in the newly formed heterocyclic ring. Among several possibilities for ortho joined functionalities those containing carbon and nitrogen are of meticulous interest, because of the numerous combinations of their different oxidation states. They permit easy accessibility of simple derivatives, provide them with exceptional versatility in heterocyclic annulations. From the literature, it was noted that *o*-amino benzaldehyde, the first and best-known member of this class of compounds have been utilized for the synthesis of various heterocycles such as pyridine derivatives [1], quinoline compounds [2], benzo pyrano/thiopyrano quinoline derivatives [3,4], thieno-quinolines [5], pyrollo-quinolines [6], indozolino quinolines [7], anthrazolines [8], naphtyridine derivatives [9,10], and so forth. An annulation reaction of heterocyclic amino aldehyde provides a synthetic entry into heterocyclic systems fused to chromene [11], pyridine [12–15], pyrazole [16–19], and quinoline nucleus [20,21]. Furthermore, Friedlander condensation has the most familiar way toward the synthesis of substituted pyridines. These literature reports and our ongoing research [22–24] prompted us for the synthesis of substituted chromeno[4,3-*b*] pyridine and their annulated heterocycles from 4-amino-2-oxo-2*H*-chromene-3-carbaldehyde. *o*-Amino aldehydes have a key scaffold for the Friedlander condensation reactions. This reaction forms a stable six-membered heterocyclic ring structure, which is capable of a synthetic entry in heterocyclic systems fused to a various heterocycle such as pyrazole, pyridine, or pyrimidine nucleus [25]. The annulation of pyridine ring on suitably functionalized heterocyclic nucleus involves the [4+2] cyclo-condensation reaction.

There were various reaction conditions for Friedlander condensation reported such as microwave assisted and HCl catalyzed [26], sulfamic acid [27],

$HClO_4$–SiO_2 [28], microwave irradiated and clay catalyzed [29], $ZnCl_2$–$SnCl_2$ [30], ionic liquid mediated and $FeCl_3$ catalyzed [31], Silver phosphor-tungstate [32], $NaHSO_4$–SiO_2 [33], NH_4OAc [34], Amberlyst-15 [35], NaOEt [36], and so forth, are well exemplified.

Furthermore, Friedlander condensation has the most familiar way toward the synthesis of substituted pyridines. The functionalized chromenopyridines and their analogs are present in numerous heterocycles with the wide spectrum of biological activities stated as follows in Figure 1. Diaryl substituted chromeno[4,3-*b*] pyridine derivative Compound **I** showed good antimicrobial potency compared with the standard antibiotics against various pathogenic microorganisms [37]. Compound **II** exhibited good anti-inflammatory and analgesic activity with low toxicity [38]. Compound **III** was reported as selective D_4 receptor antagonists and employed as novel antipsychotic drug [39]. A linear chromenopyridine derivative **IV** displays promising non-steroidal anti-inflammatory effects [40].

In literature, various methods are reported for Friedlander condensation using nanoparticles such as calcium silicate [41], nickel nanocomposite [42,43], while zinc titanate was used for one-pot three-component synthesis [44]. Metal oxides are extensively employed in the field of heterogeneous catalysis because they provide large surface area and active sites to adsorb the substrate. These active sites provide a scope for the substrate to interact. Therefore, in present communication, we have employed the mixed metal oxides such as zinc titanate ($ZnTiO_3$) in this context of reaction.

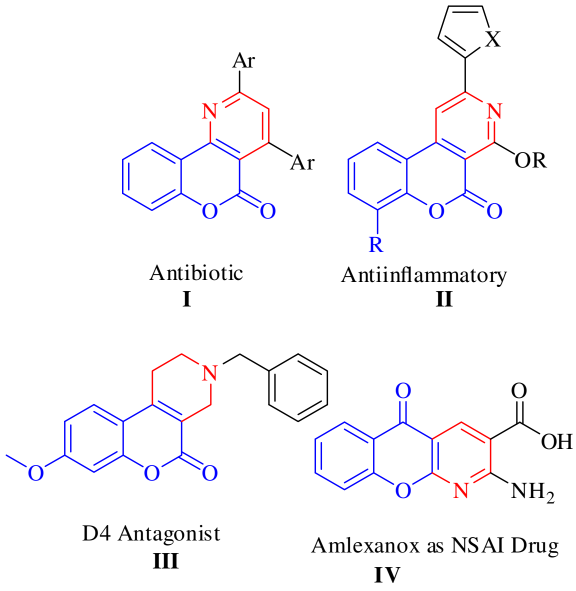

Antibiotic
I
Antiinflammatory
II
D4 Antagonist
III
Amlexanox as NSAI Drug
IV

FIGURE 1 Some biologically active chromenopyridine derivatives/drug

2 | RESULTS AND DISCUSSION

The present work focused on development of new, cost-effective, efficient, and eco-friendly approach for the synthesis of biologically active chromeno[4,3-*b*] pyridine derivatives. In continuation of our quest in organic synthesis of chromeno[4,3-*b*] pyridines by different methods we report, an easy and rapid catalytic application of zinc titanate nanoparticles.

$ZnTiO_3$ phase has been confirmed by the comparison with standard JCPDS data card No. 26-1500. The value of 2θ at 23.9, 32.7, 35.3, 40.4, and 48.9 correspond to the plane (012), (104), (110), (113), and (024). The average particle size was calculated using Scherrer formula and found to be 127 nm. The scanning electron microscopy (SEM) of the synthesized nanocrystalline zinc titanate ($ZnTiO_3$) powders prepared at 1000°C for 12 h using mechanochemical method. The powder obtained contains a large portion of agglomerates with a small particulate size. Since the agglomeration was sufficiently small and soft. It could be clearly observed that the agglomerates actually formed very small particles in nanometric range size.

Effect of dwell time on the morphology of the calcined powder was found to be quite significant. It is clearly seen that longer heat treatment led to larger particles and hard agglomeration. The particle size found to be below 100 nm for $ZnTiO_3$ samples and the agglomerates are of irregular in shape. The SEM image shows nanoparticles with good uniformity and crystallinity.

To obtain the optimal reaction conditions and stoichiometry, several experiments were conducted for representative compounds, namely, 4-amino-2-oxo-2*H*-chromene-3-carbaldehyde (1 mmol) (**1**) and acetophenone (**2a**) (1.1 mmol), 4-amino-2-oxo-2*H*-chromene-3-carbaldehyde (1 mmol) (**1**) and ethyl-methyl ketone (**4a**) (1.1 mmol), 4-amino-2-oxo-2*H*-chromene-3-carbaldehyde (1 mmol) (**1**) and 4-chloro-benzoylacetonitrile (**6a**) (1.1 mmol) by using catalyst zinc titanate ($ZnTiO_3$) (2 mol%), with different solvent conditions, the results are summarized in Table 1.

For the preliminary investigation of Friedlander condensation of 4-amino-2-oxo-2*H*-chromene-3-carbaldehyde (**1**) we have used various solvent system such as water, water/ethanol (1:1), and water/2-propanol (1:1). From the various experiments conducted concerning the solvent effect it is concluded that the solvent system containing water/2-propanol (1:1) found to be best. As in the water/2-propanol solvent mixture we got maximum yield (Table 1).

Based on these results, we have employed this optimized condition for all compounds of the series. During the course of reactions, however, we have used the catalyst 2 mol% zinc titanate, we found that the reaction is not effectively catalyzed to get a desired product. The reaction took longer time for the completion (4–6 h). Hence, we tried the reaction using 5 mol% catalyst for the reaction series and surprisingly we got good results in terms of yield and it requires shorter reaction time (2.25–3.5 h) than the previous one (Table 2).

Thus, Friedlander condensation of 4-amino-2-oxo-2*H*-chromene-3-carbaldehyde **1** with acetophenone **2a** in 2-propanol/water and zinc titanate nanoparticles (5 mol %) under reflux condition for 3.1 h furnish colorless solid in 78% yield (Scheme 1). The obtained solid was characterized by spectral and analytical methods. For instance, the ^{1}H NMR spectrum (DMSO-d_6) of the solid showed doublet at δ 8.20 (J = 8.1 Hz) for the proton present on C_4 carbon, doublet appeared at δ 7.92 (J = 7.8 Hz) corresponding to proton on C_3 position of pyridine ring due to ortho coupling. The proton appeared at δ 7.43 as a doublet (J = 8.0 Hz) due to proton at C_4 position of phenyl ring, also protons C_3 and C_5 position of pyridine ring shows doublet at δ 7.55 (J = 8.2 and 8.0 Hz) in addition, proton at C_2 and C_6 appeared as doublet at δ 8.35 (J = 8.2 Hz), while all other protons appeared in their respective region. In ^{13}C NMR spectrum (DMSO-d_6) of this solid, all aromatic carbons appeared at their respective chemical shift positions between 118 and 162. Further, the mass spectrum of this solid showed the characteristic (M^+) peak at m/z 273. The elemental analysis was in close agreement with the molecular formula $C_{18}H_{11}NO_2$. On the basis of above spectral and analytical data structure **3a** was assigned to this solid, that is, 2-phenyl-5*H*-chromeno[4,3-*b*]pyridin-5-one.

Analogously, the derivatives **3b–e** were synthesized and structures were confirmed by spectral and analytical data (Scheme 1).

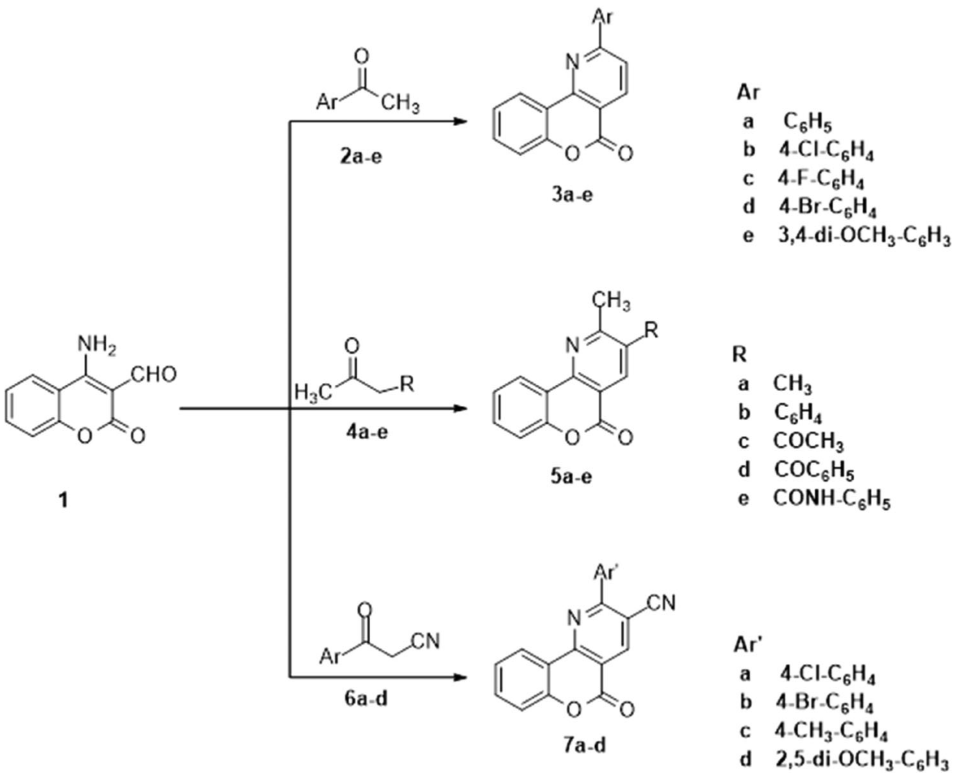
The Friedlander condensation of *o*-aminoaldehyde **1** with ketone/diketones **4a–e** yielded chromene fused pyridine annulated 2-aryl substituted heterocycles **5a–e**. In order to synthesize diverse compounds with the substrate, we have to come across the condensation with another type of condensation partner, that is, symmetric/unsymmetric carbonyl derivatives, diketones, dicarbonyl compounds, and so forth. Thus, the condensation of *o*-aminoaldehyde **1** with 2-butanone **4a** in 2-propanol/water and catalytic amount of zinc titanate (5 mol%) under reflux condition for 2.75 h yielded colorless solid in 76% yield (Scheme 1). The obtained solid was

TABLE 1 Optimization of reaction conditions for the synthesis

Entry	Catalyst	Solvent	% Yield
3a	$ZnTiO_3$	H_2O	0
		H_2O:EtOH	22
		H_2O:2-PrOH	73
5a	$ZnTiO_3$	H_2O	0
		H_2O:EtOH	32
		H_2O:2-PrOH	72
7a	$ZnTiO_3$	H_2O	0
		H_2O:EtOH	25
		H_2O:2-PrOH	68

TABLE 2 Comparative *i*-PrOH and water mediated synthesis of compounds (**3a–e**, **5a–e**, and **7a–d**) using varied catalyst concentration

		Catalyst (2 mol%)		Catalyst (5 mol%)	
Entry	Product	Time (h)	% Yield	Time (h)	% Yield
1	**3a**	5.5	73	3.1	78
2	**3b**	4.75	71	2.25	75
3	**3c**	5.25	65	2.5	71
4	**3d**	6.0	77	3.5	80
5	**3e**	5.5	78	3.25	85
6	**5a**	4.25	72	2.75	76
7	**5b**	4.75	69	2.5	74
8	**5c**	5.5	78	3.0	80
9	**5d**	5.0	69	2.5	76
10	**5e**	4.25	61	2.5	68
11	**7a**	5.25	68	3.25	75
12	**7b**	4.75	73	3.5	79
13	**7c**	4.1	64	3.2	68
14	**7d**	4.0	58	3.1	65



SCHEME 1 Synthetic pathway for the synthesis of substituted chromeno[4,3-*b*] pyridine derivatives, **3a–e**, **5a–e**, and **7a–d** Friedlander condensation by using $ZnTiO_3$ (5 mol%) nanomaterial in iPr-OH/water solvent when heated for 2.25–3.25 h

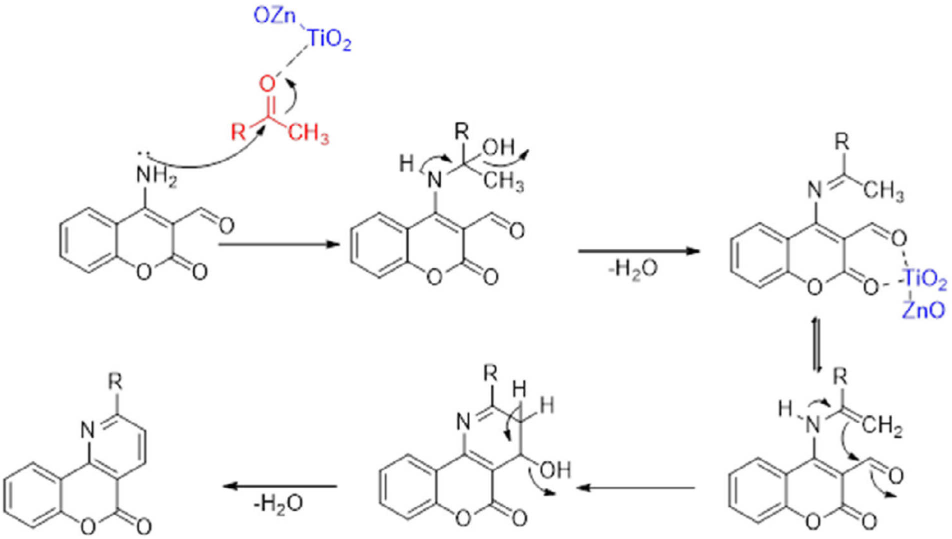
characterized by its IR, ^{1}H NMR, ^{13}C NMR, Mass Spectroscopy, and elemental analysis. For instance, ^{1}H NMR spectrum (DMSO-d_6) of the solid showed two singlets at δ 2.85 and 3.07 for six protons of two methyl groups. The proton appeared as a singlet at δ 8.95 corresponded to the proton present on the C_4 carbon with respect to pyridine ring. In ^{13}C NMR spectrum (DMSO-d_6) of this solid the signals at δ 22.3 and 26.6 corresponded to carbons of two methyl groups, while all other carbons appeared at their respective chemical shift positions between δ 115.9 and 167.2. Further, the mass spectrum of this solid showed the characteristic (M^{+}) peak at m/z 225.

On the basis of above spectral and analytical data structure **5a** was assigned to this solid, that is, 2,3-dimethyl-5*H*-chromeno[4,3-*b*]pyridin-5-one. Similarly, other derivatives **5b–e** were synthesized and structures were confirmed by spectral and analytical data. The hetero annulated ring systems are accessible from *o*-aminoaldehydes either via stepwise incorporation of the carbon and nitrogen fragments needed for completion of the pyridine moiety or by their combined introduction in one reaction step. Herein, we planned to introduce nitrile functionality into the chromenopyridines using *o*-aminoaldehyde **1** and aroylacetonitriles **6a–d**.

Thus, 4-amino-2-oxo-2*H*-chromene-3-carbaldehyde **1** when reacted with 3-oxo-3-(*p*-tolyl)propanenitrile **6c** in 2-propanol/water and catalytic amount of zinc titanate under reflux for 3.25 h afforded crystalline solid in 75% yield. The obtained solid was characterized by its IR, ^{1}H NMR, ^{13}C NMR, Mass Spectroscopy, and elemental analysis. The IR spectrum of the solid showed characteristic absorption band at 2226 cm^{-1} corresponding to —CN stretching. In ^{1}H NMR ($CDCl_3$) of this solid the two doublets (J = 7.8 Hz) at δ 8.11 and 7.43 corresponded to ortho coupled protons of pyridine annulated aromatic ring. The singlet at δ 9.09 for one proton present on C_4 with respect to pyridine nitrogen, other singlet appeared at δ 2.37 for methyl protons of 4-methyl phenyl ring. The enduring protons are appeared in their respective aromatic region. The ^{13}C NMR spectrum (DMSO-d_6) of the solid showed signal at δ 24.5 corresponded to methyl carbon of on aromatic ring, the signal at δ 118.4 corresponded to nitrile carbon, while all other aromatic carbons appeared at their respective On the basis of above spectral and analytical data structure, **7c** was assigned to this solid, that is, 5-oxo-2-(*p*-tolyl) 5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile. Analogously compounds **7a**,**b** and **7d** were synthesized and characterized by spectral and analytical data.

2.1 | Probable mechanism

In the Friedlander condensation reaction the amino group having tendency to attack on an electrophile. So electrophile must be activated. We have employed here the mixed metal oxides $ZnTiO_3$. Titanium may pull the electron cloud, which facilitates attack of amine over carbonyl easily and there is formation of imine derivative. The imine adduct contains two carbonyls, Titanium activate the aldehyde group and ring cyclization takes place leading to the target compound.



3 | CONCLUSION

In the present communication, we have reported the Friedlander condensation of *o*-aminoaldehyde **1** with various acetophenones gave 2-aryl-5*H*-chromeno[4,3-*b*]pyridin-5-one derivatives **3a–e**. Analogous reactions with CH-acidic compounds such as butan-2-one **4a**, 1-phenylpropan-2-one **4b**, pentane-2,4-dione **4c**, 1-phenylbutane-1,3-dione **4d**, and 3-oxo-*N*-phenylbutanamide **4e** permitted the synthesis of stable and diverse heterocyclic compounds.

The condensations of **1** with aroylacetonitrile **6a–e** introduce nitrile functionality at C_3 position of the chromenopyridines. It was observed that the 2/2,3-substituted chromenopyridine derivatives were synthesized by convenient, scalable, and eco-friendly route with usual procedures. The Friedlander condensation reaction was carried out by environmentally benign nanomaterial zinc titanate, which lowered the reaction time and improves the yield of the reaction. All the synthesized compounds are well characterized by spectral and analytical methods.

4 | EXPERIMENTAL SECTION

4.1 | Materials and method

The powder X-ray diffraction (PXRD) data were recorded using X-ray diffractometer (XRD), Rikagu-DMAX-250 with CuKα radiation, having $\lambda = 1.5406$ Å. Scanning Electron Microscope-JED-2300LA coupled with an Energy Dispersive Spectrometer-JED-23000La was used to check the surface morphology. All reagents are analytical grade and were used directly. All reactions were monitored by thin layer chromatography (TLC) on 25 mm silica gel 60 F254 plates (Merck, Darmstardt, Germany) using UV light (254 and 366 nm) for detection. Melting points were recorded on Gallencamp apparatus and are uncorrected. IR spectra were recorded in potassium bromide pellets using a Shimadzu IR 8400S spectrophotometer. The ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured on a Varian NMR Mercury 300 spectrometer using TMS as internal standard. Mass spectra were recorded on an Agilent UHD 6540 LC-Q-TOF mass spectrometer.

4.2 | Synthesis of zinc titanate

The synthesis of zinc titanate nanomaterial was executed by mechanochemical method. For the synthesis of $ZnTiO_3$, equimolar amount of ZnO and TiO_2 were taken. The mixture was subjected to stepwise calcination by heating until the terminal temperature in muffle furnace at the rate 10°C/min from room temperature to subsequent temperature for 12 h. After heating at higher temperature, the material was cooled and grinded with a gap of 2 h by using mortar and pestle. The grinded material was further heated at 1000°C for 20 h. The obtained powder was used for further characterization.

4.3 | General procedure for the synthesis of 4-amino-2-oxo-2*H*-chromene-3-carbaldehyde, 1 [22]

To a solution of 4-amino-2-oxo-2*H*-chromene (0.161 g, 1 mmol) in *N,N*-Dimethylformamide (DMF) (2 mL), the Vilsmeier adduct prepared from *N,N*-Dimethylformamide (1.2 mmol) and $POCl_3$ (50 mmol) was added at 0°C. The mixture was stirred at 0–25°C for 8 h (TLC, chloroform: ethanol, 9:1) and then poured over crushed ice. The yellowish solid was collected, washed, dried, and crystallized from ethanol/water (8:2):

Yield 84%, Yellowish solid, mp 183–185°C; IR spectrum, υ, cm^{-1}: 3342, 3259 (NH), 2748 (C—H aldehyde), 1745 (C═O), 1708 (C═O), 1540 (C═C). ^1H NMR (300 MHz, DMSO-d_6 δ ppm): 7.09–7.38 (m, 2H, Ar–H), 7.58–7.71 (m, 1H, Ar–H), 8.25 (dd, J = 8.1, 1.3 Hz, 1H), 9.30 (bs, 1H, —NH), 9.94 (s, 1H, CHO), 10.27 (bs, 1H, —NH). ^{13}C NMR (75 MHz, DMSO-d_6, δ ppm): 94.9, 113.3, 117.3, 124.1, 124.6, 134.8, 153.8, 157.9, 161.9, 191.5; MS: m/z 190 (M + H). Found, %: C, 63.32; H, 3.65; N, 7.23. $C_{10}H_7NO_3$. Calcd, %: C, 63.49; H, 3.73; N, 7.40. M 190.08.

4.4 | General procedure for the synthesis of 2-aryl-5*H*-chromeno[4,3-*b*] pyridin-5-one, 3a–e

A mixture of **1** (0.189 g, 1.0 mmol) and **2a–e** (1.1 mmol) in 2-propanol/water with 5 mol% of zinc titanate was heated under reflux for 2.25–3.25 h and the reaction progress was monitored by TLC (chloroform/methanol 9:1). After completion of the reaction, solvent removed *in vacuo* and the residue treated with methanol, filtered, dried under high vacuum, and recrystallized from ethanol/DMF (9: 1) to furnish compounds **3a–e** in 71%–85% yield.

4.4.1 | 2-Phenyl-5*H*-chromeno[4,3-*b*]pyridin-5-one (**3a**)

Yield: 78%, Colorless solid, mp 287–289°C. IR spectrum, υ, cm^{-1}: 1744 (C═O, ester), 1661, 1620, 1567 (C═Carom). ^1H NMR (300 MHz, DMSO-d_6, δ ppm): 7.40 (dd, J = 7.8, 8.0 Hz, 1H, Ar-H), 7.45 (d, J = 7.9 Hz, 1H, Ar-H), 7.52 (dd, J = 7.9, 8.0 Hz, 1H, Ar-H), 7.55 (m, 3H, Ar-H), 7.92 (d, J = 8.2 Hz, 1H, Ar-H), 8.21 (d, J = 8.2 Hz, 1H, Ar-H), 8.35 (m, 2H, Ar-H), 8.47 (d, J = 7.8 Hz, 1H, Ar-H). ^{13}C NMR (75 MHz, DMSO-d_6, δ (ppm): 113.5, 120.8, 124.1, 124.8, 127.1, 127.7 (2 C′ s), 128.3 (2 C′ s), 128.5, 129.6, 131.4, 138.5, 140.4, 152.6, 159.2, 159.8, 162.1. Mass spectrum, m/z: 273 [M+, 100%]. Found, %: C, 79.19; H, 4.15; N, 4.97. $C_{18}H_{11}NO_2$. Calcd, %: C, 79.11; H, 4.06; N, 5.13. M 273.29.

4.4.2 | 2-(4-Chlorophenyl)-5*H*-chromeno [4,3-*b*] pyridin-5-one (**3b**)

Yield: 75%, Pale yellow solid, mp 259–261°C. IR spectrum, υ, cm^{-1}: 1738 (C═O, ester), 1665, 1634, 1540 (C═Carom). ^1H NMR (300 MHz, DMSO-d_6, δ ppm): 7.36 (dd, J = 8.0, 8.2 Hz, 1H, Ar-H), 7.47 (d, J = 8.5 Hz, 1H, Ar-H), 7.61 (dd, J = 8.0, 8.5 Hz, 1H, Ar-H), 7.44–7.54 (m, 3H, Ar-H), 7.89 (d, J = 7.9, 1H, Ar-H), 8.05 (m, 1H, Ar-H), 8.16 (d, J = 7.9 Hz, 1H, Ar-H), 8.47 (d, J = 8.2 Hz, 1H, Ar-H). ^{13}C NMR (75 MHz, DMSO-d_6, δ (ppm): 113.5, 120.8, 124.1, 124.8, 127.1, 127.7 (2 C′ s), 128.3 (2 C′ s), 128.5, 129.6, 131.4, 138.5, 140.4, 152.6, 159.2, 159.8, 162.5. Mass spectrum, m/z: 307 [M+, 64%], 309 [M + 2, 32%]. Found, %: C, 70.32; H, 3.13; N, 4.45. $C_{18}H_{10}ClNO_2$. Calcd, %: C, 70.25; H, 3.28; N, 4.55. M 307.04.

4.4.3 | 2-(4-Fluorophenyl)-5*H*-chromeno [4,3-*b*] pyridin-5-one (**3c**)

Yield: 71%, Colorless solid, mp 263–265°C. IR spectrum, υ, cm^{-1}: 1741 (C═O, ester), 1651, 1577, 1535 (C═Carom). ^1H NMR (300 MHz, DMSO-d_6, δ ppm): 7.29 (d, J = 8.0 Hz, 2H, Ar-H), 7.43 (dd, J = 7.8, 8.1 Hz, 1H, Ar-H), 7.48 (d, J = 7.9 Hz, 1H, Ar-H), 7.55 (d, J = 8.4 Hz, 1H, Ar-H), 7.92 (d, J = 8.2, 1H, Ar-H), 8.25 (d, J = 8.4 Hz, 1H, Ar-H), 8.52 (d, J = 7.8 Hz, 1H, Ar-H) 8.54 (d, J = 8.0 Hz, 2H, Ar-H). ^{13}C NMR (75 MHz, DMSO-d_6, δ ppm) 113.5, 120.8, 124.1, 124.8, 127.1, 127.7 (2 C′ s), 128.3 (2 C′ s), 128.5, 129.6, 131.4, 138.5, 140.4, 152.6, 159.2, 159.8, 162.7. Mass spectrum, m/z: 291 [M +, 100%]. Found, %: C, 74.35; H, 3.35; N, 4.69. $C_{18}H_{10}FNO_2$. Calcd, %: C, 74.22; H, 3.46; N, 4.81. M 291.28.

4.4.4 | 2-(4-Bromophenyl)-5*H*-chromeno [4,3-*b*] pyridin-5-one (**3d**)

Yield: 80%, Pale yellow solid, mp 244–246°C. IR spectrum, υ, cm^{-1}: 1748 (C═O, ester), 1655, 1580, 1547 (C═Carom). ^1H NMR (300 MHz, DMSO-d_6, δ ppm): 7.42 (dd, J = 8.0, 8.2 Hz, 1H, Ar-H), 7.46 (d, J = 7.8 Hz, 1H, Ar-H), 7.54 (dd, J = 7.9, 8.0 Hz, 1H, Ar-H), 7.62 (d, J = 8.5 Hz, 2H, Ar-H), 7.66 (d, J = 8.2 Hz, 1H, Ar-H), 7.91 (d, J = 8.2 Hz, 1H, Ar-H), 8.38 (d, J = 8.5 Hz, 2H, Ar-H), 8.49 (d, J = 8.2 Hz, 1H, Ar-H). Mass spectrum, m/z: 350 [M+, 67%], 352 [M + 2, 86%]. Found, %: C, 61.28; H, 2.95; N, 3.92. $C_{18}H_{10}BrNO_2$. Calcd, %: C, 61.39; H, 2.86; N, 3.98. M 350.99.

4.4.5 | 2-(3,4-Dimethoxyphenyl)-5*H*-chromeno[4,3-*b*] pyridine-5-one (**3e**)

Yield: 85%, Pale yellow solid, mp 282–284°C. IR spectrum, υ, cm^{-1}: 1741 (C═O, ester), 1645, 1629, 1533 (C═Carom). ^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 3.72 (s, 6H, -OCH$_3$), 7.03 (d, J = 7.8 Hz, 1H, Ar-H), 7.42 (dd, J = 7.5, 7.9 Hz, 1H, Ar-H), 7.48 (d, J = 8.1 Hz, 1H, Ar-H), 7.54 (dd, J = 8.1, 7.9 Hz, 1H, Ar-H), 7.56 (d, J = 7.8 Hz, 1H, Ar-H), 7.64 (d, J = 8.0 Hz, 1H, Ar-H), 7.68 (s, 1H, Ar-H), 7.86 (d, J = 8.0 Hz, 1H, Ar-H), 8.51 (d, J = 7.5 Hz, 1H, Ar-H). Mass spectrum, *m*/*z*: 333 [M+, 100%]; Found, %.: C, 72.21; H, 4.38; N, 4.11. $C_{20}H_{15}NO_4$. Calcd, %: C, 72.06; H, 4.54; N, 4.20. M 333.44.

4.5 | General procedure for the synthesis of 2-methyl-3-substituted-5*H*-chromeno [4,3-*b*] pyridin-5-one, 5a–e

A mixture of **1** (0.189 g, 1.0 mmol) and corresponding carbonyl compound **4a–e** (1.1 mmol) in 2-propanol/water with 5 mol% of zinc titanate was refluxed for 2.5-3 h, the reaction progress was monitored by using TLC (chloroform/methanol 7.5:2.5). After completion of the reaction, solvent was removed *in vacuo* and residue poured over ice-cold water, filtered, dried under high vacuum, and recrystallized from ethanol/DMF (8:2) to furnish **5a–e** in 68–80% yield.

4.5.1 | 2,3-Dimethyl-5*H*-chromeno[4,3-*b*] pyridin-5-one (**5a**)

Yield: 76%, Pale yellow solid, mp 261–263°C. IR spectrum, υ, cm^{-1}: 1738 (C═O, ester), 1661, 1633, 1545 (C═Carom). ^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 2.67 (s, 3H, ─CH$_3$), 2.94 (s, 3H, ─CH$_3$), 7.37 (dd, J = 8.2, 8.4 Hz, 1H, Ar-H), 7.45 (d, J = 8.0, 7.9 Hz, 1H), 7.55 (dd, J = 8.0, 8.2 Hz, 1H, Ar-H), 8.53 (d, J = 8.4 Hz, 1H, Ar-H), 8.94 (s, 1H, Ar-H). ^{13}C NMR (75 MHz, DMSO-d_6, δ ppm) 16.8, 20.6, 112.5, 123.4, 124.1, 127.9, 128.5, 129.6, 131.4, 135.6, 149.8, 159.3, 158.7, 162.2. Mass spectrum, *m*/*z*: 225 [M+, 100%]. Found, %: C, 74.46; H, 4.85; N, 6.31. $C_{14}H_{11}NO_2$. Calcd, %: C, 74.65; H, 4.92; N, 6.22. M 225.08.

4.5.2 | 2-Methyl-3-phenyl-5*H*-chromeno [4,3-*b*] pyridin-5-one (**5b**)

Yield: 74%, Pale yellow solid, mp 291–293°C. IR spectrum, υ, cm^{-1}: 1742 (C═O, ester), 1655, 1640, 1560 (C═Carom). ^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 3.11 (s, 3H, ─CH$_3$), 7.39–7.47 (m, 5H, Ar-H), 7.44 (dd, J = 8.2, 8.5 Hz, 1H, Ar-H), 7.49 (d, J = 7.8 Hz, 1H, Ar-H), 7.59 (dd, J = 7.8, 8.2 Hz, 1H, Ar-H) 8.53 (d, J = 8.5 Hz, 1H, Ar-H), 9.07 (s, 1H, Ar-H). ^{13}C NMR (75 MHz, DMSO-d_6, δ ppm): 19.5, 113.5, 123.1, 124.3, 126.8 (2 Cs), 128.7 (3 Cs), 129.2, 129.5, 129.9, 130.0, 131.1, 136.5, 149.7159.7, 162.1, 162.4. Mass spectrum, *m*/*z*: 287 [M+, 100%]. Found, %: C, 79.55; H, 4.52; N, 4.73. $C_{19}H_{13}NO_2$. Calcd, %: C, 79.43; H, 4.56; N, 4.88. M 287.09.

4.5.3 | 3-Acetyl-2-methyl-5*H*-chromeno [4,3-*b*] pyridine-5-one (**5c**)

Yield: 80%, Pale yellow solid, mp 269–271°C. IR spectrum, υ, cm^{-1}: 1745 (C═O, ester), 1675, 1645, 1553 (C═Carom). ^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 2.49 (s, 3H, ─CH$_3$), 3.07 (s, 3H, ─CH$_3$), 7.38 (dd, J = 8.2, 8.4 Hz, 1H, Ar-H), 7.52 (d, J = 7.5 Hz, 1H, Ar-H), 7.65 (dd, J = 8.0, 8.4 Hz, 1H, Ar-H), 8.45 (d, J = 8.2 Hz, 1H, Ar-H), 9.13 (s, 1H, Ar-H). Mass spectrum, *m*/*z*: 253 [M+, 100%]. Found, %: C, 71.25; H, 4.29; N, 5.39. $C_{15}H_{11}NO_3$. Calcd, %: C, 71.14; H, 4.38; N, 5.53. M 253.07.

4.5.4 | 3-Benzoyl-2-methyl-5*H*-chromeno [4,3-*b*] pyridine-5-one (**5d**)

Yield: 76%, Colorless solid, mp 288–290°C. IR spectrum, υ, cm^{-1}: 1739 (C═O, ester), 1712 (C═O, ketone), 1645, 1634, 1540 (C═Carom). ^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 2.91 (s, 3H, ─CH$_3$), 7.38 (dd, J = 8.5, 8.0 Hz, 1H, Ar-H), 7.45 (d, J = 7.8 Hz, 1H, Ar-H), 7.57 (dd, J = 7.8, 8.0 Hz, 1H, Ar-H), 7.61 (dd, J = 7.9, 8.2 Hz, 1H, Ar-H), 7.69 (d, J = 7.9 Hz, Ar-H), 7.86 (d, J = 8.2 Hz, 1H, Ar-H), 8.53 (d, J = 8.5 Hz, 1H, Ar-H), 9.07 (s, 1H, Ar-H). Mass spectrum, *m*/*z*: 315 [M+, 100%]; Found, %: C, 76.31; H, 4.03; N, 4.39. $C_{20}H_{13}NO_3$. Calcd, %: C, 76.18; H, 4.16; N, 4.44. M 315.09.

4.5.5 | Methyl-5-oxo-*N*-phenyl-5*H*-chromeno [4,3-*b*] pyridine-3-carboxamide (**5e**)

Yield: 68%, Pale yellow solid, mp 311–313°C. IR spectrum, υ, cm^{-1}: 1738 (C═O, ester), 1669, 1626, 1566, 1531 (C═Carom). ^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 3.06 (s, 3H, ─CH$_3$), 7.13 (d, J = 8.2 Hz, 1H, Ar-H), 7.35 (dd, J = 8.0, 8.2 Hz, 2H, Ar-H), 7.41 (dd, J = 7.5, 8.1 Hz, 1H, Ar-H), 7.47 (d, J = 7.9 Hz, 1H, Ar-H), 7.51 (d, J = 8.0 Hz, 2H, Ar-H), 7.58 (dd, J = 7.5, 7.9 Hz, 1H, Ar-H), 8.53 (d, J = 8.1 Hz, 1H, Ar-H), 9.11 (s, 1H, Ar-H), 11.31 (bs, 1H,

—NH). Mass spectrum, *m*/*z*: 330 [M+, 100%]. Found, %: C, 72.88; H, 4.14; N, 8.39. $C_{20}H_{14}N_2O_3$. Calcd, %: C, 72.72; H, 4.27; N, 8.48. M 330.10.

4.6 | General procedure for the synthesis of 2-aryl-5-oxo-5*H*-chromeno[4,3-*b*] pyridine-3-carbonitrile, 7a–d

A mixture of **1** (0.189 g, 1.0 mmol) and corresponding aroylacetonitrile **6a–d** (1.1 mmol) in 2-propanol/water with 5 mol% of zinc titanate was heated under reflux for 3.1–3.5 h and the reaction progress was monitored by TLC (chloroform/methanol 9:1). After completion of the reaction, solvent was removed *in vacuo* and the residue was treated with methanol, filtered, dried under high vacuum, and recrystallized from ethanol/DMF (8:2) to furnish compounds **7a–d** in 65%–79% yield.

4.6.1 | 2-(4-Chlorophenyl)-5-oxo-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (**7a**)

Yield: 75%, Pale brown solid, mp 244–246° C. IR spectrum, *υ*, cm^{-1}: 2235 (CN, nitrile), 1746 (C=O, ester), 1650, 1633, 1553 (C=Carom). ^1H NMR (300 MHz, DMSO-d_6, δ ppm): 7. 45 (dd, $J = 8.0, 8.2$ Hz, 1H, Ar-H), 7.53 (d, $J = 7.9$ Hz, 1H, Ar-H), 7.56 (dd, $J = 7.9, 8.0$ Hz, 1H, Ar-H), 7.62 (d, $J = 7.8$ Hz, 2H, Ar-H), 8.39 (d, $J = 7.8$ Hz, 2H, Ar-H), 8.59 (d, $J = 8.2$ Hz, 1H, Ar-H), 9.13 (s, 1H, Ar-H). ^{13}C NMR (75 MHz, DMSO-d_6, δ ppm): 104.3, 114.1, 117.9, 123.7, 124.5, 127.9 (2 Cs), 128.2 (2 Cs), 128.9, 129.6, 131.0, 133.2, 135.8, 143.5, 153.2, 159.1, 162.3, 169.2. Mass spectrum, *m*/*z*: 332 [M+, 62%], 334 [M + 2 40%]. Found, %: C, 68.65; H, 2.82; N, 8.33. $C_{19}H_9ClN_2O_2$. Calcd, %: C, 68.58; H, 2.73; N, 8.42. M 332.04.

4.6.2 | 2-(4-Bromophenyl)-5-oxo-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (**7b**)

Yield: 79%, Pale brown solid, mp 296–298°C. IR spectrum, *υ*, cm^{-1}: 2238 (CN, nitrile), 1746 (C=O, ester), 1644, 1631, 1551(C=Carom). ^1H NMR (300 MHz, DMSO-d_6, δ ppm): 7.40 (dd, $J = 7.9, 8.2$ Hz, 1H, Ar-H), 7.48 (d, $J = 8.1$ Hz, 1H, Ar-H), 7.59 (dd, $J = 7.9, 8.1$ Hz, 1H, Ar-H), 7.78 (d, $J = 8.0$ Hz, 2H, Ar-H), 8.21 (d, $J = 8.0$ Hz, 2H, Ar-H), 8.57 (d, $J = 8.2$ Hz, 1H, Ar-H), 9.09 (s, 1H, Ar-H). ^{13}C NMR (75 MHz, DMSO-d_6, δ (ppm): 105.1, 114.3, 117.5, 120.8, 123.9, 124.8, 127.3 (2 Cs), 128.5, 131.7, 132.5 (2 Cs), 133.2, 136.2, 142.5, 153.9, 159.4, 162.5, 168.7. Mass spectrum, *m*/*z*: 375 [M+, 53%] 377 [M + 2, 69%]. Found, %: C, 60.64; H, 2.51; N, 7.49. $C_{19}H_9BrN_2O_2$. Calcd, %: C, 60.50; H, 2.41; N, 7.43. M 375.98.

4.6.3 | 5-Oxo-2-*p*-tolyl-5*H*-chromeno[4,3-*b*] pyridine-3-carbonitrile (**7c**)

Yield: 68%, Colorless solid, mp 268–270°C. IR spectrum, *υ*, cm^{-1}: 2235 (CN, nitrile), 1741 (C=O, ester), 1653, 1625, 1565 (C=Carom). ^1H NMR (300 MHz, DMSO-d_6, δ ppm): 2.37 (s, 3H, —CH_3), 7.31 (d, $J = 7.5$ Hz, 2H, Ar-H), 7.39 (d, $J = 7.8, 8.2$ Hz, 1H, Ar-H), 7.44 (d, $J = 7.5$ Hz, 1H, Ar-H), 7.55 (dd, $J = 7.5, 8.2$ Hz, 1H, Ar-H), 8.06 (d, $J = 7.5$ Hz, 2H, Ar-H), 8.55 (d, $J = 7.8$ Hz, 1H, Ar-H), 9.07 (s, 1H, Ar-H). ^{13}C NMR (75 MHz, DMSO-d_6, δ ppm): 20.8, 104.7, 114.5, 117.9, 123.5, 124.0, 125.2 (2 Cs), 128.1 (2 Cs), 128.7, 129.8, 131.1, 131.7, 134.9, 141.7, 153.2, 159.3, 162.4, 168.5. Mass spectrum, *m*/*z*: 312 [M+, 100%]. Found, %: C, 77.06; H, 3.71; N, 8.88. $C_{20}H_{12}N_2O_2$. Calcd, %: C, 76.91; H, 3.87; N, 8.97. M 312.32.

4.6.4 | 2-(2,5-Dimethoxyphenyl)-5-oxo-5*H*-chromeno [4,3-*b*]pyridine-3-carbonitrile (**7d**)

Yield: 65%, Pale yellow solid, mp 282–284°C; IR spectrum, *υ*, cm^{-1}: 2235 (—CN, nitrile), 1744 (C=O, ester), 1645, 1638, 1550 (C=Carom). ^1H NMR (300 MHz, DMSO-d_6, δ ppm): 3.67 (s, 6H, 2×OCH_3), 7.03–7.32 (m, 3H, Ar-H), 7.41 (dd, $J = 8.0, 8.2$ Hz, 1H, Ar-H), 7.53 (d, $J = 7.5$ Hz, 1H, Ar-H), 7.56 (dd, $J = 7.5, 8.0$ Hz, 1H, Ar-H), 8.59 (d, $J = 8.2$ Hz, 1H, Ar-H), 9.11 (s, 1H, Ar-H). Mass spectrum, *m*/*z*: 358 [M+, 100%]. Found, %: C, 70.45; H, 3.84; N, 7.79. $C_{21}H_{14}N_2O_4$. Calcd: C, 70.39; H, 3.94; N, 7.82%. M 358.35.

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No data available for this research work

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