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$InCl_3$ mediated one-pot synthesis of indol-3-yl pyridine and 2,2′-bipyridine derivatives through multi-component reaction

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ABSTRACT

A simple protocol for the efficient preparation of 2-(1*H*-Indol-3-yl)-6-methoxy-4-aryl pyridine-3,5-dicarbonitrile and 6-methoxy-4-aryl-2,2′-bipyridine-5-carbonitrile derivatives has been achieved through one-pot multi-component reaction under reflux condition. Particularly valuable features of this method include high yields of products in short reaction time and broad substrate scope. It is an efficient and promising synthetic strategy to build indol-3-yl pyridine and 2,2′-bipyridine skeletons.

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1. Introduction

Multi-component reactions (MCRs) are powerful tools in modern medicinal chemistry, enabling straightforward access to large number of structurally related, drug-like compounds[1–3] and thereby facilitating lead generation of 'privileged medicinal scaffolds.'[4–6] Hence, combined with the use of combinatorial chemistry and high throughput parallel synthesis, such reactions have constituted an increasingly valuable approach to drug discovery efforts in recent years.[7]

The 3-substituted indole nucleus is prevalent in numerous natural products and is extremely important in medicinal chemistry.[8,9] It scaffolds are found in a number of biologically active compounds especially with anticancer, anti-tumour,[10] anti-inflammatory, hypoglycemic, analgesic and anti-pyretic activities.[11] Many indole alkaloids are recognized as one of the rapidly growing groups of marine invertebrate metabolites for their broad spectrum of biological properties.[12,13]

The pyridine substructure is one of the most important heterocycle found in natural products, pharmaceuticals, and functional materials.[14] Pyridine derivatives containing multi-functional groups such as streptonigrin, streptonigrone and lavendamycin are reported as anticancer drugs, and cerivastatin is reported as the HMG-CoA enzyme inhibitors.[15] Moreover, substituted pyridines are reported as leukotriene B-4 antagonists.[16,17]

Due to the vast medicinal utility of pyridine and 3-substituted indole derivatives various methods to prepare these compounds have been reported. Literature review reveals that all published approaches involve multi-step sequences, and their usefulness is limited by the lack of generality. However, methods for the synthesis of these important compounds often suffer from tedious synthetic routes, longer reaction time, drastic reaction conditions, as well as narrow application scope of substrates. In addition, to the best of our knowledge, there have been very few reports about the synthesis of indol-3-yl derivatives including pyridine moieties.[10,16,18–21] As part of our ongoing research on the development of novel synthetic routes for biologically active heterocyclic compounds and use of green chemistry techniques in organic synthesis,[22–25] herein, we report a simple, facile and one-pot procedure for the synthesis of indol-3-yl pyridine derivatives.

2. Results and discussion

In an initial endeavor, we carried out the reaction of *p*-tolualdehyde (**1b**), malononitrile (**3**) and 3-cyanoacetyl indole (**2**)[26] with various types of Lewis acids and bases in methanol (Table 1). Excellent results were obtained with $InCl_3$ as the catalyst at reflux temperature (65 °C). Having established that $InCl_3$ was catalyst of choice, we investigated the efficacy of different solvents for the synthesis of indol-3-yl pyridine derivatives (Table 2). After systematic screening we have found that $InCl_3$/Methanol under reflux to give good yield of the product in the shorter reaction time (Scheme 1).

Table 1
Screening of various Lewis acids and bases in methanol

Entry	Base	Yield (%)[a,b]
1	$AlCl_3$	0
2	NaOH	79
3	Piperidine	0
4	Triethylamine	0
5	KOH	70
6	$InCl_3$	88

[a] Isolated yield.
[b] All reactions carried out for 1.5 h at 65°C

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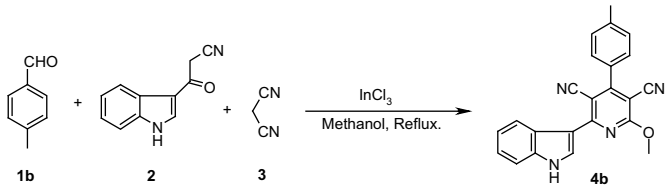
Table 2
Screening of various solvents on formation substituted pyridines using $InCl_3$

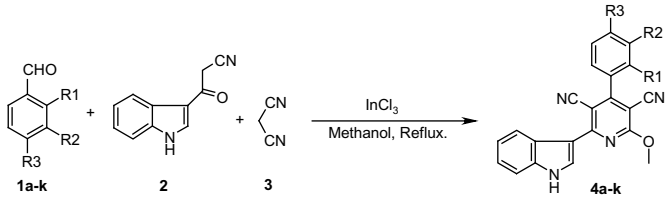
Entry	Co-Solvent	Reflux temp (°C)[a]	Yield (%)[b,c]
1	DMF	153	64
2	Dichloroethane	83	48
3	Acetonitrile	82	71
4	Water	100	74
5	Ethanol	79	78
6	Methanol	65	88

[a] Reflux tempature of the solvent.
[b] Isolated yield.
[c] All reactions carried out with 20 mol % $InCl_3$ for 1.5 h in methanol and co-solvent as 1:1 ratio.



Scheme 1.

A mixture of 3-cyanoacetyl indole (**2**) (1.0 mmol), aldehyde (**1**) (1.0 mmol) and indium trichloride (20 mol %) in methanol (30 mL) was refluxed. After complete disappearance of the both starting materials (monitored by TLC) malononitrile (**3**) (1.0 mmol) was added and the reflux was continued for 1–2 h which resulted in the formation of highly substituted pyridine derivative (Scheme 2). The feasibility of the reaction was further studied with various substituted aldehydes. On sequential addition of the substrates under optimized conditions, the reaction proceeded smoothly with a wide range of functionalized aldehydes, including those containing ether, nitro, halogens phenyl group and heterocyclic ring. However the same reaction proceeded with aliphatic aldehydes under optimized condition, we unable to get desired product and the results are summarized (Table 3).



Scheme 2. Synthesis of indol-3-yl pyridine derivatives derivatives.

Based on the above results, a plausible mechanism is proposed,[7](Scheme 3) 3-cyanoacetyl indole **2** reacts with corresponding aldehyde **1** to give a α,β unsaturated ketone **2a** and it further reacts with malononitrile **3** to yield **2b**. Michael addition product **2b** combines with methanol and $InCl_3$ to form a intermediate **2c** and its upon protonation to give on intermediate (**2d** & **2e**). Protonation of **2e** affords to yield Hantzsch dihydropyridine derivative (**2f**) with an elimination of water, finally deprotonation of **2f** leads to formation of highly substituted pyridine derivative (**4**). However in the reverse reaction, malononitrile is first allowed to react with the corresponding aldehyde followed by 3-cyanoacetyl indole attack do not lead to the formation of corresponding pyridine derivatives.

The structures of the compounds **4a–k** were confirmed through spectral analysis and elemental analysis as exemplified for compound **4g** as follows: In the IR spectrum of compound **4g**, absorptions at 3313 and 2232 cm^{-1} supported the presence of –NH and –C≡N functional groups. The ^1H NMR spectrum exhibited a broad distinguishable singlet at δ 12.22 (D_2O exchangeable) for –NH protons and a sharp distinguishable singlet appeared at δ 4.25 for methoxy protons. Aromatic protons were seen in the range of δ 7.25–8.58. A distinctive peak at δ 55.9 in the ^{13}C NMR spectrum confirmed the presence of methoxy group. The two cyano group attached carbon characteristic peaks were appeared at δ 91.8 and 96.7. The mass spectrum displayed the molecular ion $[M+H]^+$ peak at *m/z* 418.13. The structure of the compound **4g** was further established by single crystal X-ray diffraction analysis (Fig. 1).[27]

On the basis of the above results, we extended our protocol for the synthesis of 2,2′-bipyridine derivatives. Many bipyridine derivatives are capable of forming multinuclear complexes. Fused 2,2′-pyridines are useful substructures in the design of supramolecular compounds. These are chelating ligands which show particularly high affinities for transition metal ions which frequently stabilize unusual low oxidation state species because of both dπ–pπ* back-bonding by the cations and their capacity to form ligated anion radicals.[28] A mixture of 2-acetylpyridine (**5**) (1.0 mmol), aldehyde (**1**) (1.0 mmol) and indium(III)chloride (20 mol %) in 30 mL methanol was refluxed. After 30–45 min (monitored by TLC) malononitrile (**3**) (1.0 mmol) was added and the reflux was continued for 2–3 h which resulted in the formation of highly substituted 2,2′-bipyridine derivative (**6**). The substrate scope of the reaction under the optimized conditions was investigated, and the reaction was modifiable to a wide variety of substituted aldehydes (Scheme 4 and Table 4).

The structures of the compounds **6a–h** were investigated with spectral studies and elemental analysis as demonstrated for compound **6d** as follows: In the IR spectrum, the C≡N stretching frequency was appeared at 2215 cm^{-1}. In the ^1H NMR spectrum of aromatic protons were resonated in the range of *δ*: 7.35–8.67. A sharp singlet in the region *δ*: 4.19 signals confirmed the presence of methoxy proton. A sharp peak at *δ*: 94.5 corresponding to cyano group attached carbon in ^{13}C NMR spectrum and the aromatic carbons were appeared in the region *δ*: 114.1–161.1. And also methoxy carbon characteristic peak was appeared at *δ*: 54.8. A distinguishing peak was observed at *m/z:* 322.27 in the mass spectrum for $[M+H]^+$ion. Finally structure of compound **6d** was confirmed by single crystal X-ray diffraction analysis (Fig. 2).[29]

On the other hand, terephthaldialdehyde (**7**) (0.5 mmol), 3-cyanoacetyl indole (**2**) (1 mmol) and malononitrile (**3**) (1.0 mmol) in methanol under optimized condition gave 61% of product **8**. The reaction took longer time for complete formation of the product. The crude product was precipitated in ice cold water and extracted with ethyl acetate. The product was purified by column chromatography (Scheme 5).

The structure of compound (**8**) was established on the basis of elemental analysis and spectral data. In IR spectrum, stretching frequencies at 2269 and 3298 cm^{-1} confirmed the presence of C≡N and NH functional groups respectively. The ^1H NMR spectrum showed a sharp singlet at δ 4.24 for methoxy protons and broad distinct singlet in the region of δ 12.17 corresponds to NH proton (D_2O exchangeable). The aromatic proton resonated in the region of δ 7.25–8.58. In ^{13}C NMR spectrum, the apparent signal at δ 56.7 corresponds to methoxy carbon and cyano group attached carbons appeared at δ 91.9 and 97.8 respectively. The aromatic carbons were demonstrated in region of δ 112.9–164.3. In mass spectrum shows, a sharp distinguishable peak at *m/z* 625.40 corresponds to $[M+H]^+$ peak.

Due to the unique pharmacological properties of indeno pyridines, our protocol was extended to the synthesis of indenopyridine derivatives, Indenopyridines are attractive synthetic targets, because they exhibit broad range of important biological properties, such as insecticidal, phosphodiesterase inhibiting, antifungal,

Table 3
Synthesis of indol-3-yl pyridine derivatives

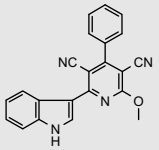
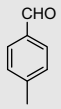
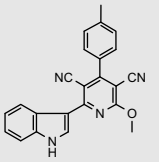
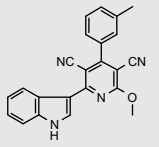
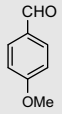
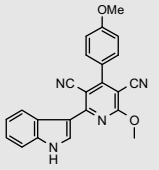
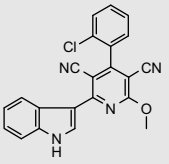
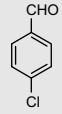
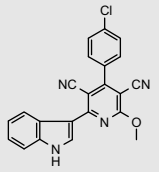
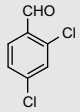
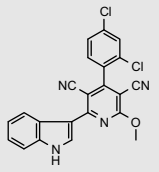
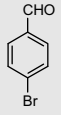
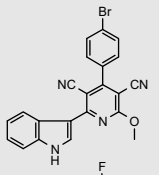
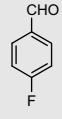
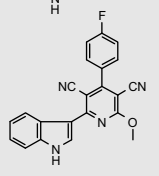
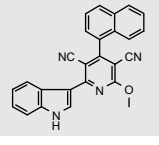
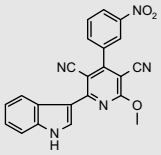
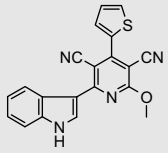
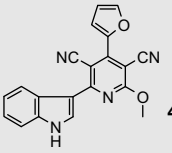
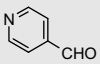
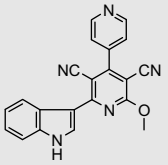
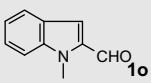
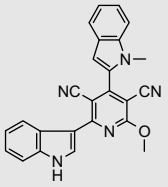
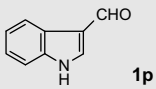
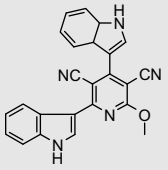
Entry	Aldehyde (**1**)	Product (**4**)[a]	Time (h)	Yield (%)[a,b]
1	 **1a**	 **4a**	2.0	85
2	 **1b**	 **4b**	1.5	88
3	 **1c**	 **4c**	2.0	84
4	 **1d**	 **4d**	1.5	90
5	 **1e**	 **4e**	3.0	74
6	 **1f**	 **4f**	2.5	79
7	 **1g**	 **4g**	3.0	76
8	 **1h**	 **4h**	2.5	77
9	 **1i**	 **4i**	3.0	74
10	 **1j**	 **4j**	1.5	89

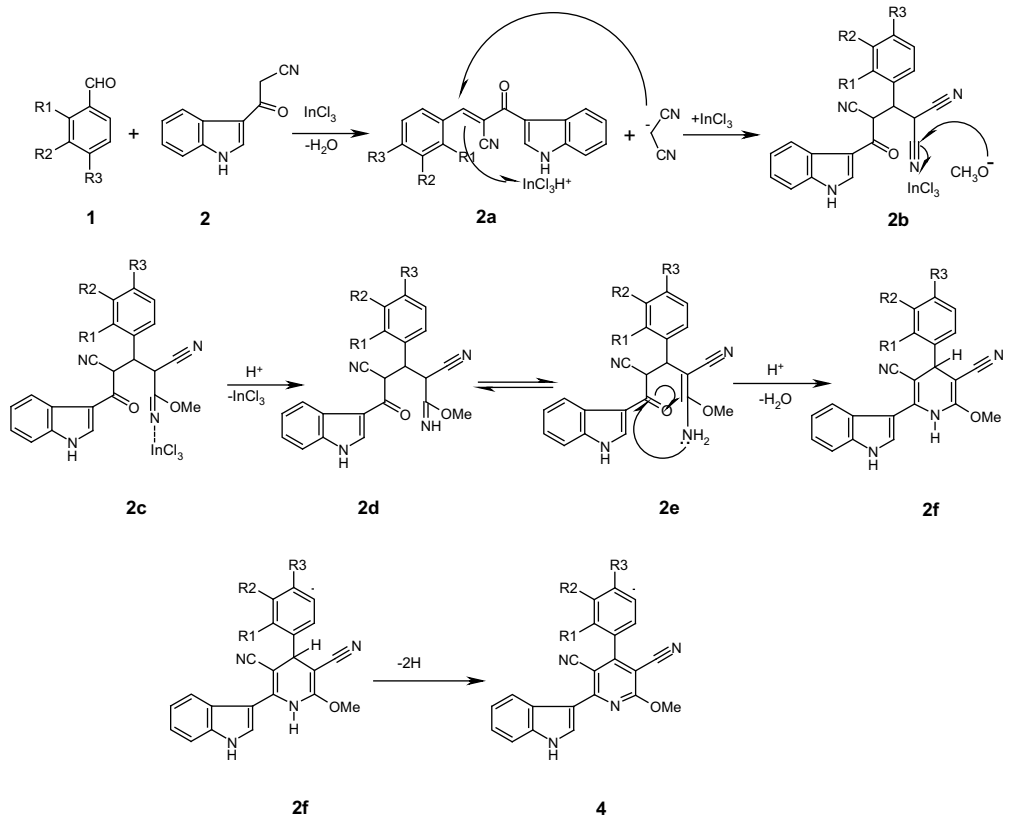
Table 3 (*continued*)

Entry	Aldehyde (**1**)	Product (**4**)[a]	Time (h)	Yield (%)[a,b]
11	 **1k**	 **4k**	3.5	70
12	 **1l**	 **4l**	3.0	61
13	 **1m**	 **4m**	3.5	72
14	 **1n**	 **4n**	3.5	63
15	 **1o**	 **4o**	4.5	69
16	 **1p**	 **4p**	4.5	69

[a] All the products characterized by NMR, IR and mass spectroscopy.
[b] Isolated yield.

antispermatogenic, antifertility, antagonistic and antiarrhythmic activities.[30] A mixture of aldehyde (1.0 mmol), 3-cyanoacetyl indole (1.0 mmol) and indium trichloride (20 mol %) in 30 mL methanol was refluxed. After 30–45 min (monitored by TLC) 2-indanone (1.0 mmol) and ammonium acetate in excess was added, finally reflux was continued for 5–6 h. On sequential addition of the substrates under optimized conditions, the reaction proceeds smoothly to form of highly substituted indenopyridines (Scheme 6). The generality of the reaction was further extended to the synthesis of various substituted indenopyridine derivatives under optimized condition (Table 5).

The structures of compounds **10a–f** were identified by spectral studies and elemental analysis. In the IR spectrum of **10g**, absorption peaks at 3316 and 2229 cm^{-1} showed the presence of –NH and –C≡N functional groups. The ^1H NMR spectrum exhibited a broad singlet at δ 8.61 (D_2O exchangeable) for –NH protons and a sharp distinct singlet showed at δ 4.20 for methylene protons. Aromatic protons were seen in the range δ 6.78–8.54. A distinguishing peak



Scheme 3. Plausible mechanism for formation of indol-3-yl pyridine derivatives.

at δ 29.7 in the ^{13}C NMR spectrum confirmed the presence of methylene carbon. The cyano group attached carbon showed a distinguishing peak at δ 104.5. The $[M+H]^+$ peak appeared at m/z 397.47 in the mass spectrum.

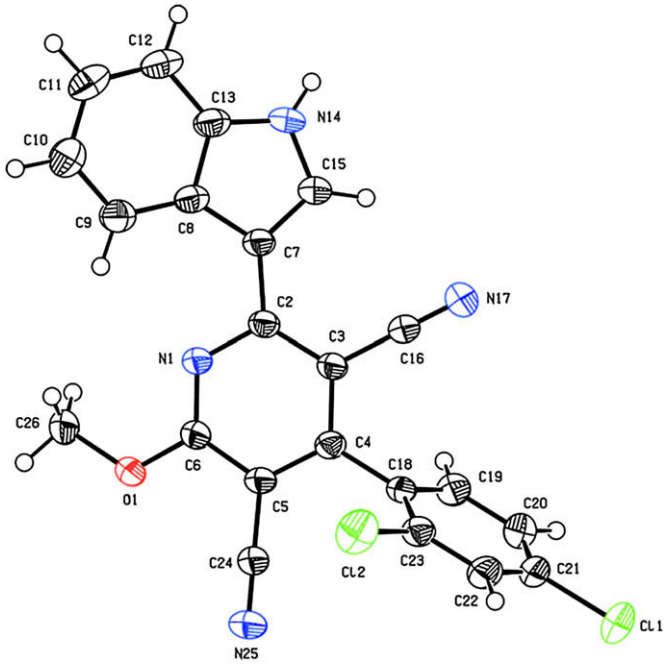
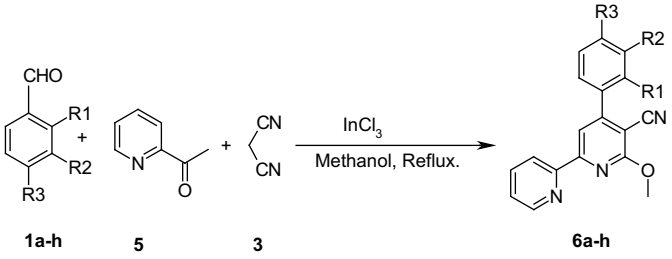


Figure 1. Ortep diagram of compound **4g**.



Scheme 4. Synthesis of 2,2′-bipyridine derivatives.

3. Conclusions

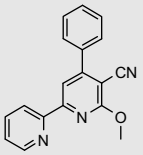
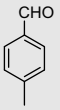
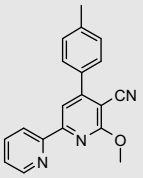
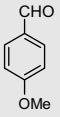
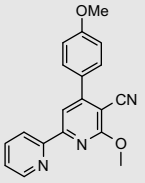
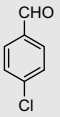
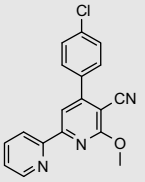
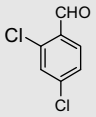
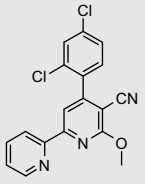
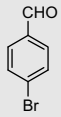
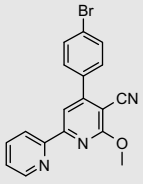
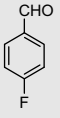
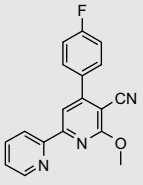
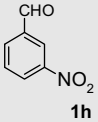
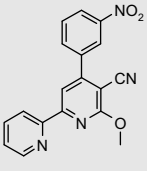
We have developed simple one-pot synthesis for the formation of substituted pyridines, a privileged medicinal scaffold through three-component reactions of structurally diverse aldehydes with 3-cyanoacetyl indole and malononitrile. By incorporating two biologically potential moieties in a single molecule will enhance the biological activity of these compounds. Further studies to delineate the scope and limitations of the present methodology are underway.

4. Experimental section

4.1. General

All the substituted aldehydes, malononitrile, 2-indanone, indole, $CDCl_3$ and DMSO-d_6 were purchased from Aldrich Chemicals. Acetic anhydride and all other reagents were purchased from S. D. Fine Chem. Limited and were used as received. Methanol was distilled from Mg/I_2 under nitrogen and stored over 3Å

Table 4
Synthesis of 2,2′-bipyridine derivatives

Entry	Aldehyde (**1**)	Product (**6**)[a]	Time (h)	Yield (%)[a,b]
1	 **1a**	 **6a**	3.0	78
2	 **1b**	 **6b**	2.5	80
3	 **1c**	 **6c**	3.0	81
4	 **1d**	 **6d**	2.5	74
5	 **1e**	 **6e**	3.0	72
6	 **1f**	 **6f**	2.0	78
7	 **1g**	 **6g**	2.5	77
8	 **1h**	 **6h**	3.0	70

[a] All the products characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy.
[b] Isolated yield.

molecular sieves was purchased from Aldrich. IR measurements were done as KBr pellets for solids using Perkin–Elmer Spectrum RXI FT-IR. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 using TMS as internal standard with JEOL 500 MHz and Bruker 500 MHz high resolution NMR spectrometer. Multiplicities were abbreviated as follows: singlet (s), doublet (d), triplet (t), multiplet (m), and broad (br). The mass spectra were recorded using a Electrospray Ionisation Method with Thermo Finnigan mass spectrometer. Melting points were determined in capillary tubes and are uncorrected. Analytical TLC was performed on pre-coated plastic sheets of silica gel G/UV-254 of 0.2 mm thickness (Macherey-Nagel, Germany). Elemental analysis data were recorded using Thermo Finnigan FLASH EA 1112 CHN instrument.

4.2. General procedure for the synthesis of indol-3-yl pyridine and 2,2′-bipyridine derivatives (4a–k and 6a–h)

A mixture of 3-cyanoacetyl indole (or) 2-acetylpyridine (1.0 mmol), aldehyde (1.0 mmol) and indium trichloride (20 mol %) in 30 mL of methanol was refluxed. After 15–30 min malononitrile (1.0 mmol) was added and the reflux was continued for appropriate time mentioned in Tables 3 and 4. After the completion of the reaction (as monitored by TLC), it was poured into water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated under vacuum. The crude product was chromatographed in silica gel (90:10 petroleum ether/ethyl acetate) and appropriate isolated yield is shown in Tables 3 and 4.

4.2.1. ***4a****. 2-(1H-Indol-3-yl)-6-methoxy-4-phenylpyridine-3,5-dicarbonitrile (Table 3, entry 1)*

Light yellow solid; mp 244–246 °C; R_f 0.23 (20% EtOAc/Petroleum ether); IR (KBr): 1153,1229, 1427, 1516, 1629, 2230, 3287 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 4.21 (s, 3H, –OC*H*$_3$), 7.22–7.24 (m, 2H, –Ar–*H*), 7.52–7.60 (m, 6H, –Ar–*H*), 8.43–8.45 (m, 1H, –Ar–*H*), 8.57 (s, 1H, –Ar–*H*), 12.17 (br s, 1H, –N*H*); ^{13}C NMR (125 MHz, DMSO-d_6): δ 56.2, 91.7, 97.0, 112.7, 113.0, 114.6, 118.3, 122.2, 122.6, 123.5, 126.4, 128.8, 129.1, 129.2, 130.9, 132.1, 134.5, 137.2, 159.3, 161.0, 164.8; MS (ESI LCQ-MS): *m*/*z* 351.20 [M+H]$^+$. Anal. Calcd for $C_{22}H_{14}N_4O$: C, 75.42; H, 4.03; N, 15.99. Found: C, 75.31; H, 4.02; N, 16.04.

4.2.2. ***4b****. 2-(1H-Indol-3-yl)-6-methoxy-4-(4-tolyl phenyl)pyridine-3,5-dicarbonitrile (Table 3, entry 2)*

Light yellow solid; mp 228–230 °C; R_f 0.30 (20% EtOAc/Petroleum ether); IR (KBr): 1145, 1224, 1306, 1422, 1516, 1620, 2221, 3325 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.41 (s, 3H, –Ar– C*H*$_3$), 4.21 (s, 3H, –OC*H*$_3$), 7.19–7.24 (m, 2H, –Ar–*H*), 7.36–7.52 (m, 5H, –Ar–*H*), 8.42 (d, 1H, *J*=8.4 Hz, –Ar–*H*), 8.55 (s, 1H, –Ar–*H*), 12.19 (br s, 1H, –N*H*); ^{13}C NMR (125 MHz, DMSO-d_6): δ 21.0, 55.5, 91.3, 96.7, 112.2, 112.3, 114.0, 117.7, 121.6, 122.0, 122.9, 125.9, 128.2, 128.5, 129.2, 131.0, 131.1, 136.4, 140.2, 159.0, 160.5, 164.3; MS (ESI LCQ-MS): *m*/*z* 365.20 [M+H]$^+$. Anal. Calcd for $C_{23}H_{16}N_4O$: C, 75.81; H, 4.43; N, 15.38. Found: C, 75.90; H, 4.42; N, 15.33.

4.2.3. ***4c****. 2-(1H-Indol-3-yl)-6-methoxy-4-(3-methylphenyl) pyridine-3,5-dicarbonitrile (Table 3, entry 3)*

Pale yellow solid; mp 286–288 °C; R_f 0.23 (20% EtOAc/Petroleum ether); IR (KBr): 1163, 1237, 1358, 1434, 1553, 1617, 2366, 3262 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.37 (s, 3H, –Ar–C*H*$_3$), 4.18 (s, 3H, –OC*H*$_3$), 7.20–7.26 (m, 2H, –Ar–*H*), 7.34–7.36 (m, 3H, –Ar–*H*), 7.43 (t, 1H, *J*=7.6 Hz, –Ar–*H*), 7.52 (d, 1H, *J*=7.6 Hz, –Ar–*H*), 8.42 (d, 1H, *J*=8.4 Hz, –Ar–*H*), 8.55 (s, 1H, –Ar–*H*), 12.14 (br s, 1H, –N*H*); ^{13}C NMR (125 MHz, DMSO-d_6): δ 20.9, 55.7, 91.3, 96.6, 112.2, 112.4, 114.1, 117.7, 121.7, 122.1, 123.0, 125.7, 125.8, 128.6, 128.9, 131.0, 131.3, 133.9, 136.5, 138.0, 158.9, 160.7, 164.3; MS (ESI LCQ-MS): *m*/*z* 365.20 [M+H]$^+$. Anal. Calcd for $C_{23}H_{16}N_4O$: C, 75.81; H, 4.43; N, 15.38. Found: C, 75.72; H, 4.44; N, 15.43.

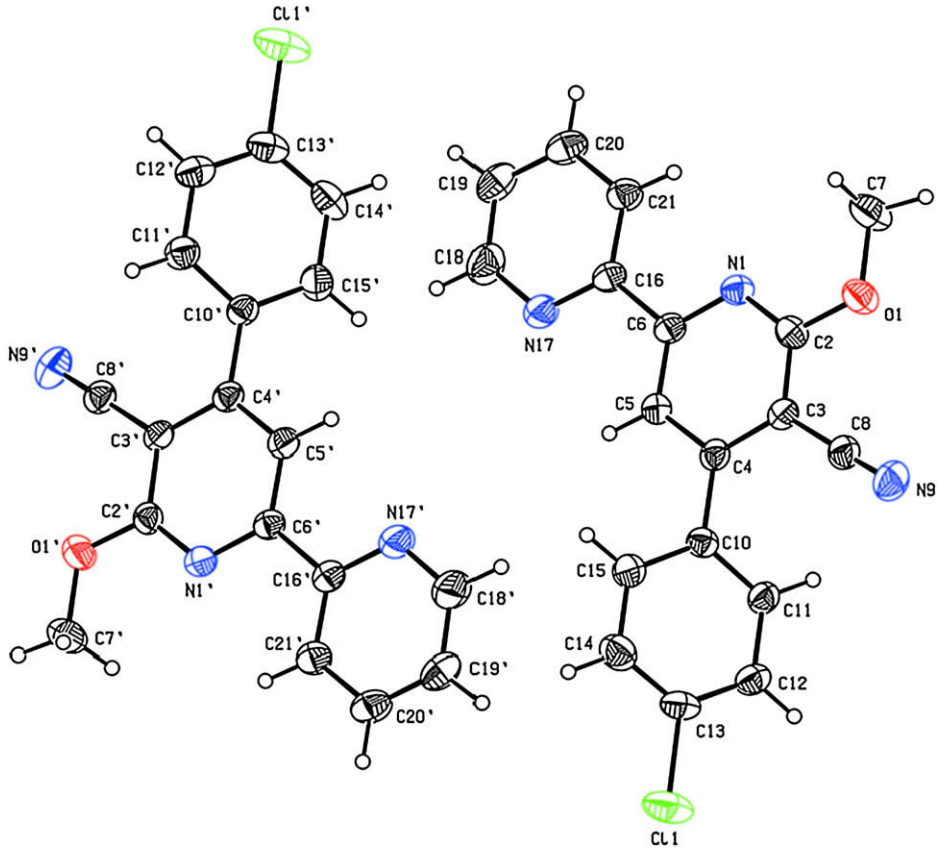
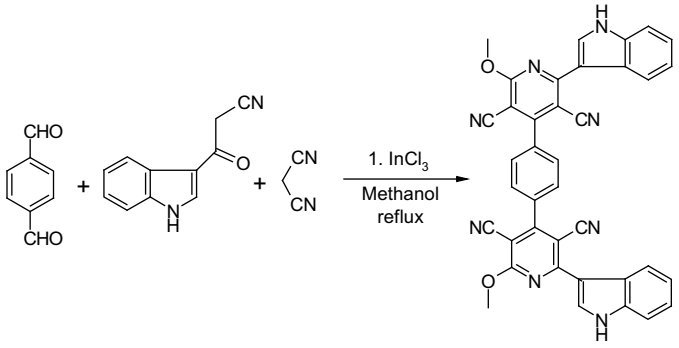


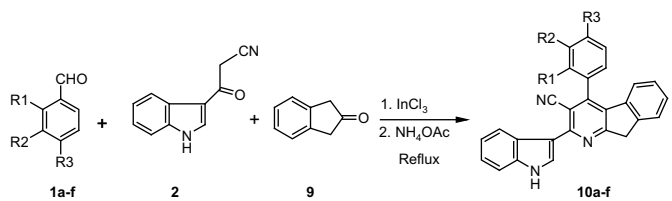
Figure 2. Ortep diagram of compound **6d**.

4.2.4. ***4d****. 2-(1H-Indol-3-yl)-6-methoxy-****4****(****4****methoxyphenyl) pyridine-3,5-dicarbonitrile (Table 3, entry 4)*

Yellow solid; mp 268–270 °C; R_f 0.23 (20% EtOAc/Petroleum ether); IR (KBr): 1163, 1237, 1358, 1434, 1553, 1617, 2366, 3262 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 3.80 (s, 3H, –OCH_3), 4.20 (s, 3H, –OCH_3), 7.06 (d, 2H, J=8.4 Hz, –Ar–H), 7.12 (d, 1H, J=8.2 Hz, –Ar–H), 7.19–7.22 (m, 1H, –Ar–H), 7.43 (d, 2H, J=8.4 Hz, –Ar–H), 7.56 (d, 1H, J=8.4 Hz, –Ar–H), 8.41–8.43 (m, 1H, –Ar–H), 8.58 (s, 1H, –Ar–H), 12.31 (br s, 1H, –NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 55.2, 55.7, 91.1, 96.4, 112.2, 112.7, 114.1, 117.7, 121.7, 122.0, 122.9, 126.0, 128.9, 130.7, 131.9, 132.8, 135.4, 137.0, 158.8, 159.4, 164.2; MS (ESI LCQ-MS): m/z 381.27 $[M+H]^+$. Anal. Calcd for $C_{23}H_{16}N_4O_2$: C, 72.62; H, 4.24; N, 14.73. Found: C, 72.72; H, 4.22; N, 14.69.



Scheme 5. Synthesis of bis(indol-3-yl pyridine) derivatives.



Scheme 6. Synthesis of indenopyridine derivatives.

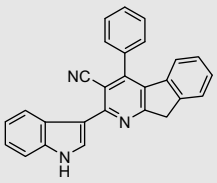
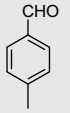
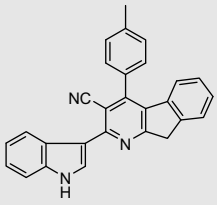
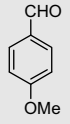
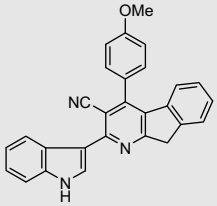
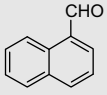
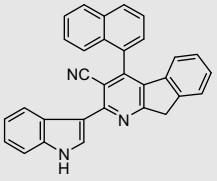
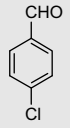
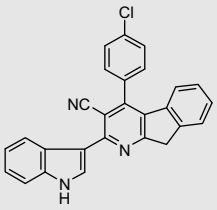
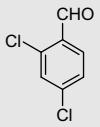
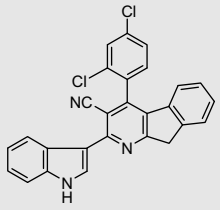
4.2.5. ***4e****. 4-(2-Chlorophenyl)-2-(1H-indol-3-yl)-6-methoxy pyridine-3,5-dicarbonitrile (Table 3, entry 5)*

Pale yellow solid; mp 214–216 °C; R_f 0.31 (20% EtOAc/Petroleum ether); IR (KBr): 1090, 1145, 1221, 1420, 1519, 2219, 3325 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 4.25 (s, 3H, –OCH_3), 7.23–7.26 (m, 2H, –Ar–H), 7.53–7.63 (m, 4H, –Ar–H), 7.71 (d, 1H, J=8.4 Hz, –Ar–H), 8.47–8.49 (m, 1H, –Ar–H), 8.58 (s, 1H, –Ar–H), 12.41 (br s, 1H, –NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 55.9, 91.9, 97.0, 112.1, 112.6, 113.4, 116.8, 121.9, 122.1, 123.2, 125.7, 127.9, 129.9, 130.4, 131.0, 131.5, 132.1, 133.0, 136.6, 158.3, 158.8, 164.2; MS (ESI LCQ-MS): m/z 385.17 $[M+H]^+$. Anal. Calcd for $C_{22}H_{13}ClN_4O$: C, 68.67; H, 3.41; N, 9.21. Found: C, 68.75; H, 3.40; N, 9.17.

4.2.6. ***4f****. 4-(4-Chlorophenyl)-2-(1H-indol-3-yl)-6-methoxy pyridine-3,5-dicarbonitrile (Table 3, entry 6)*

Pale yellow solid; mp 260–262 °C; R_f 0.31 (20% EtOAc/Petroleum ether); IR (KBr): 1093, 1222, 1366, 1423, 1490, 1517, 1573, 2222, 3329 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 4.21 (s, 3H, –OCH_3), 7.23–7.25 (m, 2H, –Ar–H), 7.53 (d, 1H, J=8.4 Hz, –Ar–H), 7.62 (q, 4H, J=8.4 Hz, –Ar–H), 8.43 (d, 1H, J=8.4 Hz, –Ar–H), 8.56 (s, 1H, –Ar–H), 12.15 (br s, 1H, –NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 55.7, 91.3, 96.6, 112.1, 112.4, 114.0, 117.6, 121.8, 122.0, 123.0, 125.6, 128.8, 130.2, 130.6, 131.3, 132.7, 135.4, 136.5, 158.8, 159.3, 164.2; MS (ESI LCQ-MS): m/z 385.20 $[M+H]^+$. Anal. Calcd for $C_{22}H_{13}ClN_4O$: C, 68.67; H, 3.41; N, 9.21. Found: C, 68.59; H, 3.42; N, 9.25.

Table 5
Synthesis of indenopyridine derivatives

Entry	Aldehyde (**1**)	Product (**10**)[a]	Time (h)	Yield (%)[b]
1	 **1a**	 **10a**	6.0	79
2	 **1b**	 **10b**	6.0	80
3	 **1c**	 **10c**	5.5	81
4	 **1d**	 **10d**	6.5	78
5	 **1e**	 **10e**	5.5	75
6	 **1f**	 **10f**	6.0	74

[a] All the products characterized by IR, NMR and Mass spectroscopy.
[b] Isolated yield.

4.2.7. ***4g****. 4-(2,4-Chlorophenyl)-2-(1H-indol-3-yl)-6-methoxy pyridine-3,5-dicarbonitrile (Table 3, entry 7)*

Pale yellow solid; mp 272–274 °C; R_f 0.31 (20% EtOAc/Petroleum ether); IR (KBr): 1145, 1225, 1310, 1422, 1522, 2232, 3313 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 4.25 (s, 3H, –OCH_3), 7.25–7.26 (m, 2H, –Ar–*H*), 7.54–7.56 (m, 1H, –Ar–*H*), 7.66–7.71 (m, 2H, –Ar–*H*), 7.96 (d, 1H, *J*=1.55 Hz, –Ar–*H*), 8.46–8.48 (m, 1H, –Ar–*H*), 8.58 (s, 1H, –Ar–*H*), 12.22 (br s, 1H, –N*H*); ^{13}C NMR (125 MHz, DMSO-d_6): δ 55.9, 91.8, 96.7, 112.0, 112.5, 113.3, 116.8, 121.9, 122.1, 123.2, 125.7, 128.2, 129.5, 131.5, 131.8, 131.9, 132.3, 136.1, 136.5, 157.2, 158.8, 164.1; MS (ESI LCQ-MS): *m*/*z* 419.13 $[M+H]^+$. Anal. Calcd for $C_{22}H_{12}Cl_2N_4O$: C, 63.02; H, 2.88; N, 16.91. Found: C, 62.91; H, 2.88; N, 16.9.

4.2.8. ***4h****. 4-Bromophenyl-2-(1H-indol-3-yl)-6-methoxypyridine-3,5-dicarbonitrile (Table 3, entry 8)*

Pale yellow solid; mp 238–240 °C; R_f 0.31 (20% EtOAc/Petroleum ether); IR (KBr): 1145, 1235, 1288, 1435, 1522, 1636, 2253, 3222 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 4.22 (s, 3H, –OCH_3), 7.22–7.27 (m, 2H, –Ar–*H*), 7.53–7.58 (m, 3H, –Ar–*H*), 7.80 (d, 2H, *J*=8.4 Hz, –Ar–*H*), 8.43 (d, 1H, *J*=8.4 Hz, –Ar–*H*), 8.56 (s, 1H, –Ar–*H*), 12.14 (brs, 1H, –N*H*); ^{13}C NMR (125 MHz, DMSO-d_6): δ 55.7, 91.3, 96.6, 112.2, 112.7, 114.2, 115.8, 117.8, 121.7, 122.0, 123.0, 126.0, 130.4, 131.3, 131.4, 132.0, 137.0, 158.8, 159.6, 162.2, 164.2, 164.3; MS (ESI LCQ-MS): *m*/*z* 431.13 $[M+H]^+$. Anal. Calcd for $C_{22}H_{13}BrN_4O$: C, 61.55; H, 3.05; N, 13.05. Found: C, 61.44; H, 3.06; N, 13.09.

4.2.9. ***4i****. 4-(4-Fluorophenyl)-2-(1H-indol-3-yl)-6-methoxy pyridine-3,5-dicarbonitrile (Table 3, entry 9)*

Pale yellow solid; mp 256–258 °C; R_f 0.30 (20% EtOAc/Petroleum ether); IR (KBr): 1152, 1227, 1370, 1421, 1511, 1603, 2224, 3317 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 4.21 (s, 3H, –OCH_3), 7.21–7.26 (m, 2H, –Ar–*H*), 7.42 (t, 2H, *J*=9.15 Hz, –Ar–*H*), 7.52 (d, 1H, *J*=6.8 Hz, –Ar–*H*), 7.67–7.69 (m, 2H, –Ar–*H*), 8.43 (d, 1H, *J*=8.4 Hz, –Ar–*H*), 8.56 (s, 1H, –Ar–*H*), 12.08 (br s, 1H, –N*H*); ^{13}C NMR (125 MHz, DMSO-d_6): δ 55.7, 91.5, 96.8, 112.1, 114.1, 115.7, 116.0, 117.7, 121.8, 122.1, 123.1, 125.8, 130.3, 131.3, 131.4, 136.5, 158.8, 159.6, 161.6, 164.9; MS (ESI LCQ-MS): *m*/*z* 369.27 $[M+H]^+$. Anal. Calcd for $C_{22}H_{13}FN_4O_7$: C, 71.73; H, 3.56; N, 15.21. Found: C, 71.62; H, 3.57; N, 15.26.

4.2.10. ***4j****. 2-(1H-Indol-3-yl)-6-methoxy-4-(1-naphthyl)pyridine-3,5-dicarbonitrile (Table 3, entry 10)*

Yellow solid; mp 240.242 °C; R_f 0.21 (20% EtOAc/Petroleum ether); IR (KBr): 1148, 1228, 1422, 1514, 1633, 2235, 3244 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 4.27 (s, 3H, –OCH_3), 7.20–7.28 (m, 2H, –Ar–*H*), 7.47–7.70 (m, 6H, –Ar–*H*), 8.06–8.15 (m, 2H, –Ar–*H*), 8.53–8.56 (m, 2H, –Ar–*H*), 12.15 (br s, 1H, –N*H*); ^{13}C NMR (125 MHz, DMSO-d_6): δ 55.8, 92.9, 97.9, 112.2, 112.5, 117.4, 121.0, 121.85, 122.2, 123.2, 124.5, 125.4, 126.7, 127.0, 127.5, 128.6, 129.8, 130.4, 131.4, 131.7, 133.0, 136.6, 158.9, 159.9, 164.4; MS (ESI LCQ-MS): *m*/*z* 351.20 $[M+H]^+$. Anal. Calcd for $C_{26}H_{16}N_4O$: C, 75.42; H, 4.03; N, 15.99. Found: C, 75.31; H, 4.02; N, 16.04.

4.2.11. ***4k****. 2-(1H-Indol-3-yl)-6-methoxy-4-(3-nitrophenyl) pyridine-3,5-dicarbonitrile (Table 3, entry 11)*

Yellow solid; mp 242–244 °C; R_f 0.08 (20% EtOAc/Petroleum ether); IR (KBr): 1098, 1236, 1349, 1433, 1531, 1620, 2216, 3386 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 4.28 (s, 3H, –OCH_3), 7.28–7.31 (m, 2H, –Ar–*H*), 7.57–7.59 (m, 1H, –Ar–*H*), 7.94 (t, 1H, *J*=7.6 Hz, –Ar–*H*), 8.14 (d, 1H, *J*=7.6 Hz, –Ar–*H*), 8.48–8.50 (m, 2H, –Ar–*H*), 8.62 (s, 2H, –Ar–*H*), 12.21 (br s, 1H, –N*H*); ^{13}C NMR (125 MHz, DMSO-d_6): δ 55.9, 91.5, 96.6, 112.1, 112.6, 114.0, 117.6, 121.9, 122.1, 123.2, 123.9, 125.3, 125.8, 130.7, 131.6, 135.4, 135.5, 136.6, 147.7, 158.1, 158.9, 164.2; MS (ESI LCQ-MS): *m*/*z* 395.13 $[M+H]^+$. Anal. Calcd for $C_{22}H_{13}N_5O_3$: C, 66.83; H, 3.31; N, 17.71. Found: C, 66.74; H, 3.32; N, 17.75.

4.2.12. ***4l****. 2-(1H-indol-3-yl)-6-methoxy-4-(2-thienyl)pyridine-3,5-dicarbonitrile (Table 3, entry 12)*

Yellow solid; mp 226–228 °C; R_f 0.76 (40% AcOEt/Petroleum ether); IR (KBr): 1134, 1226, 1475, 1514, 2222, 3268 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 4.17 (s, 3H, –OCH_3), 7.19–7.24 (m, 1H, –Ar–*H*), 7.28 (t, 1H, *J*=4.6 Hz, –Ar–*H*), 7.50 (d, 1H, *J*=7.6 Hz, –Ar–*H*), 7.58 (d, 1H, *J*=3.1 Hz, –Ar–*H*), 7.95 (d, 1H, *J*=4.6 Hz, –Ar–*H*), 8.38 (d, 1H, *J*=6.9 Hz, –Ar–*H*), 8.56 (s, 1H, –Ar–*H*), 11.67 (br s, 1H, –N*H*); ^{13}C NMR (125 MHz, DMSO-d_6): δ 56.3, 91.7, 97.1, 112.6, 113.2, 114.8, 118.5,

122.6, 123.6, 126.5, 128.5, 131.6, 132.2, 132.6, 133.2, 137.4, 153.6, 159.7, 165.1; MS (EI): *m*/*z* 357.20 [M^++H^+]. Anal. Calcd for $C_{20}H_{12}N_4OS$: C, 67.40; H, 3.39; N, 15.72. Found: C, 67.31; H, 3.38; N, 15.74.

4.2.13. ***4m****. 4-(2-Furyl)-2-(1H-indol-3-yl)-6-methoxypyridine-3,5-dicarbonitrile (Table 3, entry 13)*

Yellow solid; mp 234–236 °C; R_f 0.72 (40% AcOEt/Petroleum ether); IR (KBr): 1150, 1229, 1424, 2221, 3301 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 4.15 (s, 3H, –OCH_3), 6.84–6.86 (m, 1H, –Ar–*H*), 7.17–7.22 (m, 2H, –Ar–*H*), 7.42 (d, 1H, *J*=3.1 Hz, –Ar–*H*), 7.49 (d, 1H, *J*=7.6 Hz, –Ar–*H*), 8.11 (s, 1H, –Ar–*H*), 8.11 (d, 1H, *J*=7.6 Hz, –Ar–*H*), 8.55 (s, 1H, –Ar–*H*), 12.39 (br s, 1H, –N*H*); ^{13}C NMR (125 MHz, DMSO-d_6): δ 56.3, 87.8, 93.4, 112.6, 113.1, 113.4, 115.0, 117.4, 118.9, 122.2, 122.6, 123.5, 126.5, 132.7, 137.3, 145.6, 146.7, 160.3, 162.8, 165.6; MS (EI): *m*/*z* 341.33 [M^++H^+]. Anal. Calcd for $C_{20}H_{12}N_4O_2$: C, 67.40; H, 3.39; N, 15.72. Found: C, 67.31; H, 3.38; N, 15.74.

4.2.14. ***4n****. 2-(1H-indol-3-yl)-6-methoxy-4,4′-bipyridine-3,5-dicarbonitrile (Table 3, entry 14)*

Yellow solid; mp 172–175 °C; R_f 0.62 (40% AcOEt/Petroleum ether); IR (KBr): 1233, 1461, 1552, 1617, 2198, 3132 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 4.23 (s, 3H, –OCH_3), 7.24–7.26 (m, 2H, –Ar–*H*), 7.53–7.55 (m, 1H, –Ar–*H*), 7.63–7.64 (m, 2H, –Ar–*H*), 8.44–8.46 (m, 1H, –Ar–*H*), 8.57 (s, 1H, –Ar–*H*), 8.81–8.83 (m, 2H, –Ar–*H*), 12.18 (br s, 1H, –N*H*); ^{13}C NMR (125 MHz, DMSO-d_6): δ 56.4, 91.5, 96.5, 112.6, 113.1, 114.3, 117.9, 122.5, 122.6, 123.8, 123.7, 126.3, 132.2, 137.1, 142.3, 150.7, 158.7, 159.5, 164.7; MS (EI): *m*/*z* 352.20 [M^++H^+]. Anal. Calcd for $C_{21}H_{13}N_5O$: C, 71.79; H, 3.73; N, 19.93. Found: C, 71.70; H, 3.74; N, 19.96.

4.2.15. ***4o****. 2-(1H-indol-3-yl)-6-methoxy-4-(1-methyl-1H-indol-2-yl)pyridine-3,5-dicarbonitrile (Table 3, entry 15)*

Yellow solid; mp 242–245 °C; R_f 0.75 (40% AcOEt/Petroleum ether); IR (KBr): 1155, 1227, 1373, 1437, 1523, 1566, 2227, 3285 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 3.74 (s, 3H, –NCH_3), 4.25 (s, 3H, –OCH_3), 6.77 (s, 1H, –Ar–*H*), 6.91 (s, 1H, –Ar–*H*), 7.11–7.15 (m, 2H, –Ar–*H*), 7.26–7.28 (m, 2H, –Ar–*H*), 7.53–7.57 (m, 2H, –Ar–*H*), 8.48–8.49 (m, 1H, –Ar–*H*), 8.63 (s, 1H, –Ar–*H*), 12.20 (br s, 1H, –N*H*); ^{13}C NMR (125 MHz, DMSO-d_6): δ 31.6, 56.4, 93.2, 98.2, 111.1, 111.2, 113.1, 114.6, 118.1, 120.8, 121.6, 122.4, 123.6, 123.7, 127.3, 132.3, 132.7, 137.1, 138.7, 152.0, 161.6, 164.9, 166.2; MS (EI): *m*/*z* 404.33 [M^++H^+]. Anal. Calcd for $C_{25}H_{17}N_5O$: C, 74.43; H, 4.25; N, 17.36. Found: C, 74.34; H, 4.26; N, 17.39.

4.2.16. ***4p****. 2,4-di-1H-indol-3-yl-6-methoxypyridine-3,5-dicarbonitrile (Table 3, entry 16)*

Yellow solid; mp 230–233 °C; R_f 0.41 (40% AcOEt/Petroleum ether); IR (KBr): 1147, 1227, 1304, 1519, 1555, 1611, 2222, 3263, 3364 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 4.22 (s, 3H, –OCH_3), 7.13 (t, 1H, *J*=6.9 Hz, –Ar–*H*), 7.21–7.24 (m, 3H, –Ar–*H*), 7.52–7.54 (m, 2H, –Ar–*H*), 7.57 (d, 1H, *J*=7.6 Hz, –Ar–*H*), 7.96 (s, 1H, –Ar–*H*), 8.44–8.46 (m, 1H, –Ar–*H*), 8.59 (s, 1H, –Ar–*H*), 10.89 (br s, 1H, –N*H*), 11.87 (br s, 1H, –N*H*); ^{13}C NMR (125 MHz, DMSO-d_6): δ 56.1, 91.7, 97.7, 109.0, 112.8, 112.9, 113.0, 115.6, 119.2, 120.5, 120.7, 122.1, 122.6, 122.8, 123.4, 125.3, 126.6, 129.0, 132.0, 136.7, 137.1, 155.3, 159.8, 162.6, 165.5; MS (EI): *m*/*z* 390.20 [M^++H^+]. Anal. Calcd for $C_{24}H_{15}N_5O$: C, 74.02; H, 3.88; N, 17.98. Found: C, 74.11; H, 3.87; N, 17.95.

4.2.17. ***6a****. 6-Methoxy-4-phenyl-2,2′-bipyridine-5-carbonitrile (Table 4, entry 1)*

White solid; mp 168–170 °C; R_f 0.8 (40% AcOEt/Petroleum ether); IR (KBr): 1197, 1266, 1463, 1547, 1580, 2221 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.20 (s, 3H, Ar–OCH_3), 7.35–7.37 (m, 1H, –Ar–*H*), 7.50–7.52 (m, 3H, –Ar–*H*), 7.69–7.71 (m, 2H, –Ar–*H*), 7.83–7.85 (m, 1H, –Ar–*H*), 8.24 (s, 1H, –Ar–*H*), 8.45 (d, 1H, *J*=7.6 Hz, Ar–*H*), 8.68 (d, 1H, *J*=3.8 Hz, Ar–*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 54.7, 94.7, 114.5, 115.7, 122.1, 124.9, 128.6, 129.0, 130.1, 136.2, 137.2, 149.5, 154.3, 156.5, 157.1, 165.1; MS (ESI LCQ-MS): *m*/*z* 288.20 [M+H]$^+$. Anal. Calcd for $C_{18}H_{13}N_3O$: C, 75.25; H, 4.56; N, 14.63. Found: C, 75.08; H, 4.57; N, 14.59.

4.2.18. ***6b****. 6-Methoxy-4-(4-methylphenyl)-2,2′-bipyridine-5-carbonitrile (Table 4, entry 2)*

White solid; mp 174–176 °C; R_f 0.82 (40% AcOEt/Petroleum ether); IR (KBr): 1141, 1265, 1359, 1441, 1548, 2219, 2945 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.41 (s, 3H, –Ar–CH_3), 4.18 (s, 3H, Ar–OCH_3), 7.30 (d, 2H, *J*=8.4 Hz, –Ar–*H*), 7.33–7.36 (m, 1H, –Ar–*H*), 7.60 (d, 2H, *J*=7.6 Hz, –Ar–*H*), 7.82–7.85 (m, 1H, –Ar–*H*), 8.21 (s, 1H, –Ar–*H*), 8.43 (d, 1H, *J*=8.4 Hz, *Ar*–H), 8.67 (d, 1H, *J*=3.8 Hz, *Ar*–H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.6, 54.7, 94.5, 114.3, 115.9, 122.1, 124.9, 128.5, 129.7, 133.4, 137.1, 140.4, 149.5, 154.4, 156.4, 157.0, 165.1; MS (ESI LCQ-MS): *m*/*z* 302.20 [M+H]$^+$. Anal. Calcd for $C_{19}H_{15}N_3O$: C, 75.73; H, 5.02; N, 13.94. Found: C, 75.90; H, 5.00; N, 13.89.

4.2.19. ***6c****. 6-Methoxy-4-(4-methoxyphenyl)-2,2′-bipyridine-5-carbonitrile (Table 4, entry 3)*

White solid; mp 210–212 °C; R_f 0.75 (40% AcOEt/Petroleum ether); IR (KBr): 1138, 1266, 1445, 1583, 2216, 2945 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.87 (s, 3H, –Ar–OCH_3), 4.19 (s, 3H, Ar–OCH_3), 7.02 (d, 2H, *J*=9.1 Hz, –Ar–*H*), 7.34–7.37 (m, 1H, –Ar–*H*), 7.68–7.70 (m, 2H, –Ar–*H*), 7.83–7.86 (m, 1H, –Ar–*H*), 8.21 (s, 1H, –Ar–*H*), 8.44 (d, 1H, *J*=7.6 Hz, *Ar*–H), 8.68 (d, 1H, *J*=4.6 Hz, *Ar*–H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 54.7, 55.5, 94.2, 114.1, 114.4, 116.0, 122.1, 124.8, 128.5, 130.2, 137.1, 149.5, 154.5, 156.3, 156.6, 161.2, 165.2; MS (ESI LCQ-MS): *m*/*z* 318.27 [M+H]$^+$. Anal. Calcd for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76; N, 13.24. Found: C, 71.75; H, 4.77; N, 13.28.

4.2.20. ***6d****. 4-(4-Chlorophenyl)-6-methoxy-2,2′-bipyridine-5-carbonitrile (Table 4, entry 4)*

White solid; mp 216–218 °C; R_f 0.81 (40% AcOEt/Petroleum ether); IR (KBr): 1141, 1195, 1267, 1361, 1573, 2215, 2939 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.19 (s, 3H, Ar–OCH_3), 7.35–7.37 (m, 1H, –Ar–*H*), 7.47 (d, 2H, *J*=8.4 Hz, –Ar–*H*), 7.62 (d, 2H, *J*=8.4 Hz, –Ar–*H*), 7.83–7.87 (m, 1H, –Ar–*H*), 8.19 (s, 1H, –Ar–*H*), 8.43 (d, 1H, *J*=7.6 Hz, Ar–*H*), 8.67 (d, 1H, *J*=3.9 Hz, Ar–*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 54.8, 94.5, 114.1, 115.5, 122.2, 125.1, 129.3, 130.0, 134.6, 136.4, 137.2, 149.6, 154.1, 155.6, 156.8, 161.1; MS (ESI LCQ-MS): *m*/*z* 322.20 [M+H]$^+$. Anal. Calcd for $C_{18}H_{12}ClN_3O$: C, 67.19; H, 3.76; N, 13.06. Found: C, 67.32; H, 3.77; N, 13.11.

4.2.21. ***6e****. 4-(2,4-Dichlorophenyl)-6-methoxy-2,2′-bipyridine-5-carbonitrile (Table 4, entry 5)*

White solid; mp 164–166 °C; R_f 0.85 (40% AcOEt/Petroleum ether); IR (KBr): 1142, 1264, 1362, 1559, 2225, 2952 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.21 (s, 3H, Ar–OCH_3), 7.31 (d, 1H, *J*=8.4 Hz, –Ar–*H*), 7.36–7.38 (m, 2H, –Ar–*H*), 7.54 (d, 1H, *J*=2.3 Hz, –Ar–*H*), 7.84–7.87 (m, 1H, –Ar–*H*), 8.13 (s, 1H, –Ar–*H*), 8.45 (d, 1H, *J*=7.6 Hz, Ar–*H*), 8.66 (d, 1H, *J*=3.8 Hz, Ar–*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 54.8, 96.7, 115.2, 122.2, 125.1, 127.6, 130.2, 131.3, 133.3, 136.4, 137.2, 149.6, 153.9, 154.0, 156.8, 164.4; MS (ESI LCQ-MS): *m*/*z* 356.27 [M+H]$^+$. Anal. Calcd for $C_{18}H_{11}Cl_2N_3O$: C, 60.69; H, 3.11; N, 11.80. Found: C, 60.82; H, 3.10; N, 11.75.

4.2.22. ***6f****. 4-(4-Bromophenyl)-6-methoxy-2,2′-bipyridine-5-carbonitrile (Table 4, entry 6)*

White solid; mp 204–206 °C; R_f 0.83 (20% AcOEt/Petroleum ether); IR (KBr): 1245, 1363, 1448, 1546, 2220, 2924 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.21 (s, 3H, Ar–OCH_3), 7.36–7.39 (m, 1H, –Ar–*H*), 7.56–7.58 (m, 2H, –Ar–*H*), 7.64–7.66 (m, 2H, –Ar–*H*), 7.85–7.88 (m, 1H, –Ar–*H*), 8.21 (s, 1H, –Ar–*H*), 8.45 (d, 1H, *J*=8.4 Hz, Ar–*H*),

8.68 (d, 1H, *J*=4.6 Hz, Ar–*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 54.8, 94.5, 114.1, 115.4, 122.2, 124.8, 125.0, 130.2, 132.3, 135.1, 137.2, 149.6, 154.2, 155.7, 156.8, 162.8, 165.1; MS (ESI LCQ-MS): *m*/*z* 366.27 $[M+H]^+$. Anal. Calcd for $C_{18}H_{12}BrN_3O$: C, 59.03; H, 3.30; N, 11.43. Found: C, 59.21; H, 3.29; N, 11.43.

4.2.23. ***6g****. 4-(4-Fluorophenyl)-6-methoxy-2,2′-bipyridine-5-carbonitrile (Table 4, entry 7)*

White solid; mp 198–200 °C; R_f 0.81 (40% AcOEt/Petroleum ether); IR (KBr): 1146, 1224, 1364, 1437, 15,554, 2218 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.19 (s, 3H, Ar–OC*H*$_3$), 7.18–7.21 (m, 2H, –Ar–*H*), 7.35–7.38 (m, 1H, –Ar–*H*), 7.67–7.70 (m, 2H, –Ar–*H*), 7.83–7.87 (m, 1H, –Ar–*H*), 8.19 (s, 1H, –Ar–*H*), 8.44 (d, 1H, *J*=7.6 Hz, Ar–*H*), 8.67 (d, 1H, *J*=3.8 Hz, Ar–*H*); ^{13}C NMR (125 MHz, $CDCl_3$): 54.8, 94.5, 114.3, 115.6, 116.1, 116.2, 122.2, 125.0, 130.6, 130.7, 137.2, 149.5, 154.2, 155.9, 156.6, 162.9, 164.9, 165.1; MS (ESI LCQ-MS): *m*/*z* 306.20 $[M+H]^+$. Anal. Calcd for $C_{18}H_{12}FN_3O$: C, 70.81; H, 3.96; N, 13.76. Found: C, 70.99; H, 3.95; N, 13.71.

4.2.24. ***6h****. 6-Methoxy-4-(3-nitrophenyl)-2,2′-bipyridine-5-carbonitrile (Table 4, entry 8)*

White solid; mp 226–227 °C; R_f 0.67 (40% AcOEt/Petroleum ether); IR (KBr): 1014, 1278, 1356, 1552, 2219 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.24 (s, 3H, Ar–OC*H*$_3$), 7.39–7.41 (m, 1H, –Ar–*H*), 7.72 (t, 1H, *J*=7.2 Hz, Ar–*H*), 7.87 (t, 1H, *J*=7.2 Hz, Ar–*H*), 8.04 (d, 1H, *J*=7.6 Hz, Ar–*H*), 8.28 (s, 1H, –Ar–*H*), 8.37 (d, 1H, *J*=8.4 Hz, Ar–*H*), 8.47 (d, 1H, *J*=7.6 Hz, Ar–*H*), 8.54 (s, 1H, –Ar–*H*), 8.71 (d, 1H, *J*=2.3 Hz, Ar–*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.0, 96.1, 114.2, 115.0, 122.3, 123.7, 124.8, 125.3, 130.2, 134.5, 137.3, 137.9, 149.6, 153.8, 154.3, 157.4, 165.1; MS (ESI LCQ-MS): *m*/*z* 333.27 $[M+H]^+$. Anal. Calcd for $C_{18}H_{12}N_4O$: C, 65.61; H, 3.64; N, 16.86. Found: C, 65.22; H, 3.63; N, 16.81.

4.3. Procedure for synthesis of bis(indol-3-yl pyridine) derivatives

A mixture of 3-cyanoacetyl indole (1 mmol), dialdehyde (0.5 mmol) and indium trichloride (20 mol %) in 30 mL of methanol was refluxed. After 15 min malononitrile (1 mmol) was added and the reflux was continued for 5 h. After the completion of the reaction (as monitored by TLC), it was poured into water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated under vacuum. The crude product was chromatographed (60:40 petroleum ether/ethyl acetate) and isolated yield was 68%.

4.3.1. Phenyl 1,4-bis(2-(1H-indol-3-yl)-6-methoxypyridine-3,5-dicarbonitrile)

Yellow solid; mp<350 °C; R_f .38 (60% EtOAc/Petroleum ether); IR (KBr): 1371, 1465, 1565, 2370, 3234, 3347 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 4.24 (s, 6H, Ar–OC*H*$_3$), 7.25–7.27 (m, 4H, –Ar–*H*), 7.53–7.56 (m, 2H, –Ar–*H*), 7.68 (s, 2H, –Ar–*H*), 7.74 (d, 2H, *J*=8.4 Hz), 7.82 (d, 2H, *J*=8.4 Hz), 8.45 (d, 2H, *J*=8.4 Hz, –Ar–*H*), 8.58 (s, 2H, –Ar–*H*), 12.17 (br s, 2H, –N*H*); ^{13}C NMR (125 MHz, DMSO-d_6): δ 56.7, 91.9, 97.8, 112.9, 113.8, 118.9, 122.8, 123.9, 126.5, 128.8, 130.9, 133.6, 137.4, 157.8, 159.8, 161.8, 164.3; MS (ESI LCQ-MS): *m*/*z* 625.40 $[M+H]^+$. Anal. Calcd for $C_{38}H_{24}N_8O_2$: C, 73.07; H, 3.87; N, 17.94. Found: C, 73.19; H, 3.88; N, 17.89.

4.4. General procedure for the synthesis of indenopyridine derivatives

A mixture of 3-cyanoacetyl indole (1 mmol), aldehyde (1 mmol) and indium trichloride (20 mol %) in 30 mL of methanol was refluxed. After 15–30 min 2-indanone (1 mmol) and ammonium acetate in excess was added and then reflux was continued for appropriate time mentioned as in Table 5. After the completion of the reaction (as monitored by TLC), it was poured into water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated under vacuum. The crude product was chromatographed (90:10, petroleum ether/ethyl acetate) and appropriate isolated yield was shown in Table 5.

4.4.1. ***10a****. 2-(1H-Indol-3-yl)-4-phenyl-9H-indeno[2,1-b]pyridine-3-carbonitrile (Table 4, entry 1)*

Light brown solid; mp 298–300 °C; R_f 0.31 (20% EtOAc/Petroleum ether); IR (KBr): 1102, 1377, 1467, 1598, 2180, 3344, 3394 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.21 (s, 2H, –Ar–C*H*$_2$), 6.74 (d, 1H, *J*=7.6 Hz, –Ar–*H*), 7.15 (t, 1H, *J*=7.6 Hz, –Ar–*H*), 7.25 (s, 1H, –Ar–*H*), 7.30–7.34 (m, 3H, –Ar–*H*), 7.45 (d, 3H, *J*=7.6 Hz, –Ar–*H*), 7.58 (t, 3H, *J*=7.6 Hz, –Ar–*H*), 8.29 (d, 1H, *J*=3.0 Hz, –Ar–*H*), 8.52–8.56 (m, 1H, –Ar–*H*), 8.61 (br s, 1H, –N*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 29.7, 104.0, 111.4, 114.3, 118.4, 121.6, 122.3, 123.0, 123.3, 125.2, 126.4, 127.2, 127.3, 128.1, 129.3, 129.7, 130.3, 133.9, 135.8, 136.3, 137.9, 141.4, 147.0, 155.4, 168.4; MS (ESI LCQ-MS): *m*/*z* 384.47 $[M+H]^+$. Anal. Calcd for $C_{27}H_{17}N_3$: C, 84.57; H, 4.47; N, 10.96. Found: C, 87.50; H, 4.48; N, 11.01.

4.4.2. ***10b****. 2-(1H-Indol-3-yl)-4-(4-methylphenyl)-9H-indeno[2,1-b]pyridine-3-carbonitrile (Table 4, entry 2)*

Light brown solid; mp 201–203 °C; R_f 0.4 (20% EtOAc/Petroleum ether); IR (KBr): 1234, 1433, 1532, 2229, 3052, 3316 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.51 (s, 3H, –Ar–C*H*$_3$), 4.20 (s, 2H, –Ar–C*H*$_2$), 6.78 (d, 1H, *J*=8.5 Hz), 7.10 (t, 1H, *J*=7.6 Hz, –Ar–*H*), 7.29–7.32 (m, 3H, –Ar–*H*), 7.38–7.43 (m, 5H, –Ar–*H*), 7.57 (d, 1H, *J*=7.6 Hz), 8.28 (d, 1H, *J*=3.0 Hz), 8.52–8.54 (m, 1H, –Ar–*H*), 8.61 (br s, 1H, –N*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.6, 29.7, 104.5, 111.3, 114.4, 118.7, 121.5, 122.3, 123.1, 123.2, 125.1, 126.5, 127.0, 127.1, 127.8, 128.2, 129.5, 130.0, 132.5, 136.3, 138.3, 139.5, 141.4, 148.7, 155.3, 168.1; MS (ESI LCQ-MS): *m*/*z* 397.47 $[M+H]^+$. Anal. Calcd for $C_{28}H_{19}N_3$: C, 84.71; H, 4.82; N, 10.57. Found: C, 84.68; H, 4.81; N, 10.52.

4.4.3. ***10c****. 2-(1H-Indol-3-yl)-4-(4-methoxyphenyl)-9H-indeno[2,1-b]pyridine-3-carbonitrile (Table 4, entry 3)*

Yellow solid; mp 228–230 °C; R_f 0.2 (20% EtOAc/Petroleum ether); IR (KBr): 1304, 1490, 1600, 1657, 2373, 3362 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.81 (s, 3H, –Ar–OC*H*$_3$), 4.18 (s, 2H, –Ar–C*H*$_2$), 6.62 (d, 1H, *J*=7.6 Hz, –Ar–*H*), 7.10–7.20 (m, 5H, –Ar–*H*), 7.27–7.31 (m, 1H, –Ar–*H*), 7.44–7.49 (m, 3H, –Ar–*H*), 7.59 (d, 1H, *J*=6.9 Hz, –Ar–*H*), 8.25 (d, 1H, *J*=3.1 Hz, –Ar–*H*), 8.37 (d, 1H, *J*=3.1 Hz, –Ar–*H*), 11.76 (br s, 1H, –N*H*); ^{13}C NMR (125 MHz, DMSO-d_6): δ 36.0, 55.4, 114.1, 114.3, 122.5, 123.0, 123.2, 124.8, 125.0, 125.4, 126.8, 127.1, 127.2, 127.3, 128.9, 130.2, 130.3, 130.4, 133.2, 134.0, 139.6, 139.8, 142.1, 142.6, 145.4, 152.3, 159.6, 161.7; MS (ESI LCQ-MS): *m*/*z* 413. 46 $[M+H]^+$. Anal. Calcd for $C_{28}H_{19}N_3O$: C, 81.34; H, 4.63; N, 10.16. Found: C, 81.23; H, 4.64; N, 10.20.

4.4.4. ***10d****. 2-(1H-Indol-3-yl)-4-(1-napthyl)-9H-indeno[2,1-b] pyridine-3-carbonitrile (Table 4, entry 4)*

Yellow solid; mp 208–211; R_f 0.22 (20% EtOAc/Petroleum ether); IR (KBr): 1122, 1234, 1420, 1532, 2220, 3387 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.27 (ABq, 2H, *J*=8.9 Hz, –Ar–C*H*$_2$), 6.86 (t, 1H, *J*=7.6 Hz, –Ar–*H*), 7.20 (t, 1H, *J*=6.9 Hz, –Ar–*H*), 7.32–7.39 (m, 4H, –Ar–*H*), 7.44–7.47 (m, 2H, –Ar–*H*), 7.54–7.58 (m, 3H, –Ar–*H*), 7.68 (t, 1H, *J*=8.4 Hz, –Ar–*H*), 8.00 (d, 1H, *J*=8.4 Hz, –Ar–*H*), 8.09 (d, 1H, *J*=8.4 Hz, –Ar–*H*), 8.31 (d, 1H, *J*=2.9 Hz, –Ar–*H*), 8.60 (br s, 1H, –N*H*), 8.62–8.65 (m, 1H, –Ar–*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 29.6, 104.6, 111.7, 113.8, 118.4, 121.2, 122.2, 122.8, 122.9, 124.7, 124.9, 125.7, 126.4, 126.5, 126.6, 127.0, 127.1, 127.6, 127.9, 128.8, 129.8, 130.1, 130.6, 133.1, 133.6, 136.6, 137.9, 141.2, 146.7, 155.8, 168.0; MS (ESI LCQ-MS): *m*/*z* 434.40 $[M+H]^+$. Anal. Calcd for $C_{31}H_{19}N_3$: C, 85.89; H, 4.42; N, 9.69. Found: C, 85.83; H, 4.43; N, 9.64.

4.4.5. ***10e.*** *2-(1H-Indol-3-yl)-4-(4-chlorophenyl)-9H-indeno[2,1-b]pyridine-3-carbonitrile (Table 4, entry 5)*

Yellow solid; mp 208–211; R_f 0.37 (20% EtOAc/Petroleum ether); IR (KBr):1275, 1345, 1521, 1608, 2347, 3312 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 4.20 (s, 2H, –Ar–CH_2), 6.71 (d, 1H, J=7.6 Hz, –Ar–*H*), 7.12 (t, 1H, J=7.6 Hz, –Ar–*H*), 7.25–7.30 (m, 3H, –Ar–*H*), 7.46–7.51 (m, 3H, –Ar–*H*), 7.58 (t, 3H, J=7.6 Hz, –Ar–*H*), 8.30 (d, 1H, J=2.9 Hz, –Ar–*H*), 8.52–8.55 (m, 1H, –Ar–*H*), 10.80 (br s, 1H, –N*H*); ^{13}C NMR (125 MHz, DMSO-d_6): δ 26.6, 103.1, 111.6, 113.1, 118.3, 120.8, 121.7, 121.9, 122.5, 124.9, 126.2, 127.7, 127.8, 128.0, 128.5, 129.3, 133.7, 135.3, 136.4, 137.6, 141.0, 146.6, 155.5, 168.0; MS (ESI LCQ-MS): m/z 418.40 $[M+H]^+$. Anal. Calcd for $C_{27}H_{16}ClN_3$: C, 77.60; H, 3.86; N, 10.06. Found: C, 77.51; H, 3.87; N, 10.11.

4.4.6. ***10f.*** *2-(1H-Indol-3-yl)-4-(2, 4-dichlorophenyl)-9H-indeno[2,1-b]pyridine-3-carbonitrile (Table 3, entry 6)*

Yellow solid; mp 272–274 °C; R_f 0.33 (20% EtOAc/Petroleum ether); IR (KBr): 1080, 1491, 1575, 1649, 2237, 3373, 3420 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.18 (ABq, 2H, J=9.0 Hz, –Ar–CH_2), 6.61 (d, 1H, J=8.4 Hz, –Ar–*H*), 7.18 (t, 1H, J=7.6 Hz, –Ar–*H*), 7.31–7.39 (m, 4H, –Ar–*H*), 7.47–7.52 (m, 2H, –Ar–*H*), 7.60 (d, 1H, J=7.6 Hz, –Ar–*H*), 7.70 (d, 1H, J=1.6 Hz, –Ar–*H*), 8.32 (d, 1H, J=3.1 Hz, –Ar–*H*), 8.56–8.58 (m, 1H, –Ar–*H*), 8.61 (br s, 1H, –N*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 35.6, 108.8, 112.5, 117.0, 120.3, 120.5, 122.1, 122.5, 123.3, 124.0, 125.4, 126.9, 127.5, 128.8, 129.2, 132.8, 133.3, 136.4, 138.5, 141.8, 143.3, 145.5, 154.8, 162.5; MS (ESI LCQ-MS): m/z 452.33 $[M+H]^+$. Anal. Calcd for $C_{27}H_{15}Cl_2N_3$: C, 71.69; H, 3.34; N, 9.29. Found: C, 71.77; H, 3.35; N, 9.23.

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Supplementary data

Supplementary data associated with this article can be found in online version, at doi:10.1016/j.tet.2009.06.097.

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