Spectral Assignments and Reference Data

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Synthesis and NMR spectral assignments of indol-3-yl pyridines through one-pot multi-component reaction

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Asimple protocol for the efficient preparation of 6-(ferrocene-1-yl)-2-(indol-3-yl)pyridine and 2-(1*H*-indol-3-yl)-6-(2-thienyl)pyridine derivatives has been achieved through multi-component reaction, and these compounds were thoroughly characterised by 2D NMR spectral techniques. Copyright © 2010 John Wiley & Sons, Ltd.

Supporting information may be found in the online version of this article.

Keywords: ^{1}H NMR; ^{13}C NMR; 2D NMR; indol-3-yl pyridines; 3-cyanoacetyl indoles

Introduction

The structural diversity and biological importance of nitrogen containing heterocycles have made them attractive targets for synthesis over many years. They are found in various natural products and have been identified as products of chemical and biological importance.[1,2] 3-Substituted indole scaffolds are found in a number of biologically active compounds especially with anticancer, antitumour,[3] anti-inflammatory, hypoglycemic, analgesic, and antipyretic activities.[4] On the other hand, pyridine substructure is one of the most important heterocycles found in natural products, pharmaceuticals, and functional materials.[5] 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.[6]

The wide-ranging biological activity associated with 3-substituted indoles and pyridines derivatives, both naturally occurring and synthetic, ensures that the synthesis of this important ring system remains a topic of current interest.[7–10] As part of our ongoing research on the development of novel synthetic routes for the synthesis of biologically active heterocyclic compounds[11–13] herein, we report the synthesis,[14] ^{1}H and ^{13}C NMR spectral assignment of 6-(ferrocene-1-yl)-2-(indol-3-yl)pyridine and (1*H*-indol-3-yl)-6-(2-thienyl)pyridine derivatives through 2D NMR spectral techniques in solution.

Results and Discussion

The structure of compounds **4A**–**E** was established based on the detailed spectroscopic studies, and the elemental analysis as exemplified for compound **4B** as follows: stretching frequencies at 3416 and 2246 cm^{-1} in the IR spectrum confirm the presence of –NH and –C≡N functional groups. The ^{1}H NMR spectrum showed chemical shift of δ = 11.14 ppm (brs, D_2O exchangeable) which corresponds to –NH proton, and the aromatic protons resonated in the region of δ = 7.23–8.70 ppm. The three sharp distinct peaks appearing in the region of δ = 68.4, 70.0, 71.1, and 82.5 ppm correspond to ferrocenyl ring carbons in the ^{13}C NMR spectrum and the aromatic carbons appeared in the region of δ = 112.0–162.7 ppm. The mass spectrum displayed the molecular ion $[M + H]^+$ peak at *m/z* 494.20 (Scheme 1)

The structure of compounds **6A**–**F** was confirmed through spectral and elemental analysis. In the IR spectrum of compound **6B**, absorptions at wave numbers 3314 and 2214 cm^{-1} confirmed the presence of –NH and –C≡N functionalities. The ^{1}H NMR spectrum exhibited a broad singlet at δ = 11.83 ppm (D_2O exchangeable) for –NH protons and a sharp distinguishable singlet at δ = 2.38 ppm for methyl protons. Aromatic protons were seen in the region of δ = 7.22–8.51 ppm. A characteristic peak at δ = 21.4 ppm in the ^{13}C NMR spectrum confirmed the presence of methyl carbon. The cyano group attached carbon showed a characteristic peak at δ = 100.7 ppm. The mass spectrum displayed the molecular ion $[M + H]^+$ peak at *m/z* 392.27 (Scheme 2).

Due to the vast medicinal applications of the substituted pyridine derivatives, it is worthwhile to characterise these compounds with the aid of 1D and 2D NMR spectral studies such as ^{1}H–^{1}H COSY, HETCOR, HSQC, and HMBC. In order to assign a chemical shift value to each proton and carbon, atom numbering was assigned to all derivatives of compounds **4A**–**E** and**6A**– **F**.

The chemical shift value of each proton assigned to compounds **4A**–**E** is summarised in Table 1. Noticeable differences in chemical shift values due to the substituents present in the compound **4A**–**E** were observed. The HETCOR and HSQC correlation spectra gave the

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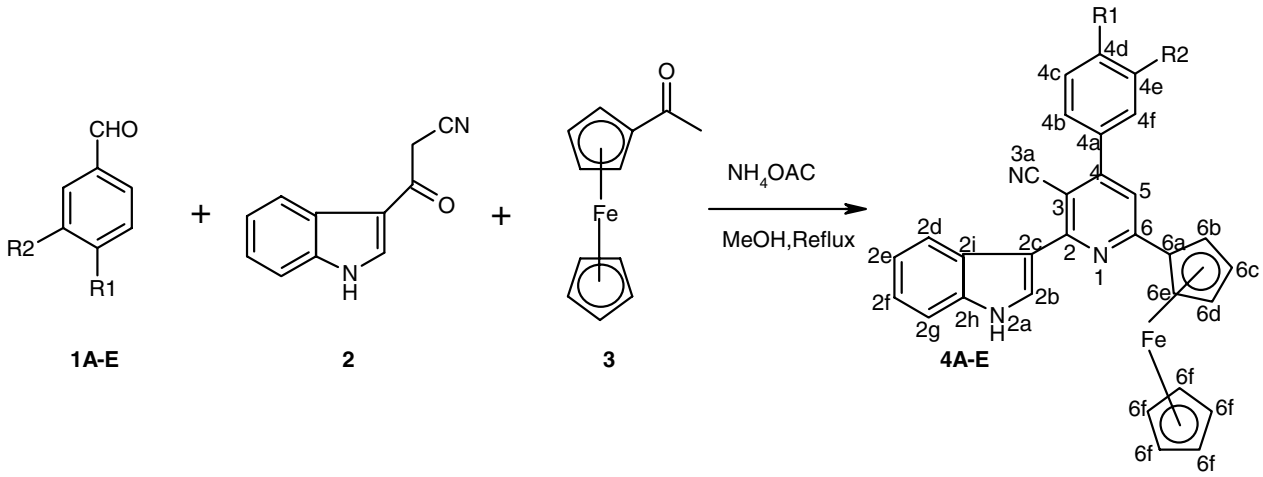


Aldehydes	R_1	R_2	Product[a]	Time(h)	Yield(%)[b]
1A	H	H	4A	6.0	72
1B	CH_3	H	4B	6.5	76
1C	Br	H	4C	7.5	70
1D	F	H	4D	7.0	74
1E	H	NO_2	4E	7.5	75

[a]The products were characterized by NMR, IR, MASS and elemental analysis.

[b]Isolated yield.

Scheme 1. Synthesis of 6-(ferrocene-1-yl)-2-(indol-3-yl)pyridine derivative **4A**–**E** from various aldehydes.

same information about $^{1}H-^{13}C$ correlation connected through one bond, whereas the HMBC correlation spectrum contained the information on the $^{1}H-^{13}C$ correlation connected through two and three bonds. By combining the HETCOR/HSQC and HMBC correlation spectra, the ^{13}C chemical shifts for all compounds were assigned and are summarised in Tables 2 and 3 (see the supporting information).

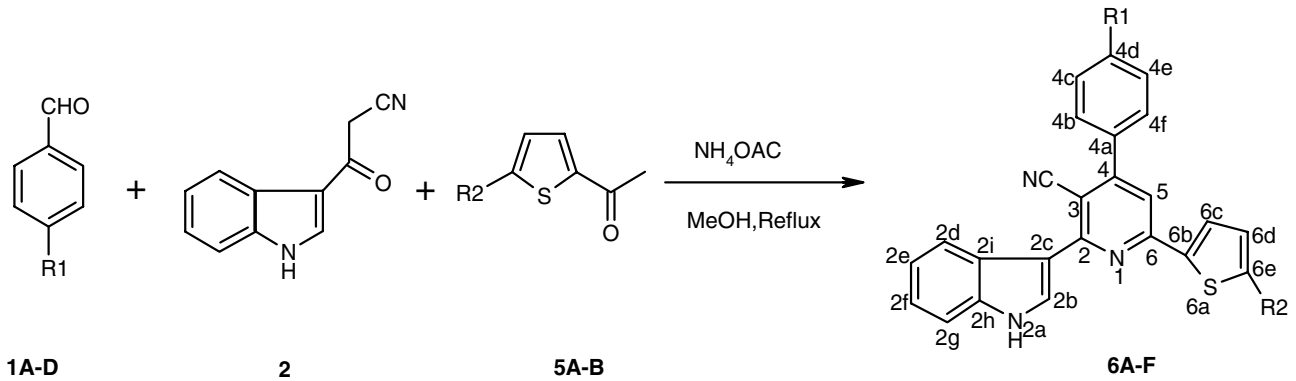
Based on the detailed 2D NMR spectral studies, the structural assignments were made for the compounds **4A**–**E** as exemplified for compound **4B** as follows: From the literature, the peaks appearing at $\delta = 5.11, 4.54$ and 4.13 ppm correspond to ferrocenyl ring protons. The effect of pyridine ring was manifested by distinct chemical shifts of ferrocene ring protons $\delta = 5.11$ and 4.54 ppm. The observation of sharp singlet at 4.13 ppm can be recognised as the cyclopentadiene ring, connected only to the iron atom. A broad distinguishable singlet appearing at $\delta = 11.77$ ppm with D_2O exchange corresponds to the indolyl –NH proton. The peaks at $\delta = 8.39$ and 7.51 ppm did not show any cross-correlation in the aromatic region of $^{1}H-^{1}H$ COSY spectrum. Based on the splitting pattern, the proton chemical shifts were assigned as H-2b ($\delta = 8.39$ ppm) and H-5 ($\delta = 7.51$ ppm). Based on the cross-peak correlations in $^{1}H-^{1}H$ COSY spectrum, splitting pattern, integral values, and coupling constants in the ^{1}H NMR spectrum, the indolyl ring and phenyl ring protons were assigned. The indolyl ring protons appeared at $\delta = 8.70$ and 7.23 ppm and the aromatic protons were observed at $\delta = 7.36$ and 7.56 ppm.

From the proton assignments in Table 1 and the HETCOR/HSQC spectra, the chemical shift of carbons was assigned based on their one-bond coupling with hydrogen. The remaining quaternary carbon signals were assigned through HMBC spectra. In a similar fashion, the NMR structural assignments were made for the compounds **6A**–**F** based on the 2D NMR spectral studies. The proton chemical shift and coupling constant data are documented in Table 4. The carbon chemical shifts and HMBC correlations of compounds (**6A**–**F**) are summarised in Tables 5 and 6, respectively.

Finally, we have carried out ^{15}N NMR spectral studies on compounds **4A**–**E** and **6A**–**F**; however, we were able to observe ^{15}N signal for the compound **6B** only. The distinct singlet appearing at $\delta = -126.69$ ppm corresponds to indole –NH nitrogen in the ^{15}N NMR spectrum (with reference to nitromethane), whereas the other nitrogens were not observed owing to their long relaxation times.

Conclusions

In summary, we have demonstrated a simple method for the synthesis of indol-3-yl pyridine derivatives through multi-component reaction employing structurally diverse aldehydes with 3-cyanoacetyl indole and 2-acetyl thiophene (or) 1-acetyl



1A-D **2** **5A-B** **6A-F**

Aldehydes	R_1	R_2	Product[a]	Time(h)	Yield(%)[b]
1A	H	H	6A	6.0	72
1B	CH_3	H	6B	6.5	76
1C	OMe	H	6C	7.5	70
1D	F	H	6D	6.5	71
1A	H	Br	6E	7.0	74
1B	CH_3	Br	6F	7.5	75

[a]The products were characterized by NMR, IR, MASS and elemental analysis.

[b]Isolated yield.

Scheme 2. Synthesis of 6-(indol-3-yl)-(2-thienyl)pyridine derivative **6A–F** from various aldehydes.

ferrocene. ^{1}H and ^{13}C NMR chemical shift values for the newly synthesised indol-3-yl pyridine derivatives were assigned using 2D NMR techniques.

Experimental

General

All the substituted aldehydes, 1-acetyl ferrocene, 2-acetyl thiophene, indole, and DMSO-d_6 were purchased from Aldrich Chemicals. Acetic anhydride and other reagents were procured from S. D. Fine Chemicals Ltd. (India), and were used as received. IR spectra were taken as KBr pellets for solids on a Perkin Elmer spectrum RXI FT-IR.

All NMR experiments were made on a JEOL ECA-500 MHz high resolution FT-NMR spectrometer operating at frequencies 500.16 MHz (^{1}H), 125.77 (^{13}C), and 50.68 (^{15}N). An amount of 30 mg of compounds was dissolved in 0.7 ml of DMSO-d_6. Tetramethylsilane was used an internal reference standard for the assignment of ^{1}H and ^{13}C chemical shifts. ^{15}N chemical shifts were given with reference to nitro methane as an internal standard. All the NMR spectra were recorded at 298 K. JEOL-Delta software package (version 4.3.6) was used for the purpose of NMR pulse sequences and data processing.

The experimental parameters chosen for 1D ^{1}H/^{13}C NMR were as follows: spectral width 15/250 ppm, number of data points 16,384/32,768, number of scans 8/200, acquisition time 1.3/0.83 s, relaxation delay 5/2 s, and 90° pulse width 12.5/10.2 µs. The experimental parameters chosen for ^{15}N NMR were as follows: spectral width 600 ppm, number of data points 16,384, number scan 1000, acquisition time 0.54 s, relaxation delay 5 s and 90° pulse width 25.4 µs. Exponential multiplication was applied before Fourier transformation in both cases.

^{1}H–^{1}H COSY: COSY spectra were obtained using the gradient version of dqf cosy pulse sequence of the JEOL-Delta software. The spectra resulted from 1024 (F_2) × 256 (F_1) data matrix size with one scan per t_1 increment. A spectral width of 15 ppm was used in both F_1 and F_2 dimensions.

^{1}H–^{13}C HETCOR: HETCOR spectra were recorded using the standard hector pulse program of the JEOL-Delta software. The acquisition parameters were as follows: spectra resulted from 1024 × 128 data matrix size with eight scans per t_1 increment. A spectra width of 180 ppm in F_2 and 15 ppm in F_1 was recorded.

^{1}H–^{13}C HSQC: The one-bond correlation of ^{1}H and ^{13}C was tracked using the phase sensitive HSQC pulse sequence of the JEOL-Delta software. The experiments were optimised for the one-bond coupling constant ($^1J_{CH}$) as 140 Hz. The spectra were obtained from 1024 × 256 data matrix size with four scans per t_1 increment. A spectral width of 15 ppm in F_2 and 180 ppm in F_1 was recorded.

Table 1. ^{1}H chemical shifts of compounds **4A**–**E** in DMSO-d_6

Entry	2a	2b	2d	2e	2f	2g
4A	11.77 (brs, 1H, –*NH*)	8.32–8.33 (m, 1H, –Ar–*H*)	8.52–8.53 (m, 1H, –Ar–*H*)	7.15–7.24 (m, 3H, –Ar–*H*)		7.15–7.24 (m, 3H, –Ar–*H*)
4B	11.14 (brs, 1H, –*NH*)	8.39 (m, 1H, –Ar–*H*)	8.70 (d, 1H, $J = 7.7$ Hz, –Ar–*H*)	7.23–7.31 (m, 3H, –Ar–*H*)		7.23–7.31 (m, 3H, –Ar–*H*)
4C	11.78 (brs, 1H, –*NH*)	8.33–8.34 (m, 1H, –Ar–*H*)	8.51 (s, 1H, –Ar–*H*)	7.15–7.24 (m, 2H, –Ar–*H*)		7.44–7.51 (m, 3H, –Ar–*H*)
4D	11.76 (brs, 1H, –*NH*)	8.31–8.33 (m, 1H, –Ar–*H*)	8.51 (s, 1H, –Ar–*H*)	7.15–7.24 (m, 3H, –Ar–*H*)		7.15–7.24 (m, 3H, –Ar–*H*)
4E	11.79 (brs, 1H, –*NH*)	8.35–8.36 (m, 1H, –Ar–*H*)	8.52–8.53 (m, 1H, –Ar–*H*),	7.21–7.26 (m, 2H, –Ar–*H*)		7.52–7.61 (m, 2H, –Ar–*H*)

Entry	4b	4c	4d	5	6b/6e	6c/6d	6f′
4A	7.50–7.56 (m, 4H, –Ar–*H*)	7.50–7.56 (m, 4H, –Ar–*H*)	7.50–7.56 (m, 4H, –Ar–*H*)	7.71–7.73 (m, 2H, –Ar–*H*)	5.21 (s, 2H, –fc–*H*)	4.57(s, 2H, –fc–*H*)	4.11 (s, 5H, –fc–*H*)
4B	7.56–7.58 (m, 2H, –Ar–*H*)	7.36–7.38 (m, 2H, –Ar–*H*)	–	7.51 (d, 1H, $J = 7.7$ Hz, –Ar–*H*)	5.11 (s, 2H, –fc–*H*)	4.54 (s, 2H, –fc–*H*)	4.13 (s, 5H, –fc–*H*)
4C	7.44–7.51 (m, 3H, –Ar–*H*)	7.74–7.76 (m, 2H, –Ar–*H*)	–	7.66–7.68 (m, 1H, –Ar–*H*)	5.19 (s, 2H, –fc–*H*)	4.56 (s, 2H, –fc–*H*)	4.10 (s, 5H, –fc–*H*)
4D	7.41–7.52 (m, 3H, –Ar–*H*)	7.72–7.78 (m, 2H, –Ar–*H*)	–	7.41–7.52 (m, 3H, –Ar–*H*)	5.21 (s, 2H, –fc–*H*)	4.57 (s, 2H, –fc–*H*)	4.10 (s, 5H, –fc–*H*)
4E	8.19 (s, 1H, –Ar–*H*)	6.47–6.52 (m, 2H, –Ar–*H*)	7.52–7.61 (m, 2H, –Ar–*H*)	7.88 (s, 1H, –Ar–*H*)	5.23 (s, 2H, –fc–*H*)	4.60 (s, 2H, –fc–*H*)	4.12 (s, 5H, –fc–*H*)

Table 2. ^{13}C chemical shifts of compound **4A**–**E** in DMSO-d_6

Entry	2	3	4	5	6	4	2b	2c	2d	2e	2f	2g	2h	2i
4A	163.0	99.7	154.3	116.0	157.5	154.3	129.7	114.8	122.8	123.2	121.5	111.5	136.3	126.8
4B	162.7	99.1	154.2	115.5	157.7	154.2	128.3	113.8	122.5	122.6	120.9	112.0	136.7	126.9
4C	163.2	99.2	153.1	116.1	157.5	153.1	128.9	113.5	122.2	123.8	121.3	112.6	136.7	126.9
4D	163.0	99.3	154.3	116.3	157.5	154.3	128.9	113.6	122.2	122.9	121.2	112.6	136.8	126.9
4E	162.3	99.0	151.9	116.0	157.5	151.9	128.6	113.4	122.2	122.9	121.2	112.4	136.7	126.8

Entry	3a	4a	4b	4c	4d	6a	6b/6e	6c/6d	6f′
4A	119.8	137.5	128.7	128.9	127.6	82.4	71.2	68.5	70.1
4B	120.0	134.6	129.5	128.7	139.6	82.5	71.4	68.4	70.0
4C	119.9	136.9	131.6	132.2	123.8	82.5	71.7	68.8	70.3
4D	119.6	137.5	129.4	129.2	130.1	82.6	71.6	68.6	70.3
4E	119.5	139.0	124.5/135.9	148.3/130.7	124.1	82.3	71.6	68.8	70.2

Table 3. ^{1}H chemical shift and HMBC correlation of compounds **4A**–**E** in DMSO-d_6

Entry	4A		4B		4C		4D		4E	
Proton	δ^1H	m	δ^1H	HMBC	δ^1H	HMBC	δ^1H	HMBC	δ^1H	HMBC
2a	11.77	–	11.14	–	11.78	–	11.76	–	11.79	–
2b	8.32–8.33	2c,2h,2i	8.39–8.40	2c,2h,2i	8.33–8.34	2c,2h,2i	8.31–8.33	2c,2h,2i	8.35–8.36	2c,2h,2i
2d	8.52–8.53	2e,2h,2i	8.70	2e,2h,2i	8.51	2e,2h	8.51	2e	8.53–8.53	2e
2e	7.15–7.24	–	7.23–7.31	–	7.15–7.24	2i 2g,2h	7.15–7.24	2g,2i 2h	7.21–7.26	2d 2g
2f										
2g	7.15–7.24	2h,2i	7.23–7.31	–	7.44–7.51	2e,2i	7.15–7.24	–	7.52–7.61	2f,2h,2i
4b	7.50–7.56	4c,4d	7.56–7.58	4,4d,4c	7.44–7.51	4, 4a	7.41–7.52	4c	6.47–6.52, 8.12	4,4c
4c	7.50–7.56	4b	7.36–7.38	4b, 4a	7.74–7.76	4b, 4d	7.72–7.78	4a,4b,4d	6.47–6.52	–
4d	7.50–7.56	4b	–	–	–	–	–	–	7.52–7.61	–
5	7.71–7.73	3,4,6,6a	7.51	3,4	7.66–7.68	3, 4	7.41–7.52	3,4	7.88	3
6b/6e	5.21	6a,6c	5.11	6a,6c	5.19	6a,6c	5.21	6a,6c	5.23	6a,6c
6c/6d	5.47	6a,6b	4.54	6a,6b	4.56	6a,6b	4.57	6a,6b	4.60	6a,6b
6f′	4.11	–	4.13	–	4.10	–	4.10		4.12	

^{1}H–^{13}C HMBC: The gradient version of HMBC experiments were recorded in order to sketch the long-range (two and three bonds) ^{1}H–^{13}C correlations. The long-range coupling constant ($^{n}J_{CH}$) optimised was 8 Hz. The spectra resulted from 2048 × 256 data matrix size with eight scans per t_1 increment. A spectral width of 15 ppm in F_2 and 180 ppm in F_1 was recorded.

2D correlation spectra were recorded in order to track ^{1}H–^{1}H and ^{1}H–^{13}C correlations. A relaxation delay of 1.5 s was used in all the 2D experiments.

Mass spectra were recorded with Thermo Finnigan mass spectrometer using an electrospray ionisation method. Melting points were determined in capillary tubes and are uncorrected. Analytical TLC was performed on precoated 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.

General procedure for the synthesis of 6-(ferrocene-1-yl)-2-(indol-3-yl)pyridine derivatives (4A–E)

A mixture of 1-acetyl ferrocene (1 mmol), aldehyde (1 mmol), and ammonium acetate in methanol was refluxed. After the complete disappearance of the starting materials (monitored by TLC), 3-cyanoacetyl indole was added and the reflux was continued for appropriate time mentioned as in Table 1. After the completion of the reaction as monitored by TLC, the reaction mixture 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, and the appropriate isolated yield of the pure product is shown in Table 1.

*6-(Ferrocene-1-yl)-2-(1H-indol-3-yl)-4-(phenyl)nicotinonitrile (**4A**)*

Deep red colour semisolid; R_f 0.38 (20% AcOEt/petroleum ether); IR (KBr): 1170, 1247, 1445, 1521, 2227, 3421 cm^{-1}; MS (EI): m/z = 480.20 [$M^+ + H^+$]; Anal. Calcd for $C_{30}H_{21}FeN_3$: C 75.17, H 4.42, N 8.77. Found: C 75.06, H 4.43, N 8.79.

*6-(Ferrocene-1-yl)-2-(1H-indol-3-yl)-4-(4-methylphenyl)nicotinonitrile (**4B**)*

Deep red colour semisolid; R_f 0.42 (20% AcOEt/petroleum ether); IR (KBr): 1119, 1223, 1435, 1526, 1559, 3325 cm^{-1}; MS (EI): m/z = 494.20 [$M^+ + H^+$]; Anal. Calcd for $C_{31}H_{23}FeN_3$: C 75.47, H 4.70, N 8.52. Found: C 75.37, H 4.71, N 8.54.

*6-(Ferrocene-1-yl)-2-(1H-indol-3-yl)-4-(4-bromophenyl)nicotinonitrile (**4C**)*

Deep red colour semisolid; R_f 0.51 (20% AcOEt/petroleum ether); IR (KBr): 1168, 1252, 1454, 1642, 2236, 3427 cm^{-1}; MS (EI): m/z =

Table 4. ^{1}H chemical shift of compounds **6A–F** in DMSO-d_6

Entry	2a	2b	2d	2e	2f	2g
6A	11.83 (brs, 1H, –*NH*)	8.40 (s, 1H, –Ar–*H*)	8.12 (d, 1H, $J = 3.9$ Hz, –Ar–*H*)	7.22–7.24 (m, 3H, –Ar–*H*)		7.57 (m, 4H, –Ar–*H*)
6B	11.83 (brs, 1H, –*NH*)	8.39 (s, 1H, –Ar–*H*)	8.10 (s, 1H, –Ar–*H*)	7.22–7.24 (m, 3H, –Ar–*H*)		7.52 (d, 1H, $J = 8.0$ Hz, –Ar–*H*)
6C	11.82 (brs, 1H, –*NH*)	8.37 (s, 1H, –Ar–*H*)	8.08 (d, 1H, $J = 3.8$ Hz, –Ar–*H*)	7.20–7.23 (m, 3H, –Ar–*H*)		7.51 (d, 1H, $J = 8.0$ Hz, –Ar–*H*)
6D	11.84 (brs, 1H, –*NH*)	8.37 (s, 1H, –Ar–*H*)	8.08 (d, 1H, $J = 3.9$ Hz, –Ar–*H*)	7.19–7.24 (m, 3H, Ar–*H*)		7.77–7.83 (m, 3H, –Ar–*H*)
6E	11.85 (brs, 1H, –*NH*)	8.38–8.42 (m, 2H, –Ar–*H*)	7.85 (s, 1H, –Ar–*H*)	7.24–7.27 (m, 3H, –Ar–*H*)		7.52 (s, 4H, –Ar–*H*)
6F	11.83 (brs, 1H, –*NH*)	8.37–8.39 (m, 1H, –Ar–*H*)	7.79 (d, 1H, $J = 3.9$ Hz, –Ar–*H*)	7.21–7.28 (m, 3H, –Ar–*H*)		7.52 (d, 3H, $J = 8.4$ Hz, –Ar–*H*)

Entry	4b	4c	4d	5	6c	6d	6e
6A	7.73 (d, 2H, $J = 6.0$ Hz, –Ar–*H*)	7.57 (m, 4H, –Ar–*H*)	7.57 (m, 4H, –Ar–*H*)	7.90 (s, 1H, –Ar–*H*)	8.52 (d, 1H, $J = 6.8$ Hz, –Ar–*H*)	7.22–7.24 (m, 3H, –Ar–*H*)	7.81 (d, 1H, $J = 4.5$ Hz, –Ar–*H*)
6B	7.62 (d, 2H, $J = 7.6$ Hz, –Ar–*H*)	7.36 (d, 2H, $J = 7.6$ Hz, –Ar–*H*)	–	7.86 (s, 1H, –Ar–*H*)	8.51 (d, 1H, $J = 8.4$ Hz, –Ar–*H*)	7.22–7.24 (m, 3H, –Ar–*H*)	7.81 (d, 1H, $J = 4.5$ Hz, –Ar–*H*)
6C	7.69 (d, 2H, $J = 8.4$ Hz, –Ar–*H*)	7.01 (d, 2H, $J = 8.4$ Hz, –Ar–*H*)	–	7.84 (s, 1H, –Ar–*H*)	8.49 (d, 1H, $J = 6.8$ Hz, –Ar–*H*)	7.20–7.23 (m, 3H, –Ar–*H*)	7.79 (d, 1H, $J = 4.6$ Hz, –Ar–*H*)
6D	7.77–7.83 (m, 3H, –Ar–*H*)	7.39 (d, 2H, $J = 8.4$ Hz, –Ar–*H*)	–	7.87 (s, 1H, –Ar–*H*)	8.49 (d, 1H, $J = 6.8$ Hz, –Ar–*H*)	7.19–7.24 (m, 3H, Ar–*H*)	7.52 (d, 1H, $J = 4.5$ Hz, –Ar–*H*)
6E	7.66 (s, 2H, –Ar–*H*)	7.52 (s, 4H, –Ar–*H*)	7.52 (s, 4H, –Ar–*H*)	7.79 (s, 1H, –Ar–*H*)	8.38–8.42 (m, 2H, –Ar–*H*)	7.24–7.27 (m, 3H, –Ar–*H*)	–
6F	7.52 (d, 3H, $J = 8.4$ Hz, –Ar–*H*)	7.27 (d, 2H, $J = 7.6$ Hz, –Ar–*H*)	–	7.71 (s, 1H, –Ar–*H*)	8.34 (s, 1H, –Ar–*H*)	7.21–7.28 (m, 3H, –Ar–*H*)	–

Table 5. ^{13}C chemical shift of compounds **6A–F** in DMSO-d_6

Entry	2	3	4	5	6	2b	2c	2d	2e	2f	2g	2h	2i
6A	157.8	100.8	154.5	114.9	155.5	129.3	113.0	128.9	123.0	121.4	112.6	136.3	126.6
6B	157.8	100.7	154.2	114.9	155.4	129.5	113.0	128.9	123.0	121.3	112.6	136.8	126.6
6C	161.0	100.6	155.1	114.7	161.1	129.3	113.0	128.7	123.0	121.3	112.6	136.9	126.6
6D	164.5	100.8	157.7	114.9	162.5	129.3	112.9	128.9	123.1	121.4	112.6	136.9	126.6
6E	157.8	101.2	153.1	114.5	155.5	129.2	112.8	129.2	123.0	121.5	112.6	136.9	126.5
6F	157.8	101.1	153.0	112.8	155.4	129.3	114.3	129.1	122.9	121.4	112.6	136.7	126.5

Entry	3a	4a	4b	4c	4d	6b	6c	6d	6e
6A	119.5	144.2	129.4	129.2	130.2	137.3	122.3	129.3	131.7
6B	119.7	140.1	129.8	129.3	142.2	134.2	122.3	129.8	131.4
6C	119.8	144.2	130.9	114.8	154.1	131.5	122.3	129.5	130.7
6D	119.5	144.1	131.8 (d, $J^2_{C-F} = 38.3$ Hz)	116.1 (d, $J^1_{C-F} = 85.9$ Hz)	154.2 (d, $J^1_{C-F} = 85.9$ Hz)	133.6	122.3	129.5	131.7
6E	119.4	145.9	129.3	129.1	130.2	117.6	122.1	132.8	137.1
6F	119.5	140.0	129.2	129.7	145.8	117.4	122.1	132.8	134.1

Table 6. ^{1}H chemical shift and HMBC correlation in DMSO-d_6 of compounds **6A–F**

Entry	6A		6B		6C		6D		6E		6F	
Proton	δ^1H	HMBC	δ^1H	HMBC	δ^1H	HMBC	δ^1H	HMBC	δ^1H	HMBC	δ^1H	HMBC
2a	11.83	–	11.83	2b,2c,2h	11.82	–	11.84	–	11.85	2c,2h,2i	11.83	–
2b	8.40	2c,2h,2i	8.39	2c,2h,2i	8.37	2c,2h,2i	8.37	2c,2h,2i	8.38–8.42	2c,2h,2i	8.37–8.39	2h,2i
2d	8.12	–	8.10	–	8.08	–	8.08	–	7.85	–	7.79	–
2e	7.22–7.24	2i	7.22–7.24	–	7.20–7.23	2i	7.19–7.24	2g,2i	7.24–7.27	2d	7.21–7.28	–
2f	7.22–7.24	2g,2h	7.22–7.24	–	7.20–7.23	2e,2g,2h	7.19–7.24	2h	7.24–7.27	2g	7.21–7.28	–
2g	7.57	2f,2h,2i	7.52	2f,2i	7.51	2e,2i	7.77–7.83	–	7.52	2f,2h,2i	7.52	2f,2i
4b	7.73	4c,4d	7.62	4,4a,4c	7.69	4	7.77–7.83	4c	7.66	4,4c	7.52	4,4a,4c
4c	7.57	4b	7.36	4b, $-CH_3$	7.01	–	7.39	4a,4b,4d	7.52	–	7.27	–
4d	7.57	4b	–	–	–	–	–	–	7.52	–	–	–
5	7.90	3,4,6,6b	7.86	3,4,6b	7.84	3,4a,6	7.87	3,4a,6b	7.79	3,4a,6	7.71	3,6
6c	8.52	6b	8.51	–	8.49	–	8.49	–	8.38–8.42	–	8.34	–
6d	7.22–7.74	6c	7.22–7.24	–	7.20–7.23	–	7.19–7.24	6c	7.24–7.27	6c	7.21–7.28	–
6e	7.81	6d	7.81	–	7.79	–	7.52	6c	–	–	–	–

558.07 [$M^+ + H^+$]; Anal. Calcd for $C_{30}H_{20}BrFeN_3$: C 64.54, H 3.61, N 7.53. Found: C 64.62, H 3.60, N 7.55.

*6-(Ferrocene-1-yl)-2-(1H-indol-3-yl)-4-(4-fluorophenyl)nicotinonitrile (**4D**)*

Deep red colour semisolid; R_f 0.56 (20% AcOEt/petroleum ether); IR (KBr): 1142, 1348, 1567, 1638, 2236, 3422 cm^{-1}; MS (EI): $m/z = 498.07$ [$M^+ + H^+$]; Anal. Calcd for $C_{30}H_{20}FFeN_3$: C 72.45, H 4.05, N 8.45. Found: C 72.56, H 4.06, N 8.43.

*6-(Ferrocene-1-yl)-2-(1H-indol-3-yl)-4-(3-nitrophenyl)nicotinonitrile (**4E**)*

Deep red colour semisolid; R_f 0.45 (20% AcOEt/petroleum ether); IR (KBr): 1052, 1246, 1451, 1621, 2238, 3452 cm^{-1}; MS (EI): $m/z = 526.13$ [$M^+ + H^+$]; Anal. Calcd for $C_{30}H_{20}FeN_4O$: C 68.72, H 3.84, N 10.68. Found: C 68.63, H 3.85, N 10.65.

General procedure for the synthesis of 2-(indol-3-yl)-6-(2-thienyl)pyridine derivatives (6A–F)

A mixture of 2-acetyl thiophene (1 mmol), aldehyde (1 mmol), and ammonium acetate in MeOH was refluxed. After the complete disappearance of starting materials (monitored by TLC), 3-cyanoacetyl indole was added and the reflux was continued for appropriate time mentioned as in Table 2. After the completion of the reaction (as monitored by TLC), the solid was filtered and then dried. The crude solid was recrystallised with ethanol and appropriate isolated yield was shown in Table 2.

*2-(1H-indol-3-yl)-4-phenyl-6-(2-thienyl)nicotinonitrile (**6A**)*

Yellow solid; mp 248–250 °C; R_f 0.37 (20% AcOEt/petroleum ether); IR (KBr): 1136, 1231, 1566, 2216, 3302 cm^{-1}; MS (EI): $m/z = 378.27$ [$M^+ + H^+$]; $C_{24}H_{15}N_3S$. Anal. Calcd. for $C_{24}H_{15}N_3S$: C 76.37, H 4.01, N 11.13. Found: C 76.20, H 4.00, N 11.16.

*2-(1H-indol-3-yl)-4-(4-methylphenyl)-6-(2-thienyl)nicotinonitrile (**6B**)*

Yellow solid; mp 283–285 °C; R_f 0.40 (20% AcOEt/petroleum ether); IR (KBr): 1528, 1652, 2214, 2930, 3314 cm^{-1}; MS (EI): $m/z = 392.27$ [$M^+ + H^+$]; $C_{25}H_{17}N_3S$. Anal. Calcd for $C_{25}H_{17}N_3S$: C 76.70, H 4.38, N 10.73. Found: C 76.82, H 4.36, N 10.70.

*2-(1H-indol-3-yl)-4-(4-methoxylphenyl)-6-(2-thienyl)nicotinonitrile (**6C**)*

Yellow solid; mp 218–220 °C; R_f 0.29 (20% AcOEt/petroleum ether); IR (KBr): 1248, 1516, 1635, 2370, 2918, 3309 cm^{-1}; MS (EI): $m/z = 408.20$ $[M^+ + H^+]$; $C_{25}H_{17}N_3OS$. Anal. Calcd for $C_{25}H_{17}N_3OS$: C 73.69, H 4.21, N 10.31. Found: C 73.54, H 4.20, N 10.34.

*4-(4-Fluorophenyl)-2-(1H-indol-3-yl)-6-(2-thienyl)nicotinonitrile (**6D**)*

Yellow solid; mp 288–290 °C; R_f 0.46 (20% AcOEt/petroleum ether); IR (KBr): 1025, 1428, 1620, 2369, 2922, 3304 cm^{-1}; MS (EI): $m/z = 396.33$ $[M^+ + H^+]$; $C_{24}H_{14}FN_3S$. Anal. Calcd for $C_{24}H_{14}FN_3S$: C 72.89, H 3.57, N 10.63. Found: C 72.75, H 3.56, N 10.66.

*6-(5-Bromo-2-thienyl)-2-(1H-indol-3-yl)-4-phenylnicotinonitrile (**6E**)*

Yellow solid; mp 208–210 °C; R_f 0.37 (20% AcOEt/petroleum ether); IR (KBr): 1421, 1623, 2210, 3413 cm^{-1}; MS (EI): $m/z = 456.13$ $[M^+ + H^+]$; $C_{24}H_{14}BrN_3S$. Anal. Calcd for $C_{24}H_{14}N_3BrS$: C 63.16, H 3.09, N 9.21. Found: C 63.08, H 3.10, N 9.24.

*6-(5-Bromo-2-thienyl)-2-(1H-indol-3-yl)-4-(4-methylphenyl)nicotinonitrile (**6F**)*

Yellow solid; mp 234–236 °C; R_f 0.34 (20% AcOEt/petroleum ether); IR (KBr): 1528, 1652, 2214, 2930, 3314 cm^{-1}; MS (EI): $m/z = 470.20$ $[M^+ + H^+]$; $C_{25}H_{16}BrN_3S$. Anal. Calcd for $C_{25}H_{16}BrN_3S$: C 63.83, H 3.43, N 8.93. Found: C 63.93, H 3.42, N 8.95.

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Supporting information

Supporting information may be found in the online version of this article.

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