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Synthesis and anti-inflammatory activity of 3-indolyl pyridine derivatives through one-pot 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 has been achieved through one-pot multi-component reaction under reflux condition. These compounds showed a good anti-inflammatory activity. Also a series of *bis*-Hantzsch dihydropyridine derivatives were synthesized and they exhibit analgesic activity.

Keywords. Multi component reaction; 3-cyanoacetyl indole; malononitrile; pyridine synthesis; anti-inflammatory activity; analgesic activity.

1. Introduction

Functionalized nitrogen-heterocycles play a predominant role in medicinal chemistry and they have been intensively used as scaffolds for drug development. Multi-component reactions (MCR's) have emerged as a powerful tool for delivering the molecular diversity needed in the combinatorial approaches for the preparation of bioactive heterocyclic compounds.[1] Multi-component reactions, such as the Biginelli,[2] Passerini,[3] Ugi,[4] and Hantzsch, provide a wide variety of important heterocycles.[5] For example, the Hantzsch reaction provides dihydropyridines with activity against calcium channels, multidrug resistance (MDR) proteins, 5-hydroxytryptamine(5-HT) receptors, and anti-inflammatory targets.[6–7]

The pyridine nucleus is prevalent in numerous natural products and is extremely important in chemistry of biological systems.[8] It plays a key role catalysing both biological and chemical systems. In many enzymes of living organisms it is the prosthetic pyridine nucleotide (NADP) that is involved in various oxidation–reduction processes. Other evidence of the potent activity of pyridine in biological systems is its presence in the important vitamins niacin and pyridoxine (vitamin B6) and also in highly toxic alkaloids such as nicotine.[9–11] The pyridine substructure is one of the most important heterocycles found in natural products, pharmaceuticals, and functional materials.[12] 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 inhibitor.[8] Moreover, substituted pyridines are reported as leukotriene B-4 antagonists.[13–15]

3-Substituted indole is the one of the 'privileged medicinal scaffold,' found in many biologically active compounds and natural products.[16,17] Through appropriate functional group modifications, these scaffolds are capable of providing ligands for a number of functionally and structurally discrete biological receptors. 3-Substitued indole scaffolds are found in a number of biologically active compounds especially with anticancer, anti-tumour,[18] hypoglycemic, anti-inflammatory, analgesic and anti-pyretic activities (figure 1).[19–20]

The wide-ranging biological activity associated with many pyridine and 3-substituted indole derivatives, both naturally occurring and synthetic, ensures that the synthesis of this important ring system remains a topic of current interest. Various methods for the preparation of these compounds have been reported. However, these methods suffer from tedious synthetic routes, longer reaction time, drastic reaction conditions, as well as narrow substrate scope.[21–25] There have been very few reports about the synthesis of indol-3-yl derivatives including pyridine moieties.[9,18,22–23,26] As part of our ongoing research on the development of novel synthetic routes for the synthesis of biologically active hetero-

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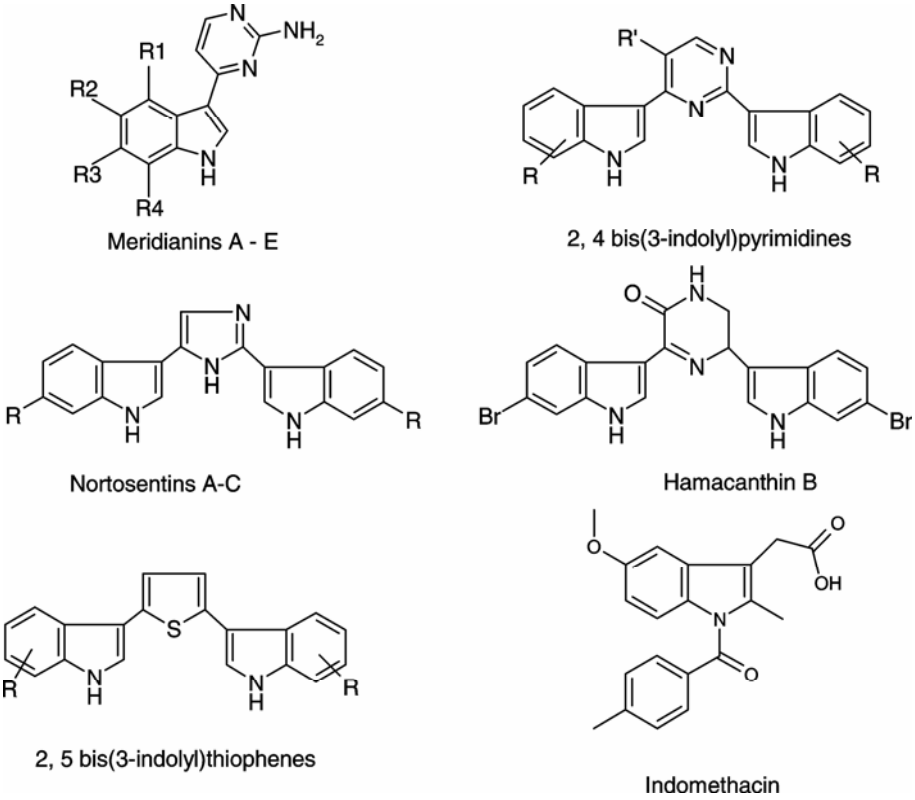


Figure 1. Representatives of 3-substituted indole derivatives

cyclic compounds and use of green chemical techniques in organic synthesis,[27,28] we report here a simple and facile one pot procedure for the synthesis of indol-3-yl pyridine derivatives in aqueous media under reflux condition.

2. Experimental

2.1 *General*

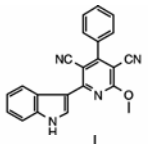
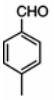
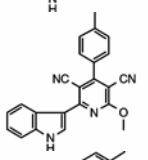
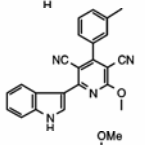
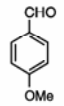
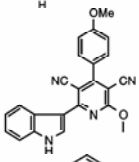
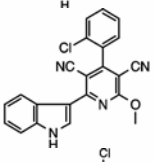
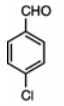
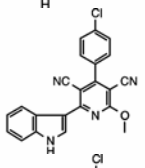
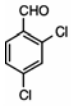
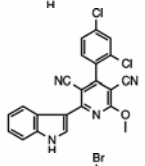
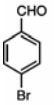
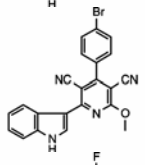
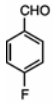
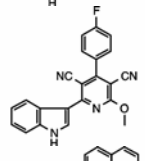
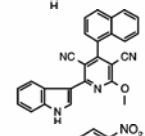
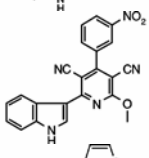
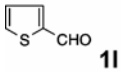
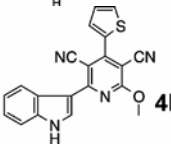
All the substituted aldehydes, malononitrile, 2-indanone, indole, $CDCl_3$ and DMSO-d_6 were purchased from Aldrich Chemicals. Acetic anhydride and all other reagents were purchased from S.D. Fine Chemicals Limited and were used as received. Methanol was distilled from Mg/I_2 under nitrogen and stored over 3 Å molecular sieves purchased from Aldrich. IR measurements were done as KBr pellets for solids using Perkin Elmer Spectrum RXI FT–IR. The ^1H 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 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.

2.2 *General procedure for the synthesis of indol-3-yl pyridine and 2,2′-bipyridine derivatives* **(4a–p)**

A mixture of 3-cyanoacetyl indole (1·0 mmol), aldehyde (1·0 mmol), malononitrile(1·0 mmol) and freshly prepared sodium methoxide (1·0 mmol) (or) sodium hydroxide (1·2 mmol) in 30 mL of methanol : water (2 : 1) was refluxed. After the completion of the reaction (as monitored by TLC), it was poured into water, filtered and then dried. The crude product was further purified by recrystallization with ethanol and the appropriate isolated yield shown in table 1.

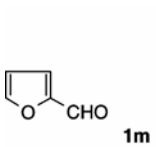
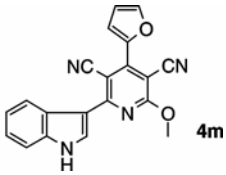
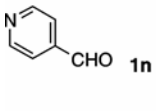
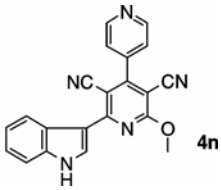
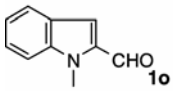
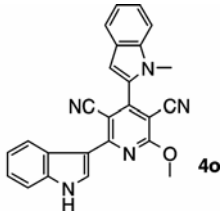
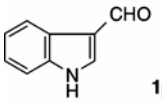
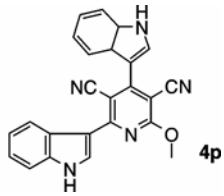
2.2a *2-(1H-Indol-3-yl)-6-methoxy-4-phenylpyridine-3,5-dicarbonitrile (table 1, entry 1)* **4a**: Light yellow solid; m.p. 244–246°C; R_f 0·23 (20%

Table 1. Synthesis of indol-3-yl pyridine derivatives.

Entry	Aldehyde (1)	Product (**4**)[a]	Time (h)	Yield (%)[b]
1	 **1a**	 **4a**	1·5	89
2	 **1b**	 **4b**	1·0	91
3	 **1c**	 **4c**	1·5	86
4	 **1d**	 **4d**	1·5	91
5	 **1e**	 **4e**	2·5	79
6	 **1f**	 **4f**	2·0	81
7	 **1g**	 **4g**	2·0	81
8	 **1h**	 **4h**	2·0	79
9	 **1i**	 **4i**	2·0	79
10	 **1j**	 **4j**	1·0	81
11	 **1k**	 **4k**	3·0	72
12	 **1l**	 **4l**	2·5	68

(*Contd*...)

Table 1. (*Contd…*)

Entry	Aldehyde (1)	Product (**4**)[a]	Time (h)	Yield (%)[b]
13	 **1m**	 **4m**	2·5	77
14	 **1n**	 **4n**	2·5	66
15	 **1o**	 **4o**	4·0	70
16	 **1p**	 **4p**	4·5	73

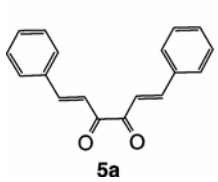
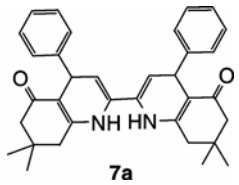
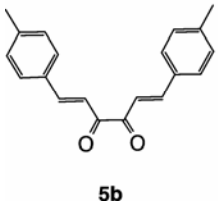
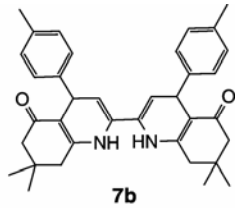
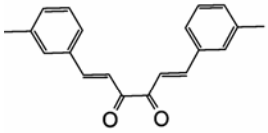
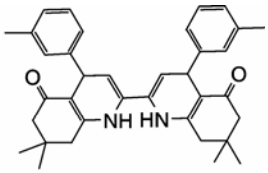
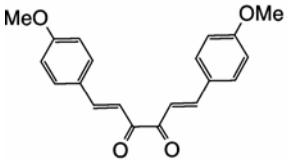
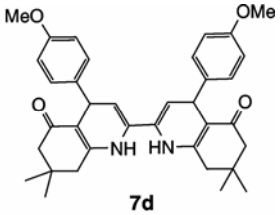
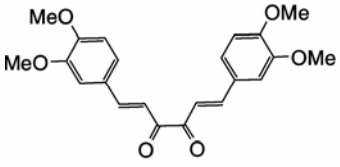
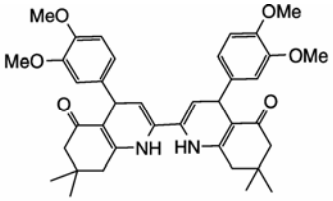
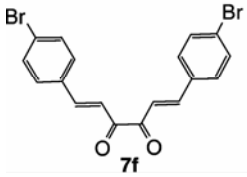
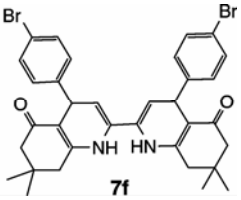
[a]All the products were characterized by NMR, IR and mass spectroscopy. [b]Isolated yield

EtOAc/petroleum ether); IR (KBr): 1153, 1229, 1427, 1516, 1629, 2230, 3287 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 4·21 (*s*, 3H, –OCH_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 (*brs*, 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.

2.2b *2-(1H-Indol-3-yl)-6-methoxy-4-(4-tolyl phenyl) pyridine-3,5-dicarbonitrile (table 2, entry 2)* **4b**: Light yellow solid; m.p. 228–230°C; R_f 0.30 (20% EtOAc/Petroleum ether); IR (KBr): 1145, 1224, 1306, 1422, 1516, 1620, 2221, 3325 cm^{-1} ^1H NMR (500 MHz, DMSO-d_6): δ 2·41 (*s*, 3H, –Ar-CH_3) 4·21 (*s*, 3H, –OCH_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 (*brs*, 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.

2.2c *2-(1H-Indol-3-yl)-6-methoxy-4-(3-methyl-phenyl)pyridine-3,5-dicarbonitrile (table 1, entry 3)* **4c**: Pale yellow solid; m.p. 286–288°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 2·37 (*s*, 3H, –Ar-CH_3) 4·18 (*s*, 3H, –OCH_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 (*brs*, 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 $C_{23}H_{16}N_4O$:

Table 2. Synthesis of 7,7,7′,7′-tetramethyl-4,4′-*bis*(aryl)-4,6,7,8,4′,6′,7′,8′-octahydro-1H,1H-[2,2′]biquinolinyl-5,5′-dione derivatives

Entry	Cinnamil	Product (7)[a]	Time (h)	Yield (5%)[b]
1	 **5a**	 **7a**	12·0	55
2	 **5b**	 **7b**	11·0	56
3	 **5c**	 **7c**	11·5	48
4	 **5d**	 **7d**	12·0	58
5	 **5e**	 **7e**	11·0	52
6	 **7f**	 **7f**	14·0	42

[a]The products were characterized by IR, NMR, mass and elemental analysis. [b]Isolated yield.

C 75·81 H 4·43 N 15·38. Found: C 75·72 H 4·44 N 15·43.

2.2d *2-(1H-Indol-3-yl)-6-methoxy-4(4methoxy-phenyl) pyridine -3,5-dicarbonitrile (table 1, entry 4)* **4d**: Yellow solid; m.p. 268–270°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 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 (*brs*, 1H, –N*H*); ^{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.

2.2e *4-(2-Chlorophenyl)-2-(1H-indol-3-yl)-6-methoxypyridine-3,5-dicarbonitrile (table 1, entry 5)* **4e***:* Pale yellow solid; m.p. 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 (*brs*, 1H, –N*H*); ^{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.

2.2f *4-(4-Chlorophenyl)-2-(1H-indol-3-yl)-6-methoxypyridine-3,5-dicarbonitrile (table 1, entry 6)* **4f***:* Pale yellow solid; m.p. 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 (*brs*, 1H, –N*H*); ^{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.

2.2g *4-(2,4-Chlorophenyl)-2-(1H-indol-3-yl)-6-methoxy pyridine-3,5-dicarbonitrile (table 1, entry 7)* **4g***:* Pale yellow solid; m.p. 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 (*brs*, 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.

2.2h 4-(*4-Bromophenyl)-2-(1H-indol-3-yl)-6-methoxypyridine-3,5-dicarbonitrile (table 1, entry 8)* **4h***:* Pale yellow solid; m.p. 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.

2.2i *4-(4-Fluorophenyl)-2-(1H-indol-3-yl)-6-methoxypyridine-3,5-dicarbonitrile (table 1, entry 9)* **4i**: Pale yellow solid; m.p. 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 (*brs*, 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.

2.2j *2-(1H-Indol-3-yl)-6-methoxy-4-(1-naphthyl) pyridine-3,5-dicarbonitrile (table 1, entry 10)* **4j**: Yellow solid; m.p. 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 (*brs*, 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.

2.2k *2-(1H-Indol-3-yl)-6-methoxy-4-(3-nitrophenyl) pyridine-3,5-dicarbonitrile (table 1, entry 11)* **4k***:* Yellow solid; m.p. 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 (*brs*, 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.

2.2l *2-(1H-Indol-3-yl)-6-methoxy-4-(2-thienyl) pyridine-3,5-dicarbonitrile (table 1, entry 12)* **4l***:* Yellow solid; m.p. 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 (*brs*, 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.

2.2m *4-(2-Furyl)-2-(1H-indol-3-yl)-6-methoxy-pyridine-3,5-dicarbonitrile (table 1, entry 13)* **4m***:* Yellow solid; m.p. 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 (*brs*, 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.

2.2n *2-(1H-Indol-3-yl)-6-methoxy-4,4′-bipyridine-3,5-dicarbonitrile (table 1, entry 14)* **4n***:* Yellow solid; m.p. 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 (*brs*, 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.

2.2o *2-(1H-Indol-3-yl)-6-methoxy-4-(1-methyl-1H-indol-2-yl)pyridine-3,5-dicarbonitrile (table 1, entry 15)* **4o***:* Yellow solid; m.p. 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 (*brs*, 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.

2.2p *2,4-Di-1H-indol-3-yl-6-methoxypyridine-3,5-dicarbonitrile (table 1, entry 16)* **4p***:* Yellow solid; m.p. 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 (*brs*, 1H, –N*H*), 11·87 (*brs*, 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.

2.3 *Synthesis of 6,6′-bis-(1H-indol-3-yl)-4-4′-diaryl-[2,2′]bipyridinyl-5,5′-dicarbonitrile*

A mixture of dimedone (2 mmol), cinnamil (1 mmol) and 5 g of ammonium acetate under neat condition was refluxed at 120°C for appropriate time mentioned as in table 2. After the completion of the reaction (as monitored by TLC), it was poured into water and then filtered washed with acetone and then dried. The obtained crude solid was purified further by recrystallisation with DMF and appropriate isolated yield is shown in table 2.

2.3a *7,7,7′,7′-Tetramethyl-4,4′-diphenyl-4,6,7,8,4′,6′,7′,8′-octahydro-1H,1H-[2,2′]biquinolinyl-5,5′-dione (Table 2, entry 1)* **7a**: Yellow solid; m.p. 293–296°C; R_f 0·81 (40% AcOEt/Petroleum ether); IR (KBr): 1126, 1314, 1384, 1485, 1587, 2934, 3340 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0·86 (*s*, 6H, –C*H*$_3$), 0·94 (*s*, 6H, –C*H*$_3$), 1·88 (*Abq*, 4H, *J* = 8·2 Hz, –C*H*), 2·35 (*s*, 4H, –C*H*$_2$), 4·42 (*d*, 2H, *J* = 5·3 Hz, dihydropyridyl–C*H*), 5·26 (*d*, 2H, *J* = 5·3 Hz, dihydropyridyl-C=C*H*), 7·05 (*m*, 2H, Ar-*H*), 7·13 (*d*, 4H, *J* = 7·6 Hz, Ar-*H*), 7·18 (*m*, 4H, Ar-*H*), 8·15 (*brs*, 2H, –*NH*); ^{13}C NMR (125 MHz, DMSO-d_6): δ 27·6, 29·2, 29·6, 32·6, 38·2, 41·8, 50·8, 107·2, 117·1, 119·3, 127·6,128·2, 128·5, 128·8, 128·9, 129·2, 129·8, 131·6, 133·5, 136·2, 141·3, 143·2, 144·8, 150·2, 158·2, 162·2, 183·1, 195·2; MS (ESI LCQ-MS): *m/z* 505·47 [$M^+ + H^+$]. Anal. Calcd. for $C_{34}H_{36}N_2O_2$: C 80·92 H 7·19 N 5·55. Found: C 80·81 H 7·22 N 5·52.

2.3b *7,7,7′,7′-Tetramethyl-4,4′-bis(4-methylphenyl)-4,6,7,8,4′,6′,7′,8′-octahydro-1H,1H-[2,2′]biquinolinyl-5,5′-dione (table 2, entry 2)* **7b**: Yellow solid; m.p. 185–187°C; R_f 0·84 (40% AcOEt/petroleum ether); IR (KBr): 1057, 1128, 1386, 1490, 1588, 2935, 3320 cm^{-1} ^{1}H NMR (500 MHz, DMSO-d_6): δ 0·91 (*s*, 6H, –C*H*$_3$), 0·97 (*s*, 6H, –C*H*$_3$), 1·93 (*Abq*, 4H, *J* = 8·6 Hz, –C*H*), 2·19 (*s*, 6H, Ar-C*H*$_3$), 2·29 (*s*, 4H, –C*H*$_2$), 4·58 (d, 2H, *J* = 6·1 Hz, dihydropyridyl-C*H*), 6·63 (*d*, 2H, *J* = 4·5 Hz, dihydropyridyl-C=C*H*), 7·18 (*m*, 4H, Ar-*H*), 7·67 (*d*, 4H, *J* = 7·6 Hz, Ar-*H*), 8·55 (*brs*, 2H, –*NH*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21·0, 21·5, 27·5, 29·2, 29·6, 32·6, 38·1, 41·7, 50·7, 107·3, 117·1, 119·4, 127·9, 128·5, 128·8, 128·9, 129·3, 129·7, 131·7, 133·7, 136·3, 141·5, 143·3, 144·9, 150·2, 183·2, 195·3; MS (ESI LCQ-MS): *m/z* 533·47 [$M^+ + H^+$]. Anal. Calcd. for $C_{36}H_{40}N_2O_2$: C 81·17 H 7·57 N 5·26. Found: C 80·28 H 7·52 N 5·23.

2.3c *7,7,7′,7′-Tetramethyl-4,4′-bis(4-methoxyphenyl)-4,6,7,8,4′,6′,7′,8′-octahydro-1H,1H-[2,2′]biquinolinyl-5,5′-dione (table 2, entry 3)* **7c**: Yellow solid; m.p. 226–228°C; R_f 0·6 (40% AcOEt/petroleum ether); IR (KBr): 1176, 1257, 1445, 1562, 3014, 3129 cm^{-1} ^{1}H NMR (500 MHz, DMSO-d_6): δ 1·02 (*s*, 6H, –C*H*$_3$), 1·08 (*s*, 6H, –C*H*$_3$), 2·15 (*Abq*, 4H, *J* = 8·1 Hz, –C*H*), 2·36 (*s*, 4H, –C*H*$_2$), 3·75 (*s*, 6H, Ar-OC*H*$_3$), 4·78 (*d*, 2H, *J* = 5·6 Hz, dihydropyridyl-C*H*), 6·24 (*m*, 2H, dihydropyridyl-C=C*H*), 6·81 (*m*, 4H, Ar-*H*), 6·88 (*m*, 2H, Ar-*H*), 7·50 (*m*, 2H, Ar-*H*) 8·55 (*brs*, 2H, –*NH*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 27·5, 28·3, 29·2, 29·7, 32·6, 37·6, 41·7, 50·7, 55·2, 55·4, 107·4, 113·6, 113·9, 114·4, 115·7, 119·0, 127·2, 129·1, 129·5, 130·4, 133·7, 138·6, 144·6, 150·1, 158·4, 161·9, 183·1, 195·3; MS (ESI LCQ-MS): *m/z* 565·20 [$M^+ + H^+$]. Anal. Calcd. for $C_{36}H_{40}N_2O_4$: C 76·57 H 7·14 N 4·96. Found: C 76·66 H 7·17 N 4·98.

2.3d *7,7,7′,7′-Tetramethyl-4,4′-bis(4-chlorophenyl)-4,6,7,8,4′,6′,7′,8′-octahydro-1H,1H-[2,2′]biquinolinyl-5,5′-dione (table 2, entry 4)* **7d**: Yellow solid; m.p. 286–289°C; R_f 0·81 (40% AcOEt/petroleum ether); IR (KBr): 1319, 1384, 1484, 1590, 2928, 3352 cm^{-1} ^{1}H NMR (500 MHz, DMSO-d_6): δ 0·85 (*s*, 6H, –C*H*$_3$), 0·95 (*s*, 6H, –C*H*$_3$), 1·89 (*Abq*, 4H, *J* = 9·2 Hz, –C*H*), 2·35 (*s*, 4H, –C*H*$_2$), 4·46 (*d*, 2H, *J* = 4·6 Hz, dihydropyridyl-C*H*), 5·52 (*d*, 2H, *J* = 4·6 Hz, dihydropyridyl-C=C*H*), 7·14 (*m*, 4H, *J* = 8·4 Hz, Ar-*H*), 7·25 (*d*, 4H, *J* = 8·4 Hz, Ar-*H*), 8·22 (*brs*, 2H, –*NH*); ^{13}C NMR (125 MHz, DMSO-d_6): δ 27·3, 28·1, 29·0, 29·5, 32·4, 37·4, 41·5, 50·8, 55·1, 55·3, 107·2, 113·4, 113·8, 114·2, 115·5, 119·1, 127·1, 129·2, 129·4, 130·5, 133·5, 138·5, 144·5, 150·2, 158·2, 161·7, 183·3, 195·4; MS (ESI LCQ-MS): *m/z* 573·20 [$M^+ + H^+$]. Anal. Calcd. for $C_{34}H_{34}Cl_2N_2O_2$: C 71·20 H 5·98 N 4·88. Found: C 71·28 H 5·95 N 4·87.

2.3e *7,7,7′,7′-Tetramethyl-4,4′-bis(3,4-dimethoxyphenyl)-4,6,7,8,4′,6′,7′,8′-octahydro-1H,1H-[2,2′]biquinolinyl-5,5′-dione (table 2, entry 5)* **7e***:* Yellow solid; m.p. 211–214°C; R_f 0·35 (40% AcOEt/petroleum ether); IR (KBr): 1345, 1212, 1496, 1575, 2945, 3345 cm^{-1} ^{1}H NMR (500 MHz, DMSO-d_6): δ 1·07 (*s*, 6H, –CH_3), 1·12 (*s*, 6H, –CH_3), 2·12 (*Abq*, 4H, J = 8·6 Hz, –C*H*), 2·31 (*s*, 4H, –CH_2), 3·68 (*s*, 6H, Ar-OCH_3), 3·73 (*s*, 6H, Ar-OCH_3), 4·76 (*d*, 2H, J = 5·6 Hz, dihydropyridyl–C*H*), 6·21 (*m*, 2H, dihydropyridyl-C=C*H*), 6·85 (*m*, 2H, Ar-*H*), 6·94 (*m*, 2H, Ar-*H*), 7·56 (*m*, 2H, Ar-*H*) 8·59 (*brs*, 2H, –N*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 27·8, 28·6, 29·4, 29·9, 32·8, 37·7, 42·3, 51·5,55·8, 56·1, 56·2, 56·8, 108·1, 113·8, 114·0, 114·6, 115·8, 119·1, 127·2, 129·3, 129·7, 130·7, 133·9, 138·9, 144·5, 150·4, 159·3, 162·4, 184·5, 196·5; MS (ESI LCQ-MS): *m/z* 625·40 [$M^+ + H^+$]. Anal. Calcd for $C_{38}H_{44}N_2O_6$: C 73·05 H 7·10 N 4·48. Found: C 73·18 H 7·16 N 4·52.

2.3f *7,7,7′,7′-Tetramethyl-4,4′-bis(4-bromophenyl)-4,6,7,8,4′,6′,7′,8′-octahydro-1H,1H-[2,2′]biquinolinyl-5,5′-dione (table 2, entry 6)* **7f***:* Yellow solid; m.p. 282–284°C; R_f 0·79 (40% AcOEt/petroleum ether); IR (KBr): 1189, 1259, 1426, 1559, 2975, 3189 cm^{-1} ^{1}H NMR (500 MHz, DMSO-d_6): δ 0·89 (*s*, 6H, –CH_3), 0·95 (*s*, 6H, –CH_3), 2·08 (*Abq*, 4H, J = 8·1 Hz, –C*H*), 2·32 (*s*, 4H, –CH_2), 4·91 (*d*, 2H, J = 5·6 Hz, dihydropyridyl-C*H*), 6·21 (*m*, 2H, dihydropyridyl-C=C*H*), 7·08–7·12 (*m*, 2H, Ar-*H*), 7·18–7·22 (*m*, 4H, Ar-*H*), 7·48 (*m*, 2H, Ar-*H*) 8·47 (*brs*, 2H, –N*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 26·8, 27·2, 29·1, 29·7, 32·4, 37·3, 41·5, 50·3, 107·1, 112·7, 113·5, 114·1, 115·3, 118·3, 126·3, 128·6·6, 129·9, 130·7, 133·3, 138·3, 144·1, 149·8, 157·2, 160·5, 182·9, 194·3; MS (ESI LCQ-MS): *m/z* 663·28 [$M^+ + H^+$]. Anal. Calcd. for $C_{34}H_{34}Br_2N_2O_4$: C 61·64 H 5·17 N 4·23. Found: C 61·75 H 5·15 N 4·21.

3 Biological evaluation of newly synthesized compounds

3.1 *Anti inflammatory activity of indol-3-yl pyridine derivatives*

The anti-inflammatory activities of various synthesized compounds were evaluated against carrageenan-induced paw oedema in rats. The inflammation was readily produced in rats in the form of paw oedema with the help of irritants such as carrageenan. Carrageenan-induced paw oedema is a useful model to assess the contribution of mediators involved in vascular changes associated with acute inflammation. Carrageenan is sulphated polysaccharides obtained from sea weed (rhodophyceae) and when injected causes the release of histamine 5-HT, bradykininins and prostaglandins. It produce inflammation and oedema.

3.1a *Preparation of 1% carrageenan solution:* Carrageenan (1 g) was dissolved in 0.9% saline and the maximum volume administered to the rat was kept as 0·1 ml. The effects of drugs on paw oedema induced by carrageenan are shown in table 3. Almost all the drugs showed a maximum anti-inflammatory effect and reduction in swelling. On the basis of these results, it can be concluded that greater anti-inflammatory activity was achieved with all the compounds, especially **4h**, **4i** exhibit almost similar action as that of the standard. The anti-inflammatory activity of the synthesized 3-substituted indole derivatives was compared with indomethacin. The experiment was maintained up to four hours.

3.2 *Analgesic activity of bis(indol-3yl dihydropydine) derivatives*

The analgesic activities of various synthesized compounds were evaluated against acetic acid-induced writhing test-induced in Albinomice. Glacial acetic acid (GAA)-induced writhing 1% GAA solution was injected (ip) and following this typical abdominal writhing response was observed. The number of writhes over a period of 20 min following GAA injection was counted. The data for drug treated groups were compared with appropriate controls for statistical significance. The results were analysed by student's 't' test. The 't' value of at least 0·05 or less was considered as level of significance.

3.2a *Materials and methods:* Animals: Albinomice 25–30 g; Drugs/chemicals: 1% acetic acid; 2% Tween 80: Aspirin Std Drug (50 m/kg); Synthetic compounds: **7a–f**.

3.2b *Acetic acid-induced writhing test*[5]*:* The prescreened animals were divided into 5 groups of 6 animals each. Aspirin in doses of 50 mg/kg, suspended in 2% Tween 80 was used as the standard drug and administered orally. Writhing was induced

Table 3. Anti-inflammatory activity of indol-3-yl pyridine derivatives.

Group	Doses (mg/kg)	Paw volume (mean ± SEM)					Percentage of inhibition			
		0 min	60 min	120 min	180 min	240 min	60 min (%)	120 min (%)	180 min (%)	240 min (%)
(1) (control)	2·5% Tween80	0·682 ± 0·033	0·672 ± 0·028	0·674 ± 0·025	0·670 ± 0·028	0·663 ± 0·012	00	00	00	00
(2) Indomethacin	Indomethacin 10 mg/kg	0·678 ± 0·012	0·632 ± 0·032	0·540 ± 0·022	0·430 ± 0·010	0·360 ± 0·022	5·95	19·88	35	45·7
4a(3)	20 mg/kg	0·667 ± 0·010	0·637 ± 0·022	0·573 ± 0·031	0·501 ± 0·021	0·380 ± 0·032	5·2	14·9	25	42·6
4b(4)	20 mg/kg	0·643 ± 0·033	0·622 ± 0·032	0·551 ± 0·021	0·460 ± 0·032	0·390 ± 0·021	7·4	18·2	31·3	41·7
4c(5)	20 mg/kg	0·651 ± 0·022	0·625 ± 0·018	0·543 ± 0·018	0·455 ± 0·018	0·385 ± 0·018	6·9	19·4	32	41·9
4d(6)	20 mg/kg	0·668 ± 0·012	0·631 ± 0·021	0·550 ± 0·032	0·453 ± 0·019	0·400 ± 0·012	6·1	18·3	32·2	39·7
4e(7)	20 mg/kg	0·661 ± 0·010	0·621 ± 0·018	0·543 ± 0·012	0·451 ± 0·031	0·390 ± 0·018	7·5	19·4	32·6	41·2
4f(8)	20 mg/kg	0·643 ± 0·033	0·616 ± 0·042	0·533 ± 0·018	0·438 ± 0·021	0·380 ± 0·012	8·3	20·9	34·6	41·2
4g(9)	20 mg/kg	0·657 ± 0·022	0·621 ± 0·031	0·551 ± 0·019	0·459 ± 0·019	0·390 ± 0·031	7·6	18·2	31·5	41·2
4h(10)	20 mg/kg	0·648 ± 0·033	0·612 ± 0·021	0·512 ± 0·018	0·428 ± 0·042	0·350 ± 0·026	8·9	24	36·1	47·2
4i(11)	20 mg/kg	0·659 ± 0·041	0·621 ± 0·026	0·532 ± 0·019	0·430 ± 0·032	0·345 ± 0·026	7·6	21	35·8	48·0
4j(12)	20 mg/kg	0·669 ± 0·029	0·627 ± 0·038	0·543 ± 0·018	0·452 ± 0·042	0·390 ± 0·038	6·7	19·4	32·6	41·2
4k(13)	20 mg/kg	0·642 ± 0·021	0·613 ± 0·018	0·531 ± 0·032	0·451 ± 0·019	0·385 ± 0·032	8·7	21·2	32·7	42
4l(14)	20mg/kg	0·671 ± 0·021	0·620 ± 0·011	0·521 ± 0·016	0·450 ± 0·033	0·370 ± 0·036	7·7	22·7	32·8	45·0
4m(15)	20 mg/kg	0·670 ± 0·021	0·621 ± 0·020	0·520 ± 0·020	0·448 ± 0·040	0·385 ± 0·012	7·5	22·8	33·1	42·6
4n(16)	20 mg/kg	0·669 ± 0·032	0·618 ± 0·022	0·522 ± 0·029	0·440 ± 0·022	0·390 ± 0·038	8·0	22·5	34·3	41·2
4o(17)	20 mg/kg	0·649 ± 0·020	0·617 ± 0·032	0·513 ± 0·033	0·450 ± 0·026	0·380 ± 0·042	8·2	23·8	32·8	40·4
4p(18)	20 mg/kg	0·662 ± 0·019	0·619 ± 0·036	0·532 ± 0·030	0·430 ± 0·042	0·365 ± 0·032	7·8	21·1	35·8	44·5

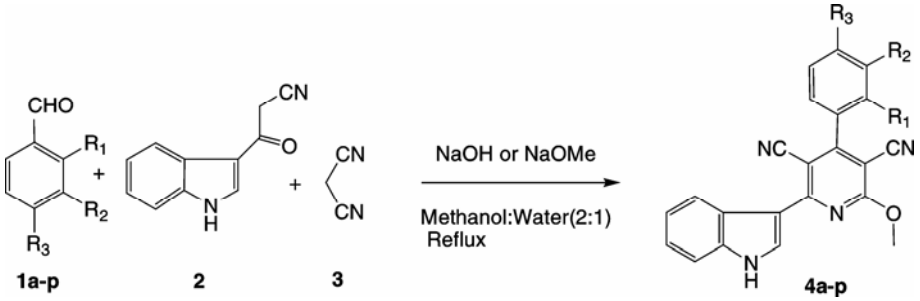
10 min later by intraperetoneal injection of 0·1 ml of 1% acetic acid in distilled water. The number of writhes was counted for 10 min immediately after the acetic acid injection. The percentage protection was calculated. Then the grouped animals received the standard and test drug as follows.

Group-1: Received subcutaneously 2% Tween 80 and served as control.

Group-2: The standard group received intra-peretoneally 50 mg/kg of the bodyweight of aspirin.

Table 4. Analgesic activity of *bis*(indol-3yl dihydropydine) derivatives.

Group	Animal weight (g)	Dose (mg/kg)	Writhing response	Inhibition (%)
1 (control)	25	1% Acetic acid	38·00 ± 0·70	00
2 (aspirin)	30	50 mg/kg	10·50 ± 0·64	72·36
3 (**7a**)	30	100 mg/kg	12·50 ± 0·86	67·10
4 (**7b**)	30	100 mg/kg	11·75 ± 0·75	69·07
5 (**7c**)	30	100 mg/kg	11·25 ± 0·28	70·39
6 (**7d**)	30	100 mg/kg	12·15 ± 0·75	68·02
7 (**7e**)	30	100 mg/kg	11·25 ± 0·75	70·22
8 (**7f**)	30	100 mg/kg	10·75 ± 0·70	71·71



Scheme 1. Synthesis of indol-3-yl pyridine derivatives

Group-3–8: The **3–8** groups received drugs **7a–f** (100 mg/kg) respectively. All the above test compounds were dissolved in 2% Tween 80 and administered orally. Writhing was induced 30 min later by intraperetoneal injections of 0·1 ml of 1% acetic acid in distilled water the number of writhes was counted for 10 min immediately after the acetic acid injection. The percentage protection was calculated.

Writhing method is one of the most common tests for evaluating the analgesic efficacy of drugs/compound in rodents. Narcotic analgesic inhibits both the types of pain, while NSAIDS such as paracetamol aspirin inhibit only the peripheral pain.

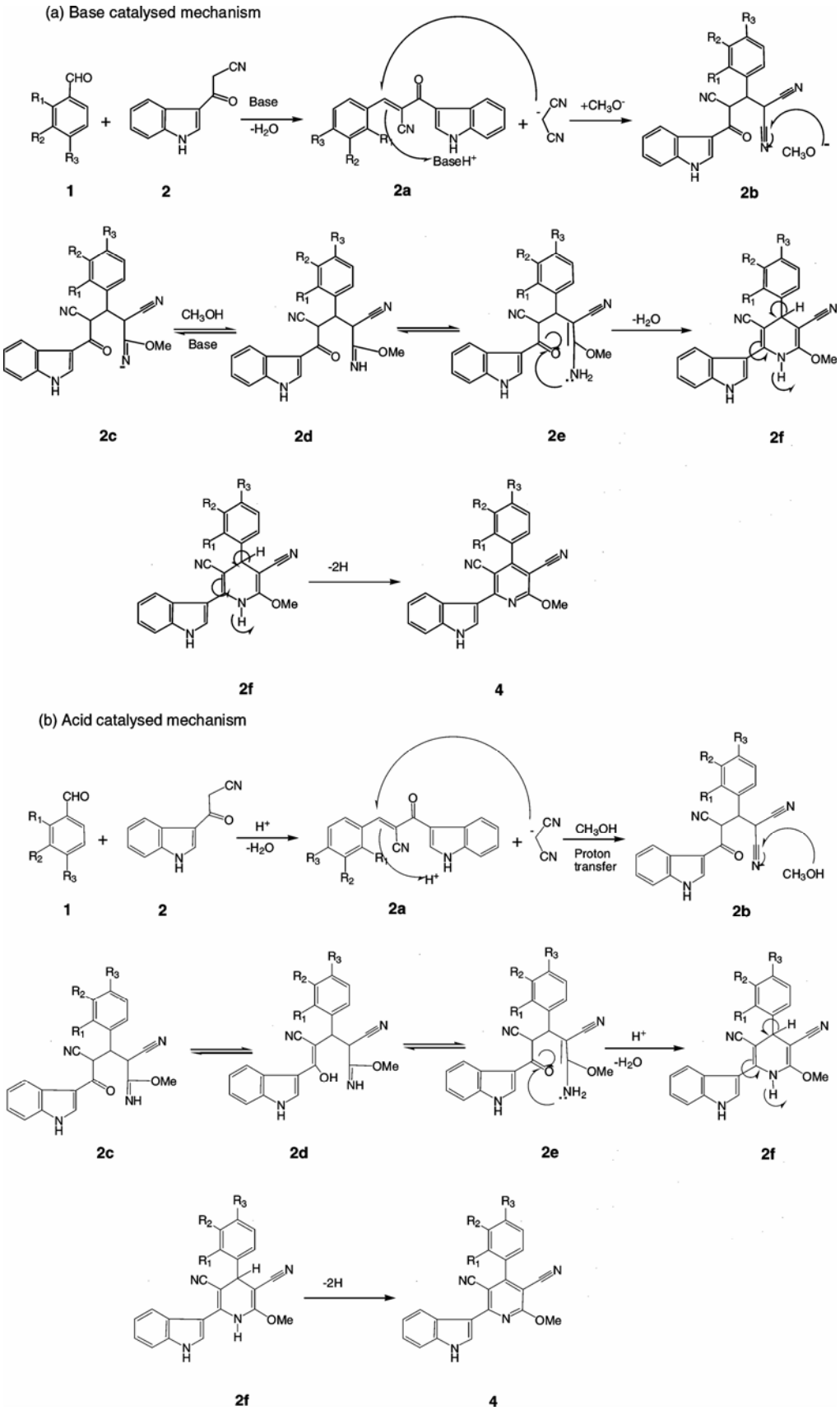
The abdominal constriction response induced by glacial acetic acid is a sensitive procedure to establish peripherally acting analgesics. This response is thought to involve local peritoneal receptors. The number of writhing observed during a 10 min period in control group was 38·00 ± 0.70 which corresponds with the finding of other workers.

The compounds **7c, 7e** and **7f** significantly reduced the number of writhes. Analgesic activity of the synthesized *bis*-Hantzsch dihydropyridine derivatives was compared with aspirin and found to be having significant activity.

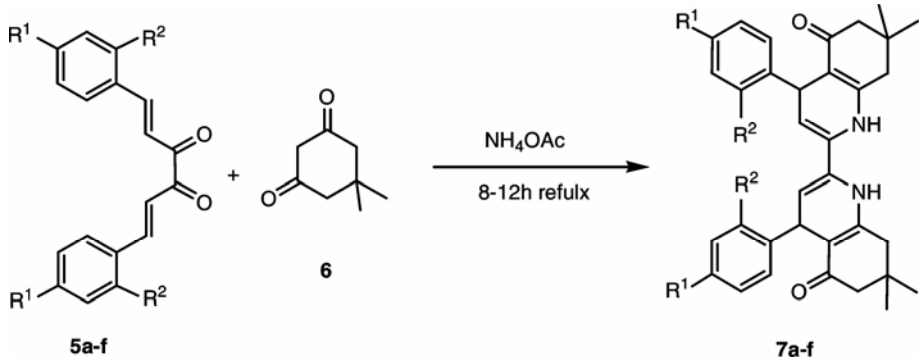
4. Results and discussion

In our previous report, we demonstrated that a mixture of substituted aldehyde, 3-cyanoacetyl indole and malononitrile in $InCl_3$/methanol under reflux condition for 2–6 h, afforded indol-3-yl pyridine derivatives in good yields.[26] To further optimize conditions we extended the generality of our methodology, we explored an alternative procedure, which resulted in an operationally efficient process. Thus, instead of heating the reaction in $InCl_3$/methanol, the reaction mixture was refluxed in freshly prepared NaOMe (or) NaOH in methanol : water (2 : 1) ratio to give best yield of indol-3-yl pyridine derivatives in shorter reaction time. The isolation of the product was very simple and easy, without employing any purification technique like column chromatography. It was pretty much straightforward as the solid precipitated was filtered and then dried. The crude was further purified by recrystallisation with ethanol to afford highly pure substituted indol-3-yl pyridine derivative (scheme 1).

The substrate scope of the reaction under the optimized conditions was investigated, and the reaction was amenable to a wide variety of conditions on various aldehydes. On sequential addition of



Scheme 2. A plausible mechanism for the formation of synthesis of indol-3-yl pyridine derivatives



Scheme 3. Synthesis of 7,7′,7′-tetramethyl-4,4′-*bis*(aryl)-4,6,7,8,4′,6′,7′,8′-octahydro-1H,1H-[2,2′]biquinolinyl-5,5′-dione derivatives.

the substrates under optimized conditions, the reaction proceeded smoothly with a wide range of functionalized aldehydes, including those containing ether nitro, halogens and polyaromatic spacers and the results are summarized in table 1.

Based on the above results, a plausible base and acid catalysed mechanism was proposed for the formation indol-3-yl pyridine derivatives (scheme 2).[7] Initially, 3-cyano acetyl indole reacts with corresponding aldehyde **(1a–k)** to give a α, β unsaturated ketone **(2a)** and on further it reacts with malononitrile **(2b)** followed by methoxide or methanol attack **(2c)** to give an intermediate **(2d** and **2e)**, which upon protonation yields Hantzsch dihydro pyridine derivative **(2g)**. The later deprotonation afford to yield pyridine **(4)** derivative. However in the reverse reaction, malononitrile is first allowed to react with the corresponding aldehyde followed by 3-cyanoacetyl indole attack did not lead to the formation of corresponding pyridine derivatives (scheme 2).

The structures of the compounds **4a–p** were established through IR, ^{1}H NMR, ^{13}C NMR and elemental analysis as exemplified for compound **4g** as follows: In the IR spectrum absorptions at 3222 and 2253 cm^{-1} supported the presence of –NH and –C≡N functional groups. The ^{1}H NMR spectrum exhibited a broad distinguishable singlet at δ 12·14 (D_2O exchangeable) for –NH protons and a sharp distinguishable singlet appeared at δ 4·22 for methoxy protons. Aromatic protons were seen in the range of δ 7·22–8·56. A distinctive peak at δ 55·7 in the ^{13}C NMR spectrum confirmed the presence of methoxy group. The two cyano groups attached carbon characteristic peaks were appeared at δ 91·3 and 96·6. The mass spectrum displayed the molecular ion $[M + H]^+$ peak at *m/z* 431·3. The structure of the compound **4g** was further established by single crystal X-ray diffraction analysis (figure 2)[27].

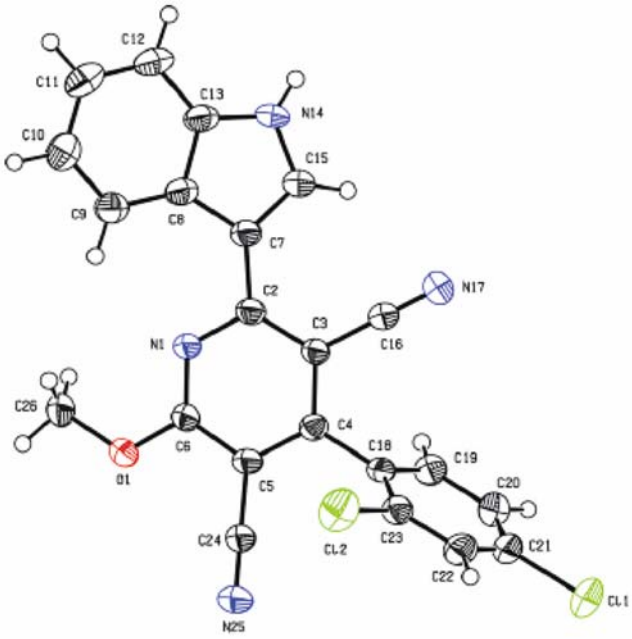


Figure 2. ORTEP diagram of compound **4g**.

Based on above results, we extended our protocol to the reaction with 1,6-diarylhexa-l,5-diene-3,4dione, dimedone and ammonium acetate under reflux condition which gave *bis*(indol-3yl dihydropydine) derivatives in moderate yields (scheme 3). Under optimized conditions, the reaction proceeded smoothly with a wide range of functionalized cinnamils, including those containing ethers, chlorine and hydrocarbons and the results are summarized in table 2.

The structure of compounds **(7a–f)** were examined based on the detailed spectroscopic studies as exemplified for compound **7b** as follows: In the IR spectrum of compound **(7b)** showed stretching frequencies at 3320 and 1588 cm^{-1} for –NH and C=O bonds. The ^{1}H NMR spectrum showed chemical

shift of δ: 8·55 (*brs*, D_2O exchangeable) corresponds to NH protons. The doublet in chemical shift region of δ: 4·78 and 6·63 corresponds to dihydropyridine ring protons. The sharp two singlets appeared in the region if δ: 183·2 and 195·3 correspond to carbonyl carbons. The aromatic carbons resonated in the region of δ: 117·1–150·2. The mass spectrum showed distinguishable singlet peak at *m/z* 533·47.

5. Conclusions

In conclusion, we have synthesized indol-3-yl pyridine in better yields *via* one pot multi-component reaction. These compounds showed good anti-inflammatory activity in comparison with the standard drug indomethacin. Also, we have prepared series of *bis*-Hantzsch dihydropyridine derivatives. These compounds showed a good analgesic activity when compared with asprin. Further studies to delineate the scope and limitations of the present methodology are underway.

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