Microwave-Assisted One-Pot Synthesis of Pyrazolo[3,4-*b*]indoles and New Isoxazolo[5,4-*b*]indoles via Copper-Catalyzed Intramolecular C–N/C–O Bond Formation

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Received 1 August 2011; revised 19 September 2011

Abstract: A facile one-pot, two-step synthesis of highly substituted pyrazolo[3,4-*b*]indoles and isoxazolo[5,4-*b*]indoles was developed via microwave-assisted, copper-catalyzed intramolecular heterocyclization (involving C–N/C–O bond formation) from 3-acetyl-2-chloroindoles in good to excellent yields.

Key words: copper catalysis, 3-acyl-2-chloroindoles, pyrazolo[3,4-*b*]indoles, isoxazolo[5,4-*b*]indoles, intramolecular heteroarylation

Nitrogen- and oxygen-containing heterocycles are being given great attention due to their role in the pharmaceutical industry and their occurrence in natural, biologically active[1] organic compounds, as well as in drugs such as Celebrex[2] and Viagra.[3] Moreover, pyrazole and isoxazole[4] nuclei are prominent structural motifs found in several natural products and synthetic compounds with vital medicinal value, and also the indole system is found in numerous natural products as well as in therapeutics.[5] The synthesis of fused indoles has therefore become an important research field and several synthetic methods have been developed.[6] The core structure of a fused indole is present in numerous biologically active indole derivatives, such as mitomycin and vincamine.[7] We were interested in developing an efficient synthetic method for biologically important indoles fused with pyrazole and isoxazole frameworks through copper-catalyzed intramolecular C–N and C–O bond formation.

During the past century, cross-coupling reactions have emerged as a powerful tool in organic synthesis,[8] in particular the copper-mediated Ullmann reaction[9] (N-arylation of amine) and the Goldberg reaction[10] (N-arylation of amide); however, these reactions have limitations, such as high reaction temperatures and the necessity to use stoichiometric amounts of copper, and several modifications have been introduced to overcome these shortcomings for the construction of carbon–carbon, carbon–nitrogen and carbon–oxygen bonds.[11–14] The success of these results prompted us to examine copper-catalyzed N-heteroarylation and O-heteroarylation in the synthesis of pyrazolo[3,4-*b*]indoles and isoxazolo[5,4-*b*]indoles, especially for 3-acyl-2-chloroindoles as starting materials.

SYNTHESIS 2011, No. 23, pp 3878–3886
Advanced online publication: 21.10.2011
DOI: 10.1055/s-0031-1289572; Art ID: Z75511SS

A survey of the literature disclosed that the pyrazolo[3,4-*b*]indole skeleton (Figure 1) has been found to display antiviral activity against HCMV (human cytomegalovirus)[15c] and the reported synthetic methods were poorly accomplished without further details involving applicability and scope.[15] Recently, Ila and co-workers reported[16] the synthesis of pyrazolo[3,4-*b*]indoles through a palladium-catalyzed intramolecular cyclization. To the best of our knowledge, however, this is the first report on the synthesis of highly substituted, new isoxazolo[5,4-*b*]indoles and pyrazolo[3,4-*b*]indoles via microwave-assisted one-pot, two-step, copper-catalyzed intramolecular O-heteroarylation and N-heteroarylation.

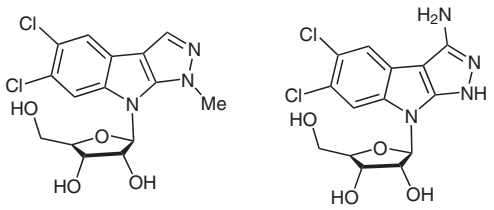
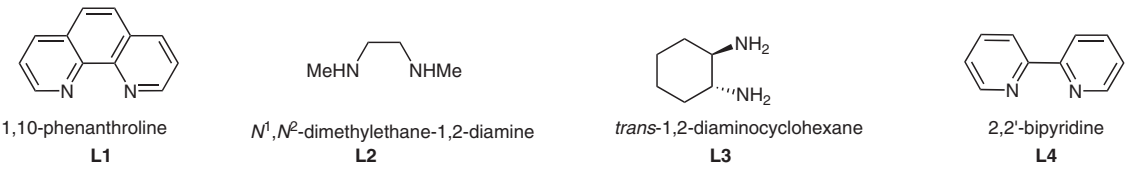


Figure 1 (2*R*,3*S*,4*R*,5*R*)-2-(5,6-Dichloropyrazolo[3,4-*b*]indol-8(1*H*)-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol nucleosides having antiviral and cytotoxic activity

To obtain the best optimized reaction conditions for the synthesis of pyrazolo[3,4-*b*]indoles and isoxazolo[5,4-*b*]indoles, we initiated our investigation with conventional heating, as shown in Tables 1 and 2, respectively. These data show the effect of various parameters, such as different copper sources (CuI, CuBr, CuCl, Cu_2O), ligands (see Figure 2), bases (Cs_2CO_3, K_2CO_3, K_3PO_4, Et_3N, *t*-BuOK) and solvents (DMSO, DMF, NMP, MeOH, toluene, MeCN) at various temperatures, on the efficiency of the reaction.

Gratifyingly, in our initial experiments we noticed that good yields could be achieved in the presence of a copper(I) iodide/*trans*-1,2-diaminocyclohexane catalyst system with potassium carbonate as base and *N*-methyl-2-pyrrolidinone (NMP) as solvent at 160 °C for the formation of 8-ethyl-3-methyl-1-phenyl-1,8-dihydropyrazolo[3,4-*b*]indole in 62% yield (Table 1, entry 9) and 8-ethyl-3-methyl-8*H*-isoxazolo[5,4-*b*]indole in 66% yield (Table 2, entry 5) by conventional heating.



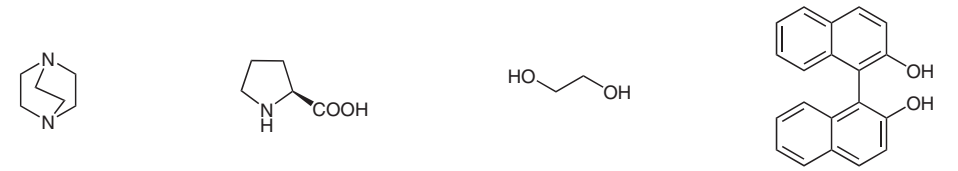
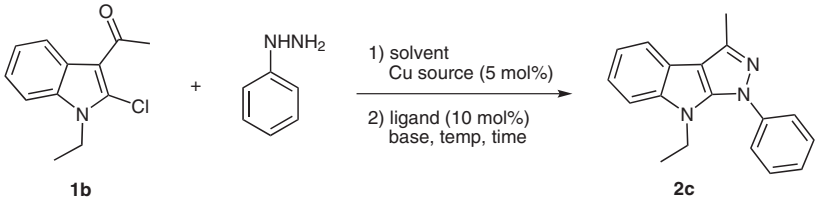


Figure 2 Selected ligands used in copper-catalyzed intramolecular heterocyclization

Table 1 Optimization of the Copper-Catalyzed Synthesis of 8-Ethyl-3-methyl-1-phenyl-1,8-dihydropyrazolo[3,4-*b*]indole (**2c**)



1b **2c**

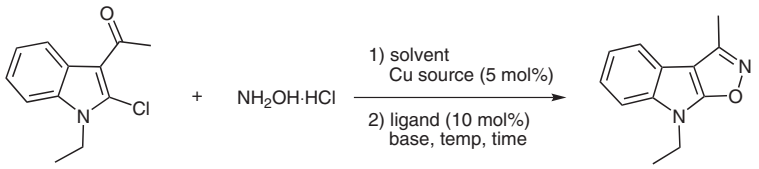
Microwave heating								Conventional heating		
Entry	Catalyst	Ligand	Base	Solvent	Temp (°C)	Time (min)	Yield (%)	Temp (°C)	Time (h)	Yield (%)
1	–	–	K_2CO_3	DMSO	120	60	–	150	24	–
2	CuO	**L1**	K_2CO_3	DMSO	120	60	–	150	24	–
3	Cu_2O	**L1**	K_2CO_3	DMSO	120	60	20	150	24	17
4	CuI	**L1**	K_2CO_3	DMSO	120	60	38	150	24	–
5	CuI	**L2**	Et_3N	DMF	120	60	–	150	24	–
6	CuI	**L3**	Cs_2CO_3	DMSO	120	60	45	110	24	–
7	CuI	**L4**	*t*-BuOK	MeOH	120	60	–	100	24	–
8	CuCl	**L5**	K_2CO_3	MeCN	120	60	25	100	24	–
9	**CuI**	**L3**	**K_2CO_3**	**NMP**	**120**	**20**	**92**	**160**	**24**	**62**
10	CuI	**L3**	Cs_2CO_3	NMP	120	30	86	160	24	65
11	CuI	**L3**	K_3PO_4	NMP	120	30	71	160	24	52
12	CuI	**L3**	*t*-BuOK	NMP	120	30	52	160	24	47
13	CuBr	**L3**	K_2CO_3	NMP	120	30	36	160	24	30
14	CuCl	**L3**	K_2CO_3	NMP	120	30	10	160	24	–
15	CuI	**L6**	Et_3N	toluene	120	30	–	110	24	–
16	CuI	**L7**	Cs_2CO_3	DMF	120	30	–	160	24	–
17	CuI	**L8**	Et_3N	DMF	120	30	–	160	24	–
18	Cu_2O	**L3**	Et_3N	DMF	120	30	–	160	24	–
19	CuI	–	K_2CO_3	NMP	120	30	20	160	24	12
20	–	**L3**	K_2CO_3	NMP	120	30	–	150	24	–
21	CuI	**L2**	K_2CO_3	NMP	120	30	83	150	24	67

Having an interest in the application of microwave irradiation technology,[17] we used microwave heating to speed up the optimized reaction, at first conducting the synthesis of the pyrazolo[3,4-*b*]indoles and isoxazolo[5,4-*b*]indoles in a single step in one pot. After several experiments, we concluded that better yields could be achieved by stepwise cyclization. Thus, the one-pot, two-step, copper-catalyzed intramolecular N-heteroarylation and O-heteroarylation procedure was developed. We found that the reaction was completed in the second step within 10–15 minutes and the isolated yields were 92% for **2c** (Table 1, entry 9) and 90% for **3b** (Table 2, entry 5). Finally, we found that the best reaction conditions for the formation of pyrazolo[3,4-*b*]indoles and isoxazolo[5,4-*b*]indoles in the second step involves 5 mol% of copper(I) iodide, 10 mol% of *trans*-1,2-diaminocyclohexane, 2.0 equivalents of potassium carbonate as base and NMP as solvent. By employing the optimal reaction conditions in the second step, we synthesized various pyrazolo[3,4-*b*]indoles **2** and isoxazolo[5,4-*b*]indoles **3** in good to excellent yields, as shown in Tables 3 and 4, respectively.

With our successfully developed method for the synthesis of pyrazolo[3,4-*b*]indoles and isoxazolo[5,4-*b*]indoles, we concluded that an electron-withdrawing group present in position 1 of the 3-acetyl-2-chloroindoles **1** produced excellent yields, as shown for the formation of **2d** (95%) and **2p** (93%) in Table 3, and **3c** (96%) and **3h** (94%) in Table 4, relative to electron-releasing groups. The structure of compound **2a** was also determined by X-ray crystallography.[18] The ORTEP diagram of **2a** is shown in Figure 3.

In conclusion, we have described a rapid, convenient and high-yielding method for the synthesis of an array of pyrazolo[3,4-*b*]indoles and isoxazolo[5,4-*b*]indoles via microwave-assisted one-pot, two-step, copper-catalyzed intramolecular heteroarylation involving C–N/C–O bond formation.

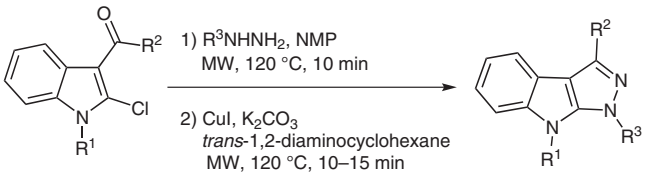
Table 2 Optimization of the Copper-Catalyzed Synthesis of 8-Ethyl-3-methyl-8*H*-isoxazolo[5,4-*b*]indole (**3b**)



1b **3b**

Microwave heating								Conventional heating		
Entry	Catalyst	Ligand	Base	Solvent	Temp (°C)	Time (min)	Yield (%)	Temp (°C)	Time (h)	Yield (%)
1	CuI	**L8**	K_2CO_3	DMSO	120	60	15	150	24	7
2	Cu_2O	**L7**	K_2CO_3	DMSO	120	60	–	150	24	–
3	Cu_2O	**L6**	K_2CO_3	DMSO	120	60	15	160	24	17
4	CuI	**L4**	K_2CO_3	DMSO	120	60	38	160	24	5
5	**CuI**	**L3**	**K_2CO_3**	**NMP**	**120**	**20**	**90**	**160**	**24**	**66**
6	CuI	**L5**	Cs_2CO_3	dioxane	120	60	45	110	24	–
7	CuI	**L1**	*t*-BuOK	MeOH	120	60	–	70	24	–
8	CuCl	**L2**	K_2CO_3	MeCN	120	60	25	70	24	–
9	CuI	**L3**	Cs_2CO_3	DMF	120	20	55	160	24	32
10	CuI	**L3**	Cs_2CO_3	NMP	120	30	87	110	24	65
11	CuI	**L3**	K_3PO_4	NMP	120	30	83	160	24	52
12	CuI	**L3**	*t*-BuOK	DMF	120	30	49	160	24	47
13	CuBr	**L3**	K_2CO_3	toluene	120	30	10	110	24	30
14	CuCl	**L3**	K_2CO_3	NMP	120	30	17	110	24	–
15	CuI	**L5**	Et_3N	NMP	120	30	–	110	24	–
16	CuI	**L7**	Cs_2CO_3	DMF	120	30	–	160	24	–
17	CuI	**L8**	Et_3N	DMF	120	30	–	160	24	–
18	CuCl	**L3**	Et_3N	DMSO	120	30	–	160	24	–

Table 3 Synthesis of Pyrazolo[3,4-*b*]indoles[a]



1 2

Product	R^1	R^2	R^3	Time (min)	Yield[b] (%)
2a	H	Me	Ph	10	89
2b	Et	Me	H	10	92
2c	Et	Me	Ph	10	94
2d	Bn	Me	Ph	10	95
2e	Bu	Me	Ph	10	93
2f	*n*-Hex	Me	Ph	10	89
2g	Bu	Me	3-$O_2NC_6H_4$	15	86
2h	*n*-Hex	Me	3-$O_2NC_6H_4$	15	83
2i	Bu	Me	4-ClC_6H_4	10	89
2j	Bu	Me	4-NCC_6H_4	10	87
2k	Bu	Me	3-Tol	10	86
2l	*n*-Hex	H	Ph	15	88
2m	H	H	Ph	15	82
2n	Et	H	Ph	13	86
2o	Bu	H	Ph	10	86
2p	Bn	H	Ph	10	93

[a] Reaction conditions: (1) 3-acyl-2-chloroindole **1** (0.5 mmol, 1.0 equiv), R^3NHNH_2 (0.5 mmol, 1.0 equiv), NMP (0.5 mL), MW, 120 °C; (2) CuI (5 mol%), *trans*-1,2-diaminocyclohexane (10 mol%), K_2CO_3 (2.0 equiv), MW, 120 °C.
[b] Yield refers to the column-purified product.

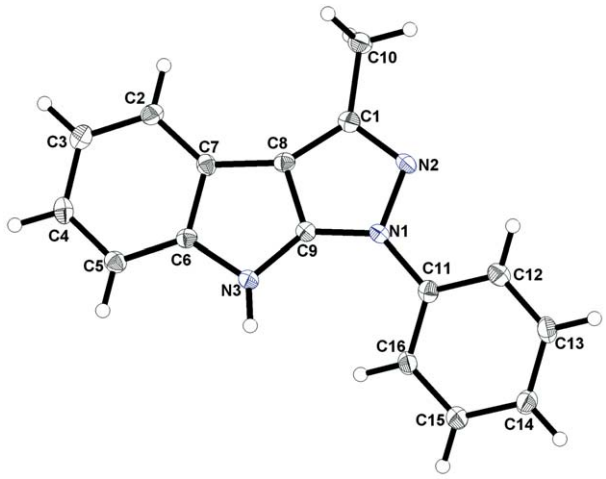
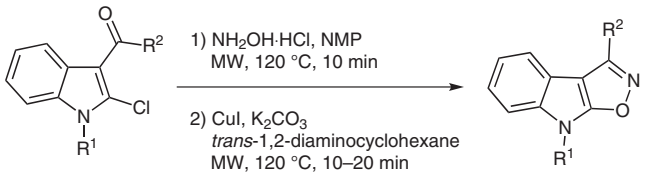


Figure 3 ORTEP diagram of **2a**

Table 4 Synthesis of Isoxazolo[5,4-*b*]indoles[a]



1 3

Product	R^1	R^2	Time (min)	Yield[b] (%)
3a	H	Me	20	86
3b	Et	Me	15	90
3c	Bn	Me	10	96
3d	Bu	Me	10	93
3e	*n*-Hex	Me	10	89
3f	H	H	15	82
3g	Et	H	13	86
3h	Bn	H	13	94
3i	Bu	H	10	86
3j	*n*-Hex	H	15	88

[a] Reaction conditions: (1) 3-acyl-2-chloroindole **1** (0.5 mmol, 1.0 equiv), $NH_2OH·HCl$ (0.5 mmol, 1.0 equiv), NMP (0.5 mL), MW, 120 °C; (2) CuI (5 mol%), *trans*-1,2-diaminocyclohexane (10 mol%), K_2CO_3 (2.0 equiv), MW, 120 °C.
[b] Yield refers to the column-purified product.

The procedure does not require an inert atmosphere. All the products obtained were purified by column chromatography using silica gel (100–200 mesh) with EtOAc–hexane as the eluent. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ with TMS at 400 MHz and 100 MHz, respectively, on a Bruker DRX 400 instrument. The chemical shifts are reported in ppm downfield to TMS ($\delta = 0$ ppm) for ^{1}H NMR and relative to the central $CDCl_3$ resonance ($\delta = 77.0$ ppm) for ^{13}C NMR spectra. The coupling constants, *J*, are given in Hz. IR spectra were recorded on a Jasco FT/IR-5300 spectrophotometer. The X-ray diffraction measurements were carried out at 298 K on a Bruker Smart Apex CCD automated diffractometer using graphite monochromated Mo Kα ($\lambda = 0.71073$ Å) radiation with CAD4 software, or the X-ray intensity data were measured at 298 K on a Bruker Smart Apex CCD diffractometer equipped with a graphite monochromator and a Mo Kα fine-focus sealed tube ($\lambda = 0.71073$ Å). Elemental analyses were recorded on a Thermo Finnigan Flash EA 1112 analyzer at the School of Chemistry, University of Hyderabad. Mass spectra were recorded on a Shimadzu LCMS-2010A mass spectrometer. Melting points were measured in open capillary tubes and are uncorrected. Microwave reactions were performed with an LG (MG 607APR)^{TM} 900 W domestic microwave oven.

8-Ethyl-3-methyl-1-phenyl-1,8-dihydropyrazolo[3,4-*b*]indole (2c); Typical Procedure

A domestic microwave oven was charged with 3-acetyl-2-chloro-1-ethyl-1*H*-indole (100 mg, 0.5 mmol, 1.0 equiv), $PhNHNH_2$ (48 mg, 0.5 mmol, 1.0 equiv) and NMP (0.5 mL) in an open vessel. The vessel was heated at 120 °C for 10 min (fixed hold time) in the microwave oven. Then, to the preformed hydrazone solution, K_2CO_3 (124

mg, 1.0 mmol, 2.0 equiv), CuI (4 mg, 0.025 mmol, 0.05 equiv) and *trans*-1,2-diaminocyclohexane (5 mg, 0.05 mmol, 0.1 equiv) were added. The reaction vessel was again heated at 120 °C for 10 min (fixed hold time) in the microwave oven. The reaction mixture was filtered through Celite® and purified by column chromatography (EtOAc–hexane) to give **2c** as a colorless viscous liquid; yield: 117 mg (94%).

IR (KBr): 3051, 2928, 2854, 1595, 1564, 1520, 1494, 1454, 1375, 1321, 1261, 1165, 1103, 1020, 742 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 7.2 Hz, 1 H), 7.62–7.61 (m, 2 H), 7.56–7.52 (m, 2 H), 7.46–7.44 (m, 1 H), 7.31–7.24 (m, 3 H), 4.08 (q, *J* = 7.2 Hz, 2 H), 2.68 (s, 3 H), 1.13 (t, *J* = 4.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.4, 142.5, 141.7, 139.3, 129.2, 127.8, 124.9, 121.9, 119.0, 110.0, 109.7, 38.6, 29.7, 22.7.

LC-MS (positive mode): *m*/*z* = 276 $[M + H]^+$.

Anal. Calcd for $C_{18}H_{17}N_3$: C, 78.52; H, 6.22; N, 15.26. Found: C, 78.65; H, 6.25; N, 15.07.

3-Methyl-1-phenyl-1,8-dihydropyrazolo[3,4-*b*]indole (2a)
Yield: 113 mg (89%); colorless solid; mp 161–163 °C.

IR (KBr): 3223, 3063, 2928, 2878, 1682, 1670, 1593, 1560, 1502, 1450, 1404, 1302, 1263, 1224, 1113, 1076, 1026, 1003, 754, 692 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.48 (s, 1 H), 7.72–7.67 (m, 3 H), 7.45 (t, *J* = 7.2 Hz, 2 H), 7.38–7.26 (m, 1 H), 7.25–7.20 (m, 3 H), 2.68 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.7, 142.1, 141.6, 139.1, 129.1, 125.4, 122.5, 121.9, 121.3, 120.3, 119.0, 118.4, 117.5, 112.0, 111.2, 31.8.

LC-MS (positive mode): *m*/*z* = 248 $[M + H]^+$.

Anal. Calcd for $C_{16}H_{13}N_3$: C, 77.71; H, 5.30; N, 16.99. Found: C, 77.65; H, 5.36; N, 16.85.

8-Ethyl-3-methyl-1,8-dihydropyrazolo[3,4-*b*]indole (2b)
Yield: 92 mg (92%); brown viscous liquid.

IR (KBr): 2924, 2860, 1633, 1599, 1452, 1375, 1338, 1269, 1269, 1091, 1018, 740 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 8.0 Hz, 1 H), 7.32–7.24 (m, 2 H), 7.11 (t, *J* = 8.0 Hz, 1 H), 4.18 (q, *J* = 8.0 Hz, 2 H), 2.63 (s, 3 H), 1.45 (t, *J* = 4.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.8, 144.3, 130.9, 123.4, 120.2, 119.5, 118.6, 108.6, 107.3, 38.1, 13.7, 11.5.

LC-MS (positive mode): *m*/*z* = 200 $[M + H]^+$.

Anal. Calcd for $C_{12}H_{13}N_3$: C, 72.33; H, 6.58; N, 21.09. Found: C, 72.21; H, 6.52; N, 21.18.

8-Benzyl-3-methyl-1-phenyl-1,8-dihydropyrazolo[3,4-*b*]indole (2d)
Yield: 112 mg (95%); pale brown solid; mp 271–273 °C.

IR (KBr): 3061, 2926, 1718, 1593, 1562, 1494, 1454, 1323, 1157, 1113, 1022, 1005, 740, 696 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.76–7.75 (m, 1 H), 7.37–7.34 (m, 2 H), 7.33–7.32 (m, 3 H), 7.25–7.24 (m, 1 H), 7.19–7.18 (m, 6 H), 6.84–6.83 (m, 1 H), 5.21 (s, 2 H), 2.66 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 146.5, 143.2, 141.7, 138.9, 136.4, 129.7, 129.1, 128.7, 127.7, 127.4, 126.0, 125.3, 124.8, 122.4, 122.2, 120.6, 119.9, 119.0, 118.4, 110.2, 47.4, 13.8.

LC-MS (positive mode): *m*/*z* = 338 $[M + H]^+$.

Anal. Calcd for $C_{23}H_{19}N_3$: C, 81.87; H, 5.68; N, 12.45. Found: C, 81.65; H, 5.75; N, 12.32.

8-Butyl-3-methyl-1-phenyl-1,8-dihydropyrazolo[3,4-*b*]indole (2e)
Yield: 112 mg (93%); pale brown, viscous liquid.

IR (KBr): 2926, 2858, 1686, 1554, 1448, 1161, 1107, 1018, 744 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.54–7.50 (d, *J* = 8.0 Hz, 1 H), 7.45–7.41 (m, 2 H), 7.29–7.28 (m, 2 H), 7.26–7.24 (m, 1 H), 7.23–7.21 (m, 3 H), 4.01–3.97 (m, 2 H), 2.76 (s, 3 H), 1.04–1.00 (m, 2 H), 0.90–0.87 (m, 2 H), 0.68 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.7, 142.7, 141.6, 139.0, 132.3, 129.2, 128.0, 125.3, 121.9, 120.2, 119.8, 119.0, 109.8, 108.4, 43.6, 31.0, 19.7, 14.1, 13.6, 13.4.

LC-MS (positive mode): *m*/*z* = 304 $[M + H]^+$.

Anal. Calcd for $C_{20}H_{21}N_3$: C, 79.17; H, 6.98; N, 13.85. Found: C, 79.26; H, 6.89; N, 13.68.

8-Hexyl-3-methyl-1-phenyl-1,8-dihydropyrazolo[3,4-*b*]indole (2f)
Yield: 106 mg (89%); colorless viscous liquid.

IR (KBr): 3362, 2926, 2854, 1599, 1558, 1523, 1493, 1454, 1157, 1028, 740, 698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.40–8.39 (m, 1 H), 7.32–7.28 (m, 8 H), 4.27–4.23 (m, 2 H), 2.71 (s, 3 H), 1.83–1.39 (m, 2 H), 1.37–1.23 (m, 4 H), 0.93–0.91 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.7, 141.6, 139.2, 129.5, 129.2, 128.3, 127.9, 126.9, 125.6, 125.3, 121.8, 120.1, 119.8, 119.0, 115.3, 109.8, 43.8, 31.0, 28.9, 26.1, 22.3, 13.8.

LC-MS (positive mode): *m*/*z* = 332 $[M + H]^+$.

Anal. Calcd for $C_{22}H_{25}N_3$: C, 79.72; H, 7.60; N, 12.68. Found: C, 79.63; H, 7.55; N, 12.59.

8-Butyl-3-methyl-1-(3-nitrophenyl)-1,8-dihydropyrazolo[3,4-*b*]indole (2g)
Yield: 119 mg (86%); pale yellow solid; mp 225–227 °C.

IR (KBr): 2959, 2930, 2866, 1614, 1554, 1523, 1475, 1442, 1352, 1165, 1107, 1026, 879, 798, 752 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.46 (t, *J* = 4.0 Hz, 1 H), 8.27–8.25 (m, 1 H), 8.01–8.00 (m, 1 H), 7.99–7.77 (m, 2 H), 7.75–7.25 (m, 3 H), 4.10 (t, *J* = 6.0 Hz, 2 H), 2.66 (s, 3 H), 1.56–1.53 (m, 2 H), 1.08–1.04 (m, 2 H), 0.73 (t, *J* = 9.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.5, 146.4, 143.4, 142.9, 140.5, 130.2, 129.9, 122.4, 122.1, 121.7, 120.7, 119.7, 118.6, 113.1, 110.2, 44.2, 31.0, 19.7, 13.6, 13.4.

LC-MS (positive mode): *m*/*z* = 349 $[M + H]^+$.

Anal. Calcd for $C_{20}H_{20}N_4O_2$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.85; H, 5.71; N, 16.21.

8-Hexyl-3-methyl-1-(3-nitrophenyl)-1,8-dihydropyrazolo[3,4-*b*]indole (2h)
Yield: 132 mg (83%); red viscous liquid.

IR (KBr): 2926, 2854, 1622, 1529, 1462, 1350, 1150, 1022, 966, 875, 740 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.45 (t, *J* = 4.0 Hz, 1 H), 8.26–8.01 (m, 1 H), 7.99–7.77 (m, 1 H), 7.75–7.72 (m, 2 H), 7.61–7.50 (m, 2 H), 7.34–6.95 (m, 1 H), 4.11–4.08 (m, 2 H), 2.66 (s, 3 H), 1.59–1.53 (m, 2 H), 0.91–0.90 (m, 5 H), 0.88–0.76 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.5, 143.0, 140.5, 130.2, 129.1, 129.0, 122.4, 121.7, 120.7, 120.5, 119.1, 118.7, 113.2, 110.2, 109.0, 44.4, 31.9, 31.0, 29.3, 22.6, 14.0, 13.7.

LC-MS (positive mode): *m*/*z* = 377 $[M + H]^+$.

Anal. Calcd for $C_{22}H_{24}N_4O_2$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.25; H, 6.38; N, 14.75.

8-Butyl-1-(4-chlorophenyl)-3-methyl-1,8-dihydropyrazolo[3,4-*b*]indole (2i)
Yield: 120 mg (89%); pale green, viscous liquid.

IR (KBr): 3248, 3051, 2932, 2860, 1672, 1612, 1493, 1466, 1402, 1300, 1091, 1028, 831, 744 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80–7.74 (m, 2 H), 7.72–7.70 (m, 3 H), 7.32–7.24 (m, 3 H), 4.11–4.08 (m, 2 H), 2.65 (s, 3 H), 1.49–1.45 (m, 2 H), 1.04–1.01 (m, 2 H), 0.71 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.3, 143.7, 143.0, 142.8, 133.3, 124.0, 122.4, 120.0, 119.8, 119.1, 118.3, 112.3, 111.3, 111.2, 110.4, 44.2, 31.8, 29.3, 19.7, 13.7.

LC-MS (positive mode): *m*/*z* = 338/340 $[M + H]^+$.

Anal. Calcd for $C_{20}H_{20}ClN_3$: C, 71.10; H, 5.97; N, 12.44. Found: C, 71.25; H, 5.88; N, 12.35.

4-(8-Butyl-3-methylpyrazolo[3,4-*b*]indol-1(8*H*)-yl)benzonitrile (2j)
Yield: 114 mg (87%); brown viscous liquid.

IR (KBr): 3251, 2926, 2854, 1590, 1564, 1520, 1494, 1454, 1375, 1325, 1280, 1166, 1110, 1020, 742 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80–7.74 (m, 2 H), 7.72–7.70 (m, 3 H), 7.31–7.24 (m, 3 H), 4.10–4.08 (q, *J* = 7.2 Hz, 2 H), 2.63 (s, 3 H), 1.50–1.42 (m, 2 H), 1.04–0.95 (m, 2 H), 0.72 (t, *J* = 4.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.3, 143.7, 143.0, 142.8, 133.3, 124.0, 120.7, 119.8, 119.1, 118.3, 112.2, 111.2, 110.4, 44.2, 30.9, 29.3, 19.7, 13.7, 13.4.

LC-MS (positive mode): *m*/*z* = 329 $[M + H]^+$.

Anal. Calcd for $C_{21}H_{20}N_4$: C, 76.80; H, 6.14; N, 17.06. Found: C, 76.89; H, 6.08; N, 17.18.

8-Butyl-3-methyl-1-*m*-tolyl-1,8-dihydropyrazolo[3,4-*b*]indole (2k)
Yield: 109 mg (86%); pale yellow, viscous liquid.

IR (KBr): 3051, 2957, 2930, 2868, 1676, 1645, 1610, 1520, 1464, 1390, 1197, 1159, 1107, 1008, 744 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74–7.72 (m, 1 H), 7.41–7.20 (m, 7 H), 4.02–3.98 (m, 2 H), 2.64 (s, 3 H), 2.44 (s, 3 H), 1.50–1.46 (m, 2 H), 1.06–1.01 (m, 2 H), 0.71 (t, *J* = 4.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.7, 142.7, 141.8, 139.3, 139.1, 128.8, 128.6, 125.8, 122.1, 121.7, 120.1, 119.8, 118.9, 109.8, 43.6, 31.0, 29.7, 21.3, 19.7, 13.7, 13.4.

LC-MS (positive mode): *m*/*z* = 318 $[M + H]^+$.

Anal. Calcd for $C_{21}H_{23}N_3$: C, 79.46; H, 7.30; N, 13.24. Found: C, 79.35; H, 7.26; N, 13.36.

8-Hexyl-1-phenyl-1,8-dihydropyrazolo[3,4-*b*]indole (2l)
Yield: 100 mg (88%); brown viscous liquid.

IR (KBr): 3059, 2928, 2856, 1711, 1599, 1566, 1523, 1493, 1456, 1375, 1159, 1109, 1018, 740, 698 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01–7.99 (m, 1 H), 7.76–7.74 (m, 4 H), 7.60–7.44 (m, 1 H), 7.29–7.22 (m, 4 H), 4.03–3.99 (m, 2 H), 1.51–1.44 (m, 2 H), 1.14–1.10 (m, 6 H), 1.00–0.76 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.7, 142.7, 141.6, 139.2, 129.2, 128.9, 128.3, 127.9, 125.3, 121.8, 120.1, 119.8, 119.0, 109.8, 109.7, 43.8, 31.0, 28.9, 26.1, 22.3, 13.7.

LC-MS (positive mode): *m*/*z* = 318 $[M + H]^+$.

Anal. Calcd for $C_{21}H_{23}N_3$: C, 79.46; H, 7.30; N, 13.24. Found: C, 79.35; H, 7.33; N, 13.16.

1-Phenyl-1,8-dihydropyrazolo[3,4-*b*]indole (2m)
Yield: 106 mg (82%); colorless solid; mp 167–169 °C.

IR (KBr): 3425, 3246, 3057, 2939, 2876, 2546, 1668, 1599, 1502, 1462, 1404, 1302, 1263, 1113, 1026, 985, 927, 754, 696, 657 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.32 (s, 1 H), 7.97 (s, 1 H), 7.76–7.52 (m, 3 H), 7.40–7.38 (m, 2 H), 7.30–7.25 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.9, 142.2, 141.9, 139.1, 129.5, 125.3, 122.4, 120.8, 120.2, 119.0, 118.4, 112.0, 111.1.

LC-MS (negative mode): *m*/*z* = 232 $[M - H]^+$.

Anal. Calcd for $C_{15}H_{11}N_3$: C, 77.23; H, 4.75; N, 18.01. Found: C, 77.32; H, 4.68; N, 17.95.

8-Ethyl-1-phenyl-1,8-dihydropyrazolo[3,4-*b*]indole (2n)
Yield: 108 mg (86%); colorless viscous liquid.

IR (KBr): 3040, 2930, 2852, 1702, 1590, 1552, 1520, 1490, 1450, 1370, 1150, 1109, 1012, 742, 689 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75–7.63 (m, 1 H), 7.63–7.61 (m, 2 H), 7.56–7.52 (m, 2 H), 7.45 (d, *J* = 8.0 Hz, 1 H), 7.31–7.24 (m, 4 H), 4.08 (q, *J* = 8.0 Hz, 2 H), 1.14 (t, *J* = 4.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.4, 143.2, 141.7, 138.9, 136.4, 129.7, 128.7, 127.7, 126.0, 125.3, 124.8, 122.4, 121.0, 119.9, 118.4, 47.3, 21.0.

LC-MS (positive mode): *m*/*z* = 262 $[M + H]^+$.

Anal. Calcd for $C_{17}H_{15}N_3$: C, 78.13; H, 5.79; N, 16.08. Found: C, 78.25; H, 5.72; N, 16.18.

8-Butyl-1-phenyl-1,8-dihydropyrazolo[3,4-*b*]indole (2o)
Yield: 99 mg (86%); light brown, viscous liquid.

IR (KBr): 3031, 2948, 2854, 1580, 1564, 1529, 1494, 1434, 1355, 1310, 1261, 1145, 1130, 1010, 742 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75–7.73 (m, 1 H), 7.59–7.58 (m, 2 H), 7.54–7.50 (m, 2 H), 7.45–7.41 (m, 1 H), 7.29–7.21 (m, 4 H), 4.01–3.99 (m, 2 H), 1.04–1.00 (m, 2 H), 0.90–0.87 (m, 2 H), 0.69–0.65 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.7, 142.8, 141.5, 138.7, 134.5, 129.3, 128.2, 125.4, 122.1, 120.3, 119.7, 119.1, 109.9, 109.7, 43.5, 31.0, 22.7, 19.7, 14.1.

LC-MS (positive mode): *m*/*z* = 290 $[M + H]^+$.

Anal. Calcd for $C_{19}H_{19}N_3$: C, 78.86; H, 6.62; N, 15.26. Found: C, 78.51; H, 6.57; N, 14.41.

8-Benzyl-1-phenyl-1,8-dihydropyrazolo[3,4-*b*]indole (2p)
Yield: 111 mg (93%); brown solid; mp 257–259 °C.

IR (KBr): 2932, 2150, 1682, 1504, 1404, 1300, 1172, 1114, 1026, 985, 927, 850, 752, 700, 657 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75–7.74 (m, 1 H), 7.41–7.40 (m, 6 H), 7.39–7.36 (m, 2 H), 7.35–7.34 (m, 3 H), 7.28–7.19 (m, 3 H), 5.23 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.5, 143.3, 141.7, 138.9, 136.4, 129.7, 129.1, 128.7, 128.1, 127.6, 127.4, 126.1, 125.4, 124.9, 122.4, 122.2, 121.0, 120.5, 120.0, 119.1, 118.4, 47.5.

LC-MS (positive mode): *m*/*z* = 324 $[M + H]^+$.

Anal. Calcd for $C_{22}H_{17}N_3$: C, 81.71; H, 5.30; N, 12.99. Found: C, 81.62; H, 5.35; N, 12.81.

8-Ethyl-3-methyl-8*H*-isoxazolo[5,4-*b*]indole (3b); Typical Procedure

A domestic microwave oven was charged with 3-acetyl-2-chloro-1-ethyl-1*H*-indole (100 mg, 0.5 mmol, 1.0 equiv), $NH_2OH{\cdot}HCl$ (31 mg, 0.5 mmol, 1.0 equiv) and NMP (0.5 mL) in an open vessel. The vessel was heated at 120 °C for 10 min (fixed hold time) in the microwave oven. Then, to the preformed oxime solution, K_2CO_3 (124 mg, 1.0 mmol, 2.0 equiv), CuI (4 mg, 0.025 mmol, 0.05 equiv) and *trans*-1,2-diaminocyclohexane (5 mg, 0.05 mmol, 0.1 equiv) were added. The reaction vessel was again heated at 120 °C for 15 min (fixed hold time) in the microwave oven. The reaction mixture was filtered through Celite® and purified by column chromatography (EtOAc–hexane) to give **3b** as a pale yellow, viscous liquid; yield: 81 mg (90%).

IR (KBr): 3035, 2915, 2862, 1702, 1590, 1552, 1520, 1490, 1450, 1370, 1150, 1109, 1012, 742, 689 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.34–8.32 (m, 1 H), 7.58–7.54 (m, 1 H), 7.47–7.45 (m, 1 H), 7.32–7.26 (m, 1 H), 4.49–4.45 (m, 2 H), 2.00 (s, 3 H), 1.47 (t, *J* = 4.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.1, 144.1, 130.9, 128.3, 123.7, 120.7, 118.6, 108.7, 107.5, 37.8, 22.5, 13.4.

LC-MS (positive mode): *m*/*z* = 201 $[M + H]^+$.

Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.06; H, 6.11; N, 13.85.

3-Methyl-8*H*-isoxazolo[5,4-*b*]indole (3a)

Yield: 76 mg (86%); colorless viscous liquid.

IR (KBr): 3342, 2931, 2222, 1691, 1657, 1509, 1455, 1333, 1260, 1111, 992, 915, 746 cm^{-1}.

^1H NMR (400 MHz, CDCl3): δ = 9.25 (s, 1 H), 8.33–8.32 (m, 1 H), 7.55–7.54 (m, 3 H), 2.03 (s, 3 H).

^{13}C NMR (100 MHz, CDCl3): δ = 147.6, 144.1, 139.8, 133.8, 128.4, 126.4, 121.2, 120.8, 111.4, 29.6.

LC-MS (negative mode): *m*/*z* = 171 $[M - H]^+$.

Anal. Calcd for C10H8N2O: C, 69.76; H, 4.68; N, 16.27. Found: C, 69.85; H, 4.61; N, 16.12.

8-Benzyl-3-methyl-8*H*-isoxazolo[5,4-*b*]indole (3c)

Yield: 88 mg (96%); red-brown solid; mp 221–223 °C.

IR (KBr): 3408, 3061, 2926, 2854, 1950, 1712, 1651, 1612, 1493, 1467, 1367, 1317, 1170, 1122, 1080, 1030, 752, 700 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.38 (m, 2 H), 7.36–7.35 (m, 3 H), 7.34–7.26 (m, 1 H), 7.24–7.21 (m, 2 H), 7.21–7.20 (m, 1 H), 5.23 (s, 2 H), 2.68 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.9, 139.2, 135.9, 135.0, 132.9, 130.2, 128.7, 128.4, 127.7, 126.4, 126.2, 124.1, 123.0, 121.7, 108.9, 43.8, 14.2.

LC-MS (positive mode): *m*/*z* = 263 $[M + H]^+$.

Anal. Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.68; H, 5.45; N, 10.56.

8-Butyl-3-methyl-8*H*-isoxazolo[5,4-*b*]indole (3d)

Yield: 85 mg (93%); colorless solid; mp 168–170 °C.

IR (KBr): 3048, 2925, 1632, 1490, 1444, 1367, 1322, 1210, 1160, 1090, 1017, 930, 772 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.41–8.39 (m, 1 H), 7.32–7.28 (m, 3 H), 4.27–4.24 (m, 2 H), 2.70 (s, 3 H), 1.84–1.78 (m, 2 H), 1.45 (m, 2 H), 0.99 (t, *J* = 9.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.0, 128.1, 126.0, 123.4, 122.8, 122.2, 121.2, 113.3, 109.3, 43.8, 34.0, 31.4, 20.0, 13.7.

LC-MS (negative mode): *m*/*z* = 227 $[M - H]^+$.

Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.56; H, 7.12; N, 12.36.

8-Hexyl-3-methyl-8*H*-isoxazolo[5,4-*b*]indole (3e)

Yield: 82 mg (89%); brown viscous liquid.

IR (KBr): 3053, 2930, 2858, 1649, 1493, 1450, 1377, 1336, 1209, 1178, 1099, 933, 746 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.41–8.39 (m, 1 H), 7.32–7.28 (m, 3 H), 4.26–4.22 (m, 2 H), 2.70 (s, 3 H), 1.83–1.80 (m, 2 H), 1.40–1.27 (m, 5 H), 0.90–0.81 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.9, 126.0, 123.4, 122.8, 122.2, 113.2, 109.3, 44.0, 31.3, 30.8, 29.3, 26.4, 22.5, 13.9.

LC-MS (positive mode): *m*/*z* = 257 $[M + H]^+$.

Anal. Calcd for $C_{16}H_{20}N_2O$: C, 74.97; H, 7.86; N, 10.93. Found: C, 75.12; H, 7.81; N, 10.85.

8*H*-Isoxazolo[5,4-*b*]indole (3f)

Yield: 72 mg (82%); colorless viscous liquid.

IR (KBr): 3387, 2943, 2222, 1687, 1651, 1504, 1448, 1302, 1265, 1113, 985, 925, 750 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.98 (s, 1 H), 7.67–7.65 (m, 1 H), 7.39–7.28 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.7, 138.5, 133.5, 126.9, 124.5, 122.9, 119.1, 111.3.

LC-MS (positive mode): *m*/*z* = 159 $[M + H]^+$.

Anal. Calcd for $C_9H_6N_2O$: C, 68.53; H, 3.82; N, 17.71. Found: C, 68.21; H, 3.91; N, 17.65.

8-Ethyl-8*H*-isoxazolo[5,4-*b*]indole (3g)

Yield: 77 mg (86%); light brown, viscous liquid.

IR (KBr): 3061, 2926, 2858, 2222, 1670, 1614, 1516, 1456, 1396, 1350, 1232, 1084, 1028, 742 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 8.0 Hz, 1 H), 7.38–7.27 (m, 4 H), 4.32 (q, *J* = 8.0 Hz, 2 H), 1.44 (t, *J* = 4.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.4, 126.9, 125.5, 124.0, 122.7, 119.2, 110.1, 108.2, 105.3, 39.4, 14.6.

LC-MS (negative mode): *m*/*z* = 185 $[M - H]^+$.

Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.85; H, 5.48; N, 15.12.

8-Benzyl-8*H*-isoxazolo[5,4-*b*]indole (3h)

Yield: 86 mg (94%); red solid; mp 216–218 °C.

IR (KBr): 3447, 2934, 2879, 2156, 1682, 1664, 1504, 1404, 1302, 1114 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.71–7.69 (m, 1 H), 7.35–7.29 (m, 6 H), 7.28 (s, 1 H), 7.12–7.10 (m, 2 H), 5.44 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.0, 139.2, 135.0, 132.9, 130.2, 128.7, 128.4, 127.7, 126.4, 126.2, 124.1, 123.0, 121.7, 108.9, 56.4.

LC-MS (negative mode): *m*/*z* = 247 $[M - H]^+$.

Anal. Calcd for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.31; H, 4.82; N, 11.15.

8-Butyl-8*H*-isoxazolo[5,4-*b*]indole (3i)

Yield: 78 mg (86%); colorless viscous liquid.

IR (KBr): 3051, 2932, 2872, 2222, 1653, 1506, 1458, 1404, 1302, 1263, 1113, 1030, 848, 750 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.70–7.68 (m, 1 H), 7.37–7.28 (m, 4 H), 4.27–4.26 (m, 2 H), 1.83–1.79 (m, 2 H), 1.43–1.38 (q, *J* = 4.0 Hz, 2 H), 0.99 (t, *J* = 4.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.5, 133.0, 126.4, 123.9, 122.7, 119.1, 114.2, 110.4, 44.0, 31.4, 19.9, 13.6.

LC-MS (positive mode): *m*/*z* = 215 $[M + H]^+$.

Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.68; H, 6.51; N, 13.21.

8-Hexyl-8*H*-isoxazolo[5,4-*b*]indole (3j)
Yield: 80 mg (88%); colorless viscous liquid.

IR (KBr): 3366, 2924, 2852, 1626, 1452, 1383, 1155, 1030 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.41–8.39 (m, 1 H), 7.32–7.28 (m, 4 H), 4.26–4.22 (m, 2 H), 1.83–1.80 (m, 2 H), 1.35–1.32 (m, 5 H), 0.92–0.89 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.0, 131.2, 126.0, 123.5, 122.9, 122.3, 118.7, 113.3, 109.3, 44.2, 31.3, 30.7, 29.4, 26.5, 14.0.

LC-MS (positive mode): *m*/*z* = 243 $[M + H]^+$.

Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.21; H, 7.56; N, 11.65.

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Primary Data for this article are available online at http://www.thieme-connect.com/ejournals/toc/synthesis and can be cited using the following DOI: 10.4125/pd0020th.

Acknowledgment

We gratefully acknowledge DST for financial assistance (Project number: SR/S1/OC-70/2008) and for providing the single-crystal X-ray diffractometer facility in our school. A.S.K. thanks UGC for a Senior Research Fellowship and P.V.A.R. thanks CSIR for a Junior Research Fellowship. A.S.K. also thanks Rambabu Bolligarla and Saikat Sen for helping with the crystal studies.

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(18) The crystal data of compound **2a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 832662. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44 (1223)336033; E-mail: deposit@ccdc.cam.ac.uk] or via www.ccdc.cam.ac.uk/data_request/cif.
Compound **2a**: $C_{16}H_{13}N_3$, M = 247.29; unit cell parameters: a = 13.2646(12) Å, b = 14.7200(13) Å, c = 15.4448(14) Å, α = 104.423(2)°, β = 107.550(2)°, γ = 112.102(2)°, space group $P1$.