Palladium-Mediated Direct Synthesis of N-Substituted 4-Methyl- and 4-Ethylisoquinolone Derivatives

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Received 14 February 2008; revised 11 June 2008

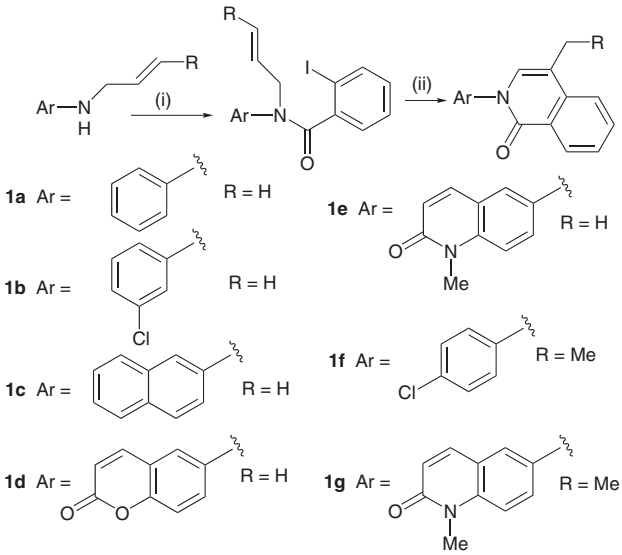
Abstract: N-Substituted 4-methyl- and 4-ethylisoquinolone derivatives are prepared from different *N*-allylbenzamide derivatives in a single step through a ligand-free palladium-mediated intramolecular Heck cyclization.

Key words: isoquinolones, Heck cyclization, intramolecular cyclization, palladium acetate

Substituted isoquinolones are important from both synthetic and application points of view. The isoquinolone moiety is found in several alkaloids and other pharmacologically important compounds.[1–13] Isoquinolones have been employed as useful intermediates in the synthesis of indenoisoquinolines, protoberberines, and dibenzoquinolizines. These are of much interest in medicinal chemistry. Due to their biological and pharmacological importance, several methods have been reported for the synthesis of isoquinolone derivatives.[14–19] Only few methods have utilized palladium catalyst. Paladium-catalyzed[20,21] reactions have been extensively used for carboannulation[22–25] and heteroannulation[26–35] processes. Several research groups have reported the synthesis of aromatic heterocycles via palladium-catalyzed annulation of internal alkynes.[36,37] Others have shown that palladium-catalyzed cyclizations are valuable synthetic tools for the preparation of a wide variety of heterocycles using vinylic compounds, terminal alkynes, allenes, and other substrates. In continuation of our work on palladium-catalyzed cyclization[38–40] we report here a straightforward protocol for the synthesis of hitherto unreported substituted isoquinolone derivatives.

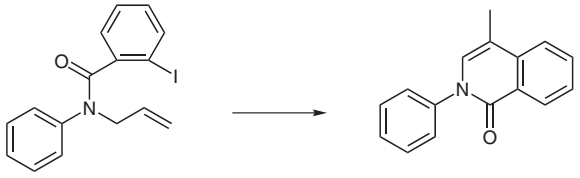
The Heck precursors **1a**–**g** were synthesized in one step by the reaction between *N*-allyl derivatives of the corresponding amines obtained with 2-iodobenzoyl chloride in anhydrous dichloromethane in the presence of triethylamine and a catalytic amount of DMAP as outlined in Scheme 1.

When the intramolecular Heck reaction was carried out with substrate **1a** (Table 1) in the presence of 10 mol% of $Pd(OAc)_2$ as catalyst, KOAc (2.5 equiv) as base and tetrabutylammonium bromide as a promoter in DMF at about 80 °C for one hour, we obtained the corresponding N-substituted 4-methylisoquinolone derivative **2a** in 90% yield.



Scheme 1 *Reagents and conditions*: (i) 2-iodobenzoyl chloride, anhyd CH_2Cl_2, Et_3N, DMAP (cat.), r.t.; (ii) $Pd(OAc)_2$, Bu_4NBr, KOAc, anhyd DMF, Δ.

Table 1 Cyclization of **1a** to **2a**[a]



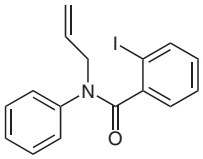
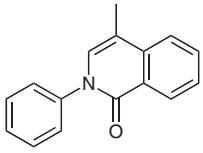
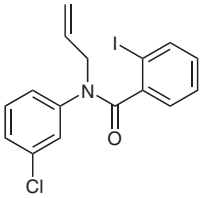
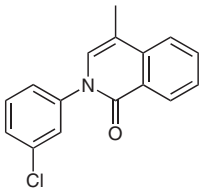
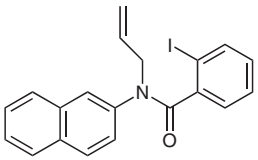
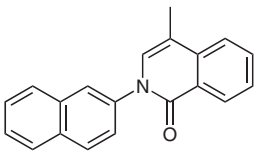
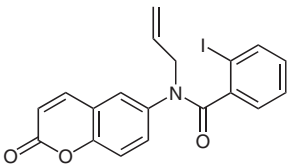
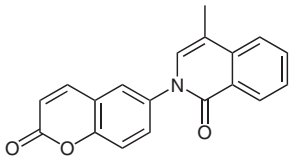
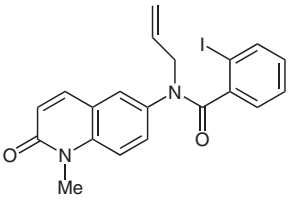
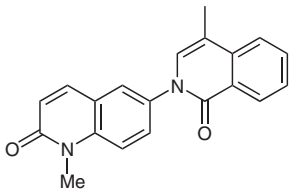
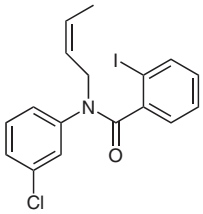
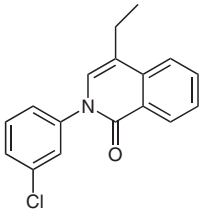
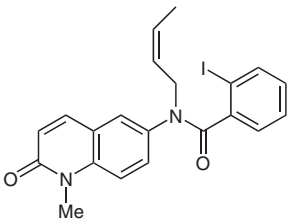
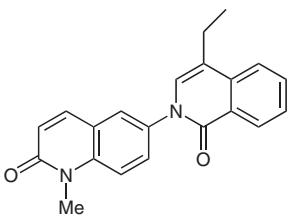
Entry	Catalyst[b]	Base[c]	Solvent	Yield (%)
1	$Pd(OAc)_2$	KOAc	DMF	95
2	$Pd(OAc)_2$	K_2CO_3	DMF	50
3	$Pd(OAc)_2$	Cs_2CO_3	DMF	65
4	$Pd(OAc)_2$	Et_3N	DMF	–[d]
5	$Pd(OAc)_2$	KOAc	MeCN	–[d]
6	$PdCl_2$	KOAc	DMF	45

[a] Bu_4NBr (TBAB) was used as the promoter. All the reactions were performed at 80 °C for 1–1.3 h.
[b] Amount of catalyst used: 10 mol%.
[c] Amount of base used: 2.50 equiv.
[d] No reaction.

SYNTHESIS 2008, No. 18, pp 2991–2995
Advanced online publication: 22.08.2008
DOI: 10.1055/s-2008-1067244; Art ID: Z04508SS

We have examined the influence of factors such as the nature of the base, solvent, catalyst, and the temperature on the formation of the cyclized product **2a**. With increase of temperature the yield of the product decreases due to extensive decomposition of the starting material. We have also examined the influence of the base like Cs_2CO_3, K_2CO_3, and triethylamine. KOAc proved to be the most effective base for the cyclization. Changing the solvent neither reduced the reaction time nor improved the yield of the reaction. Use of a low-boiling solvent such as

Table 2 Compounds **2** Prepared

Entry	Precursor	Time (h)	Product	Yield (%)
1	 **1a**	1	 **2a**	95
2	 **1b**	1.1	 **2b**	85
3	 **1c**	1.1	 **2c**	90
4	 **1d**	1.2	 **2d**	80
5	 **1e**	1.3	 **2e**	85
6	 **1f**	1	 **2f**	75
7	 **1g**	1.2	 **2g**	70

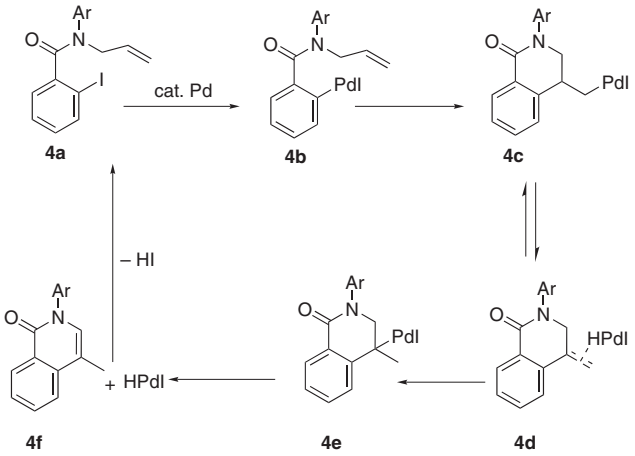
MeCN did not give any cyclized product. We have also examined the influence of $PdCl_2$ as a catalyst, and in this case the reaction is found to be very slow. However, we obtained the same product **2a** in low yield. Results are summarized in Table 1.

Substrates **1b–e** were treated similarly with $Pd(OAc)_2$ and KOAc in DMF for 1–1.3 hours to afford different N-substituted 4-methylisoquinolone derivatives (Table 2).

The substrates **1f**,**g** gave the corresponding N-substituted 4-ethylisoquinolone derivatives. However, when the reaction was carried out with monosubstituted *N*-allyl-2-iodobenzamide (**3a**) no cyclized product was obtained, instead it afforded the deiodinated product **3b** (Scheme 2).

Scheme 2

Usually a ligand such as PPh_3 is necessary[41] for carrying out this type of palladium-mediated Heck cyclization. However, no ligand is needed for achieving this type of reaction reported here. Mechanistically, these reactions appear to proceed as depicted in Scheme 3.



Scheme 3

In conclusion, we have achieved an expedious synthesis of hitherto unreported N-substituted 4-methyl- and 4-ethylisoquinolone derivatives through a ligand-free palladium-mediated intramolecular Heck cyclization.

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a PerkinElmer L 120-000A spectrometer. ^{1}H NMR (400 MHz) spectra were recorded on a Bruker DPX-400 spectrometer in $CDCl_3$ with TMS as internal standard. Silica gel [(60–120, 230–400 mesh), Spectrochem, India] was used for chromatographic separation. Silica gel G [E-Merck (India)] was used for TLC. Petroleum ether (PE) refers to the fraction boiling at 60–80 °C.

Substituted *N*-Allylbenzamide Derivatives 1; *N*-Allyl-2-iodo-*N*-phenylbenzamide (1a); Typical Procedure

A solution of 2-iodobenzoyl chloride (300 mg, 1.12 mmol) in anhyd CH_2Cl_2 (10 mL) was added dropwise to a stirred solution of *N*-allylaniline (150 mg, 1.12 mmol) in anhyd CH_2Cl_2 (10 mL) in the presence of DMAP (5 mg) and Et_3N (2 mL), and the mixture was stirred for 2 h. After completion of the reaction, the mixture was washed with H_2O (3 × 15 mL) and dried (Na_2SO_4). The solvent was removed and the residual mass was purified by column chromatography over silica gel using PE–EtOAc (20:1) as eluent to afford the desired compound **1a**; pale yellow liquid; yield: 387 mg (95%).

IR (film): 1651, 1595 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.52 (d, *J* = 5.96 Hz, 2 H), 5.16–5.24 (m, 2 H), 5.97–6.00 (m, 1 H), 6.79–6.84 (m, 1 H), 6.98 (dd, *J* = 7.6, 1.5 Hz, 1 H), 7.05–7.10 (m, 2 H), 7.14–7.16 (m, 4 H), 7.65 (d, *J* = 7.96 Hz, 1 H).

MS: *m*/*z* = 363 (M$^+$).

Anal. Calcd for $C_{16}H_{14}INO$: C, 52.91; H, 3.89; N, 3.86. Found: C, 53.02; H, 3.96; N, 3.90.

***N*-Allyl-*N*-(3-chlorophenyl)-2-iodobenzamide (1b)**

Pale yellow liquid; yield: 85%.

IR (film): 1651, 1590 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.50 (d, *J* = 4.9 Hz, 2 H), 5.12–5.25 (m, 2 H), 5.95–6.03 (m, 1 H), 6.85–6.89 (m, 1 H), 6.93–7.20 (m, 6 H), 7.66 (d, *J* = 7.84 Hz, 1 H).

MS: *m*/*z* = 397 (M$^+$).

Anal. Calcd for $C_{16}H_{13}ClINO$: C, 48.33; H, 3.30; N, 3.52. Found: C, 48.42; H, 3.37; N, 3.48.

***N*-Allyl-2-iodo-*N*-(naphthalen-2-yl)benzamide (1c)**

Yellow liquid; yield: 85%.

IR (film): 1650, 1628 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.60 (d, *J* = 5.76 Hz, 2 H), 5.11–5.25 (m, 2 H), 6.01–6.11 (m, 1 H), 6.73–6.77 (m, 1 H), 6.98–7.00 (m, 2 H), 7.28 (d, *J* = 1.6 Hz, 1 H), 7.41–7.48 (m, 2 H), 7.57–7.85 (m, 5 H).

MS: *m*/*z* = 413 (M$^+$).

Anal. Calcd for $C_{20}H_{16}INO$: C, 58.13; H, 3.90; N, 3.39. Found: C, 58.26; H, 3.95; N, 3.43.

***N*-Allyl-2-iodo-*N*-(2-oxo-2*H*-chromen-6-yl)benzamide (1d)**

Yellow liquid; yield: 80%.

IR (film): 1731, 1651 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.51 (d, *J* = 5.04 Hz, 2 H), 5.09–5.22 (m, 2 H), 5.96–6.00 (m, 1 H), 6.36 (d, *J* = 9.6 Hz, 1 H), 6.83 (t, *J* = 7.24 Hz, 1 H), 7.04–7.13 (m, 3 H), 7.28–7.36 (m, 2 H), 7.53 (d, *J* = 9.6 Hz, 1 H), 7.63 (d, *J* = 7.9 Hz, 1 H).

MS: *m*/*z* = 431 (M$^+$).

Anal. Calcd for $C_{19}H_{14}INO_3$: C, 52.97; H, 3.24; N, 3.29. Found: C, 53.10; H, 3.29; N, 3.34.

***N*-Allyl-2-iodo-*N*-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yl)benzamide (1e)**

Yellow liquid; yield: 90%.

IR (film): 1651, 1646 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.60 (s, 3 H), 4.53 (d, *J* = 5.36 Hz, 2 H), 5.17–5.22 (m, 2 H), 5.97–6.07 (m, 1 H), 6.65 (d, *J* = 9.4 Hz, 1 H), 6.80–6.84 (m, 1 H), 7.04–7.15 (m, 3 H), 7.35–7.38 (m, 2 H), 7.49 (d, *J* = 9.4 Hz, 1 H), 7.62 (d, *J* = 8.0 Hz, 1 H).

MS: *m*/*z* = 444 (M^+).

Anal. Calcd for $C_{20}H_{17}IN_2O_2$: C, 54.07; H, 3.86; N, 6.31. Found: C, 54.16; H, 3.94; N, 6.35.

_N_-(But-2-enyl)-_N_-(3-chlorophenyl)-2-iodobenzamide (1f)
Pale yellow liquid; yield: 85%.

IR (film): 1651, 1589 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.54 (s, 3 H), 4.08 (s, 2 H), 5.34 (s, 2 H), 6.83–6.87 (m, 1 H), 7.02–7.24 (m, 6 H), 7.64 (d, *J* = 7.72 Hz, 1 H).

MS: *m*/*z* = 411 (M^+).

Anal. Calcd for $C_{17}H_{15}ClINO$: C, 49.60; H, 3.67; N, 3.40. Found: C, 49.67; H, 3.65; N, 3.43.

_N_-(But-2-enyl)-2-iodo-_N_-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yl)benzamide (1g)
Yellow liquid; yield: 80%.

IR (film): 1651, 1646 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.60 (s, 3 H), 3.62 (s, 3 H), 4.05 (s, 2 H), 5.56 (s, 2 H), 6.63 (d, *J* = 9.5 Hz, 1 H), 6.79–6.83 (m, 1 H), 7.34–7.33 (m, 5 H), 7.47 (d, *J* = 9.5 Hz, 1 H), 7.60 (d, *J* = 7.9 Hz, 1 H).

MS: *m*/*z* = 458 (M^+).

Anal. Calcd for $C_{21}H_{19}IN_2O_2$: C, 55.04; H, 4.18; N, 6.11. Found: C, 55.15; H, 4.24; N, 6.16.

Heck Reaction of Substituted _N_-Allylbenzamide Derivatives 2; 4-Methyl-2-phenylisoquinolin-1(2*H*)-one (2a); Typical Procedure
A mixture of *N*-allyl-2-iodo-*N*-phenylbenzamide (100 mg, 0.275 mmol), TBAB (220 mg, 0.69 mmol), KOAc (40 mg, 0.4 mmol), $Pd(OAc)_2$ (2.5 mg, 1.1×10^{-4} mmol), and anhyd DMF (5 mL) was heated at 80 °C for 1 h. After completion of the reaction, H_2O (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined CH_2Cl_2 extracts were washed with H_2O (3 × 15 mL) and dried (Na_2SO_4). The solvent was removed and the residual mass was purified by column chromatography over silica gel using PE–EtOAc (20:1) as eluent to afford the compound **2a**; colorless solid; yield: 58 mg (90%); mp 102–104 °C.

IR (KBr): 1662, 1627 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.30 (d, *J* = 0.6 Hz, 3 H), 7.02 (d, *J* = 0.6 Hz, 1 H), 7.30–7.52 (m, 5 H), 7.54–7.59 (m, 1 H), 7.63 (d, *J* = 7.9 Hz, 1 H), 7.71–7.75 (m, 1 H), 8.50 (d, *J* = 7.88 Hz, 1 H).

MS: *m*/*z* = 235 (M^+).

Anal. Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.59. Found: C, 81.81; H, 5.62; N, 5.64.

2-(3-Chlorophenyl)-4-methylisoquinolin-1(2*H*)-one (2b)
Colorless solid; yield: 85%; mp 118–120 °C.

IR (KBr): 1665, 1630 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.30 (s, 3 H), 6.98 (s, 1 H), 7.33–7.46 (m, 4 H), 7.53–7.56 (m, 1 H), 7.62 (d, *J* = 7.9 Hz, 1 H), 7.72–7.76 (m, 1 H), 8.49 (d, *J* = 7.9 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.01, 142.77, 137.77, 135.13, 133.06, 130.57, 129.61, 129.06, 128.58, 127.74, 127.58, 126.66, 125.64, 123.64, 112.95, 15.76.

HRMS: *m*/*z* calcd for $C_{16}H_{12}ClNO$ $[M + H]^+$: 270.0680; found: 270.0703.

Anal. Calcd for $C_{16}H_{12}ClNO$: C, 71.25; H, 4.48; N, 5.19. Found: C, 71.35; H, 4.58; N, 5.24.

4-Methyl-2-(naphthalen-2-yl)isoquinolin-1(2*H*)-one (2c)
Colorless solid; yield: 90%; mp 110–112 °C.

IR (KBr): 1660, 1625 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.33 (d, *J* = 0.6 Hz, 3 H), 7.10 (d, *J* = 0.6 Hz, 1 H), 7.47–7.59 (m, 4 H), 7.65 (d, *J* = 7.9 Hz, 1 H), 7.73–7.82 (m, 1 H), 7.87–7.97 (m, 4 H), 8.53 (d, *J* = 7.80 Hz, 1 H).

MS: *m*/*z* = 269 (M^+).

Anal. Calcd for $C_{20}H_{15}NO$: C, 84.19; H, 5.30; N, 4.91. Found: C, 84.29; H, 5.37; N, 4.96.

4-Methyl-2-(2-oxo-2*H*-chromen-6-yl)isoquinolin-1(2*H*)-one (2d)
Colorless solid; yield: 80%; mp 186–190 °C.

IR (KBr): 1731, 1659 cm^{-1}.

H NMR (400 MHz, $CDCl_3$): δ = 2.32 (s, 3 H), 6.47 (d, *J* = 9.52 Hz, 1 H), 7.01 (s, 1 H), 7.44 (d, *J* = 9.52 Hz, 1 H), 7.48–7.78 (m, 6 H), 8.49 (d, *J* = 7.80 Hz, 1 H).

MS: *m*/*z* = 303 (M^+).

Anal. Calcd for $C_{19}H_{13}NO_3$: C, 75.24; H, 4.32; N, 4.62. Found: C, 75.36; H, 4.40; N, 4.67.

4-Methyl-2-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yl)isoquinolin-1(2*H*)-one (2e)
Colorless solid; yield: 85%; mp 198–200 °C.

IR (KBr): 1651, 1649 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.33 (s, 3 H), 3.76 (s, 3 H), 6.75 (d, *J* = 9.4 Hz, 1 H), 7.00 (s, 1 H), 7.45 (d, *J* = 9.4 Hz, 1 H), 7.54–7.58 (m, 1 H), 7.64–7.68 (m, 4 H), 7.74–7.77 (m, 1 H), 8.50 (d, *J* = 7.8 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.53, 162.35, 139.69, 138.85, 137.79, 135.98, 133.07, 129.89, 129.60, 128.95, 127.58, 126.89, 126.57, 123.66, 123.00, 121.37, 115.40, 113.02, 30.03, 15.77.

MS: *m*/*z* = 316 (M^+).

Anal. Calcd for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.86. Found: C, 76.08; H, 5.15; N, 8.90.

2-(3-Chlorophenyl)-4-ethylisoquinolin-1(2*H*)-one (2f)
Colorless solid; yield: 75%; mp 120–122 °C.

IR (KBr): 1660, 1625 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.4 Hz, 3 H), 2.75 (q, *J* = 7.4 Hz, 2 H), 6.95 (s, 1 H), 7.30–7.55 (m, 5 H), 7.69–7.75 (m, 2 H), 8.50 (d, *J* = 8.0 Hz, 1 H).

MS: *m*/*z* = 283 (M^+).

Anal. Calcd for $C_{17}H_{14}ClNO$: C, 71.96; H, 4.97; N, 4.94. Found: C, 80.08; H, 5.02; N, 5.01.

4-Ethyl-2-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yl)isoquinolin-1(2*H*)-one (2g)
Colorless solid; yield: 70%; mp 205–207 °C.

IR (KBr): 1651, 1649 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (t, *J* = 7.5 Hz, 3 H), 2.74 (q, *J* = 7.5 Hz, 2 H), 3.76 (s, 3 H), 6.75 (d, *J* = 9.5 Hz, 1 H), 7.01 (s, 1 H), 7.46 (d, *J* = 9.6 Hz, 1 H), 7.48–7.67 (m, 5 H), 7.71–7.77 (m, 1 H), 8.51 (d, *J* = 8.1 Hz, 1 H).

MS: m/z = 330 (M^+).

Anal. Calcd for $C_{21}H_{18}N_2O_2$: C, 76.34; H, 5.49; N, 8.48. Found: C, 76.44; H, 5.55; N, 8.53.

Acknowledgment

We thank the DST (New Delhi) and the CSIR (New Delhi) for financial assistance. Two of us (S.C. and K.R.) are thankful to the CSIR (New Delhi) for fellowships.

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