

An Efficient Synthesis of 2,4-Disubstituted Quinolines by Electrophile-Mediated Cyclization Reactions of 2-Isocyanostyrene Derivatives

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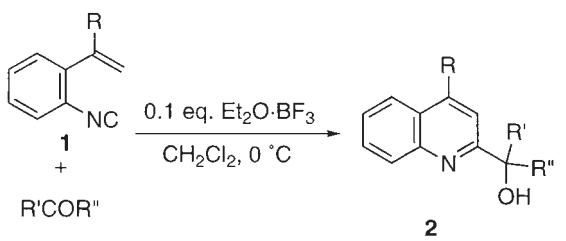
A novel quinoline synthesis starting with 2-isocyanostyrene derivatives is described. The treatment of 2-isocyanostyrene derivatives with aldehydes (or acetone) in the presence of a catalytic amount of diethyl ether–boron trifluoride afforded quinoline derivatives carrying a 1-hydroxyalkyl substituent at the 2-position. The use of acetaldehyde diethyl acetal or phenyloxirane as an electrophile under the same conditions gave the corresponding quinoline derivatives, carrying the 1-ethoxyethyl or 2-hydroxy-2-phenylethyl substituent at the 2-position, respectively. 2-Isocyanostyrene derivatives reacted with *N*,*N*-dimethyliminium salts without any catalyst to give 2-(1-dimethylaminoalkyl)quinolines.

We recently showed that 1-(2-isocyanophenyl)pyrroles reacted with aldehydes (or ketones), acetals, or oxiranes in the presence of catalytic amounts of diethyl ether–boron trifluoride to afford pyrrolo[1,2-*a*]quinoxalines carrying an oxyalkyl substituent, such as 1-hydroxyalkyl,[1,2] 1-alkoxyalkyl,[2] or 2-hydroxyalkyl,[2] at the 4-position, respectively. We also described that 4-(1-dialkylaminoalkyl)pyrrolo[1,2-*a*]quinoxalines could be prepared by treating 1-(2-isocyanophenyl)pyrroles with various iminium salts without any catalyst.[3] In an attempt to broaden the scope of these reactions, we examined an analogous electrophile-mediated cyclization using 2-isocyanostyrene derivatives **1** with the expectation that the reaction might produce quinolines carrying one of these functionalized substituents at the 2-position,[4] **2**–**6**. In this paper, we would like to report on the results of that study. A large number of general synthetic methods of quinoline derivatives have been reported.[5] However, the availability of a new method for their general preparation would seem to be attractive because of their importance in synthetic,[6] medicinal,[7,8] and natural-product chemistries.[9]

The treatment of 2-isocyanostyrene derivatives **1** with aldehydes in dichloromethane at 0 °C in the presence of a 0.1 molar amount of diethyl ether–boron trifluoride led to the formation of quinoline rings with the introduction of a 1-hydroxyalkyl group at the 2-position (Scheme 1), and the corresponding desired products **2** were obtained in the yields summarized in Table 1. The reactions of 2-isocyano-α-phenylstyrene (**1a**) gave moderate-to-fair yields of the desired products (entries 1 and 2). However, when methoxy group(s) were substituted on



Scheme 1.

Table 1. Preparation of 2-(1-Hydroxyalkyl)quinolines **2**

Entry	**1**	R′COR″	**2** (Yield/%)[a]
1	**1a** (R = Ph)	EtCHO	**2a** (52)
2	**1a**	*i*-PrCHO	**2b** (58)
3	**1b** [R = 4-(MeO)C_6H_4]	EtCHO	**2c** (66)
4	**1b**	*i*-PrCHO	**2d** (82)
5	**1b**	MeCOMe	**2e** (6)
6	**1c** [R = 3,4-$(MeO)_2C_6H_3$]	EtCHO	**2f** (72)
7	**1d** (R = Me)	EtCHO	**2g** (39)

a) Isolated yields after purification by preparative TLC on SiO_2.

the α-phenyl group, somewhat better results were obtained (entries 3, 4, and 6). Although the reaction of **1b** with acetone under the same conditions gave the desired product **2e**, the yield was very low (entry 5). Furthermore, the use of 2-isocyano-α-methylstyrene (**1d**) gave a rather poor result (entry 7). This may be due to the lower nucleophilicity of the methylethenyl group.

The preparation of 2-(1-ethoxyethyl)quinolines **3a** and **3c** was achieved by the treatment of 2-isocyanostyrene derivatives **1a** and **1c** with acetaldehyde diethyl acetal in the presence of diethyl ether–boron trifluoride under conditions similar to those described for the preparation of **2**, as shown in Scheme 2. However, the yields of these products were low to moderate.

Subsequently, a similar treatment of 2-isocyanostyrene derivatives **1** with phenyloxirane was carried out. The reaction was found to give 2-(2-hydroxy-2-phenylethyl)quinolines **4**, as illustrated in Scheme 3. While the reaction using 2-isocyano-α-(4-methoxyphenyl)styrene (**1b**) gave a moderate yield of the desired product **4b**, α-(3,4-dimethoxyphenyl)-2-isocyanostyrene (**1c**) gave a much better result.

The portionwise addition of a catalyst, which was very effective for preparing substituted pyrrolo[1,2-*a*]quinoxalines,[1,2] could not be used in any cases of the above-mentioned present reactions, because TLC analyses of the reactions showed that the starting materials were completely consumed within 20 min in all cases.

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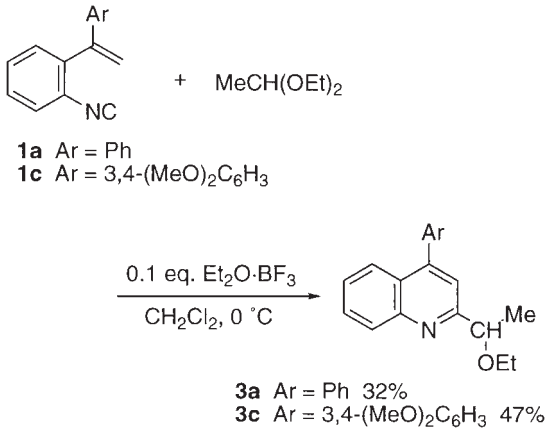
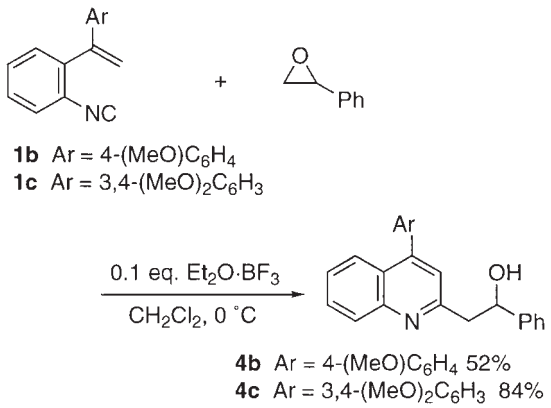
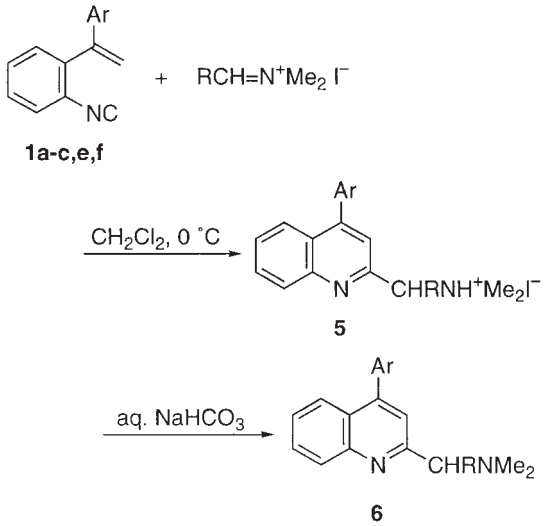


Scheme 2.



Scheme 3.

As expected, 2-(1-dimethylammonioalkyl)- and 2-(1-dimethylaminoalkyl)quinolines, **5** and **6**, could be obtained by the treatment of 2-isocyanostyrenes **1** with iminium salts without any catalyst, as illustrated in Scheme 4. Thus, reactions of 2-isocyanostyrene derivatives **1b**, **1c**, and **1e** with *N*,*N*-dimethylmethyleneammonium iodide (Eschenmoser's salt) underwent smoothly at 0 °C, and the addition of anhydrous diethyl ether, followed by filtration, gave the corresponding (quinolin-2-ylmethyl)ammonium iodide (**5b**, **5c**, and **5e**) in fair-to-good to excellent yields, as summarized in Table 2 (entries 2–4). These salts were then treated with saturated anhydrous sodium hydrogencarbonate to give 2-(dimethylaminomethyl)quinolines **6** in excellent yields, after extraction with dichloromethane, followed by purification by column chromatography on silica gel. In the reactions of **1a** and **1f** with Eschenmoser's salt, no



Scheme 4.

attempt was made to isolate (quinolin-2-ylmethyl)ammonium iodides. The reaction mixtures were directly treated with saturated anhydrous sodium hydrogencarbonate to give the corresponding 2-(dimethylaminomethyl)quinolines **6a** and **6f** (entries 1 and 5). The reaction of isocyanide **1c** with *N*,*N*-dimethylpropylideneammonium iodide[10] proceeded sluggishly, even at room temperature to afford only a low yield of 2-[1-(dimethylamino)propyl]quinoline **6g**, after a workup with saturated anhydrous sodium hydrogencarbonate (entry 6).

The present reactions leading to 2-functionalized quinolines **2**–**6** are thought to proceed via an attack of the isocyano carbon of *o*-isocyanostyrenes **1** to activated electrophiles, followed by an intramolecular combination of the resulting cation center and the β-carbon atom of the styrenes, in a similar manner as illustrated for the formation of pyrrolo[1,2-*a*]quinolines from 1-(2-isocyanophenyl)pyrroles in our previous papers.[1–3]

In summary, an efficient synthesis of quinolines carrying a functionalized substituent at the 2-position, which are otherwise accessible with difficulty, based on the electrophile-mediated cyclization of 2-isocyanostyrene derivatives, has been demonstrated. The ready availability of the starting isocyanides, which were prepared from commercially available *o*-aminoacetophenone, and the ease of operation make the present quinoline synthesis attractive.

Experimental

General. The melting points were determined on a Laboratory Devices MEL-TEMP II melting-point apparatus and are uncorrect-

Table 2. Preparation of 2-(1-Aminoalkyl)quinolines **5** and **6**

Entry	Isocyanide **1**	R in iminium salt	Temp/°C	**5** (Yield/%)[a)]	**6** (Yield/%)[b)]
1	**1a**	H	0	—	**6a** (49)[c)]
2	**1b**	H	0	**5b** (76)	**6b** (95)
3	**1c**	H	0	**5c** (95)	**6c** (95)
4	**1e** [Ar = 2,6-(MeO)$_2$C$_6$H$_3$]	H	0	**5e** (74)	**6e** (95)
5	**1f** [Ar = 2,4,6-(MeO)$_3$C$_6$H$_2$]	H	0	—	**6f** (55)[c)]
6	**1c**	Et	rt	—	**6g** (28)[c)]

a) Isolated yields after recrystallization. b) Isolated yields after purification by chromatography on SiO_2. c) Overall yields from **1**.

ed. The IR spectra were recorded on a Perkin-Elmer 1600 Series FT IR spectrometer. The ^{1}H NMR spectra were determined using $SiMe_4$ as an internal reference with a JEOL JNM-GX270 FT NMR spectrometer operating at 270 MHz in $CDCl_3$. Low-resolution mass spectra were recorded on a JEOL AUTOMASS 20 spectrometer (Center for Joint Research and Development, this University). High-resolution mass spectra were performed on a JEOL JMS-AX505 HA spectrometer (Faculty of Agriculture, this University). Thin-layer chromatography (TLC) was carried out on Merck Kieselgel 60 PF_{254}. All of the solvents used were dried over appropriate drying agents and distilled under argon prior to use. All of the reactions were carried out under argon.

Starting Materials. The starting isocyanides **1** were prepared from 1-amino-2-(1-arylethenyl)benzenes or 1-amino-2-(1-methylethenyl)benzene (commercially available) by formylation with formic acid in refluxing toluene, followed by dehydration of the resulting formamides with $POCl_3/Et_3N$ in THF at 0 °C. 1-Amino-2-(1-arylethenyl)benzenes were prepared by the action of arylmagnesium bromides, generated from appropriate aryl bromide and magnesium, upon *o*-aminoacetophenone, followed by thermolytic dehydration[11] of the resulting 1-(2-aminophenyl)-1-arylethanols. The physical, spectral, and analytical data for new compounds follow.

1-(2-Aminophenyl)-1-phenylethanol: mp 88–90 °C (hexane–Et_2O); IR (KBr disk) 3527, 3464, 3370, and 1621 cm^{-1}; ^{1}H NMR δ 1.87 (3H, s), 3.73 (3H, br), 6.64 (1H, d, $J = 7.4$ Hz), 6.86 (1H, t, $J = 7.4$ Hz), 7.11 (1H, t, $J = 7.4$ Hz), 7.2–7.35 (3H, m), and 7.35–7.45 (3H, m). Found: C, 78.82; H, 7.10; N, 6.30%. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57%.

1-Amino-2-(1-phenylethenyl)benzene: mp 83–85 °C (hexane–Et_2O); IR (KBr disk) 3476, 3381, and 1615 cm^{-1}; ^{1}H NMR δ 3.03 (2H, br), 5.35 (1H, d, $J = 1.3$ Hz), 5.79 (1H, d, $J = 1.3$ Hz), 6.70 (1H, d, $J = 7.9$ Hz), 6.79 (1H, td, $J = 7.9$ and 1.3 Hz), 7.15 (1H, td, $J = 7.9$ and 1.3 Hz), and 7.25–7.4 (6H, m). These spectral data were identical to those reported in the literature.[12]

***N*-[2-(1-Phenylethenyl)phenyl]formamide:** mp 86–89 °C (hexane–Et_2O); IR (KBr disk) 3266, 1694, and 1668 cm^{-1}; ^{1}H NMR δ 5.32 and 5.36 (combined 1H, 2s), 5.89 and 5.95 (combined 1H, 2s), 7.05–7.4 (10H, m), and 8.15–8.55 (1H, m). Found: C, 80.67; H, 5.87; N, 5.99%. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27%.

1-Isocyano-2-(1-phenylethenyl)benzene (1a): An oil; R_f 0.75 (1:2 EtOAc–hexane); IR (neat) 2122 cm^{-1}; ^{1}H NMR δ 5.40 (1H, s), 5.87 (1H, s), and 7.25–7.4 (9H, m); MS *m*/*z* (%) 205 (M^+, 87) and 204 (100). Found: *m*/*z* 205.0916. Calcd for $C_{15}H_{11}N$: M, 205.0891.

1-(2-Aminophenyl)-1-(4-methoxyphenyl)ethanol: An oil; R_f 0.25 (1:2 EtOAc–hexane); IR (neat) 3456, 3382, and 1611 cm^{-1}; ^{1}H NMR δ 1.86 (3H, s), 3.7–3.85 and 3.78 (combined 6H, br and s), 6.64 (1H, dd, $J = 7.9$ and 1.3 Hz), 6.8–6.9 (3H, m), 7.12 (1H, t, $J = 7.9$ Hz), 7.30 (2H, d, $J = 8.9$ Hz), and 7.37 (1H, d, $J = 7.9$ Hz). Found: C, 73.86; H, 7.14; N, 5.66%. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76%.

1-Amino-2-[1-(4-methoxyphenyl)ethenyl]benzene: An oil; R_f 0.75 (1:2 EtOAc–hexane); IR (neat) 3466, 3375, and 1607 cm^{-1}; ^{1}H NMR δ 3.58 (2H, br), 3.80 (3H, s), 5.23 (1H, s), 5.69 (1H, m), 6.85 (1H, d, $J = 8.6$ Hz), 7.15–7.4 (6H, m), and 7.30 (1H, d, $J = 8.6$ Hz). Found: C, 79.87; H, 6.61; N, 6.16%. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22%.

***N*-{2-[1-(4-Methoxyphenyl)ethenyl]phenyl}formamide:** mp 72–73 °C (toluene); IR (KBr disk) 3314, 1694, and 1605 cm^{-1}; ^{1}H NMR δ 3.80 (3H, s), 5.20 and 5.23 (combined 1H, 2s), 5.78 and 5.83 (combined 1H, 2s), 6.84 (2H, d, $J = 8.9$ Hz), 7.15–7.4 (7H, m), and 8.15–8.6 (1H, m). Found: C, 75.81; H, 6.00; N, 5.32%. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53%.

1-Isocyano-2-[1-(4-methoxyphenyl)ethenyl]benzene (1b): An oil; R_f 0.65 (1:2 EtOAc–hexane); IR (neat) 2123 and 1607 cm^{-1}; ^{1}H NMR δ 3.80 (3H, s), 5.27 (1H, d, $J = 1.0$ Hz), 5.77 (1H, d, $J = 1.0$ Hz), 6.84 (2H, d, $J = 8.9$ Hz), 7.18 (2H, d, $J = 8.9$ Hz), and 7.3–7.45 (4H, m); MS *m*/*z* (%) 235 (M^+, 100). Found: *m*/*z* 235.1012. Calcd for $C_{16}H_{13}NO$: M, 235.0997.

1-(2-Aminophenyl)-1-(3,4-dimethoxyphenyl)ethanol: An oil; R_f 0.20 (1:2 EtOAc–hexane); IR (neat) 3477, 3379, and 1614 cm^{-1}; ^{1}H NMR δ 1.86 (3H, s), 3.5–4.2, 3.82, and 3.84 (combined 9H, br, s, and, s, respectively), 6.64 (1H, d, $J = 6.6$ Hz), 6.7–6.8 (2H, m), 6.85 (1H, t, $J = 7.6$ Hz), 7.06 (1H, d, $J = 2.0$ Hz), 7.13 (1H, t, $J = 7.6$ Hz), and 7.37 (1H, d, $J = 7.6$ Hz). Found: C, 70.29; H, 6.96; N, 5.08%. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12%.

1-Amino-2-[1-(3,4-dimethoxyphenyl)ethenyl]benzene: mp 145–147 °C (hexane–Et_2O); IR (KBr disk) 3464, 3372, and 1607 cm^{-1}; ^{1}H NMR δ 3.56 (2H, br s), 3.84 (3H, s), 3.87 (3H, s), 5.26 (1H, d, $J = 1.3$ Hz), 5.69 (1H, d, $J = 1.3$ Hz), 6.68 (1H, d, $J = 8.2$ Hz), 6.7–6.8 (2H, m), 6.86 (1H, dd, $J = 8.2$ and 2.0 Hz), 6.96 (1H, d, $J = 2.0$ Hz), 7.05–7.2 (2H, m). Found: C, 75.09; H, 6.88; N, 5.28%. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49%.

***N*-{2-[1-(3,4-Dimethoxyphenyl)ethenyl]phenyl}formamide:** mp 125–127 °C (toluene); IR (KBr disk) 3340 and 1694 cm^{-1}; ^{1}H NMR δ 3.84 (3H, s), 3.88 (3H, s), 5.23 and 5.26 (combined 1H, 2s), 5.79 and 5.85 (combined 1H, 2s), 6.7–6.95 (3H, m), 7.1–7.45 (4H, m), 8.15–8.6 (2H, m). Found: C, 71.96; H, 6.13; N, 4.93%. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94%.

1-[1-(3,4-Dimethoxyphenyl)ethenyl]-2-isocyanobenzene (1c): mp 79–81 °C (Et_2O–hexane–CH_2Cl_2); IR (KBr disk) 2124 and 1601 cm^{-1}; ^{1}H NMR δ 3.85 (3H, s), 3.88 (3H, s), 5.31 (1H, s), 5.79 (1H, s), 6.70 (1H, dd, $J = 8.2$ and 2.0 Hz), 6.78 (1H, d, $J = 8.2$ Hz), 6.87 (1H, d, $J = 2.0$ Hz), and 7.3–7.45 (4H, m); MS *m*/*z* (%) 265 (M^+, 100). Found: C, 76.71; H, 5.43; N, 5.20%. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28%.

***N*-[2-(1-Methylethenyl)phenyl]formamide:** mp 60–61 °C (toluene–hexane); IR (KBr disk) 3275 and 1667 cm^{-1}; ^{1}H NMR δ 2.05 and 2.07 (combined 3H, 2s), 5.00 and 5.03 (combined 1H, 2s), 5.36 and 5.40 (combined 1H, 2s), 7.05–7.3 (4H, m), 7.61 (1H, br), and 8.3–8.7 (1H, m). Found: C, 74.54; H, 7.02; N, 8.64%. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69%.

1-Isocyano-2-(1-methylethenyl)benzene (1d): An oil; R_f 0.78 (1:2 EtOAc–hexane); IR (neat) 2122 cm^{-1}; ^{1}H NMR δ 2.10 (3H, s), 5.07 (1H, s), 5.29 (1H, s), and 7.2–7.35 (4H, m); MS *m*/*z* (%) 143 (M^+, 100). Found: *m*/*z* 143.0719. Calcd for $C_{10}H_9N$: M, 143.0735.

1-(2-Aminophenyl)-1-(2,6-dimethoxyphenyl)ethanol: mp 95–97 °C (hexane–Et_2O); IR (KBr disk) 3479, 3443, 3345, 1635, and 1611 cm^{-1}; ^{1}H NMR δ 2.03 (3H, s), 3.65 (6H, s), 4.39 (1H, br s), 5.83 (2H, br s), 6.55–6.65 (4H, m), 6.95–7.05 (2H, m), and 7.21 (1H, t, $J = 8.2$ Hz). Found: C, 70.25; H, 6.94; N, 5.04%. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12%.

1-Amino-2-[1-(2,6-dimethoxyphenyl)ethenyl]benzene: mp 134–138 °C (hexane–Et_2O); IR (KBr disk) 3451, 3361, 1628, and 1612 cm^{-1}; ^{1}H NMR δ 3.75 (6H, s), 4.01 (2H, br s), 5.39 (1H, d, $J = 2.1$ Hz), 5.64 (1H, d, $J = 2.1$ Hz), 6.55–6.7 (4H, m), 7.00 (1H, t, $J = 7.6$ Hz), 7.12 (1H, d, $J = 7.6$ Hz), and 7.19 (1H, t, $J = 8.2$ Hz). Found: C, 75.16; H, 6.80; N, 5.41%. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49%.

***N*-{2-[1-(2,6-Dimethoxyphenyl)ethenyl]phenyl}formamide:** mp 163–165 °C (toluene); IR (KBr disk) 3326, 1693, and 1613 cm^{-1}; ^1H NMR δ 3.78 and 3.81 (combined 6H, 2s), 5.46 and 5.48 (combined 1H, 2d, $J = 1.3$ Hz each), 5.52 and 5.55 (combined 1H, 2d, $J = 1.3$ Hz each), 6.57 and 6.59 (combined 2H, d, $J = 8.6$ Hz each), 7.0–7.25 (4H, m), 7.32 and 7.39 (combined 1H, 2d, $J = 7.6$ Hz each), and 8.25–8.7 (2H, m). Found: C, 71.97; H, 6.33; N, 4.85%. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94%.

1-[1-(2,6-Dimethoxyphenyl)ethenyl]-2-isocyanobenzene (1e): mp 123–124 °C (hexane–Et_2O–CH_2Cl_2); IR (KBr disk) 2128 and 1634 cm^{-1}; ^1H NMR δ 3.71 (6H, s), 5.62 (1H, d, $J = 1.5$ Hz), 5.82 (1H, d, $J = 1.5$ Hz), 6.57 (2H, d, $J = 8.6$ Hz), and 7.15–7.35 (5H, m); MS m/z (%) 265 (M^+, 51) and 250 (100). Found: C, 76.74; H, 5.61; N, 5.21%. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28%.

1-(2-Aminophenyl)-1-(2,4,6-trimethoxyphenyl)ethanol: mp 147–149 °C (hexane–Et_2O–CH_2Cl_2); IR (KBr disk) 3479, 3379, and 1606 cm^{-1}; ^1H NMR δ 2.00 (3H, s), 3.64 (6H, s), 3.80 (3H, s), 4.3–4.6 (1H, br), 5.4–5.6 (2H, br), 6.18 (2H, s), 6.55–6.65 (2H, m), and 6.9–7.0 (2H, m). Found: C, 67.30; H, 7.01; N, 4.70%. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62%.

1-Amino-2-[1-(2,4,6-trimethoxyphenyl)ethenyl]benzene: mp 102–103 °C (hexane–Et_2O); IR (KBr disk) 3445, 3362, and 1602 cm^{-1}; ^1H NMR δ 3.72 (6H, s), 3.80 (3H, s), 4.00 (2H, br s), 5.37 (1H, d, $J = 1.5$ Hz), 5.60 (1H, d, $J = 1.5$ Hz), 6.15 (2H, s), 6.55–6.7 (2H, m), 6.99 (1H, td, $J = 7.6$ and 1.6 Hz), and 7.10 (1H, dd, $J = 7.6$ and 1.6 Hz). Found: C, 71.61; H, 6.07; N, 4.91%. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91%.

***N*-{2-[1-(2,4,6-Trimethoxyphenyl)ethenyl]phenyl}formamide:** mp 115–117 °C (toluene); IR (KBr disk) 3390 and 1698 cm^{-1}; ^1H NMR δ 3.76, 3.78, and 3.80 (combined 9H, 3s), 5.4–5.55 (2H, m), 6.135 and 6.144 (combined 2H, 2s), 7.0–7.4 (4H, m), and 8.2–8.7 (2H, m). Found: C, 68.87; H, 6.30; N, 4.45%. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47%.

1-Isocyano-2-[1-(2,4,6-trimethoxyphenyl)ethenyl]benzene (1f): mp 128–129 °C (hexane–Et_2O–CH_2Cl_2); IR (KBr disk) 2123 and 1601 cm^{-1}; ^1H NMR δ 3.69 (6H, s), 3.82 (3H, s), 5.58 (1H, d, $J = 1.3$ Hz), 5.76 (1H, d, $J = 1.3$ Hz), 6.14 (2H, s), and 7.15–7.35 (4H, m); MS m/z (%) 295 (M^+, 98) and 280 (100). Found: C, 73.03; H, 5.93; N, 4.82%. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74%.

Typical Procedure for the Preparation of 2-(1-Hydroxyalkyl)quinolines 2. 2-(1-Hydroxypropyl)-4-phenylquinoline (2a): To a stirred solution of **1a** (0.21 g, 1.0 mmol) and propanal (58 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) at 0 °C under argon was added $Et_2O \cdot BF_3$ (14 mg, 0.10 mmol). After 20 min, CH_2Cl_2 (10 mL) and aqueous saturated $NaHCO_3$ (15 mL) were added. The layers were separated. The aqueous layer was extracted with CH_2Cl_2 twice (10 mL each). The combined extracts were washed with brine, dried over anhydrous K_2CO_3, and evaporated. The residue was purified by column chromatography on SiO_2 (1:3 EtOAc–hexane) to give **2a** (0.14 g, 52%): a viscous oil; R_f 0.18 (1:3 EtOAc–hexane); IR (neat) 3381 and 1591 cm^{-1}; ^1H NMR δ 1.01 (3H, t, $J = 7.3$ Hz), 1.75–1.85 (1H, m), 1.95–2.05 (1H, m), 4.90 (2H, br s), 7.27 (1H, s), 7.45–7.55 (6H, m), 7.72 (1H, t, $J = 8.2$), 7.88 (1H, d, $J = 8.3$ Hz), and 8.14 (1H, d, $J = 8.3$ Hz); MS m/z (%) 263 (M^+, 0.16), 261 (1.9), 246 (13), and 235 (100). Found: C, 82.08; H, 5.37; N, 6.27%. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 5.32; N, 6.08%.

2-(1-Hydroxy-2-methylpropyl)-4-phenylquinoline (2b): mp 115–116 °C (hexane–Et_2O); IR (KBr disk) 3382 and 1591 cm^{-1}; ^1H NMR δ 0.79 (3H, d, $J = 6.6$ Hz), 1.15 (3H, d, $J = 6.6$ Hz), 2.1–2.25 (1H, m), 4.78 (1H, br s), 4.86 (1H, br s), 7.25 (1H, s), 7.45–7.55 (6H, s), 7.72 (1H, t, $J = 8.3$ Hz), 7.90 (1H, d, $J = 8.3$ Hz), and 8.14 (1H, d, $J = 8.3$ Hz); MS m/z (%) 277 (M^+, 3.2) and 194 (100). Found: C, 82.05; H, 6.97; N, 4.81%. Calcd for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05%.

2-(1-Hydroxypropyl)-4-(4-methoxyphenyl)quinoline (2c): A viscous oil; R_f 0.13 (1:5 EtOAc–hexane); IR (neat) 3390 and 1614 cm^{-1}; ^1H NMR δ 1.01 (3H, t, $J = 7.3$ Hz), 1.7–1.85 (1H, m), 2.0–2.1 (1H, m), 3.90 (3H, s), 4.90 (2H, br s), 7.05 (2H, d, $J = 8.9$ Hz), 7.24 (1H, s), 7.4–7.55 (3H, m), 7.71 (1H, t, $J = 8.2$ Hz), 7.93 (1H, d, $J = 8.2$ Hz), and 8.13 (1H, d, $J = 8.2$ Hz); MS m/z (%) 293 (M^+, 1.5) and 265 (100). Found: C, 77.79; H, 6.72; N, 4.88%. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77%.

2-(1-Hydroxy-2-methylpropyl)-4-(4-methoxyphenyl)quinoline (2d): mp 117–118 °C (hexane–Et_2O); IR (KBr disk) 3382 and 1609 cm^{-1}; ^1H NMR δ 0.79 (3H, d, $J = 6.8$ Hz), 1.14 (3H, d, $J = 6.8$ Hz), 2.0–2.5 (1H, m), 3.89 (3H, s), 4.76 (1H, br s), 4.84 (1H, br s), 7.06 (2H, d, $J = 8.6$ Hz), 7.23 (1H, s), 7.4–7.55 (3H, m), 7.71 (1H, t, $J = 8.2$ Hz), 7.93 (1H, d, $J = 8.2$ Hz), and 8.13 (1H, d, $J = 8.2$ Hz); MS m/z (%) 307 (M^+, 6.6), 306 (19), and 236 (100). Found: C, 77.96; H, 6.88; N, 4.32%. Calcd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56%.

2-(1-Hydroxy-1-methylethyl)-4-(4-methoxyphenyl)quinoline (2e): A viscous oil; R_f 0.05 (1:5 EtOAc–hexane); IR (neat) 3390 and 1604 cm^{-1}; ^1H NMR δ 1.57 (1H, br s), 1.63 (6H, s), 3.91 (3H, s), 7.07 (2H, d, $J = 8.4$ Hz), 7.35 (1H, s), 7.4–7.5 (3H, m), 7.71 (1H, t, $J = 8.3$ Hz), 7.92 (1H, d, $J = 8.3$ Hz), and 8.12 (1H, d, $J = 8.3$ Hz); MS m/z (%) 293 (M^+, 8.9) and 278 (100). Found: C, 77.72; H, 6.61; N, 4.62%. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77%.

4-(3,4-Dimethoxyphenyl)-2-(1-hydroxypropyl)quinoline (2f): mp 109–110 °C (hexane–Et_2O); IR (KBr disk) 3390 and 1604 cm^{-1}; ^1H NMR δ 1.02 (3H, t, $J = 7.4$ Hz), 1.75–1.85 (1H, m), 2.0–2.1 (1H, m), 3.92 (3H, s), 3.98 (3H, s), 3.95–4.05 (2H, m), 7.0–7.1 (3H, m), 7.27 (1H, s), 7.49 (1H, ddd, $J = 7.3$, 6.9, and 1.3 Hz), 7.73 (1H, ddd, $J = 8.6$, 7.3 and 1.3 Hz), 7.96 (1H, d, $J = 7.3$ Hz), and 8.14 (1H, d, $J = 8.6$ Hz); MS m/z (%) 323 (M^+, 6.6) and 295 (100). Found: C, 74.22; H, 6.70; N, 4.32%. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33%.

2-(1-Hydroxypropyl)-4-methylquinoline (2g): A viscous oil; R_f 0.16 (1:5 EtOAc–hexane); IR (neat) 3382 and 1604 cm^{-1}; ^1H NMR δ 0.93 (3H, t, $J = 7.3$ Hz), 1.75–1.85 (1H, m), 1.95–2.05 (1H, m), 2.71 (3H, s), 4.8–4.85 (2H, m), 7.17 (1H, s), 7.55 (1H, t, $J = 8.0$ Hz), 7.70 (1H, d, $J = 8.0$ Hz), 7.98 (1H, d, $J = 8.0$ Hz), and 8.07 (1H, d, $J = 8.0$ Hz); MS m/z (%) 201 (M^+, 0.15), 199 (7.5), 184 (19), and 173 (100). Found: C, 77.54; H, 7.61; N, 6.86%. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96%.

Isocyanides **1a** and **1c** were allowed to react with acetaldehyde diethyl acetal in the presence of diethyl ether–boron trifluoride (0.1 eq.) as described for the preparation of **2a**. Similar workups and purification gave **3a** and **3c**, respectively.

2-(1-Ethoxyethyl)-4-phenylquinoline (3a): A viscous oil; R_f 0.35 (1:5 EtOAc–hexane); IR (neat) 1591 and 1108 cm^{-1}; ^1H NMR δ 1.22 (3H, t, $J = 7.4$ Hz), 1.58 (3H, d, $J = 6.9$ Hz), 3.45–3.6 (2H, m), 4.75 (1H, q, $J = 7.4$ Hz), 7.45–7.6 (7H, m), 7.70 (1H, t, $J = 8.2$ Hz), 7.91 (1H, d, $J = 8.2$ Hz), and 8.13 (1H, d, $J = 8.2$ Hz); MS m/z (%) 277 (M^+, 0.09) and 233 (100). Found: C, 82.14; H, 6.93; N, 5.05%. Calcd for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05%.

4-(3,4-Dimethoxyphenyl)-2-(1-ethoxyethyl)quinoline (3c): A viscous oil; R_f 0.35 (1:2 EtOAc–hexane); IR (neat) 1620, 1608,

1593, 1256, and 1107 cm^{-1}; ^1H NMR δ 1.24 (3H, t, $J = 6.9$ Hz), 1.58 (3H, d, $J = 6.6$ Hz), 3.45–3.6 (2H, m), 3.92 (3H, s), 3.98 (3H, s), 4.75 (1H, q, $J = 6.9$ Hz), 7.0–7.15 (3H, m), 7.48 (1H, t, $J = 8.2$ Hz), 7.54 (1H, s), 7.70 (1H, t, $J = 8.2$ Hz), 7.98 (1H, d, $J = 8.2$ Hz), and 8.12 (1H, d, $J = 8.2$ Hz); MS m/z (%) 337 (M^+, 0.07) and 293 (100). Found: C, 74.73; H, 6.65; N, 4.05%. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15%.

Isocyanides **1b** and **1c** were allowed to react with phenyloxirane in the presence of diethyl ether–boron trifluoride (0.1 eq.), as described for the preparation of **2a**. Similar workups and purification gave **4b** and **4c**, respectively.

2-(2-Hydroxy-2-phenylethyl)-4-(4-methoxyphenyl)quinoline (4b): A viscous oil; R_f 0.33 (1:5 EtOAc–hexane); IR (neat) 3390 and 1607 cm^{-1}; ^1H NMR δ 3.17 (2H, d, $J = 5.9$ Hz), 3.90 (3H, s), 4.76 (1H, d, $J = 5.9$ Hz), 5.14 (1H, m), 7.04 (2H, d, $J = 8.6$ Hz), 7.2–7.3 (6H, m), 7.36 (2H, d, $J = 8.6$ Hz), 7.48 (1H, dd, $J = 8.2$ and 7.3 Hz), 7.71 (1H, dd, $J = 8.2$ and 7.3 Hz), 7.93 (1H, dd, $J = 8.2$ and 1.3 Hz), and 8.12 (1H, d, $J = 8.2$ Hz); MS m/z (%) 355 (M^+, 5.2), 353 (25), and 234 (100). Found: C, 81.13; H, 5.96; N, 3.94%. Calcd for $C_{24}H_{21}NO_2$: C, 81.10; H, 5.96; N, 3.94%.

4-(3,4-Dimethoxyphenyl)-2-(2-hydroxy-2-phenylethyl)quinoline (4c): A viscous oil; R_f 0.10 (1:5 EtOAc–hexane); IR (neat) 3390 and 1603 cm^{-1}; ^1H NMR δ 3.18 (2H, d, $J = 6.3$ Hz), 3.90 (3H, s), 3.97 (3H, s), 4.76 (1H, d, $J = 6.3$ Hz), 5.1–5.2 (1H, m), 6.95–7.05 (3H, m), 7.2–7.3 (6H, m), 7.49 (1H, t, $J = 8.6$ Hz), 7.72 (1H, t, $J = 8.6$ Hz), 7.95 (1H, t, $J = 8.6$ Hz), and 8.13 (1H, d, $J = 8.6$ Hz); MS m/z (%) 385 (M^+, 5.2), 383 (75), and 264 (100). Found: C, 77.77; H, 6.13; N, 3.59%. Calcd for $C_{25}H_{23}NO_3$: C, 77.90; H, 6.01; N, 3.63%.

Typical Procedure for the Preparation of (Quinolinylmethyl)ammonium Iodides 5. [4-(4-Methoxyphenyl)quinolin-2-ylmethyl]dimethylammonium Iodide (5b): To a stirred solution of *N*,*N*-dimethylmethyleneammonium iodide (Eschenmoser's salt; 0.24 g, 1.3 mmol) in CH_2Cl_2 (4 mL) at 0 °C under argon was added dropwise a solution of **1b** (0.28 g, 1.3 mmol) in CH_2Cl_2 (1 mL). After 1.5 h anhydrous Et_2O (20 mL) was added. The white precipitate was collected by filtration and recrystallized from EtOH to give **5b** (0.41 g, 76%): mp 204–206 °C; IR (KBr disk) 3400–2250 and 1611 cm^{-1}; ^1H NMR δ 3.04 (6H, s), 3.90 (3H, s), 4.60 (2H, s), 7.07 (2H, d, $J = 9.1$ Hz), 7.25 (1H, s), 7.5–7.65 (3H, m), 7.73 (1H, s), 7.77 (1H, t, $J = 7.6$ Hz), 8.04 (1H, t, $J = 7.6$ Hz), and 8.20 (1H, d, $J = 7.6$ Hz). Found: C, 54.04; H, 4.98; N, 6.47%. Calcd for $C_{19}H_{21}IN_2O$: C, 54.30; H, 5.04; N, 6.67%.

[4-(3,4-Dimethoxyphenyl)quinolin-2-ylmethyl]dimethylammonium Iodide (5c): mp 215–221 °C (EtOH); IR (KBr disk) 3400–2500 and 1605 cm^{-1}; ^1H NMR δ 3.00 (6H, s), 3.97 (3H, s), 4.01 (3H, s), 4.58 (2H, s), 7.02 (1H, d, $J = 8.2$ Hz), 7.1–7.2 (2H, m), 7.27 (1H, s), 7.59 (1H, t, $J = 8.2$ Hz), 7.78 (1H, t, $J = 8.2$ Hz), 7.91 (1H, s), 8.11 (1H, d, $J = 8.2$ Hz), and 8.17 (1H, d, $J = 8.2$ Hz). Found: C, 53.06; H, 4.88; N, 5.96%. Calcd for $C_{20}H_{23}IN_2O_2$: C, 53.34; H, 5.15; N, 6.22%.

[4-(2,6-Dimethoxyphenyl)quinolin-2-ylmethyl]dimethylammonium Iodide (5e): mp 111–115 °C (EtOH); IR (KBr disk) 3400–2500 and 1603 cm^{-1}; ^1H NMR δ 3.06 (6H, s), 3.67 (6H, s), 4.59 (2H, s), 6.72 (2H, d, $J = 8.2$ Hz), 7.4–7.6 (5H, m), 7.73 (1H, t, $J = 8.2$ Hz), and 8.20 (1H, d, $J = 8.2$ Hz). Found: C, 53.24; H, 5.16; N, 6.20%. Calcd for $C_{20}H_{23}IN_2O_2$: C, 53.34; H, 5.15; N, 6.22%.

2-[(Dimethylamino)methyl]-4-phenylquinoline (6a). Isocyanide **1a** (0.21 g, 1.0 mmol) was allowed to reacted with Eschenmoser's salt (0.19 g, 1.0 mmol) in CH_2Cl_2 (5 mL) in a manner similar to that described for the preparation of **5b**. The reaction mixture was treated with saturated aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 twice (10 mL each). The combined extracts were dried over anhydrous K_2CO_3 and evaporated. The residue was purified by column chromatography on SiO_2 (1:5 EtOAc–hexane) to give **6a** (0.13 g, 49%): a viscous oil; R_f 0.02 (1:5 EtOAc–hexane); IR (neat) 1614 cm^{-1}; ^1H NMR δ 2.37 (6H, s), 3.80 (2H, s), 7.15–7.3 (3H, m), 7.4–7.55 (4H, m), 7.69 (1H, t, $J = 8.6$ Hz), 7.90 (1H, d, $J = 8.6$ Hz), and 8.15 (1H, d, $J = 8.6$ Hz); MS m/z (%) 263 (M + 1, 56), 262 (M^+, 24), and 219 (100). Found: C, 82.32; H, 7.00; N, 10.37%. Calcd for $C_{18}H_{18}N_2$: C, 82.41; H, 6.92; N, 10.68%.

2-[(Dimethylamino)methyl]-4-(4-methoxyphenyl)quinoline (6b). Iodonium salt **5b** (0.25 g, 0.6 mmol) was treated with saturated aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 twice (10 mL each). The combined extracts were dried over anhydrous K_2CO_3 and evaporated. The residue was purified by column chromatography on silica gel (1:5 EtOAc–hexane) to give **6b** (0.17 g, 95%): a viscous oil; R_f 0.08 (1:5 EtOAc–hexane); IR (neat) 1609 cm^{-1}; ^1H NMR δ 2.37 (6H, s), 3.80 (2H, s), 3.90 (3H, s), 7.04 (2H, d, $J = 8.6$ Hz), 7.4–7.55 (4H, m), 7.68 (1H, t, $J = 7.3$ Hz), 7.94 (1H, d, $J = 7.3$ Hz), and 8.14 (1H, d, $J = 7.3$ Hz); MS m/z (%) 292 (M^+, 0.07) and 249 (100). Found: C, 77.97; H, 6.96; N, 9.57%. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58%.

4-(3,4-Dimethoxyphenyl)-2-[(dimethylamino)methyl]quinoline (6c). This compound was prepared from **5c** in a manner similar to that described for the preparation of **6b**. **6c**: a viscous oil; R_f 0.05 (1:5 EtOAc–hexane); IR (neat) 1603 cm^{-1}; ^1H NMR δ 2.40 (6H, s), 3.85 (2H, s), 3.92 (3H, s), 3.98 (3H, s), 6.95–7.15 (3H, m), 7.49 (1H, td, $J = 7.9$ and 1.3 Hz), 7.55 (1H, s), 7.70 (1H, td, $J = 7.9$ and 1.3 Hz), 7.97 (1H, dd, $J = 7.9$ and 1.3 Hz), and 8.12 (1H, dd, $J = 7.9$ and 1.3 Hz); MS m/z (%) 322 (M^+, 0.22) and 279 (100). Found: C, 74.53; H, 7.02; N, 8.67%. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69%.

4-(2,6-Dimethoxyphenyl)-2-[(dimethylamino)methyl]quinoline (6e). This compound was prepared from **5d** in a manner similar to that described for the preparation of **6b**. **6d**: a viscous oil; R_f 0.05 (1:5 EtOAc–hexane); IR (neat) 1605 cm^{-1}; ^1H NMR δ 2.36 (6H, s), 3.63 (6H, s), 3.82 (2H, s), 6.69 (2H, d, $J = 8.3$ Hz), 7.35–7.65 (5H, m), and 8.12 (1H, d, $J = 8.2$ Hz); MS m/z (%) 322 (M^+, 2.8) and 279 (100). Found: C, 74.32; H, 6.87; N, 8.65%. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69%.

2-[(Dimethylamino)methyl]-4-(2,4,6-trimethoxyphenyl)-quinoline (6f). This compound was prepared from **1f** and Eschenmoser's salt under conditions similar to those described for the preparation of **6a**. **6f**: a viscous oil; R_f 0.20 (acetone); IR (neat) 1613 cm^{-1}; ^1H NMR δ 2.35 (6H, s), 3.62 (6H, s), 3.80 (2H, s), 3.90 (3H, s), 6.26 (2H, s), 7.36 (1H, t, $J = 8.2$ Hz), 7.45 (1H, s), 7.50 (1H, d, $J = 8.2$ Hz), 7.62 (1H, t, $J = 8.2$ Hz), and 8.10 (1H, d, $J = 8.2$ Hz); MS m/z (%) 352 (M^+, 0.11) and 309 (100). Found: C, 71.27; H, 6.90; N, 7.77%. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95%.

4-(3,4-Dimethoxyphenyl)-2-[1-(dimethylamino)propyl]quinoline (6g). To a stirred solution of *N*,*N*-dimethylpropylideneammonium iodide, generated in situ from propanal (38 mg, 0.65 mmol), dimethylamine hydrochloride (53 mg, 0.65 mmol), NaI (0.21 g, 1.4 mmol), Me_3SiCl (0.15 g, 1.4 mmol), and Et_3N (0.14 g, 1.4 mmol) in MeCN (1.4 mL) under the Risch's conditions,[10] at room temperature was added dropwise a solution of **1c** (0.17 g, 0.65 mmol) in MeCN (2 mL). After 2 h the reaction mixture was worked up in a similar manner as described for the preparation of **6a**. The crude product was purified by column chromatography on SiO_2 (acetone)

to give **6g** (64 mg, 28%): a viscous oil; R_f 0.20 (acetone); IR (neat) 1604 cm^{-1}; ^1H NMR δ 0.80 (3H, t, $J = 7.3$ Hz), 1.9–2.1 (2H, m), 2.31 (6H, s), 3.45 (1H, dd, $J = 8.9$ and 4.6 Hz), 3.92 (3H, s), 3.97 (3H, s), 6.95–7.15 (3H, m), 7.41 (1H, s), 7.47 (1H, t, $J = 8.2$ Hz), 7.69 (1H, t, $J = 8.2$ Hz), 7.96 (1H, d, $J = 8.2$ Hz), and 8.16 (1H, d, $J = 8.2$ Hz); MS m/z (%) 350 (M^+, 0.04) and 292 (100). Found: C, 75.33; H, 7.52; N, 7.76%. Calcd for $C_{22}H_{26}N_2O_2$: C, 75.40; H, 7.48; N, 7.99%.

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