Tetrahedron Vol 44, No. 11, pp 3391 to 3398, 1988
Printed in Great Britain

0040-4020/88 $3.00 + .00

Synthesis of Isoquinolines Bearing Differentially Functionalized Nitrogen Substituents at Positions 3 and 4 through Amine Displacement on a 4-Nitro-3-(*p*-toluenesulfonyloxy)isoquinoline†

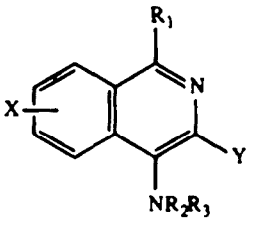
Jeffery S. Hinkle and O. William Lever, Jr.

Research Laboratories, Ortho Pharmaceutical Corporation
Raritan, New Jersey 08869

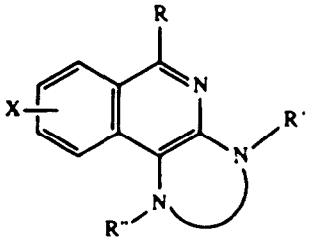
(*Received in USA 29 January* 1988)

Abstract. A method for the synthesis of isoquinolines functionalized with differentiated nitrogen substituents at positions 3 and 4 is described. The method involves tosylation of a 3-hydroxy-4-nitroisoquinoline and subsequent tosylate displacement by amine nucleophiles to give 3-amino-4-nitroisoquinoline derivatives, the products of specific C-O bond cleavage. Reduction of the 4-nitro group and elaboration of the resulting 4-amino moiety provides the differentiated 3- and 4-amino functions, not readily available by other methods. Appropriately substituted compounds are amenable to further transformations, illustrated by their conversion to imidazo[5,4-c]isoquinoline derivatives. Additional studies on the tosylate displacement indicated that thiol displacement also occurs by scission of the C-O bond to give a 3-thioether derivative, and that reactions of the 4-nitro-3-tosyloxyisoquinoline system with certain other nucleophiles, including alcohols, did not proceed readily.

We became interested in the synthesis of 3-amino isoquinoline derivatives as part of an ongoing investigation of isoquinoline compounds possessing interesting pharmacological activity. In particular, we required access to a series of isoquinolines 1 functionalized with differentiated nitrogen substituents at positions 3 and 4. These compounds are 3-amino isosteres of our 4-substituted isoquinolin-3-ol (2) cardiovascular agents,[1] and may also serve as intermediates to a variety of other heterocycles of potential interest including tricyclic systems (3). A review of the literature indicated that the requisite diamino isoquinolines have not been well described, in spite of the significant body of chemistry reported on the ubiquitous isoquinoline ring system.[2] In fact, synthetic reports of isoquinolines substituted at both the 3- and 4-positions with nitrogen functionality (1) include only compounds also containing heteroatom substituents at the 1-position (oxygen,[3] nitrogen[4] or halogen[5]). The synthetic methodologies employed in these reports were not useful for the preparation of our target compounds 1. We therefore sought a practical method to produce 3,4-diamino isoquinoline derivatives with a key requirement that our synthetic strategy include the ability to differentiate between the 3 and 4 nitrogen substituents for further elaboration.



1 Y = NR_4R_5
2 Y = OH; X = 6,7-$(OMe)_2$; R_1 = Me

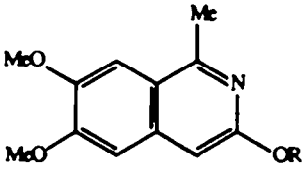


3

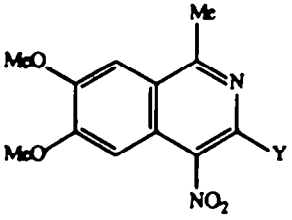
An attractive approach to our target compounds involved the preparation of 4-nitroisoquinoline derivatives bearing a leaving group at the 3-position which could be displaced by various amines. This would provide 3-amino-4-nitro analogs and permit differentiation between the 3 and 4 nitrogen substituents through reduction of the 4-nitro group and subsequent elaboration of the 4-amino function. We initially contemplated using chloride as the leaving group, but discovered that 3-chloro-4-nitroisoquinolines are not readily obtained. For example, 3-chloroisoquinoline undergoes nitration at the 5-position rather than at the desired 4-position.[6] Furthermore, although 3-hydroxy-4-nitroisoquinoline 6 is readily available by nitration of 4 as

†Dedicated to Professor Edward C. Taylor on the occasion of his 65th birthday.

previously reported from our laboratories,[1] we were unable to convert **6** to the chloro compound **7** by standard methods (phosphorous oxychloride, phosphorous pentachloride). We next considered activation of the 3-hydroxy group of **6** through conversion to the *p*-toluenesulfonate. Although tosylates of nitrophenols are subject to nucleophilic attack, cleavage of either the carbon-oxygen or the sulfur-oxygen bond can occur.[7,8] Successful sulfonate ester displacements in heteroaromatic systems appear to be limited to certain purine[9] and pyrimidine[10] derivatives. It has been reported that 2-tosyloxypyridine is unreactive toward secondary amines and that the corresponding methanesulfonate undergoes S-O cleavage.[10] Thus, although we anticipated that the 4-nitro group would activate the isoquinoline derivative **8** for reaction with amine nucleophiles, the regiochemical preference for C-O versus S-O bond cleavage could not be readily predicted.

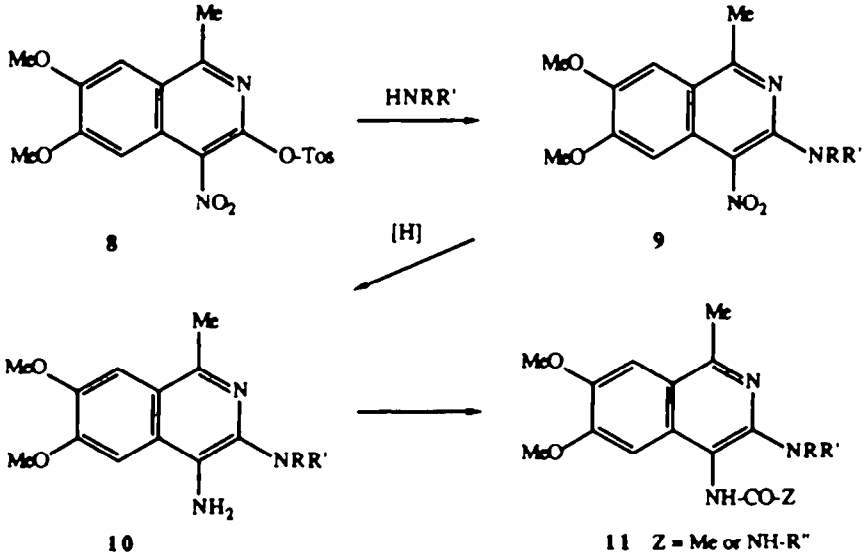


4 R = H
5 R = $SO_2C_6H_4$-4-Me



6 Y = OH
7 Y = Cl
8 Y = $OSO_2C_6H_4$-4-Me

Tosylation of **6** using *p*-toluenesulfonyl chloride in methylene chloride with triethylamine and a catalytic amount of dimethylaminopyridine proceeded smoothly at room temperature to provide the highly crystalline 3-*O*-tosyl derivative **8** in good yield. We were gratified to find that tosylate **8** reacts with a variety of amines in toluene at reflux and undergoes specific C-O bond cleavage to provide the 3-amino compounds **9** (Scheme 1, Table 1). Within the limits of our ability to detect the isoquinolinol **6** by thin layer chromatography (tlc), we did not observe any competitive attack by the amines on sulfur. As expected, activation by the 4-nitro group was essential. Tosylation of **4** provides the corresponding tosylate **5**, but this compound fails to undergo nucleophilic displacement by amines under the conditions employed with **8** and is recovered unchanged.



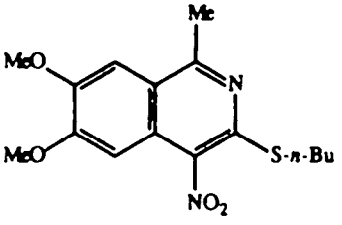
8 **9**

10 **11** Z = Me or NH-R"

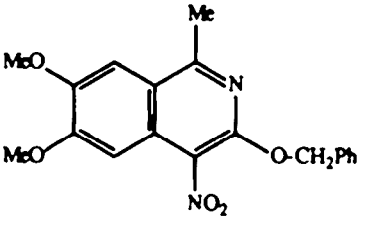
Scheme 1

Secondary amines provided compounds **9** (R,R'≠H) in good yields with only minor side products. Primary amines reacted more slowly and provided **9** (R=H) in somewhat lower yields. Tlc monitoring of the reaction with primary amines indicated that a polar decomposition product began forming before starting material was completely consumed. Yields for all of the primary amines were not fully optimized through variation of reaction times. A number of attempts to provide the parent 3-amino-4-nitroisoquinoline **9** (R,R'=H) by direct nucleophilic displacement with ammonia or ammonium acetate were unsuccessful, presumably due to instability of the product.

We also investigated the displacement of the tosylate **8** with other nucleophiles. Butane-1-thiol successfully provided the 3-thioether derivative **12**, but alcohols and even alkoxides reacted poorly if at all. For example, sodium methoxide gave no isolable 3-methoxy compound and benzyl alcohol under mildly basic conditions gave the isoquinolinyl benzyl ether **13** in only a 4% isolated yield. Displacement of the tosylate with amides, potassium phthalimide, sodium azide, thioamides, and thioureas also did not proceed readily, and in general the starting tosylate was recovered, indicating that attack at sulfur was still not competive.

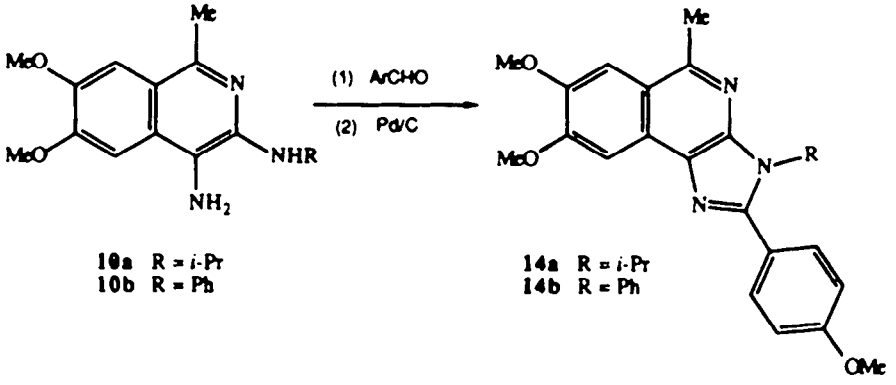


12



13

With a variety of compounds **9** in hand, we were able to differentially functionalize the 3 and 4 nitrogen substituents (Scheme 1). Catalytic reduction of **9** gave the 4-amino compounds **10** (Table 2). The 4-amino group may be functionalized by a variety of standard methods, including acylation with acid chlorides or with isocyanates (*cf.* **11**; Table 2). The potential of derivatives **10** for synthesis of more elaborate ring systems is illustrated by treatment of **10a** and **10b** with anisaldehyde followed by dehydrogenation of the intermediate aminals with palladium on carbon to give the corresponding [5,4-c]-imidazoisoquinoline systems **14a** and **14b**.

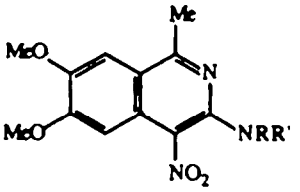


10a R = *i*-Pr
10b R = Ph

14a R = *i*-Pr
14b R = Ph

In conclusion, our synthetic strategy utilizing nucleophilic displacement of the tosylate in 4-nitro-3-tosyloxyisoquinolines provides access to a variety of 3-amino-4-nitroisoquinoline derivatives. These compounds may be used to allow differentiation of the 3 and 4 nitrogen substituents for subsequent elaboration to more complex systems. Extension of this tosylate displacement to other heterocyclic systems is currently under investigation.

Table 1



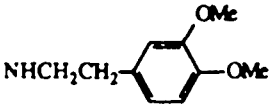
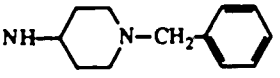
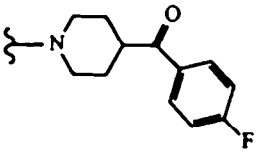
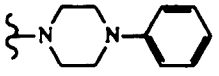
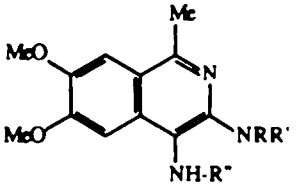
Compound No.	NRR'
9a	NHMe
9b	NH-*n*-Bu
9c	NH-CH_2Ph
9d	
9e	$NHCH_2CH_2NMe_2$
9f	NH-*i*-Pr
9g	$NHCH(Me)CH_2CH_2CH_2NEt_2$
9h	
9i	NHPh
9j	$N(Me)_2$
9k	$N(Et)_2$
9l	$N(Et)CH_2CH_2NMe_2$
9m	
9n	
9o	N(Me)Ph
9p	$NHNH_2$

Table 2



Compound No.	R	R'	R"
10a	*i*-Pr	H	H
10b	Ph	H	H
10c	Me	Me	H
11a	Me	Me	COMe
11b	Ph	H	CONH(*n*-Bu)
11c	Me	Me	CONH(*n*-Bu)
11d	Ph	H	CONH(allyl)
11e	Me	Me	CONH(allyl)

EXPERIMENTAL

Melting points (mp) were determined on a Thomas-Hoover apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Nicolet 5DXB FT-IR spectrophotometer and are expressed in cm^{-1}. Proton nuclear magnetic resonance (^1H NMR) spectra were obtained on Varian FT-80A or Varian XL-400 spectrometers and chemical shifts are reported in delta (δ) units downfield from tetramethylsilane (TMS) as internal standard. Mass spectra were obtained on a Finnigan 1015D quadrupole mass spectrometer coupled to a Finnigan 9500 gas chromatograph or on a Finnigan MAT 8230 double focusing high resolution mass spectrometer. Elemental analyses were obtained on a Perkin Elmer 240C for C, H, and N, and at Atlantic Microlabs, Atlanta, GA for other elements (S, F).

6,7-Dimethoxy-1-methyl-3-[(4-methylphenylsulfonyl)oxy]-4-nitroisoquinoline (8). Triethylamine (21.5 mL, 2 eq) and 4-(*N,N*-dimethylamino)pyridine (1.9 g, 0.2 eq) were added to a stirred slurry of 6,7-dimethoxy-1-methyl-4-nitroisoquinolin-3-ol[1] (6, 20.5 g, 77.6 mMol) in methylene chloride (600 mL) at room temperature under a nitrogen atmosphere. To this mixture was added *p*-toluenesulfonyl chloride (18.0 g, 1.15 eq) and the slurry was stirred at room temperature under nitrogen for 5 hours. The mixture was filtered and the precipitate was washed with methylene chloride to provide an initial portion (15.2 g) of **8** as a yellow solid. The filtrate was washed successively with 1N HCl (2 x 300 mL) and water (2 x 150 mL), dried ($MgSO_4$), and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with methylene chloride as eluent (R_f 0.8 in 98:2 methylene chloride/methanol) to give an additional 13.2 g of the product (total yield 87%): mp 236-238 °C (dec); IR (KBr) 1617, 1599 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.96 (d, J = 7.9 Hz, 2H), 7.35 (d, J = 7.9 Hz, 2H), 7.22 (s, 1H), 7.12 (s, 1H), 4.03 (s, 3H), 3.99 (s, 3H), 2.82 (s, 3H), 2.48 (s, 3H); LRMS (DCI), m/z (rel. int.), 419 (MH^+, 100), 248 (45).

Anal. Calcd. for $C_{19}H_{18}N_2O_7S$: C, 54.54; H, 4.34; N, 6.69; S, 7.66. Found: C, 54.80; H, 4.28; N, 6.81; S, 7.62.

6,7-Dimethoxy-1-methyl-3-methylamino-4-nitroisoquinoline (9a). An excess of 40% aqueous methylamine (6 mL, 30 eq) was added to a stirred slurry of tosylate **8** (1.00 g, 2.39 mmol) in toluene (50 mL) and the mixture was heated under reflux for 12 hours. The mixture was then stirred at room temperature for 12 hours and the orange precipitate was collected by filtration, washed with ether, and purified by column chromatography on silica gel with methylene chloride as eluent to give 0.39 g (59%) of compound **9a** as an orange powder, mp 233-234 °C; IR (KBr) 1619, 1592, 1512 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.6 - 9.3 (br m, 1H), 8.54 (s, 1H), 7.16 (s, 1H), 4.03 (s, 3H), 3.96 (s, 3H), 3.26 (d, J = 5.7 Hz, 3H), 2.79 (s, 3H); LRMS (DCI), m/z (rel. int.), 278 (MH^+, 100).

Anal. Calcd. for $C_{13}H_{15}N_3O_4 \cdot 1/4\ H_2O$: C, 55.41; H, 5.54; N, 14.91. Found: C, 55.52; H, 5.74; N, 14.48.

3-(*n*-Butylamino)-6,7-dimethoxy-1-methyl-4-nitroisoquinoline (9b). An excess of *n*-butylamine (0.8 mL, 4 eq) was added to a stirred slurry of tosylate **8** (1.00 g, 2.39 mmol) in toluene (50 mL) and the mixture was heated under reflux overnight. After cooling to room temperature, the precipitate was removed by filtration, washed with toluene, and purified by column chromatography on silica gel with methylene chloride as eluent to give 0.52 g (68%) of compound **9b** as an orange powder, mp 160-161 °C; IR (KBr) 1624, 1598, 1577, 1498 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.6 - 9.3 (br t, 1H; D_2O exchangeable), 8.53 (s, 1H), 7.16 (s, 1H), 4.03 (s, 3H), 3.96 (s, 3H), 3.75 (d of t, appears as q, J = 6.4 Hz, 2H; collapses to t, J = 6.9 Hz upon D_2O exchange), 2.78 (s, 3H), 1.9 - 1.2 (m, 4H), 0.98 (t, J = 6.7 Hz, 3H); LRMS (DCI), m/z (rel. int.), 320 (MH^+, 100), 290 (34).

Anal. Calcd. for $C_{16}H_{21}N_3O_4$: C, 60.18; H, 6.63; N, 13.16. Found: C, 60.41; H, 6.92; N, 13.15.

3-Benzylamino-6,7-dimethoxy-1-methyl-4-nitroisoquinoline (9c). Following the method described above for **9b**, compound **9c** was obtained in 69% yield from tosylate **8** and benzylamine as an orange solid, mp 240-241 °C; IR (KBr) 1617, 1587, 1519, 1503 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.7 - 9.4 (br m, 1H), 8.50 (s, 1H), 7.4 - 7.2 (m, 5H), 7.17 (s, 1H), 4.96 (d, J = 6.0 Hz, 2H), 4.02 (s, 3H), 3.95 (s, 3H), 2.78 (s, 3H); LRMS (DCI), m/z (rel. int.), 354 (MH^+, 100).

Anal. Calcd. for $C_{19}H_{19}N_3O_4$: C, 64.38; H, 5.42; N, 11.89. Found: C, 64.03; H, 5.47; N, 11.75.

6,7-Dimethoxy-3-[2-(3,4-dimethoxyphenyl)ethyl]amino-1-methyl-4-nitroisoquinoline (9d). To a mixture of tosylate **8** (1.00 g, 2.39 mmol) in toluene (50 mL) was added 2-(3,4-dimethoxyphenyl)ethylamine (1.61 mL, 1.5 eq) and triethylamine (1.3 mL, 4 eq), and the resulting mixture was heated to reflux under a nitrogen atmosphere for 12 hours. The mixture was cooled to room temperature, evaporated under reduced pressure, and purified by column chromatography on silica gel with methylene chloride as eluent to give 0.93 g (91%) of the product as an orange solid, mp 180-182 °C; IR (KBr) 1588, 1512 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.49 (br t, 1H), 8.59 (s, 1H), 7.23 (s, 1H), 6.85 - 6.80 (m, 3H), 4.07 (s, 3H), 4.02 (t, J = 7.0 Hz, 2H), 4.01 (s, 3H), 3.91 (s, 3H), 3.86 (s, 3H), 2.99 (t, J = 7.0 Hz, 2H), 2.82 (s, 3H); LRMS (DCI), m/z (rel. int.), 428 (MH^+, 100), 259 (20).

Anal. Calcd. for $C_{22}H_{25}N_3O_6$: C, 61.82; H, 5.90; N, 9.83. Found: C, 61.55; H, 5.63; N, 9.63.

6,7-Dimethoxy-3-[2-(dimethylamino)ethyl]amino-1-methyl-4-nitroisoquinoline (9e). Following the method described above for **9b**, compound **9e** was obtained in 88% yield from tosylate **8** and 2-(dimethylamino)ethylamine as an orange solid, mp 218-219 °C; IR (KBr) 1618, 1590, 1524, 1504 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.7 - 9.4 (br m, 1H), 8.50 (s, 1H), 7.15 (s, 1H), 4.03 (s, 3H), 3.96 (s, 3H), 3.82 (t, J = 6.3 Hz, 2H), 2.79 (s, 3H), 2.60 (t, J = 6.3 Hz, 2H), 2.33 (s, 6H); LRMS (DCI), m/z (rel. int.), 335 (MH^+, 100).

Anal. Calcd. for $C_{16}H_{22}N_4O_4$: C, 57.47; H, 6.63; N, 16.76. Found: C, 57.31; H, 6.68; N, 16.45.

6,7-Dimethoxy-1-methyl-4-nitro-3-(2-propylamino)isoquinoline (9f). Isopropylamine was added in portions (5 x 2 mL, total 20 eq) over two days to a stirred slurry of tosylate **8** (2.5 g, 6 mmol) in toluene (150 mL) which was heated under reflux. After cooling to room temperature, the mixture was evaporated and the residue purified by column chromatography on silica gel with methylene chloride as eluent to give 1.75 g (95%) of the product **9f** as an orange powder, mp 219-220 °C; IR (KBr) 1587 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.38 (br d, 1H), 8.59 (s, 1H), 7.21 (s, 1H), 4.72 (m, 1H), 4.06 (s, 3H), 3.99 (s, 3H), 2.80 (s, 3H), 1.35 (d, J = 6.0 Hz, 6H); LRMS (DCI), m/z (rel. int.), 306 (MH^+, 100).

Anal. Calcd. for $C_{15}H_{19}N_3O_4 \cdot 1/4H_2O$: C, 58.15; H, 6.34; N, 13.56. Found: C, 58.05; H, 6.43; N, 13.44.

3-[2-(5-Diethylamino)pentyl]amino-6,7-dimethoxy-1-methyl-4-nitroisoquinoline (9g). Following the method described above for 9d using 2-amino-5-diethylaminopentane as the amine, compound 9g was obtained as an orange solid in 79% yield, mp 85-87 °C; IR (KBr) 1588, 1513 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.41 (d, J = 9 Hz, 1H), 8.60 (s, 1H), 7.21 (s, 1H), 4.70 (m, 1H), 4.06 (s, 3H), 3.99 (s, 3H), 2.79 (s, 3H), 2.50 (q, J = 7.2 Hz, 4H), 2.51 - 2.43 (m, 2H), 1.72 - 1.62 (m, 2H), 1.62 - 1.52 (m, 2H), 1.32 (d, J = 6.5 Hz, 3H), 1.00 (t, J = 7.2 Hz, 3H); LRMS (DCI), m/z (rel. int.), 405 (MH^+, 100).

Anal. Calcd. for $C_{21}H_{23}N_4O_4$: C, 62.35; H, 7.97; N, 13.85. Found: C, 62.20; H, 8.05; N, 13.62.

3-[(1-Benzyl)-4-piperidinyl]amino-6,7-dimethoxy-1-methyl-4-nitroisoquinoline (9h). Following the method described above for 9d using 4-amino-1-benzylpiperidine as the amine, compound 9h was obtained as an orange solid in 83% yield, mp 188-189 °C; IR (KBr) 1615, 1589, 1525, 1504 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.4 (br d, 1H), 8.53 (s, 1H), 7.4 - 7.2 (m, 5H), 7.15 (s, 1H), 4.6 - 4.2 (m, 1H), 4.02 (s, 3H), 3.95 (s, 3H), 3.52 (s, 2H), 3.1 - 1.5 (m, 8H), 2.78 (s, 3H); LRMS (DCI), m/z (rel. int.), 436 (M^+, 20), 418 (75), 401 (65), 172 (100).

Anal. Calcd. for $C_{24}H_{28}N_4O_4$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.12; H, 6.43; N, 12.54.

6,7-Dimethoxy-1-methyl-4-nitro-3-phenylaminoisoquinoline (9i). To a mixture of tosylate 8 (3.00 g, 7.17 mmol) in toluene (100 mL) was added an excess of aniline (8 mL), and the resulting mixture was heated to reflux under a nitrogen atmosphere for 24 hours. The mixture was cooled to room temperature and filtered, and the precipitate was washed with methylene chloride. The combined filtrates were evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel with methylene chloride as eluent to give 1.83 g (75%) of the product as an orange solid, mp 200-201 °C; IR (KBr) 1589, 1574, 1507, 1497, 1482 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.36 (s, 1H), 7.8 - 7.2 (m, 7H), 4.04 (s, 3H), 3.99 (s, 3H), 2.77 (s, 3H); LRMS (DCI), m/z (rel. int.), 340 (MH^+, 100).

Anal. Calcd. for $C_{18}H_{17}N_3O_4$: C, 63.71; H, 5.05; N, 12.38. Found: C, 63.78; H, 5.06; N, 12.07.

6,7-Dimethoxy-3-(*N*,*N*-dimethyl)amino-1-methyl-4-nitroisoquinoline (9j). An excess of 40% aqueous dimethylamine (1.1 mL, 4 eq) was added to tosylate 8 (1.00 g, 2.39 mmol) in toluene (50 mL) and the mixture was heated under reflux for 8 hours. The mixture was then cooled, washed with 1N HCl (2 x 75 ml), and the organic layer was dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel with methylene chloride as the eluent to provide 9j (0.69 g, 99%) as a red solid: mp 170-171°C; IR (KBr) 1621, 1585, 1504 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.68 (s, 1H), 7.12 (s, 1H), 4.00 (s, 3H), 3.96 (s, 3H), 3.12 (s, 6H), 2.76 (s, 3H); LRMS (DCI), m/z (rel. int.), 292 (MH^+, 100).

Anal. Calcd. for $C_{14}H_{17}N_3O_4$: C, 57.72; H, 5.88; N, 14.42. Found: C, 57.91; H, 5.87; N, 14.20.

3-(*N*,*N*-Diethyl)amino-6,7-dimethoxy-1-methyl-4-nitroisoquinoline (9k). Following the method described above for 9b, compound 9k was obtained in 99% yield from tosylate 8 and diethylamine as a red-orange solid, mp 130-131 °C; IR (KBr) 1624, 1576, 1513, 1490 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.46 (s, 1H), 7.11 (s, 1H), 3.99 (s, 3H), 3.96 (s, 3H), 3.48 (q, J = 7.0 Hz, 4H), 2.75 (s, 3H), 1.19 (t, J = 7.0 Hz, 6H); LRMS (DCI), m/z (rel. int.), 320 (MH^+, 100), 258 (20).

Anal. Calcd. for $C_{16}H_{21}N_3O_4$: C, 60.18; H, 6.63; N, 13.16. Found: C, 59.83; H, 6.67; N, 12.84.

6,7-Dimethoxy-3-[*N*-(2-dimethylamino)ethyl-*N*-ethyl]amino-1-methyl-4-nitroisoquinoline (9l). Following the method described above for 9d using 1.1 eq *N*,*N*-dimethyl-*N*'-ethylethylenediamine as the amine, compound 9l was obtained as an orange solid in 75% yield, mp 81-82 °C; IR (KBr) 1625, 1582, 1513, 1489 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.41 (s, 1H), 7.12 (s, 1H), 3.96 (s, 6H), 3.8 - 3.5 (m, 2H), 3.40 (q, J = 7.0 Hz, 2H), 2.75 (s, 3H), 2.7 - 2.4 (m, 2H), 2.27 (s, 6H), 1.19 (t, J = 7.0 Hz, 3H); LRMS (DCI), m/z (rel. int.), 363 (MH^+, 100).

Anal. Calcd. for $C_{18}H_{26}N_4O_4$: C, 59.65; H, 7.23; N, 15.46. Found: C, 59.70; H, 7.35; N, 15.11.

6,7-Dimethoxy-3-[4-(4-fluorobenzoyl)piperidin-1-yl]-1-methyl-4-nitroisoquinoline (9m). Following the method described above for 9d using 4-(4-fluorobenzoyl)piperidine (1.5 eq) and 8 eq of triethylamine, compound 9m was obtained as an orange solid in 92% yield, mp 193-195 °C; IR (KBr) 1685, 1621, 1600, 1575, 1505, 1485 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.01 (dd, J_1 = 8.9 Hz, J_2 = 5.4 Hz, 2H), 7.54 (s, 1H), 7.19 (s, 1H), 7.15 (d, 8.7 Hz, 2H), 4.08 - 3.95 (m, 2H), 4.02 (s, 3H), 4.00 (s, 3H), 3.55 - 3.45 (m, 1H), 3.28 - 3.19 (m, 2H), 2.79 (s, 3H), 1.98 - 1.88 (m, 4H); LRMS (DCI), m/z (rel. int.), 454 (MH^+, 100).

Anal. Calcd. for $C_{24}H_{24}FN_3O_5$: C, 63.57; H, 5.33; N, 9.27; F, 4.19. Found: C, 63.30; H, 5.33; N, 9.13; F, 4.21.

6,7-Dimethoxy-1-methyl-4-nitro-3-[(4-phenyl)piperazin-1-yl]isoquinoline (9n). An excess of 1-phenylpiperazine (1.14 mL, 3 eq) was added to a stirred slurry of tosylate 8 (1.00 g, 2.39 mmol) in toluene (50 mL) and the mixture was heated under reflux overnight. After cooling to room temperature, a precipitate (identified as tosylate salt of 1-phenylpiperazine) was removed by filtration, and the resulting filtrate was evaporated under reduced pressure and purified by column chromatography on silica gel with methylene chloride as eluent to give 0.78 g (80%) of compound 9n as a red-orange powder, mp 179-181 °C; IR (KBr) 1625, 1590, 1582, 1509, 1497, cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.43 (s, 1H), 7.3 - 7.1 (m, 2H), 7.14 (s, 1H), 7.0 - 6.8 (m, 3H), 4.00 (s, 3H), 3.98 (s, 3H), 3.66 (t, J = 5 Hz, 4H), 3.28 (t, J = 5 Hz, 4H), 2.78 (s, 3H); LRMS (DCI), m/z (rel. int.), 409 (MH^+, 100).

Anal. Calcd. for $C_{22}H_{24}N_4O_4 \cdot 1/4H_2O$: C, 63.99; H, 5.98; N, 13.57. Found: C, 63.99; H, 6.17; N, 13.30.

6,7-Dimethoxy-1-methyl-3-[*N*-methyl-*N*-phenylamino]-4-nitroisoquinoline (9o). Following the method described above for 9b using 10 eq of *N*-methylaniline as the amine, compound 9o was obtained in 85% yield as an orange solid, mp 182-184 °C; IR (KBr) 1618, 1600, 1585, 1564, 1520, 1511, 1501, 1490 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.4 - 7.1 (m, 2H), 7.20 (s, 1H), 7.14 (s, 1H), 7.1 - 6.8 (m, 3H), 4.01 (s, 3H), 3.95 (s, 3H), 3.57 (s, 3H), 2.87 (s, 3H); LRMS (DCI), m/z (rel. int.), 354 (MH^+, 100).

Anal. Calcd. for $C_{19}H_{19}N_3O_4$: C, 64.58; H, 5.42; N, 11.89. Found: C, 64.36; H, 5.40; N, 11.49.

6,7-Dimethoxy-3-hydrazino-1-methyl-4-nitroisoquinoline (9p). Following the method described above for 9b, compound 9p was obtained in 30% yield from tosylate 8 and hydrazine as an orange solid, mp 198-199 °C (dec); IR (KBr) 1617, 1576, 1562, 1514 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.48 (s, 1H), 7.37 (s, 1H), 3.89 (s, 6H), 3.28 (br s; D_2O exchangeable), 2.81 (s, 3H); LRMS (DCI), m/z (rel. int.), 279 (MH^+, 100), 249 (60), 219 (35).

Anal. Calcd. for $C_{12}H_{14}N_4O_4 \cdot 1/4H_2O$: C, 50.97; H, 5.17; N, 19.81. Found: C, 51.03; H, 5.23; N, 19.74.

4-Amino-6,7-dimethoxy-1-methyl-3-(2-propylamino)isoquinoline (10a). Nitroisoquinoline **9f** (1.65 g, 5.40 mmol) was hydrogenated in methanol (200 mL) with 10% palladium on carbon (0.60 g) at room temperature under 40 psig hydrogen for 8 hours. After filtration to remove the catalyst, the solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel with 98:2 methylene chloride/methanol as eluent to provide 1.24 g (83%) of the product as a yellowish green solid: mp 95-99 °C (dec); IR (KBr) 1637, 1624, 1590, 1574, 1506, 1487 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.12 (s, 1H), 6.85 (s, 1H), 4.2 - 4.1 (m, 1H), 4.1 - 3.7 (br s, 1H), 4.01 (s 3H), 3.98 (s, 3H), 3.6 - 3.2 (br s, 2H), 2.73 (s, 3H), 1.23 (d, J = 6.2 Hz, 6H); LRMS (DCI), m/z (rel. int.), 276 (MH^+, 100).

Anal. Calcd. for $C_{15}H_{21}N_3O_2 \cdot 1/4\ H_2O$: C, 64.38; H, 7.74; N, 15.01. Found: C, 64.24; H, 7.95; N, 14.72.

4-Amino-6,7-dimethoxy-1-methyl-3-phenylaminoisoquinoline (10b). Nitroisoquinoline **9i** (1.80 g, 5.30 mmol) was hydrogenated in methanol (250 mL) with 10% palladium on carbon (0.60 g) at room temperature under 40 psig hydrogen for 4 hours. After filtration to remove the catalyst, the solvent was evaporated under reduced pressure and the residue was triturated with ether to provide 1.44 g (88%) of the product as a green solid: mp 198-202 °C; IR (KBr) 1625, 1604, 1590, 1580, 1570, 1512, 1502, 1490, 1475 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.2 - 7.0 (m, 4H), 6.9 - 6.6 (m, 3H), 5.97 (br s, 1H), 4.06 (s, 6H), 3.9 - 3.4 (br s, 2H), 2.75 (s, 3H); LRMS (DCI), m/z (rel. int.), 310 (MH^+, 100).

Anal. Calcd. for $C_{18}H_{19}N_3O_2 \cdot 1/4\ H_2O$: C, 68.88; H, 6.26; N, 13.39. Found: C, 68.75; H, 6.13; N, 13.12.

4-Amino-6,7-dimethoxy-3-(*N*,*N*-dimethyl)amino-1-methylisoquinoline (10c). Following the method described above for **10b**, nitroisoquinoline **9j** (2.03 g, 6.97 mmol) was reduced to give 1.44 g (79%) of **10c** as a greenish yellow solid: mp 164-165 °C; IR (KBr) 1627, 1586, 1574 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.12 (s, 1H), 6.91 (s, 1H), 4.2 - 3.9 (br s, 2H), 3.98 (s, 6H), 2.76 (s, 9H); LRMS (DCI), m/z (rel. int.), 262 (MH^+, 80), 261 (M^+, 100).

Anal. Calcd. for $C_{14}H_{19}N_3O_2$: C, 64.35; H, 7.33; N, 16.08. Found: C, 63.98; H, 7.46; N, 15.73.

4-[(*N*-Acetyl)amino]-6,7-dimethoxy-3-[(*N*,*N*-dimethyl)amino]-1-methylisoquinoline (11a). Acetyl chloride (0.03 mL, 1.1 eq) was added to a stirred solution of **10c** (0.09 g, 0.34 mmol) and triethylamine (0.06 mL, 1.2 eq) in methylene chloride (5 mL). The solution was then gently refluxed under a nitrogen atmosphere for 3 hours. The resulting solution was passed through a silica gel column, eluting with methylene chloride, and the fractions with material at R_f 0.4 (98:2 methylene chloride/methanol) were combined and evaporated under reduced pressure. Trituration of the residue with ether gave **11a** (0.07 g, 67%) as an off-white solid; mp 158 °C (coalesc.), 167-168 °C; IR (KBr) 1650, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.15 (s, 1H), 7.01 (s, 0.5H), 6.92 (s, 1H), 6.79 (s, 0.5H), 4.00 (s, 3H), 3.99 (s, 3H), 3.03 (s, 3H), 2.86 (s, 3H), 2.80 (s, 3H), 2.37 (s, 3H); LRMS (DCI), m/z (rel. int.), 304 (MH^+, 100).

Anal. Calcd. for $C_{16}H_{21}N_3O_3$: C, 63.35; H, 6.98; N, 13.85. Found: C, 63.56; H, 7.11; N, 13.88.

4-[1-(3-*n*-Butyl)ureido]-6,7-dimethoxy-1-methyl-3-phenylaminoisoquinoline (11b). To a solution of **10b** (0.50 g, 1.60 mmol) in methylene chloride (25 mL) was added *n*-butylisocyanate (0.22 mL, 1.2 eq), and the resulting mixture was heated under reflux in a nitrogen atmosphere for 12 hours. The reaction mixture was then purified by column chromatography on silica gel with a gradient elution from methylene chloride to 98:2 methylene chloride/methanol to provide 0.33 g (50%) of urea **11b** as a pale yellow solid; mp 194-196 °C (coalesces & resolidifies), >375 °C (dec); IR (KBr) 1621, 1602, 1574, 1499 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.6 - 7.5 (m, 2H), 7.4 - 7.1 (m, 2H), 7.1 - 6.8 (m, 4H), 6.50 (br s, 1H), 4.95 - 4.65 (br t, 1H), 3.90 (s, 3H), 3.82 (s, 3H), 3.25 - 2.95 (m, 2H), 2.70 (s, 3H), 1.4 - 1.0 (m, 4H), 0.76 (t, J = 6 Hz, 3H); LRMS (DCI), m/z (rel. int.), 409 (MH^+, 100).

Anal. Calcd. for $C_{23}H_{28}N_4O_3$: C, 67.63; H, 6.91; N, 13.72. Found: C, 67.85; H, 7.15; N, 13.78.

4-[1-(3-*n*-Butyl)ureido]-6,7-dimethoxy-3-(*N*,*N*-dimethyl)amino-1-methylisoquinoline (11c). To a solution of **10c** (0.45 g, 1.72 mmol) in methylene chloride (25 mL) was added *n*-butylisocyanate (0.23 mL, 1.2 eq), and the resulting mixture was heated under reflux in a nitrogen atmosphere for 48 hours. The reaction mixture was filtered, the filtrate was evaporated under reduced pressure, and the residue was triturated with ether to provide 0.52 g (84%) of urea **11c** as a colorless solid; mp 225-226 °C; IR (KBr) 1632, 1625, 1575 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.30 (br s, 1H), 7.08 (s, 1H), 6.85 (s, 1H), 6.15 - 6.00 (br t, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 3.24 (s, 3H), 3.1 - 2.9 (m, 2H), 2.80 (s, 6H), 1.5 - 1.1 (m, 4H), 0.86 (t, J = 6 Hz, 3H); LRMS (DCI), m/z (rel. int.), 361 (MH^+, 100).

Anal. Calcd. for $C_{19}H_{28}N_4O_3$: C, 63.31; H, 7.83; N, 15.54. Found: C, 63.66; H, 8.02; N, 15.48.

4-[1-(3-Allyl)ureido]-6,7-dimethoxy-1-methyl-3-phenylaminoisoquinoline (11d). Allylisocyanate (0.15 mL, 1.1 eq) was added to a solution of **10b** (0.50 g, 1.6 mmol) in methylene chloride (25 mL) and the mixture was heated under reflux in a nitrogen atmosphere for 3 days. The precipitate which formed was collected by filtration and washed with methylene chloride to provide 0.44 g (69%) of urea **11d** as a colorless solid; mp 365-370 °C (dec); IR (KBr) 1635, 1610, 1575 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.89 (s, 1H), 7.83 (s, 1H), 7.49 (d, J = 7.8 Hz, 2H), 7.28 (s, 1H), 7.22 (dd, appears as t, J = 7.6 Hz, 2H), 7.19 (s, 1H), 6.82 (t, J = 7.3 Hz, 1H), 6.48 (br t, 1H), 5.96 - 5.84 (m, 1H), 5.20 (dd, J_1 = 17.3 Hz, J_2 = 1.6 Hz, 1H), 5.06 (dd, J_1 = 10.4 Hz, J_2 = 1.6 Hz, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 3.75 (m, 2H), 2.76 (s, 3H); LRMS (DCI), m/z (rel. int.), 393 (MH^+, 40), 233 (100).

Anal. Calcd. for $C_{22}H_{24}N_4O_3$: C, 67.33; H, 6.16; N, 14.28. Found: C, 67.31; H, 6.17; N, 14.05.

4-[1-(3-Allyl)ureido]-6,7-dimethoxy-3-(*N*,*N*-dimethyl)amino-1-methylisoquinoline (11e). Following the method described above for **11d** using compound **10c** as the amine, urea **11e** was obtained in 71% yield as a colorless solid; mp 238-240 °C (coalesc), 258-264 °C (dec); IR (KBr) 1625, 1575 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.14 (s, 1H), 7.11 (s, 1H), 6.04 (br s, 1H), 6.86 - 6.74 (m, 1H), 5.12 - 5.00 (m, 2H), 4.92 (br t, 1H), 4.00 (s, 3H), 3.98 (s, 3H), 3.86 - 3.80 (m, 2H), 3.02 (s, 6H), 2.79 (s, 3H); LRMS (DCI), m/z (rel. int.), 345 (MH^+, 100).

Anal. Calcd. for $C_{18}H_{24}N_4O_3$: C, 62.77; H, 7.02; N, 16.27. Found: C, 62.43; H, 6.93; N, 15.97.

3-(*n*-Butylthio)-6,7-dimethoxy-1-methyl-4-nitroisoquinoline (12). *n*-Butanethiol (0.78 mL, 3 eq), triethylamine (0.67 mL, 2 eq) and potassium carbonate (1.32 g, 4 eq) were added to a stirred suspension of tosylate **8** (1.00 g, 2.39 mmol) in toluene (50 mL) and the mixture was heated under reflux for 3 days. The mixture was cooled to room temperature, filtered, and the solids were washed with methylene chloride. The filtrate was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel with methylene chloride as the eluent to provide **12** (0.59 g, 73%) as a yellow solid: mp 130-132 °C; IR (KBr) 1622, 1562, 1557 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.44 (s, 1H), 7.17 (s, 1H),

4.01 (s, 3H), 3.99 (s, 3H), 3.26 (t, J = 7.2 Hz, 2H), 2.86 (s, 3H), 1.9 - 1.2, (m, 4H), 0.95 (t, J = 6.7 Hz, 3H); LRMS (DCI), m/z (rel. int.), 337 (MH^+, 100), 307 (96).

Anal. Calcd. for $C_{16}H_{20}N_2O_4S$: C, 57.13; H, 5.99; N, 8.33; S, 9.53. Found: C, 56.92; H, 6.15; N, 8.21; S, 9.48.

3-Benzyloxy-6,7-dimethoxy-1-methyl-4-nitroisoquinoline (13). A mixture of tosylate **8** (1.00 g, 2.39 mmol) and triethylamine (0.67 mL, 2 eq) in benzyl alcohol (50 mL) was heated to 140 °C for 48 hours. The reaction mixture was evaporated under reduced pressure, and compound **13** was obtained (0.04 g, 4% yield) from the residue after careful column chromatography on silica gel with methylene chloride as eluent, mp 212-214 °C; IR (KBr) 1574, 1518 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.50 (d, J = 7.5 Hz, 2H), 7.38 (t, J = 7.5 Hz, 2H), 7.31 - 7.26 (m, 1H), 7.19 (s, 1H), 7.11 (s, 1H), 5.61 (s, 2H), 4.02 (s, 3H), 4.00 (s, 3H), 2.87 (s, 3H); LRMS (DCI), m/z (rel. int.), 355 (MH^+, 100).

Anal. Calcd. for $C_{19}H_{18}N_2O_5 \cdot 1/2H_2O$: C, 62.80; H, 5.27; N, 7.71. Found: C, 62.80; H, 4.87; N, 7.62.

7,8-Dimethoxy-2-(4-methoxyphenyl)-5-methyl-3-(2-propyl)-3*H*-imidazo[5,4-c]isoquinoline (14a). A mixture of amine **10a** (0.50 g, 1.82 mmol) and *p*-anisaldehyde (0.25 mL, 1.1 eq) in toluene (25 mL) was heated to reflux with azeotropic water removal for 3 days. The reaction mixture was cooled to room temperature, 10% palladium on carbon (0.06g) was added, and the resulting mixture was heated to reflux for an additional 2 days. The palladium on carbon was removed via filtration, the filtrate was evaporated under reduced pressure, and the residue was triturated with ether to provide 0.55g (77%) of compound **14a** as a cream solid, mp 206-208 °C; IR (KBr) 1611, 1580, 1527, 1512, 1491, 1462 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.84 (s, 1H), 7.56 (d, J = 8.8 Hz, 2H), 7.33 (s, 1H), 6.99 (d, J = 8.8 Hz, 2H), 4.76 (sept., J = 6.7 Hz, 1H), 4.05 (s, 3H), 4.01 (s, 3H), 3.85 (s, 3H), 2.95 (s, 3H), 1.75 (d, J = 6.7 Hz, 6H); LRMS (DCI), m/z (rel. int.), 392 (MH^+, 100).

Anal. Calcd. for $C_{23}H_{25}N_3O_3$: C, 70.57; H, 6.44; N, 10.73. Found: C, 70.22; H, 6.32; N, 10.36.

7,8-Dimethoxy-2-(4-methoxyphenyl)-5-methyl-3-phenyl-3*H*-imidazo[5,4-c]isoquinoline (14b). A mixture of amine **10b** (0.40 g, 1.29 mmol) and *p*-anisaldehyde (0.17 mL, 1 eq) in toluene (25 mL) was heated to reflux under nitrogen with azeotropic water removal for 5 days. The reaction mixture was cooled to room temperature, 10% palladium on carbon (0.05g) was added, and the resulting mixture was heated to reflux under nitrogen for an additional 2 hours. The hot reaction mixture was filtered through celite, and the precipitate which formed upon cooling was collected by filtration to provide 0.10 g (18%) of compound **14b** as an off-white solid. An additional 0.10 g of precipitate was obtained by addition of ether to the filtrate (total yield 0.20 g, 36%), mp 266-268 °C; IR (KBr) 1625, 1603, 1581, 1524, 1512, 1489 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.95 (s, 1H), 7.8 - 7.1 (m, 8H), 6.82 (d, J = 8.8 Hz, 2H), 4.12 (s, 3H), 4.02 (s, 3H), 3.79 (s, 3H), 2.99 (s, 3H); LRMS (DCI), m/z (rel. int.), 426 (MH^+, 100).

Anal. Calcd. for $C_{26}H_{23}N_3O_3$: C, 73.40; H, 5.45; N, 9.88. Found: C, 73.25; H, 5.40; N, 9.41.

Acknowledgement. We wish to thank M. L. Cotter and her staff for analytical services.

REFERENCES

1. R. M. Kanojia, O. W. Lever, Jr., J. B. Press, L. Williams, H. Werblood, E. C. Giardino, R. Falotico, A. J. Tobia, *J. Med. Chem.*, submitted. See also: R. M. Kanojia, J. B. Press, O. W. Lever, Jr., L. Williams, J. J. McNally, A. J. Tobia, R. Falotico and J. B. Moore, Jr., *J. Med. Chem.* **31**, (1988), in press.
2. See for example: (a) *The Chemistry of Heterocyclic Compounds*; A. Weissberger, E. C. Taylor, Eds.; Wiley: New York, 1980; Vol. 38 (*Isoquinolines*); (b) *The Chemistry and Biology of Isoquinoline Alkaloids*; J. D. Phillipson, M. F. Roberts, M. H. Zenk, Eds.; Springer-Verlag: New York, 1985; (c) S. F. Dyke, *Rodd's Chemistry of Carbon Compounds*, Second Ed.; S. Coffey, M. F. Ansell, Eds.; Elsevier: Amsterdam, 1976; Vol. 4(F), pp 357-438; (d) P. A. Claret, *Comprehensive Organic Chemistry*; P. G. Sammes, Ed.; Pergamon: New York, 1979; Vol. 4, pp 205-232.
3. (a) C. S. Lee, Y. Hashimoto, K. Shudo, M. Nagao, *Heterocycles* **22**, 2249 (1984); (b) M. Hejsek, J. Slouka, *Pharmazie* **39**, 186 (1984); (c) A. B. Tomchin, U. Lepp, V. S. Dmitrukha, *Zh. Org. Khim.* **11**, 2407 (1975), *Chem. Abstr.* **84**:59401u (1976); (d) L. W. Deady, E. H. Kachob, *Australian J. Chem.* **39**, 2089 (1986). Ref. 3d also describes the conversion of 1-methoxyisoquinoline-3,4-diamine to a variety of imidazoisoquinolines.
4. (a) D. Rose, German Patent DE 2650226, May 11, 1978, *Chem. Abstr.* **89**:43148j (1978); (b) E. Fleckenstein, R. Mohr, German Patent DE 2347756, April 24, 1975, *Chem. Abstr.* **83**:81207m (1975); (c) See also ref. 3a.
5. (a) F. Johnson, W. A. Nasutavicus, *J. Org. Chem.* **27**, 3953 (1962); (b) See also ref. 3a.
6. C. E. Hall, A. Taurins, *Can. J. Chem.* **44**, 2473 (1966).
7. (a) H. L. Sharma, V. N. Sharma, R. L. Mital, *Australian J. Chem.* **21**, 3081 (1968); (b) Y. Takikawa, S. Yoshida, R. Sato, S. Takizawa, *Nippon Kagaku Kaishi* **4**, 631 (1976), *Chem. Abstr.* **85**:93352j (1976).
8. (a) J. F. Bunnett, J. Y. Bassett, Jr., *J. Amer. Chem. Soc.* **81**, 2104 (1959); (b) J. F. Bunnett, J. Y. Bassett, Jr., *J. Org. Chem.* **27**, 2345 (1962).
9. P. K. Bridson, W. Markiewicz, C. B. Reese, *J. Chem. Soc., Chem. Comm.* **1977**, 447.
10. S. R. James, *J. Chem. Res. (M)*, **1979**, 1579; *J. Chem. Res. (S)*, **1979**, 125.