Synthesis of 1-(4-Substituted)benzyl-6-hydroxyisoquinolines with Potential Activity on Na^+,K^+-ATPase

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The synthesis of 1-(4-substituted)benzyl-6-hydroxyisoquinolines, to be evaluated in the displacement of the specific ^{3}H-ouabain binding to Na^+,K^+-ATPase, is described. The key step involved a cyclization to the isoquinoline ring under Pictet-Gams conditions which was best performed with the 6-hydroxy group protected as the benzyl ether. When an unsaturated ester group was present in position 4 of the 1-benzyl group, this was best introduced before the cyclization step, since the Heck reaction on 1-(4-bromobenzyl)-6-hydroxyisoquinoline (**8**) with acrylic acid derivatives was not successful in all cases.

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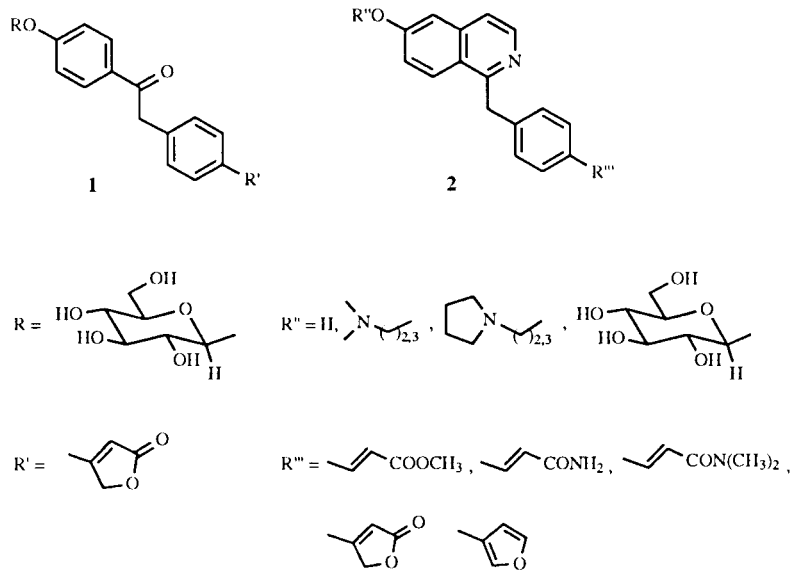
Digitalis cardiac glycosides are drugs clinically used for the treatment of congestive heart failure. Their main pharmacodynamic property is the increase of the force of myocardial contraction through the direct inhibition of the membrane bound Na^+,K^+-ATPase. However toxic effects are frequent and can be severe [2].

The search for less toxic agents has prompted a lot of work both on natural and synthetic compounds [3]. Among the latter, the deoxybenzoin derivative **1** (Figure 1) was found to inhibit Na^+,K^+-ATPase and to be a positive inotropic agent [4].

As a part of a work on compounds acting on the Na^+,K^+-ATPase we prepared some isoquinolines of general structure **2** (Figure 1), where the isoquinoline ring replaces the benzoyl part of **1**; the substituents on the benzyl and the 6-hydroxy groups are those reported to favor the interaction with the Na^+,K^+-ATPase digitalis receptor [3].

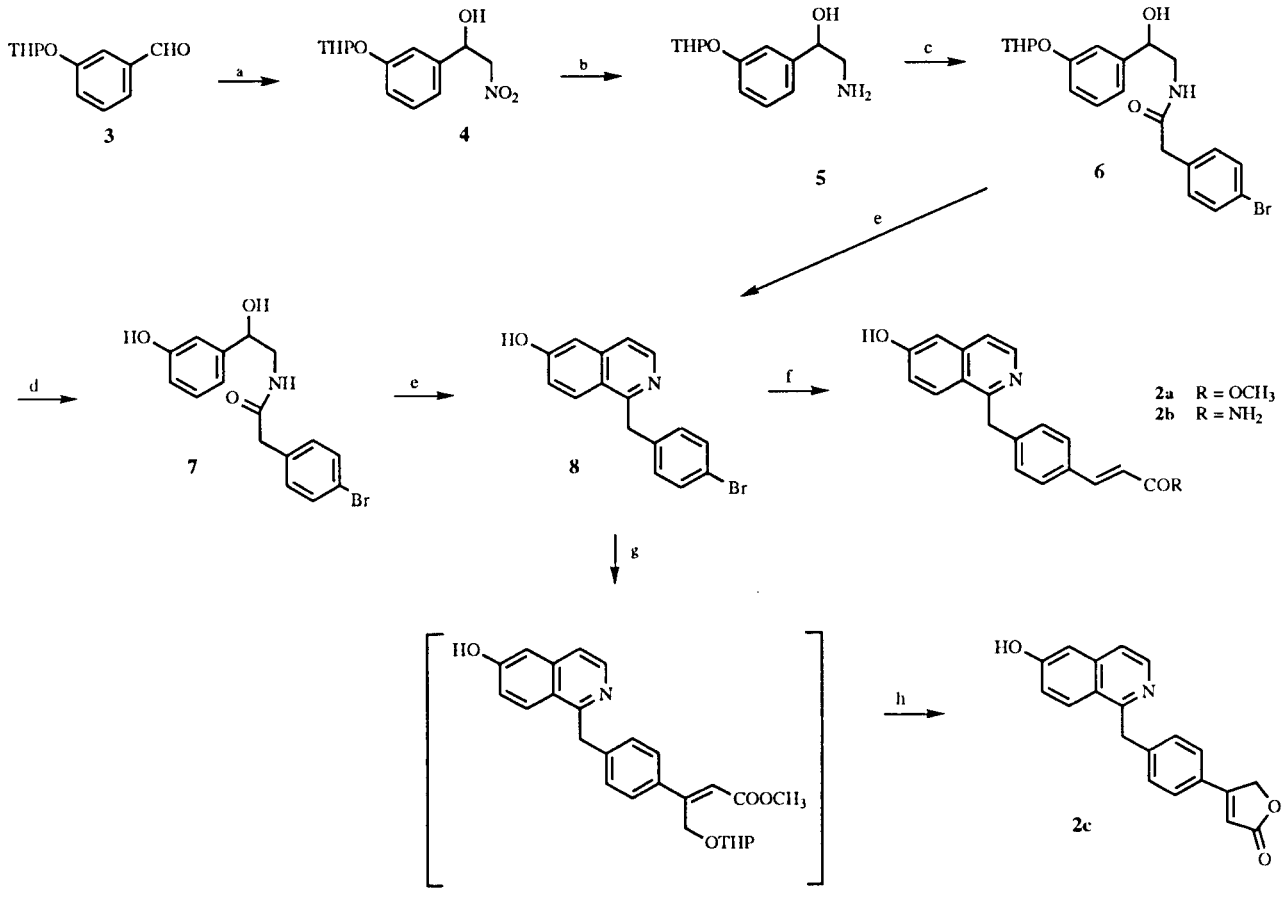
The first target was the bromo derivative **8** (Scheme 1) from which the final compounds could be prepared by Heck reactions with the appropriate olefins. The starting 3-tetrahydropyranyloxybenzaldehyde (**3**) [5] gave with nitromethane under alkaline conditions the nitroalcohol **4** which was reduced to **5** in good yields by catalytic hydrogen transfer with ammonium formate [6]; **4** and **5** were

Figure 1



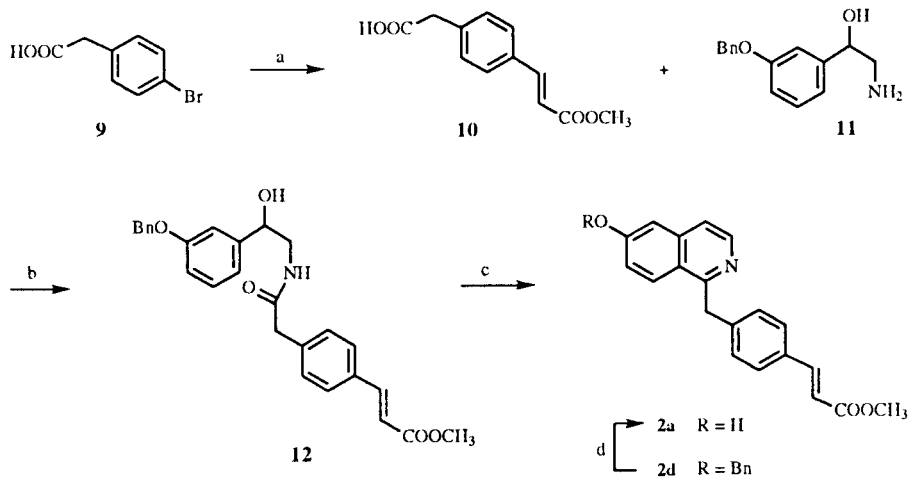
As a part of a work on compounds acting on the Na^+,K^+-ATPase we prepared some isoquinolines of general structure **2** (Figure 1), where the isoquinoline ring obtained as mixtures of diasteroisomers and used as such since the stereogenic centers are lost in the final isoquinolines.

Scheme 1



Reagents: a) CH_3NO_2, NaOH, MeOH, H_2O. b) $HCOONH_4$, Pd/C, THF, MeOH. c) 4-$BrC_6H_4CH_2COCl$, NaOH, Et_2O, H_2O. d) $(COOH)_2$, H_2O, MeOH. e) $POCl_3$, MeCN, 80°C. f) CH_2=CHCOR, $Pd(OAc)_2$, PPh_3, n-Bu_3N, DMF, 90°C. g) (E)-$THPOCH_2CH$=$CHCOOCH_3$, $Pd(OAc)_2$, n-Bu_3N, DMF, 90°C. h) PTSA, CH_2Cl_2, MeOH, 45°C.

Scheme 2



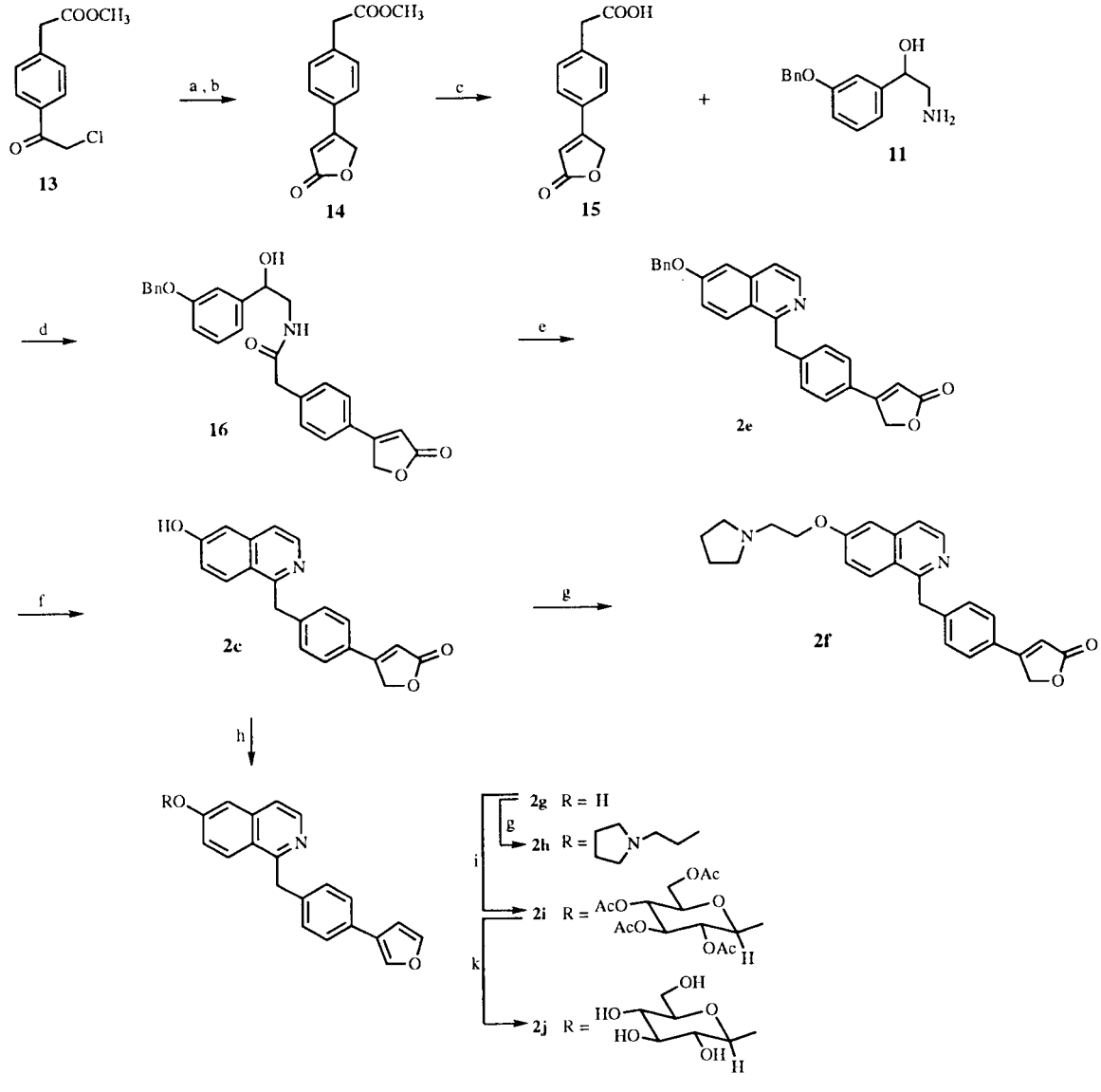
Reagents: a) CH_2=$CHCOOCH_3$, $Pd(OAc)_2$, PPh_3, DIPEA, DMF, 100°C. b) 1°: $SOCl_2$, C_6H_6, 80°C; 2°: **11**, NaOH, H_2O, dioxane. c) $POCl_3$, MeCN, 80°C. d) CF_3COOH, 50°C.

Compound **5** afforded with 4-bromophenylacetyl chloride [7] under Schotten-Baumann conditions the amide **6**. The Pictet-Gams ring closure to isoquinoline **8** proceeded in low yields, either under reflux for a few minutes (18%), according to Teitel and Brossi [8], or at room temperature for four days (30%). Other attempts at the cyclization of **6**, such as using PPE as the condensing agent [9] at different reaction temperatures, or the cyclization of the unprotected phenol **7**, did not give better results. Heck reactions [10] on compound **8** with the appropriate acrylic acid derivatives gave the desired compounds **2a** and **2b** in moderate yields while the reaction with methyl (*E*)-4-(2-tetrahydropyranyloxy)but-2-enoate followed by an acid catalyzed cyclization to the 4-substituted-2(5*H*)-furanones [11], afforded **2c** in an unacceptable 10% yield.

We then considered a new pathway to these unsaturated derivatives, *i.e.* the cyclization to isoquinoline of an intermediate with the unsaturated ester group already present on the benzylic residue and with the phenolic group protected as the more stable benzyl ether.

The unsaturated ester **10** was obtained by the Heck

Scheme 3

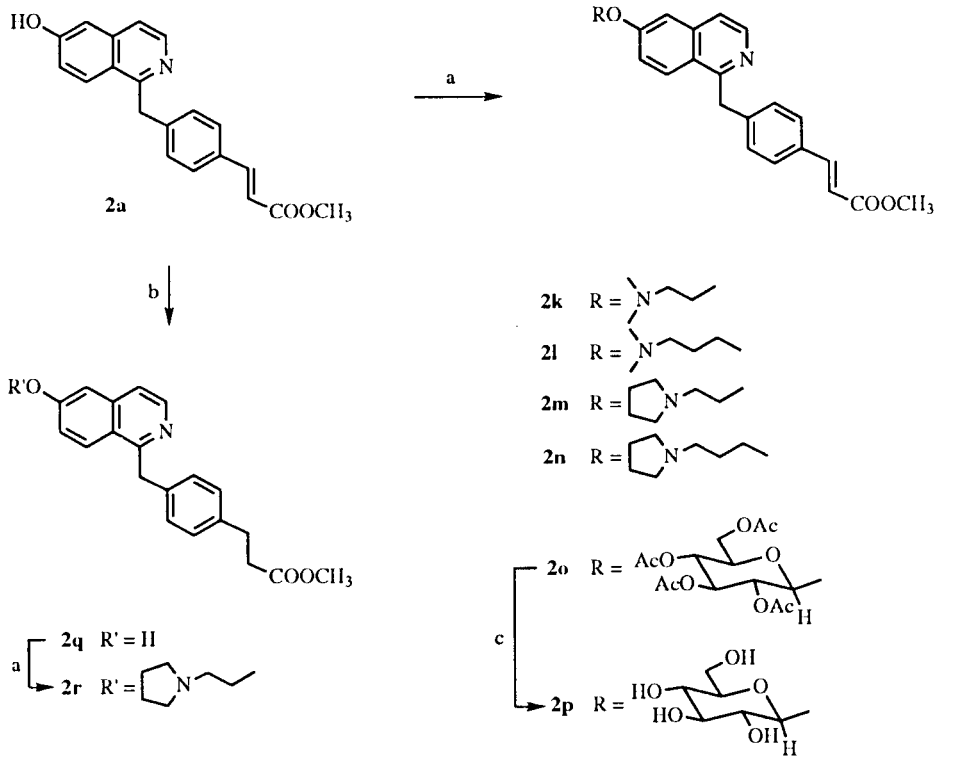


Reagents: a) $(MeO)_2POCH_2COOK$, MeCN, 60°C. b) DIPEA, LiCl, MeCN. c) HBr 48%, 100°C. d) CDI, DMF, -20°C. e) $POCl_3$, MeCN, 80°C. f) CF_3COOH, 60°C. g) 1-(2-chloroethyl)pyrrolidine, Ag_2CO_3, $PhCH_3$, 40°C. h) DIBAH, THF, -50°C. i) α-bromoacetoglucose, Ag_2CO_3, $PhCH_3$. j) NaOH, MeOH.

reaction on 4-bromophenylacetic acid (**9**) (Scheme 2); reaction of **10** with the amine **11** [12] gave the amide **12**, which under the Pictet-Gams cyclization conditions gave **2d** in 80% yield. The final deprotection of the benzyl ether in trifluoroacetic acid gave **2a** in 83% yield (47% overall yield from **9**).

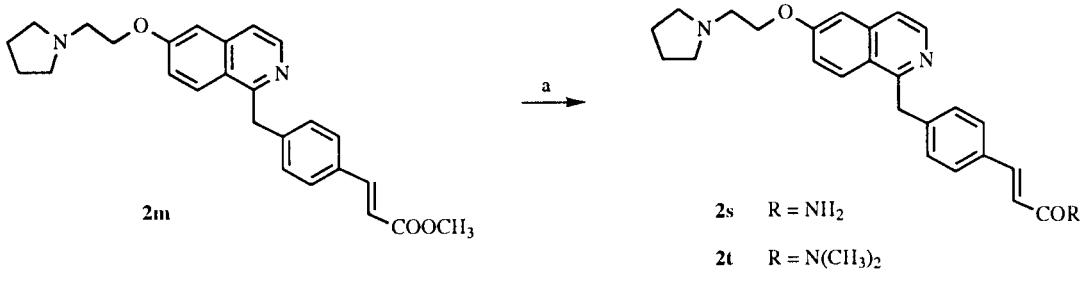
potassium dimethylphosphonoacetate followed by an intramolecular Horner reaction with diisopropylethylamine and lithium chloride [14] gave **14** in a higher yield (70%) than that obtained with the sequence reported in the literature for the same compound [13]. The amide **16** was obtained by reaction of **15**, prepared

Scheme 4



Reagents : a) RCl (**2k-n**) (or RBr (**2o**)), Ag_2CO_3, $PhCH_3$, 40°C. b) H_2, Raney Ni, EtOH. c) NaOH, MeOH.

Scheme 5



Reagents: a) NH_3 (or $HN(CH_3)_2$), MeONa, MeOH.

The approach used for the preparation of the ester **2a** was also followed for the synthesis of the analogous compound **2c** (Scheme 3). The α-chloroketone **13** [13] with

from **14** by hydrolysis with 48% hydrobromic acid [13], with **11** [12] at -20° using carbonyldiimidazole as the condensing agent. The overall yield of **2c**, starting from

15, was 45%. The reduction of the lactone **2c** to the corresponding furan **2g** was performed with DIBAH at -50° [15].

The alkylations of the phenolic group of compounds **2c** and **2g** (Scheme 3), and **2a** and **2q** (Scheme 4) with chloroalkylamines under standard conditions, such as sodium hydride or carbonate in tetrahydrofuran or *N,N*-dimethylformamide at different temperatures, gave very complex mixtures of products. Clean reactions, with yields higher than 60%, were accomplished when a heterogeneous mixture of the silver salts with an excess of the alkyl halides, as reported for 2-pyridone [16], were used. The same conditions were applied for the glycosidation of **2a** and **2g**. The hydrogenation of the unsaturated ester **2a** to **2q** (Scheme 4) was performed with Raney Nickel at atmospheric pressure.

The amides **2s** and **2t** were prepared from the easily achievable ester **2m** respectively by treatment with dry ammonia and dimethylamine in methanol with sodium methoxide as the catalyst (Scheme 5).

Compounds **2** were evaluated in the displacement of the specific ^{3}H-ouabain binding to Na^+,K^+-ATPase [17]. All showed moderate bindings, with IC_{50} values in the 10^{-4} *M* range, in contrast to natural compounds which have bindings in the 10^{-7} *M* range.

EXPERIMENTAL

Melting points were determined with a Büchi 535 capillary apparatus and are uncorrected. Elemental analyses were performed by Redox, Cologno Monzese, Italy. The ^{1}H- and ^{13}C-nmr spectra were obtained, at 300.13 and 75.48 MHz respectively, on a Bruker AC-300 instrument. Chemical shifts are expressed in ppm downfield from TMS as the internal standard. The multiplicity of carbon signals was determined using 135° DEPT experiment. Mass spectra were obtained on a INCOS-50B Finnigan spectrometer in the DEPT-EI mode at 70 eV. The ir spectra were recorded on a Perkin-Elmer 1310 spectrophotometer. The tlc were performed on silica gel plates with a fluorescent indicator (Merck, Kieselgel 60 F_{254}) and visualized both with light at 254 nm and with spraying a solution of cerium sulfate (0.2%) and ammonium molybdate (4%) in water:sulfuric acid (24:1) followed by heating.

1-(3-Tetrahydropyranyloxyphenyl)-2-nitroethanol (**4**).

To a solution of 49.50 g (0.240 mole) of 3-tetrahydropyranyloxybenzaldehyde (**3**) [5] and 25.80 ml (0.480 mole) of nitromethane in 500 ml of methanol was added 96 ml of 2.5 *M* (0.240 mole) sodium hydroxide in water, keeping the temperature below 30°. After 30 minutes at room temperature, the solution was poured into 2.5 l of water containing 13.8 ml (0.240 mole) of acetic acid cooled at 0°. The solution was extracted with ethyl acetate. The organic phase was washed with water, aqueous 5% sodium hydrogen carbonate and then dried. The solvent was evaporated. The residue was purified on a silica gel column (8 x 30 cm). Gradient elution with *n*-hexane containing increasing amounts of ethyl acetate (10 to 25%) afforded 48.10 g (75%) of **4**, as a clear pale yellow oil; ^{1}H nmr (deuteriochloroform): δ (ppm) 1.60-1.85 (m, 3 H, THP), 1.85-2.10 (m, 3 H, THP), 2.91 (m, 1 H, OH), 3.62-3.70 (m, 1 H, OC*H*H), 3.88-3.99 (m, 1 H, OCH*H*), 4.52-4.70 (m, 2 H, CH_2NO_2), 5.48 (m, 2 H, C*H*OH and OCHO), 7.02-7.11 (m, 2 H, phenyl H-4,6), 7.14 (bs. 1H, phenyl H-2), 7.36 (t, J = 8.0 Hz, 1 H, phenyl H-5).

Anal. Calcd. for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.30; H, 6.49; N, 5.11.

1-(3-Tetrahydropyranyloxyphenyl)-2-aminoethanol (**5**).

To a solution of 28.10 g (0.105 mole) of **4** in 400 ml of methanol and 400 ml of tetrahydrofuran were added 6.00 g of 10% palladium on charcoal and then 33.10 g (0.525 mole) of ammonium formate. After stirring at room temperature for 8 hours, the mixture was diluted with 5.0 l of diethyl ether and filtered. The solvent was evaporated to yield 21.90 g (88%) of **5**, as a viscous pale yellow oil, pure by tlc (chloroform:methanol: acetic acid, 90:7:3); ^{1}H nmr (deuteriochloroform): δ (ppm) 1.49-1.78 (m, 3 H, THP), 1.79-2.15 (m, 3 H, THP), 2.65 (b, 3 H, OH and NH_2), 2.70-3.10 (m, 2 H, CH_2N), 3.50-3.70 (m, 1 H, OC*H*H), 3.80-3.98 (m, 1 H, OCH*H*), 4.55-4.67 (m, 1 H, C*H*OH), 5.41 (m, 1 H, OCHO), 6.88-7.02 (m, 2 H, phenyl H-4,6), 7.07 (s, 1 H, phenyl H-2), 7.27 (t, J = 8.0 Hz, 1 H, phenyl H-5).

Anal. Calcd. for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.68; H, 8.20; N, 5.75.

N-[2-(3-Tetrahydropyranyloxyphenyl)-2-hydroxyethyl]-4-bromophenylacetamide (**6**).

To a vigorously stirred mixture of 21.35 g (0.090 mole) of **5** in 350 ml of diethyl ether and 72 ml of 1.25 *M* (0.090 mole) aqueous sodium hydroxide, a solution of 21.00 g (0.090 mole) of 4-bromophenylacetyl chloride [7] in 21 ml of diethyl ether was added in 20 minutes. After 30 minutes the ether layer was separated, dried and the solvent was evaporated to yield 37.10 g (95%) of **6**, as a white foam, pure by tlc (*n*-hexane:ethyl acetate, 30:70); ^{1}H nmr (deuteriochloroform): δ (ppm) 1.50-1.75 (m, 3 H, THP), 1.77-2.10 (m, 3 H, THP), 3.20-3.35 (m, 1 H, C*H*HN), 3.43 (s, 2 H, CH_2CON), 3.50-3.65 (m, 2 H, CH*H*N and OC*H*H), 3.80-3.92 (m, 1 H, OCH*H*), 3.95 (b, 1 H, OH), 4.65-4.75 (m, 1 H, C*H*OH), 5.46 (m, 1 H, OCHO), 6.17 (t, J = 6.0 Hz, 1 H, NH), 6.85-6.98 (m, 2 H, phenoxy H-4,6), 7.00 (s, 1 H, phenoxy H-2), 7.06 (d, J = 8.0 Hz, 2 H, bromophenyl H-2,6), 7.22 (t, J = 8.0 Hz, 1 H, phenoxy H-5), 7.40 (d, J = 8.0 Hz, 2 H, bromophenyl H-3,5).

Anal. Calcd. for $C_{21}H_{24}BrNO_4$: C, 58.07; H, 5.57; Br, 18.40; N, 3.22. Found: C, 57.94; H, 5.52; Br, 18.18; N, 3.10.

N-[2-(3-Hydroxyphenyl)-2-hydroxyethyl]-4-bromophenylacetamide (**7**).

To a solution of 1.00 g (2.3 mmoles) of **6** in 9 ml of methanol and 1 ml of water was added oxalic acid until *p*H 2.0 was reached. After warming at 55° for 1 hour, the solution was cooled and concentrated. The residue was taken up with ethyl acetate and washed with water. The organic phase was washed

with aqueous 5% sodium hydrogen carbonate, dried and the solvent was evaporated to yield 0.78 g (97%) of **7**, as a waxy white solid, pure by tlc (methylene chloride:ethyl acetate, 40:60); ^{1}H nmr (DMSO-d_6): δ (ppm) 3.00-3.15 (m, 1 H, C*H*HN), 3.20-3.35 (m, 1 H, CH*H*N), 3.40 (s, 2 H, CH_2CON), 4.45-4.55 (m, 1 H, C*H*OH), 5.36 (d, J = 4.0 Hz, 1 H, CHO*H*), 6.63 (d, J = 8.0 Hz, 1 H, hydroxyphenyl H-4), 6.68 (d, J = 7.8 Hz, 1 H, hydroxyphenyl H-6), 6.75 (s, 1 H, hydroxyphenyl H-2), 7.08 (t, J = 8.0 Hz, 1 H, hydroxyphenyl H-5), 7.18 (d, J = 8.5 Hz, 2 H, bromophenyl H-2,6), 7.45 (d, J = 8.5 Hz, 2 H, bromophenyl H-3,5), 8.05 (m, 1 H, NH), 9.25 (s, 1 H, phenyl OH).

Anal. Calcd. for $C_{16}H_{16}BrNO_3$: C, 54.87; H, 4.60; Br, 22.82; N, 4.00. Found: C, 54.62; H, 4.52; Br, 22.60; N, 3.87.

1-(4-Bromobenzyl)-6-hydroxyisoquinoline (**8**).

To a solution of 26.06 g (0.060 mole) of **7** in 600 ml of acetonitrile was added 38.5 ml (0.42 mole) of phosphorus oxychloride. After stirring at room temperature for 4 days, the solution was made alkaline to *p*H 9 with aqueous 20% sodium carbonate. The mixture was extracted with chloroform. The organic layer was separated, washed with water, dried and evaporated. The residue was purified on a silica gel column (7 x 30 cm). Gradient elution with methylene chloride containing increasing amount of ethyl acetate (25 to 30%) afforded 5.68 g (30%) of **8**, as a white solid, mp 235-240°; ^{1}H nmr (DMSO-d_6): δ (ppm) 4.48 (s, 2 H, CH_2), 7.08 (s, 1 H, isoquinoline H-5), 7.13 (d, J = 8.0 Hz, 1 H, isoquinoline H-7), 7.23 (d, J = 7.9 Hz, 2 H, phenyl H-2,6), 7.42 (d, J = 7.9 Hz, 2 H, phenyl H-3,5), 7.48 (d, J = 5.6 Hz, 1 H, isoquinoline H-4), 8.14 (d, J = 8.0 Hz, 1 H, isoquinoline H-8), 8.23 (d, J = 5.6 Hz, 1 H, isoquinoline H-3), 10.34 (s, 1 H, OH); ^{13}C nmr (DMSO-d_6): δ (ppm) 40.0 (t), 107.9 (d), 118.5 (d), 119.1 (s), 119.9 (d), 121.3 (s), 127.8 (d), 130.8 (d), 131.1 (d), 138.3 (s), 139.2 (s), 142.0 (d), 158.6 (s), 158.8 (s).

Anal. Calcd. for $C_{16}H_{12}BrNO$: C, 61.17; H, 3.85; Br, 25.43; N, 4.46. Found: C, 60.93; H, 3.78; Br, 25.24; N, 4.31.

General Procedure for the Reactions of 1-(4-Bromobenzyl)-6-hydroxyisoquinoline (**8**) with Acrylic Acid Derivatives. Synthesis of Methyl 4-[(6-Hydroxy-1-isoquinolinyl)methyl]-cinnamate (**2a**).

Method A.

This reaction was carried out under an atmosphere of nitrogen. A solution of 2.51 g (8.0 mmoles) of **8**, 2.90 ml (32.0 mmoles) of methyl acrylate, 5.70 ml (24.0 mmoles) of tri-*n*-butylamine, 0.090 g (0.4 mmole) of palladium acetate and 0.21 g (0.8 mmole) of triphenylphosphine in 25 ml of dry *N,N*-dimethylformamide was stirred at 90° for 44 hours. The mixture was cooled, poured into water and extracted with ethyl acetate. The organic layer was separated, washed with water, dried and evaporated. The residue was purified by flash chromatography on a silica gel column (4 x 15 cm). Elution with methylene chloride:ethyl acetate (60:40) gave a residue which was ground with diethyl ether to afford 1.30 g (51%) of **2a**, as a white solid, mp 194-195°; ir (potassium bromide): ν 1713 (C=O) cm^{-1}; ms: m/z 319 (M$^+$), 318, 258; ^{1}H nmr (DMSO-d_6): δ (ppm) 3.69 (s, 3 H, CH_3), 4.54 (s, 2 H, CH_2), 6.54 (d, J = 16.1 Hz, 1 H, CHCOO), 7.09 (d, J = 2.2 Hz, 1 H, isoquinoline H-5), 7.14 (dd, J = 2.2, 9.1 Hz, 1 H, isoquinoline H-7), 7.32 (d, J = 8.0 Hz, 2 H, phenyl H-3,5), 7.48 (d, J = 5.8 Hz, 1 H, isoquinoline H-4), 7.58 (d, J = 16.1 Hz, 1 H, phenyl CH=), 7.59 (d, J = 8.0 Hz, 2 H, phenyl H-2,6), 8.15 (d, J = 9.1 Hz, 1 H, isoquinoline H-8), 8.24 (d, J = 5.8 Hz, 1 H, isoquinoline H-3), 10.30 (s, 1 H, OH); ^{13}C nmr (DMSO-d_6): δ (ppm) 40.6 (t), 51.3 (q), 107.9 (d), 117.1 (d), 118.5 (d), 119.8 (d), 121.3 (s), 127.8 (d), 128.4 (d), 129.1 (d), 131.9 (s), 138.2 (s), 141.9 (d), 142.5 (s), 144.3 (d), 158.6 (s), 158.8 (s), 166.6 (s).

Anal. Calcd. for $C_{20}H_{17}NO_3$: C, 75.22; H, 5.37; N, 4.39. Found: C, 74.97; H, 5.38; N, 4.30.

4-[(6-Hydroxy-1-isoquinolinyl)methyl]cinnamamide (**2b**).

This compound was analogously prepared in 45% yield, using acrylamide and after purification by flash chromatography (methylene chloride:methanol 90:10) followed by grinding in methanol:water (90:10), as a white solid, mp 235-245° dec; ir (potassium bromide): ν 3300 and 3160 (NH_2), 1665 (C=O) cm^{-1}; ms: m/z 304 (M$^+$), 303, 286; ^{1}H nmr (DMSO-d_6): δ (ppm) 4.53 (s, 2 H, CH_2), 6.50 (d, J = 16.0 Hz, 1 H, CHCO), 7.09 (d, J = 2.2 Hz, 1 H, isoquinoline H-5), 7.13 (dd, J = 2.2, 9.1 Hz, 1 H, isoquinoline H-7), 7.30 (d, J = 8.0 Hz, 2 H, phenyl H-3,5), 7.32 (d, J = 16.0 Hz, 1 H, phenyl CH=), 7.42 (d, J = 8.0 Hz, 2 H, phenyl H-2,6), 7.47 (d, J = 5.7 Hz, 1 H, isoquinoline H-4), 8.14 (d, J = 9.1 Hz, 1 H, isoquinoline H-8), 8.24 (d, J = 5.7 Hz, 1 H, isoquinoline H-3), 10.35 (s, 1 H, OH); ^{13}C nmr (DMSO-d_6): δ (ppm) 40.6 (t), 107.9 (d), 118.7 (d), 119.9 (d), 121.5 (d), 121.6 (d), 127.7 (d), 128.0 (d), 129.2 (d), 132.8 (s), 138.4 (s), 139.1 (d), 141.4 (s), 141.8 (d), 158.6 (s), 159.0 (s), 166.8 (s).

Anal. Calcd. for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20. Found: C, 74.70; H, 5.35; N, 9.07.

4-{4-[(6-Hydroxy-1-isoquinolinyl)methyl]phenyl}-2(5*H*)-furanone (**2c**).

Method A.

Compound **8** (157 mg, 0.5 mmole) was reacted with 500 mg (2.5 mmoles) of methyl (*E*)-4-(2-tetrahydropyranyloxy)but-2-enoate under the conditions described above for the preparation of **2a**. After 40 hours at 90° the mixture was cooled, poured into water and extracted with chloroform. The organic layer was separated, washed with water, dried and evaporated. The residue was dissolved in 1 ml of dichloromethane and 4 ml of methanol. To the solution were added 80 mg of *p*-toluenesulfonic acid monohydrate. After 2 hours at 50°, the solution was cooled and evaporated. The residue was dissolved in ethyl acetate and washed with aqueous 5% sodium hydrogen carbonate. The organic layer was dried and evaporated. The residue was purified by flash chromatography on a silica gel column (4 x 15 cm). Elution with methylene chloride:ethyl acetate (1:1) afforded 16 mg (10%) of **2c**.

(*E*)-4-(2-Methoxycarbonylvinyl)phenylacetic Acid (**10**).

A solution of 10.75 g (0.05 mole) of 4-bromophenylacetic acid (**9**), 9.0 ml (0.10 mole) of methyl acrylate, 0.52 g (0.002 mole) of triphenylphosphine and 0.22 g (0.001 mole) of palladium acetate in 21.8 ml (0.125 mole) of diisopropylethylamine was stirred at 100° under nitrogen for 3 days. After cooling, the mixture was poured in 250 ml 1 *N* hydrochloric acid and extracted three times with ethyl acetate. The combined organic

phases were washed with 1 *N* hydrochloric acid, dried and evaporated. The residue was crystallized from acetic acid to give 8.80 g (80%) of **10**, as a white solid, mp 118-120° dec; ir (potassium bromide): ν 1725 (acid C=O), 1695 (ester C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ (ppm) 3.69 (s, 2 H, CH_2), 3.82 (s, 3 H, CH_3), 6.43 (d, J = 16.0 Hz, 1 H, CHCOO), 7.32 (d, J = 8.0 Hz, 2 H, phenyl H-2,6), 7.51 (d, J = 8.0 Hz, 2 H, phenyl H-3,5), 7.69 (d, J = 16.0 Hz, 1 H, phenyl CH=).

Anal. Calcd. for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 65.38; H, 5.38.

Methyl 4-[2-(3-Benzyloxyphenyl)-2-hydroxyethylaminocarbonylmethyl]cinnamate (**12**).

A solution of 2.20 g (0.01 mole) of **10** and 1.46 ml (0.02 mole) of thionyl chloride in 20 ml of benzene were heated at reflux for 1.5 hours. After cooling the solution was evaporated. The liquid residue was dissolved in benzene and evaporated twice to give 2.40 g (100%) of (*E*)-4-(2-methoxycarbonylvinyl)phenylacetyl chloride, as an orange solid which was used in the subsequent reaction without any further purification.

To a solution of 2.43 g (0.01 mole) of **11** [12] in 11.0 ml of 1 *N* (0.011 mole) sodium hydroxide and 20 ml of dioxane, a solution of 2.40 g of (*E*)-4-(2-methoxycarbonylvinyl)phenylacetyl chloride in 15 ml of diethyl ether and 3 ml of dioxane was added dropwise. After 1.5 hours the mixture was filtered; the solid was washed with water and dried to give 3.05 g of crude **12**. Extraction of the mother liquor with ethyl acetate gave, after evaporation of the solvent, 0.95 g of crude **12**. Grinding of the two crops with diethyl ether afforded 3.56 g (80%) of **12**, as a white solid, mp 63-68°; ^1H nmr (DMSO-d_6): δ (ppm) 3.05-3.18 (m, 1 H, C*H*HN), 3.18-3.20 (m, 1 H, CH*H*N), 3.43 (s, 2 H, CH_2CO), 3.70 (s, 3 H, CH_3), 4.50-4.60 (m, 1 H, C*H*OH), 5.05 (s, 2 H, OCH_2), 5.48 (d, J = 4.0 Hz, 1 H, OH), 6.57 (d, J = 15.9 Hz, 1 H, CHCOO), 6.80-6.90 (m, 2 H, phenoxy H-4,6), 6.95 (d, J = 1.9 Hz, 1 H, phenoxy H-2), 7.15-7.50 (m, 8 H), 7.58 (d, J = 8.0 Hz, 2 H, C=C phenyl H-2,6), 7.61 (d, J = 15.9 Hz, 1 H, phenyl CH=), 8.12 (t, J = 7.5 Hz, 1 H, NH).

Anal. Calcd. for $C_{27}H_{27}NO_5$: C, 72.79; H, 6.11; N, 3.14. Found: C, 72.50; H, 6.15; N, 3.11.

Methyl 4-[(6-Benzyloxy-1-isoquinolinyl)methyl]cinnamate (**2d**).

To a stirred and boiling solution of 2.67 g (0.006 mole) of **12** in 50 ml of acetonitrile was added dropwise 5.60 ml (0.060 mole) of phosphorus oxychloride. After 1.5 hours at reflux, the solution was cooled and aqueous 5% sodium hydrogen carbonate was added carefully until *p*H 8.0 was reached. The mixture was extracted with ethyl acetate. The organic phase was dried and the solvent evaporated. The residue was purified on a silica gel column (4 x 20 cm). Gradient elution with methylene chloride containing increasing amounts of ethyl acetate (15 to 50%) afforded 2.09 g (85%) of **2d**, as a white solid.

A sample was dissolved in boiling acetone and the solution was added with the stoichiometric amount of oxalic acid to give **2d** as the oxalate sesquihydrate, white solid, mp 150-155°; ir (potassium bromide): ν 1710 (C=O) cm^{-1}; ms: m/z 409 (M^+), 408, 318; ^1H nmr (DMSO-d_6): δ (ppm) 3.69 (s, 3 H, CH_3), 4.61 (s, 2 H, CH_2 1-isoquinolinyl), 5.25 (s, 2 H, phenyl CH_2O), 6.54 (d, J = 16.0, 1 H, CHCO), 7.30-7.64 (m, 13 H), 8.25 (d, J = 9.2 Hz, 1 H, isoquinoline H-8), 8.35 (d, J = 5.4 Hz, 1 H, isoquinoline H-3).

Anal. Calcd. for $C_{29}H_{25}NO_7 \cdot 1.5\ H_2O$: C, 66.14; H, 5.35; N, 2.66; H_2O, 5.13. Found: C, 65.99; H, 5.17; N, 2.66; H_2O, 5.00.

Methyl 4-[(6-Hydroxy-1-isoquinolinyl)methyl]cinnamate (**2a**).

Method B.

A solution of 1.84 g of **2d** in 35 ml of trifluoroacetic acid was heated at 50° for 25 hours. The solution was cooled and evaporated. The residue was taken up with aqueous 5% sodium hydrogen carbonate and extracted with ethyl acetate. The organic phase was washed with water, dried and evaporated. The residue was purified on a silica gel column (3 x 15 cm). Elution with methylene chloride:ethyl acetate (70:30) afforded 1.19 g (83%) of **2a**, as a white solid, mp 192-195°.

4-(4-Methoxycarbonylmethylphenyl)-2(5*H*)-furanone (**14**).

A mixture of 18.13 g (0.080 mole) of **13** [13] and 36.30 g of potassium *P,P*-dimethylphosphonoacetate in 420 ml of acetonitrile was refluxed with stirring for 1 hour. After cooling, the mixture was poured into aqueous 20% sodium dihydrogen phosphate and extracted with ethyl acetate. The organic phase was dried and evaporated to dryness. The residue was dissolved in dry acetonitrile and the solution, under nitrogen, was added with 13.70 ml (0.080 mole) of diisopropylethylamine and 4.07 g (0.096 mole) of lithium chloride. After stirring at room temperature for 2 hours, the mixture was poured into 400 ml of 1 *N* hydrochloric acid and extracted with ethyl acetate. The organic phase was dried and evaporated. The residue was purified on a silica gel column (8 x 30 cm). Elution with methylene chloride:ethyl acetate (80:20) afforded 13.05 g (70%) of **14**, as a white solid, mp 120-123° (lit mp 122° [13]); ^1H nmr (deuteriochloroform): δ (ppm) 3.69 (s, 2 H, CH_2COOCH_3), 3.72 (s, 3 H, CH_3), 5.22 (d, J = 4.1 Hz, 2 H, $=CCH_2O$), 6.38 (t, J = 4.1 Hz, 1 H, =CH), 7.40 (d, J = 8.0 Hz, 2 H, phenyl H-3,5), 7.49 (d, J = 8.0 Hz, 2 H, phenyl H-2,6).

4-{4-[2-(3-Benzyloxyphenyl)-2-hydroxyethylaminocarbonylmethyl]phenyl}-2(5*H*)-furanone (**16**).

To a stirred suspension, under nitrogen, of 3.27 g (0.015 mole) of **15** [13] in 60 ml of dry *N,N*-dimethylformamide at -20° was added 2.43 g (0.015 mole) of carbonyldiimidazole. After two hours, the resulting solution was added with 3.65 g (0.015 mole) of **11** [12]. After 1.5 hours at -20° the solution was allowed to warm to room temperature. The solution was poured into 100 ml of 0.5 *N* hydrochloric acid and extracted with ethyl acetate. The organic phase was dried and evaporated. The residue was purified on a silica gel column (8 x 30 cm). Gradient elution with methylene chloride containing increasing amounts of methanol (5 to 10%) afforded 4.12 g (62%) of **16**, as a white solid, mp 90-93°; ^1H nmr (DMSO-d_6): δ (ppm) 3.07-3.19 (m, 1 H, C*H*HN), 3.19-3.30 (m, 1 H, CH*H*N), 3.43 (s, 2 H, CH_2CO), 4.50-4.60 (m, 1 H, CHO), 5.05 (s, 2 H, CH_2O), 5.48 (d, J = 4.0 Hz, 1 H, OH), 5.32 (d, J = 1.8 Hz, 2H, $=CCH_2O$) 6.65 (t, = 1.8 Hz, 1H, =CH), 6.82-6.92 (m, 2 H, phenoxy H-4,6), 6.95 (d, J = 3.0 Hz, 1 H, phenoxy H-2), 7.15-7.50 (m, 8 H), 7.59

(d, J = 8.0 Hz, 2 H, C=C phenyl H-2,6), 8.12 (m, 1 H, NH).

Anal. Calcd. for $C_{27}H_{25}NO_5$: C, 73.12; H, 5.68; N, 3.16. Found: C, 72.90; H, 5.69; N, 2.99.

4-{4-[(6-Benzyloxy-1-isoquinolinyl)methyl]phenyl}-2(5*H*)-furanone (**2e**).

To a stirred and boiling solution of 4.26 g (0.096 mole) of **16** in 130 ml of acetonitrile was added dropwise 9.60 ml (0.096 mole) of phosphorus oxychloride. After 1.5 hours at reflux, the solution was cooled and aqueous 5% sodium hydrogen carbonate was added carefully until *p*H 8.0 was reached. The mixture was extracted with ethyl acetate:methanol (90:10). The organic phase was dried and the solvent was evaporated. The residue was ground with diethyl ether to give 3.32 g (85%) of **2e**, as a white solid.

A sample was dissolved in boiling acetone and the solution was added with the stoichiometric amount of oxalic acid to give **2e** as the oxalate monohydrate, white solid, mp 120-123°; ir (potassium bromide): ν 1740 (C=O) cm^{-1}; ms: m/z 407 (M^+), 406, 316; ^1H nmr (DMSO-d_6): δ (ppm) 4.64 (s, 2 H, CH_2 1-isoquinolinyl), 5.25 (s, 2 H, phenyl CH_2O), 5.31 (d, J = 1.7 Hz, 2 H, CH_2OOC), 6.62 (t, J = 1.7 Hz, 1 H, CHCO), 7.30-7.64 (m, 12 H), 8.24 (d, J = 9.4 Hz, 1 H, isoquinoline H-8), 8.35 (d, J = 5.7 Hz, 1 H, isoquinoline H-3).

Anal. Calcd. for $C_{29}H_{23}NO_7 \cdot 1\ H_2O$: C, 67.56; H, 4.89; N, 2.71; H_2O, 3.50. Found: C, 67.97; H, 4.69; N, 2.79; H_2O, 3.30.

4-{4-[(6-Hydroxy-1-isoquinolinyl)methyl]phenyl}-2(5*H*)-furanone (**2c**).

Method B.

A solution of 4.48 g (0.011 mole) of **2e** in 65 ml of trifluoroacetic acid was heated at 60° for 18 hours. The solution was cooled and evaporated. The residue was ground with aqueous 5% sodium hydrogen carbonate, filtered, washed with water and dried under vacuum. The solid was ground with ethyl acetate:methanol (90:10) and filtered to give 3.14 g (90%) of **2c**, as an off-white solid.

A sample was dissolved in methanol and tetrahydrofuran and the solution was added with the stoichiometric amount of oxalic acid. After addition of ethyl acetate, **2c** was obtained as the oxalate hemihydrate, white solid, mp (108) 221-222°; ir (potassium bromide): ν 1740 (C=O) cm^{-1}; ms: m/z 317 (M^+), 316, 257, 233; ^1H nmr (DMSO-d_6): δ (ppm) 4.61 (s, 2 H, CH_2 phenyl), 5.31 (d, J = 1.6 Hz, 2 H, CH_2O), 6.62 (d, J = 1.6 Hz, 1 H, CHCO), 7.12 (d, J = 2.3 Hz, 1 H, isoquinoline H-5), 7.15 (dd, J = 2.3, 9.1 Hz, 1 H, isoquinoline H-7), 7.41 (d, J = 8.2 Hz, 2 H, phenyl H-3,5), 7.54 (d, J = 5.8 Hz, 1 H, isoquinoline H-4), 7.59 (d, J = 8.2 Hz, 2 H, phenyl H-2,6), 8.20 (d, J = 9.1 Hz, 1 H, isoquinoline H-8), 8.25 (d, J = 5.8 Hz, 1 H, isoquinoline H-3); ^{13}C nmr (DMSO-d_6): δ (ppm) 39.9 (t), 71.0 (t), 108.1 (d), 111.8 (d), 119.0 (d), 120.4 (d), 121.0 (s), 127.1 (d), 127.7 (s), 128.2 (d), 129.2 (d), 138.7 (s), 140.3 (d), 143.1 (s), 158.2 (s), 159.4 (s), 161.6 (s), 164.7 (s), 173.8 (s).

Anal. Calcd. for $C_{22}H_{17}NO_7 \cdot 0.5\ H_2O$: C, 63.45; H, 4.35; N, 3.36; H_2O, 2.16. Found: C, 63.62; H, 4.23; N, 3.31; H_2O, 2.10.

3-{4-[(6-Hydroxy-1-isoquinolinyl)methyl]phenyl}furan (**2g**).

A solution of 475 mg (1.5 mmoles) of **2c** dissolved in 40 ml of dry tetrahydrofuran was cooled to -78°. Six ml of a 1.0 *M* solution of DIBAH in hexane were added dropwise. After 3 hours at -78° the reaction was allowed to warm to -20° and 10% aqueous sulfuric acid was added until *p*H 5 was reached. The mixture was stirred for 30 minutes at room temperature and neutralized with 5% aqueous sodium hydrogencarbonate. The mixture was extracted five times with ethyl acetate. The organic phase was dried and evaporated. The residue was purified on a silica gel column (3 x 15 cm). Gradient elution with *n*-hexane containing increasing amounts of ethyl acetate (60 to 90%) afforded 240 mg (53%) of **2g**, as a white solid.

A sample was dissolved in a mixture of ethyl acetate and tetrahydrofuran and the solution was added with the stoichiometric amount of oxalic acid to give **2g** as the oxalate hemihydrate, white solid, mp 200-203°; ir (potassium bromide): ν 1720 (C=O) cm^{-1}; ms: m/z 301 (M^+), 300, 270, 136; ^1H nmr (DMSO-d_6): δ (ppm) 4.56 (s, 2 H, CH_2), 6.87 (bs, 1 H, furan H-4), 7.15 (d, J = 2.1 Hz, 1 H, isoquinoline H-5), 7.19 (dd, J = 2.1, 9.1 Hz, 1 H, isoquinoline H-7), 7.29 (d, J = 8.0 Hz, 2 H, phenyl H-3,5), 7.48 (d, J = 8.0 Hz, 2 H, phenyl H-2,6), 7.57 (d, J = 5.9 Hz, 1 H, isoquinoline H-4), 7.69 (bs, 1 H, furan H-5), 8.07 (bs, 1 H, furan H-2), 8.24 (d, J = 9.1 Hz, 1 H, isoquinoline H-8), 8.28 (d, J = 5.9 Hz, 1 H, isoquinoline H-3); ^{13}C nmr (DMSO-d_6): δ (ppm) 39.8 (t), 108.0 (d), 108.6 (d), 118.9 (d), 120.3 (d), 121.0 (s), 125.5 (s), 125.6 (d), 128.4 (d), 128.9 (d), 129.9 (s), 137.9 (d), 138.7 (s), 139.0 (s), 140.3 (d), 144.1 (d), 158.9 (s), 159.4 (s), 161.6 (s).

Anal. Calcd. for $C_{22}H_{17}NO_6 \cdot 0.5\ H_2O$: C, 65.99; H, 4.53; N, 3.50; H_2O, 2.25. Found: C, 65.98; H, 4.40; N, 3.43; H_2O, 2.30.

3-{4-[(6β-(Tetraacetylglucopyranosyloxy-1-isoquinolinyl)-methyl]phenyl}furan (**2i**).

To a solution of 150 mg (0.5 mmole) of **2g** in 5 ml of pyridine were added 640 mg (1.55 mmoles) of freshly crystallized acetobromo-α-D-glucose and 390 mg (1.5 mmoles) of silver carbonate. The mixture was stirred in the dark for 24 hours and then filtered thoroughly washing the insoluble material with toluene. The filtrate was evaporated and the residue was purified on a silica gel column (4 x 15 cm). Elution with *n*-hexane:ethyl acetate (20:80) afforded 135 mg (43%) of **2i**, as a waxy white solid; ^1H nmr (deuteriochloroform): δ (ppm) 2.03 (s, 12 H, CH_3CO), 3.90-4.00 (m, 1 H, glucose H-5), 4.15-4.30 (m, 2 H, glucose H-6), 4.62 (s, 2 H, phenyl CH_2), 5.15-5.30 (m, 4 H, glucose H-1,2,3,4), 6.62 (d, J = 1.7 Hz, 1 H, furan H-4), 7.15-7.30 (m, 4 H, isoquinoline H-7,5 and phenyl H-3,5), 7.36 (d, J = 8.2 Hz, 2 H, phenyl H-2,6), 7.42 (t, J = 1.7 Hz, 1 H, furan H-5), 7.45 (d, J = 5.8 Hz, 1 H, isoquinoline H-4), 7.65 (d, J = 1.7 Hz, 1 H, furan H-2), 8.19 (d, J = 9.2 Hz, 1 H, isoquinoline H-8), 8.46 (d, J = 5.8 Hz, 1 H, isoquinoline H-3).

Anal. Calcd. for $C_{34}H_{33}NO_{11}$: C, 64.65; H, 5.27; N, 2.22. Found: C, 64.32; H, 5.06; N, 2.13.

3-{4-[(6β-(Glucopyranosyloxy-1-isoquinolinyl)methyl]-phenyl}furan (**2j**).

To a solution of 126 mg (0.2 mmole) of **2i** in 3 ml of methanol, cooled at 0°, was added 1.6 ml of 0.5 *M* (0.8 mmole) methanolic sodium hydroxide. After 30 minutes at 0°, the solution was neutralized with 20% aqueous acetic acid. The solution was evaporated. The residue was crystallized from ethanol to give 70 mg (75%) of **2j** as a white solid, mp 160-165° dec; ir

(potassium bromide): ν 1740 (C=O) cm^{-1}; ms: m/z 300, 260, 219, 73, 60; ^1H nmr (DMSO-d_6:methanol-d_4 1:1): δ (ppm) 3.15-3.70 (m, 6 H, glucose), 4.57 (s, 2 H, phenyl CH_2), 5.07 (m, 1 H, glucose H-1), 6.86 (bs, 1 H, furan H-4), 7.25-7.35 (m, 3 H, isoquinoline H-5 and phenyl H-3,5), 7.45-7.50 (m, 3 H, isoquinoline H-7 and phenyl H-2,6), 7.57 (d, J = 5.7 Hz, 1 H, isoquinoline H-4), 7.69 (bs, 1 H, furan H-5), 8.07 (bs, 1 H, furan H-2), 8.25 (d, J = 9.2 Hz, 1 H, isoquinoline H-8), 8.35 (d, J = 5.7 Hz, 1 H, isoquinoline-H-3).

Anal. Calcd. for $C_{26}H_{25}NO_7$: C, 67.38; H, 5.44; N, 3.02. Found: C, 67.00; H, 5.55; N, 2.91.

Methyl 3-{4-[(6-Hydroxy-1-isoquinolinyl)methyl]phenyl}propionate (**2q**).

A suspension of 207 mg (0.65 mmole) of **2a** and 1.0 g of wet Raney Nickel in 15 ml of dioxane was hydrogenated at room temperature and atmospheric pressure under stirring. After 4 hours the suspension was filtered and the resulting solution was evaporated. The residue was purified on a silica gel column (2 x 15 cm). Elution with methylene chloride:ethyl acetate (60:40) afforded a crude product which after crystallization from ethyl acetate gave 110 mg (53%) of **2q**, as a white solid, mp 143-144°; ir (potassium bromide): ν 1740 (C=O) cm^{-1}; ms: m/z 321 (M^+), 320, 290, 260, 246, 233; ^1H nmr (DMSO-d_6): δ (ppm) 2.55 (t, J = 7.7 Hz, 2 H, CH_2COO), 2.75 (t, J = 7.7 Hz, 2 H, CH_2CH_2COO), 3.54 (s, 3 H, CH_3), 4.46 (s, 2 H, CH_2 1-isoquinolinyl), 7.05-7.20 (m, 6H), 7.45 (d, J = 5.8 Hz, 1 H, isoquinoline H-4), 8.15 (d, J = 9.1 Hz, 1 H, isoquinoline H-8), 8.23 (d, J = 5.8 Hz, 1 H, isoquinoline H-3), 10.30 (s, 1 H, OH); ^{13}C nmr (DMSO-d_6): δ (ppm) 29.8 (t), 34.8 (t), 40.4 (t), 51.3 (q), 107.8 (d), 118.4 (d), 119.7 (d), 121.3 (s), 128.0 (d), 128.2 (d), 128.5 (d), 137.5 (s), 138.1 (s), 138.2 (s), 142.0 (d), 158.5 (s), 159.4 (s), 172.7 (s).

Anal. Calcd. for $C_{20}H_{19}NO_3$: C, 74.74; H, 5.96; N, 4.36. Found: C, 74.65; H, 5.93; N, 4.34.

General Procedure for the Alkylations of the 6-Hydroxyisoquinoline Derivatives. Synthesis of 4-{4-[(6-(2-(1-Pyrrolidinyl)ethoxy)-1-isoquinolinyl)methyl]phenyl}-2(5*H*)-furanone (**2f**).

A mixture of 150 mg (0.36 mmole) of **2c** and 200 mg (0.72 mmole) of silver carbonate in 4.0 ml of 1-(2-chloroethyl)pyrrolidine was stirred at 50° for 4 hours in the dark. After cooling the mixture was filtered through celite and the pad washed with toluene:methanol (90:10). The filtrate was evaporated and the residue was purified on a silica gel column (3 x 15 cm). Gradient elution with methylene chloride containing increasing amounts of methanol (5 to 10%) afforded 102 mg (68%) of **2f**.

One hundred mg of **2f** was dissolved in a mixture of ethanol and ethyl acetate and the solution was added with a stoichiometric amount of oxalic acid to give **2f** as the dioxalate sesquihydrate, white solid, mp 180-190°; ms: m/z 414 (M^+); ^1H nmr (deuterium oxide): δ (ppm) 1.95-2.30 (m, 4 H, pyrrolidine H-3), 3.20-3.33 (m, 2 H, pyrrolidine H-2), 3.72-3.82 (m, 4 H, NCH_2CH_2O and pyrrolidine H-2), 4.62 (t, J = 4.9 Hz, 2 H, OCH_2CH_2N), 4.95 (s, 2 H, phenyl CH_2), 5.32 (s, 2 H, CH_2OOC), 6.44 (s, 1 H, CHCO), 7.40 (d, J = 8.0 Hz, 2 H, phenyl H-3,5), 7.55-7.65 (m, 4 H, phenyl H-2,6 and isoquinoline H-5,7), 8.15 (d, J = 6.0 Hz, 1 H, isoquinoline H-4), 8.29 (d, J = 6.0 Hz, 1 H, isoquinoline H-3), 8.48 (d, J = 9.2 Hz, 1 H, isoquinoline H-8); ^{13}C nmr (deuterium oxide): δ (ppm) 25.5 (t), 39.5 (t), 56.2 (t), 57.4 (t), 66.7 (t), 75.4 (t), 110.4 (d), 114.9 (d), 124.9 (s), 126.2 (d), 126.5 (d), 130.6 (d), 131.5 (s), 132.4 (d), 132.9 (d), 133.6 (d), 142.0 (s), 144.9 (s), 159.0 (s), 166.1 (s), 168.0 (s), 169.0 (s), 180.6 (s).

Anal. Calcd. for $C_{30}H_{30}N_2O_{11}$•1.5 H_2O: C, 57.96; H, 5.35; N, 4.51; H_2O, 4.35. Found: C, 57.80; H, 5.38; N, 4.50; H_2O, 4.19.

3-{4-[(6-(2-(1-Pyrrolidinyl)ethoxy)-1-isoquinolinyl)methyl]phenyl}furan (**2h**).

This compound was analogously prepared as the dioxalate hydrate (from ethyl acetate), white solid, mp 169-172°; ms: m/z 398 (M^+), 283, 127; ^1H nmr (DMSO-d_6): δ (ppm) 1.85-2.00 (m, 4 H, pyrrolidine H-3), 3.30-3.35 (m, 4 H, pyrrolidine H-2), 3.55-3.65 (m, 2 H, NCH_2CH_2O), 4.43 (m, 2 H, OCH_2), 4.58 (s, 2 H, phenyl CH_2), 6.88 (bs, 1 H, furan H-4), 7.25-7.35 (m, 3 H, isoquinoline H-7 and phenyl H-3,5), 7.41 (d, J = 2.1 Hz, 1 H, isoquinoline H-5), 7.46 (d, J = 8.0 Hz, 2 H, phenyl H-2,6), 7.62 (d, J = 5.8 Hz, 1 H, isoquinoline H-4), 7.70 (bs, 1 H, furan H-5), 8.09 (bs, 1 H, furan H-2), 8.27 (d, J = 9.0 Hz, 1 H, isoquinoline H-8), 8.39 (d, J = 5.8 Hz, 1 H, isoquinoline H-3).

Anal. Calcd. for $C_{28}H_{30}N_2O_{11}$•H_2O: C, 60.39; H, 5.40; N, 4.70, H_2O, 3.02. Found: C, 60.04; H, 5.38; N, 4.56; H_2O, 2.95.

Methyl 4-{[6-(2-Dimethylaminoethoxy)-1-isoquinolinyl]methyl}cinnamate (**2k**).

This compound was analogously prepared as the dioxalate hydrate (from ethyl acetate), white solid, mp (110) 177-180°; ms: m/z 390 (M^+), 359, 301, 240, 114; ^1H nmr (DMSO-d_6): δ (ppm) 2.84 (s, 6 H, $N(CH_3)_2$), 3.54 (m, 2 H, NCH_2), 3.69 (s, 3 H, OCH_3), 4.46 (m, 2 H, OCH_2), 4.60 (s, 2 H, phenyl CH_2), 6.54 (d, J = 16.0 Hz, 1 H, CHCOO), 7.27 (d, J = 9.4 Hz, 1 H, isoquinoline H-7), 7.30 (d, J = 8.0 Hz, 2 H, phenyl H-3,5), 7.41 (s, 1 H, isoquinoline H-5), 7.57 (d, J = 16.0 Hz, 1 H, phenyl CH=), 7.59 (d, J = 8.0 Hz, 2 H, phenyl H-2,6), 7.62 (d, J = 5.7 Hz, 1 H, isoquinoline H-4), 8.24 (d, J = 9.4 Hz, 1 H, isoquinoline H-8), 8.37 (d, J = 5.7 Hz, 1 H, isoquinoline H-3).

Anal. Calcd. for $C_{28}H_{30}N_2O_{11}$•H_2O: C, 57.13; H, 5.48; N, 4.76, H_2O, 3.06. Found: C, 57.01; H, 5.38; N, 4.56; H_2O, 2.95.

Methyl 4-{[6-(3-Dimethylaminopropoxy)-1-isoquinolinyl)]methyl}cinnamate (**2l**).

This compound was analogously prepared as the dioxalate (from methanol), white solid, mp 168-172°; ms: m/z 404 (M^+), 373, 257, 229; ^1H nmr (DMSO-d_6): δ (ppm) 2.15 (m, 2 H, $CH_2CH_2CH_2$), 2.80 (s, 6 H, $N(CH_3)_2$), 3.22 (t, J = 7.8 Hz, 2 H, NCH_2), 3.69 (s, 3 H, OCH_3), 4.19 (t, J = 5.9 Hz, 2 H, OCH_2), 4.60 (s, 2 H, phenyl CH_2), 6.54 (d, J = 16.0 Hz, 1 H, CHCOO), 7.23 (dd, J = 9.3, 2.5 Hz, 1 H, isoquinoline H-7), 7.31 (d, J = 8.0 Hz, 2 H, phenyl H-3,5), 7.34 (d, J = 2.5 Hz, 1 H, isoquinoline H-5), 7.56 (d, J = 8.0 Hz, 2 H, phenyl H-2,6), 7.58 (d, J = 16.0 Hz, 1 H, phenyl CH=), 7.61 (d, J = 5.7 Hz, 1 H, isoquinoline H-4), 8.22 (d, J = 9.3 Hz, 1 H, isoquinoline H-8), 8.35 (d, J = 5.7 Hz, 1 H, isoquinoline H-3).

Anal. Calcd. for $C_{29}H_{32}N_2O_{11}$: C, 59.58; H, 5.52; N, 4.79. Found: C, 59.87; H, 5.66; N, 4.73.

Methyl 4-{[6-(2-(1-Pyrrolidinyl)ethoxy)-1-isoquinolinyl]-methyl}cinnamate (**2m**).

This compound was analogously prepared as the sesquioxalate (from methanol), white solid, mp 123-130°; ms: m/z 416 (M^+), 385, 330, 301, 241, 228; ^1H nmr (DMSO-d_6): δ (ppm) 1.93 (m, 4 H, pyrrolidine H-3), 3.33 (m, 4 H, pyrrolidine H-2), 3.60 (m, 2 H, NCH_2CH_2O), 3.69 (s, 3 H, OCH_3), 4.44 (m, 2 H, OCH_2), 4.60 (s, 2 H, phenyl CH_2), 6.54 (d, J = 16.1 Hz, 1 H, CHCOO), 7.27 (dd, J = 9.2, 2.3 Hz, 1 H, isoquinoline H-7), 7.31 (d, J = 8.0 Hz, 2 H, phenyl H-3,5), 7.41 (d, J = 2.3 Hz, 1 H, isoquinoline H-5), 7.56 (d, J = 8.0 Hz, 2 H, phenyl H-2,6), 7.58 (d, J = 16.1 Hz, 1 H, phenyl CH=), 7.62 (d, J = 5.8 Hz, 1 H, isoquinoline H-4), 8.24 (d, J = 9.2 Hz, 1 H, isoquinoline H-8), 8.37 (d, J = 5.8 Hz, 1 H, isoquinoline H-3).

Anal. Calcd. for $C_{29}H_{31}N_2O_9$: C, 63.15; H, 5.67; N, 5.08. Found: C, 62.79; H, 5.79; N, 5.00.

Methyl 4-{[6-(3-(1-Pyrrolidinyl)propoxy)-1-isoquinolinyl]-methyl}cinnamate (**2n**).

This compound was analogously prepared as the dioxalate dihydrate (from methanol), white solid, mp 89-91°; ms: m/z 430 (M^+), 399, 318, 259, 230; ^1H nmr (DMSO-d_6): δ (ppm) 1.90 (m, 4 H, pyrrolidine H-3), 2.14 (m, 2 H, $CH_2CH_2CH_2$), 3.33 (m, 4 H, pyrrolidine H-2), 3.22 (m, 2 H, $NCH_2CH_2CH_2O$), 3.69 (s, 3 H, OCH_3), 4.19 (m, 2 H, OCH_2), 4.60 (s, 2 H, phenyl CH_2), 6.54 (d, J = 16.0 Hz, 1 H, CHCOO), 7.22 (dd, J = 9.3, 2.5 Hz, 1 H, isoquinoline H-7), 7.31 (d, J = 8.0 Hz, 2 H, phenyl H-3,5), 7.33 (d, J = 2.5 Hz, 1 H, isoquinoline H-5), 7.57 (d, J = 8.0 Hz, 2 H, phenyl H-2,6), 7.60 (d, J = 16.0 Hz, 1 H, phenyl CH=), 7.62 (d, J = 5.7 Hz, 1 H, isoquinoline H-4), 8.22 (d, J = 9.3 Hz, 1 H, isoquinoline H-8), 8.37 (d, J = 5.7 Hz, 1 H, isoquinoline H-3).

Anal. Calcd. for $C_{31}H_{34}N_2O_{11}$•2 H_2O: C, 57.57; H, 5.92; N, 4.33; H_2O, 5.60. Found: C, 57.40; H, 5.85; N, 4.18; H_2O, 5.85.

Methyl 3-{4-[6-(2-(1-Pyrrolidinyl)ethoxy)-1-isoquinolinyl)-methyl]phenyl}propionate (**2r**).

This compound was analogously prepared as the dioxalate (from methanol/acetone), white solid, mp 120-126°; ir (potassium bromide): ν 1723 (C=O) cm^{-1}; ms: m/z 418 (M^+), 387, 303, 260, 230; ^1H nmr (DMSO-d_6): δ (ppm) 1.93 (m, 4 H, pyrrolidine H-3), 2.54 (t, J = 7.6 Hz, 2 H, CH_2COO), 2.75 (t, J = 7.6 Hz, 2 H, CH_2CH_2COO), 3.0-4.0 (b, 4 H, pyrrolidine H-2), 3.53 (s, 3 H, CH_3), 3.63 (m, 2 H, NCH_2CH_2O), 4.44 (m, 2 H, CH_2O), 4.52 (s, 2 H, CH_2 1-isoquinolinyl), 7.07 (m, J = 8.1 Hz, 2 H, phenyl H-2,6), 7.16 (m, J = 8.1 Hz, 2 H, phenyl H-3,5), 7.28 (dd, J = 9.1, 2.4 Hz, 1 H, isoquinoline H-7), 7.40 (d, J = 2.4 Hz, 1 H, isoquinoline H-5), 7.61 (d, J = 5.7 Hz, 1 H, isoquinoline H-4), 8.25 (d, J = 9.1 Hz, 1 H, isoquinoline H-8), 8.36 (d, J = 5.7 Hz, 1 H, isoquinoline H-3).

Anal. Calcd. for $C_{30}H_{34}N_2O_{11}$: C, 60.19; H, 5.73; N, 4.68. Found: C, 60.13; H, 5.78; N, 4.68.

Methyl 4-[(6β-Tetraacetylglucopyranosyloxy-1-isoquinolinyl)-methyl]cinnamate (**2o**).

To a solution of 0.32 g (1.0 mmole) of **2a** in 5 ml of toluene and 2 ml of pyridine were added 1.34 g (3.1 mmoles) of freshly crystallized α-bromoacetoglucose and 0.69 g (2.5 mmoles) of silver carbonate. The mixture was stirred in the dark for 24 hours and then filtered thoroughly washing the insoluble material with toluene. The filtrate was evaporated and the residue was purified on a silica gel column (4 x 15 cm). Gradient elution with diethyl ether containing increasing amounts of ethyl acetate (10 to 20%) afforded 0.30 g (46%) of **2o**, as a waxy white solid; ^1H nmr (deuteriochloroform): δ (ppm) 2.03 (s, 12 H, CH_3CO), 3.78 (s, 3 H, OCH_3), 3.93-4.00 (m, 1 H, glucose H-5), 4.10-4.30 (m, 2 H, glucose H-6), 4.62 (s, 2 H, phenyl CH_2), 5.10-5.35 (m, 4 H, glucose H-1,2,3,4), 6.47 (d, J = 16.0 Hz, 1 H, CHCOO), 7.20 (dd, J = 9.2, 2.4 Hz, 1 H, isoquinoline H-7), 7.25-7.30 (m, 3 H, phenyl H-3,5 and isoquinoline H-5), 7.42 (d, J = 8.0 Hz, 2 H, phenyl H-2,6), 7.49 (d, J = 5.7 Hz, 1 H, isoquinoline H-4), 7.62 (d, J = 16.0 Hz, 1 H, phenyl CH=), 8.07 (d, J = 9.2 Hz, 1 H, isoquinoline H-8), 8.46 (d, J = 5.7 Hz, 1 H, isoquinoline H-3).

Anal. Calcd. for $C_{34}H_{35}NO_{12}$: C, 62.86; H, 5.43; N, 2.16. Found: C, 62.49; H, 5.27; N, 2.08.

Methyl 4-[(6β-Glucopyranosyloxy-1-isoquinolinyl)methyl]-cinnamate (**2p**).

To a solution of 195 mg (0.3 mmole) of **2o** in 3 ml of methanol, cooled at 0°, was added 2.4 ml of 0.5 *M* (1.2 mmoles) methanolic sodium hydroxide. After 30 minutes at 0°, the solution was neutralized with 20% aqueous acetic acid. The solution was evaporated. The residue was crystallized from ethanol to give 102 mg (70%) of **2p** as a white solid, mp 169-174°; ir (potassium bromide): ν 1710 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6:methanol-d_4 1:1): δ (ppm) 3.15-3.70 (m, 6 H, glucose), 3.69 (s, 3 H, CH_3), 4.60 (s, 2 H, phenyl CH_2), 5.07 (m, 1 H, glucose H-1), 6.54 (d, J = 16.1 Hz, 1 H, CHCOO), 7.29-7.33 (m, 3 H, isoquinoline H-7 and phenyl H-3,5), 7.45 (d, J = 2.3 Hz, 1 H, isoquinoline H-5), 7.54-7.60 (m, 4 H, isoquinoline H-4, phenyl CH= and phenyl H-2,6), 8.24 (d, J = 9.2 Hz, 1 H, isoquinoline H-8), 8.34 (d, J = 5.7 Hz, 1 H, isoquinoline H-3).

Anal. Calcd. for $C_{26}H_{27}NO_8$: C, 64.86; H, 5.65; N, 2.91. Found: C, 64.50; H, 5.45; N, 2.80.

4-{[6-(2-(1-Pyrrolidinyl)ethoxy)-1-isoquinolinyl]methyl}-cinnamamide (**2s**).

A solution of 517 mg (1.2 mmoles) of **2m** and 143 mg (2.64 mmoles) of sodium methoxide in 10 ml of 5 *M* (50 mmoles) methanolic ammonia was stirred at room temperature for 24 hours. The solution was evaporated. The residue was taken up with chloroform:ethanol (80:20) and washed with water. The organic phase was dried and evaporated. The residue was purified on a silica gel column (3 x 15 cm). Elution with chloroform:methanol:26% aqueous ammonia (89:10:1) afforded 190 mg (39%) of **2s**, as a white solid, mp 161-165°, hemihydrate; ir (potassium bromide): ν 1660 (C=O) cm^{-1}; ms: m/z 401 (M^+), 286, 264, 241, 218; ^1H nmr (DMSO-d_6): δ (ppm) 1.66 (m, 4 H, pyrrolidine H-3), 2.50 (m, 4 H, pyrrolidine H-2), 2.83 (t, J = 5.6 Hz, 2 H, CH_2CH_2O), 4.19 (t, J = 5.6 Hz, 2 H, CH_2O), 4.56 (s, 2 H, phenyl CH_2), 6.49 (d, J = 15.9 Hz, 1 H, =CHCO), 7.04 (bs, 1 H, isoquinoline H-5), 7.10-7.55 (m, 6 H), 7.58 (d, J = 5.8 Hz, 1 H, isoquinoline H-4), 8.18 (d, J = 9.2 Hz, 1 H, isoquino-

line H-8), 8.33 (d, J = 5.8 Hz, 1 H, isoquinoline H-3).

Anal. Calcd. for $C_{25}H_{27}N_3O_2 \cdot 0.5\ H_2O$: C, 73.14; H, 6.87; N, 10.24; H_2O, 2.19. Found: C, 73.04; H, 6.97; N, 10.04; H_2O, 2.01.

N,N-Dimethyl-4-{[6-(2-(1-pyrrolidinyl)ethoxy)-1-isoquinolinyl]-methyl}cinnamamide (**2t**).

A solution of 270 mg (0.63 mmole) of **2m** and 27 mg (0.50 mmole) of sodium methoxide in 10 ml of 10% (v/v) methanolic dimethylamine was stirred at room temperature for 3 days. The solution was evaporated. The residue was taken up with chloroform:ethanol (8:2) and washed with water. The organic phase was dried and evaporated. The residue was purified on a silica gel column (3 x 15 cm). Elution with chloroform:methanol:26% aqueous ammonia (89:10:1) afforded 135 mg (31%) of **2t**, as a white solid.

A sample was dissolved in acetone and the solution was added with the stoichiometric amount of oxalic acid to give **2t** as the dioxalate hemihydrate, white solid, mp 116-123°; ir (potassium bromide): ν 1633 (C=O) cm^{-1}; ms: m/z 429 (M^+), 399, 333, 300, 278, 241; ^1H nmr (DMSO-d_6): δ (ppm) 1.93 (m, 4 H, pyrrolidine H-3), 2.90 (s, 3 H, NCH_3), 3.11 (s, 3 H, NCH_3), 3.20-3.50 (m, 4 H, pyrrolidine H-2), 3.63 (m, 2 H, CH_2CH_2O), 4.45 (m, 2 H, CH_2O), 4.62 (s, 2 H, phenyl CH_2), 7.09 (d, J = 15.8 Hz, 1 H, =CHCO), 7.28-7.33 (m, 3 H, phenyl H-2,6 and isoquinoline H-7), 7.38 (d, J = 15.8 Hz, 1 H, phenyl CH=), 7.40 (bs, 1 H, isoquinoline H-5), 7.57 (d, J = 8.0 Hz, 2 H, phenyl H-3,5), 7.63 (d, J = 5.7 Hz, 1 H, isoquinoline H-4), 8.23 (d, J = 8.2 Hz, 1 H, isoquinoline H-8), 8.38 (d, J = 5.7 Hz, 1 H, isoquinoline H-3).

Anal. Calcd. for $C_{25}H_{27}N_3O_2 \cdot 0.5\ H_2O$: C, 73.14; H, 6.87; N, 10.24; H_2O, 2.19. Found: C, 73.04; H, 6.97; N, 10.04; H_2O, 2.01.

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