An Efficient Synthesis of the New Benzo[*c*]pyrido[2,3,4-*kl*]acridine Skeleton

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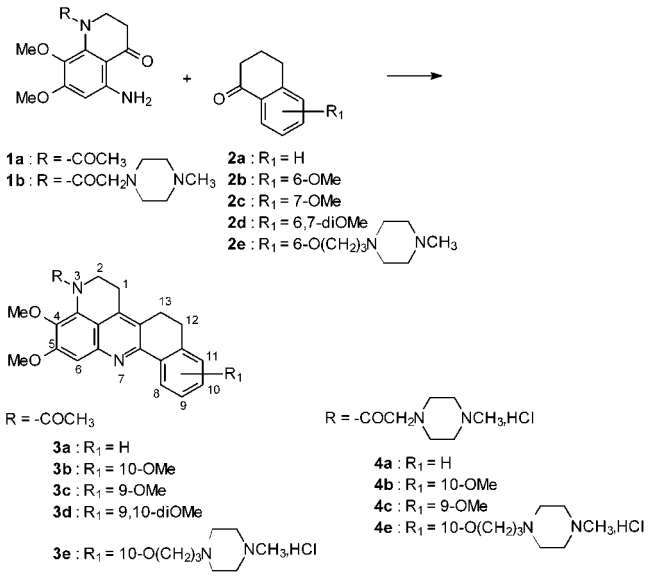
Abstract: A series of molecules of therapeutic interest, possessing the new skeleton of 1*H*-benzo[*c*]pyrido[2,3,4-*kl*]-acridine with acyl or aminoacyl and methoxy or aminoalkoxy substituents on the aromatic homocycles were synthesized by means of a Friedländer-type reaction. The requisite 5-aminodihydroquinoline-4-ones **1**, whose preparation is described, were reacted with the appropriate α-tetralones **2** using an acidic catalyst (PPTS) under azeotropic conditions. Optimized reaction time and yield depend on temperature, which must not be below 90 °C.

DNA topoisomerases I and II are nuclear enzymes able to break and religate the sugar−phosphate bonds of DNA and adjust the topological states of the DNA helix during cellular processes. Mammalian topoisomerase poisons and topoisomerase inhibitors have been recognized as effective cancer chemotherapeutics. They have recently received considerable attention,[1−7] particularly with regard to the biological activity of camptothecin, a specific inhibitor of topoisomerase I. This natural compound and other topoisomerase-interacting drugs exhibit common structural elements that have been considered as essential for their activity, particularly quinoline-based heterocyclic systems. Herein, we report the synthesis of the new fused pentacyclic skeleton named 2,3,12,13-tetrahydro-1*H*-benzo[*c*]pyrido[2,3,4-*kl*]acridine, containing quinoline, as a potential topoisomerase ligand.

One of the most generally used methods for preparing substituted quinolines is the Friedländer synthesis,[8−11] in which an aromatic *o*-aminoaldehyde or ketone is condensed with an aldehyde or ketone containing at least one methylene group α to the carbonyl. An extension of this reaction was envisaged to elaborate the 1*H*-benzo-[*c*]pyrido[2,3,4-*kl*]acridine skeleton, which was chosen from the structural analysis of natural topoisomerase inhibitors such as DHDMC[12] (or 5,6-dihydro-8-desmethylcoralyne), an isoquino[3,2-*a*]isoquinoline, and shermilamin,[13] a pyrido[4,3,2-*de*]quinoline. In this case, the prerequisite aminoketone is a 5-amino-7,8-dimethoxy-2,3-dihydro-1*H*-quinolin-4-one **1** that can be opposed to an α-tetralone **2** (Scheme 1).

Scheme 1



This paper describes the synthesis of the 5-amino-2,3-dihydro-1*H*-quinolin-4-ones **1a** and **1b** and their subsequent use in the Friedländer-type synthesis of the 2,3,12,13-tetrahydro-1*H*-benzo[*c*]pyrido[2,3,4-*kl*]acridines **3** and **4**.

The synthesis of **1a** (Scheme 2) began with the conversion of 2,3-dimethoxybenzoic acid into 2,3-dimethoxyaniline **6** (95% yield) via urethane **5**, prepared as described by White[14] using Yamada's modification[15] of the Curtius rearrangement[16] and hydrolyzed under basic conditions. The anilinopropionic acid **7** was obtained by a regioselective nucleophilic attack on carbon 3 of *β*-propiolactone[17,18] in acetonitrile. Cyclization into dihydroquinolinone **8** was completed with PPA before acetylation of the amino group to suppress the susceptibility of the amine to oxidative conditions during nitration (**10a**) and to allow for the spontaneous cyclodehydration of the

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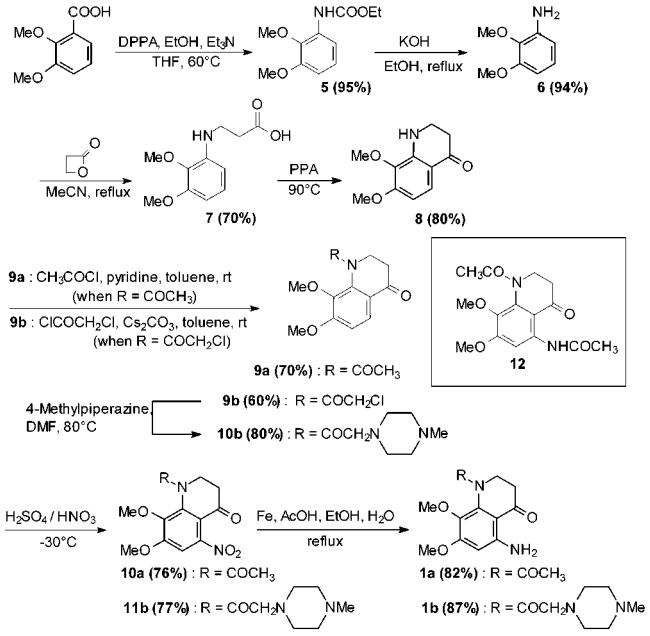
Scheme 2



condensation product during the Friedländer reaction.[17] The regioselectivity of nitration was ascertained by 2D ROESY NMR. Reduction to the corresponding amine **1a** was carried out with iron powder.[19,20] Aminoquinolinone **1b** was obtained using the same strategy (Scheme 2): amidification of **8** followed by nucleophilic substitution with 4-methylpiperazine provided dihydroquinolinone **10b**, whose nitration and subsequent reduction yielded dihydroquinolinone **1b**.

The cyclization reaction between **1a**,**b** and substituted tetralones **2a**−**e** was carried out in acid-catalyzed medium, excluding extreme conditions (absence of solvent, temperature ranging from 150 to 220 °C) and classical basic catalysis (KOH; NaOEt; Triton B; piperidine), which appeared unsuccessful here. However, using acetic acid as solvent and catalyst in the reaction of the enolizable ketone **2a** with **1a** led to acetylation of the 5-NH_2 of this latter compound (amide **12**) rather than to the Schiff base intermediate. The preparation of pentacyclic compounds **3a**−**d** was conveniently carried out using toluene as solvent and pyridinium *p*-toluenesulfonate (PPTS) with azeotropic distillation of water (method A). In the case of **3e**, a toluene/ethanol (2:1) mixture was used (method B) due to the insolubility of ketone **2e** in toluene; under these conditions, reaction took place in 5 days instead of 24 h due to the lower temperature of the ternary azeotrope (68 °C vs 84 °C). The reaction for **4a**−**c**,**e** (method C) was completed in 4 h by using butan-1-ol (azeotropic temperature: 93 °C).

These conditions were used to prepare compounds **3a**−**e** and proved that this method gave a significantly higher yield at a temperature about 90 °C and a lower reaction time than classically found (Table 1).

Experimental Section

General Methods. Melting points were determined with a capillary melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz respectively.

Table 1. Preparation of 3a−e and 4a−c,e under Acidic Catalysis

1	2	3 or 4	cond[a]	time (h)	yield (%)	mp (°C) (solvent)
a	**a**	**3a**	A	24	58	204 (water)
			C	4	67	
a	**b**	**3b**	A	24	62	210 (ethanol)
			C	5.5	81	
a	**c**	**3c**	A	24	65	210 (ethanol)
			C	3.5	79	
a	**d**	**3d**	A	24	54	246 (ethanol)
			C	5	85	
a	**e**	**3e**	B	120	60	214 (ethanol−ether)
			C	2	48	
b	**a**	**4a**	C	12	75	230−232 (methanol−ether)
b	**b**	**4b**	C	12	72	227 (methanol−ether)
b	**c**	**4c**	C	12	75	222−225 (methanol−ether)
b	**e**	**4e**	C	24	78	>250 (ethanol−ether)

[a] Method A: azeotropic distillation; solvent, toluene; catalyst, PPTS. Method B: azeotropic distillation; solvent, toluene/ethanol (2:1); catalyst, PPTS. Method C: azeotropic distillation; solvent, butan-1-ol; catalyst, PPTS.

Chemical shifts are reported in ppm downfield from TMS. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; p, pentet; m, multiplet; b, broad. Coupling constants are given in hertz. Elemental analyses were performed by the Service Central d'Analyse-Département Analyse Elémentaire, CNRS, F-69390 Vernaison. Dimethylformamide was distilled from CaH_2 and stored over 3 Å molecular sieves. Tetrahydrofuran was distilled over sodium benzophenone before use.

Materials. The preparation of *N*-(ethoxycarbonyl)-3,4-dimethoxyaniline[14] **5** and 2,3-dimethoxyaniline[14] **6** have been described previously.

3-(2,3-Dimethoxyphenylamino)propionic Acid (7). A solution of **6** (5.4 g, 35.3 mmol) in acetonitrile (10 mL) was heated to reflux, and *β*-propiolactone (2.21 mL, 35.3 mmol) was then added. The mixture was refluxed for 24 h. After concentration of the solution, the residue was dissolved in 10% aqueous potassium carbonate. The resulting brown solution was washed with ether. The aqueous fraction was acidified up to pH 4 (6 N HCl) and extracted several times with ethyl acetate. The organic layers were washed with saturated aqueous sodium chloride and dried over magnesium sulfate. After removal of the solvent, the crude product was recrystallized from cyclohexane to yield 3.78 g (70%) of **7** as a beige solid: mp 88 °C; IR (KBr) 3406, 1713, 1608, 1514, 1477, 1452 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.68 (t, J = 6.5, 2H), 3.49 (t, J = 6.4, 2H), 3.79 (s, 3H), 3.83 (s, 3H), 6.35 (d, J = 8.3, 2H), 6.55 (bs, 2H), 6.94 (t, J = 8.3, 1H). Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22. Found: C, 58.62; H, 6.66; N, 6.34.

7,8-Dimethoxy-2,3-dihydro-1*H*-quinolin-4-one (8). Compound **7** (5 g, 22.2 mmol) was added portionwise to stirred PPA (100 g) at 90 °C. After being stirred for 20 min, the dark brown mixture was poured into ice. The resulting red solution was extracted several times with ethyl acetate. The organic layers were washed with 10% aqueous potassium carbonate and saturated aqueous sodium chloride and then dried over magnesium sulfate. The concentrate was purified by chromatography (silica gel, 50% ethyl acetate−heptane) and recrystallized from cyclohexane to give 4 g (80%) of **8** as beige crystals: mp 92 °C; IR (KBr) 3376, 1667, 1608, 1519, 1484, 1459 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.67 (t, J = 6.9, 2H), 3.57 (t, J = 6.9, 2H), 3.83 (s, 3H), 3.90 (s, 3H), 4.93 (bs, 1H), 6.39 (d, J = 8.8, 1H), 7.64 (d, J = 9.0, 1H). Anal. Calcd for $C_{11}H_{13}NO_3$ (0.25 H_2O): C, 62.40; H, 6.43; N, 6.62. Found: C, 62.41; H, 6.32; N, 6.65.

1-Acetyl-7,8-dimethoxy-2,3-dihydro-1*H*-quinolin-4-one (9a). Acetyl chloride (3.6 mL, 49.7 mmol) was added dropwise to a solution of **8** (3.43 g, 16.5 mmol) in toluene (10 mL) and pyridine (4.33 mL, 53.8 mmol). After being stirred overnight at room temperature, the mixture was partitioned between ethyl acetate and water. The organic layer was washed with 1 N HCl, water, and saturated aqueous sodium chloride and was dried

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over magnesium sulfate. After removal of the solvent, the crude product was recrystallized from cyclohexane to yield 2.4 g (70%) of **9a** as a pale yellow solid: mp 107 °C; IR (KBr) 1687, 1663 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.14 (s, 3H), 2.83 (m, 2H), 3.41 (t, J = 11.1, 1H), 3.75 (s, 3H), 3.97 (s, 3H), 5.06 (d, J = 11.1, 1H), 6.90 (d, J = 8.8, 1H), 7.77 (d, J = 8.8, 1H). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.71; H, 6.05; N, 5.51.

1-(2-Chloroacetyl)-7,8-dimethoxy-2,3-dihydro-1*H*-quinolin-4-one (9b). Chloroacetyl chloride (14.8 mL, 185 mmol) was added dropwise to a suspension of **8** (6.04 g, 29 mmol) and cesium carbonate (16.63 g, 51 mmol) in toluene (60 mL). After being stirred overnight at room temperature, the mixture was diluted with ethyl acetate and washed with water, 1 N HCl, and saturated aqueous sodium chloride. The organic layer was dried over magnesium sulfate. Removal of the solvent gave an oily product, which precipitated in diisopropyl ether. After washing of the crude product with diisopropyl ether, recrystallization from toluene yielded 5 g (60%) of **9b** as a white solid: mp 166−168 °C; IR (KBr) 1686, 1661, 1590, 1496, 1460, 1440 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.76 (m, 2H), 3.49 (m, 1H), 3.75 (s, 3H), 3.98 (s, 3H), 4.22 (s, 1H), 4.24 (s, 1H), 5.04 (m, 1H), 6.92 (d, J = 8.9, 1H), 7.81 (d, J = 8.6, 1H). Anal. Calcd for $C_{13}H_{14}ClNO_4$: C, 55.04; H, 4.97; N, 4.94. Found: C, 55.04; H, 5.00; N, 4.85.

1-[2-(4-Methylpiperazin-1-yl)acetyl]-7,8-dimethoxy-2,3-dihydro-1*H*-quinolin-4-one (10b). 4-Methylpiperazine (8.5 mL, 76 mmol) was added to a solution of **9b** (9.80 g, 34.5 mmol) in dry DMF (50 mL), and the mixture was stirred overnight at 80 °C. The mixture was diluted with 1 N HCl and extracted several times with ethyl acetate. The aqueous layer was made basic using potassium carbonate and extracted several times with ethyl acetate. The organic layers were washed with saturated aqueous sodium chloride and dried over magnesium sulfate. Concentration yielded an oily product that precipitated in a mixture of ether−petroleum ether. Recrystallization from cyclohexane−diisopropyl ether gave 9.60 g (80%) of **10b** as white crystals: mp 156−157 °C; IR (KBr) 1668, 1667, 1592, 1496, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.18 (s, 3H), 2.18−2.70 (m, 10H), 3.31 (s, 1H), 3.33 (s, 1H), 3.50 (m, 1H), 3.73 (s, 3H), 3.94 (s, 3H), 4.92 (m, 1H), 6.87 (d, J = 9.0, 1H), 7.76 (d, J = 8.0, 1H). Anal. Calcd for $C_{18}H_{25}N_3O_4$ (0.5 H_2O): C, 60.66; H, 7.35; N, 11.79. Found: C, 60.87; H, 7.36; N, 11.76.

General Procedure for Nitration. Compound **9a** or **10b** (n mmol) was gradually added to a well-cooled (−30 °C) mixture of nitric acid (d = 1.41) (30.n mmol) and sulfuric acid (16.n mmol). After being warmed to −10 °C, the solution was poured into ice and diluted with ethyl acetate. The layers were separated, and the yellow organic layer was washed with 10% aqueous potassium carbonate, water, and saturated aqueous sodium chloride and dried over magnesium sulfate before removal of the solvent.

1-Acetyl-7,8-dimethoxy-5-nitro-2,3-dihydro-1*H*-quinolin-4-one (10a): yield 76%; yellow solid mp 203 °C (ethanol); IR (KBr) 1694, 1671, 1589, 1542, 1500, 1461, 1348 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.15 (s, 3H), 2.81 (m, 2H), 3.55 (bs, 1H), 3.84 (s, 3H), 4.00 (s, 3H), 4.96 (bs, 1H), 6.98 (s, 1H). Anal. Calcd for $C_{13}H_{14}N_2O_6$: C, 53.06; H, 4.80; N, 9.52. Found: C, 53.12; H, 4.75; N, 9.59.

7,8-Dimethoxy-1-[2-(4-methylpiperazin-1-yl)acetyl]-5-nitro-2,3-dihydro-1*H*-quinolin-4-one (11b). The crude oily product was precipitated in diisopropyl ether: yield 77%; yellow solid; mp 147−149 °C (toluene−diisopropyl ether); IR (KBr) 1693, 1668, 1592, 1537, 1498, 1375 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.24 (s, 3H), 2.20−2.60 (m, 8H), 2.77 (t, J = 6.3, 2H), 3.25−3.41 (m, 2H), 3.69 (bs, 1H), 3.82 (s, 3H), 3.98 (s, 3H), 4.81 (bs, 1H), 6.96 (s, 1H). Anal. Calcd for $C_{18}H_{24}N_4O_6$: C, 55.09; H, 6.16; N, 14.28. Found: C, 54.98; H, 5.91; N, 14.03.

General Procedure for Reduction. A mixture of **10a** or **11b** (n mmol), iron powder (8.n mmol) and 37% HCl (0.15.n mmol) in a mixture of acetic acid/ethanol/water (2:2:1) (20 mL) was refluxed for 15 min. The warmed solution was filtered through Celite and washed with water. The filtrate was extracted with chloroform, and the layers were separated. The dark green organic layer was washed with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride and dried over magnesium sulfate. Filtration and removal of the solvent gave the crude product, which was recrystallized from 2-propanol−ether (**1a**) or toluene (**1b**).

1-Acetyl-5-amino-7,8-dimethoxy-2,3-dihydro-1*H*-quinolin-4-one (1a): yield 82%; yellowish solid; mp 173 °C; IR (KBr) 3415, 3303, 1651, 1629, 1610, 1549, 1494, 1471, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.11 (s, 3H), 2.51 (dd, J = 18.1; 2.1, 1H), 2.81 (m, 1H), 3.26 (td, J = 13.1, 3.6, 1H), 3.62 (s, 3H), 3.88 (s, 3H), 4.99 (dd, J = 12.2, 5.0, 1H), 6.00 (s, 1H), 6.57 (bs, 2H). Anal. Calcd for $C_{13}H_{16}N_2O_4$ (0.5 H_2O): C, 57.13; H, 6.27; N, 10.25. Found: C, 57.16; H, 6.32; N, 10.11.

5-Amino-7,8-dimethoxy-1-[2-(4-methylpiperazin-1-yl)-acetyl]-2,3-dihydro-1*H*-quinolin-4-one (1b): yield 87%; beige solid; mp 198 °C; IR (KBr) 3385, 3383, 1671, 1623, 1547, 1494, 1455 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.17 (s, 3H), 2.30−2.75 (m, 10H), 3.15 (d, J = 15.6, 1H), 3.30 (bs, 1H), 3.39 (d, J = 15.6, 1H), 3.57 (s, 3H), 3.84 (s, 3H), 4.92 (m, 1H), 5.97 (s, 1H), 6.58 (bs, 2H). Anal. Calcd for $C_{18}H_{26}N_4O_4$ (0.5 H_2O): C, 58.21; H, 7.33; N, 15.08. Found: C, 58.33; H, 7.28; N, 15.01.

1-Acetyl-5-acetylamino-7,8-dimethoxy-2,3-dihydro-1*H*-quinolin-4-one (12). α-Tetralone **2e** (0.33 g, 2.2 mmol) diluted in acetic acid (5 mL) was added to a refluxing solution of **1a** (0.5 g, 1.9 mmol) in glacial acetic acid (5 mL). The mixture was stirred at reflux for 5 h. Removal of the solvent gave the crude product, which was subjected to chromatography (silica gel, 20% acetone−30% toluene−cyclohexane). The concentrate was recrystallized from ethanol to yield 230 mg (40%) of **12** as a beige solid: mp 180 °C; IR (KBr) 1699, 1673, 1650, 1608, 1580, 1508, 1466, 1449 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.11 (s, 3H), 2.24 (s, 3H), 2.62 (m, 1H), 2.81−2.94 (m, 1H), 3.30−3.37 (m, 1H), 3.69 (s, 3H), 3.98 (s, 3H), 4.98−5.05 (m, 1H), 8.40 (s, 1H), 12.05 (s, 1H); MS (EI) m/e 306 (M^+, 42), 275 (18), 249 (35), 207 (100). Anal. Calcd for $C_{15}H_{18}N_2O_5$: C, 58.82; H, 5.92; N, 9.15. Found: C, 58.97; H, 5.60; N, 9.06.

6-[3-(4-Methylpiperazin-1-yl)propoxy]-3,4-dihydro-2*H*-naphthalen-1-one (2e). Potassium carbonate (3.4 g, 24 mmol) was added to a solution of 6-hydroxytetralone (1 g, 6.1 mmol) in dry DMF (10 mL), and the mixture was stirred for 30 min at room temperature. Then 1-(3-chloropropyl)-4-methylpiperazine dihydrochloride (1.23 g, 4.9 mmol) was added. The mixture was stirred overnight at 80 °C, diluted with water, and extracted several times with ethyl acetate. The organic layers were washed with saturated aqueous sodium chloride and dried over magnesium sulfate. Concentration followed by chromatography (silica gel, 15% methanol−5% ammoniacal dichloromethane) gave 0.75 g (75%) of **2e** as a brown oil: IR (KBr) 1675, 1599, 1569, 1493, 1459 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.90 (p, J = 6.4, 2H), 2.01 (p, J = 6.4, 2H), 2.21 (s, 3H), 2.41−2.53 (m, 12H), 2.82 (t, J = 6.0, 2H), 3.98 (t, J = 6.4, 2H), 6.61 (d, J = 2.6, 1H), 6.72 (dd, J = 8.7, 2.6, 1H), 7.90 (d, J = 8.6, 1H). Anal. Calcd for $C_{18}H_{26}N_2O_2$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.49; H, 8.66; N, 9.28.

Synthesis of Quinolines 3a−d. Method A. A solution of **1a** (0.5 g, 1.89 mmol), PPTS (0.47 g, 1.89 mmol), and the appropriate tetralone **2a**−**d** (2.84 mmol) in toluene (10 mL) was heated under reflux using a Dean−Stark trap. The precipitate obtained after cooling was collected by filtration and washed successively with toluene and ether.

Synthesis of Quinolines 3a−d. Method C. A solution of **1a** (0.5 g, 1.89 mmol), PPTS (0.70 g, 2.84 mmol), and the appropriate tetralone **2a**−**d** (5.67 mmol) in butan-1-ol (10 mL) was heated under reflux using a Dean−Stark trap. After cooling, the solvent was evaporated and the residue was triturated with ether. After the precipitate was washed with ether, the crude product was subjected to chromatography (silica gel, 2% methanol−dichloromethane−TFA (5 drops)). Solids were additionally recrystallized.

3-Acetyl-4,5-dimethoxy-2,3,12,13-tetrahydro-1*H*-benzo[*c*]pyrido[2,3,4-*kl*]acridine (3a): yellow solid; IR (KBr) 1673, 1641, 1594, 1487 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.14 (s, 3H), 2.99 (s, 4H), 3.12 (m, 3H), 3.87 (s, 3H), 4.10 (s, 3H), 5.23 (bs, 1H), 7.28 (d, J = 6.7, 1H); 7.42 (p, J = 7.3, 1.3, 2H), 7.58 (s, 1H), 8.52 (dd, J = 7.0, 2.0, 1H); ^{13}C NMR ($CDCl_3$) δ 171.43, 156.61, 149.98, 142.93, 142.07, 140.13, 131.32, 130.54, 128.01, 127.96, 127.78, 126.99, 126.24, 116.55, 103.01, 61.05, 56.60, 41.94, 27.48, 23.54, 22.02; MS (EI) m/e 374 (M^+, 62), 331 (27), 316 (100). Anal. Calcd for $C_{23}H_{22}N_2O_3$ (0.5 TFA, 0.5 H_2O): C, 65.47; H, 5.38; N, 6.36. Found: C, 65.55; H, 5.11; N, 6.60.

3-Acetyl-4,5,10-trimethoxy-2,3,12,13-tetrahydro-1*H*-benzo[*c*]pyrido[2,3,4-*kl*]acridine (3b): bright yellow solid; IR (KBr) 1681, 1641, 1599, 1576, 1508, 1487, 1456 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.17 (s, 3H), 2.99 (s, 4H), 3.18 (m, 3H), 3.88 (s, 3H), 3.90 (s, 3H), 4.12 (s, 3H), 5.22 (bs, 1H), 6.84 (d, J = 2.3, 1H), 7.03 (dd, J = 9.1, 2.6, 1H), 8.16 (s, 1H), 8.7 (d, J = 12.1, 1H); ^{13}C NMR ($CDCl_3$) δ 171.37, 163.61, 158.28, 153.5, 148.22, 146.85, 142.53, 136.45, 130.41, 128.35, 125.96, 119.68, 116.06, 114.29, 113.53, 99.97, 61.21, 57.10, 55.63, 41.90, 28.02, 27.67, 23.37, 22.07; MS (EI) *m/e* 404 (M^+, 51), 361 (17), 346 (100). Anal. Calcd for $C_{24}H_{24}N_2O_4$ (TFA): C, 60.23; H, 4.86; N, 5.40. Found: C, 60.25; H, 4.85; N, 5.49.

3-Acetyl-4,5,9-trimethoxy-2,3,12,13-tetrahydro-1*H*-benzo[*c*]pyrido[2,3,4-*kl*]acridine (3c): beige solid; IR (KBr) 1661, 1617, 1587, 1504, 1482, 1429 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.14 (s, 3H), 2.94 (s, 4H), 3.14 (m, 3H), 3.86 (s, 3H), 3.96 (s, 3H), 4.10 (s, 3H), 5.24 (bs, 1H), 6.94 (dd, J = 8.5, 2.8, 1H), 7.20 (d, J = 8.2, 1H), 7.42 (s, 1H), 8.10 (d, J = 2.8, 1H); ^{13}C NMR ($CDCl_3$) δ 171.85, 159.03, 154.63, 152.31, 144.10, 141.21, 138.00, 135.65, 131.25, 128.82, 127.93, 125.90, 116.72, 116.36, 109.73, 106.57, 61.04, 56.14, 55.56, 42.23, 27.07, 27.02, 24.19, 22.18; MS (EI) *m/e* 404 (M^+, 56), 361 (26), 346 (100). Anal. Calcd for $C_{24}H_{24}N_2O_4$: C, 71.27; H, 5.98; N, 6.92. Found: C, 71.05; H, 5.96; N, 6.98.

3-Acetyl-4,5,9,10,-tetramethoxy-2,3,12,13-tetrahydro-1*H*-benzo[*c*]pyrido[2,3,4-*kl*]acridine (3d): pale yellow solid; IR (KBr) 1662, 1618, 1583, 1511, 1487, 1462 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.14 (s, 3H), 2.96−3.17 (m, 7H), 3.85 (s, 3H), 3.96 (s, 3H), 4.07 (s, 6H), 5.23 (bs, 1H), 6.77 (s, 1H), 7.40 (s, 1H), 8.07 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 171.87, 154.57, 152.38, 150.41, 148.36, 144.12, 140.88, 137.70, 132.17, 128.01, 127.35, 125.10, 115.91, 110.44, 108.58, 106.42, 61.05, 56.14, 56.11, 55.98, 42.26, 27.48, 27.04, 24.18, 22.20; MS (EI) *m/e* 434 (M^+, 82), 391 (13), 376 (100). Anal. Calcd for $C_{25}H_{26}N_2O_5$ (0.5 H_2O): C, 67.70; H, 6.14; N, 6.32. Found: C, 67.87; H, 5.97; N, 6.42.

Synthesis of Quinoline 3e. Method B. A solution of **1a** (2 g, 7.57 mmol), PPTS (0.95 g, 3.79 mmol), and tetralone **2e** (1.14 g, 3.79 mmol) in 15 mL of a mixture of toluene/ethanol (2:1) was heated under reflux using a Dean−Stark trap. The precipitate formed after cooling to room temperature was collected by filtration and washed successively with toluene and ether. The crude product was subjected first to chromatography (silica gel, 10% methanol−dichloromethane) and then to preparative HPLC (C_{18}, 4.6 × 150 mm, 5 μm, 100 Å MeOH 34%−H_2O 66%−TFA 0.1%). Evaporation of the appropriate fraction (t_R = 14.87 min) afforded **3e** as a beige solid. Saturated methanol with HCl was added to a solution of this solid in methanol to yield **3e** as the hydrochloride.

Synthesis of Quinoline 3e. Method C. A solution of **1a** (0.7 g, 2.65 mmol), PPTS (0.33 g, 1.3 mmol) and tetralone **2e** (0.4 g, 1.3 mmol) in butan-1-ol (10 mL) was heated under reflux using a Dean−Stark trap. After being cooled to room temperature, the mixture was diluted with 1 N HCl and extracted several times with ethyl acetate. The aqueous layer was made basic using potassium carbonate and extracted several times with ethyl acetate. The organic layers were washed with saturated aqueous sodium chloride and dried over magnesium sulfate. Removal of the solvent gave the crude product, which was subjected to chromatography (silica gel, 10% methanol−dichloromethane).

3-Acetyl-4,5-dimethoxy-10-[3-(4-methylpiperazin-1-yl)-propoxy]-2,3,12,13-tetrahydro-1*H*-benzo[*c*]pyrido[2,3,4-*kl*]-acridine hydrochloride (3e): IR (KBr) 1673, 1651, 1610, 1585, 1484, 1462 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.02 (s, 3H), 2.80−3.07 (m, 17H), 3.37−3.42 (m, 5H), 3.77 (s, 3H), 4.00 (s, 3H), 4.12 (t, J = 5.6, 2H), 4.73 (bs, 1H), 6.94 (s, 1H), 6.98 (d, J = 8.9, 1H), 7.37 (s, 1H), 8.33 (d, J = 8.6, 1H); ^{13}C NMR (DMSO-d_6) δ 170.07, 160.05, 157.50, 155.04, 150.52, 142.08, 140.98, 139.97, 127.55, 126.04, 125.05, 115.65, 114.90, 113.63, 113.46, 104.90, 65.24, 60.43, 56.14, 53.19, 53.05, 50.62, 49.15, 48.77, 48.15, 42.20, 39.28, 26.81, 26.00, 24.51, 23.21, 21.97; MS (EI) *m/e* 530 (M^+, 56), 460 (57), 391 (100). Anal. Calcd for $C_{31}H_{38}N_4O_4$·2HCl (0.5 H_2O, TFA): C, 54.54; H, 5.83; N, 7.71; Cl, 9.76. Found: C, 54.76; H, 5.55; N, 7.43; Cl, 9.46.

Synthesis of Quinolines 4a−c,e. Method C. A solution of **1b** (0.5 g, 1.38 mmol), PPTS (0.52 g, 2.07 mmol), and the appropriate tetralone **2a**−**c**,**e** (4.14 mmol) in butan-1-ol (10 mL) was heated under reflux using a Dean−Stark trap. The mixture was cooled to room temperature, made basic using 10% aqueous potassium carbonate, and diluted with ethyl acetate, and the layers were separated. The dark red organic layer was washed with saturated aqueous sodium chloride and dried over magnesium sulfate. Removal of the solvent gave an oily product that precipitated in ether. After filtration and washing with ether, the crude product was subjected to chromatography (silica gel, 5% methanol−dichloromethane (**4a**−**c**), 30% methanol−dichloromethane to 50% methanol−1% ammoniacal dichloromethane (**4e**)). Evaporation of the appropriate fraction gave quinolines as bases. Dichloromethane saturated with HCl was added to a solution of these bases in dichloromethane to yield quinolines **4** as hydrochlorides.

3-[2-(4-Methylpiperazin-1-yl)acetyl]-4,5-dimethoxy-2,3,-12,13-tetrahydro-1*H*-benzo[*c*]pyrido[2,3,4-*kl*]acridine hydrochloride (4a): yellow solid; IR (KBr) 1687, 1634, 1595, 1519, 1484, 1415 cm^{-1}; ^1H NMR (DMSO-d_6, 60 °C) δ 2.82 (s, 3H), 3.07 (s, 4H), 3.34−3.51 (m, 11H), 3.92 (s, 3H), 4.11 (s, 3H), 4.22 (m, 3H), 7.52 (m, 3H), 8.03 (s, 1H), 8.70 (d, J = 6.7, 1H); MS (CI) *m/e* 473 (M + 1), 501 (M + 29). Anal. Calcd for $C_{28}H_{32}N_4O_3$·3HCl (2 H_2O): C, 54.41; H, 6.36; N, 9.06; Cl, 17.21. Found: C, 54.74; H, 6.20; N, 9.09; Cl, 17.21.

3-[2-(4-Methylpiperazin-1-yl)acetyl]-4,5,10-trimethoxy-2,3,12,13-tetrahydro-1*H*-benzo[*c*]pyrido[2,3,4-*kl*]acridine hydrochloride (4b): yellow solid; IR (KBr) 1687, 1635, 1611, 1574, 1512, 1486, 1456 cm^{-1}; ^1H NMR (DMSO-d_6, 60 °C) δ 2.80 (s, 3H), 3.06 (s, 4H), 3.20−3.55 (m, 11H), 3.91 (s, 3H), 3.95 (s, 3H), 4.11 (s, 3H), 4.22 (m, 3H), 7.11 (m, 2H), 8.15 (s, 1H), 8.73 (s, 1H); MS (CI) *m/e* 503 (M + 1), 531 (M + 29). Anal. Calcd for $C_{29}H_{34}N_4O_4$·3HCl (2.5 H_2O): C, 53.01; H, 6.44; N, 8.52; Cl, 16.18. Found: C, 53.74; H, 6.21; N, 8.64; Cl, 16.39.

3-[2-(4-Methylpiperazin-1-yl)acetyl]-4,5,9-trimethoxy-2,3,12,13-tetrahydro-1*H*-benzo[*c*]pyrido[2,3,4-*kl*]acridine hydrochloride (4c): yellow solid; IR (KBr) 1682, 1634, 1591, 1573, 1523, 1487, 1462 cm^{-1}; ^1H NMR (DMSO-d_6, 60 °C) δ 2.83 (s, 3H), 3.01−3.06 (m, 4H), 3.35−3.60 (m, 10H), 3.93 (s, 3H), 4.00 (s, 3H), 4.12 (s, 3H), 4.30 (m, 3H), 7.17 (d, J = 8.2, 1H), 7.41 (d, J = 8.2, 1H), 8.29 (s, 1H), 8.36 (s, 1H); MS (CI) *m/e* 503 (M + 1), 531 (M + 29). Anal. Calcd for $C_{29}H_{34}N_4O_4$·2.5HCl (4.5 H_2O): C, 51.61; H, 6.79; N, 8.30; Cl, 13.13. Found: C, 51.40; H, 6.01; N, 8.35; Cl, 12.85.

3-[2-(4-Methylpiperazin-1-yl)acetyl]-4,5-dimethoxy-10-[3-(4-methylpiperazin-1-yl)propoxy]-2,3,12,13-tetrahydro-1*H*-benzo[*c*]pyrido[2,3,4-*kl*]acridine hydrochloride (4e): yellow solid; IR (KBr) 1687, 1635, 1612, 1575, 1512, 1488, 1456 cm^{-1}; MS (CI) *m/e* 629 (M + 1), 657 (M + 29). Anal. Calcd for $C_{36}H_{48}N_6O_4$·5HCl (3.5 H_2O): C, 49.46; H, 6.91; N, 9.61; Cl, 20.27. Found: C, 49.47; H, 6.69; N, 9.67; Cl, 20.33.

Supporting Information Available: ^1H NMR spectra for **7**, **8**, **9a**,**b**, **10a**,**b**, **11b**, **1a**,**b**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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