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Reactivity of Pyrido[4,3,2-*kl*]acridines: Regioselective Formation of 6-Substituted Derivatives

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Abstract: Pyrido[4,3,2-*kl*]acridines represent a new class of heterocycles, isomers of marine alkaloids. The 7*H*-pyrido-[4,3,2-*kl*]acridine reacts as an electron rich heterocycle, and in particular via electrophilic substitution such as H/D exchange and the Vilsmeier−Haack reaction. The reaction is fully regioselective and gives the corresponding 6-substituted derivatives. The pyrido[4,3,2-*kl*]acridin-4-one reacts with amines and thiol, via 1,4-Michael addition to give the 6-amino or 6-thio analogues in a very efficient way. Molecular calculations account for the observed regioselectivity.

Pyrido[2,3,4-*kl*]acridines constitute a large family of marine alkaloids isolated from sponges and ascidians (Figure 1).[1]

Most of these molecules display significant cytotoxicities against various cancer lines and deserve to be further evaluated as antitumor agents. Accessibility from natural sources constitutes one major drawback to the therapeutical development of this class of alkaloids. Therefore various strategies have been designed for the chemical synthesis of pyrido[2,3,4-*kl*]acridines, allowing the synthesis and biological screening of nonnatural alkaloids.[2] We are interested in the synthesis and reactivity of the pyrido[4,3,2-*kl*]acridine skeleton, isomer of the marine alkaloids, which only differs by the position of the nitrogen on ring D. This heterocycle is also found in necatorone, alkaloid isolated from fungi.[3] Necatorone and other pyrido[4,3,2-*kl*]acridines have been prepared by us and others.[4−9]The chemical reactivity of such condensed

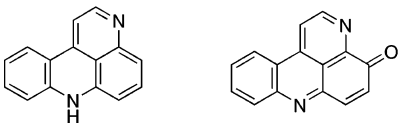

FIGURE 1. General skeletons of marine pyrido[2,3,4-*kl*]-acridine alkaloids.

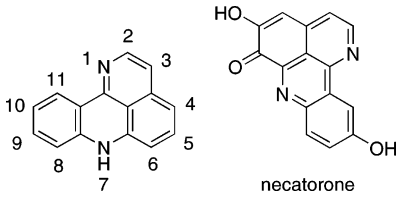

FIGURE 2. Pyrido[4,3,2-*kl*]acridines.

nitrogen heterocycles has been largely unexplored. There is only mention by Stevens in 2003 of the use of the Heck reaction between chloro-substituted quinoacridines and acrylic acid derivatives, and of the Suzuki-Miyaura reaction between triflate-substituted quinoacridines and alkylboranes.[10] In an effort to prepare pyridoacridine derivatives bearing various substituents in the search for antitumor agents, we investigated the chemical reactivity of the 4-methoxypyrido[4,3,2-*kl*]acridine nucleus and its 4-one analogue. We describe in this paper the synthesis of a series of functionalized derivatives prepared by chemical modifications of the heterocycle. We also discuss the chemical reactivity of pyrido[4,3,2-*kl*]acridines in the light of molecular calculations.

The starting compound 4-methoxypyrido[4,3,2-*kl*]acridine (**3**) has been prepared by a two-step synthesis starting from 9-chloro-2-methoxyacridine (**1**) and involving a regioselective cyclodehydration step (Scheme 1).[9]

Considering that pyrido[4,3,2-*kl*]acridine is an electron-rich heterocycle, electrophilic substitution reactions were investigated (Scheme 2). In a first approach we studied the H−D exchange in trifluoroacetic acid-*d*. The reaction was performed at room temperature and compound **3-D** was isolated in 62% yield. The reaction is fully regioselective, with introduction of one deuterium at position 6. The position of the deuterium was established by NOE experiments.[11] Irradiation of the 4-methoxy group (δ 3.87 ppm) resulted in an enhancement of the singlet at 7.15 ppm that was therefore attributed to H-5. To introduce a C substituent, we performed the Vilsmeier−Haack reaction (DMF−$POCl_3$). The reaction proceeded smoothly

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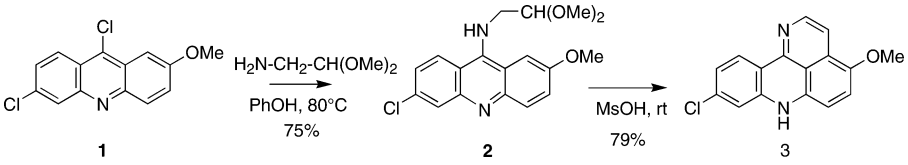
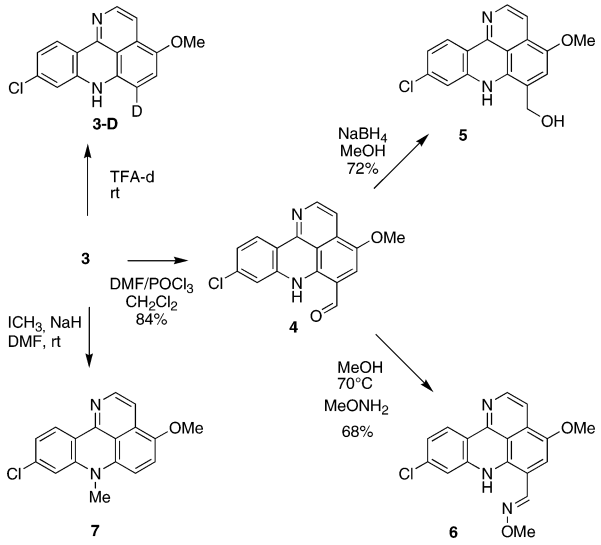
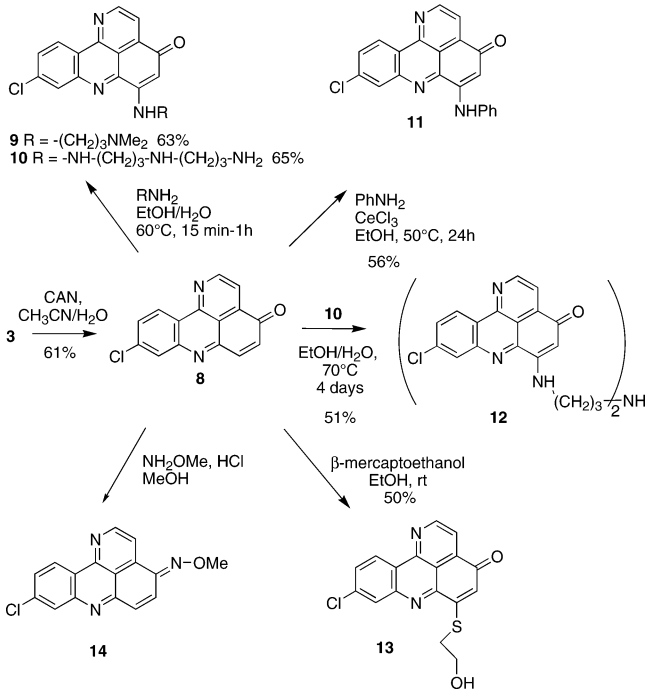
SCHEME 1



SCHEME 2. Preparation of 6-Substituted 7*H*-9-Chloro-4-methoxypyrido[4,3,2-*kl*]acridines



SCHEME 3. Preparation of 6-Substituted 4*H*-9-Chloropyrido[4,3,2-*kl*]acridin-4-ones



in CH_2Cl_2 and the formyl derivative **4** was isolated in 84% yield. The product is characterized by two singlets at 6.99 (H-5) and 9.80 ppm (CHO). The formyl derivative **4** can be further functionalized. Reduction of the carbonyl group with sodium borohydride afforded the corresponding hydroxymethyl derivative **5** in 75% yield. Compound **5** is characterized by NMR by a singlet at 4.66 ppm integrating for 2 protons. Compound **4** was also reacted with methoxyamine to form the methyl-substituted oxime **6** in 68% yield. NOE experiments indicated the exclusive formation of the E isomer. Molecular modeling calculations (Insight Discover II, cvff force field) corroborate this preferential conformation in which there is stabilization due to hydrogen bonding between the oxime nitrogen and the heterocyclic N7-H. This is confirmed by the strong NOE observed between H-5 and the oxime hydrogen.

Due to its high acidic character the N7-H proton can be easily abstracted. N-Alkylation of **3** proceeded smoothly in the presence of methyl iodide and sodium hydride. Compound **7** was obtained in 76% yield. The *N*-methyl group is characterized by NMR by a singlet at 3.47 ppm. NOE experiments confirm the presence of the methyl group at the N-7 position, and irradiation of the *N*-methyl singlet results in the enhancement of the signals at 6.65 and 7.12 ppm (H-6 and H-8, respectively).

Oxidative demethylation of compound **3** by CAN in a CH_3CN/water mixture formed the corresponding pyrido-[4,3,2-*kl*]acridin-4-one (**8**) in 80% yield. This compound is characterized in NMR by the high coupling constant ($J = 10.3$ Hz) observed for protons 5 and 6 that appeared as two doublets at 7.87 and 6.96 ppm, respectively. This is in accordance with a quinone-type structure for ring C. The pyrido[4,3,2-*kl*]acridin-4-one (**8**) is very close structurally to the second general skeleton displayed by the natural alkaloids and is therefore of major interest. Considering that this heterocycle may react as a quinone-type derivative we studied the reactivity of **8** with various nucleophiles (Scheme 3). Compound **8** reacted at room temperature in the presence of a large excess of primary aliphatic amines to give the 4-enones **9** and **10** in 63% and 65% yield, respectively. It should be noticed that reoxidation of the 1,4 Michael addition products to the quinone forms occurs spontaneously. As previously published, addition of a weaker nucleophile, aniline, required the presence of a Lewis acid ($CeCl_3$) as catalyst to give after 1 day compound **11** in 56% yield.[11] Dimeric structure **12**, which may act as a DNA bis-intercalating drug, was obtained in 51% yield by coupling **10** with **8**.

In a similar way, thiol (β-mercaptoethanol) reacted at position 6 to give compound **13** in 50% yield. As observed for addition of amine, reoxidation occurred spontaneously. The reaction proceeds smoothly at room temperature.

Unlike what has been observed with amines, methoxyamine reacted in a 1−2 addition process to give the oxime ether **14** in 47% yield.

To give an insight into the reactivity of 7*H*-4-methoxypyrido[4,3,2-*kl*]acridine (**3**) and the 4*H*-pyrido[4,3,2-*kl*]acridin-4-one (**8**), the structures of these compounds have been optimized at the B3LYP/6-31G* level with the Gaussian98 package. The orbital molecular and charge population (NBO population) have been computed at the same level.

The analysis of the structure exhibits a short C6−C5 distance of 1.351 Å for compound **8** vs 1.412 Å for compound **3**. This short distance is in agreement with the NMR data (J_{4-5} = 10.3 Hz).

For compound **3**, the comparison of the charge population of the possible reactive carbons C5, C6, and C8 exhibits no difference (−0.29e for all three carbons) and so a charge control cannot explain the observed regioselectivity. On the other hand, the HOMO orbital rationalizes the experimental reactivity observed for **3** with an important weight of the p_z orbital of the C6 carbon and no contribution from the C8 and C5 carbons.

For compound **8**, the results are also in excellent agreement with the experimental reactivity but with a balanced charge and orbital control. Indeed, the C6 carbon has a more accentuated electrophilic character with a deficit of 0.10e compared to that of the C5 carbon. Likewise, the LUMO orbital of this compound shows a more important weight of the C6 carbon compared to the C5 carbon also in agreement with the experimental data.

Thus, the regioselectivity of compound **3** is explained by a strong orbital control while for compound **8** both orbital and charge control favored the selectivity.

In conclusion, we have observed a total regioselectivity in the reactivity of both 4*H*-pyrido[4,3,2-*kl*]acridin-4-one and 7*H*-4-methoxypyrido[4,3,2-*kl*]acridine, giving access to a series of 6-functionalized derivatives. The biological properties of the new compounds are under investigation and will be published elsewhere.

Experimental Section

Compounds **3**[9] and **3-D**[11] were prepared as previously described.

9-Chloro-6-formyl-4-methoxy-7*H*-pyrido[4,3,2-*kl*]acridine (4). To a solution of compound **3** (0.200 g, 0.72 mmol) in CH_2Cl_2 (20 mL) was added an equimolar mixture of DMF and $POCl_3$ (150 equiv). After being stirred for 24 h at 60 °C, the solution was neutralized by adding 10 M NaOH. The residue was warmed 15 min at 60 °C and diluted with 30 mL of H_2O, and the solution was extracted with dichloromethane. The organic layers were collected, washed with water, dried over sodium sulfate, and concentrated under vacuum. Compound **4** was precipitated by adding pentane and was obtained in 84% yield (0.186 g, 0.60 mmol). Mp 248−252 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.29 (1H, s, N−H), 9.80 (1H, s, ArCHO), 8.59 (1H, d, J = 5.8 Hz, H-2), 8.57 (1H, d, J = 8.3 Hz, H-11), 7.57 (1H, d, J = 5.8 Hz, H-3), 7.24 (1H, d, J = 1.8 Hz, H-8), 7.19 (1H, dd, J = 8.6 and 1.9 Hz, H-10), 6.99 (1H, s, H-5), 3.94 ppm (3H, s, O−CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.2 (CO), 151.1 (C), 149.2 (CH), 145.1 (C), 138.6 (C), 138.4 (C), 138.0 (C), 134.5 (C), 126.6 (CH), 124.0 (CH), 120.2 (C), 118.7 (C), 116.6 (CH), 112.2 (CH), 110.2 (CH), 109.7 (C), 56.1 ppm (CH_3). HRMS (EI) *m/z* calcd for $C_{17}H_{11}N_2O_2{}^{35}Cl$ 310.0509, found 310.0498.

9-Chloro-6-hydroxymethyl-4-methoxy-7*H*-pyrido[4,3,2-*kl*]acridine (5). $NaBH_4$ (0.111 g, 2.8 mmol) was added to a solution of compound **4** (0.091 g, 0.29 mmol) in MeOH (85 mL). After the solution was stirred for 2 h at room temperature, the product was precipitated by adding 120 mL of water. The solid formed was filtered off and washed with H_2O. Compound **5** was thus obtained in 75% yield (0.068 g; 0.21 mmol). Mp 190 °C dec .^{1}H NMR (300 MHz, DMSO-d_6) δ 9.46 (1H, s, N−H), 8.27 (1H, d, J = 8.3 Hz, H-11), 8.16 (1H, d, J = 5.9 Hz, H-2), 7.45 (1H, d, J = 1.9 Hz, H-8), 7.24 (1H, d, J = 5.9 Hz, H-3), 7.28 (1H, s, H-5), 6.99 (1H, dd, J = 8.3 and 2.0 Hz, H-10), 5.28 (1H, t, J = 5.3 Hz, OH), 4.66 (2H, d, J = 5.3 Hz, CH_2), 3.94 ppm (3H, s, O−CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ 150.2 (C), 144.1 (C), 143.3 (CH), 141.8 (C), 135.7 (C), 129.3 (C), 126.9 (C), 126.0 (CH), 120.3 (CH), 119.2 (C), 118.2 (C), 117.3 (C), 115.1 (CH), 111.4 (CH), 110.9 (CH), 59.5 (CH_2), 55.8 ppm (CH_3). HRMS (LSIMS, Cs^+, mNBA) *m/z* (M + H)$^+$ calcd for $C_{17}H_{14}N_2O_2{}^{35}Cl$ 313.0744, found 313.0745.

9-Chloro-4-methoxy-6-(methoxyiminomethylene)-7*H*-pyrido[4,3,2-*kl*]acridine (6). A stoichiometric mixture of the aldehyde **4** (0.015 g, 0.049 mmol) and *O*-methyl oxyamine hydrochloride (0.004 g, 0.049 mmol) in anhydrous MeOH (2 mL) was refluxed for 2 h. The solution was diluted with water (10 mL) and **6** was extracted with dichloromethane (50 mL). The organic layers were collected, washed with water, dried over sodium sulfate, and concentrated under vacuum. Compound **6** was precipitated by adding pentane and was obtained in 68% yield (0.011 g, 0.033 mmol). Mp 221−224 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.93 (1H, s, N−H), 8.51 (1H, d, J = 7.6 Hz, H-11), 8.33 (1H, d, J = 6.0 Hz, H-2), 8.20 (1H, s, ArCH=N), 7.44 (1H, d, J = 5.9 Hz, H-3), 7.07 (1H, dd, J = 8.6 and 1.9 Hz, H-10), 6.95 (1H, d, J = 1.9 Hz, H-8), 6.74 (1H, s, H-5), 4.04 (3H, s, O−CH_3), 3.88 ppm (3H, s, N−O−CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ 149.9 (C), 149.6 (CH), 145.7 (CH), 144.4 (C), 140.0 (C), 136.2 (C), 131.5 (C), 129.4 (C), 126.1 (CH), 122.0 (CH), 118.8 (C), 118.6 (C), 116.0 (CH), 111.3 (CH), 110.9 (CH), 105.5 (C), 62.1 (CH_3), 55.8 ppm (CH_3). HRMS (EI) *m/z* calcd for $C_{18}H_{14}N_3O_2{}^{35}Cl$ 339.0774, found 339.0765.

9-Chloro-4-methoxy-7-methylpyrido[4,3,2-*kl*]acridine (7). NaH (0.008 g, 0.20 mmol) was added to a solution of compound **3** (0.054 g, 0.19 mmol) in DMF (5 mL). Methyl iodide (24 μL, 0.38 mmol) was added, and after 100 min of stirring at room temperature, the product was precipitated by adding 200 mL of water. The solid formed was filtered off and washed with H_2O. Compound **7** was thus obtained in 76% yield (0.043 g; 0.145 mmol). Mp 221−222 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (1H, d, J = 8.5 Hz, H-11), 8.35 (1H, d, J = 5.8 Hz, H-2), 7.52 (1H, d, J = 5.8 Hz, H-3), 7.12 (1H, d, J = 1.7 Hz, H-8), 7.04 (1H, dd, J = 8.5 and 1.7 Hz, H-10), 7.01 (1H, d, J = 8.7 Hz, H-5), 6.65 (1H, d, J = 8.6 Hz, H-6), 3.96 (3H, s, O−CH_3), 3.47 ppm (3H, s, N−CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ 149.0 (C), 144.9 (C), 143.9 (CH), 142.7 (C), 136.6 (C), 134.2 (C), 127.9 (C), 126.3 (CH), 120.2 (CH), 119.4 (C), 119.3 (C), 113.5 (CH), 111.1 (CH), 110.8 (CH), 104.7 (CH), 55.7 (CH_3), 33.3 ppm (CH_3). HRMS (electrospray) *m/z* (M + H)$^+$ calcd for $C_{17}H_{14}N_2O^{35}Cl$ 297.0795, found 297.0798.

9-Chloro-4*H*-pyrido[4,3,2-*kl*]acridin-4-one (8). To compound **3** (0.327 g, 1.14 mmol) dissolved in a 2/1 acetonitrile/water mixture (260 mL) was added CAN (1.997 g, 3.64 mmol). The solution was stirred at room temperature of 1 h and then was poured into a 5/1 ethyl acetate/water mixture (600 mL). The aqueous layer was separated and extracted three times with ethyl acetate. The organic layers were collected, washed with water and brine, and dried over sodium sulfate. After evaporation to dryness, the residue was triturated in diethyl ether to give **8** (0.258 g, 0.96 mmol) as a yellow solid in 80% yield. Mp 186−188 °C (lit.[11] mp 184−190 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.41 (1H, d, J = 4.6 Hz, H-2), 9.05 (1H, d, J = 8,7 Hz, H-11), 8.23 (1H, d, J = 2 Hz, H-8), 8.19 (1H, d, J = 4.5 Hz, H-3), 7.87 (1H, d, J = 10.3 Hz, H-5), 7.76 (1H, dd, J = 8.7 and 2 Hz, H-10), 6.96 ppm (1H, d, J = 10.3 Hz, H-6).

9-Chloro-6-(3-(dimethylamino)-1-propylamino)-4*H*-pyrido[4,3,2-*kl*]acridin-4-one (9). To a solution of compound **8** (0.02 g; 0.075 mmol) in 10 mL of a EtOH/H_2O (4/1) mixture was added an excess of 3-(dimethylamino)-1-propylamine (0.5 mL; 3.9 mmol). The solution was stirred at 60 °C for 15 min. The solution was then acidified by addition of 11 N HCl and washed twice with CH_2Cl_2. The aqueous layer was neutralized by adding aqueous NaOH and extracted with dichloromethane. The organic layer was dried over sulfate sodium and evaporated under vacuum. Compound **9** was obtained in 63% yield (0.017 g; 0.047 mmol). Mp 225−228 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.26 (1H, d, J = 4.4 Hz, H-2), 8.97 (1H, d, J = 8.7 Hz, H-11), 8.2−8.1 (3H, m, H-8, H-3 and N−H), 7.72 (1H, dd, J = 8.7 and 2 Hz, H-10), 5.85 (1H, s, H-5), 3.57 (2H, q, J = 6.2 Hz, H-1′), 2.89 (2H, t, J = 6.2 Hz, H-3′), 2.63 (6H, s, 2 Me), 2.18 ppm (2H, q, J = 6.2 Hz, H-2′). ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.3 (C=O), 155.7 (CH), 152.2 (C), 147.2 (C), 146.8 (C), 146.1 (C), 137.2 (C), 136.2 (C), 130.3 (CH), 129.7 (CH), 125.6 (CH), 124.4 (C), 119.8 (CH), 115.8

(C), 100.1 (CH), 56.4 (CH_2), 44.1 (CH_2), 40.6 (2 CH_3), 30.1 ppm (CH_2). HRMS (LSIMS, Cs^+, mNBA) *m/z* $(M + H)^+$ calcd for $C_{20}H_{20}N_4O^{35}Cl$ 367.1326, found 367.1320. UV/vis (EtOH 95%) λ_{max} (ϵ) 236 (29 800), 284 (19 200), 312 (10 600), 358 (9 930), 473 (5 320).

9-Chloro-6-[(3-propylaminopropyl)amino]-4*H*-pyrido-[4,3,2-*kl*]acridin-4-one (10). To compound **8** (0.02 g, 0.075 mmol) dissolved in 15 mL of EtOH/H_2O (4/1) mixture was added an excess of bis(3-aminopropyl)amine (0.5 mL, 3.6 mmol). The solution was stirred at 60 °C for 1 h. The solution was then acidified by addition of 11 N HCl and washed twice with CH_2Cl_2. The aqueous layer was neutralized by adding aqueous NaOH and extracted with dichloromethane. The organic layer was dried over sulfate sodium and evaporated under vacuum. Compound **10** was obtained in 65% yield (0.019 g; 0.048 mmol). Mp 75−78 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.32 (1H, d, J = 4.5 Hz, H-2), 9.06 (1H, d, J = 8.8 Hz, H-11), 8.20 (1H, d, J = 2.0 Hz, H-8), 8.19 (1H, d, J = 4.6 Hz, H-3), 8.09 (1H, N−H), 7.77 (1H, dd, J = 8.7 and 2.0 Hz, H-10), 5.91 (1H, s, H-5), 3.56−3.47 (2H, m), 2.90−2.75 (6H, m), 1.99 (2H, quint, J = 6.3 Hz and 6.5 Hz), 1.76 ppm (2H, quint, J = 6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.0 (C=O), 155.7 (CH), 147.2 (C), 147.0 (C), 146.8 (C), 146.3 (C), 136.9 (C), 136.5 (C), 129.9 (CH), 129.3 (CH), 125.7 (CH), 124.4 (C), 119.8 (CH), 115.8 (C), 99.7 (C), 48.7 (CH_2), 48.4 (CH_2), 42.1 (CH_2), 40.9 (CH_2), 34.1 (CH_2), 29.9 ppm (CH_2). HRMS (electrospray) *m/z* $(M + H)^+$ calcd for $C_{21}H_{23}N_5O^{35}Cl$ 396.1591, found 396.1597. UV−vis (EtOH 95%) λ_{max} (ϵ) 236 (29 900), 284 (17 500), 312 (8 010), 358 (7 640), 473 (2 890).

Bis[3-(*N*,*N*′-(9-chloro-4*H*-pyrido[4,3,2-*kl*]acridin-4-one-6-yl))aminopropyl]amine (12). A stoichiometric mixture of compound **8** (0.0032 g, 0.012 mmol) and compound **10** (0.0049 g, 0.012 mmol) in a EtOH/H_2O (4/1) mixture (6 mL) was refluxed for 4 days. The solution was then cooled to 0 °C and the solid that formed was filtered off and washed with water. Compound **12** was thus obtained in 51% yield (0.004 g, 0.006 mmol). Mp 183−185 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.23 (2H, d, J = 4.5 Hz, H-2), 8.84 (2H, d, J = 8.7 Hz, H-11), 8.06 (2H, d, J = 4.5 Hz, H-3), 8.03 (2H, d, J = 1.8 Hz, H-8), 7.74 (2H, s, N−H), 7.57 (2H, dd, J = 8.7 and 1.8 Hz, H-10), 5.78 (2H, s, H-5), 3.54 (4H, q, J = 5.9 Hz, CH_2), 2.98 (4H, t, J = 6.2 Hz, CH_2), 2.09 ppm (4H, quint, J = 6.3 Hz, CH_2). MS (EI) *m/z* 659.3 (M^+). HRMS (electrospray) *m/z* $(M + H)^+$ calcd for $C_{36}H_{28}N_7O_2^{35}Cl_2$ 660.1682, found 660.1681.

9-Chloro-6-(2-hydroxyethylthio)-4*H*-pyrido[4,3,2-*kl*]acridin-4-one (13). β-Mercaptoethanol (0.011 mL, 0.15 mmol) was added to a suspension of **8** (0.019 g; 0.075 mmol) in EtOH (5 mL), and the solution was stirred for 5 h at room temperature. The solution was diluted with water (10 mL) and extracted with ethyl acetate. The organic layers were collected, washed with H_2O, dried over sodium sulfate, and concentrated. Compound **13** was precipitated by adding a mixture of Et_2O/pentane and obtained after filtration in 50% yield (0.013 g, 0.038 mmol). Mp 223−225 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.38 (1H, d, J = 4.4 Hz, H-2), 9.05 (1H, d, J = 9.1 Hz, H-11), 8.29 (1H, d, J = 2 Hz, H-8), 8.18 (1H, d, J = 4.4 Hz, H-3), 7.8 (1H, dd, J = 9.1 and 2.0 Hz, H-10), 6.76 (1H, s, H-5), 4.06 (2H, t, J = 6.2 Hz, H-1′), 3.24 ppm (2H, t, J = 6.2 Hz, H-2′). ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.1 (C=O), 157.6 (C), 155.8 (CH), 146.3 (C), 145.9 (C), 135.9 (C), 133.9 (C), 130.1 (CH), 128.9 (CH), 127.0 (C), 125.4 (CH), 123.8 (CH), 123.3 (C), 120.1 (C), 108.1 (C), 58.5 (CH_2), 33.2 ppm (CH_2). HRMS (EI) *m/z* calcd for $C_{17}H_{11}N_2O_2^{35}ClS$ 342.0229, found 342.0234. UV/vis (EtOH 95%) λ_{max} (ϵ) 230 (13 450), 282 (8 270), 377 (4 510).

9-Chloro-4-methoxyimino-4*H*-pyrido[4,3,2-*kl*]acridine (14). To a solution of compound **8** (0.050 g, 0.187 mmol) in 25 mL of a EtOH/H_2O (4/1) mixture was added an excess of *O*-methyl oxyamine hydrochloride (1.5 g, 18.0 mmol). The solution was stirred at 60 °C for 1 day. The solution was evaporated under vacuum, diluted with water, and extracted in CH_2Cl_2. The organic layer was dried over sodium sulfate and evaporated under vacuum. Compound **14** was precipitated by adding pentane and obtained after filtration in 47% yield (0.026 g, 0.088 mmol). Mp 214−216 °C. ^{1}H NMR (300 MHz, $CDCl_3$):δ 9.09 (1H, d, J = 5.0 Hz, H-2), 8.94 (1H, d, J = 8.7 Hz, H-11), 8.21 (1H, d, J = 5.0 Hz, H-3), 8.10 (1H, d, J = 2.0 Hz, H-8), 7.65 (1H, dd, J = 8.7 and 2.0 Hz, H-10), 7.60 (1H, d, J = 10.1 Hz, H-5), 7.60 (1H, d, J = 10.1 Hz, H-6), 4.24 ppm (3H, s, CH_3). HRMS (EI) *m/z* calcd for $C_{16}H_{10}N_3O^{35}Cl$ 295.0512, found 295.0481.

Supporting Information Available: ^{1}H NMR spectra of compounds **4**−**7**, **9**, **10**, **13**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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