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Unexpected Reactivity of the 9-Aminoacridine Chromophore in Guanidylation Reactions

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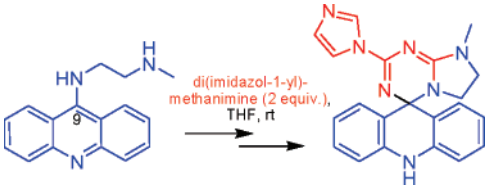


The 9-aminoacridine chromophore is an important building block of DNA-targeted chemotherapeutic agents. The success of 1-[2-(acridin-9-ylamino)ethyl]-1,3-dimethylthiourea as a carrier group in cytotoxic platinum−intercalator conjugates prompted us to explore the synthesis of an analogous guanidine-functionalized acridine. In a successful effort to generate such a derivative, various methods of guanidylation were employed, which demonstrate that the acridine C9−N9 linkage is highly susceptible to electrophilic and nucleophilic attack. The newly established reactivities provide efficient pathways to novel cyclic and spirocyclic acridine derivatives.

Acridine derivatives have a broad range of applications as chemotherapeutic agents in the treatment of cancer and protozoal diseases. The primary biological target of acridines is genomic DNA, to which they bind through intercalation to inhibit crucial DNA-processing enzymes, such as human and bacterial topoisomerases.[1] The DNA-binding affinity and the dynamic properties of the intercalator−DNA complex are two important factors that modulate the biological activity of these agents. These parameters can be optimized by tuning the electronics of the acridine chromophore, which also affects its basicity, and by introducing pendant, nonintercalating groups.[1] The latter include side chains, especially in the 4 and 9 positions of the polyaromatic system, which often produce specific and/or nonspecific interactions with the DNA grooves.[2]

The compound 1-[2-(*acr*idin-9-yl*am*ino)ethyl]-1,3-dimethyl*thiou*rea (ACRAMTU), a 9-aminoacridine derivative modified with a thiourea side chain (Figure 1), has shown promising cytotoxicity in various cancer cell lines.[3] Its protonated form ($pK_a \approx 9.8$) intercalates into DNA regiospecifically, with the thiourea moiety residing in the minor groove.[4] While the compound proved to be moderately active by itself, it produces its true cytotoxic potential as a DNA-targeted carrier ligand in platinum−intercalator hybrid agents, in which thiourea sulfur is modified with a DNA-metalating group.[5,6] To establish structure−activity relationships within these conjugates, we are making systematic changes to the acridine ligand. We were particularly interested in the guanidine analogue of ACRAMTU in which thiourea S has been replaced with imino NH (Figure 1). The synthetic studies leading to this molecule, which reveal unexpected reactivity features of the 9-aminoacridine chromophore, are reported in this paper.

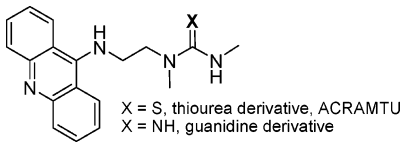
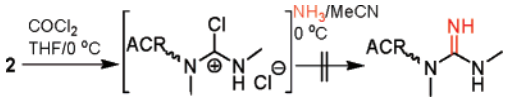


FIGURE 1. Structure of ACRAMTU and its guanidine analogue.

When undertaking a survey of the guanidine synthetic organic literature, it appeared that the target molecule might be accessible via direct transformation of the thiourea sulfur in ACRAMTU into guanidine imine [the thiourea derivative, **2**, can be conveniently synthesized by reacting *N*-acridin-9-yl-*N*′-methylethane-1,2-diamine (**1**) with methylisothiocyanate;[5] Scheme 1]. Several guanidylation reactions have been described that involve Lewis acid-promoted desulfuration,[7] oxidation,[8,9] or alkylation[10] of thiourea sulfur and subsequent reaction of the reactive intermediate with ammonia or a primary/secondary amine. Unfortunately, all attempts to generate the target molecule directly from compound **2** by the above-mentioned methodologies were unsuccessful. Desulfuration of **2** with phosgene, for instance, and ammoniolysis of the resulting chloroformamidinium salt at low temperatures[11] did not give the desired product:



Instead, the reaction leads to cyclization due to intramolecular nucleophilic attack of the exocyclic 9-amino nitrogen on the reactive formamidinium carbon, giving compound **3** (Scheme 1), which was isolated as the guanidinium chloride salt (the second equivalent of HCl released in this condensation is bound by the base added; here, NH_3).

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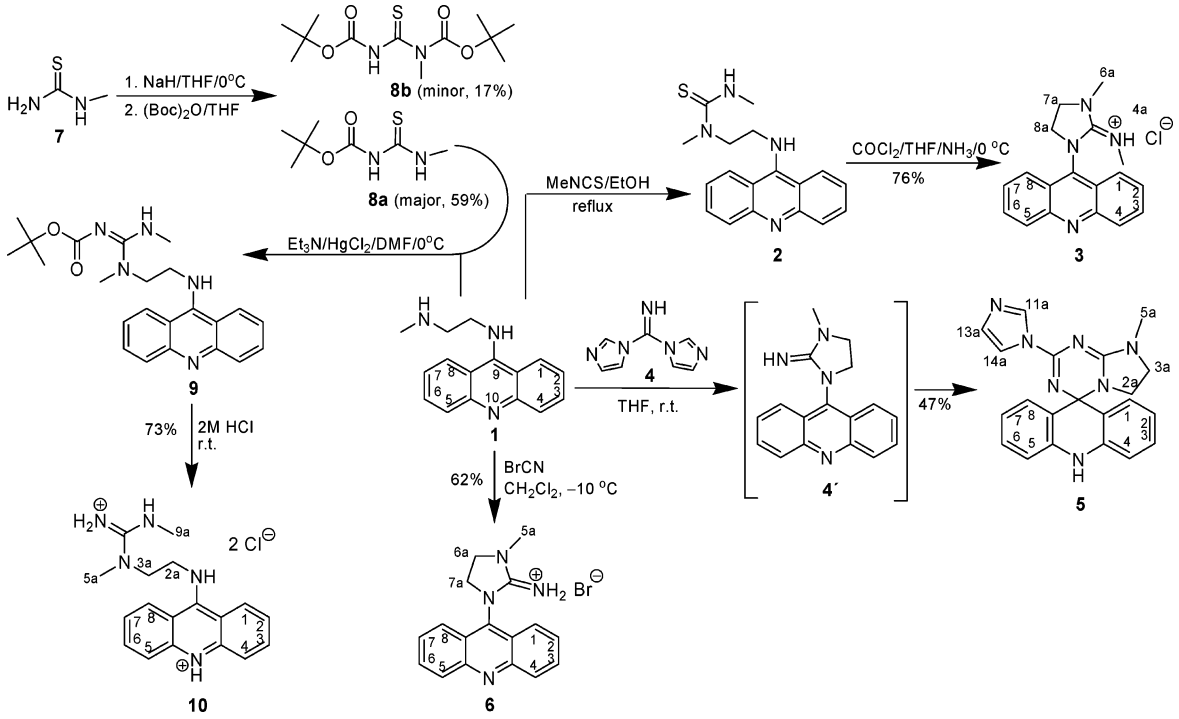
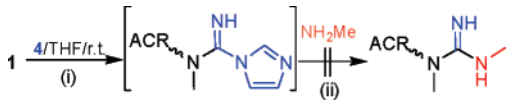
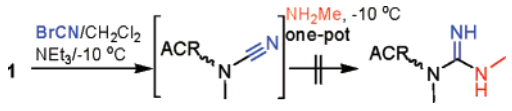
SCHEME 1



Next, we attempted the stepwise buildup of the guanidine moiety starting from precursor **1**. The first strategy involved sequential replacement of imidazole in di(imidazol-1-yl)methanimine (**4**), a versatile guanidylating reagent,[12] by (i) the secondary amino group in **1** and (ii) methylamine:



According to the literature, reactions of **4** with 1 equiv of secondary alkylamine at room temperature afford the monosubstituted intermediates in 60−80% yield, which can be isolated and reacted with a second equivalent of amine to give the desired guanidine.[12] However, in the case of amine **1**, this reaction leads to the formation of an unusual spirocyclic product, **5** (Scheme 1), which indicates the consumption of 2 equiv of reagent **4**. Retrosynthetic analysis of compound **5** indicates that the first equivalent must have yielded a cyclized product **4′** similar to compound **3**, which could not be isolated because the species reacts readily with a second equivalent of **4** via release of one imidazole group to afford **5**. (Initially, equimolar amounts of **1** and **4** were reacted, and the stoichiometry was subsequently optimized by applying 2 equiv of reagent **4**.) Finally, conversion of **1** into the cyanamide by use of cyanogen bromide[13] at −10 °C in the presence of base, followed by treatment of the reactive intermediate with methylamine in a one-pot reaction, failed to produce the guanidine derivative of ACRAMTU:



As in the previous cases, this method leads to formation of a five-membered ring affording compound **6**, the hydrobromide salt of the nonisolable intermediate **4′** implicated in the formation of **5** (Scheme 1). The only strategy to avoid cyclization and feasible pathway to the target guanidine involved addition of the secondary amino group in precursor **1** to Boc-activated *N*-methylthiourea (**8a**)[14] after desulfuration with $HgCl_2$,[15] followed by treatment of the Boc-modified intermediate **9** with dilute acid, giving the dihydrochloride salt of 1-[2-(acridin-9-ylamino)ethyl]-1,3-dimethylguanidine (**10**) (Scheme 1).

The present study reveals two unusual reactivity features of the 9-aminoacridine chromophore, which can be considered the result of the high nucleophilicity of exocyclic N9 and electrophilicity of C9 directly attached to it. The former reactivity leads to cyclization due to intramolecular nucleophilic attack of N9 on the activated formamidinium, guanidyl, and cyanamide carbon to produce compounds **3**, **5** (via **4′**), and **6**, respectively. Formation of a five-membered ring is apparently favored over reaction with external nucleophiles (amines), prohibiting the formation of compound **10**. Furthermore, the inherently basic conditions in these systems produced by the external amines (**3**, **6**) or by the basic guanidyl imino group (**5**) have the potential to deprotonate the 9-amino nitrogen, thereby increasing the nucleophilicity of N9. While formation of five-membered cyclic guanidines from 1,2-diamines has been observed previously,[16] cyclization of **1** should be unfavorable because of the loss of resonance stabilization between N9 and the aromatic system, as implicated by the molecular structures of **3** and **6**. The disruption of N9 conjugation has consequences for the basicity,

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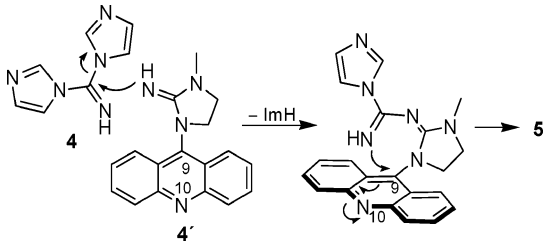
SCHEME 2



DNA affinity, and biological activity of these agents (see discussion below).

On the other hand, transformation of C9 in **4′**, the free-base form of **6** implicated in the formation of **5**, into an sp^3-hybridized spiro carbon, demonstrates that this ring atom is highly susceptible to nucleophilic attack. Ab initio calculations on compound **4′**, indeed, indicate that C9 carries the highest positive charge of the polyaromatic ring atoms, whereas a high negative charge is localized on the guanidine imino nitrogen (Supporting Information). Scheme 2 shows the proposed mechanism of formation for **5**. The first step involves nucleophilic attack of guanidine nitrogen on reagent **4** and release of imidazole (ImH). This produces an intermediate in which the modified 9-guanidyl residue and the acridine chromophore are essentially orthogonal to each other, positioning the imino nitrogen in close proximity to the reactive C9. In the final step, (concerted) proximal nucleophilic attack of the imino nitrogen on C9 and proton transfer to N10 then leads to the formation of a six-membered dihydrotriazine ring to afford the spiro compound, **5**. Spiro compounds incorporating the (9-amino)dihydroacridine moiety are rare, and only structures modified with five-membered heterocyclic rings at the 9-position have been reported in the literature.[17,18] The present synthesis provides a convenient way to introduce a six-membered triazine-type ring at C9, a structural motif previously unknown in this type of compound.

The molecular structures of compounds **3**, **5**, **6**, and **10** were determined by single-crystal X-ray crystallography. In the structure of **3** (Figure S9a, Supporting Information), which was first predicted on the basis of scalar connectivities in heteronuclear 2-D NMR spectra, the acridine and guanidinium rings adopt an almost perpendicular orientation with an angle of 87.88° between mean planes. The 9-amino nitrogen deviates significantly from planarity, as can be expected for a partial $sp^2 \rightarrow sp^3$ rehybridization due to disruption of conjugation with the polyaromatic ring system. Characteristically, nitrogen is displaced by 0.244 Å from the plane through the adjacent carbon atoms. Note that the exocyclic guanidine nitrogen and not the 9-aminoacridine is protonated in this molecule. Similar structural details are observed in the guanidinium cation of compound **6** (Figure S9b). The crystal structure of compound **5** confirms the spirocyclic nature of this molecule (Figure S9c). It indicates the loss of aromaticity of the central ring and the associated bent geometry of the 9,10-dihydroacridine, in which the angle between the mean planes through the outermost phenyl rings is 26.93°. In contrast, the structure of dicationic **10** in the solid state confirms the desired open-chain structure containing a protonated classical 9-aminoacridine moiety and a terminal guanidinium group (Figure S9d).

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TABLE 1. Summary of Chemical and Biological Characterization for 3, 6, and 10

compd	pK_{a1}, pK_{a2}[a]	K_{app}[b] (M^{-1})	IC_{50}[c] (μM)
3	2.6, 9.4	$<10^3$	>100
6	2.7, 7.9	5.1×10^3	>100
10	8.9, >12	1.5×10^4	10.26

[a] Spectrophotometric and ^{1}H NMR spectroscopic pH titrations. pK_{a1} and pK_{a2} reflect the protonation of the endocyclic acridine and guanidine nitrogen, respectively. [b] Apparent binding constant in calf thymus DNA. [c] Concentrations of drug needed to inhibit proliferation of H460 lung cancer cells by 50%; average of two experiments.

Compounds **3**, **6**, and **10** were further characterized in solution to assess their utility as DNA targeted agents, and their cytotoxicities were determined in H460 lung cancer cells. Unlike the acridinium/guanidinium salts, spiro compound **5** proved to be insoluble in biologically relevant buffers, consistent with the fact that none of its nitrogen atoms is protonable at pH 7, and it was not included in this study. Relevant data are summarized in Table 1. An important finding is that compounds **3** and **6** exist as *mono*cations at physiological pH, whereas derivative **10** forms a *di*cation. This can be attributed to the dramatically decreased proton affinities of the acridine chromophores' endocyclic nitrogens in **3** and **6** compared to **10** (Table 1), a consequence of the geometry-enforced disruption of electronic communication between the acridine chromophores and the 9-amino nitrogens, which have become part of the cyclic guanidinium moieties. These critical differences ultimately affect the DNA binding and biological activity of the molecules. The classical 9-aminoacridine derivative **10** showed the highest DNA-binding affinity and proved to be the only compound that showed an appreciable cytotoxic effect in H460 lung cancer cells in vitro. In addition to the less favorable electrostatics in **3** and **6**, the steric hindrance produced by the bulky guanidyl groups may not allow efficient intercalation of the acridine moiety into the DNA base stack, potentially limiting the agents' cytotoxic potential.

In conclusion, in a successful effort to synthesize the guanidine analogue of the anticancer active 9-aminoacridine derivative ACRAMTU, we encountered unexpected reactivity features of the acridine C9−N9 linkage. On the basis of our observations, new methodologies were developed that allow the formation of two novel structural motifs in this class of compounds: (i) incorporation of N9 into a five-membered cyclic guanidinium group and (ii) transformation of C9 into a spiro carbon as part of a triazine-type heterocycle. Further application of these methodologies will lead to novel acridines of potential biological interest.

Experimental Section

(*Z*)-*N*-[1-(Acridin-9-yl)-3-methylimidazolidin-2-ylidene]methanamine Hydrochloride, 3. To a solution of 1-[2-(acridin-9-ylamino)ethyl]-1,3-dimethylthiourea (**2**) (127 mg, 0.39 mmol) in 5 mL of dry tetrahydrofuran (THF) was added dropwise phosgene (1.41 mL, 1.93 M solution in toluene) at 0 °C. The mixture was stirred for 2 h at this temperature and for another 1 h at room temperature. The solvents and excess phosgene were removed under vacuum. The hygroscopic residue was dissolved in 120 mL of dry acetonitrile, and into the solution was bubbled ammonia gas for 2 h. Solvent was evaporated, and the residue was recrystallized from ethanol to afford the product as yellow needles. Yield 98 mg (76%); mp 238−239.5 °C; ^{1}H NMR (D_2O) δ 8.09 (4H, two overlapping d), 7.92 (2H, t, J = 8.7 Hz), 7.78 (2H, t, J = 7.5 Hz), 4.17 (H7a

and H8a, 4H, m), 3.27 (H6a, 3H, s), 1.98 (H4a, 3H, s); ^{13}C-{H} NMR (D_2O) δ 158.2, 148.8, 140.1, 132.26, 129.0, 128.6, 123.6, 122.3, 51.6, 49.8, 32.9, 29.1; ESI-MS (MeOH, +ve mode) *m/z* 291.9 $[M]^+$. Anal. ($C_{18}H_{19}N_4Cl \cdot 0.5C_2H_5OH$) C, H, N: calcd 65.23, 6.34, 16.01; found 65.52, 6.19, 15.77.

2′-(1*H*-Imidazol-1-yl)-8′-methyl-7′,8′-dihydro-6′*H*,10*H*-spiro-[acridine-9,4′-imidazo[1,2-*a*][1,3,5]triazine], 5. To precursor **1** (251.1 mg, 1.0 mmol) in 10 mL of dry THF was added di(imidazol-1-yl)methanimine (**4**) (338.3 mg, 2.1 mmol). The mixture was allowed to stir at room temperature for 10 h and then stored at −4 °C for several days. The resulting yellow crystals were filtered off, washed with cold THF and ether, and dried under vacuum. Yield 173 mg (47%); mp 261.5−262.5 °C; ^{1}H NMR (DMF-d_7) δ 9.58 (NH, 1H, s), 8.40 (H11a, 1H, t), 7.71 (H13a, 1H, t, J = 1.13 Hz), 7.42 (H1 and H8, 2H, d, J = 7.85 Hz), 7.26 (H3 and H6, 2H, t, J = 7.55 Hz), 7.04 (H4 and H5, 2H, d, J = 7.77 Hz), 6.98 (H14a, 1H, t), 6.94 (H2 and H7, 2H, t, J = 7.42 Hz), 3.42 (H3a, 2H, t, J = 8.73 Hz), 3.02 (H5a, 3H, s), 2.95 (H2a, 2H, t, J = 8.12 Hz); ^{13}C-{H} NMR (DMF-d_7) δ 159.6, 149.8, 138.9, 136.6, 129.6, 129.5, 128.8, 121.4, 120.7, 117.3, 114.7, 74.0, 46.6, 42.5, 31.1. Anal. ($C_{21}H_{19}N_7 \cdot 0.25$THF) C, H, N: calcd 67.50, 5.40, 25.04; found 67.55, 5.14, 25.40.

1-(Acridin-9-yl)-3-methylimidazolidin-2-imine Hydrobromide, 6. To a solution of compound **1** (251 mg, 1.0 mmol) in 10 mL of dry CH_2Cl_2 was added 0.2 mL of triethylamine. After the yellow solution was cooled to −10 °C, BrCN (111.2 mg, 1.05 mmol) was added slowly to the stirred solution; the temperature was not allowed to rise above −5 °C. When the addition was complete, the mixture was stirred for another 1.5 h. Solvent was removed, and the residue was washed with a small amount of ice-cold water and dried in vacuum. After recrystallization from hot ethanol, compound **6** was obtained as a yellow microcrystalline solid. Yield 221 mg (62%); mp 270−271.5 °C; ^{1}H NMR (D_2O) δ 8.48 (4H, overlapping d), 8.40 (2H, t), 8.09 (2H, t), 4.46 (H7a, 2H, m), 4.32 (H6a, 2H, m), 3.29 (H5a, 3H, s); ^{13}C-{H} NMR (D_2O) δ 157.4, 148.1, 141.4, 138.6, 130.4, 125.3, 124.2, 120.8, 51.3, 49.8, 32.4; ESI-MS (MeOH, +ve mode) *m/z* 277.0 $[M]^+$. Anal. ($C_{17}H_{17}N_4Br \cdot 0.1C_2H_5OH$) C, H, N: calcd 57.10, 4.90, 15.48; found 56.73, 4.73, 15.28.

***N*-Methyl-*N*′-*tert*-butoxycarbonylthiourea, 8a, and *tert*-Butyl-*tert*-butoxycarbonyl carbamothioyl(methyl)carbamate, 8b.** A mixture of *N*-methylthiourea (**7**) (1.69 g, 18.7 mmol) and NaH (0.9 g, 22.5 mmol, 60% in mineral oil) in 550 mL of dry THF was stirred for 15 min under Ar at 0 °C. To the solution was added di-*tert*-butyl dicarbonate (4.25 g, 19.5 mmol), and stirring was continued for another 30 min. A white slurry formed within 30 min, which was stirred for another 3 h at room temperature. The reaction mixture was quenched with 50 mL of saturated aqueous $NaHCO_3$, poured into 450 mL of water, and extracted with ethyl acetate (5 × 150 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The reaction mixture was separated on an alumina column with ethyl acetate/hexane (1:5) to afford 2.11 g (59%) of **8a** (R_f = 0.39), and 0.95 g (17%) of **8b** (R_f = 0.50) as white and pale yellow solids, respectively. **8a**: ^{1}H NMR ($CDCl_3$) δ 9.68 (1H, br s), 7.92 (1H, br s), 3.17 (3H, d), 1.48 (9H, s); ^{13}C-{H} NMR ($CDCl_3$) δ 180.5, 151.9, 83.7, 32.0, 28.0. **8b**: ^{1}H NMR ($CDCl_3$) δ 12.14 (1H, br s), 3.58 (3H, s), 1.55 (9H, s), 1.51 (9H, s); ^{13}C-{H} NMR ($CDCl_3$) δ 181.2, 154.4, 150.1, 85.4, 82.4, 31.3, 28.0, 27.9.

***tert*-Butyl-{[2-(acridin-9-ylamino)ethyl]methylamino(methylamino)methylene} carbamate, 9.** Boc-protected thiourea **8** (460.0 mg, 2.41 mmol), precursor **1** (668.1 mg, 2.66 mmol), and 0.75 mL of triethylamine were dissolved in 12 mL of dry *N*,*N*-dimethylformamide (DMF). The solution was cooled to 0 °C and solid $HgCl_2$ (723.0 mg, 2.66 mmol) was added. The mixture was stirred for 1 h at this temperature and another 4 h at room temperature until the yellow slurry had turned black. DMF was removed at 30 °C in vacuum, and the residue was redissolved in ethyl acetate, filtered through Celite, and dried over Na_2SO_4 overnight. After the solvent was removed, the crude product thus obtained was purified by flash chromatography on an alumina column with methanol/ethyl acetate/hexanes (1:2:2) as the mobile phase, which yielded **8** as a yellow microcrystalline powder. Yield 730 mg (74.0%); ^{1}H NMR (MeOH-d_4) δ 8.27 (2H, br s), 7.51 (4H, br s), 7.19 (2H, br s), 4.02 (2H, t), 3.70 (2H, t), 2.80 (3H, s), 2.65 (3H, s), 1.37 (9H, s); ^{13}C-{H} NMR (MeOH-d_4) δ 161.1, 132.3, 78.9, 38.0, 30.5, 29.3, 26.0, 24.3.

1-[2-(Acridin-9-ylamino)ethyl]-1,3-dimethylguanidine Dihydronitrate, 10. Compound **9** (730 mg, 1.79 mmol) was dissolved in 200 mL of 2 M HCl, and the mixture was stirred at room temperature for 12 h. Acid was removed under vacuum, and the resulting residue was dissolved in a minimum amount of ethanol. Ether was added into the solution to precipitate the product as a yellow microcrystalline solid, which was filtered and dried under vacuum at 60 °C for 2 days. Yield 510 mg (73%); mp 260.5−261.5 °C; ^{1}H NMR (D_2O) δ 8.11 (H1/H8, 2H, d, J = 8.59 Hz), 7.95 (H3/H6, 2H, t, J = 6.90 Hz), 7.61 (H4/H5, 2H, d, J = 8.61 Hz), 7.55 (H2/H7, 2H, t, J = 6.91 Hz), 4.32 (H2a, 2H, t, J = 5.58 Hz), 3.59 (H3a, 2H, t, J = 5.41 Hz), 2.37 (H5a, 3H, s), 2.12 (H9a, 3H, s); ^{13}C-{H} NMR (D_2O) δ 159.3, 156.4, 139.2, 136.1, 124.9, 124.5, 118.9, 112.4, 50.6, 46.2, 36.1, 27.9; ESI-MS (MeOH, +ve mode) *m/z* 308.1 $[M - H]^+$. Anal. ($C_{18}H_{23}Cl_2N_5 \cdot H_2O \cdot 0.5C_2H_5OH$) C, H, N: calcd 54.15, 6.69, 16.62; found 53.69, 6.46, 16.48.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for the new compounds, X-ray crystallographic details in CIF format, views of compounds **3**, **5**, **6**, and **10** in the solid state, results of the ab initio calculations, and experimental details for the pH and DNA−drug titrations and cell proliferation assays. This material is available free of charge via the Internet at http://pubs.acs.org.

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