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Synthesis of 13-acylamino-huprines: different behavior of diastereomeric 13-methanesulfonamido-huprines on PPA-mediated hydrolysis

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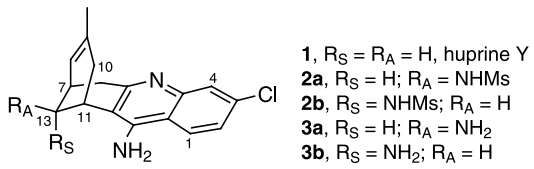
Abstract—Two diastereomeric pairs of rationally designed huprines additionally substituted at position 13 with a formamido or an acetamido group have been synthesized as potential high affinity acetylcholinesterase inhibitors. The synthetic sequence involves hydrolysis of two diastereomeric 13-methanesulfonamido-huprines, followed by acylation of the resulting diastereomeric amines. In the hydrolysis reaction, carried out with PPA under harsh conditions, significant amounts of cyclized or rearranged by-products were also formed, depending on the stereochemistry of the starting compound.

1. Introduction

Huprines have recently emerged as a novel class of high affinity central acetylcholinesterase (AChE) inhibitors of interest for the treatment of Alzheimer's disease, which have shown to be superior in terms of affinity, potency and selectivity to most of the currently approved drugs for this disorder. This is probably due to their extended binding near the active site of AChE.[1–5] By the moment, the most powerful huprines are the so-called huprine Y [(−)-**1**, Fig. 1] and its 9-ethyl analogue, huprine X. The last one binds to the human enzyme with one of the highest affinities yet reported for a reversible AChE inhibitor (inhibition constant K_I 26 pM).



1, $R_S = R_A = H$, huprine Y
2a, $R_S = H$; $R_A = NHMs$
2b, $R_S = NHMs$; $R_A = H$
3a, $R_S = H$; $R_A = NH_2$
3b, $R_S = NH_2$; $R_A = H$

Figure 1. Structures of huprine Y, 13-methanesulfonamido-huprines **2a**,**b** and 13-amino-huprines **3a**,**b**.

On the basis of molecular modeling studies[1–3,6] and the 3D X-ray diffraction analysis of a complex of *Torpedo californica* AChE-huprine X,[7] we designed a new series of huprines, functionalized at position 13 with a formamido or acetamido group as new AChE inhibitors. These compounds, with more extended binding near the active site of AChE are expected to have higher AChE affinities. We recently described the synthesis of compounds **2a**,**b** (Fig. 1) as advanced intermediates for the synthesis of these new 13-acylamino-huprines,[8] which requires cleavage of the methanesulfonamido group of **2a**,**b** followed by acylation of the resulting primary amines **3a**,**b**.

Although arene- and alkane-sulfonyl groups have been used to protect amines, removal of these protective groups is not an easy task, and usually requires drastic conditions that may not be compatible with other functional groups present in the substrate. To solve this problem, many alternative deprotection procedures have been developed. However, most of them are not general, strongly depending on the nature of the aryl or alkyl rest bound to the sulfur atom and on the degree of substitution of the nitrogen atom.[9–26] Thus, most methods allow the cleavage of arenesulfonamides, mainly *p*-toluenesulfonamides, while very few methods have been reported for the cleavage of methanesulfonamides. Regarding the degree of substitution at the nitrogen atom, most methods allow the deprotection of sulfonamides of secondary amines (usually aromatic), while they completely fail to cleave sulfonamides of primary amines (especially aliphatic). To the best of our knowledge, only three examples of cleavage of methane- or alkanesulfonamides derived from aliphatic primary amines (the substitution pattern of compounds **2a**,**b**) have been reported, involving acidic conditions (Zn/HOAc at room temperature[12] or $MeSO_3H/H_2O$ at 135 °C[11]) or photolytic

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cleavage,[26] the amines being always obtained in low to moderate yields (20–66%).

In this paper, we report the unprecedented hydrolysis of the *N*-monosubstituted methanesulfonamides **2a** and **2b** using PPA to the corresponding amines **3a** and **3b**, as well as the formation of important amounts of cyclized or rearranged by-products, depending on the configuration at position 13 of the starting methanesulfonamides, and the conversion of the amines **3a** and **3b** into the rationally designed new huprines **18a**, **18b**, **19a** and **19b**.

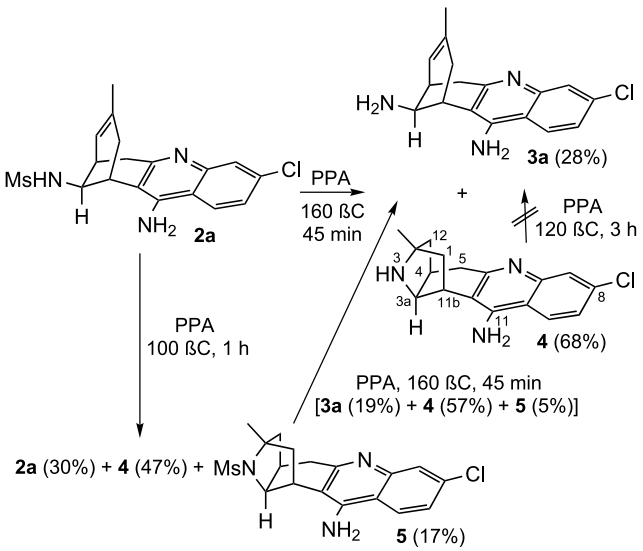
2. Results and discussion

Initial attempts to hydrolyze **2b**, on reaction with $MeSO_3H/H_2O$ at 135 °C or with Zn/HOAc under different reaction conditions, left the starting material unchanged. In view of these disappointing results and the low yield of the above mentioned photolytic deprotection method, we tried other methodologies. HBr has proved to be efficient in the deprotection of methanesulfonamides derived from primary aromatic amines.[9] Unfortunately, reaction of **2b** with 48% aq. HBr under reflux led to a complex mixture of products. Sulfuric acid has been commonly used to cleave many methanesulfonamides of primary aromatic amines.[9] However, reaction of a 1:1 diastereomeric mixture of **2a** and **2b** with a 1:1 mixture H_2SO_4/H_2O for 30 min under reflux left the starting material unchanged. Fortunately, the use of polyphosphoric acid (PPA) for the hydrolysis of **2a** afforded better results. Under the best reaction conditions (**2a** and PPA, 160 °C, 45 min), amine **3a** was obtained in 28% yield together with the pentacyclic amine **4** (68% yield) (entry 5, Table 1), which were separated by column chromatography (Scheme 1).

Table 1. Conditions and products in the reaction of methanesulfonamides **2a** and **5** with PPA

Entry	Compound	Conditions		Reaction products (%)			
		T (°C)	*t* (h)	**2a**	**3a**	**4**	**5**
1	**2a**	100	1	30		47	17
2	**2a**	115	2		13	56	6
3	**2a**	140	1.5		22	72	
4	**2a**	140	15			61	
5	**2a**	160	0.75		28	68	
6	**2a**	200	0.33		23	57	
7	**5**	160	0.75		19	57	5

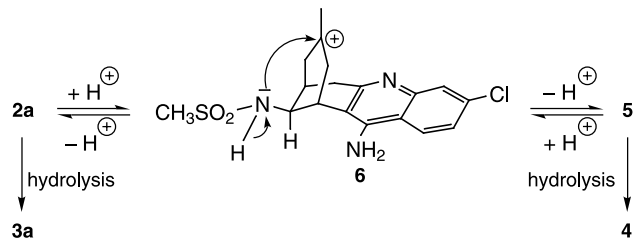
Interestingly, when this reaction was carried out at 100 °C for 1 h, **4** was again the main product (47% yield), and no amine **3a** was obtained, pentacyclic methanesulfonamide **5** (17% yield) and starting **2a** (30%) being isolated instead (entry 1, Table 1). The increase in temperature (115 °C) and reaction time (2 h) led to a total consumption of **2a** and to the formation of the desired amine **3a** (13% yield), while the yield of amine **4** increased and that of **5** greatly decreased (entry 2, Table 1). When the reaction was carried out at 140 °C for 1.5 h, **3a** and **4** were obtained in 22 and 72% yield, respectively, while increasing the reaction time to 15 h, **4** was the only isolated product (entries 3 and 4, Table 1). Finally, when the reaction was carried out at



Scheme 1. Reaction of methanesulfonamides **2a** and **5** with PPA.

200 °C for 20 min, **3a** and **4** were obtained in 23 and 57% yield, respectively (entry 6, Table 1).

When methanesulfonamide **5** was reacted with PPA at 160 °C for 45 min, the amines **3a** and **4** were obtained in 19 and 57% yield, respectively, after column chromatography, together with a small amount of unreacted **5** (entry 7, Table 1) (Scheme 1). However, **4** could not be converted into the desired amine **3a** under similar reaction conditions. From these results, we can conclude that methanesulfonamide **5** is formed from **2a** in a reversible process under the reaction conditions. The conversion of **2a** to **5** can take place by protonation of the C=C double bond at the less substituted carbon atom to give a tertiary carbocation followed by intramolecular addition of the sulfonamido nitrogen atom and deprotonation (Scheme 2).



Scheme 2. Possible mechanistic pathway for the formation of **4** and **5** from **2a**.

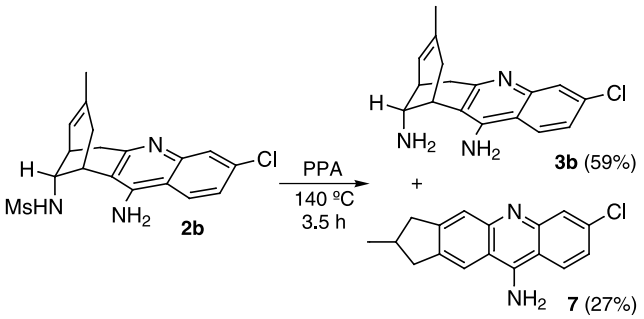
Hydrolysis of methanesulfonamides **2a** and **5** would lead to amines **3a** and **4**, respectively. The interconversion of **5** and **2a** under the reaction conditions explains the formation of both amines **3a** and **4** in the reactions of sulfonamides **2a** or **5** with PPA at 160 °C. The failure of amine **4** to give amine **3a** on reaction with PPA supports the intermediacy of sulfonamide **2a** in the formation of amine **3a** from sulfonamide **5**.

The conversion of **2a** to **5** seems to be faster than its hydrolysis to **3a**, since **5** is formed from **2a** at temperatures around 100 °C, while formation of **3a** from **2a** requires higher temperatures (around 115 °C). Also, not

unexpectedly, hydrolysis of the *N*,*N*-disubstituted methanesulfonamide **5** to **4** (47% yield from **2a** and PPA at 100 °C) appears to be faster than hydrolysis of the *N*-monosubstituted methanesulfonamide **2a** to **3a** (not formed under the same reaction conditions, entry 1, Table 1).

Contrary to **2b**, the reaction of **2a** with 48% aq. HBr (using phenol as solvent under reflux for 7 h)[27] afforded the amines **3a** and **4** in 24 and 53% yield, after column chromatography.

A completely different behavior towards PPA was exhibited by the diastereomeric methanesulfonamide **2b**. Thus, treatment of **2b** with PPA at 100 °C for 1–4 h left the starting material unchanged, but the increase in the reaction time to 15 h led to the formation of the desired amine **3b** in 46% yield, together with a by-product, which was characterized as aminocyclopentaacridine **7** (Scheme 3, entries 1 and 2, Table 2).



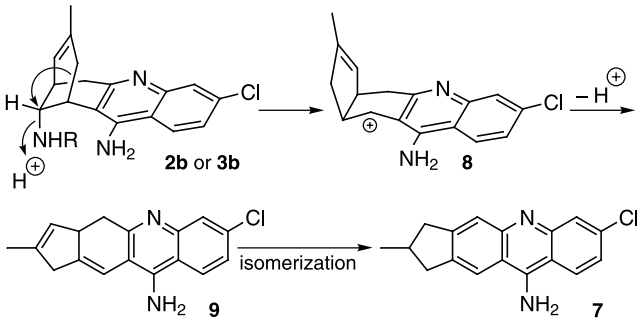
Scheme 3. Reaction of methanesulfonamide **2b** with PPA.

Table 2. Conditions and products in the reaction of methanesulfonamide **2b** with PPA

Entry	Conditions		Reaction products		
	T (°C)	*t* (h)	**2b**	**3b**	**7**
1	100	1 (4)	100 (84)		
2	100	15		46	12
3	130	3.75	7	37	21
4	130	4.5		57	26
5	140	3.5		59	27
6	150	1.75		50	33

Increasing the reaction temperature to 130–140 °C with reaction times of 3.5–4.5 h higher yields of both **3b** and **7** were obtained (entries 3–5, Table 2). Under the best reaction conditions (**2b** and PPA, 140 °C, 3.5 h), **3b** and **7** were obtained in 59 and 27% yield, respectively (Scheme 3 and entry 5, Table 2). When the reaction was carried out at 150 °C, a slightly lower yield of **3b** and a slightly higher yield of **7** were obtained (entry 6, Table 2).

In this case, the *anti*-arrangement of the 13-methanesulfonamido group and the propeno bridge of **2b** prevents any transannular reaction. However, the *antiperiplanar* arrangement of the C10–C11 sigma bond and the methanesulfonamido group favors the formation of by-product **7**, which can be rationalized on the basis of a concerted 1,2-migration of C10 from C11 to the vicinal position 13 of **2b**, which becomes electron poor by the departure of the protonated sulfonamido group. Deprotonation of the resulting carbocation **8** and C=C double bond isomerization would give the more stable compound **7**, containing a more extended aromatic system (Scheme 4).

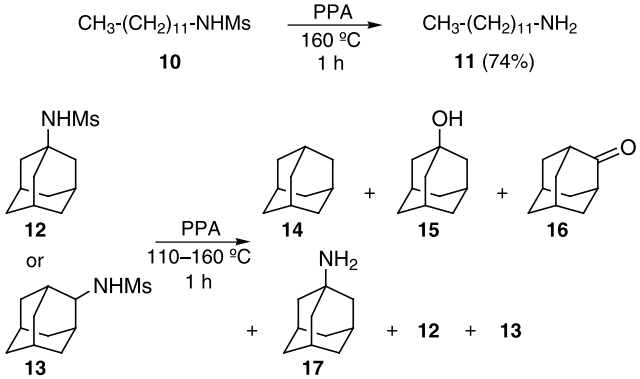


Scheme 4. Possible mechanistic pathway for the formation of **7** from **2b** or **3b**.

In sharp contrast with the results obtained in the **a** series, in this case, the hydrolysis product **3b** was always the main reaction product, thus indicating that hydrolysis is easier than rearrangement to **7**.

The increase in the yield of **7** together with the decrease in the yield of **3b** when this reaction was carried out at 150 °C (compare entries 5 and 6, Table 2) may be indicative of the alternative formation of **7** from **3b**, a transformation that could take place through the mechanism shown in Scheme 4, being R=H.

To assess the scope of this procedure of hydrolysis of methanesulfonamides derived from aliphatic primary amines, three known methanesulfonamides with different degree of substitution at the α-nitrogen position were submitted to the PPA hydrolysis conditions: *N*-dodecyl-,[28] *N*-(1-adamantyl)-,[29] and *N*-(2-adamantyl)-methanesulfonamide,[29] **10**, **12**, and **13**, respectively. Reaction of **10** with PPA at 160 °C for 1 h proceeded efficiently, affording the expected amine in 74% yield (Scheme 5). Lower reaction temperatures (110 or 140 °C) left significant amounts of starting material unchanged (89 and 30%, respectively). In sharp contrast, reaction of adamantylmethanesulfonamides **12** and **13** with PPA at 110 °C for 1 h gave similar mixtures not containing the expected amines. Thus, GC–MS and ^{13}C NMR analysis of the mixtures obtained from **12** and **13** revealed the presence of adamantane,

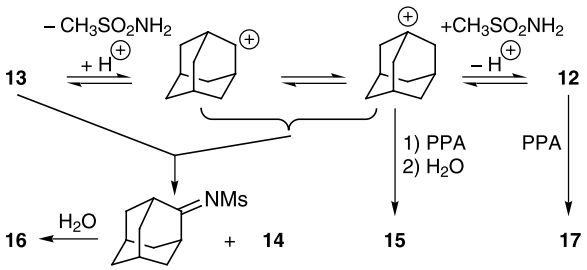


Scheme 5. Reaction of methanesulfonamides **10**, **12**, and **13** with PPA.

1-adamantanol, 2-adamantanone, **12**, and **13** (the area ratios by GC–MS are shown in Table 3) (Scheme 5). The presence of sulfonamides **12** and **13** in both mixtures indicates that these compounds may be interconverting under the reaction conditions, probably through the intermediacy of 1- and 2-adamantyl carbocations (Scheme 6). Formation of adamantane could be explained from 1- or 2-adamantyl cations by hydride abstraction, while 2-adamantanone could be formed from **13** by transfer of a hydride from position 2 to an adamantyl carbocation, followed by hydrolysis of the resulting imino derivative (Scheme 6). The ratio adamantane/2-adamantanone in these reactions is not significant since part of the volatile adamantane could have been lost during the isolation step. 1-Adamantanol could arise from 1-adamantyl carbocation on reaction with PPA followed by hydrolysis during the basic aqueous work-up (Scheme 6).

Table 3. Conditions and products in the reaction of methanesulfonamides **12** and **13** with PPA

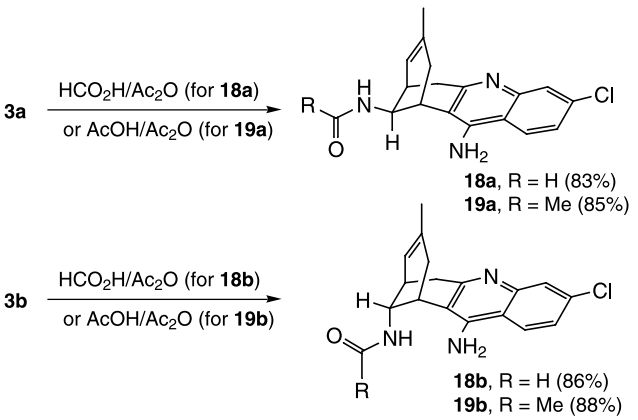
Entry	Compound	Conditions	Reaction products (relative areas by GC–MS)					
		T (°C)	**12**	**13**	**14**	**15**	**16**	**17**
1	**12**	110	36.0	10.8	8.5	15.8	28.8	
2	**13**	110	13.4	3.9	12.2	17.8	52.7	
3	**12**	160			2.2		43.7	19.4
4	**13**	160			11.8		49.6	11.4



Scheme 6. Possible mechanistic pathways for the formation of compounds **12**–**17** from **12** or **13**.

Under more forcing conditions (160 °C), **12** and **13** were fully transformed to give as before similar mixtures containing adamantane and 2-adamantanone, as well as 1-adamantylamine (Scheme 5 and Table 3). In these cases, the formation of 1-adamantanol was not detected, although other unidentified minor by-products were also formed. Although the formation of 1-adamantylamine from **13** is in accord with the previously mentioned interconversion between **12** and **13**, it is not clear why formation of 2-adamantylamine is not observed.

With the diastereomeric amines **3a** and **3b** in hand, we carried out their conversion in good yields into the corresponding 13-formamido (**18a** and **18b**) and 13-acetamido (**19a** and **19b**) derivatives on reaction with HCO_2H/Ac_2O or $AcOH/Ac_2O$ mixtures, respectively (Scheme 7). While the acetamido derivatives were routinely transformed into the corresponding hydrochlorides by treating them with a methanolic solution of HCl, partial hydrolysis of the formamido derivatives was observed when they were submitted to the same reaction conditions.



Scheme 7. Synthesis of 13-formamido and 13-acetamido-huprines **18a**, **18b**, **19a** and **19b** from the diastereomeric amines **3a** and **3b**.

Consequently, the formamido derivatives were characterized as the free base instead of the corresponding hydrochlorides as usual for other huprines.

All of the new compounds have been fully characterized on the basis of IR, ^1H NMR, ^{13}C NMR and MS spectra, and elemental analysis and/or HRMS. Assignment of the NMR spectra was performed with the aid of COSY $^1H/^1H$ and HETCOR $^1H/^{13}C$ experiments and by comparison with related compounds.[1,2,8]

3. Conclusion

In conclusion, we have carried out for the first time a PPA-mediated hydrolysis of *N*-alkyl methanesulfonamides (**2a** and **2b** to amines **3a** and **3b**) in low to moderate yields. Under the strong acidic reaction conditions, competitive side-reactions involving the sulfonamido group at position 13 occur, whose course depends on the stereochemistry of the starting sulfonamides **2a**,**b**. Also, hydrolysis of the *N*,*N*-dialkylmethanesulfonamide **5** took place in medium yield. The method was successfully applied to the hydrolysis of *N*-dodecylmethanesulfonamide, while it failed with *N*-(1-adamantyl)- and *N*-(2-adamantyl)-methanesulfonamide. Thus, the scope of the PPA hydrolysis of methanesulfonamides derived from aliphatic amines seems to be limited by the tendency of the starting sulfonamides to give carbocationic intermediates, from which by-products may be easily derived.

Also, we have prepared the 13-formamido-huprines **18a** and **18b** and the 13-acetamido-huprines **19a** and **19b**, the first examples of a new class of rationally designed huprines with a potentially increased binding near the active site of the enzyme AChE relative to the parent 13-unsubstituted huprines. The AChE inhibitory activity of these compounds, together with that of huprines **2a** and **2b** will be evaluated and reported elsewhere.

4. Experimental

4.1. General

Melting points were determined in open capillary tubes with

a MFB 595010M Gallenkamp melting point apparatus. 500 MHz ^{1}H NMR spectra, and 75.4 and 100.6 MHz ^{13}C NMR spectra were recorded on Varian Inova 500, Varian Gemini 300 and Varian Mercury 400 spectrometers, respectively. The chemical shifts are reported in ppm (δ scale) relative to internal TMS, and coupling constants are reported in Hertz (Hz). Assignments given for the NMR spectra of the new compounds are based on the following experiments: DEPT and COSY ^{1}H/^{1}H (standard procedures), COSY ^{1}H/^{13}C (HMQC sequence with an indirect detection probe). In the case of **7**, also a COSY ^{1}H/^{13}C (gHMBC sequence) was performed. The *syn* (*anti*) notation of the amino or acylamino group at position 13 of compounds **3b** (**3a**), **18b** (**18a**) and **19b** (**19a**) means that the substituent at position 13 is on the same (different) side of the quinoline moiety with respect to the cyclohexene ring. Routine MS spectra were taken on ThermoQuest Trace MS and Hewlett–Packard 5988A spectrometers using the chemical ionization (CH_4) or the electron impact techniques (70 eV, for **7**), respectively: only significant ions are given. HRMS were performed on a Micromass Autospec spectrometer. GC–MS spectra of the crude products of the hydrolyses of compounds **12** and **13** were performed on a Hewlett–Packard 5988A spectrometer, introducing the samples through a gas chromatograph Hewlett–Packard model 5890 Series II, equipped with a 30-meter HP-5 (5% diphenyl-95% dimethyl-polysiloxane) column [10 psi, initial temperature: 50 °C (2 min), then heating at a rate of 10 °C/min till 320 °C, then isothermic for 5 min], and using the electron impact technique (70 eV). IR spectra were run on a FT/IR Perkin–Elmer model 1600 spectrophotometer. Absorption values are expressed as wave-numbers (cm^{-1}); only the most intense absorption bands are given. Flash column chromatography was performed on silica gel 60 AC.C (35–70 mesh, SDS, ref 2000027). Thin-layer chromatography (TLC) was performed with aluminum-backed sheets with silica gel 60 F_{254} (Merck, ref 1.05554), and spots were visualized with UV light and 1% aqueous solution of $KMnO_4$. PPA (H_3PO_4 equivalent approx. 115%) was purchased from Aldrich. Analytical grade solvents were used for crystallization, while pure for synthesis solvents were used in the reactions, extractions and column chromatography. NMR spectra of all of the new compounds and routine mass spectra of **7** were performed at the Serveis Científico-Tècnics of the University of Barcelona, while routine and high resolution mass spectra of the rest of new compounds were carried out at the Mass Spectrometry Laboratory of the University of Santiago de Compostela (Spain) and the elemental analyses of compounds **7**, **18a**, **18b**, **19a** and **19b** were carried out at the Mycroanalysis Service of the IIQAB (CSIC, Barcelona, Spain).

4.1.1. 12,*anti*-13-Diamino-3-chloro-6,7,10,11-tetrahydro-9-methyl-7,11-methanocycloocta[*b*]quinoline dihydrochloride (3a·2HCl) and 11-amino-8-chloro-2,3,3a,4,5,11b-hexahydro-2-methyl-1*H*-2,4-methanopyrrolo[3,2-*a*]-acridine dihydrochloride (4·2HCl). Methanesulfonamide **2a** (240 mg, 0.64 mmol) was added in portions over a 5 min period to stirred PPA (3.65 g) at 160 °C. The reaction mixture was thoroughly stirred at this temperature for 45 min, cooled to room temperature and treated with ice up to a total volume of 10 mL. The resulting suspension was alkalinized with NaOH pellets (pH=12) and extracted with AcOEt (4×50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, and evaporated at reduced pressure, to give a yellowish solid residue (194 mg) which was submitted to flash column chromatography (SiO_2, 8.0 g, hexane/AcOEt/MeOH mixtures, containing 0.3% of Et_3N). On elution with AcOEt/MeOH 96:4, 94:6 and 90:10, pure amine **3a** (33 mg) and mixture of amine **3a**/amine **4** in an approximate ratio of 6:4 (^{1}H NMR, 13 mg), a mixture of **3a/4** in an approximate ratio of 15:85 (82 mg, 28% total yield of **3a**), and pure amine **4** (55 mg, 68% total yield of **4**), were successively isolated.

Dihydrochloride of **3a**. A solution of pure **3a** (18 mg, 60 μmol) in MeOH (3 mL) was treated with a solution of HCl in MeOH (0.48 M, 0.8 mL, 0.38 mmol), heated at 70 °C for 30 min and evaporated at reduced pressure, to give **3a**·2HCl (22 mg) as a yellowish solid: mp>300 °C (dec.) (MeOH); R_f (**3a**, free base) 0.09 (SiO_2, CH_2Cl_2/MeOH, 9:1, containing 0.5% of 25% aq. NH_4OH); IR (KBr) ν 3500–2500 (max. at 3384, 3176 and 2910), 1654, 1630, 1587 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 1.67 (s, 3H, 9-CH_3), 2.12 (d, J=19.5 Hz, 1H, 10-H_{endo}), 2.56 (broad dd, J=19.5 Hz, J'=5.5 Hz, 1H, 10-H_{exo}), 2.92 (m, 1H, 7-H), 3.10 (dd, J=18.0 Hz, J'=1.5 Hz, 1H, 6-H_{endo}), 3.44 (dd, $J\approx$18.0 Hz, J'=5.5 Hz, 1H, 6-H_{exo}), 3.59 (m, 1H, 11-H), 3.79 (m, 1H, 13-H), 4.84 (s, NH^++NH_2+NH_3^+), 5.55 (broad d, J=4.5 Hz, 1H, 8-H), 7.64 (dd, J=9.0 Hz, J'=2.0 Hz, 1H, 2-H), 7.78 (d, J=2.0 Hz, 1H, 4-H), 8.39 (d, $J\approx$9.0 Hz, 1H, 1-H); ^{13}C NMR (75.4 MHz, CD_3OD) δ 23.3 (CH_3, 9-CH_3), 30.1 (CH, C11), 30.6 (CH_2, C10), 31.6 (CH, C7), 35.7 (CH_2, C6), 49.2 (CH, C13), 113.0 (C, C11a), 115.3 (C, C12a), 119.2 (CH, C4), 120.1 (CH, C8), 126.5 (CH, C1), 128.0 (CH, C2), 135.9 (C, C9), 139.7 (C, C4a), 141.0 (C, C3), 151.0 (C) and 156.8 (C) (C5a and C12); *m/z* (CI) 328 [$(M+C_2H_5)^+$, 20], 302 (39) and 300 (100) [$(M+H)^+$], 301 (34), 299 (40), 285 (13) and 283 (32) [$(M-NH_2)^+$], 264 [$(M-Cl)^+$, 64]. HRMS calcd for $C_{17}H_{19}ClN_3$ [$(M+H)^+$]: 300.1268. Found: 300.1253.

Dihydrochloride of **4**. A solution of pure **4** (200 mg, 0.67 mmol) in MeOH (10 mL) was treated with a solution of HCl in MeOH (0.48 M, 8.4 mL, 4.03 mmol), heated at 70 °C for 30 min and evaporated at reduced pressure, to give **4**·2HCl (229 mg) as a yellowish solid: mp>300 °C (dec.) (MeOH); R_f (**4**, free base) 0.02 (SiO_2, CH_2Cl_2/MeOH, 9:1, containing 0.5% of 25% aq. NH_4OH); IR (KBr) ν 3500–2500 (max. at 3360, 3190 and 2867), 1654, 1635, 1594 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 1.54 (dd, $J\approx$12.5 Hz, $J'\approx$3.0 Hz, 1H, 1-H_{endo}), 1.62 (s, 3H, 2-CH_3), superimposed in part 1.64 (dd, J=13.5 Hz, J'=6.0 Hz, 1H, 12-H_{endo}), 2.28 (ddd, J=13.5 Hz, J'=12.0 Hz, J''=3.0 Hz, 1H, 12-H_{enx}), 2.70 (ddd, $J\approx J'\approx$12.5 Hz, J''=3.5 Hz, 1H, 1-H_{exo}), 3.09 (m, 1H, 4-H), 3.23 (broad dd, $J\approx$19.0 Hz, $J'\approx$1.5 Hz, 1H, 5-H_{exo}), 3.41 (dd, J=19.0 Hz, J'=6.0 Hz, 1H, 5-H_{endo}), 3.72 (dm, J=11.5 Hz, 1H, 11b-H), 4.36 (dd, $J\approx J'\approx$5.0 Hz, 1H, 3a-H), 4.85 (s, NH^++NH_2+NH_2^+), 7.63 (dd, J=9.0 Hz, J'=2.0 Hz, 1H, 9-H), 7.82 (d, J=2.0 Hz, 1H, 7-H), 8.40 (d, $J\approx$9.0 Hz, 1H, 10-H); ^{13}C NMR (100.6 MHz, CD_3OD) δ 18.5 (CH_3, 2-CH_3), 29.6 (CH_2, C5), 32.0 (CH, C11b), 32.9 (CH, C4), 39.2 (CH_2, C12), 42.9 (CH_2, C1), 60.1 (CH, C3a), 70.6 (C, C2), 111.8 (C, C11a), 115.3 (C, C10a), 119.3 (CH, C7), 126.5 (CH, C10),

128.1 (CH, C9), 139.9 (C, C6a), 141.1 (C, C8), 149.1 (C) and 157.5 (C) (C5a and C11); *m/z* (CI) 328 [(M+C_2H_5)$^+$, 18], 302 (34) and 300 (100) [(M+H)$^+$], 301 (30), 299 (35), 283 [(M−NH_2)$^+$, 12], 264 [(M−Cl)$^+$, 56]. HRMS calcd for $C_{17}H_{19}ClN_3$ [(M+H)$^+$]: 300.1268. Found: 300.1257.

4.1.2. 11-Amino-8-chloro-2,3,3a,4,5,11b-hexahydro-3-methanesulfonyl-2-methyl-1*H*-2,4-methanopyrrolo[3,2-*a*]-acridine hydrochloride (5·HCl). This reaction was carried out as described for **3a**, from methanesulfonamide **2a** (220 mg, 0.58 mmol) and PPA (3.50 g), heating at 120 °C for 1 h. A yellowish solid (200 mg) was obtained, which was submitted to flash column chromatography (SiO_2, 6.4 g, hexane/AcOEt/MeOH mixtures, containing 0.3% of Et_3N). On elution with hexane/AcOEt 40:60, pure **5** (31 mg) and mixture **5/2a** in an approximate ratio of 3:7 (^{1}H NMR, 21 mg, 17% total yield of **5**) were successively isolated. On elution with hexane/AcOEt 30:70, sulfonamide **2a** (52 mg, 30% total yield) was isolated. Finally, on elution with AcOEt/MeOH 90:10, pure amine **4** (82 mg, 47% yield) was isolated.

Hydrochloride of **5**. A solution of pure **5** (44 mg, 0.12 mmol) in MeOH (3 mL) was treated with a solution of HCl in MeOH (0.48 M, 0.75 mL, 0.36 mmol), heated at 60 °C for 30 min and evaporated at reduced pressure, to give **5**·HCl (45 mg) as a yellowish solid: mp>300 °C (dec.) (MeOH); R_f (**5**, free base) 0.59 (SiO_2, CH_2Cl_2/MeOH, 9:1, containing 0.5% of 25% aq. NH_4OH); IR (KBr) ν 3500–2500 (max. at 3373, 3227 and 2931), 1669, 1636, 1591, 1308, 1140, 1086 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 1.28 (dd, J=11.5 Hz, J'=3.0 Hz, 1H, 1-H$_{endo}$), 1.36 (dd, J=12.5 Hz, J'=6.0 Hz, 1H, 12-H$_{endo}$), 1.65 (s, 3H, 2-CH_3), 2.28 (ddd, $J\approx J'\approx$12.5 Hz, J''=3.0 Hz, 1H, 12-H$_{enx}$), 2.66 (ddd, J=J'=11.5 Hz, J''=3.0 Hz, 1H, 1-H$_{exo}$), 2.92 (m, 1H, 4-H), 3.12 (s, 3H, CH_3SO_2), 3.15 (broad d, $J\approx$19.0 Hz, 1H, 5-H$_{exo}$), 3.36 (dd, $J\approx$19.0 Hz, $J'\approx$6.0 Hz, 1H, 5-H$_{endo}$), 3.47 (dm, J=11.5 Hz, 1H, 11b-H), 4.38 (dd, $J\approx J'\approx$5.0 Hz, 1H, 3a-H), 4.86 (s, NH^++NH_2), 7.61 (dd, J=9.0 Hz, J'=2.0 Hz, 1H, 9-H), 7.77 (d, J=2.0 Hz, 1H, 7-H), 8.36 (d, J=9.0 Hz, 1H, 10-H); ^{13}C NMR (75.4 MHz, CD_3OD) δ 19.2 (CH_3, 2-CH_3), 30.7 (CH_2, C5), 33.4 (CH, C11b), 34.7 (CH, C4), 43.5 (CH_2, C12), 44.1 (CH_3, CH_3SO_2), 47.1 (CH_2, C1), 62.8 (CH, C3a), 69.9 (C, C2), 114.2 (C, C11a), 115.0 (C, C10a), 119.1 (CH, C7), 126.3 (CH, C10), 127.7 (CH, C9), 139.6 (C, C6a), 140.6 (C, C8), 149.4 (C) and 157.3 (C) (C5a and C11); *m/z* (CI) 406 [(M+C_2H_5)$^+$, 15], 380 (35) and 378 (96) [(M+H)$^+$], 379 (31), 377 (33), 344 (30) and 342 (47) [(M−Cl)$^+$], 300 (17) and 298 (34) [(M−CH_3SO_2)$^+$], 285 (35) and 283 (100) [(M−CH_3SO_2NH)$^+$], 249 [(M−CH_3SO_2NH−Cl+H)$^+$, 29]. HRMS calcd for $C_{18}H_{21}ClN_3O_2S$ [(M+H)$^+$]: 378.1043. Found: 378.1028.

4.1.3. 12,*syn*-13-Diamino-3-chloro-6,7,10,11-tetrahydro-9-methyl-7,11-methanocycloocta[*b*]quinoline dihydrochloride, (3b·2HCl) and 10-amino-7-chloro-2,3-dihydro-2-methyl-1*H*-cyclopenta[*b*]acridine (7). This reaction was carried out as described for **3a**, from methanesulfonamide **2b** (285 mg, 0.75 mmol), added over a 30 min period and PPA (3.75 g), heating at 140 °C for 3.5 h. A yellowish solid (234 mg) was obtained, which was submitted to flash column chromatography (SiO_2, 7.5 g, hexane/AcOEt/MeOH mixtures containing 0.3% of Et_3N). On elution with hexane/AcOEt 60:40 and AcOEt/MeOH 95:5, compound **7** (58 mg, 27% yield) and amine **3b** (132 mg, 59% yield) were isolated, respectively, as yellowish solids.

Dihydrochloride of **3b**. A solution of pure **3b** (206 mg, 0.69 mmol) in MeOH (10 mL) was treated with a solution of HCl in MeOH (0.48 M, 8.6 mL, 4.13 mmol), and the solvent was evaporated at reduced pressure, to give **3b**·2HCl (245 mg) as a yellowish solid. The analytical sample was obtained by precipitation in AcOEt/MeOH 1:2.5 followed by drying of the solid material at 80 °C/1 Torr for 2 days: mp>300 °C (dec.) (AcOEt/MeOH 1:2.5); R_f (**3b**, free base) 0.08 (SiO_2, CH_2Cl_2/MeOH, 9:1, containing 1% of 25% aq. NH_4OH); IR (KBr) ν 3500–2500 (max. at 3379, 3190 and 2926), 1654, 1635, 1587 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 1.63 (s, 3H, 9-CH_3), 2.18 (broad d, J=18.0 Hz, 1H, 10-H$_{endo}$), 2.75 (broad dd, J=18.0 Hz, J'=4.5 Hz, 1H, 10-H$_{exo}$), 3.01 (m, 1H, 7-H), 3.09 (d, J=19.0 Hz, 1H, 6-H$_{endo}$), 3.23 (dd, J=19.0 Hz, J'=5.5 Hz, 1H, 6-H$_{exo}$), 3.57 (m, 1H, 11-H), 3.92 (dd, J=3.5 Hz, J'=2.5 Hz, 1H, 13-H), 4.85 (s, NH^++NH_2+NH_3^+), 5.62 (broad d, J=6.0 Hz, 1H, 8-H), 7.64 (dd, J=9.0 Hz, J'=2.0 Hz, 1H, 2-H), 7.82 (d, J=2.0 Hz, 1H, 4-H), 8.40 (d, $J\approx$9.0 Hz, 1H, 1-H); ^{13}C NMR (75.4 MHz, CD_3OD) δ 22.7 (CH_3, 9-CH_3), 30.1 (CH_2, C6), 30.8 (CH, C7), 31.2 (CH, C11), 36.7 (CH_2, C10), 50.4 (CH, C13), 109.7 (C, C11a), 115.5 (C, C12a), 119.3 (CH, C4), 123.4 (CH, C8), 126.5 (CH, C1), 128.0 (CH, C2), 135.4 (C, C9), 139.8 (C, C4a), 141.0 (C, C3), 150.7 (C) and 157.8 (C) (C5a and C12); *m/z* (CI) 328 [(M+C_2H_5)$^+$, 17], 302 (35) and 300 (100) [(M+H)$^+$], 301 (33), 299 (37), 285 (16) and 283 (38) [(M−NH_2)$^+$], 264 [(M−Cl)$^+$, 60]. HRMS calcd for $C_{17}H_{19}ClN_3$ [(M+H)$^+$]: 300.1268. Found: 300.1253.

Compound **7**. Mp 248–250 °C (dec.) (isopropanol); R_f 0.38 (SiO_2, CH_2Cl_2/MeOH, 9:1, containing 1% of 25% aq. NH_4OH); IR (KBr) ν 3473, 2953, 2927, 1654, 1607, 1561, 1474, 1453, 1249 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 1.18 (d, J=7.0 Hz, 3H, 2-CH_3), 2.60 (ddq, J=J'=J''=7.0 Hz, 1H, 2-H), 2.66 (dd, $J\approx$16.0 Hz, $J'\approx$7.5 Hz, 1H, 1-H$_\alpha$), 2.68 (dd, $J\approx$15.5 Hz, $J'\approx$7.5 Hz, 1H, 3-H$_\alpha$), 3.19 (dd, $J\approx$16.0 Hz, J'=4.5 Hz, 1H, 1-H$_\beta$), 3.20 (dd, $J\approx$15.5 Hz, $J'\approx$4.5 Hz, 1H, 3-H$_\beta$), 4.85 (s, NH_2), 7.22 (dd, $J\approx$9.5 Hz, $J'\approx$2.0 Hz, 1H, 8-H), 7.57 (s, 1H, 4-H), 7.75 (d, $J\approx$2.0 Hz, 1H, 6-H), 7.98 (s, 1H, 11-H), 8.19 (d, J=9.5 Hz, 1H, 9-H); ^{13}C NMR (75.4 MHz, CD_3OD) δ 20.6 (CH_3, 2-CH_3), 36.4 (CH, C2), 41.4 (CH_2, C1), 42.0 (CH_2, C3), 112.0 (C, C9a), 113.1 (C, C10a), 117.3 (CH, C11), 120.9 (CH, C4), 123.2 (CH, C8), 125.2 (CH, C6), 125.6 (CH, C9), 137.3 (C, C7), 141.4 (C, C11a), 147.9 (C, C5a), 148.6 (C, C4a), 151.1 (C, C3a), 152.5 (C, C10); *m/z* (EI) 284 (34) and 282 (100) (M$^{\cdot+}$), 283 (26), 281 (19), 269 (13) and 267 (39) [(M−CH_3)$^+$], 268 (13), 266 (21), 232 [(M−Cl−CH_3)$^{\cdot+}$, 13]; *m/z* (CI) 285 (37) and 283 (100) [(M+H)$^+$], 284 (37), 282 (56), 247 [(M−Cl)$^+$, 47]. Anal. calcd for $C_{17}H_{15}ClN_2$·3/5H_2O: C, 69.55; H, 5.56; N, 9.54; Cl, 12.08. Found: C, 69.31; H, 5.34; N, 9.35; Cl, 12.37.

4.1.4. PPA hydrolysis of *N*-dodecylmethanesulfonamide. This reaction was carried out as described for **3a**, from methanesulfonamide **10** (200 mg, 0.76 mmol) and PPA

(3.80 g), heating at 160 °C for 1 h, obtaining pure *N*-dodecylamine (105 mg, 74% yield) as a brown oil.

4.1.5. PPA hydrolysis of *N*-(1-adamantyl)methanesulfonamide, 12, and *N*-(2-adamantyl)methanesulfonamide, 13. *Conditions 1*. This reaction was carried out as described for **3a**, from methanesulfonamide **12** or **13** (200 mg, 0.87 mmol) and PPA (4.47 g), heating at 110 °C for 1 h. GC–MS and ^{13}C NMR analysis of the crude products obtained from **12** and **13** (80 and 74 mg, respectively) revealed that they consisted of a mixture of adamantane, **14** (t_R=8.3 min), 1-adamantanol, **15** (t_R=11.1 min), 2-adamantanone, **16** (t_R=12.1 min), methanesulfonamide **12** (t_R=19.9 min), and methanesulfonamide **13** (t_R=20.1 min). For the GC–MS relative areas of these compounds see Table 3.

Conditions 2. This reaction was carried out as described for **3a**, from methanesulfonamide **12** (200 mg, 0.87 mmol) or **13** (179 mg, 0.78 mmol) and PPA (3.60 and 3.45 g, respectively), heating at 160 °C for 1 h. GC–MS and ^{13}C NMR analysis of the crude products obtained from **12** and **13** (43 and 67 mg, respectively) revealed that they consisted mainly of a mixture of adamantane, **14**, 1-adamantylamine, **17** (t_R=10.7 min), and 2-adamantanone, **16**. For the GC–MS relative areas of these compounds see Table 3.

4.1.6. 12-Amino-3-chloro-*anti*-13-formamido-6,7,10,11-tetrahydro-9-methyl-7,11-methanocycloocta[*b*]quinoline (18a). Ac_2O (682 μL, 738 mg, 7.23 mmol) was added to a solution of amine **3a** (108 mg, 0.36 mmol) in HCO_2H (1 mL, 1.22 g, 26.5 mmol), and the reaction mixture was heated under reflux for 45 min, allowed to reach room temperature and concentrated in vacuo. The resulting residue was taken in MeOH (5 mL) and treated with a saturated aqueous solution of $NaHCO_3$ (10 mL). The organic solvent was evaporated at reduced pressure, and the resulting aqueous suspension was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated at reduced pressure, to give formamide **18a** (98 mg, 83% yield) as a white solid: mp 254–256 °C (AcOEt); R_f 0.51 (SiO_2, CH_2Cl_2/MeOH 85:15, containing 1% of 25% aq. NH_4OH); IR (KBr) ν 3424, 3386, 3151, 2876, 1694, 1671, 1606, 1566, 1488 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.59 (s, 3H, 9-CH_3), 1.97 (d, J=18.0 Hz, 1H, 10-H_{endo}), 2.46 (ddm, J≈18.0 Hz, J'=4.5 Hz, 1H, 10-H_{exo}), 2.64 (m, 1H, 7-H), 3.10 (dm, J=17.5 Hz, 1H, 6-H_{endo}), 3.32 (dd, J=17.5 Hz, J'=5.5 Hz, 1H, 6-H_{exo}), 3.42 (m, 1H, 11-H), 4.42 (m, 1H, 13-H), 4.76 (broad s, 2H, NH_2), 5.48 (dm, J=5.0 Hz, 1H, 8-H), 5.88 (broad d, J=6.5 Hz, 1H, HCON*H*), 7.34 (dd, J=9.0 Hz, J'=2.0 Hz, 1H, 2-H), 7.63 (d, J=9.0 Hz, 1H, 1-H), 7.87 (broad s, 1H, 4-H), 8.28 (s, 1H, *H*CONH), a very small signal at δ 5.30 ppm corresponding to CH_2Cl_2 was also observed; ^{13}C NMR (75.4 MHz, $CDCl_3$+CD_3OD) δ 23.0 (CH_3, 9-CH_3), 30.0 (CH, C11), 30.4 (CH_2, C10), 32.9 (CH, C7), 38.5 (CH_2, C6), 46.2 (CH, C13), 113.1 (C, C11a), 115.0 (C, C12a), 121.1 (CH, C1), 122.4 (CH, C8), 124.8 (CH, C2), 125.2 (CH, C4), 133.7 (C, C9), 135.4 (C, C4a), 145.8 (C, C3), 148.3 (C) and 155.4 (C) (C5a and C12), 161.7 (C, HCONH); *m*/*z* (CI) 356 [(M+C_2H_5)$^+$, 17], 330 (37) and 328 (100) [(M+H)$^+$], 329 (28), 327 (20), 294 (17), 292 [(M−Cl)$^+$, 16]. HRMS calcd for $C_{18}H_{19}ClN_3O$ [(M+H)$^+$]: 328.1217. Found: 328.1217. Anal. calcd for $C_{18}H_{18}ClN_3O$·1/2H_2O·0.07CH_2Cl_2: C, 63.32; H, 5.63; N, 12.26; Cl, 11.79. Found: C, 63.34; H, 5.46; N, 12.10; Cl, 11.84.

4.1.7. 12-Amino-3-chloro-*syn*-13-formamido-6,7,10,11-tetrahydro-9-methyl-7,11-methanocycloocta[*b*]quinoline (18b). It was prepared as described for **18a**. Starting from a solution of amine **3b** (121 mg, 0.40 mmol) in HCO_2H (1 mL, 1.22 g, 26.5 mmol) and Ac_2O (756 μL, 818 mg, 8.01 mmol) with a reaction time of 1 h, formamide **18b** (113 mg, 86% yield) was obtained as a yellowish solid: mp 252–253 °C (dec.) (hexane/AcOEt 1:1); R_f 0.17 (SiO_2, CH_2Cl_2/MeOH 9:1, containing 1% of 25% aq. NH_4OH); IR (KBr) ν 3351, 3246, 2903, 1637, 1560, 1489 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.55 (s, 3H, 9-CH_3), 2.08 (broad d, J=17.0 Hz, 1H, 10-H_{endo}), 2.70 (dm, J≈17.0 Hz, 1H, 10-H_{exo}), 2.86 (m, 1H, 7-H), 2.96 (broad d, J≈19.0 Hz, 1H, 6-H_{endo}), superimposed in part 3.14 (dd, J=19.0 Hz, J'=6.0 Hz, 1H, 6-H_{exo}), 3.16 (m, 1H, 11-H), 4.58 (m, 1H, 13-H), 4.75 (broad s, 2H, NH_2), 5.54 (dm, J=4.0 Hz, 1H, 8-H), 5.7–6.0 (broad signal, 1H, HCON*H*), 7.34 (m, 1H, 2-H), 7.60 (m, 1H, 1-H), 7.83 (broad s, 1H, 4-H), 8.16 (s, 1H, *H*CONH), signals corresponding to AcOEt were also observed; ^{13}C NMR (75.4 MHz, $CDCl_3$+CD_3OD) δ 22.7 (CH_3, 9-CH_3), 31.3 (CH, C7), 32.2 (CH, C11), 33.0 (CH_2, C6), 35.8 (CH_2, C10), 46.5 (CH, C13), 111.0 (C, C11a), 115.1 (C, C12a), 122.2 (CH, C1), 124.2 (CH, C8), 124.9 (CH, C2), 125.0 (CH, C4), 132.5 (C, C9), 135.5 (C, C4a), 145.4 (C, C3), 149.4 (C) and 155.4 (C) (C5a and C12), 161.9 (C, HCONH); *m*/*z* (CI) 356 [(M+C_2H_5)$^+$, 16], 330 (35) and 328 (100) [(M+H)$^+$], 329 (25), 294 (55), 292 [(M−Cl)$^+$, 22]. HRMS calcd for $C_{18}H_{19}ClN_3O$ [(M+H)$^+$]: 328.1217. Found: 328.1215. Anal. calcd for $C_{18}H_{18}ClN_3O$·2/5H_2O·1/2AcOEt: C, 63.37; H, 6.06; N, 11.09; Cl, 9.35. Found: C, 63.66; H, 5.74; N, 11.40; Cl, 8.93.

4.1.8. *anti*-13-Acetamido-12-amino-3-chloro-6,7,10,11-tetrahydro-9-methyl-7,11-methanocycloocta[*b*]quinoline hydrochloride (19a·HCl). It was prepared as described for **18a**, but using AcOH instead of HCO_2H. Thus, starting from a solution of amine **3a** (100 mg, 0.33 mmol) in AcOH (1 mL, 1.05 g, 17.5 mmol) and Ac_2O (62 μL, 67 mg, 0.66 mmol), acetamide **19a** (96 mg, 85% yield) was obtained as a brown solid.

Hydrochloride of **19a**. A solution of pure **19a** (96 mg, 0.28 mmol) in MeOH (2 mL) was treated with a solution of HCl in MeOH (0.48 M, 1.95 mL, 0.94 mmol), stirred at room temperature for 5 min and evaporated at reduced pressure, to give the corresponding hydrochloride (110 mg) as a yellowish solid: mp>300 °C (dec.) (AcOEt/MeOH 4:1); R_f (**19a**, free base) 0.37 (SiO_2, CH_2Cl_2/MeOH 85:15, containing 1% of 25% aq. NH_4OH); IR (KBr) ν 3500–2500 (max. at 3323, 3150 and 2923), 1675, 1589, 1541 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 1.63 (s, 3H, 9-CH_3), 1.92 (broad d, J=18.5 Hz, 1H, 10-H_{endo}), 2.02 (s, 3H, C*H*$_3$-CONH), 2.53 (broad dd, J=18.5 Hz, J'=5.0 Hz, 1H, 10-H_{exo}), 2.68 (m, 1H, 7-H), 2.98 (dd, J=18.0 Hz, J'=1.5 Hz, 1H, 6-H_{endo}), 3.39 (dd, J=18.0 Hz, J'=5.5 Hz, 1H, 6-H_{exo}), 3.49 (m, 1H, 11-H), 4.16 (m, 1H, 13-H), 4.84 (s, NH^++NH_2), 5.51 (dm, J=4.5 Hz, 1H, 8-H), 7.60 (dd,

J=9.0 Hz, J'=2.0 Hz, 1H, 2-H), 7.74 (d, J=2.0 Hz, 1H, 4-H), 8.13 (d, J=7.5 Hz, 1H, CH_3CONH), 8.35 (d, J=9.0 Hz, 1H, 1-H); ^{13}C NMR (75.4 MHz, CD_3OD) δ 22.6 (CH_3, CH_3CONH), 23.4 (CH_3, 9-CH_3), 30.6 (CH, C11), 31.1 (CH_2, C10), 32.8 (CH, C7), 36.5 (CH_2, C6), 48.3 (CH, C13), 114.7 (C, C11a), 115.1 (C, C12a), 119.1 (CH, C4), 121.9 (CH, C8), 126.3 (CH, C1), 127.7 (CH, C2), 135.4 (C, C9), 139.6 (C, C4a), 140.6 (C, C3), 151.8 (C) and 156.9 (C) (C5a and C12), 173.5 (C, CH_3CONH); *m/z* (CI) 344 (13) and 342 (32) [$(M+H)^+$], 306 [$(M-Cl)^+$, 9]. HRMS calcd for $C_{19}H_{21}ClN_3O$ [$(M+H)^+$]: 342.1373. Found: 342.1361. Anal. calcd for $C_{19}H_{20}ClN_3O{\cdot}HCl{\cdot}2.65H_2O$: C, 53.57; H, 6.22; N, 9.86; Cl, 16.64. Found: C, 53.18; H, 6.06; N, 9.48; Cl, 17.03.

4.1.9. *syn*-13-Acetamido-12-amino-3-chloro-6,7,10,11-tetrahydro-9-methyl-7,11-methanocycloocta[*b*]quinoline hydrochloride (19b·HCl). It was prepared as described for **18a**, but using AcOH instead of HCO_2H. Thus, starting from a solution of amine **3b** (101 mg, 0.34 mmol) in AcOH (1 mL, 1.05 g, 17.5 mmol) and Ac_2O (62 μL, 67 mg, 0.66 mmol) with a reaction time of 1.25 h, acetamide **19b** (101 mg, 88% yield) was obtained as a brown solid.

Hydrochloride of **19b**. A solution of pure **19b** (101 mg, 0.30 mmol) in MeOH (2 mL) was treated with a solution of HCl in MeOH (0.48 M, 2 mL, 0.96 mmol), stirred at room temperature for 1 h and evaporated at reduced pressure, to give the corresponding hydrochloride (121 mg) as a yellowish solid: mp>300 °C (dec.) (isopropanol/AcOEt/MeOH 3:2:0.5); R_f (**19b**, free base) 0.22 (SiO_2, CH_2Cl_2/MeOH 85:15, containing 1% of 25% aq. NH_4OH); IR (KBr) ν 3500–2500 (max. at 3351, 3190 and 2922), 1654, 1646, 1587 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 1.60 (s, 3H, 9-CH_3), 1.91 (s, 3H, CH_3CONH), 2.09 (broad d, J=18.0 Hz, 1H, 10-H_{endo}), 2.69 (ddm, J=18.0 Hz, J'=4.5 Hz, 1H, 10-H_{exo}), 2.84 (broad d, J=18.5 Hz, 1H, 6-H_{endo}), 2.88 (m, 1H, 7-H), 3.22 (dd, J=18.5 Hz, J'=5.0 Hz, 1H, 6-H_{exo}), 3.30 (m, 1H, 11-H), 4.31 (m, 1H, 13-H), 4.84 (s, $CH_3CONH+NH_2+NH^+$), 5.57 (broad d, J=6.0 Hz, 1H, 8-H), 7.61 (dd, J=9.0 Hz, J'=2.0 Hz, 1H, 2-H), 7.77 (d, J=2.0 Hz, 1H, 4-H), 8.37 (d, J=9.0 Hz, 1H, 1-H); ^{13}C NMR (100.6 MHz, CD_3OD) δ 22.5 (CH_3, CH_3CONH), 22.9 (CH_3, 9-CH_3), 30.9 (CH_2, C6), 31.7 (CH, C7), 32.5 (CH, C11), 36.9 (CH_2, C10), 48.9 (CH, C13), 112.4 (C, C11a), 115.5 (C, C12a), 119.2 (CH, C4), 124.8 (CH, C8), 126.4 (CH, C1), 127.9 (CH, C2), 135.0 (C, C9), 139.7 (C, C4a), 140.8 (C, C3), 152.1 (C) and 157.8 (C) (C5a and C12), 173.6 (C, CH_3CONH); *m/z* (CI) 344 (7) and 342 (19) [$(M+H)^+$], 306 [$(M-Cl)^+$, 6]. HRMS calcd for $C_{19}H_{21}ClN_3O$ [$(M+H)^+$]: 342.1373. Found: 342.1361. Anal. calcd for $C_{19}H_{20}ClN_3O{\cdot}HCl{\cdot}H_2O$: C, 57.58; H, 5.85; N, 10.60; Cl, 17.89. Found: C, 57.88; H, 5.72; N, 10.15; Cl, 17.64.

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