7-Substituted pyrrolo[2,3-*d*]pyrimidines for the synthesis of new 1-deazapyrimido[1,2,3-*cd*]purines

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Few examples of new heterocyclic 1-deazapyrimido[1,2,3-*cd*]purine derivatives were synthesized by intramolecular cyclization of methyl 7-(oxiran-2-ylmethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxylates. The latter were obtained by iodolactonization of 7-allylpyrrolo[2,3-*d*]pyrimidine-6-carboxylic acids.

Introduction

Pyrimidine and purine rings are widely spread in nature and are the basis of numerous biologically active substances. Condensed pyrimidine compounds are thus of high interest both in organic and in pharmaceutical chemistry [1,2], and the search for new or improved approaches to synthesize these compounds is a highly relevant task**.**

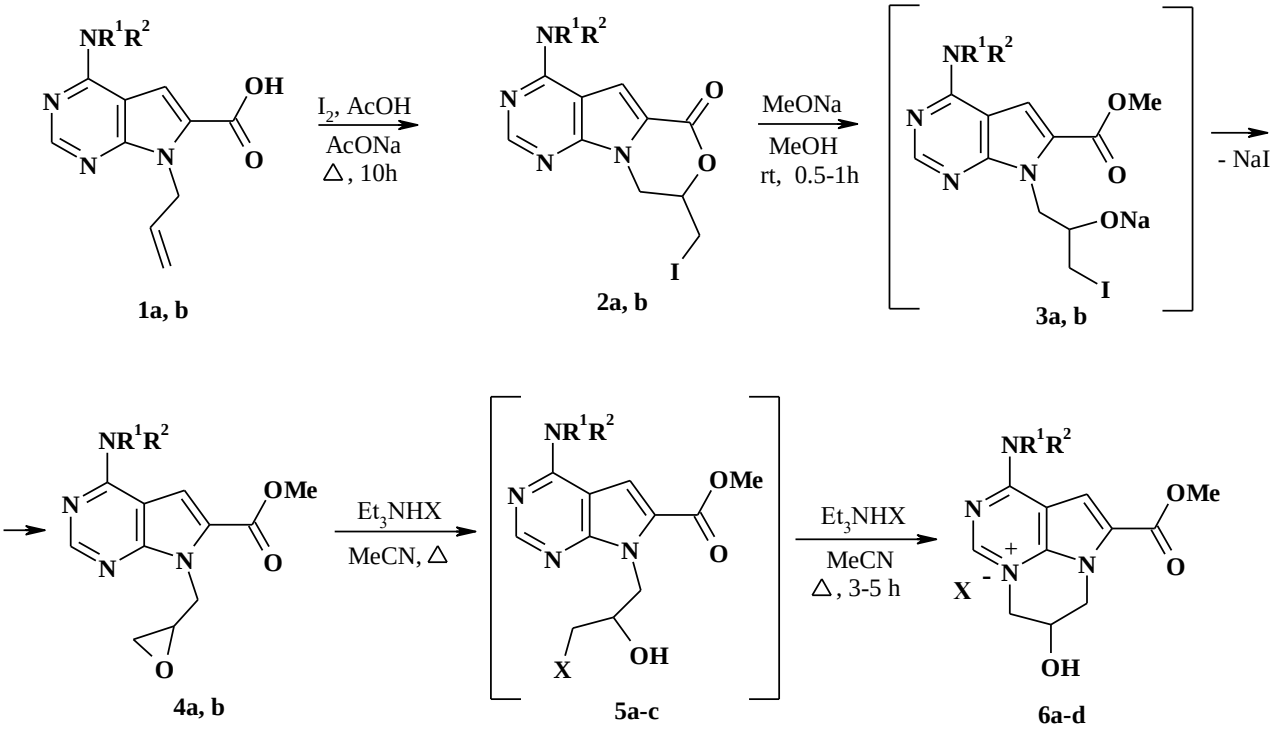
Among tricyclic purine derivatives, the compounds in which the third ring is connected to the N3 and N9 atoms of the purine motif are particularly interesting [3,4]. A natural pyrimido[1,2,3-*cd*]purine-8,10(9*H*)-dione was for example isolated from the South China Sea gorgonian *Subergorgia suberosa* [5]. Tricyclic xanthine derivatives were described as selective adenosine A1 receptor antagonists (PSB-63) [6-8], and purine cyclonucleosides modified with sugar residues were reported to exhibit antiviral properties [9-11].

Synthesis of tricyclic derivatives having pyrrolo[2,3-*d*]pyrimidine (7-deazapurine) moiety in which the third ring comprises the nitrogen atoms of pyrrole and pyrimidine units has been described back in 1963 [12]. No other examples of such systems in literature This compound is to the best of our knowledge the sole example of such derivatives described in the literature. In the present work we propose a convenient approach for the synthesis of the new tricyclic 1-deazapyrimido[1,2,3-*cd*]purine moiety (4,5-dihydro-3*H*-2a,7-diaza-5a-azoniaacenaphthylene). This method is based on the use of an intramolecular cyclisation of

pyrrolo[2,3-*d*]pyrimidine derivatives substituted in the position 7.

Results and discussion

The synthesis of the targeted 10-amino-5-hydroxy-5,6-dihydro-4*H*-1-deazapyrimido-[1,2,3-*cd*]purin-7-ium salts **6** was performed according to **Scheme 1**. Starting reactants were the previously reported 4-aminosubstituted 7-allylpyrrolo[2,3-*d*]pyrimidine-6-carboxylic acids **1a, b** [13]. Interaction of **1a, b** with iodine led to the formation of the iodolactonization products 8-iodomethylpyrimido [5',4':4,5] pyrrolo[2,1-*c*][1,4]oxazines **2a, b.**



1-4 NR^1R^2 = NMe_2 (**a**), morpholin-4-yl (**b**); **5** NR^1R^2 =NMe_2 (**a, b**), morpholin-4-yl (**c**), **X** = Cl (**a, c**), Br (**b**); **6** NR^1R^2 = NMe_2 (**a-c**), morpholin-4-yl (**d**), **X** = Cl (**a**), Br (**b**), ClO_4 (**c, d**).

Scheme 1. Synthesis of 5,6-dihydro-4*H*-1-deazapyrimido[1,2,3-*cd*]purin-7-ium salts **6a-d**.

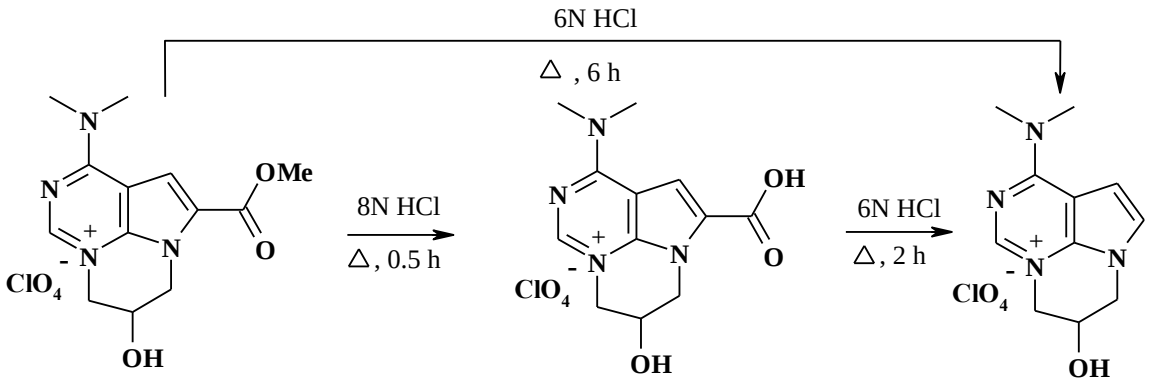
The structure of compounds **2a,b** was easily confirmed by conventional NMR analysis. The characteristic signal of the CH_2I group in the ^1H NMR spectra appeared as two doublet of doublets at 3.59, 4.04 ppm and 3.65, 4.07 ppm, and the signal of the adjacent aliphatic CH resonated at 4.88-4.93 ppm. In the ^{13}C NMR spectra, the signal of the C-8 atom appears at 76.7 ppm, and the signal of the iodomethyl carbon atom resonates at 4.5 ppm. Moreover, a comparison of the spectral characteristics of the pyrimido[5',4':4,5]pyrrolo[2,1-c][1,4]oxazines **2a,b** with those of the known relative compounds such as the 3-iodomethyl-3,4-dihydro-1*H*-2-benzopyran-1-one [14, 15] and the 3-iodomethyl-3,4-dihydro-1*H*-[1,4]oxazino

[4,3-*a*]indol-1-one [16], allowed to confirm the formation of the lactone cycle.

Treatment of the oxazines **2a, b** with sodium methylate led to a nucleophilic attack at the carbonyl group with the simultaneous lactone cycle splitting, possibly inducing the formation of intermediates **3a, b**. The latter undergo a cyclisation reaction, thus leading to the formation of the methyl 7-(oxiran-2-ylmethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxylates **4a, b**. The heating of **4a, b** in acetonitrile in the presence of triethylammonium chloride (or bromide) induces the opening of the oxirane cycle, thus giving the intermediates **5a-c,** which finally give new 5,6-dihydro-4*H*-1-deazapyrimido[1,2,3-*cd*]purin-7-ium salts **6a-d** after an intramolecular cyclisation.

The formation of the compounds **6** was previously described [17-19] by reaction of adenine derivatives with epichlorohydrin, but the low selectivity of the adenine alkylation process allowed the isolation of only small quantities of such quaternarized compounds. The formation of quaternary salts was also reported by alkylation of 7-azaindole [20], 1-deazapurine [21], adenine [22, 23], indolo[2,3-*b*]quinoxaline [24].

To synthesize the 2-unsubstituted 1-deazapyrimido[1,2,3-*cd*]purin-7-ium salt, the compound **6c** was subjected to acidic hydrolysis to form the carboxylic acid **7**. The decarboxylation of **7** led to the unsubstituted tricyclic salt **8** (**Scheme 2)**. It is worth noting that compound **8** can be directly prepared from the salt **6c** by refluxing in a 6N HCl solution.



Scheme 2. Synthesis of 5,6-dihydro-4*H*-1-deazapyrimido[1,2,3-*cd*]purin-7-ium salt **8**.

Heteroaromatic salts containing imidazolium, pyridinium or isoquinolinium rings have been described as inhibitors of acetylcholinesterase (AChE) [25, 26]. AChE catalyzes the hydrolysis of acetylcholine and plays a key role in the termination of the transmission of nerve impulses. Acetylcholinesterase inhibitors are used in treatment of neurodegenerative diseases including Alzheimer's disease. The inhibitory

activity of the 1-deazapyrimido[1,2,3-*cd*]purine derivatives described in this paper against AChE was thus evaluated. Previously obtained results showed that these compounds can inhibit AChE, with IC_{50} values in the micromolar range.

Conclusions

An effective method for the synthesis of new tricyclic derivatives exhibiting a pyrrolo[2,3-*d*]pyrimidine (7-deazapurine) core was developed. The application of this approach to the synthesis of the 1-deazapyrimido[1,2,3-*cd*]purine (4,5-dihydro-3*H*-2a,7-diaza-5a-azoniaacenaphthylene) derivative was described.

Experimental part

The ^{1}H NMR spectra were obtained on Bruker Avance DRX-500 (500 MHz) and Varian Unity plus 400 (400 MHz) using solutions in DMSO-d_6. The ^{13}C NMR spectra were recorded in DMSO-d_6 solutions on Bruker Avance DRX-500 (125 MHz) spectrometer. The spectra were referenced relative to internal TMS. APT experiments were used to assign ^{13}C chemical shifts. Elemental analysis was carried out in the analytical laboratory of IBOPC NASU. Monitoring of the reaction progress and purity of the synthesized compounds was performed by TLC on Silufol UV-254 plates.

Constant values for *7-allyl-4-(dimethylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid* **1a** are given in [13].

7-Allyl-4-morpholin-4-yl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid **1b** was synthesized according to [13]. It was isolated as a white powder with 73% yield; mp 224-226ºC (dec). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 3.72-3.74 (4H, m, $N(CH_2)_2$ morpholine), 3.89-3.91 (4H, m, $O(CH_2)_2$ morpholine), 4.69 (1H, d, *J* 17.6) and 5.01 (1H, d, *J* 10.4, $NCH_2CH=C\underline{H}_2$), 5.15-5.17 (2H, m, NCH_2); 5.93-6.01 (1H, m, $NCH_2C\underline{H}=CH_2$), 7.46 (1H, s, H-5), 8.29 (1H, s, H-2), 13.12 (1H, br s, OH); ^{13}C NMR (125 MHz, DMSO-d_6), δ: 45.1, 45.8 ($N(CH_2)_2$ morpholine and NCH_2), 66.5 ($O(CH_2)_2$ morpholine), 101.8 (C), 111.4 (C-5), 115.9 ($NCH_2CH=\underline{C}H_2$), 125.0 (C), 135.2 ($NCH_2\underline{C}H=CH_2$), 153.3 (CH), 153.8 (C), 157.8 (C), 162.7 (C). Anal. calcd for $C_{14}H_{16}N_4O_3$: C, 58.33; H, 5.59; N, 19.43. Found: C, 58.39; H, 5.50; N, 19.38.

4-(Dimethylamino)-8-(iodomethyl)-8,9-dihydro-6H-pyrimido[5',4':4,5]pyrrolo[2,1-c][1,4]oxazin-6-one ***(2a)***. A mixture of 7-allylpyrrolo[2,3-*d*]pyrimidine-6-carboxylic acid **1a** (4.9 g, 20 mmol), iodine (10.15 g, 40 mmol), and sodium acetate (6.56.2 g, 80 mmol) in acetic acid (50 mL) was heated under stirring for 10h at 100ºC. The formed precipitate was separated by filtration. It was treated with a 0.1N solution of $Na_2S_2O_3$ (100 ml), and then with a saturated solution of $NaHCO_3$ at 50-60ºC

for 30 min. The precipitate was once more separated by filtration, washed with water and recrystallized from acetonitrile. Yield 6.14 g, 83% as a white crystals; mp 184-186°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 3.25-3.37 (6H, m, $N(CH_3)_2$), 3.59 (1H, dd, *J* 11.2, 6.4 Hz), 3.65 (1H, dd, *J* 4.8, 11.2 Hz, CH_2I), 4.03 (1H, dd, *J* 12.8, 10.8 Hz), 4.73 (1H, dd, *J* 2.4, 12.8 Hz, NCH_2), 4.88-4.90 (1H, m, CH), 7.53 (1H, s, H-5), 8.26 (1H, s, H-2); ^{13}C NMR (125 MHz, DMSO-d_6), δ: 4.5 (CH_2I), 43.2 (NCH_2), 76.7 (CH), 103.7 (C), 110.6 (C-5), 119.1 (C), 150.5 (C), 154.7 (C-2), 158.1 (C), 158.6 (C). The signal of $N(CH_3)_2$ overlaps with DMSO. Anal. calcd for $C_{12}H_{13}IN_4O_2$: C, 38.73; H, 3.52; I, 34.10; N, 15.05. Found: C, 38.79; H, 3.47; I, 34.18; N, 15.15.

8-(Iodomethyl)-4-morpholin-4-yl-8,9-dihydro-6H-pyrimido[5',4':4,5]pyrrolo[2,1-c][1,4]oxazin-6-one ***(2b)*** was obtained analogously as **2a**. Yield 78% as white crystals; mp 173-175°C (dec). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 3.58-3.74 (6H, m, $N(CH_2)_2$ morpholine and CH_2I), 3.89-3.93 (4H, m, $O(CH_2)_2$ morpholine), 4.04 (1H, dd, *J* 11.4, 6.2 Hz), 4.07 (1H, dd, *J* 5.8, 11.4 Hz, CH_2I), 4.73 (1H, dd, *J* 12.6, 10.6 Hz), 4.76 (1H, dd, *J* 2.6, 12.6 Hz, NCH_2), 4.90-4.93 (1H, m, CH), 7.64 (1H, s, H-5), 8.32 (1H, s, H-2); ^{13}C NMR (125 MHz, DMSO-d_6), δ: 4.5 (CH_2I), 43.2 (NCH_2), 45.9 ($N(CH_2)_2$ morpholine), 66.5 ($O(CH_2)_2$ morpholine), 76.7 (CH), 103.4 (C), 109.6 (C-5), 119.8 (C), 150.9 (C), 154.4 (C-2), 157.8 (C), 158.5 (C). Anal. calcd for $C_{14}H_{15}IN_4O_3$: C, 40.60; H, 3.65; I, 30.64; N, 13.53. Found: C, 40.58; H, 3.70; I, 30.69; N, 13.47.

Methyl 4-(dimethylamino)-7-(oxiran-2-ylmethyl)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylate ***(4a)***. A mixture of oxazine **2a** (3.72 g, 10 mmol) and MeONa (0.54 g, 10 mmol) in methanol (30 mL) was stirred for 30 min at 20-25°C. The solvent was evaporated under vacuum, and the residue was treated with water (20 ml). The precipitate was separated by filtration and recrystallized from methanol. Yield 2.00 g, 73% as white crystals; mp 125-127°C (dec). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 2.36 (1H, dd, *J* 4.4, 2.4 Hz) and 2.67 (1H, dd, *J* 4.0, 4.4 Hz, CH_2O), 3.27-3.34 (7H, m, $N(CH_3)_2$, CH), 3.85 (1H, s, OCH_3), 4.68 (1H, dd, *J* 14.0, 4.8 Hz) and 4.76 (1H, dd, *J* 4.4, 14.0 Hz, NCH_2), 7.42 (1H, s, H-5), 8.24(1H, s, H-2); ^{13}C NMR (125 MHz, DMSO-d_6), δ: 44.3 (CH_2O), 45.4 (NCH_2), 50.4 (CH), 52.1 (OCH_3), 102.1 (C), 111.6 (C-5), 123.6 (C), 153.3 (C), 154.1 (C-2), 158.1 (C), 161.6 (C). The signal of $N(CH_3)_2$ overlaps with DMSO. Anal. calcd for $C_{13}H_{16}N_4O_3$: C, 56.51; H, 5.84; N, 20.28. Found: C, 56.61; H, 5.79; N, 20.36.

Methyl 4-morpholin-4-yl-7-(oxiran-2-ylmethyl)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylate ***(4b)*** A mixture of oxazine **2b** (4.14 g, 10 mmol) and MeONa (0.54 g, 10 mmol) in methanol (50 mL) was stirred for 1 hr at 20-25°C. The formed precipitate was separated by filtration, washed with water and recrystallized from acetonitrile.

Yield 2.7 g, 85% as white crystals; mp 156-158°C (dec). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 2.35 (1H, dd, *J* 4.0, 2.2 Hz), 2.67 (1H, dd, *J* 3.8, 4.0 Hz, CH_2O), 3.73-3.81 (4H, m, $N(CH_2)_2$ morpholine), 3.84-3.91 (7H, m, $O(CH_2)_2$ morpholine and OCH_3), 4.71 (1H, dd, *J* 14.4, 4.8 Hz), 4.78 (1H, dd, *J* 4.4, 14.4 Hz, NCH_2), 7.50 (1H, s, H-5), 8.30(1H, s, H-2); ^{13}C NMR (125 MHz, DMSO-d_6), δ: 44.3 (CH_2O), 45.4, 45.9 ($N(CH_2)_2$ morpholine and NCH_2), 50.4 (CH), 52.2 (OCH_3), 66.4 ($O(CH_2)_2$ morpholine), 101.9 (C), 110.6 (C-5), 124.3 (C), 153.8 (C), 154.1 (C-2), 157.9 (C), 161.5 (C). Anal. calcd for $C_{15}H_{18}N_4O_4$: C, 56.60; H, 5.70; N, 17.60. Found: C, 56.69; H, 5.81; N, 20.16.

General procedure for the preparation of *5,6-dihydro-4H-1-deazapyrimido[1,2,3-cd]purin-7-ium salts* ***6a-d.*** A mixture of one of the compounds **4a,b** (5 mmol) and triethylammonium chloride (bromide) (10 mmol) in acetonitrile (30 ml) was refluxed for 3-5 h. The formed precipitate was separated by filtration. To form compounds **6c,d,** the precipitated salts were dissolved in water (20 ml) and a saturated solution of $NaClO_4$ (5 ml) was added. The formed precipitate was separated by filtration and washed with water.

*8-(Dimethylamino)-4-hydroxy-2-(methoxycarbonyl)-4,5-dihydro-3H-2a,7-diaza-5a-azoniaacenaphthylene chloride (**6a**).* Yield 78% as white crystals; mp 213-215°C (dec). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 3.44 (3H, s, NCH_3), 3.58 (3H, s, NCH_3), 3.89 (1H, s, OCH_3), 4.30-4.59 (2H, m, NCH_2), 4.44-4.47 (1H, m) and 4.30-4.59 (2H, m, NCH_2, CH), 5.94-5.98 (1H, m, OH), 7.69 (1H, s, H-1), 8.76 (1H, s, H-6); ^{13}C NMR (125 MHz, DMSO-d_6), δ: 39.8 (NCH_3), 41.0 (NCH_3), 50.1 (NCH_2), 50.6 (NCH_2), 52.7 (OCH_3), 59.2 (CH), 100.7 (C), 113.2 (C-1), 125.5 (C), 138.3 (C), 147.5 (C-6), 156.9 (C), 160.6 (C). Anal. calcd for $C_{13}H_{18}ClN_4O_3$: C, 49.76; H, 5.78; Cl, 11.30; N, 17.86. Found: 49.68; H, 5.82; Cl, 11.30; N, 17.93.

*8-(Dimethylamino)-4-hydroxy-2-(methoxycarbonyl)-4,5-dihydro-3H-2a,7-diaza-5a-azoniaacenaphthylene bromide (**6b**).* Yield 71% as white crystals; mp 2214-223°C (dec). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 3.45 (3H, s, NCH_3), 3.59 (3H, s, NCH_3), 3.90 (1H, s, OCH_3), 4.32-4.36 (2H, m, NCH_2), 4.37-4.44 (1H, m) and 4.66-4.69 (2H, m, NCH_2, CH), 5.82-5.85 (1H, m, OH), 7.69 (1H, s, H-1), 8.78 (1H, s, H-6); ^{13}C NMR (125 MHz, DMSO-d_6), δ: 39.8 (NCH_3), 41.2 (NCH_3), 50.2 (NCH_2), 50.6 (NCH_2), 52.8 (OCH_3), 59.2 (CH), 100.7 (C), 113.0 (C-1), 125.5 (C), 138.3 (C), 147.6 (C-6), 157.0 (C), 160.6 (C). Anal. calcd for $C_{13}H_{18}BrN_4O_3$: C, 43.59; H, 5.06; Br, 22.31; N, 15.64. Found: 43.64; H, 5.09; Br, 22.41; N, 15.71

*8-(Dimethylamino)-4-hydroxy-2-(methoxycarbonyl)-4,5-dihydro-3H-2a,7-diaza-5a-azoniaacenaphthylene perchlorate (**6c**).* Yield 82% as white crystals; mp 200-202°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 3.45 (3H, s,

NCH_3), 3.59 (3H, s, NCH_3), 3.90 (1H, s, OCH_3), 4.29-4.44 (3H, m) and 4.66-4.69 (2H, m, $2NCH_2$, CH), 5.82-5.83 (1H, m, OH), 7.70 (1H, s, H-1), 8.73(1H, s, H-6). Anal. calcd for $C_{13}H_{18}ClN_4O_7$: C, 41.33; H, 4.80; Cl, 9.38; N, 14.83. Found: 41.37; H, 4.76; Cl, 9.45; N, 14.89.

*4-Hydroxy-2-(methoxycarbonyl)-8-morpholin-4-yl-4,5-dihydro-3H-2a,7-diaza-5a-azoniaacenaphthylene perchlorate (**6d**).* Yield 74% as white crystals; mp 191-193ºC (dec). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 3.75-3.83 (4H, m, $N(CH_2)_2$ morpholine), 3.91 (1H, s, OCH_3), 4.11-4.15 (7H, m, $O(CH_2)_2$ morpholine), 4.31-4.37 (2H, m, NCH_2), 4.43-4.46 (1H, m) and 4.67-4.69 (2H, m, NCH_2, CH), 5.83-5.85 (1H, m, OH), 7.82 (1H, s, H-1), 8.77 (1H, s, H-6); Anal. calcd for $C_{15}H_{20}ClN_4O_8$: C, 42.92; H, 4.80; Cl, 8.44; N, 13.35. Found: 42.85; H, 4.85; Cl, 8.51; N, 13.39.

*2-Carboxy-8-(dimethylamino)-4-hydroxy-4,5-dihydro-3H-2a,7-diaza-5a-azoniaacenaphthylene perchlorate (**7**).* A suspension of **6c** (0.38 g, 1 mmol) in 8N hydrochloric acid (3 ml) was refluxed for 30 min, and then was left for 12 h at 20-25ºC. The formed precipitates was separated by filtration, washed with water and recrystallized from water. Yield 0.27 g, 75% as white crystals; mp 232-234ºC (dec). ^{1}H NMR (500 MHz, DMSO-d_6), δ: 3.43 (3H, s, NCH_3), 3.57 (3H, s, NCH_3), 4.29-4.32 (2H, m, NCH_2), 4.39-4.42 (1H, m) and 4.68-4.71 (2H, m, NCH_2, CH), 5.77-5.80 (1H, m, OH), 7.62 (1H, s, H-1), 8.71 (1H, s, H-6); 13.71 (1H, br s, OH); ^{13}C NMR (125 MHz, DMSO-d_6), δ: 39.7 (NCH_3), 41.1 (NCH_3), 50.1 (NCH_2), 50.6 (NCH_2), 59.5 (CH), 100.7 (C), 110.3 (C-1), 130.5 (C), 137.6 (C), 146.6 (C-6), 156.9 (C), 162.1 (C). Anal. calcd for $C_{12}H_{16}ClN_4O_7$: C, 39.62; H, 4.43; Cl, 9.75; N, 15.40. Found: 39.72; H, 4.46; Cl, 9.83; N, 15.46.

*8-(Dimethylamino)-4-hydroxy-4,5-dihydro-3H-2a,7-diaza-5a-azoniaacenaphthylene perchlorate (**8**).*

Method A. A suspension of **7** (0.18 g, 0.5 mmol) in 6N hydrochloric acid (3 ml) was refluxed for 2 h, and left for 12 h at 20-25ºC. The formed precipitate was separated by filtration, washed with water and recrystallized from water. Yield 0.1 g, 63% as a white crystals; mp 155-157ºC.

Method B. A suspension of **6c** (0.19 g, 0.5 mmol) in 6N hydrochloric acid (5 ml) was refluxed for 6 h, and left for 12 h at 20-25ºC. The formed precipitates was separated by filtration, washed with water and recrystallized from water. Yield 0.08 g, 50% as a white crystals; mp 155-157ºC.

The characteristics of the compound **8** obtained by both methods are identical. ^{1}H NMR (500 MHz, DMSO-d_6), δ: 3.37 (3H, s, NCH_3), 3.52 (3H, s, NCH_3), 4.22-4.29 (2H, m, NCH_2), 4.34-4.47 (2H, m, NCH_2), 4.64-4.66 (1H, m, CH), 5.89-5.91 (1H, m, OH), 6.97 (1H, d, *J* 2.2 Hz, H-1), 7.52 (1H, d, *J* 2.2 Hz, H-2), 8.67 (1H, s, H-6); ^{13}C NMR (125 MHz, DMSO-d_6), δ: 39.2

(NCH_3), 41.0 (NCH_3), 49.4 (NCH_2), 50.7 (NCH_2), 59.4 (CH), 101.4 (C), 104.6 (C-1), 126.2 (C-2), 136.2 (C), 145.1 (C-6), 156.6 (C). Anal. calcd for $C_{11}H_{16}ClN_4O_5$: C, 41.32; H, 5.04; Cl, 11.09; N, 17.52. Found: 41.40; H, 5.08; Cl, 11.12; N, 17.59.

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