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Regioselective synthesis of angular nitrogen polyheterocycles: dipyrido[3,2-*a*:2′,3′-*c*]quinolino[2,3-*h*]phenazines

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Abstract—Novel polyaza heterocycles, dipyrido[3,2-*a*:2′,3′-*c*]quinolino[2,3-*h*]phenazines, were synthesized via a regiocontrolled condensation between 5,6-phendione and 3,4-diaminoacridine derivatives.

DNA may adopt a variety of multistranded structures, double-, triple- or quadruple-stranded. There is growing interest in the design of ligands binding specifically to one type of the multistranded structures, both as antitumor agents or tools for molecular biology.[1] Ligands that bind strongly to quadruplexes (G-quadruplexes or G-4 structures) may modulate telomerase activity in cancer cells and induce cell death.[2] Ligands with triplex specificity are useful to promote and stabilize the formation of triple helices in antigene strategy.[3,4] A large diversity of structures has been tested as triplex or quadruplex specific binders. In this context linear and angular extended fused polyaza heterocycles appeared very promising. They interact by intercalation between base triplets/quadruplexes or lay on the top of the quadruplex region. To overcome the low solubility in water of these polyheterocycles, polar substituents, mainly amino side-chains, were added to the central structure.

It appeared interesting to combine the DNA intercalating properties of the acridine nucleus with the nuclease activity of [1,10]phenanthroline ligands, to design a novel family of angular DNA binders. We recently reported the synthesis of novel tetraaza heptacycle benzo[*b*]phenanthrolino[1,10][5,6-*j*]phenanthroline **I**.[5] The key step was the reaction of 5-amino[1,10]phenanthroline with 3-amino-4-hydroxymethyl acridine, precursor of quinone-imine-methide type reactive intermediate. The major drawback of the method is the three-step synthesis of the acridine key-intermediate that is not compatible with the presence of unprotected or acid sensitive substituents.

We therefore considered the synthesis of a novel heterocycle: dipyrido[3,2-*a*:2′,3′-*c*]quinolino[2,3-*h*]phenazine **II**, that only differs from **I** by the presence of five heterocyclic nitrogens. Phenazine fused heterocycles, which are prepared by condensation of an *ortho*-diamino cycle with an *ortho*-diketo derivative, have been studied as metal ligands,[6–10] DNA nucleases[11] or anticancer agents.[12]

We report here the synthesis of angular extended metal ligands, dipyrido[3,2-*a*:2′,3′-*c*]quinolino[2,3-*h*]phenazines bearing various substituents.

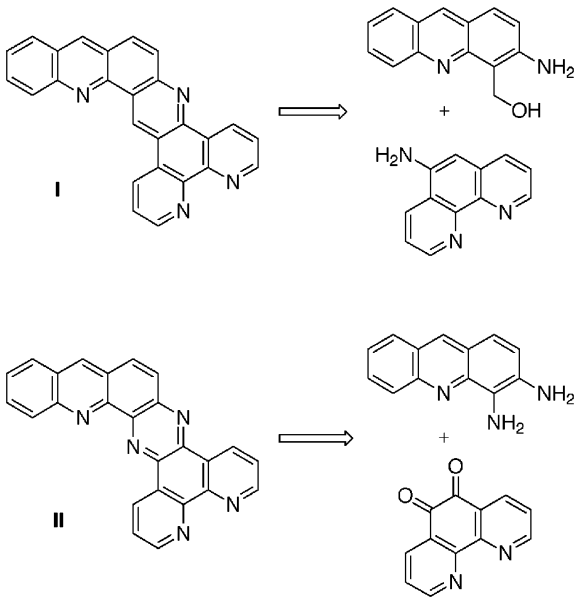

Figure 1.

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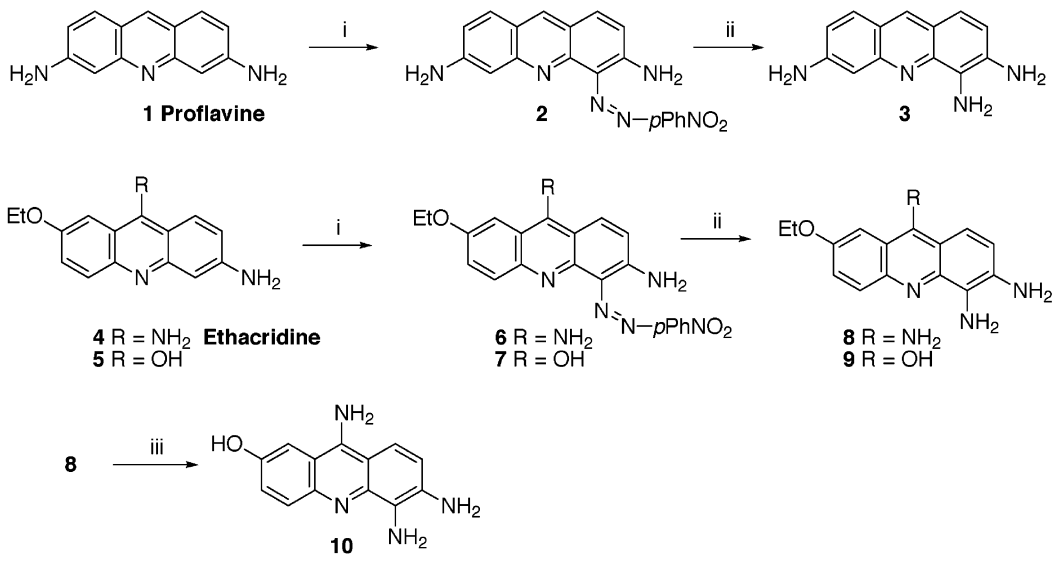
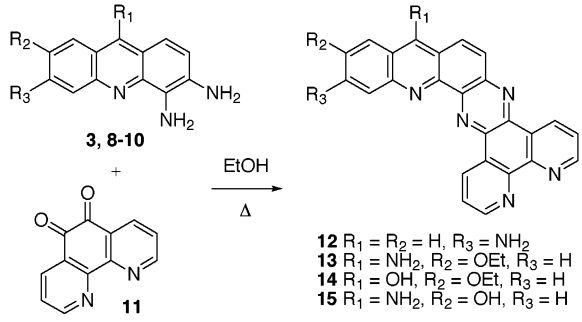


Scheme 1. Preparation of the *ortho*-diaminoacridine synthons. (i) *p*-nitrophenyl diazonium, $NaBF_4$, MeOH, 0°C; (ii) $Na_2S_2O_4$, pH 7 phosphate buffer, rt; (iii) $AlCl_3$, xylene, 90°C.

As shown in Fig. 1, the synthesis of **II** involves condensation of 3,4-diaminoacridine derivatives with the phen-5,6-dione. We designed a regioselective two-step synthesis (Scheme 1) to prepare the *ortho*-diaminoacridine key intermediates from commercially available 3,6-diaminoacridine **1** (proflavine) and 6,9-diamino-2-ethoxyacridine **4** (ethacridine). As reported previously,[13] proflavine or ethacridine react with *p*-nitrobenzenediazonium salt to give the corresponding 3-amino-4-*p*-nitrophenylazo compounds **2** and **6** in 70 and 80% yields, respectively. The reaction is fully regioselective and does not require protection of the other amino substituents. In the case of proflavine, the reaction allows the dessymmetrization of the molecule as the electrophilic substitution only proceeds in one side of the molecule because of the strong electron withdrawing effect of the diazo group that prevents a second substitution to occur. We extended this electrophilic reaction to the 9-hydroxy analogue of ethacridine **5** to prepare the diazo compound **7** in 93% yield. Reduction of the diazo group with sodium dithionite afforded the *ortho*-diamines **3**, **8** and **9** in moderate to good yields (45–70%). Cleavage of the 2-ethoxy group of **8** to give 2-hydroxy-5,6,9-triaminoacridine **10** was achieved in 88% yield by refluxing **8** in xylene in the presence of $AlCl_3$.

The final condensation of the *ortho*-diamine (**3**, **8**–**10**) with phen-5,6-dione **11**[14] was achieved by refluxing stoichiometric amounts of the two compounds in ethanol (Scheme 2). Pentaaza heptacycles **12**–**15** were thus obtained in good yields (64–89%). The structures of all new compounds were assessed by ^1H and ^{13}C NMR, and mass spectrometry.[15]

As a conclusion, we have devised a general and very efficient route to variously substituted angular pentaaza heptacyclic compounds derived from the corresponding phenanthroline and acridine. The presence of amino and/or hydroxy groups will now allow introduction of



Scheme 2.

various side-chains on the intercalating heterocycles in order to improve their solubility in water and modulate their interaction with DNA. In preliminary experiments (data not shown), compounds **12** and **13** were shown to exhibit DNA cleavage properties similarly to those known for phenanthroline in the presence of Cu(I).

Acknowledgements

This work was supported by the Centre National pour la Recherche Scientifique (CNRS), in the framework of Laboratoire Européen Associé (LEA) and COST D14 action, as well as by the Institut Universitaire de France (IUF). We also acknowledge the MENRT for a grant for F.C.

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15. Typical procedures. Synthesis of **12**.
Synthesis of 3,4-diaminoacridine synthon **3**. To a solution of azo compound **2**[13] (0.5 g, 1.4 mmol) in DMF (15 mL) was slowly added a solution of $Na_2S_2O_4$ (0.3 M in pH 7 phosphate buffer, 250 mM, 40 mL). After 5 h of stirring at rt; the solution was poured into water (400 mL) and the pH was adjusted to pH 8 by adding NH_4OH. Extraction with AcOEt afforded **3** in 70% yield.
Formation of 15-amino-dipyrido[3,2-*a*:2′,3′-*c*]quinolino-[2,3-*h*]phenazine **12**. A stoichiometric mixture (0.67 mmol) of **3** and 5,6-phendione **11** in absolute EtOH (30 mL) was refluxed for 1 h. After cooling, the solid that formed was filtered and washed with absolute EtOH. Compound **12** was thus obtained in 89% yield. Mp> 350°C; ^{1}H NMR (200 MHz, DMSO-d_6, five drops TFA-*d*) 10.50 (1H, d, $J=8.2$ Hz), 9.83 (1H, d, $J=7.9$ Hz), 9.44–9.37 (3H, m), 8.55–8.45 (2H, m), 8.38–8.31 (1H, m), 8.25 (1H, d, $J=9.3$ Hz), 8.16 (1H, d, $J=9.3$ Hz), 7.38 (2H, m); ^{13}C NMR (75 MHz, TFA-*d*) 157.5, 149.5 (CH), 149.4 (CH), 146.9, 145.6 (CH), 143.3, 142.7, 141.5 (CH), 141.0 (CH), 140.6, 140.3, 138.9, 137.3, 134.4, 133.3 (CH), 132.7 (CH), 130.3, 130.0, 128.5 (CH), 128.3 (CH), 127.7 (CH), 126.6, 124.4 (CH), 123.7; MS (positive FAB, glycerol) m/z 399 $(M+1)^+$.
13. (81% yield). Mp>350°C; ^{1}H NMR (300 MHz, DMSO-d_6) 9.92 (1H, d, $J=7.5$ Hz), 9.67 (1H, d, $J=7.7$ Hz), 9.34 (2H, m), 8.78 (1H, d, $J=9.2$ Hz), 8.25 (1H, d, $J=9.2$ Hz), 8.09 (2H, s, NH_2), 7.98–7.80 (4H, m), 7.58 (1H, d, $J=8.8$ Hz), 4.35 (2H, q, CH_2), 1.56 (3H, t, CH_3; ^{13}C NMR (75 MHz, TFA-*d*) 162.87, 150.44 (CH), 150.13 (CH) 147.70, 143.62, 142.39, 141.32 (CH), 141.03, 139.72, 138.64, 137.43,135.92, 133.96 (CH), 130.83, 129.15 (CH), 129.00 (CH), 128.48 (CH), 127.46 (CH), 122.94 (CH), 121.40, 121.17, 115.81, 114.02, 110.26, 102.47 (CH), 66.93 (CH_2), 14.03 (CH_3); MS (positive FAB, glycerol) m/z 443.2 $(M+1)^+$.
14. (64% yield). Mp>350°C; ^{1}H NMR (300 MHz, TFA-*d*) 11.20 (1H, d, $J=8.3$ Hz), 11.13 (1H, d, $J=8.7$ Hz), 10.19 (2H, m), 9.81 (1H, d, $J=9.8$ Hz), 9.33–9.22 (4H, m), 8.88–8.82 (2H, m), 5.21 (2H, q, CH_2), 2.40 (3H, t, CH_3); ^{13}C NMR (75 MHz, TFA-*d*) 167.81, 150.45 (CH), 149.96 (CH), 147.59, 143.49, 142.32 (CH), 141.28, 141.02 (CH), 139.65, 138.58, 137.28, 135.77, 133.65 (CH), 130.66, 130.36, 129.01 (CH), 128.86 (CH), 128.31 (CH), 127.39 (CH), 122.86 (CH), 121.32, 117.82, 115.73, 114.03, 102.56 (CH), 66.71 (CH_2), 14.03 (CH_3); MS (positive FAB, glycerol) m/z 444.2 $(M+1)^+$.
15. (74% yield). Mp>350°C; ^{1}H NMR (300 MHz, DMSO-d_6, five drops TFA) 10.47 (1H, d, $J=8.3$ Hz), 9.83 (1H, d, $J=7.6$ Hz), 9.44 (2H, m), 8.73 (1H, d, $J=9.6$ Hz), 8.44 (2H, m), 8.22 (1H, d, $J=7.5$ Hz), 8.01 (1H, d, $J=9.6$ Hz), 7.53 (1H, s), 7.38 (1H, d, $J=7.5$ Hz); MS (positive FAB, glycerol) m/z 415.2 $(M+1)^+$.