Synthesis of New Bis(2,4-Dimethyl-5-amino-benzo[*b*][1,8]-naphthyridines) and Bis(Benzo[*b*][1,8]naphthyridones) Linked with Methylene Linear Chain

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The preparation of novel alkyl monobridged 2,4-dimethyl-5-amino-benzo[*b*][1,8]naphthyiridine and benzo[*b*][1,8]naphthyridone derivatives by phase transfer catalysis is reported.

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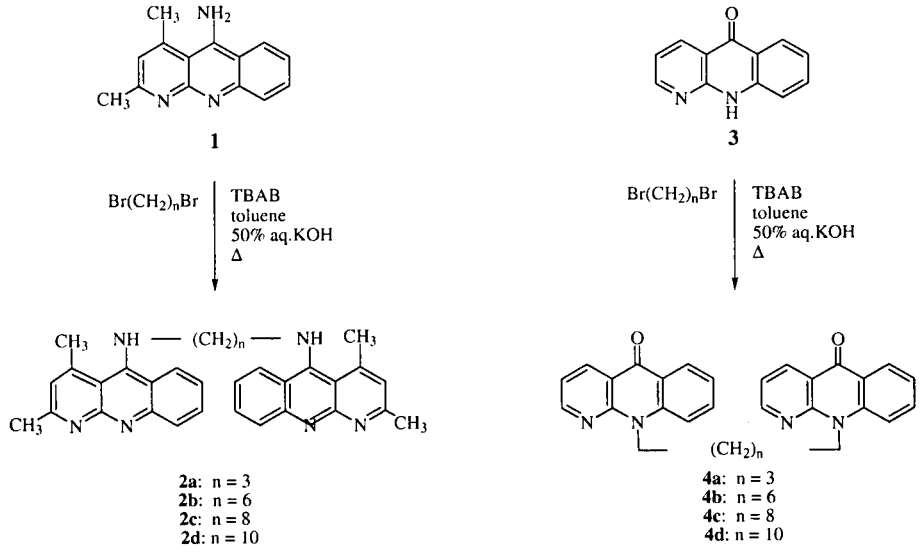
NMR studies of bis(acridine)s with methylene linker chains showed that these compounds interact with duplex DNA[1-3]. The interaction depends on the chain length. Bisintercalation occurs when the chain contains 7-10 methylene units, while only monointercalation is observed for chains with 4-6 methylene groups. Polyfunctional intercalating agents including bis(antracycline)s [4], bis(quinoline)s, tri(acridine)s [5], bis(acridine)s [6], bis(acridine-4-carboxamide)s [7] and asymmetric [4] dimers of various synthetic chromophores have been prepared. Tacrine based dimers [8], compounds with structural similarity, show cholinesterase inhibition properties, being promising candidates for palliative treatment of senile dementia of the Alzheimer's type.

The constantly increasing interest toward bisintercalating agents can be explained by their higher DNA-binding constants, slower dissociation rates and greater sequence selectivity compared with monointercalands [9]. Taking into consideration the above mentioned facts we report the preparation of new bisintercalands with potential antitumor activity, containing 2,4-dimethyl-5-amino-benzo[*b*][1,8]naphthyridine **1** or benzo[*b*][1,8]naphthyridones **3** chromophores, linked by methylene linear chains. We obtained the above mentioned bisintercalands by reaction of the corresponding heterocycles with various dibromoalkyl derivatives, in 2:1 molar ratio, using phase transfer catalysis, according to scheme 1.

Compound **1** was prepared by cyclization of 4,6-dimethyl-2-anilinonicotinonitrile in presence of $AlCl_3$.

Scheme 1



This method gives higher yields than cyclization with polyphosphoric acid [10].

As observed in the case of acridine [11], the direct alkylation of **1** proved to be considerably less efficient. Thus, we preferred the phase transfer catalysis for preparing the bis derivatives.

The ^{1}H-NMR spectra, as in the acridine case [12], can be used to distinguish between compounds **2a-2d** and **4a-4d**. The HN-C$\underline{H}_2$ protons of **2a-2d** appear in the range of 4.4-4.5 ppm, compared to 4.75-4.82 ppm, as expected for methylene groups linked at heterocyclic nitrogen of **4a-4d** (see experimental).

The mass spectra of **2a-2d** and **4a-4d** show the molecular ion that, however, is not the base peak. The fragmentation under the electron impact results in breaking of one of the C_{alkyl}-*N* bonds leading to two main fragments, the simple heterocycle and the corresponding N-alkylated heterocycle moiety, respectively. The second fragment further undergoes loss of the methylene chain (see experimental).

In conclusion, we prepared new monobridged 2,3-dimethyl-5-amino-benzo[*b*][1,8]naphthyridines and benzo[*b*][1,8]benzonaphthyridones; biological testing is now in progress to investigate their antitumoral activity.

EXPERIMENTAL

Melting points are uncorrected. Their spectra were recorded on a Perkin-Elmer Spectrum 2000 instrument (in potassium bromide) The nmr spectra were recorded on Varian, Gemini 300 spectrometer, in DMSO-d_6 (^{1}H and ^{13}C nmr spectra of compounds **2a-2d** and ^{1}H nmr spectra of compound **4a-4d**) or in trifluoroacetic acid (^{13}C nmr spectra of compounds **4a-4d**) with tetramethylsilane as internal reference. Mass spectra were performed with a Helwett Packard Trio-1 spectrometer (EI = 70 eV). Elemental analyses were performed on a Perkin-Elmer 2400 instrument. The reactions were monitored by TLC using neutral alumina plates for compounds **2a-2d** and silica gel plates for compounds **4a-4d**. The eluting system was hexane-ether 7:3 (v/v) in the first case and methanol in the second one. The visualization was performed by UV, at 254 nm.

2,4-Dimethyl-9-amino-benzo[*b*][1,8]naphthyridine (**1**).

Anhydrous aluminum chloride (2g) was added to 4 6-dimethyl-2-anilinonicotinonitrile (2.2 g, 10 mmoles) and the mixture was heated at 200°C for 30 min. The reaction mixture was cooled and then treated with 20% hydrochloric acid solution, made alkaline with 30% sodium hydroxide solution and the resulting precipitate filtered, dried and recrystallized from ethanol-ether (3:1 v/v), yield 59%, m.p. = 227-228 (225-227° [8]).

General procedure for preparing (diamino-α,ω-alkane)-5,5'-bis(2,4-dimethyl-benzo[*b*][1,8] naphthyridines) **2a-2d** and 10,10'-(alkane-α,ω–diyl)-bis(benzo[*b*][1,8]naphthyridones) **4a-4d**.

Compound **1** or **3** (10 mmoles), alkylating agent (5 mmoles) and tetrabutylammonium bromide (TBAB) (0.806 g, 5 mmoles) were added to a mixture of toluene (100 ml) and 50% aqueous solution of potassium hydroxide (50 ml). The mixture was stirred and heated at 110°C for 2 hours in case of compound **1** and at 80°C for 24 hours for compound **3**. Then the reaction mixture was cooled, the organic layer separated, washed well with water, dried and the organic solvent removed *in vacuo*. Compounds **2b-2d** were purified by extraction with hot ethanol, filtered, the organic solvent removed *in vacuo* and the residue triturated with ether. Compounds **2a** and **4a-4d** were recrystallized from dimethyl sulfoxide of spectral purity, heated at 100°C, and precipitates washed with cold ethanol.

N,N-Bis-(2,4-dimethylbenzo[*b*][1,8]naphthyridin-5-yl)-propane-1,3-diamine (**2a**).

This compound was obtained as yellow crystals in 41% yield, mp 216-218°; ^{1}H nmr: δ 10.15 (s,NH), 8.11 (d, 1H, J = 7.50), 7.49 (td, 1H, J = 7.50, 0.90), 7.39 (d, 1H, J = 7.50), 7.13 (td, 1H, J = 7.50, 0.90), 6.78 (s, 1H), 4.57 (t, 4H, J = 6.80), 2.71 (s, 3H), 2.47 (s, 3H), 2.13 (q, 2H, J = 6.80). ^{13}C nmr: δ 162.00,156.38, 150.50, 149.63, 140.30, 138.70, 132.00, 125.13, 121.80, 121.12, 120.00, 119.90, 115.20, 111.32, 42.50, 26.00, 25.50, 26.06. ms: m/z (%) 486 (29) (M^+), 264(40), 250(30), 326(35), 224 (100), 222 (22).

Anal. Calcd. for $C_{31}H_{30}N_6$: C, 76.51; H, 6.21; N, 17.27. Found: C, 76.40; H, 6.38; N, 17.38.

N,N-Bis-(2,4-dimethylbenzo[*b*][1,8]naphthyridin-5-yl)-hexane-1,6-diamine (**2b**).

This compound were obtained as yellow crystals in 61% yield, mp 143-145°; ^{1}H nmr: δ 10.10 (s,NH), 8.11 (d, 1H, J = 7.45), 7.49 (td, 1H, J = 7.45, 0.85), 7.38 (d, 1H, J = 7.45), 7.12 (td, 1H, J = 7.45, 0.85), 6.78 (s, 1H), 4.50(t ,4H, J = 7.00), 2.66 (s, 3H), 2.29 (s, 3H), 1.63 (b, 4H), 1.42 (b,4H). ^{13}C nmr: δ 162.00, 157.27, 150.23, 149.47, 138.34, 131.59, 125.06, 121.86, 121.07, 120.19, 114.83, 111.97, 42.46, 26.11, 25.70, 24.07, 23.39 ms : m/z (%) 528 (17) (M^+), 306 (9), 264 (21), 259 (25), 236 (17), 222 (24), 221 (100).

Anal. Calcd. for $C_{34}H_{36}N_6$: C,77.24; H,6.86; N,15.89. Found: C,77.35; H,7.05; N,16.12.

N,N-Bis-(2,4-dimethylbenzo[*b*][1,8]naphthyridin-5-yl)-octane-1,8-diamine (**2c**).

This compound was prepared as a yellow powder in 53% yield, mp 148-150°; ^{1}H nmr: δ 9.94 (s,NH), 8.09 (d,1H, J = 7.50), 7.50 (td, 1H, J = 7.50, 0.90), 7.34 (d,1H, J = 7.50), 7.14 (td, 1H, J = 7.50, 0.90), 6.77 (s, 1H), 4.40 (t, 4H, J = 7.00), 2.68 (s, 3H), 2.41 (s, 3H), 1.61 (q, 4H, J = 7.00), 1.28 (m, 8H). ^{13}C nmr: δ 161.08, 156.63, 149.27, 148.55, 137.41, 130.57, 124.07, 120.95, 120.05, 119.19, 113.82, 111.08, 41.58, 27.44, 25.16, 25.04, 23.14, 22.40. ms: m/z (%) 556 (20) (M^+), 335 (8), 293 (11), 279 (20), 251 (28), 221 (36), 224 (100).

Anal. Calcd. for $C_{36}H_{40}N_6$: C, 77.66; H, 7.24; N, 15.09. Found: C,77.80; H,7.12; N,15.18.

N,N-Bis-(2,4-dimethylbenzo[*b*][1,8]naphthyridin-5-yl)-decane-1,10-diamine (**2d**).

This compound was prepared as a yellow powder in 56% yield, mp 124-126°; ^{1}H nmr: δ 9.95 (s, NH), 8.07 (d, 1H,J = 7.48), 7.49 (td, 1H, J = 7.48, 0.86), 7.41 (d, 1H, J = 7. 48), 7.13 (td, 1H, J = 7.48, 0.86), 6.80 (s, 1H), 4.42 (t,4H, J = 7.00), 2.70 (s, 3H), 2.43 (s, 3H), 1.63 (q,4H, J = 7.00), 1.26 (m, 12H). ^{13}C nmr: δ 161.97, 157.78, 150.24, 148.36, 138.36, 131.65, 125.06, 121.10, 120.24, 119.01, 114. 91, 118.86, 42.56, 28.72, 28.50,

26.18, 26.04, 24.12, 23,27. ms: m/z (%) 584 (23) (M^+), 364 (9), 349 (6), 335 (7), 321 (12), 307 (13), 293 (46), 224 (100), 221(35).

Anal. Calcd. for $C_{38}H_{44}N_6$: C, 78.47; H, 7.58; N, 14.37. Found: C, 78.60; H, 7.40; N, 14.50.

10,10'-(Propane-1,3-diyl)bis(benzo[*b*][1,8]naphthyrid-5-one) (**4a**).

This compound was obtained as a brown-yellowish powder in 20% yield, mp. 240-42°; ir: ν 1637.77, 1599.02, 1491.81 cm^{-1}; ^1H nmr: δ 8.85 (dd, 1H, J = 6.3, 0.71), 8.60 (dd, 1H, J = 7.57, 1.1), 8.30 (d, 1H, J = 8.0), 7.80 (m, 2H), 7.32(m, 2H), 4.82 (t,4H J = 6.80), 2.22 (q, 2H, J = 6.80). ^{13}C nmr: δ 180.27, 151.97, 148.28, 146.4, 143.06, 142.30, 131.30, 126.06, 122.24, 119.87, 117.80, 114.51, 48.81, 31.53. ms: m/s (%) 432 (37) (M^+), 237 (45), 223 (100), 209 (31), 195 (46).

Anal. Calcd. for $C_{27}H_{20}N_4O_2$: C, 74.98; H, 4.66; N, 12.95. Found: C, 75.13; H, 4.80; N, 13.10.

10,10'-(Hexane-1,6-diyl)bis(benzo[*b*][1,8]naphthyridone) (**4b**).

This compound was prepared as a brown yellowish powder in 59% yield, mp 263-265°: ir: ν 1639.75, 1598.95, 1492.87 cm^{-1}; ^1H nmr: δ 8.81 (dd, 1H, J = 6.40, 0.75), 8.62 (dd, 1H, J = 7.60, 1.00) 8.31 (d, 1H, J = 8.1), 7.85 (m, 2H), 7.37(m, 2H), 4.76 (t,4H, J = 7.00), 1.74 (br, 4H), 1.51 (br, 4H).^{13}C nmr: δ 180.50, 150.90, 148.132, 146.70, 142.50,141.63, 131.00, 125.60, 122.80, 120.00, 118.03, 115.23, 48.81, 31.50, 30.84. ms: m/z (%) 474 (46) (M^+), 279 (13), 265 (21), 251 (9), 237 (21), 223 (38), 209 (100), 195 (75).

Anal. Calcd. for $C_{30}H_{26}N_4O_2$: C, 75.83; H, 5.60; N, 11.90. Found: C, 75.92; H, 5.80; N, 12.10.

10,10'-(octane-1,8-diyl)bis(benzo[*b*][1,8]naphthyridone) (**4c**).

This compound was obtained as a brown yellowish powder in 58% yield, mp 186-187°; ir: ν 1640.32, 1598.63, 1492.73 cm^{-1}; ^1H nmr: δ 8.83 (dd, 1H, J = 6.30, 0.72), 8.61 (dd, 1H, J = 7.40, 0.98), 7.32 (d, 1H, J = 8.30), 7.82 (m, 2H), 7.34 (m, 2H), 4.72 (t, 4H, J = 6.80), 1.68 (q,4H, J = 6.80), 1.24 (m, 8H). ^{13}C nmr: δ 178.88, 150.87, 147.06, 146.85, 142.82, 141.84, 130.06, 125.21, 122.49, 119.96, 118.76, 114.99, 48.58, 31.22, 28.94, 28.34. ms: m/z (%) 502 (26) (M^+), 293 (12), 251 (9), 237(12), 224 (46), 209 (90), 195 (100).

Anal. Calcd. for $C_{32}H_{30}N_4O_2$: C, 76.47; H, 6.02; N, 11.15. Found: C, 76.60; H, 6.18; N, 11.30.

10,10'-(decane-1,10-diyl)bis(benzo[*b*][1,8]naphthyridone) (**4d**).

This compound was obtained as a brown yellowish powder in 60% yield, mp 205-207°; ir: ν 1637.02, 1598.25, 1488.94 cm^{-1}; ^1H nmr: δ 8.85 (dd, 1H, J = 6.53, 0.81), 8.63 (dd, 1H, J = 7.6, 1.20), 8.33 (d, 1H, J = 8.2), 7.85 (m, 2H), 7.36 (m, 2H), 4.75 (t, 4H, J = 7.00), 1.72 (q, 6H, J = 7.00), 1.23 (m, 12H). ^{13}C nmr: δ 180.32, 151.82, 148.01, 147.86, 143.84, 141.38, 131.91, 126.22, 123.52, 119.75, 119.01, 115.25, 49.62, 32.34, 32.27, 29.98, 29.43. ms: m/z (%) 530 (33) (M^+), 335 (7), 311 (5), 307 (6), 293 (5), 279 (7), 265 (12), 251 (5), 237 (8), 223 (49), 209 (36), 195 (100).

Anal. Calcd. for $C_{34}H_{34}N_4O_2$: C, 76.74; H, 6.46; N, 10.56. Found: C, 76.95; H, 6.60; N, 10.80.

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