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Short Communication

Synthesis of a Boronated Naphthalimide for Potential Use in Boron Neutron Capture Therapy (BNCT)

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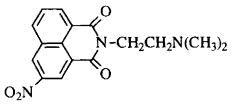
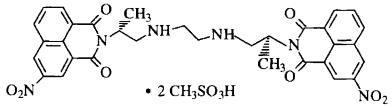
One of the most difficult aspects of treating cancer is the ability of many tumours to develop resistance to chemotherapeutic drugs.[1] An approach to circumvent this problem could be the use of certain elements such as ^{10}B which can undergo neutron capture. Boron neutron capture therapy (BNCT)[2–4] is based on the cytotoxic effect from the neutron capture reaction [$^{10}B(n, \alpha)\ ^{7}Li$]. This cytotoxic effect would be two to five times higher if the neutron capture reaction took place in the nucleus rather than in the cytoplasm or the cell membrane.[5] Therefore, boron-containing DNA intercalating/interacting molecules may serve as appropriate agents for delivery of boron-10 into the DNA of the cells. However, a targeting system should be used for selective delivery of boron compounds to the tumour cells, e.g. encapsulation of boron agents into the aqueous compartment of sterically stabilised liposomes, which in turn are conjugated to a receptor-specific ligand such as EGF, in order to enter the cell cytoplasm and minimise the accumulation of boronated agents in the healthy surrounding cells.[6]



MITONAFIDE



DMP 840

Fig. 1.

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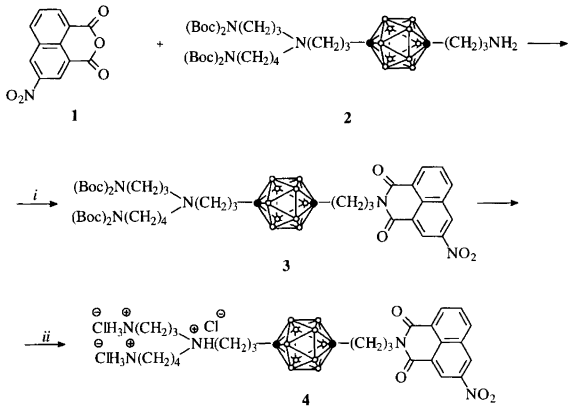
In this report, we focus our work on the synthesis of a boron-containing analogue of naphthalimides. Some naphthalimides such as Mitonafide and DMP 840 (Fig. 1) are DNA-intercalators which bind DNA with high affinity and have sequence specificity to guanine (G) and cytosine (C) bases causing single-stranded DNA breaks.[7] In addition, it is evident that the nitro or amino substituents in the chromophore rings are essential for the antitumour activity and binding.[8] Thus, the water-soluble compound **4**, containing both a *p*-carboranyl and spermidine moiety, was synthesised as the target compound for further biological evaluations.

Results

The synthesis of the boronated naphthalimide derivative was carried out by nucleophilic reaction of the corresponding polyamine with two equivalents of the required 3-nitro-1,8-naphthalic anhydride as outlined in Scheme 1. A mixture of 3-nitro-1,8-naphthalic anhydride (**1**) and the primary amine **2**[9] was heated at 80 °C in DMF for



Scheme 1. Reagents and conditions: (*i*) DMF, 80 °C, 24 h, N_2 atm; (*ii*) $HCl_{(g)}$, diethyl ether, 2 h, RT.

24 h under a nitrogen atmosphere to obtain **3** in 69% yield. This compound was purified by silica gel column chromatography using diethyl ether as the eluent. The hydrochloride salt **4** was accomplished by treatment of **3** with dry hydrogen chloride gas in diethyl ether at ambient temperature for 2 h. The lemon yellow precipitate was filtered and washed with diethyl ether to give **4** in 94% yield.

Target compound **4** will be evaluated with respect to its DNA binding capacity and also compared with other boronated DNA-intercalating agents[9–11] regarding their toxicity and DNA binding constant. The results from these studies will be published elsewhere.

Experimental

General details. ^{1}H, ^{13}C, and ^{11}B NMR spectra were recorded for samples in $CDCl_3$ (7.26 ppm, ^{1}H, 77.0 ppm, ^{13}C) or CD_3OD (3.35 ppm, ^{1}H, 49.0 ppm, ^{13}C) on a Varian XL-400 spectrometer operating at 400, 100.6 and 128.3 MHz, respectively. Boron fluoride–diethyl etherate was used as an external standard for the boron spectra. The IR spectra were obtained on a Perkin–Elmer 1600 FT-IR spectrometer. FAB-Mass spectra were recorded on a SX/SX 102A (JEOL) mass spectrometer. For column chromatography Merck Silica Gel 60 (230–400 mesh) was used. Merck Silica 60 F_{254} gel plates were used for TLC. Melting points are uncorrected and were obtained using a Büchi capillary melting point apparatus.

Compound **3.** A mixture of 3-nitro-1,8-naphthalic anhydride **1** (0.20 g, 0.82 mmol) and **2** (0.33 g, 0.42 mmol) was heated at 80 °C in DMF under a nitrogen atmosphere for 24 h. The mixture was cooled to room temperature and concentrated. The crude product was then purified by silica gel column chromatography using diethyl ether as the mobile phase to give a yellow sponge-like mass of **3** (R_f=0.68) in 69% yield (0.294 g). HRMS (NBA, FAB^+): Calc. for $C_{47}H_{78}{}^{11}B_{10}N_5O_{12}$: 1014.6578, Found: 1014.6685. ^{1}H NMR ($CDCl_3$): δ 9.29 (d, 1 H, J= 2.13 Hz, H-2 or H-4), 9.13 (d, 1 H, J=2.14 Hz, H-4 or H-2), 8.77 (d, 1 H, H-7), 8.42 (d, 1 H, H-5), 7.95 (t, 1 H, H-6), 3.99 (t, 2 H, $CH_2N_{\text{in the chromophore ring}}$), 3.52 (m, 4 H, CH_2NBoc_2), 2.30 (m, 4 H, CH_2N), 2.16 (t, 2 H, $C_{cage}CH_2CH_2CH_2N$), 1.74 (m, 2 H, $NCH_2CH_2CH_2N$), 1.60 (m, 4 H, CH_2C_{cage}), 1.49 (s, 36 H, CH_3), 1.33 (m, 4 H, $NCH_2CH_2CH_2CH_2N$), 1.25 (m, 4 H, $CH_2CH_2C_{cage}$). ^{13}C NMR ($CDCl_3$): δ 162.95 (CO), 162.34 (CO), 152. 62 (arom.), 146.40 (arom.), 135.63 (arom.), 134.53 (arom.), 131.02 (arom.), 130.16 (arom.), 129.09 (arom.), 129.00 (arom.), 124.37 (arom.), 123.04 (arom.), 82.04 (CCH_3), 79.37 and 79.11 (C_{cage}), 53.48, 52.80 and 51.21 (CH_2N), 46.31 and 45.00 (CH_2NBoc_2), 39.98 ($CH_2N_{\text{in the chromophore ring}}$); 35.52 and 35.08 ($CH_2C_{cage}$), 29.69 ($CH_2CH_2C_{cage}$), 28.10 ($CH_3$), 27.96 ($CH_2CH_2C_{cage}$), 27.03 and 26.46 ($NCH_2CH_2CH_2CH_2N$), 24.17 ($NCH_2CH_2CH_2N$). ^{11}B NMR ($CDCl_3$): δ −13.09. IR ($CDCl_3$): 2981.5, 2604.4, 1736.1, 1707.4, 1689.8, 1669.9, 1368.5 and 1131.8 cm^{-1}.

Compound **4.** A solution of **3** (0.29 g, 0.287 mmol) in dry diethyl ether (20 mL) was kept saturated with dry hydrogen chloride gas at ambient temperature for 2 h and then concentrated to half of its original volume by bubbling nitrogen through the solution. The lemon yellow precipitate was then washed with dry diethyl ether (3 × 20 mL) to give 0.19 g (94%) of **4**. M.p. 235–240 °C (decomp.). HRMS (NBA, FAB^+): Calc. for $C_{27}H_{46}{}^{11}B_{10}N_5O_4$: 614.4480. Found: 614.4495. ^{1}H NMR (CD_3OD): δ 9.30 (t, 1 H, J=2.29 Hz, H-2 or H-4), 9.13 (t, 1 H, J= 2.29 Hz, H-4 or H-2), 8.73 (td, 1 H, J=7.33 Hz, H-7), 8.61 (td, 1 H, J=8.39 Hz, H-5), 8.01 (dt, 1 H, J= 7.77 Hz, H-6), 3.99 (t, 2 H, $CH_2N_{\text{in the chromophore ring}}$), 3.29–3.08 (m, 4 H, CH_2N), 3.04–2.90 (m, 6 H, CH_2NH_3Cl and $NCH_2CH_2CH_2C_{cage}$), 2.16 (m, 2 H, $NCH_2CH_2CH_2N$), 1.82 (m, 4 H, CH_2C_{cage}), 1.67 (m, 4 H, $NCH_2CH_2CH_2CH_2N$), 1.47 (m, 4 H, $CH_2CH_2C_{cage}$). ^{13}C NMR (CD_3OD): δ 164.59 (CO), 164.03 (CO), 147.70 (arom.), 137.33 (arom.), 135.23 (arom.), 132.66 (arom.), 131.24 (arom.), 130.54 (arom.), 130.20 (arom.), 125.57 (arom.), 124.57 (arom.), 124.11 (arom.), 79.65 and 79.08 (C_{cage}), 53.80, 51.31 and 45.17 (CH_2N), 40.85 ($CH_2N_{\text{in the chromophore ring}}$), 40.05 and 37.94 ($CH_2NH_3Cl$), 36.32 and 35.27 ($CH_2C_{cage}$), 30.19 and 29.06 ($CH_2CH_2C_{cage}$), 25.60 ($NCH_2CH_2CH_2CH_2N$), 23.24 ($NCH_2CH_2CH_2N$), 22.02 ($NCH_2CH_2CH_2CH_2N$). ^{11}B NMR (CD_3OD): δ −12.34. IR (KBr): 3411.7, 2959.9, 2600.9, 1707.0, 1669.9, 1599.3, 1330.6, 1243.9 and 757.8 cm^{-1}.

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