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Towards a new family of calixarene-based podands incorporating quinolone arms. An example using nalidixic acid

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Abstract—A new calixarene-based heterocyclic podand incorporating a quinolone antibiotic, the nalidixic acid, was synthesised and fully characterised.

The highly interesting organising and carrying properties of the calixarenes have been poorly investigated in the medicinal field; only a very few number of reports, essentially patents, has been devoted to their use in this domain.[1] In order to develop calixarene-based podands shaped as potent drug carriers and dispensers, we have recently reported the synthesis and the characterisation of a penicillin-containing calix[4]arene species displaying two carboxy-protected 6-aminopenicillanic acids tethered via amide linkages on distal phenol rings.[2]

The interesting results obtained in this study brought us to develop variations in the penicillin field, actually under investigation, and with other antibiotics, such as quinolones. Thus, we present here our preliminary results in the building of a new family of calixarene-based podands displaying pendant quinolone arms at the lower rim, using the nalidixic acid as illustration.

The presence of a carboxylate function on the quinolone species led us to develop a simple strategy involving the formation of an ester linkage between the calixarene platform and the nalidixic acid. According to Scheme 1, two ways were thus available for the tethering of nalidixic acid to the lower rim of the *p*-*tert*-butylcalix[4]arene. The first one involved a pre-functionalised calixarene able to react in soft conditions with nalidixic acid; in order to avoid acidic conditions that could destroy the quinolone, we opted for an acid salt alkylation process.[3] Using DMF as solvent instead of the recommended but toxic HMPT,[4] the sodium salt of nalidixic acid **1**[5] was reacted at room temperature with the cone conformer of the 5,11,17,23-tetra(*tert*-butyl)-26,28-bis-(1-bromopropyloxy)-calix[4]-arene-25,27-diol **2**.[6] TLC monitoring of the reaction showed consumption of both reactants, with the formation of new species that we were unfortunately unable to separate properly, but which display, on the base of NMR analyses, the resonance signals of calixarene and quinolone moieties.

At the same time, we developed the opposite strategy, which involved the preliminary synthesis of a bromoalkyl ester of the nalidixic acid, followed by a base-strength-driven regioselective di-*O*-alkylation of the conic 5,11,17,23-tetra(*tert*-butyl)-calix[4]arene-25, 26, 27, 28-tetrol **5**.[7]

The bromopropyl ester of nalidixic acid **4** was thus synthesised by reaction in DMF of an excess of 1,3-dibromopropane with **1**, with a yield of ca. 70%. The reaction of **4** with calixarene **5** was performed in MeCN, using K_2CO_3 as base. TLC monitoring showed the formation of a major compound, accompanied by some degradation products, and residual **4** and **5**. The raw product was dissolved in CH_2Cl_2 and was washed with H_2O to remove inorganic material. Attempts to recover pure **3** by column chromatography failed, giving only samples for analyses.[8] A separation process involving selective precipitations in order to remove unreacted **4** and **5**, and impurities, finally afforded the desired pure podand **3** with a yield of 35% (ca. 60% by alkylation step). Similar yields were obtained with other quinolone species.

Compounds **4** and **3** were fully characterised. More precisely, the podand **3** gave satisfactory IR and ele-

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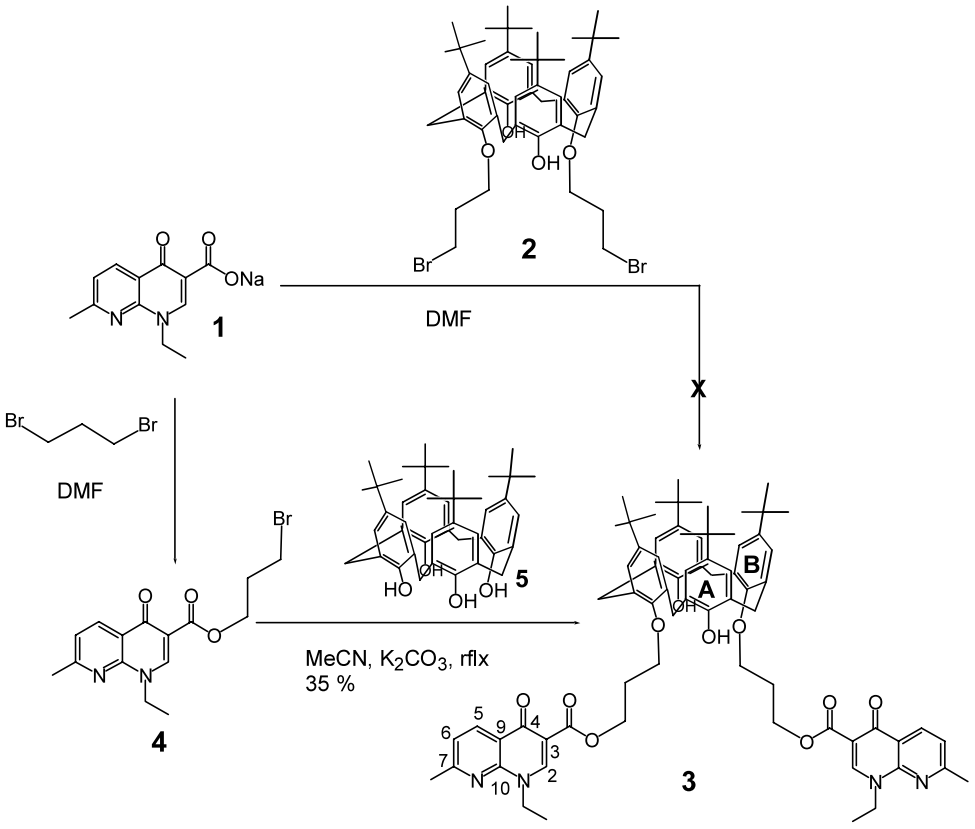

Scheme 1. Synthetic pathways evaluated for the preparation of podand **3** (numbering refers to NMR analysis).[8]

mental analyses. Electrospray mass spectrometry (positive mode) confirmed the formation of the podand with a base peak at 1193.4 amu ([**3**+H]$^+$). NMR structural analyses involved ^{1}H and ^{13}C 1D experiments, and COSY, HSQC and HMBC 2D experiments which allowed the complete attribution of the resonance signals. The ^{1}H-NMR spectrum of podand **3** was in accordance with a C_2 symmetry. The presence of an AB system at 3.300, 4.333 ppm ($J_{AB}=13$ Hz; ^{1}H NMR) and a single signal at 32.18 ppm (^{13}C NMR) attributed to the ArCH_2Ar groups, confirmed that the calixarene stayed in the cone conformation;[9] due to the presence of four ordered nitrogen atoms and four ordered oxygen atoms, this point can be of importance with regards to their potent metal complexation properties[7d] and, as recently experienced with other amphiphilic nitrogen-containing podands, to their behaviour on the air-water interface.[10]

Variation and crossing of quinolone species, improvement of reaction yields as well as purification processes are under current development. In order to verify the prodrug behaviour of the podand **3** and analogues, the lability of their ester functions in biological media are also being investigated.

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8. **Compound 4**: A mixture of sodium nalidixate **1** (0.5 g, 1.97×10^{-3} mol) and 1,3-dibromopropane (8 mL, 7.9×10^{-2} mol) in anhydrous DMF (35 mL) was stirred under Ar during 24 h. DMF was then eliminated and the solid residue was dissolved in CH_2Cl_2 and washed several times with H_2O. The organic phase was dried over Na_2SO_4, concentrated then chromatographed (SiO_2; CH_2Cl_2/CH_3OH, 5:0.1) to give **4** (recrystallised in hexane; 0.45 g; 65%). White powder. Mp: 132–134°C. IR (KBr): 1641.0 (CO); 1686.0 (COO). UV–vis ($CHCl_3$): 258 (22200); 336 (16800). ^{1}H NMR: 1.512 (t, $J=7$ Hz, 3H, CH_3CH$_2$N); 2.353 (quint, $J=6.3$ Hz, 2H, BrCH$_2$CH_2CH$_2$OCO); 2.676 (s, 3H, CH_3); 3.667 (t, $J=6.5$ Hz, 2H, BrCH_2CH$_2$CH$_2$-OCO); 4.451–4.538 (t+q, 4H, BrCH$_2$CH$_2$CH_2OCO+ CH$_3$CH_2); 7.261 (d, $J=8.2$ Hz, 1H, *H*(6)); 8.635 (s, 1H, *H*(2)); 8.644 (d, $J=8.2$ Hz, 1H, *H*(5)). ^{13}C NMR: 15.60 (*C*H$_3$CH$_2$); 25.47 (*C*H$_3$); 30.45 (Br*C*H$_2$CH$_2$CH$_2$OCO); 32.27 (BrCH$_2$*C*H$_2$CH$_2$OCO); 47.02 (CH$_3$*C*H$_2$); 62.96 (BrCH$_2$CH$_2$*C*H$_2$OCO); 112.11 (*C*(2)); 121.61 (*C*(6)); 121.97 (*C*(9)); 137.20 (*C*(5)); 149.03 (*C*(7)); 149.28 (*C*(2)); 163.13 (*C*(10)); 166.17 (BrCH$_2$CH$_2$CH$_2$O*C*O); 175.01 (*C*(4)). Elemental analysis calcd for $C_{15}H_{17}BrN_2O_3$ (352.04): C, 51.01; H, 4.85; N, 7.93; found: C, 51.06; H, 4.65; N, 7.78. ES-MS (pos. mode): 353.11 (1), 354.09 (0.15), 355.07 (1), 356.06 (0.15) [**4**+H]$^+$; 215.06 (0.8), 216.17 (0.1) [**4**-BrCH$_2$CH$_2$CH$_2$O]$^+$.

   Compound 3: A suspension of *p*-*tert*-butylcalix[4]arene **5** (0.1 g, 0.15×10^{-3} mol) and K_2CO_3 (0.85 g, 0.62×10^{-3} mol) in dry MeCN (20 mL) was refluxed under Ar during 30 min. The bromopropylnalidixate **4** (0.11 g, 0.31×10^{-3} mol) was then added. After 48 h, the solvent was evaporated to dryness and the residue was dissolved in CH_2Cl_2. Water was added and neutralised with 1 M HCl. The organic phase was dried over Na_2SO_4, concentrated, cooled then filtered. CH_2Cl_2 was evaporated to dryness and the solid residue was triturated in Et_2O to give **3** (0.065 g; 35%). White powder. Mp 131–132°C. IR (KBr): 1692 (CO); 1735 (COO). UV–vis (CH_2Cl_2): 254 (29800.0); 290 (12900); 332 (19900). ^{1}H NMR: 0.996 (s, 18H, *Me*$_3$C); 1.268 (s, 18H, *Me*$_3$C); 1.399 (t, $J=7$ Hz, 6H, CH_3CH$_2$); 2.547 (q, $J=6$ Hz, 4H, OCH$_2$CH_2CH$_2$OCO); 2.612 (s, 6H, CH_3); 3.300, 4.333 (AB, $J_{AB}=13$ Hz, 8H, ArCH_2Ar); 4.221 (t, $J=6$ Hz, 4H, OCH_2CH$_2$CH$_2$OCO); 4.31 (br q, 4H, CH_2CH$_3$); 4.885 (t, $J=6$ Hz, 4H, OCH$_2$CH$_2$CH_2OCO); 6.842 (s, 4H, Ar*H*); 7.000 (s, 4H, Ar*H*); 7.175 (d, $J=8$ Hz, 2H, *H*(6)), 7.80 (s, 2H, O*H*); 8.596 (d, $J=8$ Hz, *H*(5)); 8.62 (s, 2H, *H*(2)). ^{13}C NMR ($CDCl_3$): 15.55 (*C*H$_3$CH$_2$); 25.38 (*C*H$_3$); 29.71 (OCH$_2$*C*H$_2$CH$_2$OOC); 31.43 (*Me*$_3$C **B**); 32.09 (*Me*$_3$C **A**); 32.18 (Ar*C*H$_2$Ar); 34.17 (Me$_3$*C* **A**), 34.37 (Me$_3$*C* **B**); 46.89 (CH$_3$*C*H$_2$); 61.95 (OCH$_2$CH$_2$*C*H$_2$OCO); 72.93 (O*C*H$_2$CH$_2$CH$_2$OCO); 112.34 (*C*(3)); 121.22 (*C*(6)); 121.73 (*C*(9)); 125.43 (C_m of Ar **A**); 125.99 (C_m of Ar **B**); 127.98 (C_o of Ar **A**); 133.15 (C_o of Ar **B**); 137.06 (*C*(5)); 141.74 (C_p of Ar **A**); 147.32 (C_p of Ar **B**); 149.18 (*C*(2)); 148.96 (*C*(7)); 150.00 (C_i of Ar **B**); 151.15 (C_i of Ar **A**); 162.77 (*C*(10)); 165.51 (OCH$_2$CH$_2$CH$_2$OO*C*); 175.12 (*C*(4)). Elemental analysis calcd for $C_{74}H_{88}O_{10}N_4$ (1192.65): C, 74.47; H, 7.43; N, 4.69; found: C, 74.18; H, 7.37; N, 4.35. ES-MS (pos. mode): 1193.4 (100), 1194.4 (80), 1195.3 (30), 1196.4 (10) [**3**+H]$^+$.

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