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Synthesis of macrocyclic systems derived from di-(2-indolyl)heteroarenes

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ABSTRACT

A number of new 3,6-di-(2-indolyl)-dibenzofuran and carbazole derivatives have been prepared from dibenzofuran and carbazole linkers via the Fischer indole synthesis. The bis-indoles were successfully formylated at C3 and the resulting dicarbaldehydes were combined with diamines to generate indole based imine macrocyclic systems.

1. Introduction

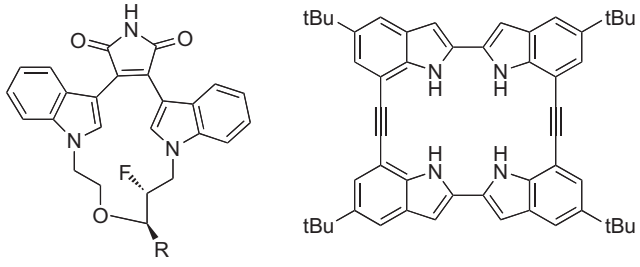
Bis-indole alkaloids are interesting heterocyclic compounds because many examples have been isolated from natural sources and display a wide range of pharmacological activity.[1] In particular, a common structural motif amongst these bis-indoles is the connection of the two indole rings via a five- or six-membered aryl or heteroaryl ring. Examples include the nortopsentins A–C, which show cytotoxicity and antifungal activity[2] and dragmacidin D, which is an inhibitor of serine/threonine protein phosphatases.[3]

In general, bis-3-indoles are perhaps the most prolific of this class, but bis-2-indoles have also attracted recent attention because of their use as tubulin polymerisation inhibitors,[4] antibacterial agents,[5] CDK inhibitors and cytotoxic agents,[6] as well as organic semiconductors[7] and light emitting compounds.[8]

Macrocyclic bis-indole systems are also of interest for pharmaceutical purposes and as receptors and chemosensors. For instance, bis(indolyl)maleimides **1** have been the focus of extensive development as protein kinase C inhibitors[9] and the macrocyclic tetraindole **2** is reported to strongly bind a range of anions[10] (Fig. 1).

In our current study, we were interested in the synthesis of bis-2-indolyls linked by structurally rigid carbazole or dibenzofuran ring systems as precursors to novel macrocycles. In addition, 3,6-diaryl or heteroaryl dibenzofurans and carbazoles have been associated with cytotoxic and antiplatelet activity,[11] and show potential as novel fluorescent probes,[12] optoelectronic materials[13] and semiconductors.[14]

Further, since indoles can be readily formylated, subsequent imine formation by reaction with amines is an effective strategy for the preparation of a diverse range of novel macrocyclic structures. Imines also show varied pharmacological effects, for example, indole-3-carbaldimines show antimicrobial activity,[15] and also can facilitate metal complexation.[16] It was therefore anticipated that this methodology of imine formation could be readily extended to our targeted 3,6-bis-(2-indolyl)-dibenzofuran and carbazole systems.



1 **2**

Fig. 1. Macrocyclic bis-indole systems.

2. Results and discussion

The synthesis of a new range of macrocyclic systems derived from 3,6-bis-(2-indolyl)-dibenzofuran and related carbazoles was approached via the Fischer indole synthesis.

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Dibenzofuran (**3a**), carbazole (**3b**) and *N*-methylcarbazole (**3c**) were acetylated under Friedel–Crafts conditions by heating at 50 °C with 2 equiv of acetyl chloride and aluminium trichloride in carbon disulfide.[17–19] The resulting dibenzofuran **4a**, carbazole **4b** and *N*-methylcarbazole **4c** were obtained in 90%, 85% and 83% yields, respectively. The aromatic ketones **4a–c** were subsequently reacted at reflux for 2 h in ethanol and glacial acetic acid with 2 equiv of phenylhydrazine to give phenylhydrazones **5a–c** in 70–80% yield (Scheme 1). Acid-catalysed cyclisation at 110 °C using methanesulfonic acid then gave the targeted 3,6-bis-(2-indolyl)-dibenzofuran **6a** and carbazoles **6b,c** in 67–75% yield. The ^{1}H NMR spectrum of dibenzofuran **6a** was characteristic for these bis-2-indoles, showing the indole H3 proton at δ 6.96 and the benzenoid protons as doublets at δ 7.42 and 7.83 and a multiplet at δ 7.13. The dibenzofuran protons were present as doublets at δ 7.55 and 8.65 and a doublet of doublets at δ 8.05 and the NH groups appeared as a broad singlet at δ 11.66. Mass spectrometry provided further structural confirmation, with the anticipated molecular ions present at 398, 397, 411 for bis-2-indoles **6a**, **6b** and **6c**, respectively.

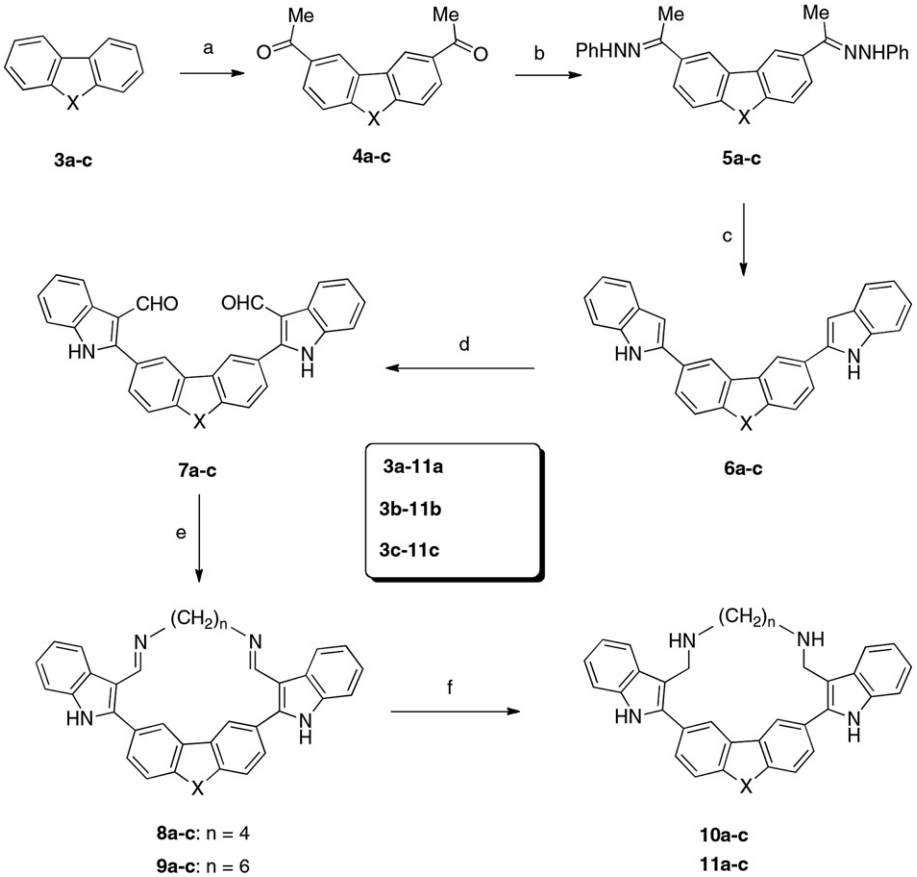
Formylation of the C3 indole positions was readily achieved using Vilsmeier–Haack conditions at 0 °C and in the presence of an excess of phosphoryl chloride. The resulting bis-indole dicarbaldehydes **7a–c** were obtained in 85–90% yield as yellow solids. Reaction at C3 was confirmed by ^{1}H NMR spectroscopy, in which the characteristic H3 protons of the precursors were absent and the new CHO protons appeared as sharp singlets at δ 10.1. The ^{13}C NMR spectra similarly displayed the expected carbonyl resonance at δ 186.0.

Schiff base condensation of the bis-indole dicarbaldehydes **7a–c** with a range of primary diamines was subsequently investigated. Heating bis-indole dicarbaldehyde **7a** at reflux with 1,2-diaminoethane in absolute ethanol for 12 h led only to recovery of the starting material. In a similar fashion, no reaction was observed upon heating with 1,2-diaminobenzene. This suggested that the rigidity of the dibenzofuran moiety necessitates the use of longer, more flexible linkers in order to produce the desired macrocycles.

Accordingly, treatment of bis-indole dicarbaldehyde **7a** with 1,4-diaminobutane at reflux for 12 h afforded the bisindolo-macrocyclic imine **8a** in 73% yield. The ^{1}H NMR spectrum showed the new imine resonance at δ 8.68 and the methylene protons at δ 1.86 and 3.76. Mass spectrometry also confirmed that the 18-membered macrocycle was formed in preference to a dimeric or other higher order system, showing a molecular ion at 506. The related analogues **8b** and **8c** were similarly prepared in good yields of 67% and 75%, respectively, upon reaction with 1,4-diaminobutane.

The diamine linker was subsequently increased by a further two methylene units. Heating bis-indole dicarbaldehydes **7a–c** with 1,6-diaminohexane overnight successfully afforded macrocyclic imines **9a–c** in 55–68%. Mass spectrometry analysis confirmed that the 20-membered macrocyclic imines were produced, displaying molecular ions at *m*/*z* 534, 533 and 547, respectively. Once again the formation of any higher order macrocycles was not evident.

Reduction of the macrocyclic imines **8a–c** and **9a–c** to give the related amine analogues **10a–c** and **11a–c**, respectively, was achieved in moderate yields of 56–65% by treatment with sodium borohydride in ethanol at room temperature for 6 h. The resulting diaza macrocycles **10a–c** and **11a–c** would be expected to show



Scheme 1. Reagents and conditions: (a) $AlCl_3$, CH_3COCl, CS_2, 50 °C, 6 h, (83–90%); (b) NH_2NHPh, EtOH, HOAc, reflux, 3 h, (70–80%); (c) methanesulfonic acid, 110 °C, 1.5 h, (67–75%); (d) $POCl_3$, DMF, 0 °C, overnight, (85–90%); (e) diamine, EtOH, reflux, 12 h, (55–75%); (f) $NaBH_4$, EtOH, rt, 6 h, (56–65%).