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Bioorganic & Medicinal Chemistry Letters 17 (2007) 1553–1557
Bioorganic & Medicinal Chemistry Letters

Bile acid-based receptors containing 2,6-bis(acylamino)pyridine for recognition of uracil derivatives

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Received 29 November 2006; revised 26 December 2006; accepted 29 December 2006
Available online 13 January 2007

Abstract—Hydrogen-bonding interactions of steroid-based cyclic and acyclic receptors containing 2,6-bis(acylamino)pyridine with uracil derivatives were studied in $CDCl_3$. Acyclic receptors show better binding behaviour as compared to cholaphanes with uracil derivatives.

The self-assembly of the two anti-parallel strands of DNA is mainly influenced by intermolecular forces which include aromatic π-stacking, hydrophobic forces, van der Waals forces and hydrogen-bonding interactions.[1] There has been considerable interest in recent years on the design of receptors for recognition of nucleobases with non-covalent interactions.[2,3] Rebek et al. introduced receptors having convergent functional groups based on Kemp's triacid for recognition of adenine derivatives.[4–9] His group also reported synthetic molecules capable of self-replication and autocatalysis.[10,11] Wilcox and Adrian prepared a receptor, having a carboxylic acid moiety with the Tröger's base spacer, capable of adenine binding with both Watson-Crick and Hoogsteen binding modes.[12]

Zimmerman and co-workers reported a molecular tweezer which complexes adenine through aromatic π-stacking and hydrogen bonding.[13]

Hamilton and Van Engen introduced a macrocycle, based on bis(acylamino)pyridine receptor, capable of binding thymine through hydrogen bonding and stacking forces.[14] Jorgenson and co-workers carried out Monte Carlo simulations with statistical perturbation theory to calculate free energy of binding in chloroform for 1-methyluracil with 2,6-diaminopyridine. The binding constant for these systems is small due to three alternate hydrogen bonds.[15,16] Sijbesma and Spek have extensively studied the complexation of diaminopyridine and diaminotriazine and their acylated derivatives with uracil/thymine derivatives through hydrogen bonding.[17] Interestingly, it was found that acylation of diaminopyridine and diaminotriazine had opposite effect on complex stabilities. High association constants were observed for complexes of 2,6-bis(acylamino)pyridines with uracil/thymine derivatives as equated to bis(acylamino)triazines. Moreover, the length of the alkyl chain of the 2,6-bis(acylamino)pyridines was found to affect the binding strength with uracil/thymine derivatives. Li et al. reported a fullerene-containing 2,6-bis(acylamino)pyridine receptor to bind uracil derivatives by hydrogen-bonding interaction with an association constant of 323 M^{-1} in $CDCl_3$.[18] It has been ascertained that 2,6-bis(acylamino)pyridine, having a donor–acceptor–donor (DAD) unit, complexes with an imide (e.g., uracil, succinimides, flavins, etc.) having acceptor–donor–acceptor unit (ADA) with association constants in $CDCl_3$ in the range of 50–500 M^{-1}, which is in accordance with the theoretical values predicted by Jorgenson et al.

The unique features of the bile acids in terms of their chiral, rigid framework and chemically different hydroxyl groups make them very appropriate compounds from the molecular engineering point of view.[19–21] Most recently, we introduced a new class of bile acid-based cyclic as well as acyclic receptors containing 2,6-bis(acylamino)pyridine for recognition of flavin analogues (Fig. 1).[22] A rigid and hydrophobic steroidal skeleton with flexible side chains for the acyclic receptor afforded ideal architecture for hydro-

Keywords: Cholaphanes; Uracil; Diaminopyridine; Hydrogen bonding; Molecular recognition.
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doi:10.1016/j.bmcl.2006.12.115

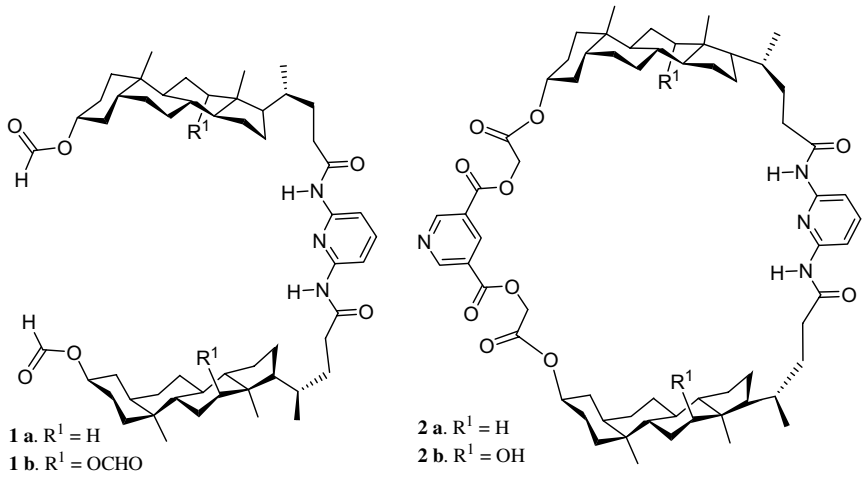
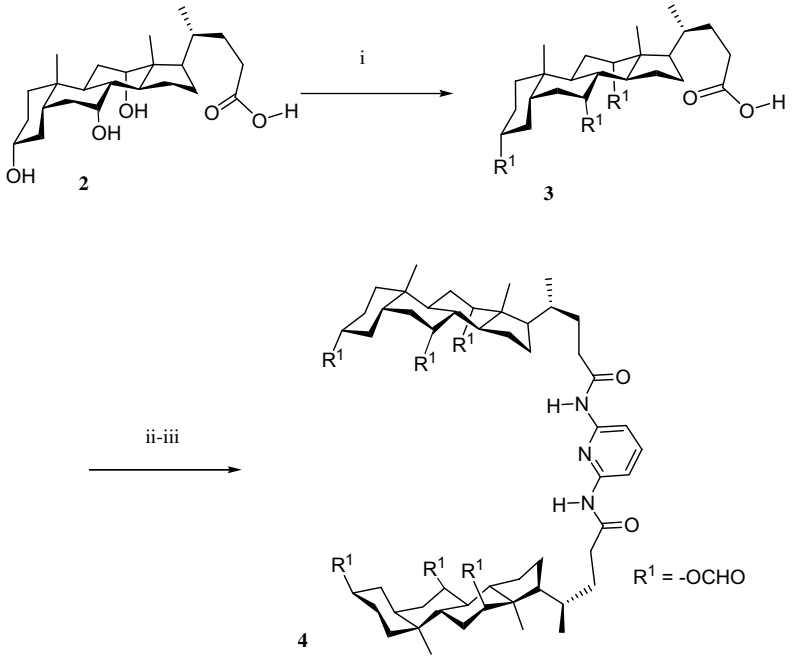


Figure 1. Steroid-based acyclic and cyclic receptors having 2,6-diaminopyridine unit.

gen-bond interactions with flavin analogues. Importantly, high association constants are observed for complexes of acyclic receptors with flavin analogues. However for the cholaphanes, due to steric hindrances, lower association constants were observed.

Nucleobases have been widely used as supramolecular motifs capable of forming strong hydrogen bonds to construct new biomaterials and complex nanostructures.[3,23–25] Earlier, we have reported the comparative binding ability of steroidal adenine with flavin and uracil derivatives.[26] In the present communication, we report the binding behaviour of acyclic and cyclic steroidal receptors containing 2,6-bis(acylamino)pyridine unit towards uracil derivatives in view of developing new steroidal materials involving DAP-uracil supramolecular motifs. The preparation of receptor **4** commenced with the formylation of cholic acid **1** with formic acid to give **3** in 98% yield (Scheme 1). Subsequent coupling of the acid chloride of **3** (2 equiv) with diaminopyridine in the presence of triethylamine gave the biscoupled product.[27] In general, nucleobases like uracil are scarcely soluble in chloroform. Attaching a long alkyl chain increases their solubility in non-polar solvents. Uracil derivatives were synthesized by selective *N*-1-alkylation of uracil with octyl bromide, methyl 3α-bromoacetyllithocholate and methyl 3α-bromoacetyldeoxycholate in the presence of potassium carbonate in dry DMF as described in (Scheme 2).[28]



Scheme 1. Reagents and conditions (and yields): (i), HCOOH, 60 °C, 4 h, (98%); (ii), $SOCl_2$, benzene, 60 °C, 4 h, (~100%); (iii), 2,6-diaminopyridine, triethylamine, THF, 0–5 °C, 12 h, (79%).