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A Novel Bile Acid-based Receptor for Recognition of Adenine Derivatives

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A deoxycholic acid-derived receptor was synthesized by incorporating uracil units at 3α and 12α positions. The receptor showed high affinity for steroidal bis-adenine derivatives in $CDCl_3$.

Keywords: Bile acid; WinEQNMR; Complexation; Hydrogen bonding; Binding constant; Adenine receptor

Recognition and selective binding of nucleobases play fundamental roles in all of the three stages of genetic information transfer: replication, transcription and protein synthesis. Hence, the design and synthesis of receptors capable of selective non-covalent recognition of nucleobases has been an area of considerable interest [1–6]. Among the various bases, adenine has received much attention because of its two different base-pairing sites, namely Watson–Crick and Hoogsteen sites [7–9]. Most of the systems designed so far for the recognition of adenine are based on Kemp's triacid (*cis*-1,3,5-trimethyl-1,3,5-cyclohexanetricarboxylic acid) [10–19]. There has been considerable interest in recent years on the design and supramolecular chemistry of bile acid-based molecular receptors [20–23]. As a part of our interest in the design of molecular receptors based on bile acids [24–26], we considered designing a receptor for adenine based on deoxycholic acid. The structural features of deoxycholic acid in terms of its rigid framework and the position of its two hydroxy groups make it a suitable scaffold for the development of a hydrophobic receptor for the binding of adenine derivatives. Rao and Maitra have reported a bile acid-derived receptor for adenine involving carboxylic groups showing relatively weak interaction [27]. We have introduced two uracil units at the 3α and 12α positions of the deoxycholic acid (receptor **1**), with a view to having strong hydrogen bonding, and selected a lipophilic steroidal bis-adenine derivative **2** to examine its binding properties, particularly the nature of the complex formation. Two types of complex formation can be envisioned in solution: (1) a 2:1 complex involving both Watson–Crick and Hoogsteen types of binding giving a noncyclic structure (Fig. 1), and (2) a 1:1 complex involving only Watson–Crick type of binding leading to a macrocyclic system (Fig. 2). Both of these structures would be important in terms of designing new types of supramolecular assemblies and their molecular recognition properties.

Compounds **1** and **2** were synthesized by following the reaction sequence given in Scheme 1 and characterized on the basis of their ^1H NMR and ESI mass spectra†. Interestingly, the ^1H NMR spectrum of receptor **1** revealed two distinct signals at 9.43 and 9.82 ppm for the acidic imide

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†**1**: ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 0.73 (s, 3H, 18-Me), 0.81 (d, 3H, 21-Me), 0.90 (s, 3H, 19-Me), 1.01–2.36 (26H, steroidal H), 3.66 (s, 3H, $-OCH_3$), 4.40–4.58 (m, 4H, 2 × CH_2—N), 4.71 (m, 1H, 3β-H), 5.16 (s, 1H, 12β-H), 5.80 (m, 2H, 2 × H-5-uracil), 7.13 (d, 1H, H-6-uracil), 7.32 (d, 1H, H-6-uracil), 9.43 (bs, 1H, —NH-uracil), 9.82 (bs, 1H, -NH-uracil); ESI mass: 733.80 (M^+ + Na). **2**: ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 0.64 (s, 3H, 18-Me), 0.70 (s, 3H, 21-Me), 0.82 (s, 3H, 19-Me), 0.97–2.38 (26H, steroidal H), 3.69 (s, 3H, $-OCH_3$), 4.78 (m, 1H, 3β-H), 4.98–5.31 (5H, 2 × CH_2-N and 12β-H), 5.64 (bs, 2H, $-NH_2$), 6.03 (bs, 2H, $-NH_2$), 7.81 (s, 1H, H-2-adenine), 7.95 (s, 1H, H-2-adenine), 8.37 (bs, 2H, H-8-adenine); ESI mass: 758.77 (M^+ +2H).

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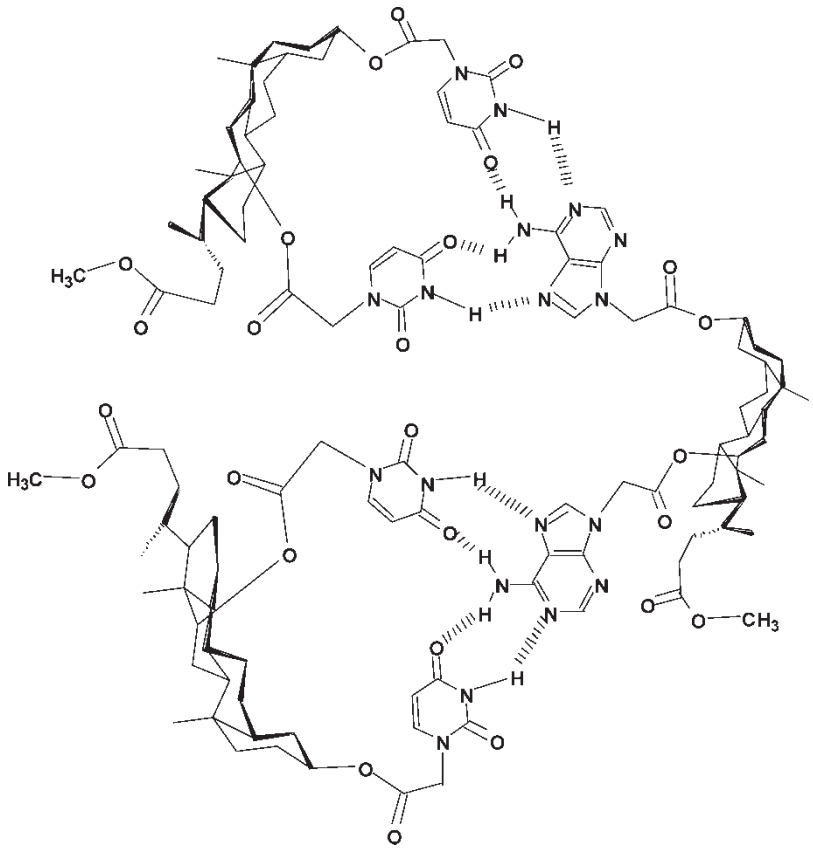


FIGURE 1 2:1 complex of receptors **1** and **2**.

protons of the two uracil units. This spectral aspect of the two N—H signals could be used in studying their binding behaviour with adenine derivatives. The complexation between receptor **1** and adenine derivative **2** was studied by a ^{1}H NMR titration experiment in $CDCl_3$, using a fixed amount of bis-uracil derivative (0.01 M). Typically, in an NMR tube containing 0.01 M solution of uracil derivative, various aliquots of 0.04 M solution of adenine derivative **2** were added, and

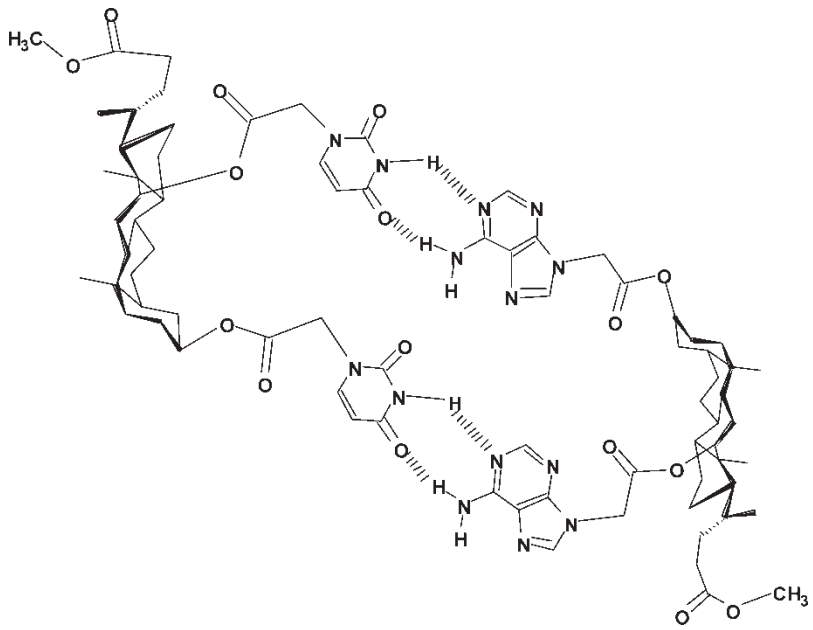
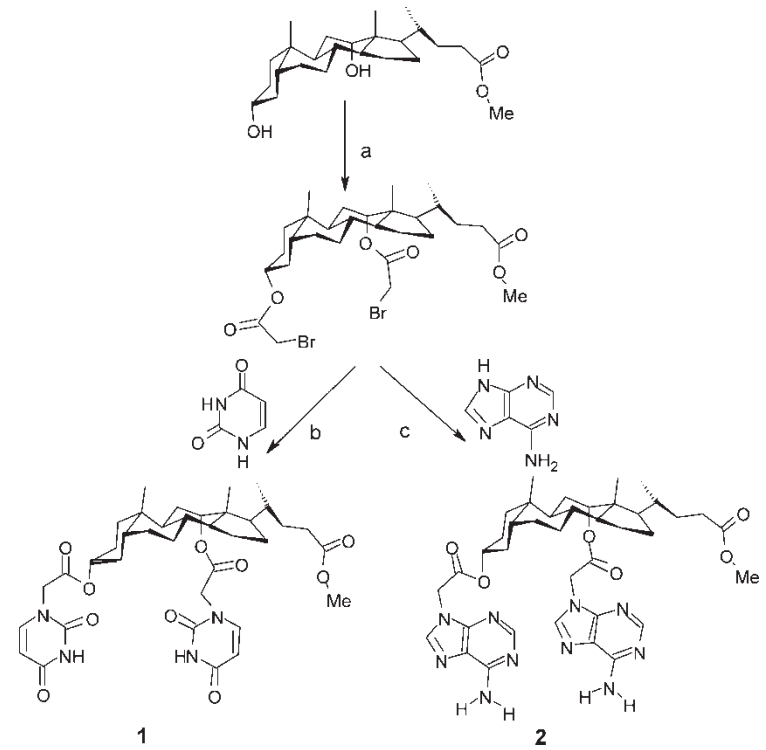


FIGURE 2 1:1 complex of receptors **1** and **2**.



SCHEME 1 Reagents and conditions: (a) $BrCH_2COBr$, anhydrous K_2CO_3, $CHCl_3$, 12 h, RT; (b) anhydrous K_2CO_3, DMF, 24 h, RT; (c) anhydrous K_2CO_3, DMF, 24 h, RT.

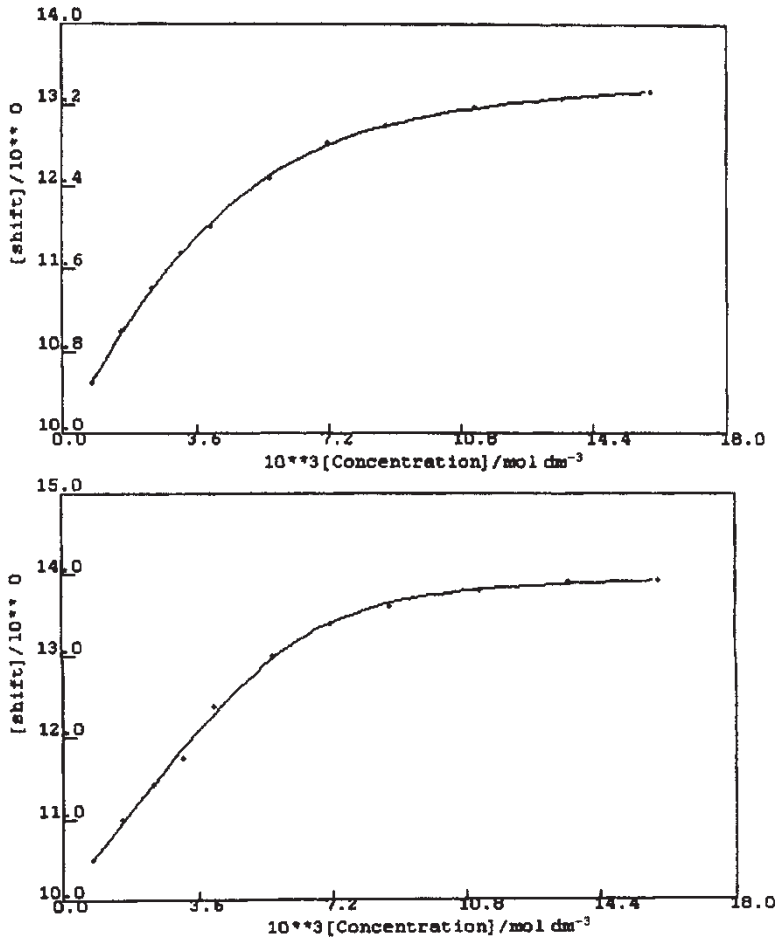


FIGURE 3 Binding isotherms for imide protons of two uracil units of receptor **1**: (a) $uracil_1$; (b) $uracil_2$.

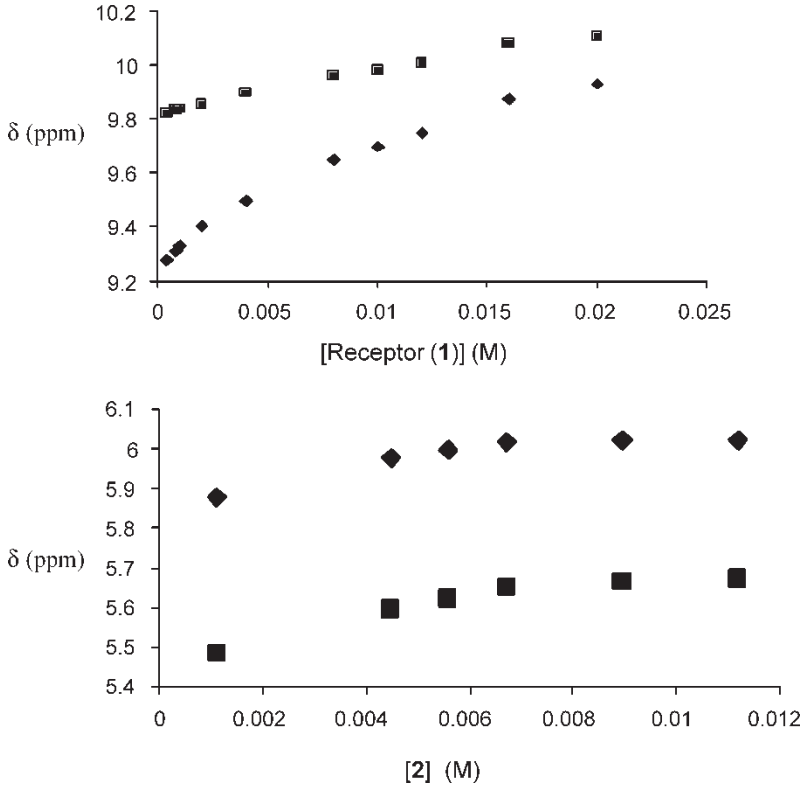


FIGURE 4 Plots of the chemical shifts of (a) the imide protons of **1** as a function of concentration and (b) the amino protons of **2** as a function of concentration.

the observed chemical shifts of the imide N—H of both the uracil units were recorded at each concentration until saturation in the chemical shift values was reached. The titration was carried out in duplicate. Inspection of the NMR titration spectral data revealed large complexation-induced shifts (CIS) of the host (uracil). Relatively small shifts were observed for the guest (adenine) protons. NMR spectra show a large downfield shift for the imide protons of the two-uracil units with saturation values of 13.33 and 13.92 ppm, respectively. Analysis of the saturation data with WinEQNMR software [28], a nonlinear regression curve-fitting program, revealed 2:1 complexation with a binding constant of $1.1690 \times 10^4\,M^{-2}$ (mean value of the binding constants of the NH of the two uracil units) (Fig. 3a,b), which ruled out the formation of a 1:1 complex (Fig. 2). This was also evident from the ^{1}H NMR spectrum of the complex, which revealed an upfield shift for both the carbon bound protons of the guest (H-2 and H-8 of adenine units). For the 1:1 complex, only one of the H-2 and H-8 protons would have shifted, and this was not observed, thus confirming the formation of a 2:1 complex. This was further confirmed by Job's plot, which showed maximum complexation at 0.33 mole fraction of **2** (Fig. 5). We have also examined the self-association of **1** and **2** through concentration-dependent ^{1}H NMR chemical shifts in $CDCl_3$ [29]. The curves obtained (Fig. 4a,b) from these titrations were fitted to a dimerization isotherm to obtain the dimerization constant (K_{dim}) [30]. None of these was found to dimerize significantly under the given experimental conditions[‡]. Furthermore, comparison of the chemical shift values of the imide and amino protons in **1** and **2**, respectively, with alkyl–uracil and alkyl–adenine ruled out intramolecular interactions in **1** and **2**.

The preferential formation of the 2:1 complex clearly indicated the ideal spacing of the two uracil units for simultaneous Watson–Crick and Hoogsteen base pairing. The high value of the binding constant obtained in this case indicates a strong association, which is comparable with the systems reported earlier involving simultaneous binding through base-pairing and aromatic stacking interactions [1,8 and 10]. Hence, the inherent features of the deoxycholate system led to a short synthetic route for a novel receptor for

[‡]The dimerization constants for **1** and **2** were measured as $12\,M^{-1}$ and $14.5\,M^{-1}$ respectively (averaged values based on monitoring two different protons on **1** and **2**).

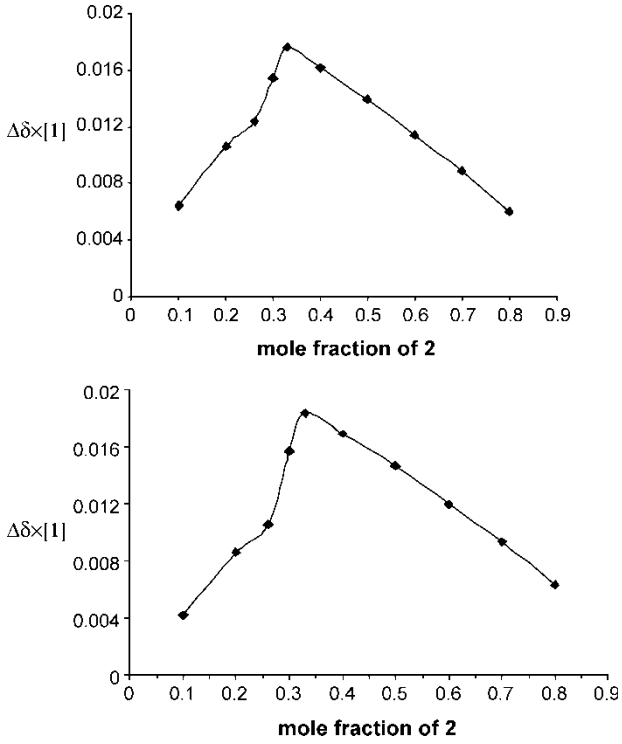


FIGURE 5 Job's plot between **1** and **2**.

adenine derivatives, which exhibits strong binding behaviour even in the absence of aromatic stacking interactions.

In conclusion, we have designed and synthesized a bile acid-based molecular tweezer bearing two uracil units showing high affinity for steroidal bis-adenine derivatives. As this bile acid-derived tweezer is more lipophilic and biocompatible than earlier reported receptors, it may be useful for recognition, extraction and separation of adenine-rich oligonucleotides in organic solvents and may find application in the selective transport of adenine-rich nucleotides across the biological membranes. Furthermore, formation of the 2:1 complex with bis-adenine derivatives indicates that this work can be extended to design receptors for the site-specific binding of nucleic acids.

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