**Water-Soluble Synthetic Receptors: Artificial Molecular Recognition**

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**Introduction**

The biotin–avidin pair, with the binding constant \((K_a)\) up to \(10^{13} – 10^{15} \text{ M}^{-1}\), is one of the strongest non-covalent bindings, and has been broadly applied in biochemistry.\(^1\) However, the relatively large size, biochemical fragility and immunogenicity of avidin protein impose limitation. Therefore, researchers have been making efforts to develop high-affinity \((K_a > 10^9 \text{ M}^{-1})\) water-soluble synthetic ligand-receptor pairs that rival the biotin–avidin pair.

**Discussion**

1. **Design of water-soluble high-affinity ligand-receptor pairs**

   In the design of ligand-receptor pairs, non-covalent binding is usually preferred over covalent binding, mainly for reversibility concerns. Typical non-covalent interactions include Coulomb interaction, H-bonding, hydrophobic interaction, and \(\pi–\pi\) interaction. Currently developed high-affinity water-soluble synthetic receptors include barrel-shaped ones, mainly utilizing hydrophobic and Coulomb interaction, and sandwich-shaped ones, utilizing hydrophobic and \(\pi–\pi\) interaction.

2. **Barrel-shaped receptors**

   Examples of barrel-shaped receptors include cucurbit[7]uril (CB[7], Fig. 1a),\(^2\) pillar[5/6]arene sulfate (P[5/6]AS)\(^3\) and corral[5]arene sulfate (SC[5]A, Fig. 1b).\(^4\) These receptors are typically cyclized oligomers, with top and bottom sides consist of hydrophilic groups that provide Coulomb interaction with ligands, and central wall of aliphatic or aromatic groups, generating a hydrophobic pocket inside the barrel. Corresponding to the receptor structure, the ligands of barrel-shaped receptors usually have a high polarity/ionized functional group attached to a hydrophobic core that fits in the receptor.

![Figure 1](image-url)

binding pocket (Fig. 1c & 1d). Their highest binding constants could reach $10^{15} - 10^{17}$ M$^{-1}$, which already surpass biotin–avidin level$^{2-4}$.

### 3. Sandwich-shaped receptors

Examples of sandwich-shaped receptors include tetralactams (Fig. 2a)$^5$ and XCage (Fig. 2b)$^6$. Their structure includes two parallel polyarene “layers” connected by amides or benzenes. These “layers” create a binding pocket that provides $\pi$-$\pi$ stacking interaction and hydrophobic interaction. For high-affinity binding, these receptors are typically more selective towards specific structures, where tetralactams bind with squarines (Fig. 2c), and XCage binds with perylenes and porphyrins (Fig. 2d). However, their binding constants are lower than barrel-shaped receptors, typically around $10^9 - 10^{11}$ M$^{-1}$.$^{5,6}$

**Figure 2.** a) tetralactam. b) tetralactam ligands. c) XCage d) XCage ligands. R = hydrophilic groups

### Summary

In conclusion, there have been several kinds of high-affinity water-soluble synthetic ligand-receptor pairs developed and applied. These pairs are small molecules and easy to access via synthetic chemistry; however, reaching the natural-level affinity and selectivity at the same time is still challenging, which is going to be the future direction in this area.

### Reference