Water-Soluble Synthetic Receptors: Artificial Molecular Recognition

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Introduction

The biotin–avidin pair, with the binding constant (K_a) up to $10^{13} – 10^{15}$ 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 ($K_a > 10^9$ 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 π–π 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 π–π 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

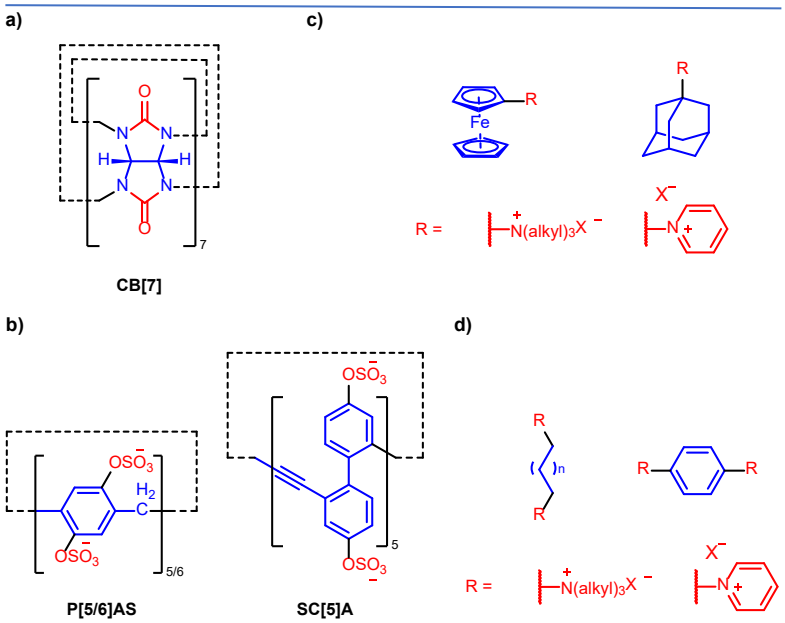

Figure 1. a) CB[7]. b) CB[7] ligands. c) P[5/6]AS and SC[5]A. d) P[5/6]AS/SC[5]A ligands.

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

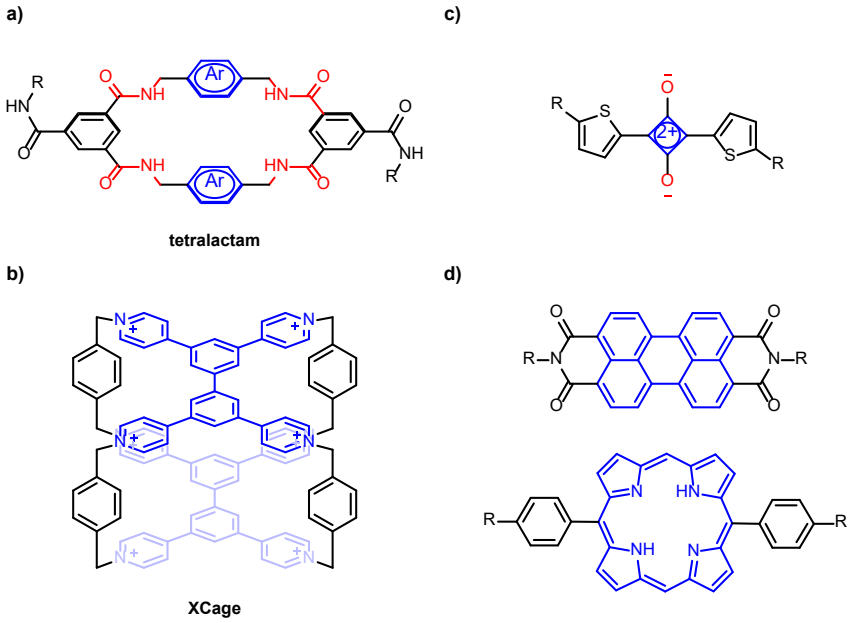

Figure 2. a) tetralactam. b) tetralactam ligands. c) XCage d) XCage ligands. R = hydrophilic groups

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 π–π 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]

Summary

In conclusion, there have been several kinds of high-affinity water-soluble synthetic ligand-receptor pairs developed and applicated. 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

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