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Synthesis of new chiral fluorescent sensors and their applications in enantioselective discrimination

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ABSTRACT

New chiral fluorescent sensors derived from tetraphenylethylene and proline hydrazide were synthesized and applied in the chiral recognition of various chiral compounds, including unprotected amino acids, acidic compounds, chiral amines and even neutral alcohols. These results demonstrated that the excellent enantioselective response ability to various chiral substrates could be attributed to the –NH moieties of pyrrolidine ring and thiourea unit which acted as hydrogen-bonding donors. This result is of potential significance in enantiomeric discrimination and high-throughput analysis of the enantiomeric purity of chiral guests.

Introduction

Molecular recognition is an important process in natural systems, especially chiral recognition, is of great significance for the fast construction of the libraries of chiral compounds in drug discovery or chiral-catalyst screening, as well as for understanding the specific interaction of molecular recognition in biological systems.[1] For instance, highly sensitive acid-responsive fluorescent probe could monitor intracellular H^+ with living cells or have great application value in reversible pH-dependent photoluminescent materials.[2] Therefore, developing a controlled and feasible technique for the determination of the enantiomeric composition of chiral compounds is of very remarkable theoretical and practical value in the field of chemistry. Up to date, there are many enantioselective methods were reported, including NMR,[3] chiral ionic liquid[4] and various separation techniques.[5] However, for these methods, complicated or expensive instruments and complexed inductive reagents are indispensable. The attachment of fluorescent groups in chiral frameworks to offer effective sensors and their application in chiral recognition have attracted keen attention because they could not only provide a real-time and low-cost method, but also greatly facilitate the combinatorial discovery of asymmetric synthesis.[6] During the past several years, a number of fluorescent sensors showed specific enantioselectivities for acidic or basic chiral compounds were reported.[7] In 2004, Pu's group reported macrocycle sensors derived from BINOL could carry out enantioselective recognition of amino acid derivatives.[8] In 2010, Pu and co-workers found the BINOL amino alcohol receptor which has very bulky tertiary hydroxyl groups could enantioselectively discriminate α-hydroxycarboxylic acids.[9] Unfortunately, they could only discern few chiral substrates.

Recently, a large number of molecules which were known as aggregation-induced emission (AIE) or aggregation-induced emission enhancement (AIEE) were reported, and have drawn sizable interests because they could provide time-efficient and feasible ways for the high through-put combinatorial screening of chiral drugs or asymmetric synthesis catalysts.[10] Zheng and co-workers incorporated chiral function groups with AIE molecules to offer receptors which could distinguish the chiral guests such as chiral amines, amino acid derivatives, and chiral acidic compounds.[11] For example, AIE containing chiral amines could enantioselectively give rise to precipitation or suspension with one enantiomer but remain a clear solution with the other enantiomer of chiral acidic substrates, and the precipitation or suspension emitted strong fluorescence but the solution did not.[12] However, rare examples of the enantioselective recognition for a variety of chiral compounds by one sensor were reported. In 2016, Zheng's group attached chiral 1,2-cyclohexyldiamines unit in tetraphenylethylene (TPE) structure by urea moiety to offer a versatile enantioselective fluorescent sensor, and it could enantioselectively discern a wide range of chiral guests including amino acids, carboxylic acids, chiral amines and even neutral compounds.[13] Herein, in continuation of our research work on enantioselective discrimination,[14] we report a new serial of chiral sensors and their applications in asymmetric discrimination.

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Proline is one of most noticeable chiral organocatalyst, because it occupies a very important role in asymmetric synthesis and can be easily modified.[15] There is no doubt that proline or proline derivatives themselves have already been proved to be effective catalysts for many reactions.[15a,16] In the field of the asymmetric synthesis, thiourea catalysts as strong hydrogen-bonding donors play very important roles and have been extensively studied.[17] These powerful and environmentally friendly catalysts have been widely applied in the production of chiral drugs, natural products, and important blocks for materials.[18] TPE is one of the most excellent fluorophores that can be synthesized with moderate yield in laboratory. Herein, we combined proline derived hydrazide with TPE by thiourea group to provide chiral sensors **4** and **5** as remarkable sensors to enantioselectively discriminate various chiral substrates.

Results and discussion

L-Proline hydrazide could be easily prepared from a cheaply available L-proline, which showed outstanding reactivity and enantioselectivity for the aldol reaction in aqueous media.[19] The attachment of proline hydrazide units in the compound **2** framework has been proved to be very superior sensors with high enantioselectivity in chiral recognition.

To treated intermediate **2** with optically pure proline hydrazides **3a** and **L-3b** could offer chiral sensors **4** and **L-5** (Scheme 1). The structures of sensors were fully characterized by NMR, MS, and polarimetry.

These chiral products were soluble in chloroform, dichloromethane, THF and ethanol, but insoluble in water. After **L-4** was dissolved in THF, the solution (2×10^{-4} M) did not emit fluorescence. When 70% fraction of water (volume ratio of water *vs* THF) was added to the solution and turbidity emerged, the solution started to emit fluorescent light. The suspension appeared when 95% fraction of water was added, and the fluorescent intensity of the suspension was increased to 946 (Fig. 1). Therefore, the sensor **L-4** is an AIE compound. The same test of **D-4** and **L-5** in mixed solvent also confirmed that they were all AIE compounds (Fig. S1 in the Supporting Information). The UV–vis spectra of all sensors were showed by Fig. S2 in the supporting information.

The enantioselective fluorescence response abilities of **L-4** to various chiral compounds in solution were tested, while the concentration ratio between sensor **L-4** and chiral reagents was kept as 1:1 in all tests. To our delight, not only chiral acidic compounds and zwitterionic amino acids could selectively affect the aggregation of sensor **L-4**, but also the basic substrates and even neutral

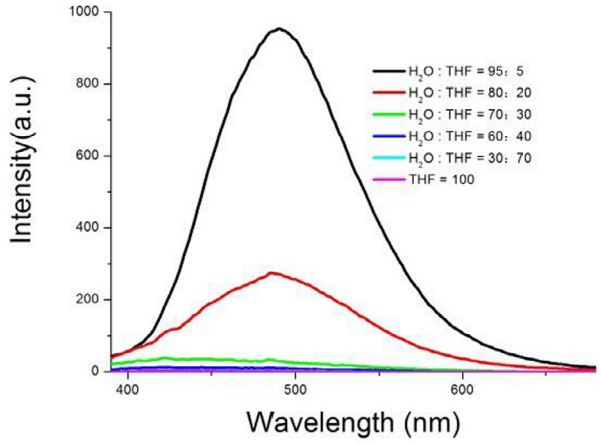
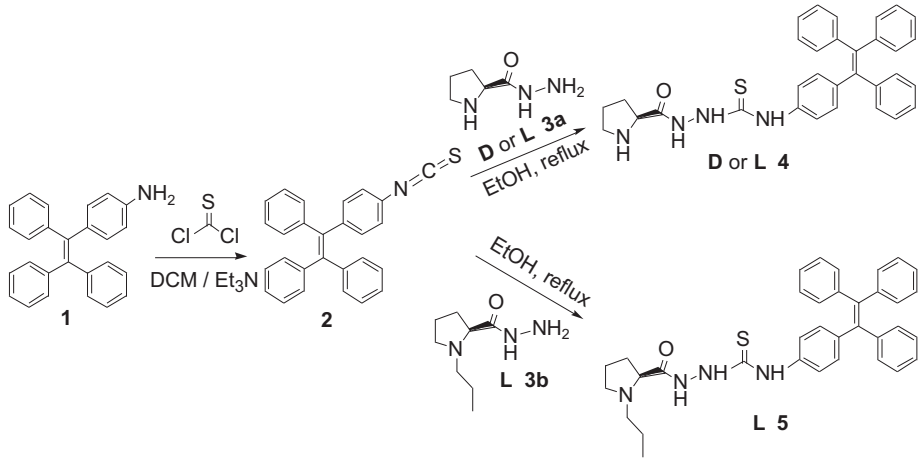


Fig. 1. Changes of the fluorescent for **L-4** (2×10^{-4} M) in THF with added water. Conditions: λex 360 nm, ex/em slits 15/5 nm.

molecules showed highly enantioselective aggregation with host **L-4** (in Table 1 and Fig. S3 in Supporting Information).

For amino acids, the mixture of **D-6** or **D-7** and receptor **L-4** gave rise to suspension but the mixture of **L-6** or **L-7** remained a clear solution in the mixed solvents of THF and water. The fluorescence intensity ratios (I_D/I_L) for the suspension vs solution were 1.9 and 4.6 for serine **6** and proline **7**, respectively (Fig. S3). As for phenylalanine **8**, their enantiomer could be differentiated by chiral sensor **L-4** with high enantioselectivity, and the fluorescence ratio of two enantiomers was $I_{D\text{-}8}/I_{L\text{-}8} = 4.5$ (Fig. 2A and Table 1). For acidic compounds, including tartaric acid **9**, BINOL **10**, two enantiomers of these substrates could be distinguished by the TPE **L-4** with good enantioselectivity. The fluorescence intensity ratios of two enantiomers of these guests were $I_{D\text{-}9}/I_{L\text{-}9} = 2.6$ and $I_{S\text{-}10}/I_{R\text{-}10} = 3.3$ (Fig. S3). For the neutral substrates **11** and **12**, **L-4** showed high enantioselectivities of 2.8 ($I_{D\text{-}11}/I_{L\text{-}11}$) and 5.8 ($I_{S\text{-}12}/I_{R\text{-}12}$) (Fig. S3 in the Supporting Information). For phenylglycinol **13**, the fluorescence ratio of two enantiomers was $I_{S\text{-}13}/I_{R\text{-}13} = 2.9$ (Fig. S3). In similar way, *R* or (*R*,*R*) isomer of 1-phenylethylamine **14** or 1, 2-cyclohexanediamine **15** induced the aggregation with **L-4**, but their *S* or (*S*,*S*) isomer did not, which gave enantioselectivities of 5 and 1.8, respectively (Table 1 and Fig. S3). These results indicated that sensor **L-4** could detect various enantiomeric pure compounds, which could probably be attributed to multiple hydrogen bonds between detected molecules and –NH groups of sensor



Scheme 1. Synthesis of the chiral sensors.