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A novel fluorescent enantioselective discrimination of lansoprazole based on a chiral *N,N′*-dioxide–Sc(III) complex

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ABSTRACT

A good chiral discrimination of lansoprazole (LAN) enantiomers was realized by a chiral *N,N′*-dioxide–Sc(III) complex, which was based on a fluorescent method through an 'off-on' process. The chiral ligand, *N,N′*-dioxide, coordinated with scandium(III) triflate forming an organic–metal complex as a chiral selector. Then the LAN enantiomers reacted with the selector and generated different signals in fluorescence. A distinct enantiomeric difference was observed with good repeatability, low detection limit, good linear range, and highly enantiomeric selectivity. At last, this study had offered a quantitative measurement of the enantiomer composition.

Chirality is a widespread and common phenomenon in life and nature.[1,2] It is well known that one enantiomer of the drug may be more active or toxic than the other. Lansoprazole (LAN, 2-(((3-methyl-4-(2,2,2-trifluoroethoxy)-2 pyridinyl) methyl)sulfinyl)-1*H*-benzimidazole) is one of the proton pump inhibitors (PPIs) being used for the treatment of gastrointestinal ulcers[3,4] and is commercially marketed as the racemic mixture. But some recent clinical and pharmacological experiments have shown that the biotransformation and pharmacokinetics were different between *R*- and *S*-LAN enantiomer and suggested that the *R*-isomer should be mainly prepared for purchase.[5] Therefore, developing methods for the recognition of LAN enantiomers would be of great significance in the enantiomer analysis of chiral drugs.

As far as we know, fluorescence, as a high selective and high sensitive method with variety of detection modes, has obtained extensive attentions in the discrimination of many chiral compounds.[6–16] Meanwhile, chiral organic–metal complex has shown its unique advantages in the applications of asymmetric catalysis, chiral separation, enantioselective discrimination, and so on.[17,18] In the fluorescent chiral recognition, various chiral copper(II) complexes have provided a high stereoselectivity to the amino acids and their derivatives.[19,20] However, very limited reports have studied on the application of other metal complexes. Chiral *N,N′*-dioxides, as excellent chiral scaffolds,[21] could coordinate with various metals and exhibit great superiority in many asymmetric reactions.[22–24]

Herein, we report our efforts on a new application of the chiral *N,N′*-dioxide **1** (Fig. 1)–Sc(III) complex in pronounced enantioselective discrimination of LAN enantiomers. The chiral recognition signals were detected by the fluorescence emission spectra, and an 'off-on' process was produced in the assay procedures. An electrochemical method was also studied in the same process to support the fluorescent discrimination.

The fluorescence emission spectrum of **1** in acetonitrile was shown in Figure 2 (excited at 286 nm). The maximum emission wavelength was at 328 nm and the intensity was gradually enhanced as the concentration increased. Noticeably, fluorescence quenching of **1** was observed in the presence of the transition metal ion Sc(III), which indicated the coordination between Sc(III) and **1**, as shown in Figure 3. Thus, the 'off' phenomenon appeared.

The maximum emission of *R*- or *S*-LAN was observed at 307 nm (Fig. 3) with the excitation wavelength of 277 nm. The peak of LAN disappeared when Sc(III) was added into the LAN solution (Fig. 3). It was due to quenching function of Sc(III) as well.

1–Sc(III) complex could not produce fluorescence until the addition of LAN enantiomers. As shown in Figure 4, cyan fluorescence was generated at the long wavelength with the excitation

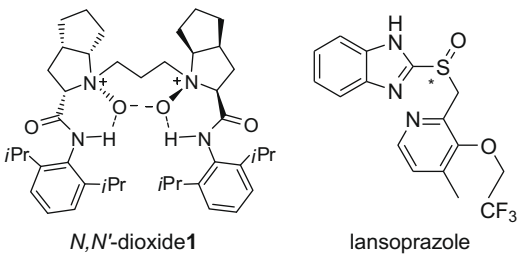

Figure 1. Structure of *N,N′*-dioxide **1** and lansoprazole.

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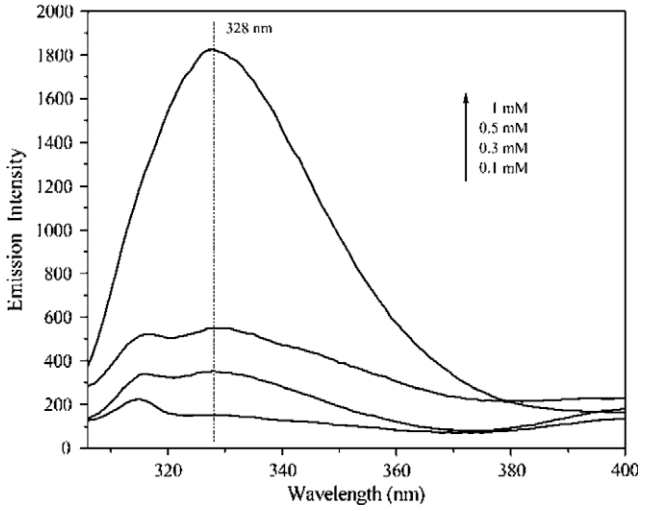

Figure 2. Concentration effect on fluorescence spectra of **1** in acetonitrile (λ_{exc} = 286 nm).

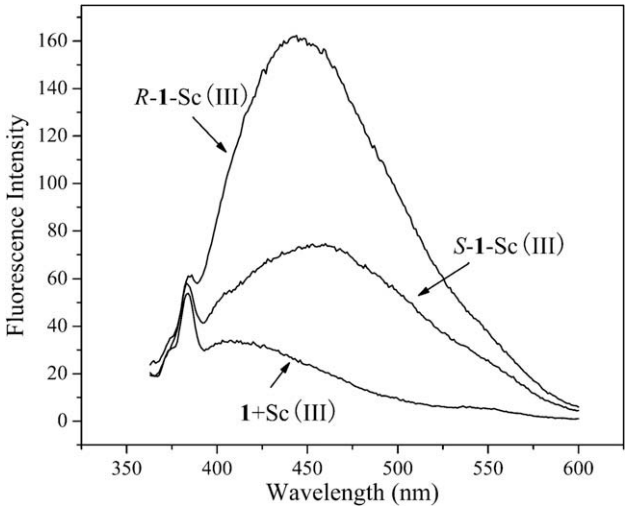

Figure 4. Fluorescence spectra of adding *S*- or *R*-LAN (both 160 μM) into acetonitrile containing **1**–Sc(III) complex (1 mM, λ_{exc} = 343 nm).

wavelength at 343 nm. Therefore, the addition of LAN 'turned on' the fluorescence. Highly enantioselective fluorescence responses were detected, with the maximum emission at 440 nm for *R*-LAN, and 460 nm for *S*-LAN. Meanwhile, in the LAN–**1**–Sc(III) complex solution, with excitation at 277 nm, the fluorescent peak of LAN at 307 nm shown in Figure 3 disappeared.

Furthermore, with the addition of LAN enantiomers into the **1**–Sc(III) complex solution, the fluorescent signal generated by *R*-LAN was much stronger than *S*-LAN did at the same concentration. Meanwhile, as the LAN concentration increased, the peak intensity which was enhanced by *R*-LAN was much stronger than that done by *S*-LAN. The results of the different concentrations of LAN enantiomers are shown in Figure 5 in which the inset reveals the plots of relative fluorescence intensity I/I_0 (I was the fluorescence intensity of the complex, and I_0 was the fluorescence intensity of the blank solvent and was taken at the same excitation wavelength as I) versus the concentration of LAN according to the results of five independent experiments. As the emission peaks shifted gradually to a longer wavelength with the increasing concentrations, the values of I and I_0 were taken at the maximum emission wavelength for each peak. The maximum enantiomeric fluorescence difference ratio ($ef = I_R/I_S$) was 2.12 at 144 μM, and the linear relative coefficients were 0.9994 for *R* and 0.9946 for *S*.

The possible reason for the enantiomeric recognition could be inferred based on some control experiments (for details, see Supplementary data). In the chiral recognition, a ternary diastereoisomeric complex of **1**–Sc(III)–*R*-LAN or **1**–Sc(III)–*S*-LAN was formed. As a result, through an external photo excitation, the maximum emission wavelength, the quantum efficiencies, and the fluorescence intensity of the two diastereoisomeric complexes might all be different, even at the same concentrations. So the **1**–Sc(III)–*R*-LAN and **1**–Sc(III)–*S*-LAN complex produced different fluorescent properties leading to the enantiomeric recognition.

The fluorescence intensity change with respect to the enantiomeric composition of *R*-LAN was studied. As the *R*-component of LAN increased, the fluorescence intensity enhanced, as shown in Figure 6. The values of I and I_0 were taken at the maximum emission wavelength for each peak. The linearly dependent coefficient was 0.9955. Hence, the **1**–Sc(III) complex could be used as a fluorescent sensor to offer a possible quantitative measurement of LAN enantiomer composition.

The electrochemical method for the chiral discrimination of lansoprazole had been studied as well, and it showed a similar result to the fluorescent consequence (for details, see the Supplementary data). According to Figure 7, a pronounced difference between the

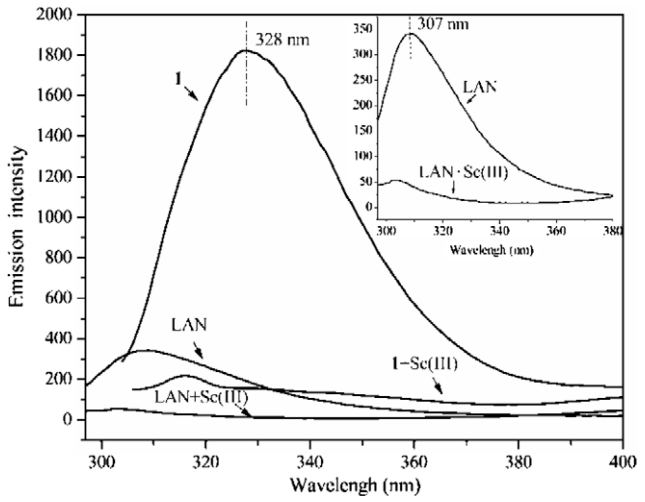

Figure 3. Fluorescence spectra of **1**, **1**+Sc(III) (both 1 mM, λ_{exc} = 286 nm), and LAN, LAN+Sc(III) (both 80 μM, λ_{exc} = 277 nm) in acetonitrile.

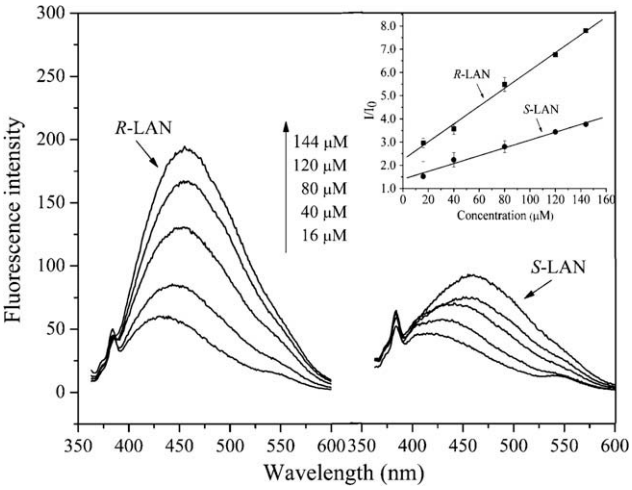

Figure 5. Concentration effect on the fluorescence spectra of *R*- and *S*-LAN adding into **1**–Sc(III) complex (1 mM) solution. Plots of fluorescence intensity versus the concentration of *R*- and *S*-LAN.

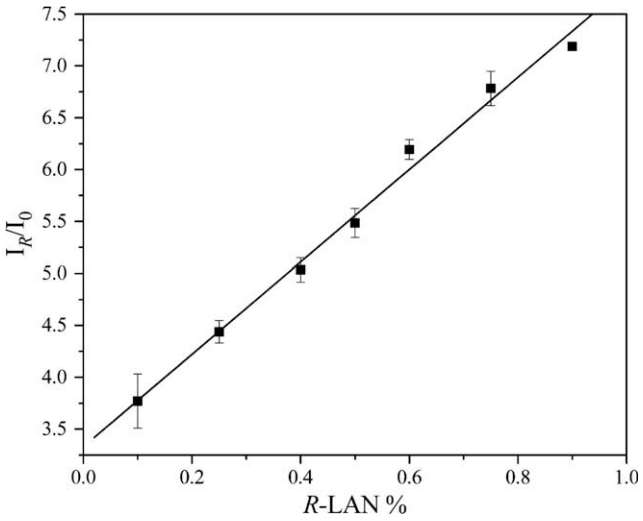

Figure 6. Relative fluorescence intensity (I/I_0) versus enantiomeric composition of *R*-LAN (the total concentration of LAN was 160 μM) in **1**–Sc(III) (1 mM) acetonitrile solution.

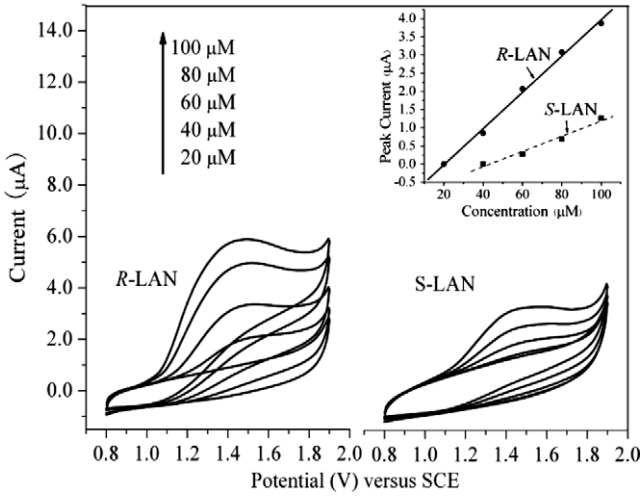

Figure 7. Concentration effect on the cyclic voltammogram for *R*- and *S*-LAN with the existence of **1**–Sc(III) complex. Inset: plots of peak current versus concentration of *R*- and *S*-LAN.

two enantiomers was displayed. *R*-LAN enhanced the peak current greater than the enantiomer *S*-LAN did. The maximum enantioselective coefficient ($\alpha = I_R/I_S$)[25] was 3.07 at 100 μM. The linear relative coefficients were 0.9976 for *R* and 0.9882 for *S*. Thus, in the electrochemical redox process, **1**–Sc(III) complex could also have its function of the enantiomeric recognition to LAN enantiomers, and the phenomenon was identical to the fluorescent results. It established another novel way to the enantioselective recognition of LAN.

In summary, we had developed an 'off-on' fluorescent method for enantioselective discrimination of LAN enantiomers, using a chiral *N*,*N*′-dioxide–Sc(III) complex as chiral selector. In the chiral discrimination, the 'off' process appeared at the formation of Sc(III) binary complex while the Sc(III) ternary complex aroused the 'on' process. The LAN enantiomers formed ternary diastereomeric complex with **1**–Sc(III) complex, producing obviously different properties in fluorescence. Furthermore, **1**–Sc(III) complex acted as a chiral selector and chiral sensor to provide a quantitative measurement of LAN enantiomer composition in fluorescence. Electrochemical redox process also supported the fluorescent recognition result. A simple, rapid, and highly enantioselective discrimination approach was produced for the LAN enantiomer composition assay of this important chiral drug. Further investigations on the application of *N*,*N*′-dioxide–metal complexes in other chiral recognition are in progress.

Acknowledgments

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Supplementary data

Supplementary data (fully detailed experiment steps and control experiments) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.04.094.

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