



# Responsive Fluorescent Coumarin–Cinnamic Acid Conjugates for $\alpha$ -Glucosidase Detection

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$\alpha$ -Glucosidase is a potent drug target for treating type II diabetes mellitus. A great number of  $\alpha$ -glucosidase inhibitors have been developed based on the molecular skeletons of bioactive natural products. However, efficient fluorescent probes for  $\alpha$ -glucosidase detection are still limited, not to mention the probes with additional inhibitory functions. In this work, aiming for the enzyme's highly specific detection, we designed and synthesized two environmentally sensitive fluorescent probes, namely, LD01 and LD02, respectively, based on conjugates of coumarin and cinnamic acid derivatives. We found a significant responsive emission enhancement upon LD02's binding to  $\alpha$ -glucosidase. These newly designed probes can act as a simple but efficient tool to evaluate the binding affinity of  $\alpha$ -glucosidase to their inhibitors.

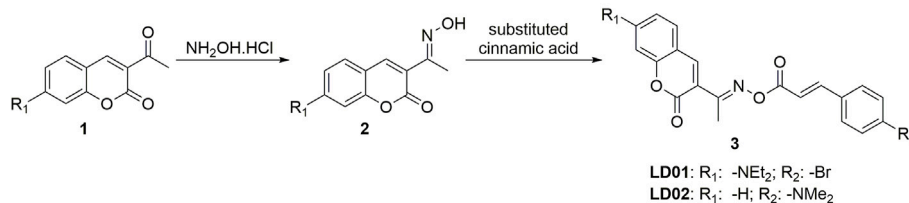
**Keywords:**  $\alpha$ -glucosidase, fluorescent probe, responsive probe, coumarin, environmentally sensitive dyes, cinnamic acid

## INTRODUCTION

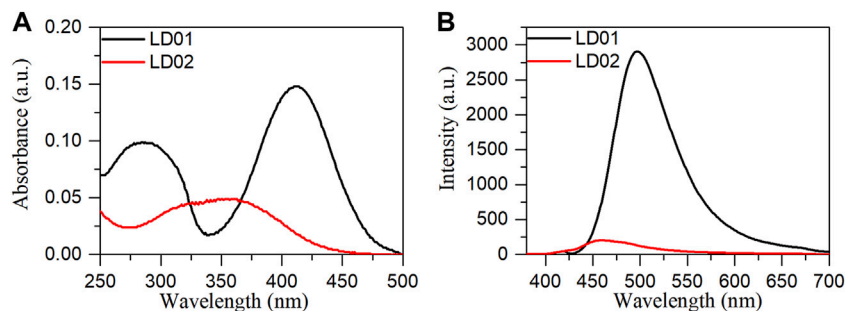
Diabetes mellitus (DM) can be categorized into three types (type I, type II, and gestational diabetes), with type II DM accounting for ninety percent of the total number of patients (Chen et al., 2015). Pathological features of type II DM are characterized by hyperglycemia arising from various causes such as a relative deficiency of insulin secretion, insulin resistance, or other malfunctioning factors on carbohydrate metabolism (Teng and Chen, 2017). Long-term high blood glucose levels in human bodies can lead to various complications, such as kidney disease, cataract, and vascular diseases (Prattichizzo et al., 2019).  $\alpha$ -Glucosidase is a membrane-bound enzyme in small intestinal epithelial cells, playing a pivotal role in the digestion of carbohydrates by direct participation in the metabolic pathway of glycogen and starch (Tang et al., 2017). Biochemically, in the last step of glycolysis, it can breakdown the  $\alpha$ -1,4 glycosidic bonds from the non-reducing saccharide chains' end, hydrolyzing the long oligosaccharide chains into single glucose. Then the digested glucose can be absorbed by the small intestine and transported to the blood. When this physiological process overacts due to excessive ingestion of carbohydrates, hyperglycemia occurs, leading to the development of DM (Guo et al., 2021).

Because of the biological and pharmacological importance of  $\alpha$ -glucosidase, a great number of natural products and synthetic compounds were developed for  $\alpha$ -glucosidase-targeting inhibition (Liu and Ma, 2017; Dhameja and Gupta, 2019; Gutiérrez-González et al., 2021; Trang et al., 2021). However, efficient probes targeting  $\alpha$ -glucosidase and the corresponding detection methods are still very rare. Up to now, only limited examples were reported in recent years about  $\alpha$ -glucosidase's molecular detection (Zhang et al., 2015; Ao et al., 2017; Kong et al., 2017; Li et al., 2018; Cheng et al.,

## The synthesis of designed molecule probes:



SCHEME 1 | Synthetic route of LD01 and LD02.

FIGURE 1 | Absorption (A) and emission (B) spectra of LD01 ( $\lambda_{\text{ex}} = 410 \text{ nm}$ ) and LD02 ( $\lambda_{\text{ex}} = 365 \text{ nm}$ ) in PBS buffer (10 mM, pH = 7.4).

2019), which are all focused on the catalytic function of  $\alpha$ -glucosidase. Because this type of technical system involved multiple steps in the sensing protocol, the quantitative detection of  $\alpha$ -glucosidase cannot be satisfactorily acquired.

Environmentally sensitive fluorescent probes are widely used for protein detection and imaging, whose responsive emissions are highly sensitive to the microenvironmental properties, such as polarity, pH, or viscosity of the surrounding medium where the dyes are located (Shvadchak et al., 2017; Dong et al., 2020; Zhou et al., 2020). Intramolecular charge transfer (ICT)-based donor- $\pi$ -acceptor dyes were found to exhibit strong emission in non-polar environments but fail to do so in highly polar solvents (Dai et al., 2020; Pal et al., 2020). Theoretically, the binding pocket of a specific target protein for such fluorescent probes may be more hydrophobic than that in aqueous solutions.

Coumarin and cinnamic acid are two types of typical natural products widely distributed in nature, harboring typical useful motifs in medicinal chemistry (Gaudino et al., 2016; Adisakwattana, 2017; Annunziata et al., 2020; Ruwizhi and Aderibigbe, 2020). Recently, Xu et al. reported that the conjugates of coumarin and cinnamic acid derivatives are potent inhibitors against  $\alpha$ -glucosidase (Xu et al., 2019). In this work, we designed and synthesized two fluorescent conjugates of dialkyl-substituted coumarin and cinnamic acid, LD01 and LD02, featuring donor- $\pi$ -acceptor structures as two environmentally sensitive probes for  $\alpha$ -glucosidase-targeting detection. We hypothesized the binding pocket inside  $\alpha$ -glucosidase may provide a relatively non-polar environment for the fluorescent probes so that intense fluorescence emission will be activated when

bound to  $\alpha$ -glucosidase. Comprehensive photophysical studies and enzyme inhibitory assays demonstrated newly designed fluorescent probe LD02 can act as a fluorescent indicator for  $\alpha$ -glucosidase, which can also serve as a potential tool for evaluating the binding affinity between  $\alpha$ -glucosidase and its inhibitors.

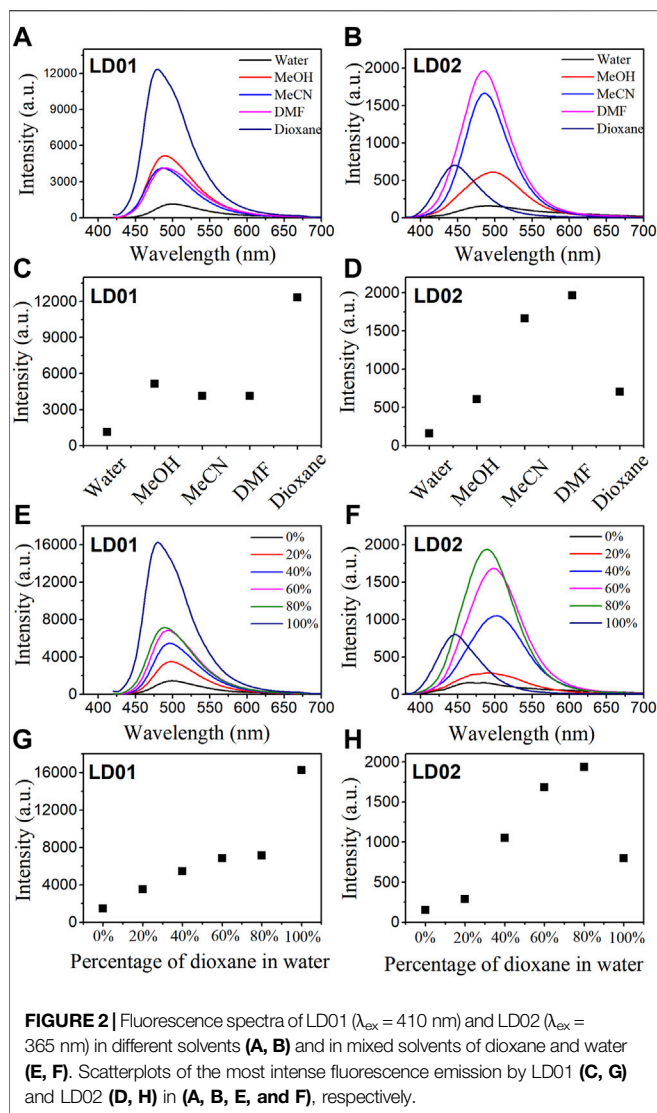
## EXPERIMENTAL

### Instruments and Reagents

All chemicals and solvents were obtained from commercial suppliers without further purification.  $\alpha$ -Glucosidase from *Saccharomyces cerevisiae* (EC 3.2.1.20) was purchased from Sigma-Aldrich. p-Nitrophenyl- $\alpha$ -D-galactopyranoside (PNPG) was obtained from Abcam. Nuclear magnetic resonance (NMR) spectra of new compounds were recorded in DMSO- $d_6$  using a Bruker Advance 500 MHz spectrometer. High-resolution mass spectrometry (HRMS) was measured on a Thermo Fisher Scientific Q Exactive Orbitrap mass spectrometer. UV-Vis absorption spectra were measured using an Hitachi 3,900 absorption spectrophotometer (Tokyo, Japan). Fluorescence spectra were recorded using an Edinburgh FLS1000 fluorescence spectrophotometer (Edinburgh, UK).

### Synthesis of LD01 and LD02

The substituted 3-acetyl-aminocoumarin derivatives (1.0 mmol) were added to a solution of hydroxylamine hydrochloride (3.0 mmol) and pyridine (0.04 mmol) in ethanol (10.0 ml), and



the mixture was stirred for 20 h at room temperature. When the reaction ended, the mixture was filtered to obtain precipitate which was then washed with ethanol to generate the substituted coumarin-based oxime product. DCC (1.1 mmol) and DMAP (0.2 mmol) were added to the solution of the substituted cinnamic acid at 0°C, and the mixture was stirred for 15 min; subsequently, the coumarin-based oxime compounds were added into the mixture and thoroughly stirred for another 12 h at room temperature. The mixture was quenched with water and extracted three times with DCM, washed with brine, and dried with magnesium sulfate. The crude product could be obtained under vacuum, and then purified by column chromatography to give the title product.

Compound LD01. Orange, solid; yield 70%; m.p. 196–198°C;  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  7.86 (s, 1H), 7.64 (d,  $J = 8.6$  Hz, 2H), 7.60–7.57 (m, 3H), 7.49 (d,  $J = 8.8$  Hz, 1H), 6.69 (dd,  $J = 8.9, 2.5$  Hz, 1H), 6.56 (d,  $J = 16.0$  Hz, 1H), 6.52 (d,  $J = 2.6$  Hz, 1H), 3.42 (q,  $J = 7.0$  Hz, 4H), 2.05 (s, 3H), 1.11 (t,  $J =$

7.0 Hz, 6H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{DMSO}-d_6$ )  $\delta$  167.89, 160.51, 156.73, 152.69, 151.18, 143.08, 141.91, 133.99, 132.31, 130.61, 130.44, 123.99, 120.58, 117.64, 109.66, 108.03, 96.61, 44.57, 14.10, 12.77; HRMS (+ESI)  $[\text{M} + \text{H}]^+$  calcd. For  $\text{C}_{24}\text{H}_{23}\text{BrN}_2\text{O}_4$ : 483.0930; found: 483.0967.

Compound LD02. Yellow, solid; yield 65%; m.p. 167–168°C;  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  8.63 (s, 1H), 7.93 (dd,  $J = 7.8, 1.6$  Hz, 1H), 7.73 (ddd,  $J = 8.7, 7.3, 1.7$  Hz, 1H), 7.46 (dt,  $J = 10.6, 6.8$  Hz, 4H), 7.40 (td,  $J = 7.6, 1.1$  Hz, 1H), 6.67 (d,  $J = 8.9$  Hz, 2H), 6.20 (d,  $J = 15.9$  Hz, 1H), 2.95 (s, 6H), 2.58 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{DMSO}-d_6$ )  $\delta$  195.51, 168.67, 158.90, 155.06, 152.02, 147.52, 145.12, 134.92, 131.24, 130.16, 125.37, 124.81, 121.99, 118.61, 116.56, 113.35, 112.20, 40.14, 30.52; HRMS (+ESI)  $[\text{M} + \text{H}]^+$  calcd. For  $\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_4$ : 377.1509; found: 377.1533.

## Photophysical Properties' Measurements

All solvents used for spectroscopic studies are spectrum pure grade. The stock solution of each sample was prepared in DMSO (1 mM), and the working solution was obtained by diluting 30  $\mu\text{L}$  of stock solutions into 3 ml of PBS buffer (10 mM, pH = 7.4) or other solvents in a quartz cuvette (1 cm  $\times$  1 cm). The absorption and emission spectra were measured at room temperature. The widths of the slits for both excitation and emission were 2 nm for all experiments.

## pH-Dependent Emission

The emission spectra of the probes in PBS buffer (pH from 3.0 to 8.0) were determined at room temperature. The pKa value was calculated using the Henderson–Hasselbalch equation (Finikova et al., 2003):

$$\text{pH} = \text{pKa} + \lg\left(\frac{[\text{A}]}{[\text{HA}]}\right).$$

## Fluorescence Titration of The Probes With $\alpha$ -Glucosidase

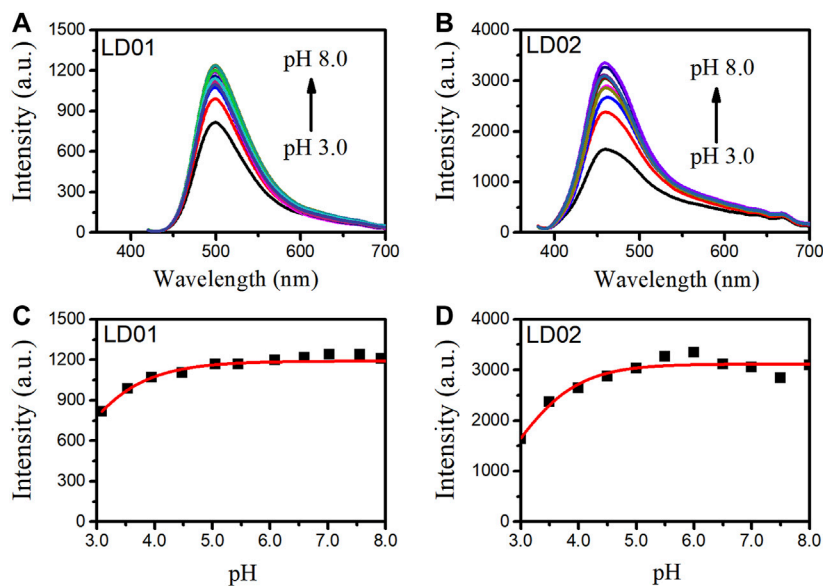
$\alpha$ -Glucosidase protein was titrated to the solution of the testing probe (LD01 or LD02) (10  $\mu\text{M}$ ), and the fluorescence emission spectra were recorded from 380 to 700 nm under excitation of 365 nm. The binding constants of  $K_a$  were obtained from a double logarithm regression curve (Wei et al., 2010):

$$\lg[(I - I_0)/I_0] = \lg K_a + n \lg[G],$$

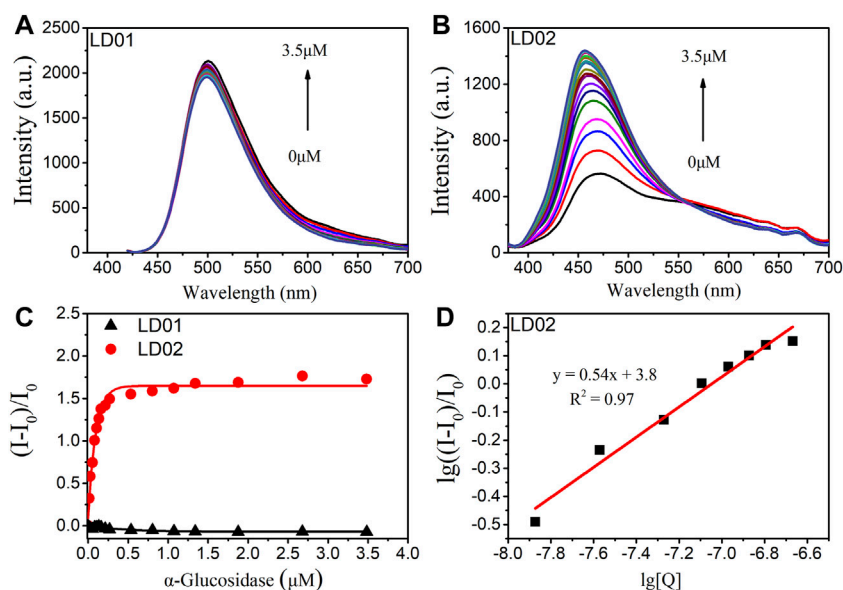
where  $I$  and  $I_0$  are the current and initial fluorescence intensity, respectively,  $K_a$  is the binding constant,  $n$  is the number of binding sites for each  $\alpha$ -glucosidase, and  $[G]$  is the total concentration of the  $\alpha$ -glucosidase protein.

## Fluorescence Competitive Binding Assay

The binding complexes of  $\alpha$ -glucosidase with LD02 were prepared by adding  $\alpha$ -glucosidase (final concentration = 3.5  $\mu\text{M}$ ) to the solution of LD02 (10  $\mu\text{M}$ ) in 10 mM PBS buffer (pH = 7.4). The dissociation constant of a competitor to  $\alpha$ -glucosidase can be determined by titrating it against binding complexes of  $\alpha$ -glucosidase with LD02, and can be calculated



**FIGURE 3** | Fluorescence spectra of LD01 (A) ( $\lambda_{\text{ex}} = 410$  nm) and LD02 (B) ( $\lambda_{\text{ex}} = 365$  nm) in buffers of various pH. Scatterplots of the most intense fluorescence emission by LD01 (C) and LD02 (D) in (A, B).



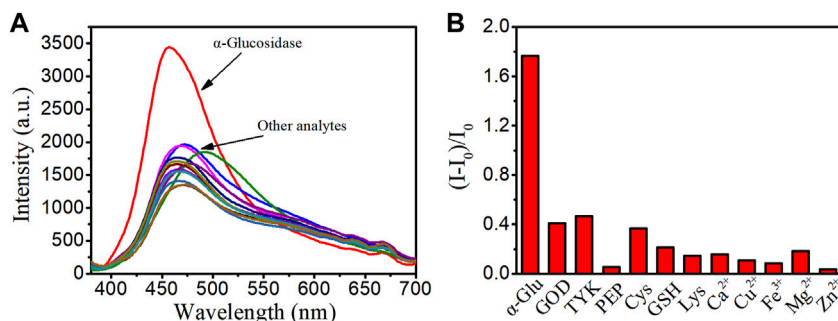
**FIGURE 4** | Fluorescence spectra of LD01 (A) and LD02 (B) (10  $\mu\text{M}$ ) in the presence of various concentrations of  $\alpha$ -glucosidase (0–3.5  $\mu\text{M}$ ) in PBS buffer. (C) Changes in  $(I-I_0)/I_0$  of LD01 ( $\lambda_{\text{ex}} = 410$  nm,  $\lambda_{\text{em}} = 500$  nm) and LD02 ( $\lambda_{\text{ex}} = 365$  nm,  $\lambda_{\text{em}} = 457$  nm) on addition of  $\alpha$ -glucosidase. (D) The linear regression line of  $\lg((I-I_0)/I_0)$  to  $\lg[Q]$ ,  $[Q]$  is the concentration of  $\alpha$ -glucosidase (mol/L).

according to the Cheng-Prusoff equation (Cheng and Prusoff, 1973).

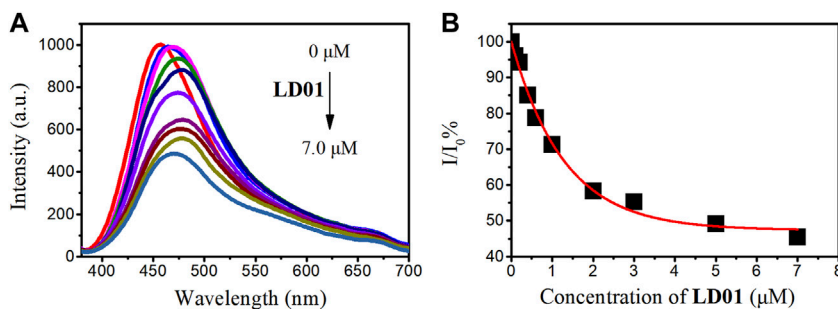
### $\alpha$ -Glucosidase Inhibition Efficiency Test of LD01 and LD02

The inhibition efficiency of LD01 and LD02 were determined according to the procedures Xu et al. reported previously (Xu

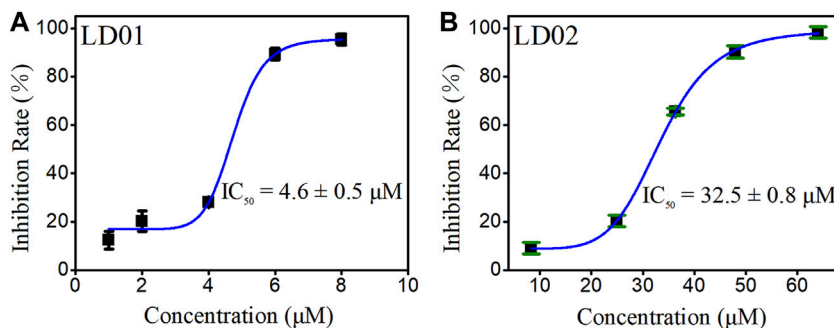
et al., 2019). Stock solutions of testing compounds were prepared in DMSO. Enzyme solution of  $\alpha$ -glucosidase (2 U/mL) was prepared in 0.1 M PBS buffer. Nitrophenol- $\alpha$ -D-glucoside (PNPG) was dissolved in 0.1 M PBS buffer (pH 6.8) to obtain the substrate solution (4 mM). In total, 10  $\mu\text{L}$  of  $\alpha$ -glucosidase (final concentration 0.1 U/mL), 130  $\mu\text{L}$  of PBS buffer, and 10  $\mu\text{L}$  of the sample solution were added into 96-well plates in succession and incubated at 37°C for 10 min. Then 50  $\mu\text{L}$  of substrate solution (PNPG final



**FIGURE 5 | (A)** Fluorescence spectra of LD02 (10  $\mu$ M) in the presence of various species:  $\alpha$ -glucosidase ( $\alpha$ -Glu) (3.5  $\mu$ M), GOD (3.5  $\mu$ M), TYK (3.5  $\mu$ M), PEP (3.5  $\mu$ M), Cys (1 mM), GSH (1 mM), Lys (1 mM),  $\text{Ca}^{2+}$  (1 mM),  $\text{Cu}^{2+}$  (1 mM),  $\text{Fe}^{3+}$  (1 mM),  $\text{Mg}^{2+}$  (1 mM), and  $\text{Zn}^{2+}$  (1 mM) in PBS buffer. **(B)** The plot of  $(I-I_0)/I_0$  in A ( $\lambda_{\text{ex}} = 365$  nm,  $\lambda_{\text{em}} = 457$  nm).



**FIGURE 6 | (A)** Fluorescent emission spectra of  $\alpha$ -glucosidase-LD02 binding complex (10  $\mu$ M of LD02 with 3.5  $\mu$ M of  $\alpha$ -glucosidase,  $\lambda_{\text{ex}} = 365$  nm) in the presence of various concentrations of LD01. **(B)** Scatterplots of the relative intensity  $I/I_0$  in A ( $\lambda_{\text{em}} = 457$  nm).



**FIGURE 7 | Plot of the inhibition rate of LD01 (A) and LD02 (B) against  $\alpha$ -glucosidase concentration.**

concentration 1 mmol/L) was added, followed by incubation at 37°C for another 30 min. The enzymatic activity was quantified by measuring the absorbance of the reaction mixture at 405 nm using a multimodel reader. The inhibition rate was calculated using the following equation:

$$\text{Inhibition rate (\%)} = [(A_1 - A_0)/A_0] \times 100\%,$$

where  $A_1$  and  $A_0$  are the absorbance values of testing samples and blank control, respectively. The  $\text{IC}_{50}$  value was obtained from a plot

of the inhibition rate *versus* the sample concentration curve. The assays were carried out in triplicate and the mean values were given.

## RESULT AND DISCUSSION

### Synthesis and Characterization of LD01 and LD02

LD01 and LD02 could be obtained through a two-step synthesis as shown in **Scheme 1**. In brief, substituted 3-acetylcoumarin



derivatives reacted with hydroxylamine hydrochloride under the basic condition to give the substituted coumarin-based oxime product, followed by acylation with corresponding cinnamic acid to produce the designed molecular probes **LD01** and **LD02**, which were well characterized by  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, and HRMS (supporting information, **Supplementary Figures S1–6**).

## Photophysical Properties' Studies

Absorption spectra of **LD01** and **LD02** were measured at room temperature in PBS buffer (pH = 7.4). **LD01** has two absorption bands at 410 nm ( $\epsilon = 14,800 \text{ M cm}^{-1}$ ) and 290 nm ( $\epsilon = 9800 \text{ M cm}^{-1}$ ) assigned to  $\pi \rightarrow \pi^*$  transitions from diethylamino-coumarin and bromo cinnamic ester moiety, respectively. **LD02** has an absorption band at around 365 nm ( $\epsilon = 4900 \text{ M cm}^{-1}$ ) resulting from the mixed  $\pi \rightarrow \pi^*$  transitions of coumarin and cinnamic ester moieties. For the emission spectra, **LD01** and **LD02** show one emission band with maximum emission at 500 and 457 nm, respectively, while exhibiting very low emission quantum yield, 5.3% for **LD01**, and 3.2% for **LD02** in PBS buffer (pH = 7.4). It has been well documented that dialkyl amine-substituted coumarin or cinnamic acid derivatives are ICT-based dyes, and their emission band or intensity is affected by the surrounding polarity. We first determined the emission spectra of **LD01** and **LD02** in various solvents of different polarities, such as water, methanol, acetonitrile, *N,N*-dimethylformamide, and dioxane (**Figures 2A–D**). The emission intensity of **LD01** accrues in an increasing order of polarity. **LD02** shows a similar tendency except for the emission of dioxane, which may result from the poor solubility of **LD02** in it. Moreover, the emission band of **LD02** shows a 40-nm blue shift in dioxane as compared to that in an aqueous buffer. We then measured the fluorescence of **LD01** and **LD02** in solvents with water and dioxane mixed at different ratios, representing different degrees of solvent polarity. As shown in **Figures 2E–H**, in the mixed solvent system, both **LD01** and **LD02**'s fluorescent emission shows a similar tendency in response to polarity change from different solvents, which suggests both **LD01** and **LD02** can be potentially used to detect  $\alpha$ -glucosidase *via* responsive emission. In the meantime, the pH effect on the emission of **LD01** and **LD02** was investigated. The emission spectra of **LD01** and **LD02** are less sensitive to pH variation (**Figure 3**) from 3.0 to 8.0 than the polarity changes; the p*K*<sub>a</sub> values of **LD01** and **LD02** were worked out to be 4.2 and 4.6 for **LD01** and **LD02**, respectively.

## Fluorescence Titration of **LD01** and **LD02** Toward $\alpha$ -Glucosidase

To confirm the  $\alpha$ -glucosidase-targeted binding interaction, fluorescence titrations were carried out by determining the emission spectra of **LD01** and **LD02** as a function of the concentration of  $\alpha$ -glucosidase. As shown in **Figure 4A**, there are no obvious emission changes observed for **LD01** after the gradual addition of  $\alpha$ -glucosidase protein up to 3.5  $\mu\text{M}$ . However, a significant enhancement of responsive fluorescence emission can be achieved for **LD02** under the

same experimental condition (**Figures 4B, C**). After the addition of 3.5  $\mu\text{M}$   $\alpha$ -glucosidase, the maximum emission intensity increased by 2.7 times, and the emission maximum of **LD02** was detected of a  $\sim 7$  nm blue shift from 457 to 450 nm, which suggests that the dimethylamine group in **LD02** may locate in the binding pocket of relative lower polarity inside  $\alpha$ -glucosidase than the aqueous surroundings. The binding constant and the rate of **LD02** to  $\alpha$ -glucosidase were obtained by the double logarithm regression curve as shown in **Figure 4D**. The value of  $\log K_a$  of **LD02** to  $\alpha$ -glucosidase was calculated to be 3.8, and the binding ratio was approximately 0.5.

## Binding Selectivity of **LD02** Toward $\alpha$ -Glucosidase

To verify the binding specificity of **LD02** toward  $\alpha$ -glucosidase, emission spectra of **LD02** in the presence of  $\alpha$ -glucosidase or various potential competitors such as other enzymes (including glucose oxidase (GOD), polyphenol oxidase (TKY), and pepsin (PEP)), and small molecules of interest (including Cys, GSH, Lys,  $\text{Ca}^{2+}$ ,  $\text{Cu}^{2+}$ ,  $\text{Fe}^{3+}$ ,  $\text{Mg}^{2+}$ , and  $\text{Zn}^{2+}$ ), were collected in 10 mM PBS buffer (pH = 7.4) at room temperature. As shown in **Figure 5**, all potential competitors tested have no obvious effect on the emission band and intensity of **LD02** compared with  $\alpha$ -glucosidase, suggesting the highly specific selectivity of **LD02** toward  $\alpha$ -glucosidase.

## Competitive Fluorescence Titration

For competitive fluorescence titration, different amounts of **LD01** were added to a solution of  $\alpha$ -glucosidase/**LD02** complex. After the addition of **LD01**, it was found that the emission of  $\alpha$ -glucosidase/**LD02** complex decreased as a function of increasing the concentration of **LD01**, indicating **LD01**'s competitive binding to the same binding pocket as **LD02** (**Figure 6**). The binding constant ( $K_a$ ) of **LD01** to  $\alpha$ -glucosidase was calculated, and the value of  $\lg K_a$  was 5.2 for **LD01**, which means **LD01** has a much stronger affinity for  $\alpha$ -glucosidase than **LD02** does. This result encouraged us to determine the inhibition efficiency of **LD01** and **LD02** against  $\alpha$ -glucosidase.

## $\alpha$ -Glucosidase Inhibitory Effect of **LD01** and **LD02**

$\alpha$ -Glucosidase inhibitory efficiency of **LD01** and **LD02** was obtained from the inhibition rate vs. concentration curves of **LD01** and **LD02** (**Figure 7**). The results showed that coumarin derivatives **LD01** and **LD02** demonstrated excellent and potent inhibitory activity against  $\alpha$ -glucosidase with the  $\text{IC}_{50}$  values of  $4.6 \pm 0.5$  and  $32.5 \pm 0.8 \mu\text{M}$ , respectively, as compared to the standard acarbose ( $\text{IC}_{50} = 856.45 \pm 5.60 \mu\text{M}$ ). In particular, **LD01** and **LD02** have a relatively stronger inhibition effect against  $\alpha$ -glucosidase than the coumarin derivatives that Xu et al. reported previously (Xu et al., 2019). In particular, the  $\text{IC}_{50}$  values of **LD01** and **LD02** have a positive correlation with the binding affinities observed from the fluorescence titration experiments, which

indicates that our fluorescent probe LD02 can be used as an applicable tool helpful in the development and screening of pharmacologically active  $\alpha$ -glucosidase inhibitors based on the candidate molecules' binding strength.

## CONCLUSION

In summary, two environmentally sensitive fluorescence agents, LD01 and LD02, based on the conjugates of substituted coumarin and cinnamic acid, were designed and synthesized. Both LD01 and LD02's fluorescent emissions show a polarity-dependent enhancement feature, as demonstrated in various solvents of different polarities, and the solvent mixture of dioxane and water. When coming to fluorescence titration, LD02 shows responsive emission changes featured with 2.7 times emission enhancement upon its binding to  $\alpha$ -glucosidase. However, LD01 does not have such changes under the same experimental conditions as LD02 does. The competitive fluorescence titration of LD01 to the  $\alpha$ -glucosidase/LD02 complex shows a gradually reduced emission as a function of increasing concentration of LD01, which suggests that LD01 can competitively bind to the same pocket of  $\alpha$ -glucosidase targeted by LD02. The binding constants of LD01 and LD02 toward  $\alpha$ -glucosidase were worked out by the fluorescence titration experiments, from which the values of  $\lg K_a$  were found to be 5.2 and 3.8 for LD01 and LD02, respectively, and positively correlated with  $IC_{50}$  values ( $4.6 \pm 0.5$  and  $32.5 \pm 0.8 \mu\text{M}$  for LD01 and LD02, respectively) as observed from the enzyme inhibitory assays. This research not only lays out a new strategy for quantitative detection of  $\alpha$ -glucosidase but also offered a potential tool for binding affinity evaluation between  $\alpha$ -glucosidase and its inhibitors, which may provide guidance for developing new  $\alpha$ -glucosidase inhibitors treating diabetes.

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## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**; further inquiries can be directed to the corresponding authors.

## AUTHOR CONTRIBUTIONS

DL: Synthesis, photophysical properties' measurement, writing—original draft, and data curation. XZ: Synthesis and analysis. XL: Investigation and analysis. Y-YZ and XZ: Enzyme inhibition test. YZ: Supervision and writing—revise and editing. ZX: Supervision, methodology, and writing—review and editing. HL: Conceptualization, formal analysis, data curation, writing—review and editing, supervision, project administration, and funding acquisition.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fchem.2022.927624/full#supplementary-material>

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