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**A new series of Salicylic acid derivatives as non-saccharide  $\alpha$ -glucosidase inhibitors and antioxidants**

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## Summary

In this study, a series of salicylic acid derivatives were designed and synthesized as novel non-saccharide  $\alpha$ -glucosidase inhibitors. Biological evaluation indicated that when compared to acarbose, compounds **T9**, **T10**, and **T32** exhibited a higher potency of  $\alpha$ -glucosidase inhibitory activity with  $IC_{50}$  values of  $0.15 \pm 0.01$  mM,  $0.086 \pm 0.01$  mM and  $0.32 \pm 0.02$  mM, respectively. Evaluation of the inhibition kinetics indicated that **T9**, **T10**, **T32**, and acarbose interacted with  $\alpha$ -glucosidase in a mixed non-competitive inhibitory manner. Moreover, **T9**, **T10**, and **T32** statically quenched the fluorescence of  $\alpha$ -glucosidase by formation of an inhibitor- $\alpha$ -glucosidase complex. The docking results showed that hydrogen bonds were generated between the test compounds and  $\alpha$ -glucosidase. The antioxidant study revealed that compound **T10** exhibited a higher antioxidant activity via scavenging 1,1-diphenyl-2-picrylhydrazyl free radical (**DPPH**), thereby inhibiting lipid peroxidation and the total reduction capacity. In brief, the salicylic acid derivatives identified in this study were promising candidates for development as novel non-saccharide  $\alpha$ -glucosidase inhibitors.

**Key words** salicylic acid derivative;  $\alpha$ -glucosidase; antioxidant; fluorescence; docking

As one of the most prevalent diseases worldwide, diabetes has become a serious public-health problem.<sup>1)</sup> Type 2 diabetes mellitus (T2DM) is increasing at an alarming rate. T2DM affects about 173 million individuals worldwide and in recent years has been associated with vascular complications that result in excess morbidity and mortality. Such complications include cardiovascular diseases, stroke, nephropathy, retinopathy, renal failure, and amputations.<sup>2,3)</sup> It is generally accepted that diabetes belongs to cardiovascular diseases (CVDs) and that cardiovascular complications are related to prevailing hyperglycemia, particularly postprandial hyperglycemia (PPHG). In several studies, it has convincingly been demonstrated that a variation in blood glucose levels as a key player in contributing to diabetic micro- and macro-vascular complications is more deleterious than chronic sustained hyperglycemia.<sup>4-6)</sup> In addition, PPHG has been identified as one of the earliest detectable abnormalities expressed in patients with diabetes.<sup>7)</sup> Therefore, it is considered a better predictor for the progression of diabetes and has been implicated in inducing oxidative stress that is recognized as a major pathophysiological link between CVD and diabetes.<sup>8,9)</sup>

Pharmacological agents that specifically decrease PPHG, including  $\alpha$ -glucosidase inhibitors (AGIs), may become therapeutics of utmost importance.<sup>10)</sup> Food starches contribute to major postprandial blood glucose levels, and represent an issue that is of significant relevance to those of Asian descent because of their specific dietary habits. Slowing down the digestion and absorption of dietary starches has shown great promise in reducing PPHG, the burden of oxidative stress, and CVD.<sup>8,9,11)</sup> This can be achieved through dietary manipulation with low-glycemic index food or by inhibition of the starch-digesting enzyme  $\alpha$ -glucosidase, which is present at the intestinal brush borders.<sup>11)</sup> Such  $\alpha$ -glucosidase inhibitors are effective for delaying and prolonging carbohydrate digestion, slowing the rate of glucose absorption, and consequently blunting the postprandial plasma glucose increase.<sup>12,13)</sup> Several AGIs, including acarbose, voglibose, and miglitol, have been effectively used in the clinic to treat T2DM and to prevent CVD in the Asian population presumably because of their specific food intake.<sup>14,15)</sup> However, only few AGIs are available commercially and their structures are similar to those with sugar, which require tedious multi-step processes for preparation. For instance, acarbose and voglibose are amino sugars, whereas miglitol is an azasugar. Therefore,

there is considerable interest in the design and synthesis of non-saccharide AGIs.<sup>16-21)</sup> Kavitha et al. investigated the binding mode of interaction of several sugar/non-saccharide AGIs at the active site of  $\alpha$ -glucosidase and developed a pharmacophore model, which represented the critical features responsible for  $\alpha$ -glucosidase inhibitory activity.<sup>17)</sup>

In our previous study, we found that several phthalimide derivatives exhibited good  $\alpha$ -glucosidase inhibitory activity.<sup>23)</sup> Based on the pharmacophore model of phthalimide compounds for  $\alpha$ -glucosidase, the phthalimide scaffold was broken apart and one carbonyl group within phthalimide was replaced with a hydroxyl group. Thus, a series of salicylic acid derivatives were explored as novel non-saccharide AGIs (Fig. 1). In the current study, a salicylic acid moiety was designed as a new scaffold, possessing similar structural characteristics as the AGIs pharmacophore model described, and a variety of alcohols and amines were conjugated with 4-(4-methylphenyl)sulfonamido salicylic acid and 4-acetylamido salicylic acid. The inhibitory activities of the designed compounds were evaluated against yeast  $\alpha$ -glucosidase and the structure-activity relationships were discussed. Compounds with prominent activities against  $\alpha$ -glucosidase were selected to further investigate the inhibition kinetics and anti-oxidation capacities. Moreover, to provide insight into the structure-activity relationship of the target compounds towards  $\alpha$ -glucosidase, fluorescence quenching analysis of  $\alpha$ -glucosidase and docking simulations of the representative compounds were performed to investigate their binding characteristics with  $\alpha$ -glucosidase.

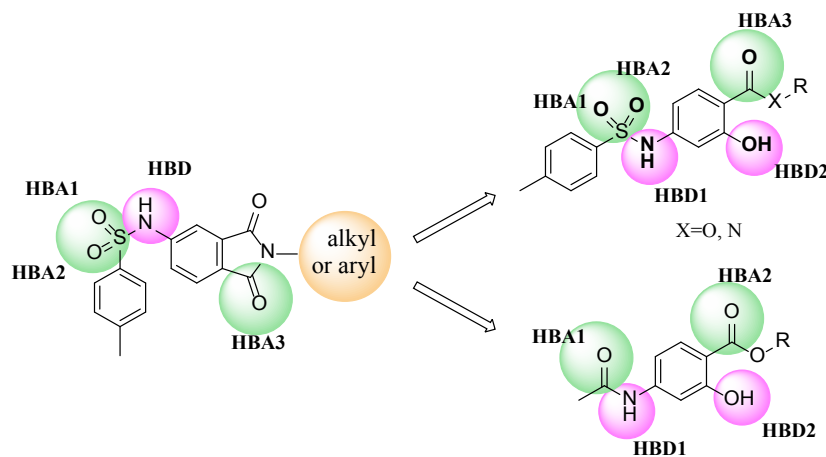


Fig. 1. Design of salicylic acid derivatives based on a new  $\alpha$ -glucosidase inhibitor of

phthalimide. HBA represent hydrogen bond acceptor, HBD represent hydrogen bond donor. (Color figure can be accessed in the online version.)

## MATERIALS AND METHODS

All materials were obtained from commercial suppliers and were used without further purification. The progress of the reaction was monitored by TLC using Qingdao Haiyang Chemical Co. Ltd, HG/T2354-92 silica Gel GF254. Purification of compounds was performed by flash column chromatography using silica gel (200-300 mesh) of Qingdao Haiyang Chemical Co. Ltd (Qingdao, China). <sup>1</sup>H-NMR (400 MHz) and <sup>13</sup>C-NMR (100 MHz) spectra were recorded with a Bruker AV400 spectrometer (Switzerland), chemical shifts were recorded in parts per million (ppm), and coupling constants (*J*) were given in Hertz. Mass spectra were obtained on a Shimadzu HPLC-MS-QP2010 instrument (Kyoto, Japan). IR spectra were recorded with a Nicolet AVATAR 330 FT-IR instrument (Madison, America).

### General procedure for the synthesis of target compounds.

A general synthetic approach for the proposed compounds **T1-T30** is depicted in Chart 1. As a starting material, 4-amino salicylic acid **1** was treated with methanol in the presence of concentrated sulfuric acid to generate methyl 4-amino salicylate **2**. Next, the phenolic hydroxyl group on the intermediate **2** was benzyl-protected by treatment with benzyl bromide to generate methyl 4-amino-2-(benzyloxy)benzoate **3**, which further underwent sulfonylation with *para*-toluenesulfonic chloride in dichloromethane in the presence of pyridine to generate methyl 2-(benzyloxy)-4-[(4-methylphenyl)sulfonamido]benzoate **4**. This was hydrolyzed with sodium hydroxide in a mixed solvent of tetrahydrofuran and water to generate the key intermediate 2-(benzyloxy)-4-[(4-methylphenyl)sulfonamido]benzoic acid **5**. The corresponding alcohols and amines were conjugated with key intermediate **5** to give rise to esters or amides, followed by deprotection of the benzyl group with palladium-carbon catalyst in a hydrogen atmosphere to obtain target compounds **T1-T30**, except **T6**, **T17**, and **T27**, for which the benzyl-deprotection was performed by treatment with titanium tetrachloride in dichloromethane.<sup>23)</sup>

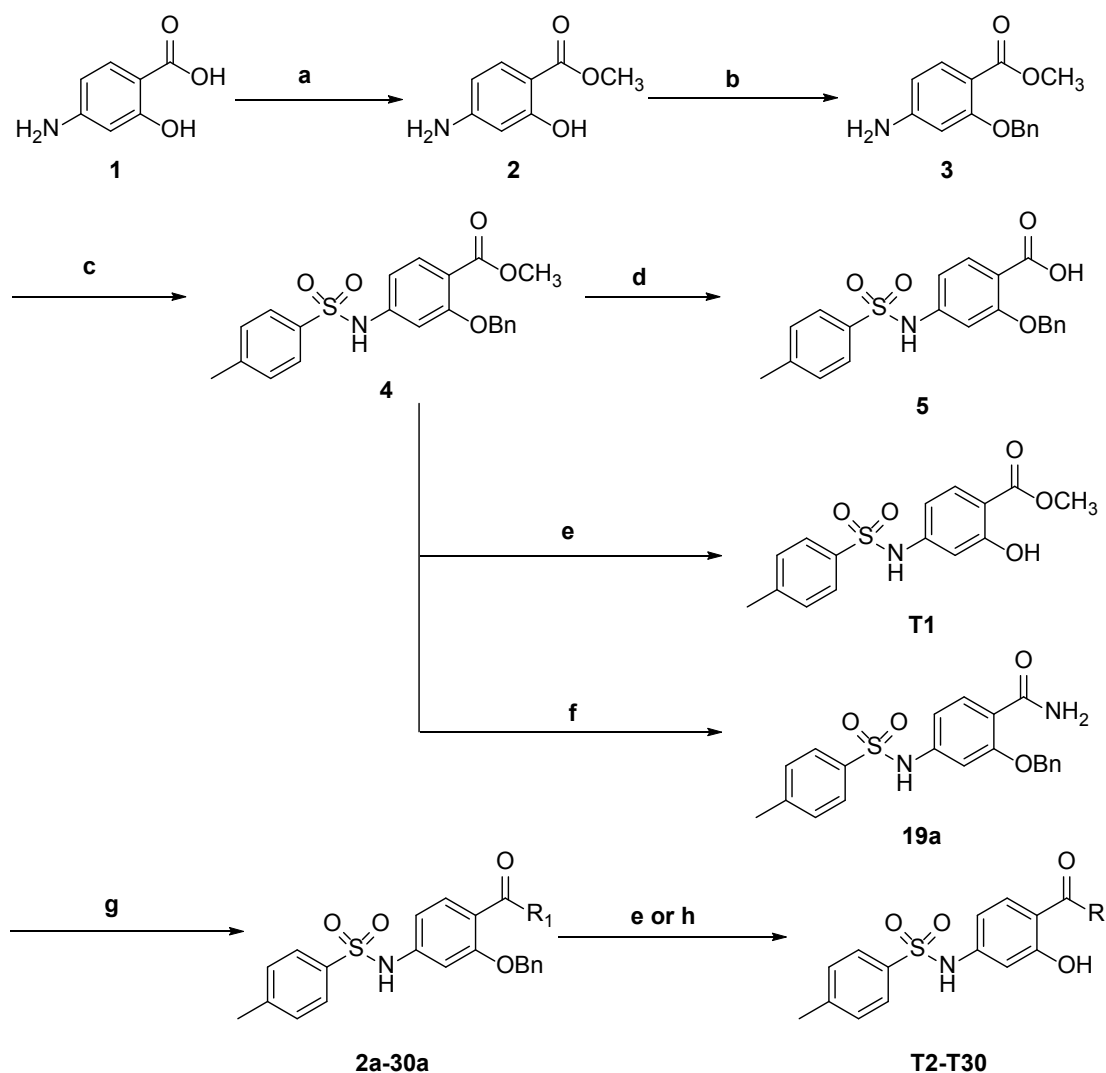


Chart 1. Synthesis of target compounds **T1-T30**. Reagents and conditions: (a) con.  $\text{H}_2\text{SO}_4$ , MeOH, reflux; (b) BnBr, NaH, DMF,  $0^\circ\text{C}$  to rt.; (c) TsCl, pyridine,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$  to rt.; (d) NaOH, THF/ $\text{H}_2\text{O}$ , rt.; (e)  $\text{H}_2$ , Pd/C, EtOH, rt.; (f) oxalyl chloride, cat. DMF, then  $\text{NH}_3 \cdot \text{H}_2\text{O}$ ; (g) alcohol or amine, HOBT, EDCI, NMM, DMF, rt.; (h)  $\text{TiCl}_4$ , DCM.

Prior to conjugation with the intermediate **5**, the hydroxyl group of 2-(4-hydroxyphenyl)ethanol **8b** and 2-(3,4-dihydroxyphenyl)ethanol **9b** were benzyl-protected using benzyl bromide in acetone in the presence of potassium carbonate to generate the corresponding compounds **8c** and **9c** as shown in Chart 2.

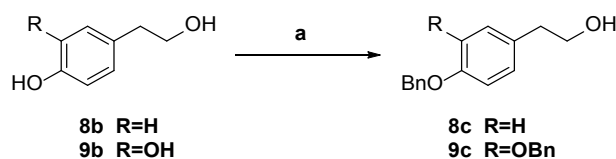


Chart 2. Synthesis of the intermediates **8c** and **9c**. Reagents and conditions: (a) BnBr,  $\text{K}_2\text{CO}_3$ , acetone, reflux.

The intermediate of the alcohol moiety for target compounds **T10** and **T11** was synthesized as shown in Chart 3. In brief, caffeic acid **10b** was esterified with methanol in the presence of concentrated sulfuric acid to generate compound **10c**, which was reacted with benzyl bromide to give rise to compound **10d**, followed by reduction with aluminium hydride, which was generated in situ from lithium aluminium hydride and benzyl bromide to generate compound **10e**.<sup>24)</sup> Based on a similar procedure, ferulic acid **11b** was converted to compounds **11e**.

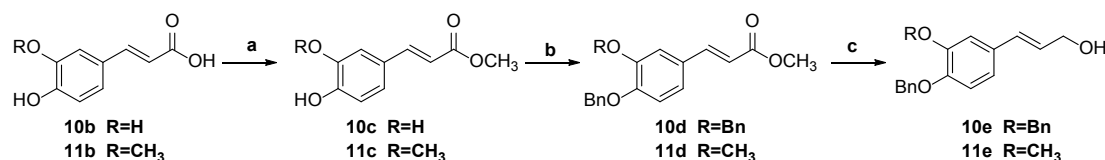


Chart 3. Synthesis of the intermediates **10e** and **11e**. Reagents and conditions: (a) con.  $\text{H}_2\text{SO}_4$ , MeOH, reflux; (b) BnBr,  $\text{K}_2\text{CO}_3$ , acetone, reflux; (c)  $\text{LiAlH}_4$ , BnBr, THF,  $0^\circ\text{C}$  to rt.

Target compounds **T31** and **T32** were synthesized via the synthetic route presented in Chart 4. In brief, methyl 4-amino-2-(benzyloxy)benzoate **3** was treated with acetyl chloride in the presence of trimethylamine to generate methyl 4-acetamido-2-(benzyloxy)benzoate **6**, which was hydrolyzed with sodium hydroxide in a mixed solvent of tetrahydrofuran and water to produce key intermediate 4-acetamido-2-(benzyloxy)benzoic acid **7**. After being condensed with alcohol and deprotection of the benzyl group, target compounds **T31** and **T32** were obtained.

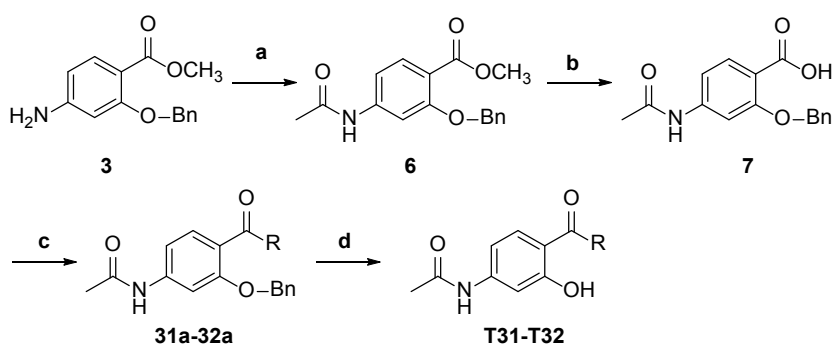


Chart 4. Synthesis of target compounds **T31-T32**. Reagents and conditions: (a) AcCl, TEA, CH<sub>2</sub>Cl<sub>2</sub>, 0°C to rt.; (b) NaOH, THF/H<sub>2</sub>O, rt.; (c) alcohol, HOBt, EDCI, NMM, DMF, rt.; (d) H<sub>2</sub>, Pd/C, EtOH.

**Synthesis of methyl 4-amino-2-hydroxybenzoate (2)** Concentrated H<sub>2</sub>SO<sub>4</sub> (5.0 mL) was slowly added to CH<sub>3</sub>OH (120.0 mL) and the mixture was stirred at room temperature for 2 hours. Then, 4-amino-2-hydroxybenzoic acid (6.00 g, 39.18 mmol) was added in one portion and the mixture was heated to reflux under N<sub>2</sub> for 20 hours. The mixture was concentrated under reduced pressure to give rise to a residue, which was first basified to pH 7 with 2.0 M NaOH, then to pH 8 with saturated NaHCO<sub>3</sub>. The resulting mixture was extracted with EtOAc (100.0 mL × 3) and the combined organic layers were washed with brine (50.0 mL × 2), dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuo to yield crude compound **2** as a light pink solid that was used for next step without further purification (6.40 g, 97.7%).

**Synthesis of methyl 4-amino-2-(benzyloxy)benzoate (3)** To a stirred solution of compound **2** (6.40 g, 38.29 mmol) in anhydrous dimethyl formamide, 60% NaH (1.70 g, 42.5 mmol) was added in portions at 0°C, and the mixture was stirred under N<sub>2</sub> for 2 hours. Subsequently, BnBr (5.00 mL, 42.10 mmol) was added dropwise after which the mixture was stirred at 0°C for 30 min, then warmed to room temperature overnight. Water (5.0 mL) was added to quench the reaction and the mixture was concentrated in vacuo to form a residue, which was dissolved with EtOAc (300.0 mL), then washed with 4 M HCl (100.0 mL × 6), the combined aqueous layers were first basified to pH 7 with 2.0 M NaOH, then to pH 8 with saturated Na<sub>2</sub>CO<sub>3</sub>. The resulting mixture was extracted with EtOAc (150.0 mL × 4) and the combined organic layers were washed with brine (100.0 mL × 3), dried over Na<sub>2</sub>SO<sub>4</sub> and



concentrated under reduced pressure to form a residue that was purified by column chromatography (petroleum ether/ethyl acetate=4:1) on silica gel to yield compound **4** as a white solid (5.30 g, 53.8%). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 7.52~7.55 (m, 3H, ArH), 7.38~7.42 (t, 2H, ArH), 7.29~7.33 (t, 1H, ArH), 6.28~6.29 (d, 1H, ArH), 6.15~6.17 (m, 1H, ArH), 5.96 (s, 2H, -NH<sub>2</sub>), 5.07 (s, 2H, -OCH<sub>2</sub>Ar), 3.68 (s, 3H, -OCH<sub>3</sub>). <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>) δ: 51.18, 70.26, 99.08, 101.34, 110.37, 126.83, 127.34, 128.89, 131.43, 136.25, 155.18, 161.69, 165.88. IR (KBr, cm<sup>-1</sup>): 3380, 2940, 2878, 1758, 1623, 1536, 1470, 1321, 1232, 1036, 835. EI-MS *m/z*: 257.1 (M<sup>+</sup>). *Anal.* Calcd for C<sub>15</sub>H<sub>15</sub>NO<sub>3</sub>: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.04; H, 5.86; N, 5.45.

**Synthesis of methyl 2-(benzyloxy)-4-[(4-methylphenyl)sulfonamido]benzoate (4)** To a stirred solution of compound **3** (5.30 g, 20.60 mmol) and pyridine (3.40 mL, 42.21 mmol) in dichloromethane (80.0 mL), paratoluensulfonyl chloride (4.32 g, 22.66 mmol) was added in portions at 0°C. After stirring at 0°C for 30 min, the mixture was warmed to room temperature overnight. Then, the mixture was washed with 2.0 M HCl, saturated NaHCO<sub>3</sub> and brine, respectively. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo to yield compound **4** as a white solid (8.20 g, 96.8%). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 10.71 (s, 1H, -SO<sub>2</sub>NH-), 7.55~7.65 (m, 3H, ArH), 7.47~7.49 (d, 2H, ArH), 7.40~7.43 (m, 2H, ArH), 7.32~7.36 (m, 3H, ArH), 6.97 (s, 1H, ArH), 6.70~6.72 (d, 1H, ArH), 5.11 (s, 2H, -OCH<sub>2</sub>Ar), 3.73 (s, 3H, -OCH<sub>3</sub>), 2.32 (s, 3H, ArCH<sub>3</sub>). <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>) δ: 21.42, 51.16, 70.29, 99.06, 108.29, 110.31, 126.80, 127.38, 128.15, 128.79, 129.12, 131.39, 136.29, 136.53, 137.46, 142.58, 161.64, 165.81. IR (KBr, cm<sup>-1</sup>): 3272, 2943, 2874, 1756, 1622, 1533, 1473, 1354, 1230, 1141, 1033, 833. EI-MS *m/z*: 411.1 (M<sup>+</sup>). *Anal.* Calcd for C<sub>22</sub>H<sub>21</sub>NO<sub>5</sub>S: C, 64.22; H, 5.14; N, 3.40; S, 7.79. Found: C, 64.20; H, 5.16; N, 3.42; S, 7.77.

**Synthesis of 2-(benzyloxy)-4-[(4-methylphenyl)sulfonamido]benzoic acid (5)** To a solution of compound **4** (8.20 g, 19.93 mmol) in tetrahydrofuran (100.0 mL), an aqueous solution of 4.0 M NaOH was added, and the mixture was stirred at room temperature for 20 hours. Under reduced pressure, the organic solvent was removed to form a residue that was extracted with EtOAc to remove impurities. The resulting aqueous layer was acidified to pH 1 with 4.0 M HCl and the precipitate was filtered and dried to yield compound **5** as an

off-white solid (7.70 g, 97.2%).  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 12.45 (s, 1H, -COOH), 10.65 (s, 1H, -SO<sub>2</sub>NH-), 7.61~7.63 (d, 2H, ArH), 7.55~7.57 (d, 1H, ArH), 7.46~7.48 (m, 2H, ArH), 7.36~7.42 (m, 2H, ArH), 7.31~7.33 (m, 3H, ArH), 6.94~6.95 (d, 1H, ArH), 6.66~6.69 (m, 1H, ArH), 5.10 (s, 2H, -OCH<sub>2</sub>Ar), 2.33 (s, 3H, ArCH<sub>3</sub>).  $^{13}\text{C-NMR}$  (DMSO- $d_6$ )  $\delta$ : 21.40, 70.31, 99.02, 108.05, 108.26, 126.77, 127.35, 128.12, 128.75, 129.08, 131.57, 136.26, 136.51, 137.42, 142.78, 161.89, 165.93. IR (KBr,  $\text{cm}^{-1}$ ): 3276, 2946, 2877, 1714, 1619, 1531, 1471, 1358, 1234, 1147, 1035, 928, 831. EI-MS  $m/z$ : 397.1 ( $\text{M}^+$ ). *Anal.* Calcd for C<sub>21</sub>H<sub>19</sub>NO<sub>5</sub>S: C, 63.46; H, 4.82; N, 3.52; S, 8.07. Found: C, 63.45; H, 4.84; N, 3.54; S, 8.05.

**Synthesis of methyl 4-acetamido-2-(benzyloxy)benzoate (6)** To a solution of compound **3** (5.00 g, 19.43 mmol) and trimethylamine (3.93 g, 38.81 mmol) in anhydrous dichloromethane (200.0 mL), acetyl chloride (1.66 mL, 23.26 mmol) was added at 0°C. Subsequently, the mixture was stirred under N<sub>2</sub> overnight at room temperature. Then, the mixture was washed with 2.0 M HCl, saturated NaHCO<sub>3</sub> and brine, respectively. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo to yield compound **6** as a light yellow solid (5.77g, 99.2%) that was used for next step without further purification.

**Synthesis of 4-acetamido-2-(benzyloxy)benzoic acid (7)** Compound **7** was prepared following the procedure that was used to generate compound **5**. From compound **6** (5.77 g, 19.28 mmol), compound **7** was obtained as an off-white solid (4.95 g, 90.1%).  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 12.36 (s, 1H, -COOH), 10.20 (s, 1H, -CONH-), 7.67~7.69 (d, 1H, ArH), 7.50~7.54 (m, 3H, ArH), 7.37~7.40 (t, 2H, ArH), 7.29~7.33 (m, 1H, ArH), 7.17~7.19 (dd, 1H, ArH), 5.13 (s, 2H, -CH<sub>2</sub>Ph), 2.05 (s, 3H, CH<sub>3</sub>CO-).  $^{13}\text{C-NMR}$  (DMSO- $d_6$ )  $\delta$ : 23.85, 70.67, 105.45, 113.06, 113.37, 126.85, 127.19, 128.32, 131.21, 136.25, 144.28, 161.24, 166.26, 168.97. IR (KBr,  $\text{cm}^{-1}$ ): 3294, 2957, 2888, 1692, 1623, 1533, 1472, 1373, 1235, 1038, 925, 836. EI-MS  $m/z$ : 285.1 ( $\text{M}^+$ ). *Anal.* Calcd for C<sub>16</sub>H<sub>15</sub>NO<sub>4</sub>: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.34; H, 5.32; N, 4.93.

**General procedure for the synthesis of compounds 8c and 9c** To a stirred solution of compound **8b** or **9b** in acetone, K<sub>2</sub>CO<sub>3</sub> (2.50 equivalent for each phenolic hydroxyl) and BnBr (1.05 equivalent for each phenolic hydroxyl) were added. The resulting mixture was heated to reflux under N<sub>2</sub> for 10 hours. The mixture was then filtered and the filtrate was

concentrated to form a residue, which was dissolved with EtOAc, washed with 2.0 M HCl, saturated NaHCO<sub>3</sub> and brine. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo to form a yellow oil that was purified by column chromatography on silica gel to generate compound **8c** or **9c**.

**Synthesis of 2-[4-(benzyloxy)phenyl]ethan-1-ol (8c)** From compound **8b** (2.00 g, 14.47 mmol), compound **8c** was obtained as a white solid (3.10 g, 93.8%).

**Synthesis of 2-[3,4-bis(benzyloxy)phenyl]ethan-1-ol (9c)** From compound **9b** (2.27 g, 14.72 mmol), **9c** was obtained as a white solid (2.70 g, 54.8%). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 7.30~7.46 (m, 10H, ArH), 6.92~6.94 (t, 2H, ArH), 6.69~6.71 (m, 1H, ArH), 5.07~5.09 (d, 4H, -CH<sub>2</sub>Ph), 4.602 (t, 1H, -OH), 3.50~3.54 (t, 2H, -OCH<sub>2</sub>-), 2.60~2.63 (t, 2H, -CH<sub>2</sub>Ar). <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>) δ: 38.82, 60.85, 70.62, 111.89, 115.66, 121.74, 126.84, 127.18, 128.59, 130.27, 136.41, 146.59, 149.43. IR (KBr, cm<sup>-1</sup>): 3339, 2953, 2854, 1623, 1533, 1450, 1368, 1235, 1073, 836. EI-MS *m/z*: 334.1 (M<sup>+</sup>). *Anal.* Calcd for C<sub>22</sub>H<sub>22</sub>O<sub>3</sub>: C, 79.02; H, 6.63. Found: C, 79.04; H, 6.62.

**General procedure for the synthesis of compound 10c and 11c** Concentrated H<sub>2</sub>SO<sub>4</sub> (1.0 mL) was added to a solution of caffeic acid **10b** or ferulic acid **11b** in methanol, and the resulting mixture was heated to reflux under N<sub>2</sub> for 12 hours. The mixture was concentrated under reduced pressure to form a residue that was purified by column chromatography to generate compound **10c** or **11c**.

**Synthesis of methyl (E)-3-(3,4-dihydroxyphenyl)acrylate (10c)** From compound **10b** (5.00 g, 27.75 mmol), compound **10c** was obtained (5.20 g, 96.5%). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 9.61 (s, 1H, ArOH), 9.16 (s, 1H, ArOH), 7.46~7.50 (d, 1H, *J*=16.0 Hz, -CH=), 7.05 (s, 1H, ArH), 6.98~7.01 (m, 1H, ArH), 6.74~6.76 (d, 1H, ArH), 6.25~6.29 (d, 1H, *J*=16.0 Hz, -CH=), 3.68 (s, 3H, -OCH<sub>3</sub>). <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>) δ: 51.81, 114.73, 114.98, 116.93, 122.85, 127.69, 143.35, 145.57, 146.11, 166.17. IR (KBr, cm<sup>-1</sup>): 3339, 2946, 2878, 1723, 1624, 1536, 1471, 1368, 1230, 1186, 918, 835. EI-MS *m/z*: 194.0 (M<sup>+</sup>). *Anal.* Calcd for C<sub>10</sub>H<sub>10</sub>O<sub>4</sub>: C, 61.85; H, 5.19. Found: C, 61.86; H, 5.17.

**Synthesis of methyl (E)-3-(4-hydroxy-3-methoxyphenyl)acrylate (11c)** From compound **11b** (6.00 g, 30.90 mmol), compound **11c** was obtained (6.15 g, 95.6%).

**General procedure for the synthesis of compounds 10d and 11d** Compounds **10d** and **11d** were prepared following the procedure that was used to prepare compounds **8c** and **9c**.

**Synthesis of methyl (*E*)-3-[3,4-bis(benzyloxy)phenyl]acrylate (10d)** From compound **10c** (5.20 g, 26.78 mmol), compound **10d** was obtained (9.50 g, 94.7%). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 7.54~7.58 (d, 1H, *J*=16.0 Hz, -CH=), 7.43~7.50 (m, 5H, ArH), 7.36~7.40 (m, 4H, ArH), 7.30~7.33 (m, 2H, ArH), 7.22~7.24 (m, 1H, ArH), 7.06~7.08 (d, 1H, ArH), 6.52~6.56 (d, 1H, *J*=16.0 Hz, -CH=), 5.19 (s, 4H, -CH<sub>2</sub>Ph×2), 3.70 (s, 3H, -OCH<sub>3</sub>). <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>) δ: 51.83, 70.68, 113.52, 114.39, 114.87, 122.16, 126.72, 126.95, 127.37, 128.59, 136.40, 143.29, 148.75, 149.28, 166.19. IR (KBr, cm<sup>-1</sup>): 3013, 2948, 2879, 1727, 1627, 1538, 1471, 1365, 1237, 1188, 1042, 906, 838. EI-MS *m/z*: 374.1 (M<sup>+</sup>). *Calcd* for C<sub>24</sub>H<sub>22</sub>O<sub>4</sub>: C, 76.99; H, 5.92. Found: C, 76.97; H, 5.93.

**Synthesis of methyl (*E*)-3-[4-(benzyloxy)-3-methoxyphenyl]acrylate (11d)** From compound **11c** (6.15 g, 29.54 mmol), compound **11d** was obtained (8.15 g, 92.5%). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 7.57~7.61 (d, 1H, *J*=16.0 Hz, -CH=), 7.37~7.45 (m, 5H, ArH), 7.30~7.35 (m, 1H, ArH), 7.21~7.23 (dd, 1H, ArH), 7.05~7.07 (d, 1H, ArH), 6.55~6.59 (d, 1H, *J*=16.0 Hz, -CH=), 5.13 (s, 2H, -CH<sub>2</sub>Ph), 3.81 (s, 3H, -OCH<sub>3</sub>), 3.70 (s, 3H, -OCH<sub>3</sub>). <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>) δ: 51.81, 56.23, 70.64, 111.12, 114.45, 114.83, 122.11, 126.83, 126.92, 127.31, 128.57, 136.44, 143.31, 145.15, 149.32, 166.23. IR (KBr, cm<sup>-1</sup>): 3019, 2940, 2873, 1725, 1621, 1534, 1473, 1366, 1232, 1183, 1039, 911, 831. EI-MS *m/z*: 298.1 (M<sup>+</sup>). *Anal.* *Calcd* for C<sub>18</sub>H<sub>18</sub>O<sub>4</sub>: C, 72.47; H, 6.08. Found: C, 72.48; H, 6.05.

**General procedure for the synthesis of compounds 10e and 11e** To a suspension of LiAlH<sub>4</sub> (1.50 equivalent) in anhydrous THF, a solution of BnBr (1.50 equivalent) in anhydrous THF was added dropwise at 0°C. After stirring for 30 min at room temperature under N<sub>2</sub>, a solution of compound **10d** or **11d** in anhydrous THF was added dropwise at 0°C. After stirring at 0°C for 2 hours, the mixture was warmed to room temperature and stirred for another 2 hours. When the reactant was completely consumed, the reaction was quenched by the addition of water (1.0 mL per gram of LiAlH<sub>4</sub>), 10% NaOH aqueous solution (2.0 mL per gram of LiAlH<sub>4</sub>), and water (3.0 mL per gram of LiAlH<sub>4</sub>) in sequence. The resulting mixture was filtered and the filtrate was concentrated in vacuo to form a residue that was purified by

column chromatography on silica gel to generate compounds **10e** or **11e**.

**Synthesis of (*E*)-3-[3,4-bis(benzyloxy)phenyl]prop-2-en-1-ol (**10e**)** From compound **10d** (9.50 g, 25.37 mmol), compound **10e** was obtained (7.50 g, 85.3%). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 7.29~7.46 (m, 10H, ArH), 7.16 (d, 1H, ArH), 6.97~6.99 (d, 1H, ArH), 6.88~6.91 (dd, 1H, ArH), 6.40~6.44 (d, 1H, *J*=16.0 Hz, -CH=), 6.20~6.24 (m, 1H, *J*=16.0 Hz, -CH=), 5.11~5.15 (d, 4H, -CH<sub>2</sub>Ph × 2), 4.80~4.83 (t, 1H, -OH), 4.06~4.08 (m, 2H, -OCH<sub>2</sub>-). <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>) δ: 63.19, 70.61, 111.15, 114.41, 119.19, 126.86, 127.21, 127.83, 128.52, 130.43, 131.70, 136.54, 148.64, 149.35. IR (KBr, cm<sup>-1</sup>): 3460, 1609, 1519, 1237, 1046, 986, 915, 823. EI-MS *m/z*: 346.1 (M<sup>+</sup>). *Anal.* Calcd for C<sub>23</sub>H<sub>22</sub>O<sub>3</sub>: C, 79.74; H, 6.40. Found: C, 79.76; H, 6.39.

**Synthesis of (*E*)-3-[4-(benzyloxy)-3-methoxyphenyl]prop-2-en-1-ol (**11e**)** From compound **11d** (8.15 g, 27.32 mmol), compound **11e** was obtained (6.18 g, 83.7%). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 7.30~7.45 (m, 5H, ArH), 7.06 (d, 1H, ArH), 6.95~6.97 (d, 1H, ArH), 6.87~6.89 (dd, 1H, ArH), 6.44~6.48 (d, 1H, *J*=16.0 Hz, -CH=), 6.24~6.28 (d, 1H, *J*=16.0 Hz, -CH=), 5.06 (s, 2H, -CH<sub>2</sub>Ph), 4.81~4.84 (t, 1H, -OH), 4.07~4.10 (m, 2H, -OCH<sub>2</sub>-), 3.78 (s, 3H, -OCH<sub>3</sub>). <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>) δ: 56.20, 63.21, 70.65, 111.16, 114.43, 119.23, 126.88, 127.25, 127.93, 128.60, 130.46, 131.73, 136.52, 145.34, 149.32. IR (KBr, cm<sup>-1</sup>): 3454, 2944, 2878, 1601, 1512, 1477, 1372, 1233, 1041, 981, 918, 816. EI-MS *m/z*: 270.1 (M<sup>+</sup>). *Anal.* Calcd for C<sub>17</sub>H<sub>18</sub>O<sub>3</sub>: C, 75.53; H, 6.71. Found: C, 75.51; H, 6.72.

**Synthesis of methyl 2-hydroxy-4-[(4-methylphenyl)sulfonamido]benzoate (**T1**)** To a solution of compound **4** (500.0 mg, 1.22 mmol) in EtOH (30.0 mL), 10% Pd/C (50.0 mg) was added. After degassing with H<sub>2</sub> for 3 times, the mixture was stirred under H<sub>2</sub> at room temperature for 12 hours. Then, the mixture was filtered through a Celite pad and the filtrate was concentrated in vacuo to give rise to a yellow residue that was purified by column chromatography (petroleum ether/ethyl acetate=5:1) to afford compound **T1** as an off-white solid (340.0 mg, 86.7%). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 10.84 (s, 1H, ArOH), 10.57 (s, 1H, -SO<sub>2</sub>NH-), 7.70~7.72 (d, 2H, ArH), 7.61~7.63 (d, 1H, ArH), 7.37~7.39 (d, 2H, ArH), 6.66~6.69 (m, 2H, ArH), 3.809 (s, 3H, -OCH<sub>3</sub>), 2.33 (s, 3H, ArCH<sub>3</sub>). <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>) δ: 21.40, 51.21, 100.65, 102.47, 108.46, 128.03, 129.08, 131.81, 136.29, 137.20, 143.03, 164.66,

168.92. IR (KBr,  $\text{cm}^{-1}$ ): 3340, 2945, 2877, 1760, 1625, 1536, 1475, 1357, 1289, 1143, 834. EI-MS  $m/z$ : 321.0 ( $\text{M}^+$ ). *Anal.* Calcd for  $\text{C}_{15}\text{H}_{15}\text{NO}_5\text{S}$ : C, 56.07; H, 4.71; N, 4.36; S, 9.98. Found: C, 56.05; H, 4.74; N, 4.35; S, 9.96.

**Synthesis of 2-(benzyloxy)-4-[(4-methylphenyl)sulfonamido]benzamide (19a)** To a solution of compound **5** (500.0 mg, 1.26 mmol) in anhydrous dichloromethane (30.0 mL), oxalyl chloride (1.07 mL, 12.50 mmol) and DMF (3 drops) were added, and the resulting mixture was stirred under  $\text{N}_2$  at room temperature for 2 hours. Subsequently, the volatiles were removed under reduced pressure, and the obtained yellow solid was redissolved in anhydrous dichloromethane (20.0 mL). The resulting solution was added dropwise to ammonium hydroxide 10 mL, and the mixture was stirred under  $\text{N}_2$  at room temperature for 2 hours. The organic solvent was removed and the residue was extracted with EtOAc (30.0 mL  $\times$  3). The combined organic layers were washed with 2.0 M HCl, saturated  $\text{NaHCO}_3$  and brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated in vacuo to give a yellow oil, which was purified by column chromatography (chloroform/ methanol=25:1) on silica gel to afford compound **19a** as a white solid (263.0 mg, 52.3%).

**General procedure for the synthesis of compound 2a-32a (except for compound 19a).** To a solution of compound **5** or compound **7** in anhydrous DMF, alcohol or amine were added (1.10 equivalent), HOBt (1.50 equivalent), EDCI (1.50 equivalent) and NMM (2.00 equivalent). After being degassed 3 times with  $\text{N}_2$ , the resulting mixture was stirred overnight at room temperature under  $\text{N}_2$ . The solvent was evaporated and the residue was redissolved in EtOAc, washed with 2.0 M HCl, saturated  $\text{NaHCO}_3$  and brine, respectively. The organic layer was dried over  $\text{Na}_2\text{SO}_4$  and concentrated in vacuo to give a crude product, which was purified by column chromatography on silica gel to afford compound **2a-32a** (except for compound **19a**).

**General procedure for the synthesis of compounds T2-T32 (except for T6, T17, and T27)** To a solution of compounds **2a-32a** (except for **6a**, **17a** and **27a**) in ethanol, 10% Pd/C was added (10% weight of the reactant). After being degassed 3 times with  $\text{H}_2$ , the resulting mixture was stirred at room temperature under  $\text{H}_2$ . The mixture was filtered through a Celite pad, and the filtrate was concentrated in vacuo to give a crude product, which was purified by

column chromatography on silica gel to afford the corresponding target compounds **T2-T32** (except for **T6**, **T17**, and **T27**).

**Synthesis of ethyl 2-hydroxy-4-[(4-methylphenyl)sulfonamido]benzoate (T2)** From compound **5** (500.0 mg, 1.26 mmol), compound **T2** was obtained (280.0 mg, 67.3%, 2 steps). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 10.83 (s, 1H, ArOH), 10.64 (s, 1H, -SO<sub>2</sub>NH-), 7.70~7.72 (d, 2H, ArH), 7.61~7.64 (d, 1H, ArH), 7.37~7.39 (d, 2H, ArH), 6.65~6.70 (m, 2H, ArH), 4.25~4.30 (q, 2H, -OCH<sub>2</sub>), 2.33 (s, 3H, ArCH<sub>3</sub>), 1.25~1.29 (t, 3H, -CH<sub>3</sub>). <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>) δ: 14.22, 21.39, 60.46, 100.63, 102.44, 108.47, 128.05, 129.09, 131.83, 136.32, 137.24, 143.05, 164.67, 169.22. IR (KBr, cm<sup>-1</sup>): 3336, 2945, 2877, 1758, 1621, 1532, 1472, 1355, 1286, 1143, 830. EI-MS *m/z*: 335.0 (M<sup>+</sup>). *Anal.* Calcd for C<sub>16</sub>H<sub>17</sub>NO<sub>5</sub>S: C, 57.30; H, 5.11; N, 4.18; S, 9.56. Found: C, 57.32; H, 5.09; N, 4.20; S, 9.55.

**Synthesis of *n*-propyl 2-hydroxy-4-[(4-methylphenyl)sulfonamido]benzoate (T3)** From compound **5** (500.0 mg, 1.26 mmol), compound **T3** was obtained (263.0 mg, 60.0%, 2 steps). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 10.84 (s, 1H, ArOH), 10.65 (s, 1H, -SO<sub>2</sub>NH-), 7.71~7.73 (d, 2H, ArH), 7.63~7.65 (d, 1H, ArH), 7.37~7.39 (d, 2H, ArH), 6.66~6.70 (m, 2H, ArH), 4.17~4.20 (q, 2H, -OCH<sub>2</sub>), 2.33 (s, 3H, ArCH<sub>3</sub>), 1.62~1.71 (m, 2H, -CH<sub>2</sub>-), 0.90~0.94 (t, 3H, -CH<sub>3</sub>). <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>) δ: 10.25, 21.35, 21.84, 68.69, 100.61, 102.43, 108.48, 128.07, 129.10, 131.85, 136.35, 137.26, 143.08, 163.82, 164.82. IR (KBr, cm<sup>-1</sup>): 3332, 2943, 2873, 1751, 1620, 1530, 1471, 1353, 1283, 1142, 829. EI-MS *m/z*: 349.1 (M<sup>+</sup>). *Anal.* Calcd for C<sub>17</sub>H<sub>19</sub>NO<sub>5</sub>S: C, 58.44; H, 5.48; N, 4.01; S, 9.18. Found: C, 58.46; H, 5.45; N, 4.03; S, 9.20.

**Synthesis of *i*-propyl 2-hydroxy-4-[(4-methylphenyl)sulfonamido]benzoate (T4)** From compound **5** (500.0 mg, 1.26 mmol), compound **T4** was obtained (245.0 mg, 55.6%, 2 steps). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 10.82 (s, 1H, ArOH), 10.71 (s, 1H, -SO<sub>2</sub>NH-), 7.70~7.72 (d, 2H, ArH), 7.59~7.61 (d, 1H, ArH), 7.37~7.39 (d, 2H, ArH), 6.67~6.70 (m, 1H, ArH), 6.64~6.65 (d, 1H, ArH), 5.08~5.14 (m, 1H, -CH-), 2.33 (s, 3H, ArCH<sub>3</sub>), 1.27~1.28 (d, 6H, -CH<sub>3</sub> × 2). <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>) δ: 21.39, 21.71, 67.10, 100.62, 102.42, 108.46, 128.08, 129.12, 131.84, 136.38, 137.28, 143.07, 164.78, 165.56. IR (KBr, cm<sup>-1</sup>): 3330, 2945, 2876, 1749, 1624, 1532, 1470, 1355, 1281, 1144, 831. EI-MS *m/z*: 349.1 (M<sup>+</sup>). *Anal.* Calcd for C<sub>17</sub>H<sub>19</sub>NO<sub>5</sub>S: C, 58.44; H, 5.48; N, 4.01; S, 9.18. Found: C, 58.42; H, 5.50; N, 4.03; S, 9.15.

**Synthesis of *n*-butyl 2-hydroxy-4-[(4-methylphenyl)sulfonamido]benzoate (T5)** From compound **5** (500.0 mg, 1.26 mmol), compound **T5** was obtained (277.0 mg, 60.4%, 2 steps). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 10.84 (s, 1H, ArOH), 10.65 (s, 1H, -SO<sub>2</sub>NH-), 7.70~7.72 (d, 2H, ArH), 7.61~7.63 (d, 1H, ArH), 7.37~7.39 (d, 2H, ArH), 6.65~6.70 (m, 2H, ArH), 4.21~4.25 (t, 2H, -OCH<sub>2</sub>), 2.33 (s, 3H, ArCH<sub>3</sub>), 1.60~1.67 (m, 2H, -CH<sub>2</sub>-), 1.34~1.35 (m, 2H, -CH<sub>2</sub>-), 0.87~0.91 (t, 3H, -CH<sub>3</sub>). <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>) δ: 13.71, 19.12, 21.41, 31.35, 64.25, 100.60, 102.41, 108.45, 128.06, 129.09, 131.84, 136.34, 137.25, 143.07, 163.80, 164.80. IR (KBr, cm<sup>-1</sup>): 3330, 2947, 2878, 1747, 1616, 1528, 1471, 1354, 1280, 1142, 824. EI-MS *m/z*: 363.1 (M<sup>+</sup>). *Anal.* Calcd for C<sub>18</sub>H<sub>21</sub>NO<sub>5</sub>S: C, 59.49; H, 5.82; N, 3.85; S, 8.82. Found: C, 59.48; H, 5.84; N, 3.83; S, 8.85.

**Synthesis of phenethyl 2-hydroxy-4-[(4-methylphenyl)sulfonamido]benzoate (T7)** From compound **5** (500.0 mg, 1.26 mmol), compound **T7** was obtained (213.0 mg, 41.5%, 2 steps). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 10.84 (s, 1H, ArOH), 10.55 (s, 1H, -SO<sub>2</sub>NH-), 7.70~7.72 (d, 2H, ArH), 7.55~7.57 (d, 1H, ArH), 7.37~7.39 (d, 2H, ArH), 7.28~7.29 (m, 4H, ArH), 7.20~7.21 (m, 1H, ArH), 6.65~6.68 (m, 2H, ArH), 4.41~4.45 (t, 2H, -OCH<sub>2</sub>-), 2.97~3.00 (t, 2H, -CH<sub>2</sub>Ph), 2.33 (s, 3H, ArCH<sub>3</sub>). <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>) δ: 21.41, 34.12, 64.29, 100.66, 102.45, 108.51, 125.53, 127.46, 128.02, 128.34, 129.03, 131.88, 136.39, 137.28, 137.93, 143.11, 163.83, 164.85. IR (KBr, cm<sup>-1</sup>): 3335, 2946, 2875, 1744, 1622, 1533, 1470, 1350, 1278, 1140, 828, 748, 686. EI-MS *m/z*: 411.1 (M<sup>+</sup>). *Anal.* Calcd for C<sub>22</sub>H<sub>21</sub>NO<sub>5</sub>S: C, 64.22; H, 5.14; N, 3.40; S, 7.79. Found: C, 64.25; H, 5.12; N, 3.42; S, 7.76.

**Synthesis of 4-hydroxyphenethyl 2-hydroxy-4-[(4-methylphenyl)sulfonamido]benzoate (T8)** From compound **5** (500.0 mg, 1.26 mmol), compound **T8** was obtained (223.0 mg, 41.8%, 2 steps). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 10.83 (s, 1H, ArOH), 10.57 (s, 1H, -SO<sub>2</sub>NH-), 9.22 (s, 1H, ArOH), 7.70~7.72 (d, 2H, ArH), 7.57~7.59 (d, 1H, ArH), 7.37~7.39 (d, 2H, ArH), 7.05~7.07 (d, 2H, ArH), 6.64~6.69 (m, 4H, ArH), 4.33~4.37 (t, 2H, -OCH<sub>2</sub>-), 2.84~2.88 (t, 2H, -CH<sub>2</sub>Ph), 2.33 (s, 3H, ArCH<sub>3</sub>). <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>) δ: 21.40, 34.14, 64.32, 100.67, 102.47, 108.52, 115.58, 128.04, 129.05, 129.96, 130.53, 131.91, 136.37, 137.26, 143.13, 155.41, 163.86, 164.87. IR (KBr, cm<sup>-1</sup>): 3340, 2948, 2876, 1742, 1619, 1532, 1469, 1348, 1275, 1140, 828. EI-MS *m/z*: 427.1 (M<sup>+</sup>). *Anal.*



Calcd for C<sub>22</sub>H<sub>21</sub>NO<sub>6</sub>S: C, 61.82; H, 4.95; N, 3.28; S, 7.50. Found: C, 61.83; H, 4.94; N, 3.26; S, 7.53.

**Synthesis of 3,4-dihydroxyphenethyl 2-hydroxy-4-[(4-methylphenyl)sulfonamido]benzoate (T9)** From compound **5** (500.0 mg, 1.26 mmol), compound **T9** was obtained (237.0 mg, 43.0%, 2 steps). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 10.83 (s, 1H, ArOH), 10.57 (s, 1H, -SO<sub>2</sub>NH-), 8.78 (s, 1H, ArOH), 8.70 (s, 1H, ArOH), 7.70~7.72 (d, 2H, ArH), 7.58~7.60 (d, 1H, ArH), 7.37~7.39 (d, 2H, ArH), 6.61~6.69 (m, 4H, ArH), 4.48~4.51 (dd, 1H, ArH), 4.31~4.35 (t, 2H, -OCH<sub>2</sub>-), 2.78~2.81 (t, 2H, -CH<sub>2</sub>Ph), 2.34 (s, 3H, ArCH<sub>3</sub>). <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>) δ: 21.42, 34.22, 64.36, 100.68, 102.48, 108.54, 115.61, 116.18, 122.46, 128.06, 129.07, 131.11, 131.94, 136.39, 137.28, 143.18, 144.13, 145.29, 163.88, 164.89. IR (KBr, cm<sup>-1</sup>): 3342, 2945, 2871, 1745, 1626, 1537, 1472, 1347, 1279, 1138, 830. EI-MS *m/z*: 443.1 (M<sup>+</sup>). *Anal.* Calcd for C<sub>22</sub>H<sub>21</sub>NO<sub>7</sub>S: C, 59.59; H, 4.77; N, 3.16; S, 7.23. Found: C, 59.61; H, 4.74; N, 3.14; S, 7.25.

**Synthesis of 3-(3,4-dihydroxyphenyl)propyl 2-hydroxy-4-[(4-methylphenyl)sulfonamido]benzoate (T10)** From compound **5** (521.0 mg, 1.31 mmol), compound **T10** was obtained (185.1 mg, 28.7%, 2 steps). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 10.87 (s, 1H, ArOH), 10.64 (s, 1H, -SO<sub>2</sub>NH-), 8.76 (s, 1H, ArOH), 8.68 (s, 1H, ArOH), 7.71~7.73 (d, 2H, ArH), 7.61~7.65 (d, 1H, ArH), 7.38~7.40 (d, 2H, ArH), 6.68~6.71 (m, 1H, ArH), 6.65~6.66 (d, 1H, ArH), 6.60~6.62 (d, 1H, ArH), 6.57~6.58 (m, 1H, ArH), 6.42~6.44 (dd, 1H, ArH), 4.17~4.20 (t, 2H, -OCH<sub>2</sub>-), 3.34~3.35 (t, 2H, -CH<sub>2</sub>Ar), 2.34 (s, 3H, ArCH<sub>3</sub>), 1.87~1.90 (m, 2H, -CH<sub>2</sub>-). <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>) δ: 21.37, 29.85, 32.58, 64.24, 100.67, 102.46, 108.55, 115.83, 116.38, 119.89, 128.06, 129.08, 131.89, 134.67, 136.34, 137.20, 143.03, 144.23, 145.45, 163.78, 164.75. IR (KBr, cm<sup>-1</sup>): 3340, 2946, 2873, 1750, 1622, 1534, 1474, 1348, 1282, 1140, 828. EI-MS *m/z*: 457.1 (M<sup>+</sup>). *Anal.* Calcd for C<sub>23</sub>H<sub>23</sub>NO<sub>7</sub>S: C, 60.38; H, 5.07; N, 3.06; S, 7.01. Found: C, 60.36; H, 5.09; N, 3.08; S, 7.00.

**Synthesis of 3-(4-hydroxy-3-methoxyphenyl)propyl 2-hydroxy-4-[(4-methylphenyl)sulfonamido]benzoate (T11)** From compound **5** (500.0 mg, 1.26 mmol), compound **T11** was obtained (164.2 mg, 28.1%, 2 steps). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 10.87 (s, 1H, ArOH), 10.64 (s, 1H, -SO<sub>2</sub>NH-), 8.73 (s, 1H, ArOH), 7.71~7.73 (d, 2H, ArH), 7.64~7.66 (d, 1H, ArH), 7.38~7.40 (d, 2H, ArH), 6.75~6.76 (d, 1H, ArH), 6.65~6.71 (m, 3H, ArH), 6.57~6.59 (dd, 1H,

ArH), 4.19~4.22 (t, 2H, -OCH<sub>2</sub>-), 3.70 (s, 3H, -OCH<sub>3</sub>), 2.56~2.60 (t, 2H, -CH<sub>2</sub>Ar), 2.34 (s, 3H, ArCH<sub>3</sub>), 1.90~1.99 (m, 2H, -CH<sub>2</sub>-). <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>) δ: 21.40, 29.82, 32.56, 56.20, 64.21, 100.65, 102.45, 108.52, 113.21, 115.28, 119.66, 128.09, 129.10, 131.85, 134.48, 136.35, 137.22, 143.08, 145.63, 147.35, 163.82, 164.78. IR (KBr, cm<sup>-1</sup>): 3342, 2949, 2875, 1747, 1620, 1530, 1476, 1347, 1277, 1141, 827. EI-MS *m/z*: 471.1 (M<sup>+</sup>). *Anal.* Calcd for C<sub>24</sub>H<sub>25</sub>NO<sub>7</sub>S: C, 61.13; H, 5.34; N, 2.97; S, 6.80. Found: C, 61.15; H, 5.32; N, 2.96; S, 6.82.

**Synthesis of 2-hydroxyethyl 2-hydroxy-4-[(4-methylphenyl)sulfonamido]benzoate (T12)** From compound **5** (500.0 mg, 1.26 mmol), compound **T12** was obtained (263.1 mg, 59.4%, 2 steps). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 10.83 (s, 1H, ArOH), 10.59 (s, 1H, -SO<sub>2</sub>NH-), 7.68~7.72 (t, 3H, ArH), 7.37~7.39 (d, 2H, ArH), 6.68~6.70 (dd, 1H, ArH), 6.65~6.66 (d, 1H, ArH), 4.90~4.93 (t, 1H, -OH), 4.23~4.26 (t, 2H, -OCH<sub>2</sub>-), 3.63~3.67 (q, 2H, -CH<sub>2</sub>O-), 2.33 (s, 3H, ArCH<sub>3</sub>). <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>) δ: 21.38, 60.76, 67.13, 100.58, 102.40, 108.43, 128.03, 129.06, 131.77, 136.30, 137.21, 142.99, 163.84, 164.65. IR (KBr, cm<sup>-1</sup>): 3358, 2951, 2876, 1750, 1624, 1536, 1475, 1350, 1252, 1143, 1046, 830. EI-MS *m/z*: 351.0 (M<sup>+</sup>). *Anal.* Calcd for C<sub>16</sub>H<sub>17</sub>NO<sub>6</sub>S: C, 54.69; H, 4.88; N, 3.99; S, 9.12. Found: C, 54.67; H, 4.89; N, 3.97; S, 9.15.

**Synthesis of 3-hydroxypropyl 2-hydroxy-4-[(4-methylphenyl)sulfonamido]benzoate (T13)** From compound **5** (500.1 mg, 1.26 mmol), compound **T13** was obtained (276.2 mg, 60.8%, 2 steps). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 10.83 (s, 1H, ArOH), 10.61 (s, 1H, -SO<sub>2</sub>NH-), 7.70~7.72 (d, 2H, ArH), 7.62~7.64 (d, 1H, ArH), 7.37~7.39 (d, 2H, ArH), 6.67~6.70 (dd, 1H, ArH), 6.65~6.66 (d, 1H, ArH), 4.58~4.60 (t, 1H, -OH), 4.28~4.31 (t, 2H, -OCH<sub>2</sub>-), 3.48~3.52 (q, 2H, -CH<sub>2</sub>O-), 2.33 (s, 3H, ArCH<sub>3</sub>), 1.79~1.83 (m, 2H, -CH<sub>2</sub>-). <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>) δ: 21.41, 31.24, 58.57, 59.98, 100.61, 102.42, 108.47, 128.05, 129.09, 131.82, 136.34, 137.26, 143.07, 163.75, 164.70. IR (KBr, cm<sup>-1</sup>): 3355, 2952, 2877, 1754, 1626, 1539, 1477, 1352, 1253, 1146, 1045, 832. EI-MS *m/z*: 365.0 (M<sup>+</sup>). *Anal.* Calcd for C<sub>17</sub>H<sub>19</sub>NO<sub>6</sub>S: C, 55.88; H, 5.24; N, 3.83; S, 8.77. Found: C, 55.87; H, 5.26; N, 3.84; S, 8.75.

**Synthesis of 4-hydroxybutyl 2-hydroxy-4-[(4-methylphenyl)sulfonamido]benzoate (T14)** From compound **5** (500.0 mg, 1.26 mmol), compound **T14** was obtained (280.9 mg, 58.9%, 2 steps). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 10.84 (s, 1H, ArOH), 10.64 (s, 1H, -SO<sub>2</sub>NH-),

7.70~7.72 (d, 2H, ArH), 7.62~7.64 (d, 1H, ArH), 7.37~7.39 (d, 2H, ArH), 6.67~6.70 (dd, 1H, ArH), 6.65~6.66 (d, 1H, ArH), 4.43~4.46 (t, 1H, -OH), 4.23~4.26 (t, 2H, -OCH<sub>2</sub>-), 3.39~3.43 (q, 2H, -CH<sub>2</sub>O-), 2.33 (s, 3H, ArCH<sub>3</sub>), 1.67~1.71 (m, 2H, -CH<sub>2</sub>-), 1.47~1.51 (m, 2H, -CH<sub>2</sub>-). <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>) δ: 21.39, 25.27, 28.76, 62.84, 65.23, 100.65, 102.46, 108.50, 128.07, 129.10, 131.85, 136.36, 137.29, 143.13, 163.67, 164.76. IR (KBr, cm<sup>-1</sup>): 3358, 2952, 2875, 1757, 1627, 1537, 1476, 1353, 1256, 1146, 1046, 833. EI-MS *m/z*: 379.1 (M<sup>+</sup>). *Anal.* Calcd for C<sub>18</sub>H<sub>21</sub>NO<sub>6</sub>S: C, 56.98; H, 5.58; N, 3.69; S, 8.45. Found: C, 56.99; H, 5.56; N, 3.67; S, 8.48.

#### **Synthesis of 2,3-dihydroxypropyl 2-hydroxy-4-[(4-methylphenyl)sulfonamido]**

**benzoate (T15)** From compound **5** (500.0 mg, 1.26 mmol), compound **T15** was obtained (158.1 mg, 33.0%, 2 steps). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 10.82 (s, 1H, ArOH), 10.56 (s, 1H, -SO<sub>2</sub>NH-), 7.68~7.72 (m, 3H, ArH), 7.37~7.39 (d, 2H, ArH), 6.65~6.70 (dd, 1H, ArH), 6.65~6.66 (d, 1H, ArH), 5.02~5.04 (d, 1H, -OH), 4.70~4.73 (t, 1H, -OH), 4.25~4.29 (dd, 1H, -CH<sub>2</sub>O-), 4.11~4.16 (dd, 1H, -CH<sub>2</sub>O-), 3.70 ~3.77 (m, 1H, -OCH-), 3.37~3.45 (m, 2H, -OCH<sub>2</sub>-), 2.33 (s, 3H, ArCH<sub>3</sub>). <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>) δ: 21.41, 64.16, 66.07, 70.64, 100.69, 102.49, 108.56, 128.09, 129.13, 131.90, 136.38, 137.31, 143.18, 163.61, 164.80. IR (KBr, cm<sup>-1</sup>): 3341, 2950, 2874, 1751, 1622, 1532, 1475, 1350, 1250, 1142, 1043, 828. EI-MS *m/z*: 381.0 (M<sup>+</sup>). *Anal.* Calcd for C<sub>17</sub>H<sub>19</sub>NO<sub>7</sub>S: C, 53.54; H, 5.02; N, 3.67; S, 8.41. Found: C, 53.55; H, 5.01; N, 3.64; S, 8.43.

#### **Synthesis of 6-hydroxyhexyl 2-hydroxy-4-[(4-methylphenyl)sulfonamido]benzoate**

**(T16)** From compound **5** (500.0 mg, 1.26 mmol), compound **T16** was obtained (480.1 mg, 64.6%, 2 steps). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 10.84 (s, 1H, ArOH), 10.64 (s, 1H, -SO<sub>2</sub>NH-), 7.70~7.72 (d, 2H, ArH), 7.61~7.63 (d, 1H, ArH), 7.37~7.39 (d, 2H, ArH), 6.67~6.70 (dd, 1H, ArH), 6.65~6.66 (d, 1H, ArH), 4.34~4.36 (t, 1H, -OH), 4.20~4.24 (t, 2H, -OCH<sub>2</sub>-), 3.37~3.38 (m, 2H, -CH<sub>2</sub>O-), 2.33 (s, 3H, ArCH<sub>3</sub>), 1.63~1.67 (m, 2H, -CH<sub>2</sub>-), 1.28~1.42 (m, 6H, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-). <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>) δ: 21.38, 25.58, 26.16, 32.07, 32.64, 63.19, 65.27, 100.68, 102.49, 108.54, 128.09, 129.11, 131.90, 136.42, 137.33, 143.17, 163.61, 164.70. IR (KBr, cm<sup>-1</sup>): 3356, 2953, 2875, 1758, 1629, 1538, 1478, 1353, 1258, 1147, 1045, 835. EI-MS *m/z*: 407.1 (M<sup>+</sup>). *Anal.* Calcd for C<sub>20</sub>H<sub>25</sub>NO<sub>6</sub>S: C, 58.95; H, 6.18; N, 3.44; S, 7.87.

Found: C, 58.93; H, 6.20; N, 3.45; S, 7.85.

**Synthesis of 2-(dimethylamino)ethyl 2-hydroxy-4-[(4-methylphenyl)sulfonamido]benzoate (T18)** From compound **5** (500.0 mg, 1.26 mmol), compound **T18** was obtained (202.1 mg, 42.3%, 2 steps). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 7.70~7.72 (d, 2H, ArH), 7.60~7.62 (d, 1H, ArH), 7.37~7.39 (d, 2H, ArH), 6.64~6.69 (m, 2H, ArH), 4.32~4.35 (t, 2H, -OCH<sub>2</sub>-), 2.62~2.65 (t, 2H, -NCH<sub>2</sub>-), 2.34 (s, 3H, ArCH<sub>3</sub>), 2.23 (s, 6H, -N(CH<sub>3</sub>)<sub>2</sub>). <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>) δ: 21.39, 46.89, 61.57, 63.03, 100.66, 102.48, 108.52, 128.07, 129.09, 131.87, 136.39, 137.26, 143.11, 163.55, 164.71. IR (KBr, cm<sup>-1</sup>): 3340, 2950, 2874, 1744, 1621, 1533, 1473, 1345, 1247, 1180, 827. EI-MS *m/z*: 378.1 (M<sup>+</sup>). *Anal.* Calcd for C<sub>18</sub>H<sub>22</sub>N<sub>2</sub>O<sub>5</sub>S: C, 57.13; H, 5.86; N, 7.40; S, 8.47. Found: C, 57.15; H, 5.84; N, 7.43; S, 8.45.

**Synthesis of 2-hydroxy-4-[(4-methylphenyl)sulfonamido]benzamide (T19)** From compound **19a** (260.1 mg, 0.66 mmol), compound **T19** was obtained (145.2 mg, 71.7%). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 13.15 (s, 1H, ArOH), 10.63 (s, 1H, -SO<sub>2</sub>NH-), 8.19 (s, 1H, -NH<sub>2</sub>), 7.75 (s, 1H, -NH<sub>2</sub>), 7.69~7.71 (d, 2H, ArH), 7.64~7.66 (d, 1H, ArH), 7.36~7.38 (d, 2H, ArH), 6.55~6.58 (m, 2H, ArH), 2.33 (s, 3H, ArCH<sub>3</sub>). <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>) δ: 21.10, 100.65, 105.13, 108.34, 127.48, 128.02, 128.91, 135.75, 136.67, 141.78, 159.38, 171.24. IR (KBr, cm<sup>-1</sup>): 3348, 3195, 2948, 2872, 1652, 1530, 1470, 1341, 1136, 825. EI-MS *m/z*: 306.0 (M<sup>+</sup>). *Anal.* Calcd for C<sub>14</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub>S: C, 54.89; H, 4.61; N, 9.14; S, 10.47. Found: C, 54.87; H, 4.63; N, 9.16; S, 10.45.

**Synthesis of 2-hydroxy-N-methyl-4-[(4-methylphenyl)sulfonamido]benzamide (T20)** From compound **5** (500.0 mg, 1.26 mmol), compound **T20** was obtained (193.0 mg, 47.8%, 2 steps). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 12.84 (s, 1H, ArOH), 10.62 (s, 1H, -SO<sub>2</sub>NH-), 8.58~8.62 (q, 1H, -NH-), 7.68~7.70 (d, 2H, ArH), 7.61~7.64 (d, 1H, ArH), 7.36~7.38 (d, 2H, ArH), 6.59 (s, 2H, ArH), 2.74~2.75 (d, 3H, -NHCH<sub>3</sub>), 2.33 (s, 3H, ArCH<sub>3</sub>). <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>) δ: 21.08, 27.23, 100.55, 104.94, 108.20, 127.39, 127.91, 128.72, 135.70, 136.61, 141.59, 159.24, 166.87. IR (KBr, cm<sup>-1</sup>): 3309, 2946, 2870, 1646, 1548, 1467, 1340, 1134, 823. EI-MS *m/z*: 320.0 (M<sup>+</sup>). *Anal.* Calcd for C<sub>15</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>S: C, 56.24; H, 5.03; N, 8.74; S, 10.01. Found: C, 56.25; H, 5.01; N, 8.72; S, 10.03.

**Synthesis of 2-hydroxy-N,N-dimethyl-4-[(4-methylphenyl)sulfonamido]benzamide (T21)** From compound **5** (500.0 mg, 1.26 mmol), compound **T21** was obtained (240.0 mg, 57.1%, 2 steps). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 10.31 (s, 1H, -SO<sub>2</sub>NH-), 9.93 (s, 1H, ArOH), 7.66~7.68 (d, 2H, ArH), 7.35~7.37 (d, 2H, ArH), 6.92~6.95 (d, 1H, ArH), 6.71~6.72 (d, 1H, ArH), 6.53~6.55 (dd, 1H, ArH), 2.81 (s, 6H, -N(CH<sub>3</sub>)<sub>2</sub>), 2.34 (s, 3H, ArCH<sub>3</sub>). <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>) δ: 21.09, 37.96, 100.27, 108.23, 109.98, 127.34, 127.88, 128.45, 135.63, 136.52, 139.84, 158.77, 170.93. IR (KBr, cm<sup>-1</sup>): 3306, 2944, 2869, 1652, 1610, 1525, 1466, 1338, 1132, 820. EI-MS *m/z*: 334.1 (M<sup>+</sup>). *Anal.* Calcd for C<sub>16</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>S: C, 57.47; H, 5.43; N, 8.38; S, 9.59. Found: C, 57.45; H, 5.44; N, 8.37; S, 9.61.

**Synthesis of N-ethyl-2-hydroxy-4-[(4-methylphenyl)sulfonamido]benzamide (T22)** From compound **5** (500.0 mg, 1.26 mmol), compound **T22** was obtained (190.1 mg, 45.1%, 2 steps). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 12.90 (s, 1H, ArOH), 10.63 (s, 1H, -SO<sub>2</sub>NH-), 8.62~8.65 (t, 1H, -NH-), 7.65~7.71 (m, 3H, ArH), 7.36~7.38 (d, 2H, ArH), 6.59~6.61 (m, 2H, ArH), 3.24~3.29 (m, 2H, -NCH<sub>2</sub>-), 2.33 (s, 3H, ArCH<sub>3</sub>), 1.07-1.08 (t, 3H, -CH<sub>3</sub>). <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>) δ: 15.61, 21.10, 35.09, 100.73, 105.36, 108.55, 127.43, 127.98, 128.97, 135.75, 136.69, 141.70, 159.43, 165.74. IR (KBr, cm<sup>-1</sup>): 3307, 2945, 2868, 1642, 1607, 1544, 1466, 1338, 1131, 820. EI-MS *m/z*: 334.1 (M<sup>+</sup>). *Anal.* Calcd for C<sub>16</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>S: C, 57.47; H, 5.43; N, 8.38; S, 9.59. Found: C, 57.48; H, 5.41; N, 8.40; S, 9.56.

**Synthesis of N,N-diethyl-2-hydroxy-4-[(4-methylphenyl)sulfonamido]benzamide (T23)** From compound **5** (500.0 mg, 1.26 mmol), compound **T23** was obtained (176.0 mg, 38.6%, 2 steps). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 10.24 (s, 1H, -SO<sub>2</sub>NH-), 9.79 (s, 1H, ArOH), 7.64~7.66 (d, 2H, ArH), 7.34~7.36 (d, 2H, ArH), 6.86~6.88 (d, 1H, ArH), 6.70~6.71 (d, 1H, ArH), 6.51~6.53 (dd, 1H, ArH), 3.09 (bs, 4H, -N(CH<sub>2</sub>)<sub>2</sub>-), 2.33 (s, 3H, ArCH<sub>3</sub>), 0.98 (s, 6H, -CH<sub>3</sub>×2). <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>) δ: 12.95, 21.12, 45.37, 100.13, 108.36, 107.84, 127.41, 128.27, 129.07, 135.71, 136.59, 137.91, 158.28, 166.88. IR (KBr, cm<sup>-1</sup>): 3304, 2942, 2866, 1648, 1607, 1521, 1464, 1332, 1127, 816. EI-MS *m/z*: 362.1 (M<sup>+</sup>). *Anal.* Calcd for C<sub>18</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub>S: C, 59.65; H, 6.12; N, 7.73; S, 8.85. Found: C, 59.67; H, 6.10; N, 7.71; S, 8.88.

**Synthesis of 2-hydroxy-4-[(4-methylphenyl)sulfonamido]-N-(n-propyl)benzamide (T24)** From compound **5** (500.0 mg, 1.26 mmol), compound **T24** was obtained (414.1 mg,

93.3%, 2 steps).  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 12.87 (s, 1H, ArOH), 10.63 (s, 1H,  $-\text{SO}_2\text{NH}-$ ), 8.64~8.67 (t, 1H,  $-\text{NH}-$ ), 7.68~7.70 (m, 3H, ArH), 7.35~7.38 (d, 2H, ArH), 6.58~6.60 (m, 2H, ArH), 3.15~3.20 (q, 2H,  $-\text{NCH}_2-$ ), 2.33 (s, 3H, ArCH $_3$ ), 1.46~1.51 (m, 2H,  $-\text{CH}_2-$ ), 0.82~0.86 (t, 3H,  $-\text{CH}_3$ ).  $^{13}\text{C-NMR}$  (DMSO- $d_6$ )  $\delta$ : 11.54, 21.07, 23.67, 42.13, 100.59, 105.18, 108.38, 127.31, 127.85, 128.79, 135.67, 136.62, 141.48, 159.29, 165.42. IR (KBr,  $\text{cm}^{-1}$ ): 3305, 2944, 2866, 1640, 1606, 1542, 1465, 1336, 1130, 820. EI-MS  $m/z$ : 348.1 ( $\text{M}^+$ ). *Anal.* Calcd for  $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_4\text{S}$ : C, 58.60; H, 5.79; N, 8.04; S, 9.20. Found: C, 58.59; H, 5.81; N, 8.06; S, 9.18.

#### **Synthesis of N-(*n*-butyl)-2-hydroxy-4-[(4-methylphenyl)sulfonamido]benzamide (T25)**

From compound **5** (500.0 mg, 1.26 mmol), compound **T25** was obtained (185.2 mg, 40.7%, 2 steps).  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 12.86 (s, 1H, ArOH), 10.60 (s, 1H,  $-\text{SO}_2\text{NH}-$ ), 8.58~8.60 (t, 1H,  $-\text{NH}-$ ), 7.64~7.70 (m, 3H, ArH), 7.35~7.38 (d, 2H, ArH), 6.57~6.60 (m, 2H, ArH), 3.21~3.22 (q, 2H,  $-\text{NCH}_2-$ ), 2.33 (s, 3H, ArCH $_3$ ), 1.44~1.48 (m, 2H,  $-\text{CH}_2-$ ), 1.25~1.30 (m, 2H,  $-\text{CH}_2-$ ), 0.84~0.88 (t, 3H,  $-\text{CH}_3$ ).  $^{13}\text{C-NMR}$  (DMSO- $d_6$ )  $\delta$ : 14.02, 20.04, 21.11, 32.48, 39.76, 100.50, 105.12, 108.29, 127.26, 127.81, 128.67, 135.61, 136.49, 141.41, 159.17, 165.33. IR (KBr,  $\text{cm}^{-1}$ ): 3306, 2943, 2866, 1638, 1603, 1540, 1463, 1336, 1131, 818. EI-MS  $m/z$ : 362.1 ( $\text{M}^+$ ). *Anal.* Calcd for  $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_4\text{S}$ : C, 59.65; H, 6.12; N, 7.73; S, 8.85. Found: C, 59.67; H, 6.11; N, 7.71; S, 8.86.

#### **Synthesis of 2-hydroxy-4-[(4-methylphenyl)sulfonamido]-N-phenylbenzamide (T26)**

From compound **5** (500.0 mg, 1.26 mmol), compound **T26** was obtained (170.1 mg, 35.4%, 2 steps).  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 12.01 (s, 1H, ArOH), 10.69 (s, 1H,  $-\text{SO}_2\text{NH}-$ ), 10.18 (s, 1H,  $-\text{NHPh}$ ), 7.80~7.82 (d, 1H, ArH), 7.71~7.73 (d, 2H, ArH), 7.61~7.63 (d, 2H, ArH), 7.32~7.39 (m, 4H, ArH), 7.09~7.12 (m, 1H, ArH), 6.74~6.75 (d, 1H, ArH), 6.66~6.69 (dd, 1H, ArH), 2.34 (s, 3H, ArCH $_3$ ).  $^{13}\text{C-NMR}$  (DMSO- $d_6$ )  $\delta$ : 21.07, 100.33, 108.17, 109.46, 121.83, 127.20, 128.17, 128.29, 128.61, 129.16, 135.53, 136.44, 138.17, 141.19, 158.98, 161.83. IR (KBr,  $\text{cm}^{-1}$ ): 3315, 2949, 2873, 1648, 1613, 1551, 1471, 1343, 1136, 825, 755, 690. EI-MS  $m/z$ : 382.1 ( $\text{M}^+$ ). *Anal.* Calcd for  $\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}_4\text{S}$ : C, 62.81; H, 4.74; N, 7.33; S, 8.38. Found: C, 62.80; H, 4.76; N, 7.35; S, 8.36.

#### **Synthesis of 2-hydroxy-N-(4-methoxyphenyl)-4-[(4-methylphenyl)sulfonamido]**

**benzamide (T28)** From compound **5** (500.0 mg, 1.26 mmol), compound **T28** was obtained

(224.0 mg, 43.2%, 2 steps).  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 12.20 (s, 1H, ArOH), 10.67 (s, 1H, -SO<sub>2</sub>NH-), 10.09 (s, 1H, -NHAr), 7.80~7.82 (d, 1H, ArH), 7.71~7.73 (d, 2H, ArH), 7.50~7.53 (d, 2H, ArH), 7.37~7.39 (d, 2H, ArH), 6.90~6.92 (d, 2H, ArH), 6.65~6.71 (m, 2H, ArH), 3.73 (s, 3H, -OCH<sub>3</sub>), 2.34 (s, 3H, ArCH<sub>3</sub>).  $^{13}\text{C-NMR}$  (DMSO- $d_6$ )  $\delta$ : 21.14, 56.02, 100.25, 108.10, 109.30, 113.96, 122.01, 127.24, 128.36, 128.76, 128.95, 135.59, 136.57, 141.03, 158.47, 158.79, 161.53. IR (KBr,  $\text{cm}^{-1}$ ): 3317, 2950, 2874, 1651, 1616, 1555, 1448, 1344, 1138, 828. EI-MS  $m/z$ : 412.1 ( $\text{M}^+$ ). *Anal.* Calcd for C<sub>21</sub>H<sub>20</sub>N<sub>2</sub>O<sub>5</sub>S: C, 61.15; H, 4.89; N, 6.79; S, 7.77. Found: C, 61.17; H, 4.88; N, 6.81; S, 7.75.

#### **Synthesis of 2-hydroxy-N-(2-hydroxyethyl)-4-[(4-methylphenyl)sulfonamido]**

**benzamide (T29)** From compound **5** (500.0 mg, 1.26 mmol), compound **T29** was obtained (187.0 mg, 33.8%, 2 steps).  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 12.70 (s, 1H, ArOH), 10.61 (s, 1H, -SO<sub>2</sub>NH-), 8.60~8.63 (t, 1H, -NH-), 7.68~7.70 (d, 3H, ArH), 7.36~7.38 (d, 2H, ArH), 6.58~6.62 (m, 2H, ArH), 4.75~4.78 (t, 1H, -OH), 3.45~3.49 (q, 2H, -OCH<sub>2</sub>-), 3.27~3.32 (m, 2H, -NCH<sub>2</sub>-), 2.34 (s, 3H, ArCH<sub>3</sub>).  $^{13}\text{C-NMR}$  (DMSO- $d_6$ )  $\delta$ : 21.11, 41.85, 61.47, 100.86, 105.51, 108.67, 127.46, 128.13, 129.20, 135.81, 136.77, 141.83, 159.62, 165.98. IR (KBr,  $\text{cm}^{-1}$ ): 3350, 2946, 2870, 1645, 1609, 1546, 1469, 1340, 1132, 1038, 823. EI-MS  $m/z$ : 350.0 ( $\text{M}^+$ ). *Anal.* Calcd for C<sub>16</sub>H<sub>18</sub>N<sub>2</sub>O<sub>5</sub>S: C, 54.85; H, 5.18; N, 8.00; S, 9.15. Found: C, 54.83; H, 5.19; N, 8.02; S, 9.14.

#### **Synthesis of 2-hydroxy-N-(2-hydroxyethyl)-N-methyl-4-[(4-methylphenyl)**

**sulfonamido]benzamide (T30)** From compound **5** (500.0 mg, 1.26 mmol), compound **T30** was obtained (115.0 mg, 25.0%, 2 steps).  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 10.27 (s, 1H, -SO<sub>2</sub>NH-), 9.86 (s, 1H, ArOH), 7.65~7.67 (d, 2H, ArH), 7.34~7.36 (d, 2H, ArH), 6.91~6.93 (d, 1H, ArH), 6.69~6.70 (d, 1H, ArH), 6.51~6.54 (dd, 1H, ArH), 4.66~4.68 (t, 1H, -OH), 3.41~3.44 (m, 2H, -OCH<sub>2</sub>-), 3.19~3.25 (m, 2H, -NCH<sub>2</sub>-), 2.84 (s, 3H, -NCH<sub>3</sub>), 2.33 (s, 3H, ArCH<sub>3</sub>).  $^{13}\text{C-NMR}$  (DMSO- $d_6$ )  $\delta$ : 21.07, 35.87, 54.98, 59.14, 100.32, 108.26, 110.14, 127.41, 128.11, 129.03, 135.74, 136.75, 139.19, 159.37, 170.16. IR (KBr,  $\text{cm}^{-1}$ ): 3348, 2943, 2868, 1650, 1608, 1525, 1467, 1328, 1130, 1035, 820. EI-MS  $m/z$ : 364.1 ( $\text{M}^+$ ). *Anal.* Calcd for C<sub>17</sub>H<sub>20</sub>N<sub>2</sub>O<sub>5</sub>S: C, 56.03; H, 5.53; N, 7.69; S, 8.80. Found: C, 56.05; H, 5.51; N, 7.67; S, 8.82.

**Synthesis of 4-hydroxyphenethyl 4-acetamido-2-hydroxybenzoate (T31)** From compound **7** (500.0 mg, 1.75 mmol), compound **T31** was obtained (214.0 mg, 39.0%, 2 steps). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 10.62 (s, 1H, ArOH), 10.24 (s, 1H, -CONH-), 9.24 (s, 1H, ArOH), 7.66~7.68 (d, 1H, ArH), 7.37 (s, 1H, ArH), 7.04~7.11 (m, 3H, ArH), 6.68~6.70 (d, 2H, ArH), 4.39~4.42 (t, 2H, -OCH<sub>2</sub>-), 2.89~2.92 (t, 2H, -CH<sub>2</sub>Ar), 2.07 (s, 3H, CH<sub>3</sub>CO-). <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>) δ: 24.51, 34.87, 64.61, 106.84, 109.07, 114.63, 116.16, 130.35, 131.11, 132.08, 144.73, 156.02, 164.83, 165.15, 170.22. IR (KBr, cm<sup>-1</sup>): 3330, 2917, 2850, 1728, 1690, 1606, 1518, 1465, 1370, 1262, 836. EI-MS *m/z*: 315.1 (M<sup>+</sup>). *Anal.* Calcd for C<sub>17</sub>H<sub>17</sub>NO<sub>5</sub>: C, 64.75; H, 5.43; N, 4.44. Found: C, 64.77; H, 5.42; N, 4.46.

**Synthesis of 3,4-dihydroxyphenethyl 4-acetamido-2-hydroxybenzoate (T32)** From compound **7** (500.0 mg, 1.75 mmol), compound **T32** was obtained (188.0 mg, 32.7%, 2 steps). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 10.61 (s, 1H, ArOH), 10.24 (s, 1H, -CONH-), 8.81 (s, 1H, ArOH), 8.72 (s, 1H, ArOH), 7.66~7.68 (d, 1H, ArH), 7.36~7.37 (d, 1H, ArH), 7.03~7.06 (dd, 1H, ArH), 6.67~6.68 (d, 1H, ArH), 6.63~6.65 (d, 1H, ArH), 6.51~6.54 (dd, 1H, ArH), 4.36~4.39 (t, 2H, -OCH<sub>2</sub>-), 2.82~2.85 (t, 2H, -CH<sub>2</sub>Ar), 2.06 (s, 3H, CH<sub>3</sub>CO-). <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>) δ: 24.45, 35.22, 64.65, 106.71, 108.89, 114.49, 116.30, 116.78, 123.18, 131.83, 132.08, 144.60, 145.11, 146.06, 164.69, 165.01, 170.13. IR (KBr, cm<sup>-1</sup>): 3334, 2944, 2875, 1731, 1692, 1607, 1521, 1466, 1264, 839. EI-MS *m/z*: 331.1 (M<sup>+</sup>). *Anal.* Calcd for C<sub>17</sub>H<sub>17</sub>NO<sub>6</sub>: C, 61.63; H, 5.17; N, 4.23. Found: C, 61.65; H, 5.16; N, 4.25.

**General procedure for the synthesis of compounds T6, T17, and T27** To a solution of compound **6a**, **17a** or **27a** in anhydrous dichloromethane, TiCl<sub>4</sub> was added (1.1 equivalent of reactant). The mixture was stirred under N<sub>2</sub> at room temperature for 30 min. Ethanol 0.5 mL was added to quench the reaction and the mixture was concentrated in vacuo to give a residue that was purified by column chromatography on silica gel to afford target compound.

**Synthesis of Benzyl 2-hydroxy-4-[(4-methylphenyl)sulfonamido]benzoate (T6)** From compound **5** (500.0 mg, 1.26 mmol), compound **T6** was obtained (258.1 mg, 52.0%, 2 steps). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 10.85 (s, 1H, ArOH), 10.57 (s, 1H, -SO<sub>2</sub>NH-), 7.71~7.73 (d, 2H, ArH), 7.65~7.68 (d, 1H, ArH), 7.42~7.44 (m, 2H, ArH), 7.36~7.39 (m, 4H, ArH), 7.31 (s, 1H, ArH), 6.68~6.70 (m, 2H, ArH), 5.31 (s, 2H, -OCH<sub>2</sub>Ar), 2.33 (s, 3H, ArCH<sub>3</sub>). <sup>13</sup>C-NMR



(DMSO- $d_6$ )  $\delta$ : 21.40, 66.08, 100.70, 102.60, 108.63, 126.79, 127.42, 128.11, 128.56, 129.17, 131.95, 135.72, 136.39, 137.33, 143.15, 164.80, 166.96. IR (KBr,  $\text{cm}^{-1}$ ): 3336, 2945, 2877, 1755, 1618, 1530, 1472, 1357, 1283, 1147, 828, 761, 697. EI-MS  $m/z$ : 397.1 ( $M^+$ ). *Anal.* Calcd for  $C_{21}H_{19}NO_5S$ : C, 63.46; H, 4.82; N, 3.52; S, 8.07. Found: C, 63.48; H, 4.81; N, 3.54; S, 8.06.

#### **Synthesis of (*E*)-cinnamyl 2-hydroxy-4-[(4-methylphenyl)sulfonamido]benzoate (T17)**

From compound **5** (500.0 mg, 1.26 mmol), compound **T17** was obtained (250.1 mg, 58.5%, 2 steps).  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 10.85 (s, 1H, ArOH), 10.60 (s, 1H, -SO<sub>2</sub>NH-), 7.68~7.72 (m, 3H, ArH), 7.46~7.48 (d, 2H, ArH), 7.32~7.39 (m, 5H, ArH), 6.74~6.78 (d, 1H,  $J=16\text{Hz}$ , =CH), 6.68~6.70 (m, 2H, ArH), 6.42~6.46 (d, 1H,  $J=16\text{Hz}$ , =CH), 4.92~4.93 (t, 2H, -OCH<sub>2</sub>-), 2.33 (s, 3H, ArCH<sub>3</sub>).  $^{13}\text{C-NMR}$  (DMSO- $d_6$ )  $\delta$ : 21.39, 64.88, 100.75, 102.57, 108.63, 120.97, 127.51, 127.96, 128.12, 128.46, 128.94, 131.93, 133.57, 135.98, 136.39, 137.27, 143.15, 163.90, 166.24. IR (KBr,  $\text{cm}^{-1}$ ): 3345, 2948, 2875, 1756, 1625, 1538, 1351, 1288, 1143, 944, 831, 765, 702. EI-MS  $m/z$ : 423.1 ( $M^+$ ). *Anal.* Calcd for  $C_{23}H_{21}NO_5S$ : C, 65.23; H, 5.00; N, 3.31; S, 7.57. Found: C, 65.22; H, 5.02; N, 3.29; S, 7.58.

#### **Synthesis of 2-hydroxy-4-[(4-methylphenyl)sulfonamido]-N-(4-nitrophenyl)benzamide (T27)**

From compound **5** (500.0 mg, 1.26 mmol), compound **T27** was obtained (235.1 mg, 44.0%, 2 steps).  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 11.61 (s, 1H, ArOH), 10.72 (s, 1H, -NHAr), 10.62 (s, 1H, -SO<sub>2</sub>NH-), 8.21~8.24 (d, 2H, ArH), 7.91~7.95 (d, 2H, ArH), 7.71~7.75 (m, 3H, ArH), 7.37~7.39 (d, 2H, ArH), 6.81~6.82 (d, 1H, ArH), 6.67~6.70 (dd, 1H, ArH), 2.34 (s, 3H, ArCH<sub>3</sub>).  $^{13}\text{C-NMR}$  (DMSO- $d_6$ )  $\delta$ : 21.09, 100.51, 108.30, 109.62, 118.98, 123.61, 128.22, 129.19, 129.36, 135.59, 136.48, 141.40, 142.96, 143.69, 156.16, 162.27. IR (KBr,  $\text{cm}^{-1}$ ): 3319, 2951, 2875, 1652, 1556, 1482, 1322, 1139, 829, 762, 697. EI-MS  $m/z$ : 427.0 ( $M^+$ ). *Anal.* Calcd for  $C_{20}H_{17}N_3O_6S$ : C, 56.20; H, 4.01; N, 9.83; S, 7.50. Found: C, 56.22; H, 4.00; N, 9.81; S, 7.51.

**$\alpha$ -Glucosidase inhibition studies** The inhibitory activities of compounds **T1-T32** against yeast  $\alpha$ -glucosidase were evaluated based on protocols previously described in the literature with slight modifications.<sup>21)</sup> Briefly,  $\alpha$ -glucosidase (G0660-750UN, from *Saccharomyces cerevisiae*, Sigma Aldrich, St. Louis, MO, USA) was dissolved in phosphate buffer (pH 6.86)

to a final concentration of 10 U/mL. The enzyme solution (15  $\mu$ L) and 60  $\mu$ L of the phosphate buffer (pH 6.86) were preincubated with 15  $\mu$ L of the target compounds at varying concentrations in DMSO at 37°C for 30 min. The reaction was triggered by the addition of 30  $\mu$ L of 4-nitrophenyl- $\alpha$ -D-glucopyranoside ( $\alpha$ -PNPG, final concentration 5.3 mM) and stopped after 30 min by the addition of 75  $\mu$ L of 1.0 M Na<sub>2</sub>CO<sub>3</sub>. The amount of released 4-nitrophenol from  $\alpha$ -PNPG was measured by determining the absorbance of the solution at 405 nm. A blank control (15  $\mu$ L of phosphate buffer instead of enzyme solution and 15  $\mu$ L of DMSO instead of test solution) and negative control (15  $\mu$ L of DMSO instead of test solution) were prepared. In each set of experiments the compound was run in triplicate. The inhibition ratio was calculated as follows:

$$\text{Inhibition (\%)} = (A_{\text{negative}} - A_{\text{sample}}) / (A_{\text{negative}} - A_{\text{blank}}) \times 100$$

Where  $A_{\text{negative}}$  was the absorbance of negative control,  $A_{\text{sample}}$  was the absorbance of sample,  $A_{\text{blank}}$  was the absorbance of blank control.

**Inhibition kinetics of  $\alpha$ -glucosidase studies** The inhibition type of compounds **T9**, **T10**, and **T32** was determined from Lineweaver-Burk plots, using an approach that has been previously described.<sup>25,26)</sup> Typically, two different concentrations of each compound around the IC<sub>50</sub> value were chosen. At each concentration, the  $\alpha$ -glucosidase activity was determined by varying the concentration of  $\alpha$ -PNPG. The enzyme reaction was performed under the above-mentioned reaction condition. The enzyme solution (40  $\mu$ L) and 20  $\mu$ L of the inhibitor were mixed with 1880  $\mu$ L phosphate buffer (pH 6.86), and pre-incubated at 37°C for 30 min. After the addition of 60  $\mu$ L  $\alpha$ -PNPG at different concentrations, the enzymatic reaction was performed at 37°C for 60s and the increase in absorbance was measured at 405 nm. Inhibition types were determined by double-reciprocal plots.<sup>27,28)</sup> Binding constants were calculated based on secondary plots of the slopes of the straight lines or vertical intercept versus the different concentration of inhibitor, respectively.

**Fluorescence quenching analysis** Fluorescence spectra were performed on a Shimadzu RF-5310pc fluorescence spectrophotometer (Shimadzu, Kyoto, Japan) equipped with a 1.0 cm quartz cuvette. Fluorescence measurements were performed at 298 K, and the excitation wavelength was set at 232 nm. The excitation and emission slit widths were set at 5.0 nm and

the emission spectra were recorded from 300 to 400 nm. Briefly, 10 mL of a diluted  $\alpha$ -glucosidase stock solution (0.6  $\mu$ M) was titrated by 3.97 mM **T9**, 2.49 mM **T10**, 6.76 mM **T32**, or 15.5 mM **acarbose** and mixed for 5 min. Subsequently, the solutions were transferred to quartz cuvettes in which the emission spectra were measured.

The fluorescence quenching data were analyzed by the Stern-Volmer equation as follows (1).<sup>29)</sup>

$$F_0/F = 1 + K_q \tau_0 [Q] = 1 + K_{SV} [Q] \quad (1)$$

where  $F_0$  and  $F$  represented the fluorescence intensities before and after addition of quencher (**T9**, **T10**, **T32**, or **acarbose**), respectively.  $K_q$  represented the bimolecular quenching constant,  $\tau_0$  represents the lifetime of the fluorophore in the absence of quencher ( $\tau_0 \approx 10^{-8}$  s),  $K_{SV}$  represents the Stern-Volmer quenching constant, and  $[Q]$  represents the concentration of quencher. Next, Eq. (1) was applied to determine the  $K_{SV}$  by linear regression of a plot of  $F_0/F$  against  $[Q]$ .

When small molecules independently bind to a set of equivalent sites on a macromolecule, the equilibrium between free and bound molecules is calculated by equation (2). The binding constant ( $K$ ) and the number of binding sites ( $n$ ) between the quencher and  $\alpha$ -glucosidase were calculated.<sup>30)</sup>

$$\lg\left(\frac{F_0 - F}{F}\right) = \lg K + n \lg [Q] \quad (2)$$

where  $F_0$  and  $F$  represent the fluorescence intensities before and after addition of quencher (**T9**, **T10**, **T32**, or **acarbose**), respectively.  $K$  represents the binding constant to a site,  $n$  represents the number of binding sites per  $\alpha$ -glucosidase molecule, and  $[Q]$  represents the concentration of the quencher.

**Molecular docking studies** Docking studies were carried to investigate the molecular binding pattern of target compounds **T9**, **T10**, and **T32** with the active site pocket of crystal structure of  $\alpha$ -glucosidase (PDB ID: 3L4V), which was downloaded from the RCSB protein Data Bank. The water molecules in  $\alpha$ -glucosidase were removed, and Gasteiger-Huckel charges and polar hydrogen atoms were added to the macromolecule. Prior to the docking studies, the structure of all inhibitors was optimized. For comparison purposes, molecular

docking studies of the standard inhibitor acarbose were also performed.

**Antioxidant activity** The antioxidant activity of target compounds **T9**, **T10**, and **T32** was evaluated towards the scavenging 1,1-diphenyl-2-picrylhydrazyl (**DPPH**) free radical, inhibiting lipid peroxidation, and total reduction capacity.

**a) DPPH radical scavenging activity** DPPH radical is based on the nitrogen atom in the center of the structure and can be stably existed in organic reagents.<sup>31)</sup> The absorbance of the DPPH radical solution after addition of anti-oxygen was reduced at a wavelength of 517 nm. A 1.00 mL aliquot of 0.08 g/mL DPPH solution was combined with 1.00 mL of the sample solution. After addition of each component, the solution was mixed well and placed at room temperature for 30 min in the dark. The control was prepared as above using 1.00 mL anhydrous ethanol instead of anti-oxygen. The absorbance was monitored at 517 nm against a blank control and the results were expressed as follows:

$$\text{DPPH radical scavenging activity (\%)} = [(A_0 - A_1)/A_0] \times 100$$

Where  $A_0$  represents the absorbance of solvent control reaction, and  $A_1$  represents the absorbance of samples with varying concentrations. All tests were performed in triplicate.

**b) Anti-lipid peroxidation activity** The anti-lipid peroxidation activity of compounds **T9**, **T10**, and **T32** was determined based on a previously described procedure with slight modifications.<sup>32,33)</sup> In brief, 0.10 mL of sample solution, 0.20 mL of yolk suspension, 0.20 mL of 25 mM FeSO<sub>4</sub> solution, and 1.50 mL of 0.1 M phosphate buffer (Na<sub>2</sub>HPO<sub>4</sub>-NaH<sub>2</sub>PO<sub>4</sub>, pH 7.45) were mixed well and incubated in water bath at 37°C for 30 min. The reaction was stopped by the addition of 1.00 mL 20% trichloroacetic acid (TCA). The solutions were shaken well and centrifuged at 3500 rpm for 15 min. Next, 2.00 mL of the supernatant was removed and 1.00 mL of 0.8% TBA was added to the removed supernatant. The mixture was heated in a water bath at 100°C for 15 min, then cooled to room temperature. The absorbance was measured at 532 nm. Experiments were performed in triplicate and ascorbic acid was used as the standard. The percentage of lipid peroxidation inhibition was calculated as follows:

$$\text{Anti-lipid peroxidation activity (\%)} = (A_0 - A_s)/A_0 \times 100$$

where  $A_0$  represents the absorbance of the control reaction, and  $A_s$  represents the

absorbance of the sample reaction.

**c) Total reduction capacity** A modified reported method was utilized to study the total reduction capacity of **T9**, **T10** and **T32**.<sup>34)</sup> In brief, 0.20 mL of sample solution, 1.00 mL of 0.2 M phosphate buffer ( $\text{NaH}_2\text{PO}_4\text{-Na}_2\text{HPO}_4$ , pH 6.6), and 1.00 mL of potassium ferric cyanide ( $\text{K}_3\text{Fe}(\text{CN})_6$ , 1%) were mixed well and incubated at 50°C for 20 min. After being cooled to room temperature, 1.00 mL of 10% trichloroacetic acid (TCA) was added to stop the reaction, and the mixture was centrifuged at 3000 rpm for 10 min. A 1.00 mL aliquot taken from the upper layer of the solution was mixed with 1.00 mL of distilled water and 0.20 mL of 0.1% ferric chloride, and the absorbance was measured at 700nm. The increase in absorbance of the reaction mixture indicated an increase in reducing power. Experiments were performed in triplicates and ascorbic acid was used as the standard. The concentration of anti-oxygen when absorbance was increased by an optical density of 0.5 was selected to compare the reduction capacity.

## RESULTS AND DISCUSSION

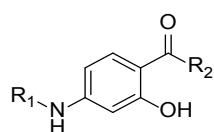
**$\alpha$ -Glucosidase inhibition studies** In the past, yeast  $\alpha$ -glucosidase has been mostly used for screening and evaluation of  $\alpha$ -glucosidase inhibitors due to its simple and convenient method.<sup>35)</sup> In this study, the  $\alpha$ -glucosidase inhibitory activity of the synthesized compounds was determined using yeast  $\alpha$ -glucosidase. The values of inhibitor concentration required for 50% inhibition of the  $\alpha$ -glucosidase activity ( $\text{IC}_{50}$ ) are listed in Table 1, and acarbose was used as the standard. The  $\text{IC}_{50}$  values indicated that the synthesized salicylic acid derivatives **T1-T32** exhibited different levels of inhibitory activity against yeast  $\alpha$ -glucosidase. The efficiency of the inhibitory activity was influenced by the variation of the substitute group of the salicylic acid derivatives.

Based on the sidechain of 4-(4-methylphenyl)sulfonamido salicylic acid derivatives, the target compounds **T1-T30** included two series: i) compounds **T1-T18**, the salicylate of various alcohols; ii) compounds **T19-T30**, the salicyamide of various amines. The different structure of the ester or amide greatly affected the inhibitory activity. Taken together, our studies indicated that salicylate was more efficient when compared to salicyamide. The

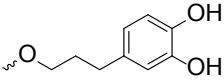
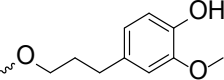
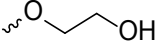
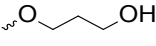
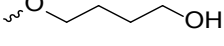
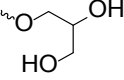
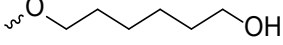
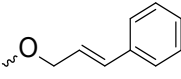
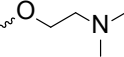







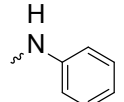
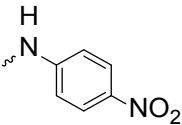
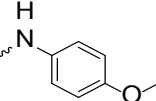
activity increased with the increase of the carbon chain. When aryl was introduced into the sidechain, the activity increased. Among compounds **T1-T30**, the inhibitory activity of compounds **T9** and **T10** was significantly higher when compared to that of acarbose ( $IC_{50} = 0.45$  mM), with  $IC_{50}$  values of 0.15 mM and 0.086 mM, respectively, which were 3-fold and 5.2-fold higher than that of acarbose.

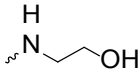
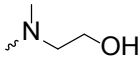
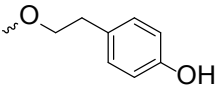
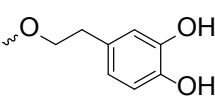
To investigate the effect of the substituent group on amino, a tosyl group was replaced by an acetyl group, and compounds **T31** and **T32** were designed and synthesized. Compound **T32** exhibited the  $IC_{50}$  value of 0.32 mM, which was 1.41-fold higher compared to that of acarbose. When comparing compounds **T8** and **T31**, we concluded that a tosyl group on amino had an advantage over the acetyl group due to its stronger electron withdrawing properties. The same conclusion could be drawn from the comparison between compounds **T9** and **T32**.

Table 1.  $IC_{50}$  values (mM) of the inhibition of  $\alpha$ -glucosidase by the target compounds.<sup>a</sup>



Compound	R <sub>1</sub>	R <sub>2</sub>	IC <sub>50</sub> / mM
T1	Ts		1.73 ± 0.14
T2	Ts		0.99 ± 0.02
T3	Ts		0.51 ± 0.03
T4	Ts		0.89 ± 0.04
T5	Ts		0.35 ± 0.02
T6	Ts		0.47 ± 0.02
T7	Ts		0.44 ± 0.03
T8	Ts		0.20 ± 0.01
T9	Ts		0.15 ± 0.01

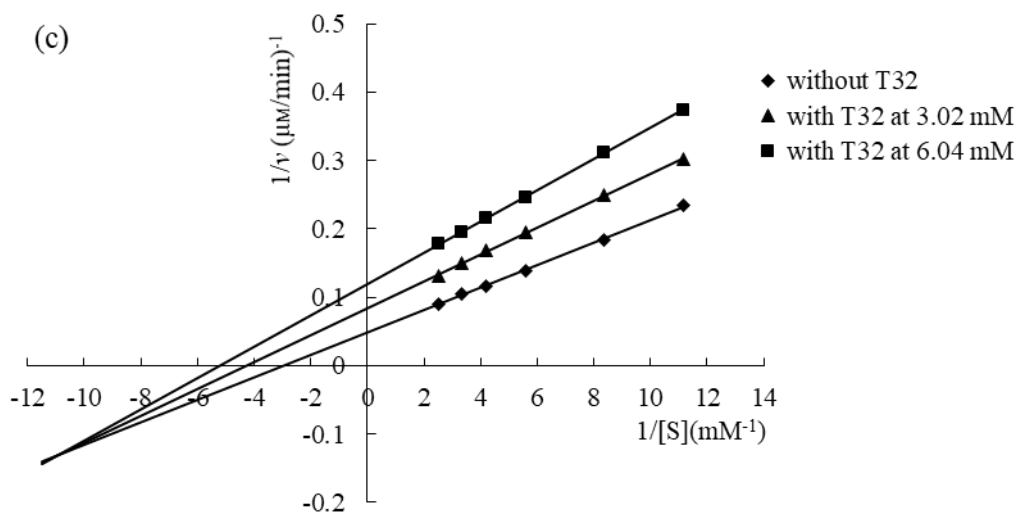
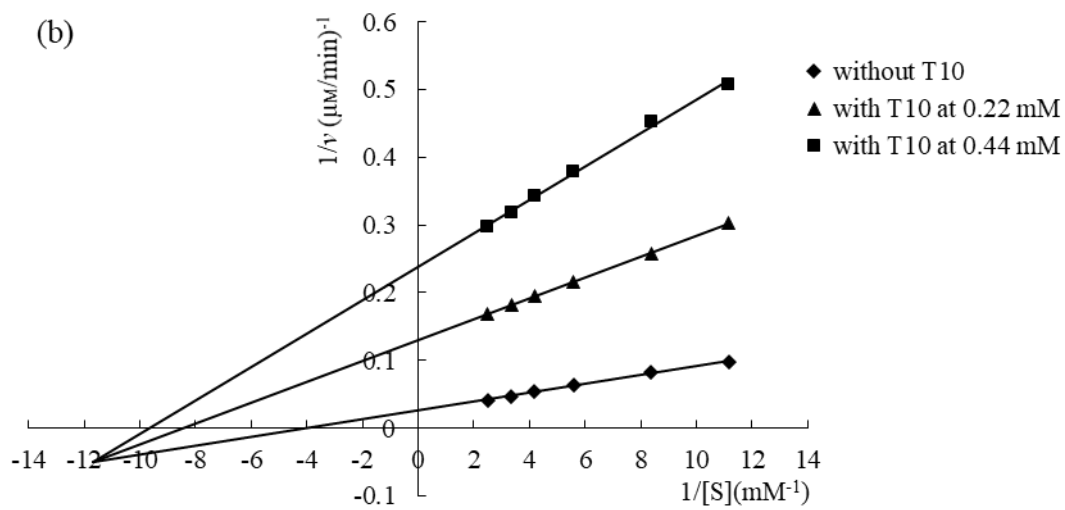
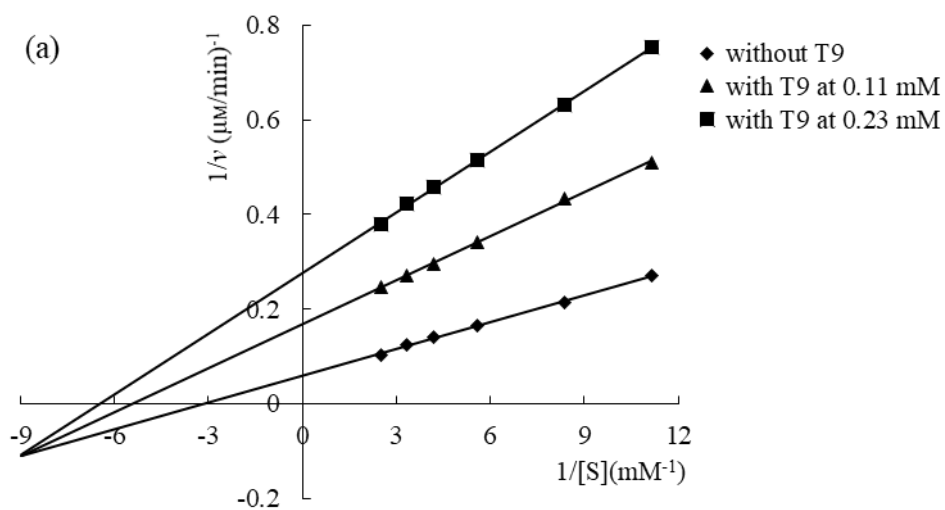
T10	Ts		$0.086 \pm 0.01$
T11	Ts		$0.95 \pm 0.04$
T12	Ts		$4.02 \pm 0.26$
T13	Ts		$3.03 \pm 0.17$
T14	Ts		$1.65 \pm 0.11$
T15	Ts		$19.24 \pm 0.75$
T16	Ts		$0.80 \pm 0.02$
T17	Ts		$0.19 \pm 0.02$
T18	Ts		$5.77 \pm 0.34$
T19	Ts		$2.51 \pm 0.28$
T20	Ts		$2.22 \pm 0.17$
T21	Ts		$6.09 \pm 0.42$
T22	Ts		$1.75 \pm 0.29$
T23	Ts		$3.58 \pm 0.34$
T24	Ts		$2.41 \pm 0.26$
T25	Ts		$2.37 \pm 0.21$
T26	Ts		$1.07 \pm 0.19$
T27	Ts		$0.61 \pm 0.04$
T28	Ts		$1.21 \pm 0.15$

T29	Ts		$7.67 \pm 0.38$
T30	Ts		$19.07 \pm 0.45$
T31	Ac		$1.25 \pm 0.20$
T32	Ac		$0.32 \pm 0.02$
Acarbose			$0.45 \pm 0.04$

<sup>a</sup> The results summarized represent the mean values for the IC<sub>50</sub> values (n=3).

**Inhibition kinetics of  $\alpha$ -glucosidase studies** To gain further insight into how salicylic acid derivatives interacted with  $\alpha$ -glucosidase, compounds **T9**, **T10**, **T32**, and acarbose were selected to investigate the inhibition kinetics based on previously described procedures.<sup>25,26)</sup> The inhibition type was determined by Lineweaver-burk plots. As shown in Fig. 2, the double reciprocal plots showed straight lines that intersected in the third quadrant, indicating that the inhibition types of compounds **T9**, **T10**, **T32** and acarbose with  $\alpha$ -glucosidase represented mixed non-competitive inhibitions. The values of free enzyme binding constant ( $K_i$ ) and enzyme-substrate complex binding constant ( $K_{is}$ ) were calculated from secondary plots of the slopes of the straight lines or vertical intercept versus the different concentration of inhibitor, respectively. The binding constants are presented in Table 2, and indicated that all three compounds and acarbose showed a stronger affinity towards the enzyme-substrate complex compared to free enzyme. The larger the  $K_i$  or  $K_{is}$  value, the weaker the inhibitory effect. For both  $K_i$  and  $K_{is}$ , the value of acarbose was the largest and that of **T10** was the smallest, **T9** had a medium value, which was consistent with the inhibitory activity against  $\alpha$ -glucosidase.





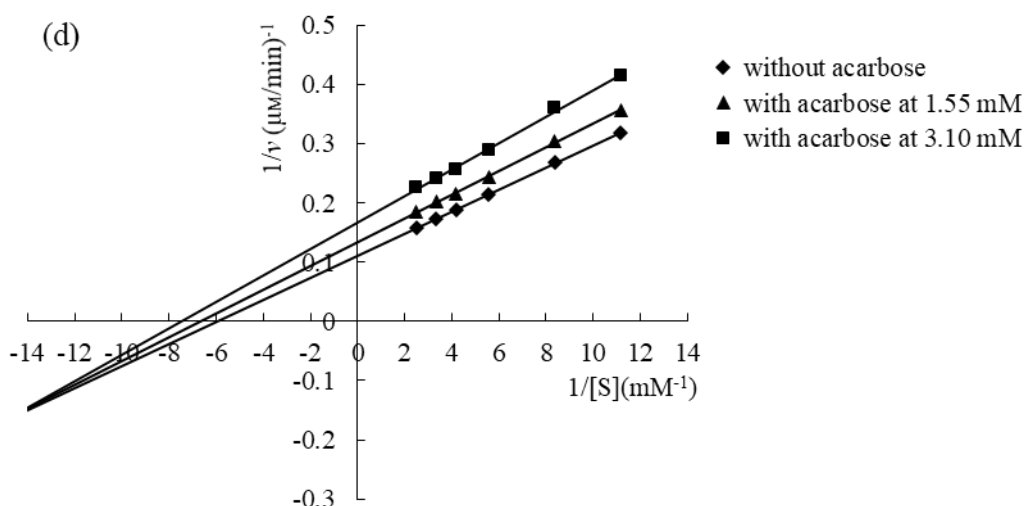


Fig. 2. Double-reciprocal plots of the inhibition kinetics of yeast  $\alpha$ -glucosidase by compounds **T9** (a), **T10** (b), **T32** (c), and **acarbose** (d).

Table 2. Binding constants of compounds **T9**, **T10**, **T32** and acarbose against  $\alpha$ -glucosidase.

Compound	$K_i$ ( $\mu\text{M}$ )	$K_{is}$ ( $\mu\text{M}$ )
<b>T9</b>	0.1792	0.0615
<b>T10</b>	0.1570	0.0520
<b>T32</b>	13.6667	4.0932
<b>acarbose</b>	15.4167	9.9358

#### Fluorescence quenching of $\alpha$ -glucosidase by compounds **T9**, **T10**, **T32**, and acarbose

Fluorescence quenching analysis was employed to investigate the intrinsic interaction mechanism of compounds **T9**, **T10**, **T32**, and **acarbose** on  $\alpha$ -glucosidase.  $\alpha$ -Glucosidase displayed a strong fluorescence peak at 332 nm, which resulted from the tyrosine residues of  $\alpha$ -glucosidase. As shown in Fig. 3, when the test compound was added, the fluorescence intensity of  $\alpha$ -glucosidase descended gradually with increasing concentrations of the test compounds. In addition, by increasing the concentrations of the test compounds, the highest emission peak around 332 nm showed no obvious red shift or blue shift, indicating that the test compounds did not affect the conformation of  $\alpha$ -glucosidase.

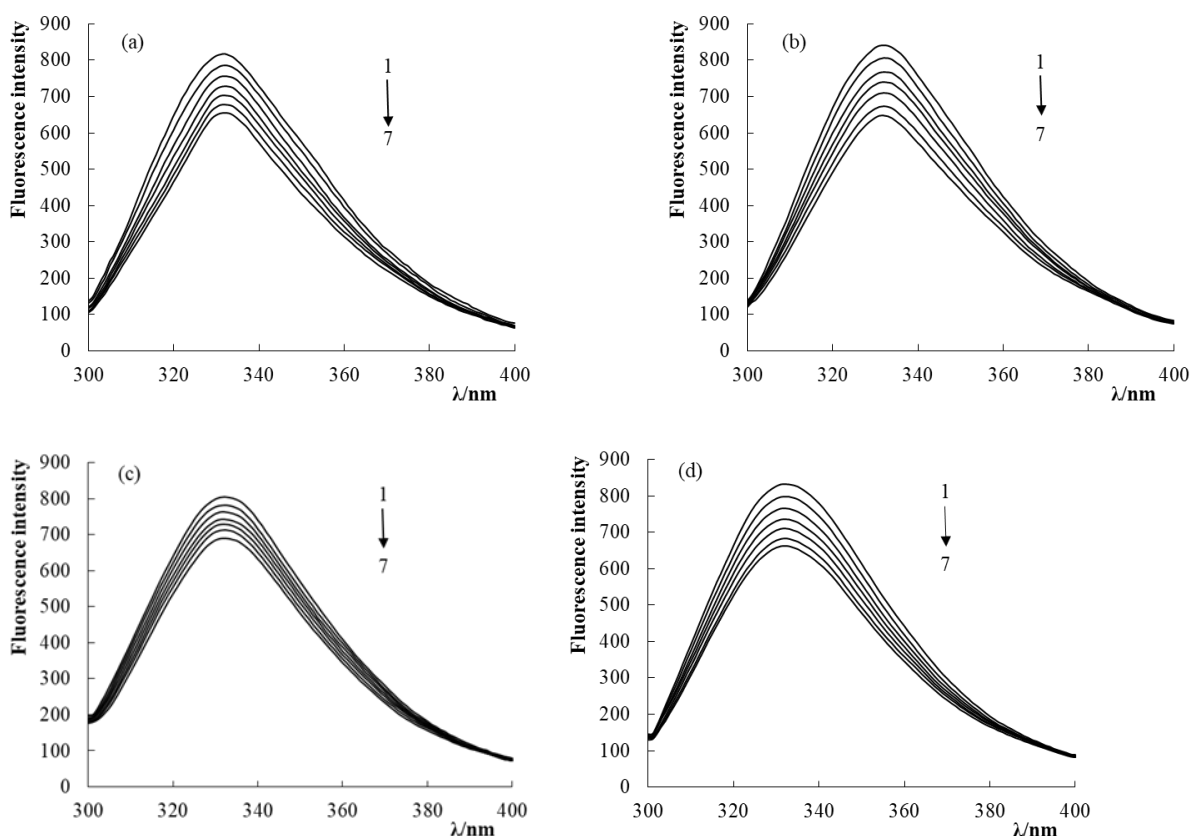


Fig. 3. Fluorescence emission spectra of  $\alpha$ -glucosidase in the presence of test compound at different concentrations. (a) compound T9, 1-7:  $C_{T9} = 0, 7.94 \times 10^{-7}, 1.59 \times 10^{-6}, 2.38 \times 10^{-6}, 3.18 \times 10^{-6}, 3.97 \times 10^{-6}, 4.76 \times 10^{-6}$  M; (b) compound T10, 1-7:  $C_{T10} = 0, 4.98 \times 10^{-7}, 9.96 \times 10^{-7}, 1.49 \times 10^{-6}, 1.99 \times 10^{-6}, 2.49 \times 10^{-6}, 2.99 \times 10^{-6}$  M; (c) compound T32, 1-7:  $C_{T32} = 0, 1.35 \times 10^{-6}, 2.70 \times 10^{-6}, 4.06 \times 10^{-6}, 5.41 \times 10^{-6}, 6.76 \times 10^{-6}, 8.11 \times 10^{-6}$  M; (d) acarbose, 1-7:  $C_{acarbose} = 0, 3.10 \times 10^{-6}, 6.20 \times 10^{-6}, 9.30 \times 10^{-6}, 1.24 \times 10^{-5}, 1.55 \times 10^{-5}, 1.86 \times 10^{-5}$  M.

For further identify the interaction mechanisms of test compounds on  $\alpha$ -glucosidase, fluorescence quenching data were calculated from the plots of  $F_0/F$  versus  $[Q]$  based on previous studies.<sup>29)</sup> For compounds **T9**, **T10**, **T32**, and acarbose, the values of  $K_q$  were determined to be  $5.23 \times 10^{12}$  L/mol·s,  $1.02 \times 10^{13}$  L/mol·s,  $1.96 \times 10^{12}$  L/mol·s and  $1.38 \times 10^{12}$  L/mol·s, respectively, which were much greater than the maximum scatter collision quenching constant  $2.0 \times 10^{10}$  L/mol·s.<sup>36)</sup> This demonstrated that fluorescence quenching caused by the test compounds was the result of static quenching by the formation of an inhibitor- $\alpha$ -glucosidase complex.

The binding constants ( $K$ ) and number of binding sites ( $n$ ) were obtained through plots of

$\lg[(F_0 - F)/F]$  versus  $\lg[Q]$ . The results presented in Table 3 show that the binding constant ( $K$ ) was **T10** > **T9** > Acarbose  $\approx$  **T32**, which further confirmed that compound **T10** was a better fluorescence quencher and more likely to connect with the enzyme. The number of binding sites ( $n$ ) of **T9**, **T10**, **T32**, and acarbose were approximately close to 1, indicating the existence of only a single binding site in  $\alpha$ -glucosidase for test compounds. Moreover, the value of  $K$  indicated that a strong interaction existed between test compounds and  $\alpha$ -glucosidase.

Table 3. Quenching constants of **T9**, **T10**, **T32**, and **acarbose** on  $\alpha$ -glucosidase.

Compound	$T$ ( $^{\circ}\text{C}$ )	$K_{SV}$ ( $\text{M}^{-1}$ )	$K_q$ ( $\text{M}^{-1}\cdot\text{s}$ )	$K$ ( $\text{M}^{-1}$ )	$n$
<b>T9</b>	25	$5.23 \times 10^4$	$5.23 \times 10^{12}$	$5.59 \times 10^4$	1.01
<b>T10</b>	25	$1.02 \times 10^5$	$1.02 \times 10^{13}$	$2.07 \times 10^5$	1.06
<b>T32</b>	25	$1.96 \times 10^4$	$1.96 \times 10^{12}$	$1.13 \times 10^4$	0.95
<b>acarbose</b>	25	$1.38 \times 10^4$	$1.38 \times 10^{12}$	$1.55 \times 10^4$	1.01

**Molecular docking studies** To provide insight into the structure-activity relationship of salicylic acid derivatives towards  $\alpha$ -glucosidase, docking simulations were carried out to investigate their binding behaviors with SYBYL-X 2.0 program. As shown in Fig. 4, compounds **T9**, **T10**, and **T32** all tend to bind with  $\alpha$ -glucosidase at the same site. Analysis of the structure of the binding site showed that compounds **T9**, **T10**, and **T32** all interacted with ASP327, ASP443, and TRP406 via hydrogen bonds. Furthermore,  $\pi$ - $\pi$  interactions were found between the benzene ring on catechol of compounds **T9**, **T10** and **T32**, and the aromatic ring on TRP406 and TRP441, which led to a better binding with active site of  $\alpha$ -glucosidase. This phenomenon may explain the better inhibitory activities of compound **T9**, **T10**, and **T32** against  $\alpha$ -glucosidase when compared to that of acarbose. Moreover, the carbon chains coupling catechol and salicylic acid were exposed in a hydrophobic region, therefore we speculated that properly increasing the length of the carbon chain might enhance the hydrophobic interaction between the target compound and the active site of  $\alpha$ -glucosidase, which was consistent with the inhibitory activity of compounds **T9** and **T10**.

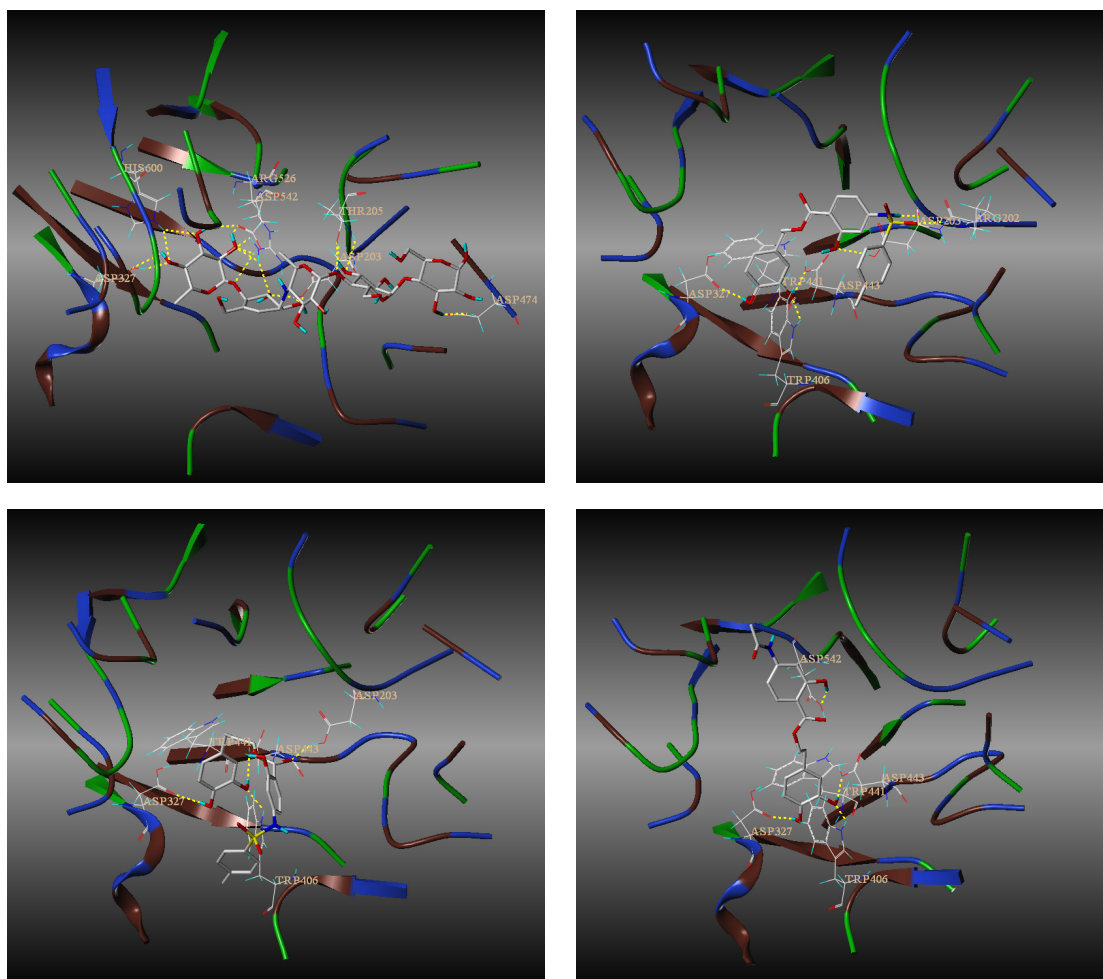


Fig. 4. Interaction diagram of compounds **acarbose**, **T9**, **T10**, and **T32** with  $\alpha$ -glucosidase (PDB ID:3L4V), respectively. Hydrogen bonds are shown as yellow dotted lines. Color indication of atoms: carbons: white; oxygen: red; hydrogen: cyan; nitrogen: blue; sulphur: yellow.

(Color figure can be accessed in the online version.)

**Antioxidant properties *in vitro*** An increasing number of studies have shown that diabetic complications are closely correlated with oxidative stress.<sup>37)</sup> Phenolic compounds are major natural antioxidants, and some natural antioxidant molecules have  $\alpha$ -glucosidase inhibitory activities.<sup>38)</sup> It has previously been reported that antioxidants and radical scavengers prevent the formation of advanced glycation end-products.<sup>39)</sup> In previous studies, it has been revealed that compounds with combined antioxidant and anti-glycosylation properties are more effective in treating diabetes.<sup>40)</sup> We coupled several phenolic compounds with salicylic acid

scaffolds for the purpose of dual-function,  $\alpha$ -glucosidase inhibitory activity, and antioxidant activity. Compounds **T9**, **T10**, and **T32** were selected to further evaluate the antioxidant properties via scavenging DPPH radical, inhibiting lipid peroxidation, and total reduction capacity. The antioxidant results are presented in Table 4. As depicted, all three compounds exhibited an excellent antioxidant ability. Compound **T9**, **T10** and **T32** showed 4.65-7.23-fold stronger activities against scavenging DPPH radical when compared to ascorbic acid. All three compounds exhibited a high potency of anti-lipid peroxidation activities and 18.2-55.6-fold higher activities were found with compounds **T9**, **T10** and **T32** compared to ascorbic acid. The total reduction capacities of compounds **T9**, **T10**, and **T32** were 2.87-3.38-fold higher compared to that of ascorbic acid. Therefore, our results indicated that the phenolic hydroxyl group was the favorable structure for scavenging reactive free radicals, anti-lipid peroxidation, and total reduction capacity. Moreover, when the same number of phenolic hydroxyl group are present, extending the carbon chain properly was beneficial to the anti-oxidation capacity, suggesting that the antioxidant activities may be associated with lipid solubility.

Table 4. Antioxidant activities of target compounds **T9**, **T10**, and **T32** *in vitro*.<sup>a</sup>

Antioxidant	DPPH radical (IC <sub>50</sub> $\mu$ M)	Anti-lipid peroxidation (IC <sub>50</sub> $\mu$ M)	Total reduction capacity ( $\mu$ M)
<b>T9</b>	3.32 $\pm$ 0.73	1.42 $\pm$ 0.03	20.08 $\pm$ 0.43
<b>T10</b>	2.79 $\pm$ 0.36	1.22 $\pm$ 0.02	18.67 $\pm$ 0.21
<b>T32</b>	4.34 $\pm$ 0.24	3.72 $\pm$ 0.02	22.02 $\pm$ 0.16
Ascorbic acid	20.16 $\pm$ 0.53	67.8 $\pm$ 0.77	63.09 $\pm$ 0.29

<sup>a</sup> The results summarized are the mean values of n=3 for IC<sub>50</sub> values.

## CONCLUSION

In summary, a series of salicylic acid derivatives were designed and synthesized as novel non-saccharide  $\alpha$ -glucosidase inhibitors. Compounds **T9**, **T10**, and **T32** exhibited a higher potency of  $\alpha$ -glucosidase inhibitory activity when compared to acarbose. All three compounds and acarbose inhibited  $\alpha$ -glucosidase in a mixed non-competitive manner, and showed a stronger affinity towards an enzyme-substrate complex compared to free enzyme.

Fluorescence analysis showed that **T9**, **T10**, and **T32** could statically quench the fluorescence of  $\alpha$ -glucosidase by formation of an inhibitor- $\alpha$ -glucosidase complex. Molecular docking studies revealed that **T9**, **T10**, and **T32** bound with  $\alpha$ -glucosidase at the same site. Hydrogen bond interactions,  $\pi$ - $\pi$  interactions, and hydrophobic interactions were found between target compounds and protein molecules. Compound **T10** showed higher antioxidant properties via scavenging **DPPH** radical, inhibiting lipid peroxidation, and total reduction capacity than compounds **T9**, **T32**, and ascorbic acid, respectively. Thus, the salicylic acid derivatives identified in this study may be promising candidates for developing novel non-saccharide  $\alpha$ -glucosidase inhibitors.

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**Conflict of Interest** The authors declare no conflict of interest.

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