Research Article

Synthesis and Biological Evaluation of New Substituted 3-[4-(Phenylsulfonamido)benzoyl]-2*H*-1-benzopyran-2-one Derivatives as α -Glucosidase Inhibitors

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A series of new substituted 3-[4-(phenylsulfonamido)benzoyl]-2*H*-1-benzopyran-2-one derivatives bearing groups methoxy, *tert*-butyl, and atoms of halogens at the *para*-position of the A-ring were synthesized and *in vitro* biological activities were evaluated as nonsugar α -glucosidase inhibitors. Most of the test compounds demonstrated significant α -glucosidase inhibitory activity relative to that of Acarbose ($IC_{50} = 29.26 \mu M$). The *para*-substitution with a methoxy group or halogens could notably increase the potency. Compounds **17**, **18**, and **23**, with IC_{50} values of $0.025 \mu M$, $0.014 \mu M$, and $0.018 \mu M$, respectively, may be of significance for the further development of new nonsugar α -glucosidase inhibitors.

1. Introduction

α -Glucosidase (EC 3.2.1.20), located in the brush-border surface membrane of intestinal cells, is a key enzyme catalyzing the final step in the digestive process of carbohydrates into glucose [1]. This enzyme has drawn a special interest in the pharmaceutical research community because the inhibition of its catalytic activity can retard the liberation of glucose from dietary complex carbohydrates and delay glucose absorption, resulting in reduced postprandial plasma blood glucose level and suppression of postprandial hyperglycemia [2]. Thus, α -glucosidase inhibitors exhibit high promise as therapeutic agents for the treatment of metabolic disorders, such as type II non-insulin-dependent diabetes mellitus, obesity, and hyperglycemia [3]. α -Glucosidase inhibitors are also known to be promising as antiviral and antitumor agents that interfere with the biosynthesis of *N*-linked oligosaccharide chains [4].

Classically, efforts for the development of a new set of α -glucosidase inhibitors have focused mainly on sugar mimics, such as disaccharides, iminosugars, carbasugars,

and thiosugars. However, numerous disadvantages exist for this strategy, including poor activity, low natural abundance, or complicated stereochemistry, which makes them difficult to approach synthetically. A more modern approach is to investigate nonsugar α -glucosidase inhibitors [5–9].

We had previously reported that 3-[4-(phenylsulfonamido)benzoyl]-2*H*-1-benzopyran-2-one derivatives [10], designed by incorporating the phenylsulfonamide chalcone substructure into the benzopyran backbone shown in Figure 1 [11], have the potential to act as a new class of nonsugar α -glucosidase inhibitors. The preliminary study on the structure-activity relationship had focused on the C-ring, which showed that the modification of this substructure with halogen or bulky groups can reduce the inhibitory activity, whereas introducing diethylamino group at C7 and methoxy and hydroxy groups at C6 and C7, respectively, can increase the potency significantly. In addition, we found that compounds bearing the methyl group displayed higher activities than those bearing a hydrogen atom, such as compounds **7u** and **7j** (Figure 1). This observation

FIGURE 1: Chemical structures of compounds **7a**, **7h**, **7i**, **7j**, and **7u**.

encouraged us to further investigate the influence of A-ring substituents on the α -glucosidase inhibitory activity of 3-[4-(phenylsulfonamido)benzoyl]-2H-1-benzopyran-2-one derivatives.

In the present study, a series of new substituted 3-[4-(phenylsulfonamido)benzoyl]-2H-1-benzopyran-2-one derivatives (Scheme 1), bearing halogen atoms, methoxy, or *tert*-butyl groups at the *para*-position of the A-ring while keeping the favorable substituents on the C-ring unchanged, were synthesized and assayed on yeast α -glucosidase to explore the effect of these substituents on the α -glucosidase inhibitory activity and obtain a comprehensive understanding of the structure-activity relationships of this class of compounds.

2. Results

The compounds **2–9** were synthesized according to the literature [12]. 4-Nitrobenzoic acid with thionyl chloride and 1,2,3-benzotriazole was refluxed to get 4-nitrobenzoyl-1,2,3-benzotriazole (**2**) as shown in Scheme 1 [12]. The resulting compound reacted with ethyl acetoacetate in the presence of sodium hydride, followed by hydrolysis to form ethyl 3-(4-nitrophenyl)-3-oxopropanoate (**3**) [13], which was subsequently reduced with stannous chloride in ethyl acetate to provide the key intermediate ethyl 3-(4-aminophenyl)-3-oxopropanoate (**4**) as shown in Scheme 1 [14]. Afterward, compound **4** was acylated with a series of *para*-substituted phenylsulfonyl chlorides to obtain ethyl 3-[4-(phenylsulfonamido)phenyl]-3-oxopropanoates (**5–9**). Lastly, compounds **5–9** were reacted separately with substituted salicylaldehydes via Knoevenagel condensation. The target compounds **10–26** were prepared as shown in Scheme 1 and seventeen target compounds were obtained in modest yields.

All target compounds were evaluated spectrophotometrically at 490 nm on yeast α -glucosidase to evaluate their potential as α -glucosidase inhibitors. Acarbose was included as a reference compound. The *in vitro* α -glucosidase inhibitory activity of the test compounds was assayed as described previously [10]. The test compounds were initially assayed for their ability to inhibit α -glucosidase at a concentration of $1 \mu g \cdot mL^{-1}$. Compounds that displayed more than 50% inhibition were selected for concentration dependent activity evaluation and calculation of IC_{50} values, as shown in Table 1.

3. Discussion

Except for compound **10** ($IC_{50} = 7.568 \mu M$) in the halogen substituted series, most of the tested compounds showed stronger inhibitory activity than that of compound **7a**, previously studied in [10] ($IC_{50} = 3.283 \mu M$). Compound **18** ($IC_{50} = 0.014 \mu M$) presented as the strongest inhibitor which was nearly 235 times higher than compound **7a**. The activities of compounds **13** ($IC_{50} = 0.075 \mu M$), **17** ($IC_{50} = 0.025 \mu M$), and **21** ($IC_{50} = 0.036 \mu M$) were increased about 3, 8, and 6 times, respectively, compared with the activity of compound **7j**, previously described in [10] ($IC_{50} = 0.199 \mu M$). This observation suggested that the halogen atoms at the *para*-position of the A-ring could greatly enhance the activity. However, this fact was contrary to the disadvantageous effect observed for the halogen groups presented on the C-ring [10].

The activity of compound **22** ($IC_{50} = 0.073 \mu M$) in the methoxy substituted series ($R_3 = OCH_3$) was 45-fold higher than that of compound **7a**. Compound **23** displayed an IC_{50} value of $0.018 \mu M$, which was 320-fold more potent than compound **7h** and was ranked as the strongest inhibitor in this series. Compounds **24** ($IC_{50} = 0.037 \mu M$) and **25** ($IC_{50} = 0.069 \mu M$) also exhibited a much better inhibitory activity compared with compounds **7i** and **7j**. Interestingly, most compounds in this series showed higher activities than those in the methyl substituted series. The activities of compounds **22**, **23**, and **24** were higher than those of compounds **7l** ($IC_{50} = 3.577 \mu M$), **7s** ($IC_{50} = 1.125 \mu M$), and **7t** ($IC_{50} = 0.347 \mu M$), respectively. All these observations indicated that the methoxy group substituted at the *para*-position of the A-ring was favorable for increasing the α -glucosidase inhibitory activity of 3-[4-(phenylsulfonamido)benzoyl]-2H-1-benzopyran-2-one derivatives.

The activity of compound **26** with *tert*-butyl group at the *para*-position of the A-ring disappeared, suggesting that this bulky group is unfavorable for binding with α -glucosidase, which is in agreement with what we had found on the C-ring [10].

4. Experimental

4.1. Chemistry. Melting points were recorded using YRT-3 melting point apparatus. The 1H -NMR spectra were recorded in DMSO- d_6 on a Bruker ARX-300 spectrometer, and chemical shifts (δ) were expressed in ppm downfield from the TMS and were used as the internal standard. Coupling constant (J) values were in Hz. The IR spectra were determined as KBr pellets on the Bruker IFS-55 spectrometer and were expressed in cm^{-1} . The progress of the reactions was monitored by TLC using several solvent systems with different polarities. The TOF-HRMS spectra were recorded on a Bruker Micro-TOFQ. All solvents and reagents were of analytical grade.

General Procedure for the Synthesis of Compounds 10–26. Compounds **5–9** (1.4 mmol) reacted with substituted salicylaldehyde (1.6 mmol) separately; five drops of piperidine, one drop of glacial acetic acid, and ethanol (10 mL) were added and stirred under reflux in an argon atmosphere for 0.5 h. The mixture was cooled to room temperature, filtered

10: R₁ = H, R₂ = H, R₃ = F11: R₁ = H, R₂ = OH, R₃ = F12: R₁ = H, R₂ = N(C₂H₅)₂, R₃ = F13: R₁ = OCH₃, R₂ = OH, R₃ = F14: R₁ = H, R₂ = H, R₃ = Cl15: R₁ = H, R₂ = OH, R₃ = Cl16: R₁ = H, R₂ = N(C₂H₅)₂, R₃ = Cl17: R₁ = OCH₃, R₂ = OH, R₃ = Cl18: R₁ = H, R₂ = H, R₃ = Br19: R₁ = H, R₂ = OH, R₃ = Br20: R₁ = H, R₂ = N(C₂H₅)₂, R₃ = Br21: R₁ = OCH₃, R₂ = OH, R₃ = Br22: R₁ = H, R₂ = H, R₃ = OCH₃23: R₁ = H, R₂ = OH, R₃ = OCH₃24: R₁ = H, R₂ = N(C₂H₅)₂, R₃ = OCH₃25: R₁ = OCH₃, R₂ = OH, R₃ = OCH₃26: R₁ = H, R₂ = N(C₂H₅)₂, R₃ = C(CH₃)₃5: R₃ = F6: R₃ = Cl7: R₃ = Br8: R₃ = OCH₃9: R₃ = C(CH₃)₃

SCHEME 1: Synthesis of 3-[4-(phenylsulfonamido)benzoyl]-2H-1-benzopyran-2-one derivatives **10–26**. Reagents and conditions: (a) SOCl₂, 1,2,3-benzotriazole, and reflux; (b) ethyl acetoacetate, NaH, THF, and rt; (c) SnCl₂, ethyl acetate, and reflux; (d) substituted benzenesulfonyl chloride, pyridine, CH₂Cl₂, –10°C, and then rt; (e) substituted salicylaldehyde, piperidine, acetic acid, EtOH, and reflux.

TABLE 1: The α -glucosidase inhibitory activity of new substituted 3-[4-(phenylsulfonamido)benzoyl]-2H-1-benzopyran-2-one derivatives.

Number	R ₁	R ₂	R ₃	IC ₅₀ (μ M) ^a
10	H	H	F	7.568 $\pm$ 0.575
11	H	OH	F	0.282 $\pm$ 0.038
12	H	N(C ₂ H ₅) ₂	F	0.085 $\pm$ 0.014
13	OCH ₃	OH	F	0.075 $\pm$ 0.012
14	H	H	Cl	1.088 $\pm$ 0.232
15	H	OH	Cl	0.171 $\pm$ 0.034
16	H	N(C ₂ H ₅) ₂	Cl	0.108 $\pm$ 0.019
17	OCH ₃	OH	Cl	0.025 $\pm$ 0.005
18	H	H	Br	0.014 $\pm$ 0.003
19	H	OH	Br	0.199 $\pm$ 0.016
20	H	N(C ₂ H ₅) ₂	Br	0.125 $\pm$ 0.035
21	OCH ₃	OH	Br	0.036 $\pm$ 0.008
22	H	H	OCH ₃	0.073 $\pm$ 0.012
23	H	OH	OCH ₃	0.018 $\pm$ 0.003
24	H	N(C ₂ H ₅) ₂	OCH ₃	0.037 $\pm$ 0.006
25	OCH ₃	OH	OCH ₃	0.069 $\pm$ 0.011
26	H	N(C ₂ H ₅) ₂	C(CH ₃) ₃	— ^b
Acarbose				29.26 $\pm$ 3.23

^aIC₅₀ values are represented as means $\pm$ SD ($n = 2-3$). ^bLess than 50% inhibition at 10 μ g/mL.

to collect the solid (if there was no precipitate, 25 mL water was added), and then washed with a small amount of ethanol. In most cases, the products were sufficiently pure. Products with impurities were purified via column chromatography, petroleum ether, and ethyl acetate systems with different polarities as eluent.

4.1.1. 3-[4-(4-Fluorophenylsulfonamido)]benzoyl]-2H-1-benzopyran-2-one (**10**). White solid, 49% yield. M.p.: 204.5–205.5°C; ¹H-NMR (DMSO-*d*₆, ppm): δ 7.22 (d, 2H, $J = 8.7$ Hz, H-3', 5'), 7.44 (m, 4H, H-6, 8, 3'', 5''), 7.73 (m, 1H, H-7), 7.83 (m, 3H, H-5, 2', 6'), 7.90 (m, 2H, H-2'', 6''), 8.34 (s, 1H, H-4), 11.03 (s, 1H, NH); IR (KBr, cm^{–1}): 3432, 3240, 1732, 1652, 1601,

1567, 1510, 1240, 1169, 838, 800; TOF-HRMS: m/z 424.0649 $[M+H]^+$ ($C_{22}H_{15}FNO_5S$ requires 424.0656).

4.1.2. 3-[4-(4-Fluorophenylsulfonamido)benzoyl]-7-hydroxy-2H-1-benzopyran-2-one (**11**). Brown solid, 54% yield. M.p.: 159-160°C; 1H -NMR (DMSO- d_6 , ppm): δ 6.76 (s, 1H, H-8), 6.82 (d, 1H, J = 8.6 Hz, H-6), 7.12 (d, 2H, J = 8.6 Hz, H-3', 5'), 7.39 (t, 2H, J = 8.8 Hz, H-3'', 5''), 7.64 (d, 1H, J = 8.6 Hz, H-5), 7.70 (d, 2H, J = 8.6 Hz, H-2'', 6''), 7.88 (dd, 2H, J = 8.8 Hz and 5.2 Hz, H-2', 6'), 8.22 (s, 1H, H-4); IR (KBr, cm^{-1}): 3474, 2924, 1730, 1601, 1228, 1166, 839, 816; TOF-HRMS: m/z 440.0599 $[M+H]^+$ ($C_{22}H_{15}FNO_6S$ requires 440.0605).

4.1.3. 3-[4-(4-Fluorophenylsulfonamido)benzoyl]-7-(*N,N*-diethylamino)-2H-1-benzopyran-2-one (**12**). Yellow solid, 51% yield. M.p.: 207-208°C; 1H -NMR (DMSO- d_6 , ppm): δ 1.13 (t, 6H, J = 6.9 Hz, $2CH_2CH_3$), 3.48 (q, 4H, J = 6.9 Hz, $2CH_2CH_3$), 6.57 (s, 1H, H-8), 6.75 (d, 1H, J = 9.0 Hz, H-6), 7.18 (d, 2H, J = 8.6 Hz, H-3', 5'), 7.43 (t, 2H, J = 8.7 Hz, H-3'', 5''), 7.56 (d, 1H, J = 9.0 Hz, H-5), 7.68 (d, 2H, J = 8.6 Hz, H-2', 6'), 7.92 (dd, 2H, J = 8.7 Hz and 5.3 Hz, H-2'', 6''), 8.17 (s, 1H, H-4), 10.90 (s, 1H, NH); IR (KBr, cm^{-1}): 3441, 3164, 2973, 1690, 1617, 1599, 1580, 1508, 1234, 1166, 827, 812; TOF-HRMS: m/z 495.1384 $[M+H]^+$ ($C_{26}H_{24}FN_2O_5S$ requires 495.1391).

4.1.4. 3-[4-(4-Fluorophenylsulfonamido)benzoyl]-7-hydroxy-6-methoxy-2H-1-benzopyran-2-one (**13**). Yellow solid, 39% yield. M.p.: 226-227°C; 1H -NMR (DMSO- d_6 , ppm): δ 3.81 (s, 3H, OCH_3), 6.84 (s, 1H, H-8), 7.22 (d, 2H, J = 8.5 Hz, H-3', 5'), 7.35 (s, 1H, H-5), 7.44 (m, 2H, H-3'', 5''), 7.77 (d, 2H, J = 8.6 Hz, H-2', 6'), 7.91 (m, 2H, H-2'', 6''), 8.22 (s, 1H, H-4), 10.89 (s, 1H, NH); IR (KBr, cm^{-1}): 3429, 3206, 2922, 1680, 1658, 1602, 1569, 1509, 1261, 1156, 840, 790; TOF-HRMS: m/z 470.0704 $[M+H]^+$ ($C_{23}H_{17}FNO_7S$ requires 470.0711).

4.1.5. 3-[4-(4-Chlorophenylsulfonamido)benzoyl]-2H-1-benzopyran-2-one (**14**). White solid, 87% yield. M.p.: 208-209°C; 1H -NMR (DMSO- d_6 , ppm): δ 7.21 (d, 2H, J = 8.7 Hz, H-3', 5'), 7.42 (m, 2H, H-6, 8), 7.66 (d, 2H, J = 8.7 Hz, H-3'', 5''), 7.73 (m, 1H, H-7), 7.84 (m, 5H, H-5, 2', 6', 2'', 6''), 8.34 (s, 1H, H-4), 11.08 (s, 1H, NH); IR (KBr, cm^{-1}): 3441, 3243, 1736, 1653, 1603, 1510, 1240, 1164, 828, 801; TOF-HRMS: m/z 440.0354 $[M+H]^+$ ($C_{22}H_{15}ClNO_5S$ requires 440.0360).

4.1.6. 3-[4-(4-Chlorophenylsulfonamido)benzoyl]-7-hydroxy-2H-1-benzopyran-2-one (**15**). Brown solid, 24% yield. M.p.: 186-187°C; 1H -NMR (DMSO- d_6 , ppm): δ 6.75 (s, 1H, H-8), 6.81 (d, 1H, J = 8.6 Hz, H-6), 7.01 (d, 2H, J = 8.6 Hz, H-3', 5'), 7.55 (d, 2H, J = 8.5 Hz, H-3'', 5''), 7.62 (d, 3H, J = 8.5 Hz, H-5, 2', 6'), 7.77 (d, 2H, J = 8.5 Hz, H-2'', 6''), 8.16 (s, 1H, H-4); IR (KBr, cm^{-1}): 3445, 1716, 1601, 1506, 1225, 1162, 850, 790; TOF-HRMS: m/z 456.0303 $[M+H]^+$ ($C_{22}H_{15}ClNO_6S$ requires 456.0309).

4.1.7. 3-(4-Chlorophenylsulfonamidobenzoyl)-7-(*N,N*-diethylamino)-2H-1-benzopyran-2-one (**16**). Brown solid, 31% yield. M.p.: >250°C; 1H -NMR (DMSO- d_6 , ppm): δ 1.13 (t, 6H,

J = 7.0 Hz, $2CH_3$), 3.47 (q, 4H, J = 7.0 Hz, $2CH_2$), 6.56 (s, 1H, H-8), 6.76 (d, 1H, J = 8.6 Hz, H-6), 7.09 (d, 2H, J = 8.2 Hz, H-3', 5'), 7.61 (m, 5H, H-5, 2', 6', 3'', 5''), 7.82 (d, 2H, J = 8.1 Hz, H-2'', 6''), 8.11 (s, 1H, H-4); IR (KBr, cm^{-1}): 3433, 3173, 2973, 1718, 1689, 1617, 1581, 1508, 1233, 1163, 825, 789; TOF-HRMS: m/z 511.1089 $[M+H]^+$ ($C_{26}H_{24}ClN_2O_5S$ requires 511.1095).

4.1.8. 3-[4-(4-Chlorophenylsulfonamido)benzoyl]-7-hydroxy 6-methoxy-2H-1-benzopyran-2-one (**17**). Yellow solid, 37% yield. M.p.: >250°C; 1H -NMR (DMSO- d_6 , ppm): δ 3.81 (s, 3H, OCH_3), 6.84 (s, 1H, H-5), 7.22 (d, 2H, J = 8.4 Hz, H-3', 5'), 7.35 (s, 1H, H-8), 7.66 (d, 2H, J = 8.4 Hz, H-3'', 5''), 7.77 (d, 2H, J = 8.5 Hz, H-2', 6'), 7.84 (d, 2H, J = 8.5 Hz, H-2'', 6''), 8.22 (s, 1H, H-4), 10.91 (s, 1H, NH); IR (KBr, cm^{-1}): 3433, 3310, 1681, 1601, 1569, 1509, 1258, 1160, 847, 827; TOF-HRMS: m/z 508.0228 $[M+Na]^+$ ($C_{23}H_{16}ClNNaO_7S$ requires 508.0234).

4.1.9. 3-[4-(4-Bromophenylsulfonamido)benzoyl]-2H-1-benzopyran-2-one (**18**). Yellow solid, 27% yield. M.p.: 205-207°C; 1H -NMR (DMSO- d_6 , ppm): δ 7.20 (d, 2H, J = 8.7 Hz, H-3', 5'), 7.42 (m, 3H, H-6, 7, 8), 7.73 (d, 1H, J = 8.6 Hz, H-5), 7.78 (m, 6H, H-2', 6', 2'', 3'', 5'', 6''), 8.34 (s, 1H, H-4); IR (KBr, cm^{-1}): 3433, 3245, 1721, 1604, 1571, 1510, 1240, 1163, 823, 758; TOF-HRMS: m/z 483.9849 $[M+H]^+$ ($C_{22}H_{15}BrNO_5S$ requires 483.9855).

4.1.10. 3-[4-(4-Bromophenylsulfonamido)benzoyl]-7-hydroxy-2H-1-benzopyran-2-one (**19**). Yellow solid, 43% yield. M.p.: 203.5-204.5°C; 1H -NMR (DMSO- d_6 , ppm): δ 6.77 (s, 1H, H-8), 6.83 (d, 1H, J = 8.6 Hz, H-6), 7.22 (d, 2H, J = 8.7 Hz, H-3', 5'), 7.66 (d, 1H, J = 8.6 Hz, H-5), 7.76 (m, 6H, H-2', 6', 2'', 3'', 5'', 6''), 8.26 (s, 1H, H-4), 10.94 (s, 1H, OH), 11.03 (s, 1H, NH); IR (KBr, cm^{-1}): 3205, 1715, 1601, 1573, 1508, 1226, 1161, 852, 805; TOF-HRMS: m/z 499.9798 $[M+H]^+$ ($C_{22}H_{15}BrNO_6S$ requires 499.9804).

4.1.11. 3-[4-(4-Bromophenylsulfonamido)benzoyl]-7-(*N,N*-diethylamino)-2H-1-benzopyran-2-one (**20**). Yellow solid, 50% yield. M.p.: 215-216°C; 1H -NMR (DMSO- d_6 , ppm): δ 1.14 (t, 6H, J = 6.9 Hz, $2CH_2CH_3$), 3.47 (q, 4H, J = 6.9 Hz, $2CH_2CH_3$), 6.58 (s, 1H, H-8), 6.76 (d, 1H, J = 8.9 Hz, H-6), 7.20 (d, 2H, J = 8.7 Hz, H-3', 5'), 7.59 (d, 1H, J = 9.0 Hz, H-5), 7.69 (d, 2H, J = 8.7 Hz, H-3'', 5''), 7.77 (q, 4H, H-2', 6', 2'', 6''), 8.17 (s, 1H, H-4), 10.95 (s, 1H, NH); IR (KBr, cm^{-1}): 3438, 3180, 2974, 1715, 1688, 1617, 1600, 1579, 1508, 1233, 1162, 823, 740; TOF-HRMS: m/z 555.0584 $[M+H]^+$ ($C_{26}H_{24}BrN_2O_5S$ requires 555.0590).

4.1.12. 3-[4-(4-Bromophenylsulfonamido)benzoyl]-7-hydroxy-6-methoxy-2H-1-benzopyran-2-one (**21**). Yellow solid, 33% yield. M.p.: >250°C; 1H -NMR (DMSO- d_6 , ppm): δ 3.81 (s, 3H, OCH_3), 6.84 (s, 1H, H-5), 7.21 (d, 2H, J = 8.6 Hz, H-3', 5'), 7.36 (s, 1H, H-8), 7.77 (m, 6H, H-2', 6', 2'', 3'', 5'', 6''), 8.22 (s, 1H, H-4), 10.93 (s, 1H, NH); IR (KBr, cm^{-1}): 3426, 3304, 2924, 1682, 1602, 1569, 1510, 1257, 1157, 823, 787; TOF-HRMS: m/z 529.9904 $[M+H]^+$ ($C_{23}H_{17}BrNO_7S$ requires 529.9910).

4.1.13. 3-[4-(4-Methoxyphenylsulfonamido)benzoyl]-2H-1-benzopyran-2-one (**22**). White solid, 58% yield. M.p.: 175.5–176.5°C; ¹H-NMR (DMSO-*d*₆, ppm): δ 3.81 (s, 3H, OCH₃), 7.11 (d, 2H, *J* = 8.9 Hz, H-3'', 5''), 7.20 (d, 2H, *J* = 8.7 Hz, H-3', 5'), 7.44 (m, 2H, H-6, 8), 7.70 (d, 1H, *J* = 8.5 Hz, H-7), 7.78 (m, 5H, H-5, 2', 6', 2'', 6''), 8.33 (s, 1H, H-4), 10.88 (s, 1H, NH); IR (KBr, cm⁻¹): 3444, 3249, 1741, 1653, 1598, 1498, 1241, 1156, 836, 801; TOF-HRMS: *m/z* 436.0849 [M+H]⁺ (C₂₃H₁₈NO₆S requires 436.0856).

4.1.14. 3-[4-(4-Methoxyphenylsulfonamido)benzoyl]-7-hydroxy-2H-1-benzopyran-2-one (**23**). Orange solid, 59% yield. M.p.: 135–145°C; ¹H-NMR (DMSO-*d*₆, ppm): δ 3.80 (s, 3H, OCH₃), 6.76 (s, 1H, H-8), 6.83 (d, 1H, *J* = 8.6 Hz, H-6), 7.10 (d, 2H, *J* = 8.9 Hz, H-3'', 5''), 7.17 (d, 2H, *J* = 8.7 Hz, H-3', 5'), 7.64 (d, 1H, *J* = 8.6 Hz, H-5), 7.73 (m, 4H, H-2', 6', 2'', 6''), 8.23 (s, 1H, H-4); IR (KBr, cm⁻¹): 3317, 3227, 1732, 1646, 1600, 1497, 1228, 1146, 850, 829; TOF-HRMS: *m/z* 452.0798 [M+H]⁺ (C₂₃H₁₈NO₇S requires 452.0805).

4.1.15. 3-[4-(4-Methoxyphenylsulfonamido)benzoyl]-7-(*N,N*-diethylamino)-2H-1-benzopyran-2-one (**24**). Yellow solid, 37% yield. M.p.: 161–162°C; ¹H-NMR (DMSO-*d*₆, ppm): δ 1.13 (s, 6H, *J* = 6.9 Hz, 2CH₃), 3.47 (s, 4H, *J* = 6.9 Hz, 2CH₂), 3.80 (s, 3H, OCH₃), 6.57 (s, 1H, H-8), 6.76 (s, 1H, H-6), 7.08 (d, 2H, *J* = 7.6 Hz, H-3'', 5''), 7.20 (d, 2H, *J* = 8.4 Hz, H-3', 5'), 7.58 (d, 1H, *J* = 8.7 Hz, H-5), 7.70 (d, 2H, *J* = 8.1 Hz, H-2', 6'), 7.78 (d, 2H, *J* = 8.4 Hz, H-2'', 6''), 8.16 (s, 1H, H-4), 10.76 (s, 1H, NH); IR (KBr, cm⁻¹): 3438, 3232, 2973, 1696, 1618, 1598, 1581, 1510, 1233, 1158, 832, 803; TOF-HRMS: *m/z* 507.1584 [M+H]⁺ (C₂₇H₂₇N₂O₆S requires 507.1591).

4.1.16. 3-[4-(4-Methoxyphenylsulfonamido)benzoyl]-7-hydroxy-6-methoxy-2H-1-benzopyran-2-one (**25**). Yellow solid, 36% yield. M.p.: 167–168°C; ¹H-NMR (DMSO-*d*₆, ppm): δ 3.80 (s, 6H, 2OCH₃), 6.84 (s, 1H, H-5), 7.11 (d, 2H, *J* = 8.9 Hz, H-3'', 5''), 7.21 (d, 2H, *J* = 8.5 Hz, H-3', 5'), 7.35 (s, 1H, H-8), 7.75 (m, 4H, H-2', 6', 2'', 6''), 8.20 (s, 1H, H-4), 10.81 (s, 1H, NH); IR (KBr, cm⁻¹): 3430, 1715, 1598, 1567, 1508, 1263, 1156, 836, 789; TOF-HRMS: *m/z* 482.0904 [M+H]⁺ (C₂₄H₂₀NO₈S requires 482.0910).

4.1.17. 3-[4-(4-*tert*-Butylphenylsulfonamido)benzoyl]-7-(*N,N*-diethylamino)-2H-1-benzopyran-2-one (**26**). Orange solid, 33% yield. M.p.: 118–120°C; ¹H-NMR (DMSO-*d*₆, ppm): δ 1.14 (t, 6H, *J* = 7.0 Hz, 2CH₃), 1.16 (s, 9H, -C(CH₃)₃), 3.46 (q, 4H, *J* = 7.0 Hz, 2CH₂), 6.57 (s, 1H, H-8), 6.75 (d, 1H, *J* = 9.0 Hz, H-6), 7.18 (d, 2H, *J* = 8.7 Hz, H-3', 5'), 7.58 (m, 3H, H-5, 2', 6'), 7.68 (d, 2H, *J* = 8.7 Hz, H-3'', 5''), 7.78 (d, 2H, *J* = 8.6 Hz, H-2'', 6''), 8.16 (s, 1H, H-4), 10.88 (s, 1H, NH); IR (KBr, cm⁻¹): 3436, 2967, 1721, 1618, 1600, 1510, 1234, 1162, 828, 788; TOF-HRMS: *m/z* 533.2105 [M+H]⁺ (C₃₀H₃₃N₂O₅S requires 533.2111).

4.2. Assay of the *In Vitro* α-Glucosidase Inhibitory Activity. A 100 μL reaction system containing 0.02 U of α-glucosidase, 67 nM sodium phosphate buffer (pH 6.8), and a test compound were preincubated at 37°C for 10 min. A negative

control in the absence of a test compound and a blank control in the absence of either an enzyme or the test compound were run simultaneously. The reaction was initiated by the addition of 0.1 M maltose, and the reaction mixture was incubated at room temperature for 10 min. Then, the 200 μL glucose-detecting agent was added, and the absorbance (A) at 490 nm was recorded on a SPECTRAMax Plus 384 reader (MD, USA). The test compounds were initially assayed for their inhibition of α-glucosidase at a concentration of 10 μg/mL. Calculate inhibition ratio according to OD value; inhibition ratio = [1 - (OD_{sample} - OD_{blank})/(OD_{negative} - OD_{blank})] × 100%. Each monoconcentration had two replicates when preliminary screened. If an inhibition ratio of more than 70% was observed, diluted 10 times and re-screened. If an inhibition ratio of re-screening was more than 70%, measured IC₅₀ value. The active compounds were consequently tested at six gradient dilute concentrations, with each concentration having two replicates. On the basis of inhibition ratio, the IC₅₀ values were calculated using 4-Parameter Logistic Model of Xlfit software.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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