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Short communication

Synthesis and evaluation of the α-glucosidase inhibitory activity of 3-[4-(phenylsulfonamido)benzoyl]-2*H*-1-benzopyran-2-one derivatives

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ABSTRACT

In the course of studies directed toward the discovery of novel non-sugar α-glucosidase inhibitors for the treatment of diabetes, a series of 3-[4-(phenylsulfonamido)benzoyl]-2*H*-1-benzopyran-2-one derivatives was synthesized and evaluated as α-glucosidase inhibitors. Most compounds showed good inhibitory activity with IC_{50} values ranging from 0.0645 μM to 26.746 μM. 7-Hydroxy-6-methoxy-3-[4-(4-methylphenylsulfonamido)benzoyl]-2*H*-1-benzopyran-2-one **7u** manifested the most potent inhibitory activity with an IC_{50} value of 0.0645 μM.

1. Introduction

α-Glucosidase (EC 3.2.1.20) is located in the brush-border surface membrane of intestinal cells. It is responsible for catalyzing the final step in the digestive process of carbohydrates [1]. Meanwhile, α-Glucosidase inhibitors can retard the gastrointestinal absorption of dietary carbohydrates by inhibiting the digestion of polysaccharides and disaccharides, thus lessening the postprandial increase in the blood glucose level [2]. Several sugar α-glucosidase inhibitors, including acarbose, voglibose, and miglitol are clinically used in the effective treatment of type 2 diabetes mellitus [3]. However, such inhibitors, which are of great structural diversity, require tedious multi-steps during preparation. Hence, greater attention is focused on non-sugar α-glucosidase inhibitors.

Flavones display extensive biological activities, including anticancer, antifungal, antiviral, and anti-inflammatory activities [4–7]. Recent studies indicate that Baicalein **1** and its analogues can effectively inhibit sucrase [8]. In the course of identifying potential α-glucosidase inhibitors from the Indian herb *Oroxylum indicum*, it was observed that extracts of this plant possess inhibitory activity, with Oroxylin A **2**, Baicalein **1,** and Chrysin **3** posing as the major isolates for the activity [9]. Actually, flavones can be considered to be structurally constrained analogues of chalcones, with the chalcone substructure incorporated into the benzopyran backbone.

Chalcones demonstrate various biological activities, including antimalarial, antifungal, anti-inflammatory, and cytotoxic activities [10–13]. Chalcones with sulfonamide substitution have recently received significant attention for their biological activities, such as their fungicidal, antimalarial, antileishmanial, and anti-interleukin-5 activities [14–17]. Seo et al. found that aminochalcones, such as **4,** exhibit α-glucosidase inhibitory activity. Encouraged by the anti-diabetic sulfonylureas, they further synthesized several phenylsulfonamide chalcones, such as **5** and **6,** which displayed higher α-glucosidase inhibitory activity compared with their corresponding amino analogues [18]. To investigate the binding mode of sulfonamide chalcone, a homology-modeled α-glucosidase protein structure was developed by Bharatham et al. The study found that the sulfonamide group interacts with Asp349, His348, and Arg212 through hydrogen bonds, and the benzene ring of phenylsulfonamide chalcone is inserted into the pocket comprised of Tyr71, Phe157, Phe158, and Phe177 through a hydrophobic interaction [19]. Thus, the phenylsulfonamide chalcone scaffold may be useful for designing new α-glucosidase inhibitors.

In this paper, a series of 3-[4-(phenylsulfonamido)benzoyl]-2*H*-1-benzopyran-2-one derivatives (Fig. 1), being structurally constrained analogues of phenylsulfonamide chalcones with the phenylsulfonamide chalcone substructure incorporated into the benzopyran backbone, was designed and synthesized to find novel non-sugar α-glucosidase inhibitors and to verify the viability of

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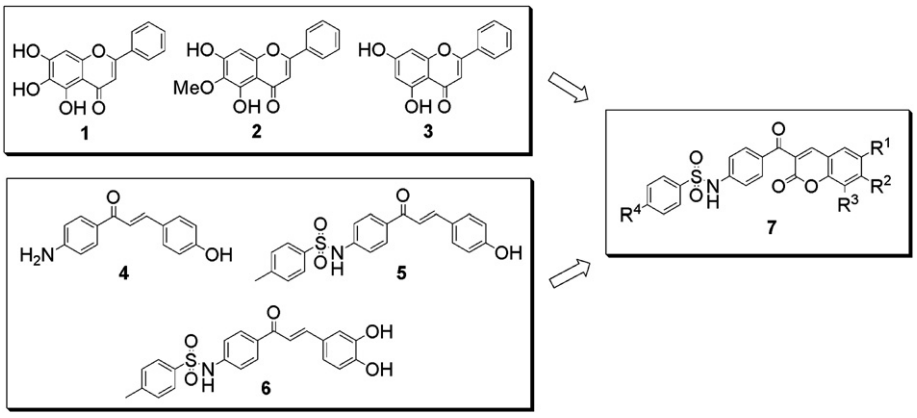


Fig. 1. Schematic diagram depicting the procedure for the design of the target compounds.

using 3-[4-(phenylsulfonamido)benzoyl]-2*H*-1-benzo-pyran-2-one as a scaffold for the design of α-glucosidase inhibitors. The α-glucosidase inhibitory activity of the synthesized compounds was evaluated on yeast α-glucosidase, and their structure–activity relationships were considered.

2. Results and discussion

2.1. Chemistry

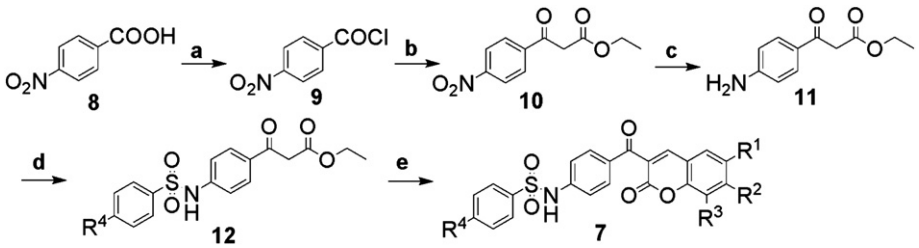
The synthesis of the target compounds (**7a–v)** is outlined in Scheme 1. The treatment of 4-nitrobenzoic acid with thionyl chloride under reflux resulted in 4-nitrobenzoyl chloride [20]. This then reacted with ethyl acetoacetate in the presence of sodium ethylate, and the resulting followed by hydrolysis to afford compound **10**, which was hydrogenated over the Pd/C catalyst to provide compound **11**. Following this, compound **11** was acylated with benzenesulfonyl chloride and 4-methylbenzenesulfonyl chloride, respectively, and the two key intermediates **12a** and **12b** were obtained [21]. Lastly, the two intermediates were reacted separately with substituted salicylaldehydes via Knoevenagel condensation, and 22 target compounds were obtained [22], the structures of which were fully supported by ^{1}H NMR, IR, and TOF-HRMS spectral data.

2.2. α-Glucosidase inhibitory activity

The in vitro inhibitory activity of the target compounds was evaluated spectrophotometrically at 490 nm on yeast α-glucosidase, as shown in Table 1. It was proven that most of the 3-[4-(phenylsulfonamido)benzoyl]-2*H*-1-benzopyran-2-one derivatives demonstrated good inhibitory activity with IC_{50} values ranging from 0.0645 μM to 26.746 μM.

In the $R^4 = H$ series, the activity of compound **7b** ($IC_{50} = 7.180$ μM) was lower than that of compound **7a** ($IC_{50} = 3.283$ μM), and compounds **7c** and **7d** had no activity, suggesting that the halogen group at the C6 position could reduce the activity. As compared to compound **7a**, compound **7f** ($IC_{50} = 7.129$ μM) with *tert*-butyl groups at C6 and C8, respectively, possessed lower activity; this bulky group might be unfavorable for binding with α-glucosidase. When C7 was substituted with the methoxy group, such as compounds **7g** and **7k**, their activities disappeared, demonstrating that the methoxy group at the C7 position was deficient for inhibitory activity. When C7 was substituted with hydroxy, the activity of compound **7h** decreased slightly with an IC_{50} value of 5.766 μM. In the case of C7 substituted with diethylamino, the activity of compound **7i** ($IC_{50} = 0.294$ μM) was enhanced 11-fold compared to that of compound **7a**. Compound **7j** ($IC_{50} = 0.199$ μM) possessed the strongest inhibitory activity of the series, and its activity was 16 times higher than that of compound **7a**, and 29 times higher than that of compound **7h**. Apparently, the methoxy group at the C6 position plays an important role in promoting the activity. By comparing two compound couples, **7h** versus **7g** and **7j** versus **7k**, it was obvious that the methylation of the hydroxy group at the C7 position had a negative impact on inhibitory activity.

In the $R^4 = CH_3$ series, by separately comparing compound **7l** ($IC_{50} = 3.577$ μM) with compounds **7m** ($IC_{50} = 4.600$ μM), **7n** ($IC_{50} = 26.746$ μM), and **7o** ($IC_{50} > 30$ μM), it was observed that the modification of benzopyranone moiety with halogen groups reduced inhibitory activity. Such a tendency might act as F < Cl < Br; a similar trend could also be found in the $R^4 = H$ series. Compound **7q** ($IC_{50} = 10.099$ μM) with tert-butyl groups at the C6 and C8 positions, possessed lower activity compared to compound **7l**, and this was in agreement with compound **7f** versus compound **7a** in the $R^4 = H$ series. Concerning compounds **7s**



Scheme 1. Synthesis of 3-[4-(phenylsulfonamido)benzoyl]-2*H*-1-benzopyran-2-one derivatives **7**. Reagents and conditions: (a) $SOCl_2$ reflux; (b) ethyl acetoacetate, EtONa in EtOH, THF, −10 °C, then rt; (c) H_2, Pd/C, EtOH, rt; (d) benzenesulfonyl/4-methylbenzenesulfonyl chloride, pyridine, CH_2Cl_2,–10 °C, then rt; (e) substituted salicylaldehyde, piperidine, acetic acid, EtOH, reflux.

Table 1
The in vitro inhibitory activity of 3-[4-(phenylsulfonamido)benzoyl]-2*H*-1-benzopyran-2-one derivatives against yeast α-glucosidase.

No	R^1	R^2	R^3	R^4	IC_{50}[a] (μM)	No	R^1	R^2	R^3	R^4	IC_{50}[a] (μM)
7a	H	H	H	H	3.283	**7l**	H	H	H	CH_3	3.577
7b	F	H	H	H	7.180	**7m**	F	H	H	CH_3	4.600
7c	Cl	H	H	H	>30[b]	**7n**	Cl	H	H	CH_3	26.746
7d	Br	H	H	H	>30[b]	**7o**	Br	H	H	CH_3	>30[b]
7e	Br	H	Br	H	>30[b]	**7p**	Br	H	Br	CH_3	7.727
7f	$C(CH_3)_3$	H	$C(CH_3)_3$	H	7.129	**7q**	$C(CH_3)_3$	H	$C(CH_3)_3$	CH_3	10.099
7g	H	OCH_3	H	H	>30[b]	**7r**	H	OCH_3	H	CH_3	>30[b]
7h	H	OH	H	H	5.766	**7s**	H	OH	H	CH_3	1.125
7i	H	$N(C_2H_5)_2$	H	H	0.294	**7t**	H	$N(C_2H_5)_2$	H	CH_3	0.347
7j	OCH_3	OH	H	H	0.199	**7u**	OCH_3	OH	H	CH_3	0.0645
7k	OCH_3	OCH_3	H	H	>30[b]	**7v**	OCH_3	OCH_3	H	CH_3	5.589

[a] IC_{50} values: the concentration of the inhibitor required to produce 50% inhibition of α-glucosidase.
[b] $IC_{50} > 30$ μM was considered to be no inhibitory activity.

($IC_{50} = 1.125$ μM), **7t** ($IC_{50} = 0.347$ μM), and **7u** ($IC_{50} = 0.0645$ μM), the activity increased remarkably in the presence of the hydroxy or diethylamino groups at the C7 position. By comparing compounds **7s** and **7u** in relation to compounds **7r** ($IC_{50} > 30$ μM) and **7v** ($IC_{50} = 5.589$ μM), respectively, it was noted that the methylation of the hydroxy group at the C7 position was not beneficial for their activities; moreover, compound **7u** with a methoxy group at the C6 position showed the strongest inhibitory activity between the two series. In general, most compounds in the $R^4 = CH_3$ series showed higher activities than those in the $R^4 = H$ series. The activities of compounds **7m**, **7n**, **7p**, **7s**, **7u**, and **7v** were higher than those of compounds **7b**, **7c**, **7e**, **7h**, **7j**, and **7k**, respectively.

Finally, by comparing compounds **7s** and **7u** in relation to compounds **19** ($IC_{50} = 0.98$ μM) and **20** ($IC_{50} = 0.40$ μM) in reference 18 [18], respectively, it was interesting to find that compound **7s** was comparable to compound **19,** whereas compound **7u** showed inhibitory activity that was 6-fold stronger than that of compound **20**.

3. Conclusion

In summary, the results showed that 3-[4-(phenylsulfonamido)benzoyl]-2*H*-1-benzopyran-2-one derivatives represent a new class of strong non-sugar α-glucosidase inhibitors and 3-[4-(phenylsulfonamido)benzoyl]-2*H*-1-benzopyran-2-one might be a suitable scaffold to use in the design of new α-glucosidase inhibitors. Among the compounds synthesized, compound **7u** showed the strongest inhibitory activity. Further investigations into the structure–activity relationships together with tests on mammalian animal models are currently in progress in our laboratory.

4. Experimental protocols

4.1. Chemistry

Melting points were recorded using YRT-3 melting point apparatus and were uncorrected. The ^{1}H 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 determined using an Agilent 1100 instrument. All solvents and reagents were of analytical grade.

4.1.1. 4-Nitrobenzoyl chloride **9**

A mixture of 4-nitrobenzoic acid **8** (150.0 g, 0.9 mol) and thionyl chloride (210 ml) was stirred under reflux for 5 h. The mixture was then condensed under reduced pressure, and a yellow solid (166.8 g) was obtained with a yield of 99.8%. The product was sufficiently pure to proceed to the next step.

4.1.2. Ethyl 3-(4-nitrophenyl)-3-oxopropanoate **10**

A solution of sodium ethylate prepared from sodium metal (13.8 g, 0.6 mol) and anhydrous ethanol (230 ml) was added dropwise to ethyl acetoacetate (117 g, 0.9 mol) at −10 °C. The solution was stirred at room temperature for 1–2 h, and a solution of 4-nitrobenzoyl chloride (167 g, 0.9 mol) in dry THF (1200 ml) was added dropwise at −10 °C. The solution was stirred at room temperature for 4–5 h. The THF was evaporated under reduced pressure. The residue was mixed with ether (1000 ml) and was then filtered. The cake was washed with ether and mixed with water (1000 ml). The mixture was warmed to 35 °C, and a solution of ammonium chloride (60 g) and 25% ammonium hydroxide (60 ml) was added. After stirring overnight, the solution was cooled to 5 °C and was left to stand for 2 h. After the filtering and drying process, 110 g of solid was obtained and it was purified by column chromatography (chloroform) to give **10** as a yellow solid (88 g, 41.2%), mp 70–72 °C (68–71 °C [23]).

4.1.3. Ethyl 3-(4-aminophenyl)-3-oxopropanoate **11**

A solution of ethyl 3-(4-nitrophenyl)-3-oxopropanoate **10** (88 g, 0.37 mol) in anhydrous ethanol (1000 ml) was hydrogenated over 10% Pd/C (1 g) at room temperature for 5 h. The solvent was filtered and evaporated under reduced pressure to produce a light yellow solid (57.3 g, 74.6%), mp 82–84 °C (84.3–84.5 °C [24]).

4.1.4. Ethyl 3-oxo-3-[4-(phenylsufonamido)phenyl]propanoate **12a**

A mixture of ethyl 3-(4-aminophenyl)-3-oxopropanoate **11** (15 g, 0.04 mol), dry pyridine (8.6 g, 0.11 mol), and dry methylene chloride (90 ml) was stirred and cooled to −10 °C. Phenylsulfonyl chloride (14.5 g, 0.08 mol) in dry methylene chloride (45 ml) was added dropwise at –5–0 °C. The mixture was then stirred at room temperature for 5 h. The solution was washed with a 5% HCl solution (23 ml × 3), and water (20 ml × 3). The organic phase was then collected and dried overnight over anhydrous Na_2SO_4. After filtering, the solvent was evaporated under reduced pressure and the residue was recrystallized from anhydrous ethanol. A white solid was obtained (22.3 g, 83%), mp 112–113 °C; ^{1}H NMR (DMSO-d_6, ppm): δ 1.14 (t, 3H, $J = 6.9$ Hz, CH_3), 4.07 (m, 4H, $2CH_2$), 7.22 (d, 2H, $J = 8.7$ Hz, arom), 7.61 (m, 3H, arom), 7.84 (m, 4H, arom), 10.97 (s, 1H, NH).

*4.1.5. Ethyl 3-[4-(4-methylphenylsulfonamido)phenyl]-3-oxopropanoate **12b***

The synthetic procedure was similar to that for **12a**. A white solid weighing 13.6 g was obtained, with a yield of 52%, mp 140–141 °C; ^{1}H NMR (DMSO-d_6, ppm): δ 1.11 (t, 3H, $J = 6.9$ Hz, CH_2CH_3), 2.33 (s, 3H, CH_3), 4.07 (m, 4H, $2CH_2$), 7.21 (d, 2H, $J = 8.7$ Hz, arom), 7.37 (d, 2H, $J = 8.1$ Hz, arom), 7.73 (d, 2H, $J = 8.1$ Hz, arom), 7.82 (d, 2H, $J = 8.7$ Hz, arom), 10.89 (s, 1H, NH).

*4.1.6. General procedure for the synthesis of compounds **7a–v***

A mixture of **12** (1.4 mmol), substituted salicylaldehyde (1.6 mmol), five drops of piperidine, one drop of glacial acetic acid, and ethanol (10 ml) was stirred under reflux in an argon atmosphere for 0.5 h. The mixture was cooled to room temperature and was filtered to collect the solid (if there was no precipitate, water (25 ml) was added), then it was washed with a small amount of ethanol. In most cases, the products were sufficiently pure. Products with impurities could be purified by column chromatography (petroleum ether–ethyl acetate 100:0–300).

*4.1.6.1. 3-[4-(phenylsulfonamido)benzoyl]-2H-1-benzopyran-2-one **7a**.* Yield 51.4%, a white solid, mp 159–161 °C; ^{1}H NMR (DMSO-d_6, ppm): δ 7.22 (d, 2H, $J = 8.7$ Hz, arom), 7.42–7.44 (m, 1H, H-8), 7.47–7.49 (m, 1H, H-6), 7.57–7.66 (m, 3H, arom), 7.70–7.72 (m, 1H, H-7), 7.81–7.88 (m, 5H, arom), 8.33 (s, 1H, H-4), 11.04 (br s, 1H, NH); IR (KBr, cm^{-1}): 3173, 1710, 1661, 1607, 1566, 1509, 1266, 1166, 851, 804; TOF-HRMS: m/z 428.0567 $[M + Na]^+$ ($C_{22}H_{15}NNaO_5S$ requires 428.0569).

*4.1.6.2. 6-Fluoro-3-[4-(phenylsulfonamido)benzoyl]-2H-1-benzopyran-2-one **7b**.* Yield 50.5%, a light yellow solid, mp 185–186 °C; ^{1}H NMR (DMSO-d_6, ppm): δ 7.22 (d, 2H, $J = 8.7$ Hz, arom), 7.56–7.70 (m, 6H, arom), 7.83–7.88 (m, 4H, arom), 8.28 (s, 1H, H-4), 11.05 (s, 1H, NH); IR (KBr, cm^{-1}): 3197, 1705, 1673, 1602, 1572, 1507, 1282, 1247, 1163, 844, 791; TOF-HRMS: m/z 446.0456 $[M + Na]^+$ ($C_{22}H_{14}FNNaO_5S$ requires 446.0474).

*4.1.6.3. 6-Chloro-3-[4-(phenylsulfonamido)benzoyl]-2H-1-benzopyran-2-one **7c**.* Yield 76.8%, a light yellow solid, mp 225–226 °C; ^{1}H NMR (DMSO-d_6, ppm): δ 7.23 (d, 2H, $J = 8.4$ Hz, arom), 7.52 (d, 1H, $J = 8.9$ Hz, H-8), 7.60–7.66 (m, 3H, arom), 7.75 (dd, 1H, $J = 8.9$ and 2.4 Hz, H-7), 7.86 (m, 4H, arom), 7.93 (d, 1H, $J = 2.4$ Hz, H-5), 8.27 (s, 1H, H-4), 11.06 (br s, 1H, NH); IR (KBr, cm^{-1}): 3200, 1705, 1673, 1600, 1280, 1238, 1163, 844, 787; TOF-HRMS: m/z 462.0175 $[M + Na]^+$ ($C_{22}H_{14}ClNNaO_5S$ requires 462.0179).

*4.1.6.4. 6-Bromo-3-[4-(phenylsulfonamido)benzoyl]-2H-1-benzopyran-2-one **7d**.* Yield 76.3%, a yellow solid, mp 223–224 °C; ^{1}H NMR (DMSO-d_6, ppm): δ 7.23 (d, 2H, $J = 8.7$ Hz, arom), 7.46 (d, 1H, $J = 8.6$ Hz, H-8), 7.57–7.66 (m, 3H, arom), 7.84–7.89 (m, 5H, arom), 8.06 (d, 1H, $J = 2.3$ Hz, H-5), 8.26 (s, 1H, H-4), 11.06 (s, 1H, NH); IR (KBr, cm^{-1}): 3235, 1753, 1649, 1598, 1513, 1214, 1156, 846, 789; TOF-HRMS: m/z 505.9674 $[M + Na]^+$ ($C_{22}H_{14}BrNNaO_5S$ requires 505.9674).

*4.1.6.5. 6, 8-Dibromo-3-[4-(phenylsulfonamido)benzoyl]-2H-1-benzopyran-2-one **7e**.* Yield 59.8%, an orange solid, mp 237–238 °C; ^{1}H NMR (DMSO-d_6, ppm): δ 7.23 (d, 2H, $J = 8.4$ Hz, arom), 7.60–7.66 (m, 3H, arom), 7.87 (m, 4H, arom), 8.07 (d, 1H, $J = 2.1$ Hz, H-5), 8.25 (s, 2H, H-4, 7), 11.07 (s, 1H, NH); IR (KBr, cm^{-1}): 3191, 1716, 1666, 1610, 1549, 1508, 1245, 1216, 1166, 850, 796; TOF-HRMS: m/z 585.8733 $[M + Na]^+$ ($C_{22}H_{13}Br_2NNaO_5S$ requires 585.8758).

*4.1.6.6. 6, 8-Di-tert-butyl-3-[4-(phenylsulfonamido)benzoyl]-2H-1-benzopyran-2-one **7f**.* Yield 67.8%, a light yellow solid, mp 237–238 °C; ^{1}H NMR (DMSO-d_6, ppm): δ 1.31 (s, 9H, $3CH_3$), 1.46 (s, 9H, $3CH_3$), 7.23 (d, 2H, $J = 8.4$ Hz, arom), 7.58–7.68 (m, 5H, arom), 7.81–7.87 (m, 4H, arom), 8.28 (s, 1H, H-4), 11.02 (s, 1H, NH); IR (KBr, cm^{-1}): 3221, 2966, 1748, 1648, 1579, 1577, 1513, 1238, 1193, 1160, 851, 792; TOF-HRMS: m/z 540.1818 $[M + Na]^+$ ($C_{30}H_{31}NNaO_5S$ requires 540.1821).

*4.1.6.7. 7-Methoxy-3-[4-(phenylsulfonamido)benzoyl]-2H-1-benzopyran-2-one **7g**.* Yield 93.3%, an orange solid, mp 207–208 °C; ^{1}H NMR (DMSO-d_6, ppm): δ 3.90 (s, 3H, OCH_3), 7.02 (d, 1H, $J = 8.4$ Hz, H-6), 7.08 (s, 1H, H-8), 7.21 (d, 2H, $J = 8.7$ Hz, arom), 7.57–7.66 (m, 3H, arom), 7.74–7.80 (m, 3H, arom), 7.86 (d, 2H, $J = 6.9$ Hz, arom), 8.29 (s, 1H, H-4), 10.99 (s, 1H, NH); IR (KBr, cm^{-1}): 3146, 1694, 1661, 1603, 1558, 1505, 1227, 1161, 840, 786; TOF-HRMS: m/z 458.0668 $[M + Na]^+$ ($C_{23}H_{17}NNaO_6S$ requires 458.0674).

*4.1.6.8. 7-Hydroxy-3-[4-(phenylsulfonamido)benzoyl]-2H-1-benzopyran-2-one **7h**.* Yield 23.5%, a yellow solid, mp 140–141 °C; ^{1}H NMR (DMSO-d_6, ppm): δ 6.70 (d, 1H, $J = 2.1$ Hz, H-8), 6.84 (dd, 1H, $J = 8.4$ and 2.1 Hz, H-6), 7.20 (d, 2H, $J = 8.7$ Hz, arom), 7.59–7.68 (m, 4H, arom), 7.76 (d, 2H, $J = 8.7$ Hz, arom), 7.86 (d, 2H, $J = 7.2$ Hz, arom), 8.24 (s, 1H, H-4), 10.93 (s, 1H, OH), 10.96 (s, 1H, NH); IR (KBr, cm^{-1}): 3218, 1714, 1600, 1507, 1227, 1159, 852, 790; TOF-HRMS: m/z 444.0510 $[M + Na]^+$ ($C_{22}H_{15}NNaO_6S$ requires 444.0518).

*4.1.6.9. 7-Diethylamino-3-[4-(phenylsulfonamido)benzoyl]-2H-1-benzopyran-2-one **7i**.* Yield 70.3%, a yellow solid, mp 110–111 °C; The ^{1}H NMR (DMSO-d_6, ppm): δ 1.15 (t, 6H, $2CH_2CH_3$), 3.48 (m, 4H, $2CH_2CH_3$), 6.58 (s, 1H, H-8), 6.76 (d, 1H, $J = 8.5$ Hz, H-6), 7.00 (d, 2H, $J = 8.5$ Hz, arom), 7.51–7.57 (m, 6H, arom), 7.80 (d, 2H, $J = 5.7$ Hz, arom), 8.07 (s, 1H, H-4); IR (KBr, cm^{-1}): 3444, 3057, 2972, 1709, 1579, 1506, 1236, 1181, 1133, 830, 791; TOF-HRMS: m/z 477.1481 $[M + H]^+$ ($C_{26}H_{24}N_2NaO_5S$ requires 477.1484).

*4.1.6.10. 7-Hydroxy-6-methoxy-3-[4-(phenylsulfonamido)benzoyl]-2H-1-benzopyran-2-one **7j**.* Yield 20.0%, a brown solid, mp 142–144 °C; ^{1}H NMR (DMSO-d_6, ppm): δ 3.81 (s, 3H, OCH_3), 6.84 (s, 1H, H-8), 7.21 (d, 2H, $J = 8.6$ Hz, arom), 7.35 (s, 1H, H-5), 7.59–7.66 (m, 3H, arom), 7.74 (d, 2H, $J = 8.6$ Hz, arom), 7.86 (d, 2H, $J = 7.0$ Hz, arom), 8.21(s, 1H, H-4), 10.74 (s, 1H, OH), 10.96(s, 1H, NH); IR (KBr, cm^{-1}): 3421, 3215, 2926, 1718, 1560, 1510, 1262, 1159, 852, 807; TOF-HRMS: m/z 474.0612 $[M + Na]^+$ ($C_{23}H_{17}NNaO_7S$ requires 474.0623).

*4.1.6.11. 6, 7-Dimethoxy-3-[4-(phenylsulfonamido)benzoyl]-2H-1-benzopyran-2-one **7k**.* Yield 92.5%, a yellow solid, mp 248–249 °C; ^{1}H NMR (DMSO-d_6, ppm): δ 3.80 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 7.16 (s, 1H, H-8), 7.22 (d, 2H, $J = 8.7$ Hz, arom), 7.37 (s, 1H, H-5), 7.59–7.66 (m, 3H, arom), 7.77 (d, 2H, $J = 8.7$ Hz, arom), 7.86 (d, 2H, $J = 6.9$ Hz, arom), 8.24 (s, 1H, H-4), 10.99 (s, 1H, NH); IR (KBr, cm^{-1}): 3424, 3251, 1723, 1652, 1604, 1558, 1506, 1268, 1239, 1163, 858, 831; TOF-HRMS: m/z 448.0780 $[M + Na]^+$ ($C_{24}H_{19}NNaO_7S$ requires 488.0780).

*4.1.6.12. 3-[4-(4-Methylphenylsulfonamido)benzoyl]-2H-1-benzopyran-2-one **7l**.* Yield 83.8%, a white solid, mp 109–110 °C; ^{1}H NMR (DMSO-d_6, ppm): δ 2.35 (s, 3H, CH_3), 7.21 (d, 2H, $J = 8.7$ Hz, arom), 7.37–7.50 (m, 4H, arom), 7.65–7.72 (m, 3H, arom), 7.81–7.88 (m, 3H, arom), 8.33 (s, 1H, H-4), 10.96 (s, 1H, NH); IR (KBr, cm^{-1}): 3226, 1731, 1652, 1598, 1509, 1244, 1186, 1159, 856, 810; TOF-HRMS: m/z 442.0731 $[M + Na]^+$ ($C_{23}H_{17}NNaO_5S$ requires 442.0725).

*4.1.6.13. 6-Fluoro-3-[4-(4-methylphenylsulfonamido)benzoyl]-2H-1-benzopyran-2-one **7m**.* Yield 39.7%, a yellow solid, mp 161–162 °C; ^{1}H NMR (DMSO-d_6, ppm): δ 2.35 (s, 3H, CH_3), 7.21 (d, 2H, $J = 8.4$ Hz,

arom), 7.39 (d, 2H, $J = 8.1$ Hz, arom), 7.55–7.61 (m, 2H, H-5, 8), 7.69 (dd, 1H, $J = 8.4$ and 2.7 Hz, H-7), 7.75 (d, 2H, $J = 8.1$ Hz, arom), 7.84 (d, 2H, $J = 8.7$ Hz, arom), 8.27 (s, 1H, H-4), 10.98 (s, 1H, NH); IR (KBr, cm^{-1}): 3218, 1754, 1597, 1513, 1251, 1188, 1154, 826, 790; TOF-HRMS: m/z 460.0623 $[M + Na]^+$ ($C_{23}H_{16}FNNaO_5S$ requires 460.0631).

4.1.6.14. 6-Chloro-3-[4-(4-methylphenylsulfonamido)benzoyl]-2H-1-benzopyran-2-one ***7n***. Yield 43.2%, a yellow solid, mp 186–187 °C; ^1H NMR (DMSO-d_6, ppm): δ 2.35 (s, 3H, CH_3), 7.22 (d, 2H, $J = 8.7$ Hz, arom), 7.38 (d, 2H, $J = 8.1$ Hz, arom), 7.53 (d, 1H, $J = 8.7$ Hz, H-8), 7.75 (m, 3H, arom), 7.84 (d, 2H, $J = 8.7$ Hz, arom), 7.93 (d, 1H, $J = 2.4$ Hz, H-5), 8.26 (s, 1H, H-4), 10.98 (s, 1H, NH); IR (KBr, cm^{-1}): 3215, 1756, 1649, 1597, 1512, 1240, 1189, 1156, 825, 789; TOF-HRMS: m/z 476.0343 $[M + Na]^+$ ($C_{23}H_{16}ClNNaO_5S$ requires 476.0336).

4.1.6.15. 6-Bromo-3-[4-(4-methylphenylsulfonamido)benzoyl]-2H-1-benzopyran-2-one ***7o***. Yield 72.6%, a yellow solid, mp 187–188 °C; ^1H NMR (DMSO-d_6, ppm): δ 2.35 (s, 3H, CH_3), 7.21 (d, 2H, $J = 8.7$ Hz, arom), 7.38 (d, 2H, $J = 7.8$ Hz, arom), 7.45 (d, 1H, $J = 9.0$ Hz, H-8), 7.75 (d, 2H, $J = 7.8$ Hz, arom), 7.84 (m, 3H, arom), 8.06 (s, 1H, H-5), 8.25 (s, 1H, H-4), 10.98 (br s, 1H, NH); IR (KBr, cm^{-1}): 3444, 3179, 1714, 1696, 1621, 1581, 1508, 1238, 1190, 1149, 854, 805; TOF-HRMS: m/z 519.9839 $[M + Na]^+$ ($C_{23}H_{16}BrNNaO_5S$ requires 519.9830).

4.1.6.16. 6, 8-Dibromo-3-[4-(4-methylphenylsulfonamido)benzoyl]-2H-1-benzopyran-2-one ***7p***. Yield 65.6%, a yellow solid, mp 227–228 °C; ^1H NMR (DMSO-d_6, ppm): δ 2.35 (s, 3H, CH_3), 7.21 (d, 2H, $J = 8.7$ Hz, arom), 7.39 (d, 2H, $J = 8.1$ Hz, arom), 7.75 (d, 2H, $J = 8.1$ Hz, arom), 7.86 (d, 2H, $J = 8.4$ Hz, arom), 8.07 (d, 1H, $J = 2.1$ Hz, H-5), 8.25 (s, 2H, H-4, 7), 10.99 (br s, 1H, NH); IR (KBr, cm^{-1}): 3244, 1747, 1655, 1600, 1510, 1240, 1184, 1160, 859, 796; TOF-HRMS: m/z 599.8918 $[M + Na]^+$ ($C_{23}H_{15}Br_2NNaO_5S$ requires 599.8915).

4.1.6.17. 6, 8-Di-tert-butyl-3-[4-(4-methylphenylsulfonamido)benzoyl]-2H-1-benzopyran-2-one ***7q***. Yield 90.0%, a white solid, mp 218–219 °C; ^1H NMR (DMSO-d_6, ppm): δ 1.32 (s, 9H, $3CH_3$), 1.39 (s, 9H, $3CH_3$), 2.35 (s, 3H, CH_3), 7.22 (d, 2H, $J = 8.7$ Hz, arom), 7.39 (d, 2H, $J = 8.4$ Hz, arom), 7.64 (d, 1H, $J = 2.1$ Hz, H-7), 7.70 (d, 1H, $J = 2.1$ Hz, H-5), 7.75 (d, 2H, $J = 8.1$ Hz, arom), 7.84 (d, 2H, $J = 8.7$ Hz, arom), 8.29 (s, 1H, H-4), 10.96 (s, 1H, NH); IR (KBr, cm^{-1}): 3182, 2962, 1722, 1689, 1659, 1601, 1510, 1238, 1186, 1162, 848, 813; TOF-HRMS: m/z 554.2033 $[M + Na]^+$ ($C_{31}H_{33}NNaO_5S$ requires 554.1977).

4.1.6.18. 7-Methoxy-3-[4-(4-methylphenylsulfonamido)benzoyl]-2H-1-benzopyran-2-one ***7r***. Yield 71.6%, a yellow solid, mp 212–213 °C; ^1H NMR (DMSO-d_6, ppm): δ 2.34 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 7.01 (d, 1H, $J = 8.7$ Hz, H-6), 7.08 (s, 1H, H-8), 7.20 (d, 2H, $J = 8.7$ Hz, arom), 7.38 (d, 2H, $J = 8.1$ Hz, arom), 7.76 (m, 5H, arom), 8.29 (s, 1H, H-4), 10.92 (s, 1H, NH); IR (KBr, cm^{-1}): 3272, 1730, 1651, 1603, 1504, 1227, 1185, 1156, 843, 810; TOF-HRMS: m/z 472.0839 $[M + Na]^+$ ($C_{24}H_{19}NNaO_6S$ requires 472.0831).

4.1.6.19. 7-Hydroxy-3-[4-(4-methylphenylsulfonamido)benzoyl]-2H-1-benzopyran-2-one ***7s***. Yield 44.0%, a dark yellow solid, mp 150–151 °C; ^1H NMR (DMSO-d_6, ppm): δ 2.34 (s, 3H, CH_3), 6.77 (s, 1H, H-8), 6.84 (d, 1H, $J = 8.4$ Hz, H-6), 7.20 (d, 2H, $J = 8.7$ Hz, arom), 7.38 (d, 2H, $J = 8.4$ Hz, arom), 7.66 (d, 1H, $J = 8.4$ Hz, H-5), 7.74 (m, 4H, arom), 8.24 (s, 1H, H-4), 10.88 (s, 1H, OH), 10.92 (s, 1H, NH); IR (KBr, cm^{-1}): 3426, 1702, 1601, 1508, 1226, 1159, 918, 813; TOF-HRMS: m/z 458.0710 $[M + Na]^+$ ($C_{23}H_{17}NNaO_6S$ requires 458.0674).

4.1.6.20. 7-Diethylamino-3-[4-(4-methylphenylsulfonamido)benzoyl]-2H-1-benzopyran-2-one ***7t***. Yield 75.3%, a yellow solid, mp 177–178 °C; ^1H NMR: (DMSO-d_6, ppm): δ 1.14 (t, 6H, $J = 6.6$ Hz, $2CH_2CH_3$), 2.34 (s, 3H, CH_3), 3.46 (m, 4H, $2CH_2CH_3$), 6.58 (s, 1H, H-8), 6.76 (d, 1H, $J = 8.8$ Hz, H-6), 7.17 (d, 2H, $J = 8.2$ Hz, arom), 7.38 (d, 2H, $J = 7.8$ Hz, arom), 7.57 (d, 1H, $J = 8.7$ Hz, H-5), 7.71 (m, 4H, arom), 8.17 (s, 1H, H-4), 10.84 (s, 1H, NH); IR (KBr, cm^{-1}): 3197, 1720, 1618, 1583, 1508, 1234, 1184, 1159, 920, 786; TOF-HRMS: m/z 513.1499 $[M + Na]^+$ ($C_{27}H_{26}N_2NaO_5S$ requires 513.1460).

4.1.6.21. 7-Hydroxy-6-methoxy-3-[4-(4-methylphenylsulfonamido)benzoyl]-2H-1-benzopyran-2-one ***7u***. Yield 22.0%, a yellow solid, mp 176–178 °C; ^1H NMR (DMSO-d_6, ppm): δ 2.34 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 6.84 (s, 1H, H-8), 7.20 (d, 2H, $J = 8.7$ Hz, arom), 7.35–7.39 (m, 3H, arom), 7.72–7.75 (m, 4H, arom), 8.20 (s, 1H, H-4), 10.73 (br s, 1H, OH), 10.87 (br s, 1H, NH); IR (KBr, cm^{-1}): 3212, 2929, 1710, 1598, 1564, 1508, 1241, 1199, 1157, 852, 816; TOF-HRMS: m/z 488.0736 $[M + Na]^+$ ($C_{24}H_{19}NNaO_7S$ requires 488.0780).

4.1.6.22. 6, 7-Dimethoxy-3-[4-(4-methylphenylsulfonamido)benzoyl]-2H-1-benzopyran-2-one ***7v***. Yield 84.8%, a fluorescein solid, mp 248–249 °C; ^1H NMR (DMSO-d_6, ppm): δ 2.35 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 7.16 (s, 1H, H-8), 7.21(d, 2H, $J = 8.7$ Hz, arom) 7.38 (d, 3H, $J = 9.1$ Hz, H-5, arom), 7.75 (m, 4H, arom), 8.24 (s, 1H, H-4), 10.91 (s, 1H, NH); IR (KBr, cm^{-1}): 3434, 3256, 1711, 1658, 1604, 1564, 1510, 1245, 1202, 1160, 871, 815; TOF-HRMS: m/z 502.0934 $[M + Na]^+$ ($C_{25}H_{21}NNaO_7S$ requires 502.0936).

4.2. Assay of the in vitro α-glucosidase inhibitory activity

A 100 μl reaction system containing 0.02 U of α-glucosidase (Sigma, G-0660), a test compound, and 67 mM potassium phosphate buffer (pH 6.8) was pre-incubated at 37 °C for 10 min. 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 glucose-detecting agent (Nanjing Jiancheng Corporation, China) was added, and the absorbance (A) at 490 nm was recorded on a SPECTRAmax Plus 384 reader (MD, USA). 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 test compounds were initially assayed for their inhibition of α-glucosidase at a concentration of 10 μg/ml.

Next, the inhibition rate was calculated by the equation % inhibition $= (A_{negative} - A_{test\ \ compound})/(A_{negative} - A_{blank})$. If an inhibition of more than 50% was observed, the compound was classified as active. The active compounds were consequently tested at eight concentrations under three times dilution, with each concentration having two replicates. The IC_{50} values were calculated using Xlfit software.

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