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Study on the synthesis and biological activities of α-substituted arylacetates derivatives

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ABSTRACT

Anisodamine was isolated from the medicinal herb, it was used in the treatment of gastrointestinal smooth muscle spasm, infective toxic shock and organophosphorus intoxication. But there is no report about anisodamine with α-glucosidase inhibitory activity. In order to find novel α-glucosidase inhibitors, a series of α-substituted arylacetates derivatives have been synthesized based on the active unit of anisodamine. In α-glucosidase assay, compound **9** in Schiff base form and compound **22** in ester form show strong inhibition against α-glucosidase with IC_{50} value of 46.81 μM and 83.76 μM, respectively. Compounds **9** and **22** exhibit comparable good antidiabetic activities as commercial drug Glimepiride. In addition, Schiff bases of α-substituted arylacetates show antitumor activities against human cancer cell lines, where compound **9** with thiourea moiety performs the best antitumor activity. We anticipate that our research will provide potential candidate scaffolds for antidiabetic drug design.

Diabetes mellitus, a common endocrine disorder disease characterized by hyperglycemia, has become a major risk to the individual's quality of life.[1,2] The number of people with diabetes has increased from 153 million (in 1980) to 347 million (in 2008).[3] Based on the WHO projection, diabetes will become the seventh leading cause of death globally by 2030.[4] Diabetes mellitus is closely associated with cardiovascular disease, as the major cause of morbidity and mortality.[5] Some serious complications also associated with diabetes mellitus, such as peripheral vascular disease, diabetic neuropathy, amputations, renal failure, stroke, and blindness, result in increasing disability, reducing life expectancy, and enormous health costs.[6] Currently, the main strategy for the treatment of diabetes is to use appropriate drugs to control postprandial hyperglycemia.[7,8] As one of six classes of antidiabetic drugs, α-glucosidase inhibitors can suppress the critical digestive enzyme to delay the hydrolysis of carbohydrates, thus reducing the level of postprandial plasma glucose.[9] α-Glucosidases (EC3.2.1.20) is a family of enzymes located in the brush border surface of small intestine that acts upon 1,4-alpha bonds.[10] This enzyme plays a vital role in maintaining the normal physiological function and participates in carbohydrate metabolism that specifically hydrolyzes the α-glucopyranoside bond to release α-glucose from the non-reducing end of the sugar.[11,12] It has been shown recently that controlling or regulating α-glucosidase activity also can suppress the diseases caused by metabolic disorders, immune responses, differentiation of nerve cells, tumor metastases, and viral infections.[13–16] Up to now, although considerable endeavors have been made to develop new α-glucosidase inhibitors for the treatment of diabetes, only a few α-glucosidase inhibitors are clinically available and they are all sugar mimics with tedious multi-steps from carbohydrates and noncarbohydrates, including 1-deoxynojirimycin **1**, acarbose **2**, and valienamine **3** (Fig. 1).[17–20] Importantly, the continuous usage of these agents should be limited because

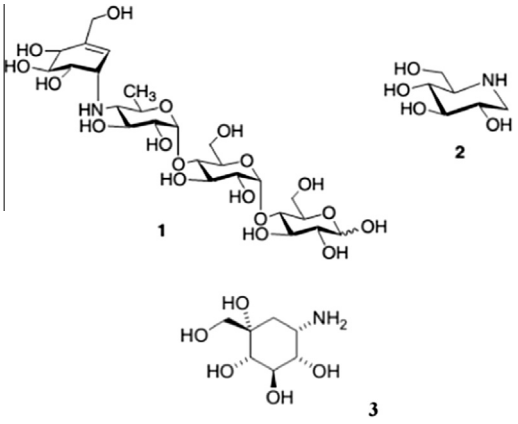

Figure 1. Structures of potent glycosidase inhibitors.

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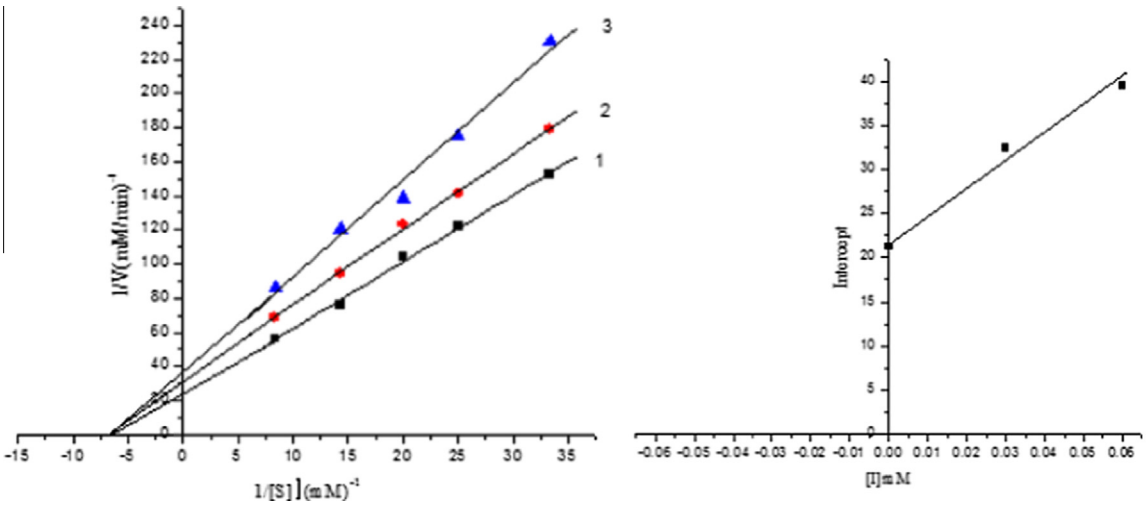
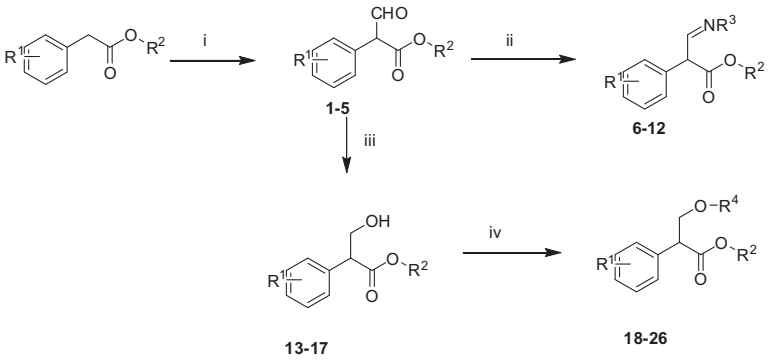


Figure 2. Lineweaver–Burk plots of the inhibition kinetics of α-glucosidase inhibitory effect by compound **9**. The inhibitor concentrations of compound **9** for curves 1–3 were 0, 30, 60 mM.



1. R^1 = H, R^2 = CH_3 ; 2. R^1 = 4-CH_3, R^2 = CH_3 ; 3. R^1 = 4-OCH_3, R^2 = CH_3 ;

4. R^1 = 4-F, R^2 = CH_2CH_3 ; 5. R^1 =4- CF_3, R^2 = CH_2CH_3 ;

6. R^1 = H, R^2 = CH_3, R^3 = $NHCSNH_2$; 7. R^1 = 4-CH_3, R^2 = CH_3, R^3 = $NHCSNH_2$;

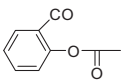
8.R^1 = 4-OCH_3, R^2 = CH_3, R^3=$NHCSNH_2$; 9. R^1=4- F, R^2=CH_2CH_3, R^3 = $NHCSNH_2$;

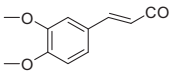
10.R^1=4-F, R^2=CH_2CH_3, R^3=OCH_3; 11. R^1 =4-CF_3, R^2 = CH_2CH_3, R^3 = $NHCSNH_2$;

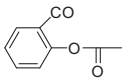
12. R^1 =4- CF_3, R^2 = CH_2CH_3, R^3 = OCH_3; 13. R^1 = H, R^2 = CH_3 ;

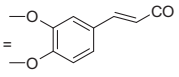
14. R^1=4-CH_3, R^2=CH_3 ; 15. R^1=4-OCH_3, R^2 = CH_3 ; 16. R^1 = 4-F, R^2 = CH_2CH_3 ;

17. R^1=4-CF_3, R^2 =CH_2CH_3 ; 18. R^1 = H, R^2 = CH_3, R^4 = PhCO;

19. R^1 = H, R^2 = CH_3, R^4 =  ;

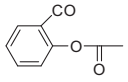
20. R^1 = H, R^2 = CH_3, R^4 = 

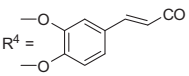
21.R^1 = 4-F, R^2 = CH_2CH_3, R^4 =  ;

22.R^1 = 4-F, R^2 = CH_2CH_3, R^4 = 

23.R^1 = 4-F, R^2 = CH_2CH_3, R^4 = PhCO ;

24. R^1 = 4-CF_3, R^2 = CH_2CH_3, R^4 =PhCO

25.R^1 = 4-CF_3, R^2 = CH_2CH_3, R^4 =  ;

26.R^1 = 4-CF_3, R^2 = CH_2CH_3, R^4 = 

Scheme 1. Synthesis of α-substituted arylacetate derivatives. Reaction conditions: (i) Ethyl formate/Na/toluene, 5% HCl; (ii) $NH_2NHCSNH_2$ EtOH/reflux, NH_2OCH_3·HCl/NaOH/EtOH/RT; (iii) $NaBH_4$/−10 °C; (iv) DCC/DMAP/DCM/−10 °C.

they may cause side effects such as flatulence, abdominal cramps, vomiting, diarrhea, serious hepatic injury, and acute hepatitis.[21,22] In recent years, much efforts have been devoted to develop effective non-sugar inhibitors of α-glucosidase from natural sources because of the high levels of natural abundance and biological efficacy.[23,24]

Schiff bases are attractive and versatile scaffolds with relevant applications in several areas, including asymmetric catalysis, chemosensors, photochemical switches, live cell imaging, or pharmacology.[25–29] Schiff bases have been reported as antiprotozoal activities, antibacterial activities, anti-HIV activities, anticonvulsant activities, antitumor activities, and anthelminthic activities, acetyl cholinesterase inhibitors, α-glucosidase inhibitors and stimulate plants growth.[30–32] Another popular scaffold is tropic acid, which is an important building block for biologically active tropane alkaloids, such as anisodamine, anisodamine and scopolamine.[33,34] They are typical acetylcholine M receptor antagonists, yet anisodamine appears to be less potent and less adverse reactions than atropine.[35] The ability to improve the microcirculation makes anisodamine in the treatment of gastrointestinal smooth muscle spasm, infective toxic shock and organophosphorus intoxication.[36] Also, anisodamine is applied in treatment of sudden deafness, acute otitis media, anaphylactoid purpura, acute alcoholism, diabetes, myocardial infarction and bronchial asthma, etc. Recently, α-substituted phenylacetic acid derivatives has been reported to the investigations of expressed antibacterial, bactericidal, insecticidal, antioxidant, anticancer, antidiabetic, anti-HIV virus, anti-inflammatory and other biological activities.[37] However, there is no report about α-substituted phenylacetic acid derivatives that performing α-glucosidase inhibitory activity. In addition, several studies have already proved that rosmarinic acid derivatives possess a number of interesting biological activities, including antioxidant, anti-inflammatory, antiviral and antibacterial effects.[38]

In this Letter, we have synthesized a series of Schiff bases of α-arylacetates and the other α-arylacetate derivatives from commercial sources with simple methods. All of the α-arylacetate derivatives have been evaluated in in vitro α-glucosidase inhibition assay, hypoglycemic assay and antitumor assay. We found that some compounds show strong inhibition against α-glucosidase, hypoglycemic activity, and even antitumor activity as well.

As described in Scheme 1, a series of α-substituted arylacetate derivatives have been synthesized followed by the literature reported.[39–42] With commercial arylacetates (**1**–**5**) as starting materials reacted with ethyl formate and sodium, α-formyl arylacetate derivatives are obtained after acidified by hydrochloric acid. With α-formyl arylacetates in hand, the addition of methoxy amine or thiosemicarbazide can provide the corresponding Schiff bases, while the presence of sodium borohydride results in α-hydroxymethyl arylacetates. The α-hydroxymethyl arylacetates can be further transformed to the corresponding esterified esters with carboxylic acids. Evidenced by full characterizations such as IR, NMR, MS and elemental analysis, these α-substituted arylacetate derivatives have been investigated by different biological assays.

Using 1-deoxynojirimycin as a positive control, the α-substituted arylacetates are examined by in vitro α-glucosidase inhibition studies.[43] The IC_{50} values of α-substituted arylacetates and their inhibition ratios of α-glucosidase are summarized in Table 1. Compared to 1-deoxynojirimycin, α-formyl arylacetate derivatives (**1**–**5**) do not show significant inhibition against α-glucosidase (Table 1, entries 1–5). After the α-formyl arylacetate derivatives transformed to their corresponding Schiff bases, the inhibition activity of compounds **6**, **7** and **8** are comparable as their precursors **1**, **2** and **3** (Table 1, entries 6–8 vs 1–3). To our surprise, compound **9**[44] shows strong inhibition against α-glucosidase with IC_{50} value of 46.81 μM and inhibition ratio of 65.27%, which are even better than those of 1-deoxynojirimycin (Table 1, entry 9 vs entry 27). However, while the R^3 group in **9** changes from thiourea to methoxy (**10**), it becomes no active to α-glucosidase (Table 1, entry 9 vs entry 10). These results indicate that the steric and electronic properties of the substituted group in Schiff bases cause great effect to their inhibition abilities. The similar results are obtained between **11** and **12** (Table 1, entries 11 and 12). For the α-hydroxymethyl arylacetates (**13**–**17**), no significant inhibition against α-glucosidase is observed (Table 1, entries 13–17). After esterification of compound **13** to **18**, **19**, **20** with different carboxylic acids, the inhibition abilities against α-glucosidase become even worse with low IC_{50} values and inhibition ratios (Table 1, entries 18–20 vs entry 13). Compared with compound **16**, there is no obvious change on the inhibition ability with its ester form **21** bearing R^4 as 2-acetoxybenzoic group or **23** bearing R^4 as benzoyl group (Table 1, entries 21 and 23). However, compound **22** bearing with R^4 as (*E*)-3-(3,4-dimethoxyphenyl)acryloyl group is a potent inhibitor against α-glucosidase with IC_{50} value of 83.76 μM, that is better than 1-deoxynojirimycin (Table 1, entry 22 vs entry 27). Once compound **17** forms the esters (**24**, **25** and **26**), their inhibition abilities become active although the inhibition ratios are not very high (Table 1, entries 24–26). Taken together, Schiff base of α-substituted arylacetate **9** and ester form of α-substituted arylacetate **22** have been found to be as potent inhibitors against α-glucosidase. Also, we found that the steric effect and electronic effect of substituted groups in α-substituted arylacetates could cause great effect to their inhibition abilities.

Kinetics of the representative α-glucosidase inhibitor was further studied to determine the type of inhibition by theanalysis of the Lineweave–Burk plots, as depicted in Figure 2. The value of $1/V$ increased with increasing concentrations of compound **9**, but the intercept on the *x*-axis remains constant, but with different gradients. This result suggests a noncompetitive inhibition of compound **9**. The K_i value for compound **9** was 65.36 μM. Hence, the inhibitor was expected to bind to a site other than the active site of α-glucosidase.

Table 1
In vitro α-glucosidase inhibitory activity of substituted phenylacetate derivatives

Entry	Compound	Inhibition ratio[a] (%)	IC_{50}[b] (μM)
1	**1**	15.32 ± 1.25	>200
2	**2**	29.29 ± 1.64	185.26 ± 3.08
3	**3**	18.42 ± 1.17	>200
4	**4**	20.38 ± 1.48	182.68 ± 2.70
5	**5**	NA	
6	**6**	19.83 ± 2.05	>200
7	**7**	20.76 ± 1.39	190.17 ± 3.52
8	**8**	14.44 ± 1.18	>200
9	**9**	65.27 ± 1.02	46.81 ± 1.17
10	**10**	NA	
11	**11**	34.05 ± 1.75	137.45 ± 2.18
12	**12**	NA	
13	**13**	28.66 ± 1.46	186.50 ± 3.46
14	**14**	14.63 ± 0.93	>200
15	**15**	NA	
16	**16**	19.22 ± 1.55	>200
17	**17**	NA	
18	**18**	12.86 ± 1.72	>200
19	**19**	13.68 ± 1.63	>200
20	**20**	11.10 ± 1.82	>200
21	**21**	15.85 ± 0.97	>200
22	**22**	47.84 ± 1.96	83.76 ± 2.07
23	**23**	27.28 ± 1.75	>200
24	**24**	16.81 ± 2.16	>200
25	**25**	14.09 ± 1.16	>200
26	**26**	29.90 ± 1.59	191.36 ± 4.03
27	1-Deoxynojirimycin	52.52 ± 1.87	109.15 ± 3.11

[a] Percent inhibition at a concentration of 100 μM.
[b] Inhibitor concentration (mean ± SD of three independent experiments) required for 50% inactivation of α-glucosidase. NA = not active.

Table 2
Effect of the selected compounds on glucose levels in diabetic rats ($n = 8$)[a]

Entry	Compound	Dose (mg/kg)	Blood glucose levels (mmol/l) (decrease %)				
			0 day	3 days	6 days	9 days	12 days
1	**9**	360	20.11 ± 2.57[b]	18.04 ± 3.97[b] (10.29%)	18.53 ± 3.26[b] (7.86%)	16.71 ± 3.00[c,d] (16.91%)	16.48 ± 3.73[c,d] (18.05%)
2	**14**	360	20.08 ± 2.39[b]	19.89 ± 3.41[b] (7.86%)	21.66 ± 3.40[b]	21.76 ± 2.59[b,e]	21.40 ± 2.61[b,e]
3	**20**	360	20.36 ± 3.40[b]	18.71 ± 3.72[b] (7.86%)	19.65 ± 3.83[b] (7.86%)	20.44 ± 3.74[b]	20.76 ± 3.69[b]
4	**22**	360	22.36 ± 4.30[b]	20.74 ± 4.31[b] (7.86%)	21.66 ± 3.40[b] (7.86%)	21.95 ± 2.71[b] (7.86%)	18.11 ± 4.66[b,e] (7.86%)
5	NG	—	7.08 ± 0.48	6.29 ± 0.57 (7.86%)	6.88 ± 0.90 (7.86%)	6.35 ± 0.64 (7.86%)	6.66 ± 1.13 (7.86%)
6	DG	20	21.55 ± 3.63[b]	21.93 ± 4.12[b]	21.95 ± 2.83[b] (7.86%)	23.26 ± 1.30[b]	23.38 ± 1.41[b]
7	GG	20	21.21 ± 2.65[b]	17.99 ± 5.15[b] (7.86%)	17.78 ± 4.55[b,d] (7.86%)	18.55 ± 3.72[b,e] (7.86%)	17.15 ± 3.35[b,e] (7.86%)
8	MG	100	20.13 ± 1.77[b]	16.49 ± 3.58[b, d] (7.86%)	15.46 ± 3.63[b,e] (7.86%)	16.73 ± 3.98[b,e] (7.86%)	15.18 ± 3.16[b,e] (7.86%)

[a] NG: normal control mice group; DG: diabetic control rats group; GG: diabetic rats treated Glimepiride group; MG: diabetic rats treated Metformin group. Each value is the mean ± SEM for eight rats in each group.
[b] $P < 0.01$ compared with normal control group at each time point.
[c] $P < 0.05$ compared with normal control group at each time point.
[d] $P < 0.05$ compared with diabetic control group at each time point.
[e] $P < 0.01$ compared with diabetic control group at each time point.

Table 3
Antitumor activities of substituted phenylacetate derivatives with different human cancer cell lines[a]

Entry	Compound	IC_{50} (mg/mL)				
		HCT-116	HepG2	BGC-823	NCI-H165	A2780
1	**1**	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$
2	**2**	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$
3	**3**	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$
4	**4**	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$
5	**5**	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$
6	**6**	3.21×10^{-6}	8.00×10^{-6}	8.18×10^{-6}	3.25×10^{-6}	$>10 \times 10^{-6}$
7	**7**	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	5.22×10^{-6}	5.34×10^{-6}	5.92×10^{-6}
8	**8**	8.80×10^{-6}	3.77×10^{-6}	$>10 \times 10^{-6}$	2.50×10^{-6}	3.40×10^{-6}
9	**9**	1.91×10^{-6}	2.18×10^{-6}	7.27×10^{-6}	1.98×10^{-6}	2.11×10^{-6}
10	**10**	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$
11	**11**	3.67×10^{-6}	5.19×10^{-6}	$>10 \times 10^{-6}$	8.05×10^{-6}	2.59×10^{-6}
12	**12**	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$
13	**13**	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$
14	**14**	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$
15	**15**	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$
16	**16**	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$
17	**17**	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$
18	**18**	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$
19	**19**	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$
20	**20**	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$
21	**21**	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$
22	**22**	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$
23	**23**	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$
24	**24**	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$
25	**25**	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$
26	**26**	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$
27	Taxol[b]	1.95×10^{-8}	1.06×10^{-8}	2.56×10^{-8}	3.17×10^{-8}	5.87×10^{-7}

[a] Human cancer cell lines: HCT-116 (colon carcinoma), HepG2 (hematoma), BGC-823 (gastric carcinoma), NCI-H165 (lung carcinoma) and A2780 (ovarian carcinoma).
[b] Taxol is a control compound.

Hypoglycemic activity of α-substituted arylacetates is examined with monitoring the blood glucose levels of diabetic rats.[45] As shown in Table 2, four α-substituted arylacetates are selected including the two potent inhibitors against α-glucosidase (compounds **9** and **22**) and two other ineffective compounds **14** and **20**. After the diabetic rats treated by compounds **9** and **22** for 12 days, significant hypoglycemic activities are observed which decrease the blood glucose levels by 18.05% and 19.01%, respectively (Table 2, entries 1 and 4). These data are comparable with the commercial antidiabetic drug Glimepiride (Table 2, entries 1, 2 vs entry 7), although they do not reach the level of Metformin (Table 2, entries 1, 2 and 8). In addition, another two compounds **14** and **20** that are unable to inhibit the α-glucosidase activity are also tested in hypoglycemic assay. However, no significant decreases of the blood glucose levels in diabetic rats are observed (Table 2, entries 2 and 3). Taken together, compounds **9** and **22** are

potent inhibitors against α-glucosidase and they have significant hypoglycemic activities as well, while compounds **14** and **20** are ineffective in either α-glucosidase inhibition assay or hypoglycemic assay. These results indicate that there might be an inherent correlation between hypoglycemic activity and α-glucosidase inhibitory activity.

Except the assays of α-glucosidase inhibitory activity and hypoglycemic activity, we also evaluate the antitumor activities of α-substituted arylacetate derivatives as shown in Table 3. In vitro 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay are employed and five human cancer cell lines HCT-116 (colon carcinoma), HepG2 (hematoma), BGC-823 (gastric carcinoma), NCI-H165 (lung carcinoma) and A2780 (ovarian carcinoma) are selected.[46] We found that the some Schiff bases of α-substituted arylacetates show antitumor activities, although they are not better than Taxol. For all five cancer cell lines, compound **9** performs the best antitumor activity among all of the Schiff bases of α-substituted arylacetates (Table 3, entry 9 vs entries 6–8 and 10–12). Compared to compound **9** bearing thiourea moiety, compound **10** bearing methoxy moiety shows no significant antitumor activity (Table 3, entry 9 vs entry 10). The similar results are observed between compound **11** and compound **12** (Table 3, entry 11 vs entry 12). These results indicate that the steric effect and electronic effect of substituted groups in α-substituted arylacetates cause great effect to their antitumor activitie.

We have successfully synthesized a series of α-substituted arylacetate derivatives. Two lead compounds (**9** and **22**) have been found to be potent inhibitors against α-glucosidase with the IC_{50} value of 46.81 μM and 83.76 μM, respectively. These two compounds also show comparable antidiabetic activities with commercial drug Glimepiride. Interestingly, we found that Schiff base of α-substituted arylacetates show antitumor activities. We also found that small changes of substituted group in α-substituted arylacetates will cause great effect to their biological properties. This work provides a simple protocol to screen the potential candidates for antidiabetic assay and we anticipate that this work will be helpful to the future antidiabetic drug design.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2016.02.055.

References and notes

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44. *Ethyl 3-(2-carbamothioylhydrazono)-2-(4-fluorophenyl)propanoate (**9**)*
White solid, mp: 141.6–143.1 °C, yield: 90.8%; IR (cm^{-1}, KBr): 3429, 2971, 1728, 1643, 1608, 1586, 1502, 1451, 1085; ^1H NMR: (DMSO-d_6, 300 MHz) δ (ppm): 9.97 (s, 1H, –NH), 7.78 (s, 2H, NH_2), 7.50 (d, 1H, J = 6.9 Hz, CH), 7.27 (d, 2H, J = 7.2 Hz, Ph-H), 7.09 (d, 2H, J = 7.2 Hz, Ph-H), 5.34 (d, 1H, J = 6.9 Hz, –CH), 4.23 (q, 2H, J = 4.2 Hz, CH_2), 1.23 (q, 3H, J = 4.2 Hz, CH_3); ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 178.6, 170.7, 161.6, 154.1, 131.6, 130.8, 118.2, 61.8, 51.6, 13.5; ^{19}F NMR (DMSO-d_6, 282 MHz) δ (ppm): 107.8. ESI-MS m/z: 284 (M+1). Anal. Calcd for $C_{12}H_{14}FN_3O_3S$: C, 50.87; H, 4.98; N, 14.83. Found: C, 50.88; H, 5.01; N, 14.82.
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