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Synthesis and α-glucosidase inhibition activity of dihydroxy pyrrolidines

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ABSTRACT

A new series of Deacetylsarmentamide **A** and **B** derivatives, amides and sulfonamides of 3,4-dihydroxypyrrolidines as α-glucosidase inhibitors were designed and synthesized. The biological screening test against α-glucosidase showed that some of these compounds have the positive inhibitory activity against α-glucosidase. Saturated aliphatic amides were more potent than the olefinic amides. Among all the compounds, **5o**/**6o** having polar –NH_2 group, **10f**/**11f** having polar –OH group on phenyl ring displayed 3–4-fold more potent than the standard drugs. Acarbose, Voglibose and Miglitol were used as standard references. The promising compounds **6i**, **5o**, **6o**, **10a**, **11a**, **10f** and **11f** have been identified. Molecular docking simulations were done for compounds to identify important binding modes responsible for inhibition activity of α-glucosidase.

Diabetes mellitus is a well-known metabolic disorder that has become a serious problem of modern society due to severe long-term health complications associated with it. In particular, type 2 diabetes (T2DM) is the most encountered form of diabetes. Glucose metabolism disturbances are major factors leading to diabetes. T2DM is characterized by an abnormal postprandial increase of blood glucose level.[1,2] Acute hyperglycemia induces vascular damage through direct action on vascular endothelium and finally causes myocardial infarction, coronary heart disease, cerebral stroke, retinopathy and severely affects the patient's quality of life.[3,4] Current oral anti-diabetic drugs approved by the U.S. FDA are mainly classified into five categories: biguanides, thiazolidinediones, sulfonylureas, meglitinides and α-glucosidase inhibitors. However, some of these drugs have unacceptable side effects in some patients or lose their effectiveness over a period of time. Therefore, the search for new anti-diabetic drugs has continued to attract considerable interest. Among these drugs, α-glucosidase inhibitors are oral anti-diabetic agents which suppress postprandial hyperglycemia by blocking the activity of α-glucosidase which is responsible for the degradation of carbohydrates. α-Glucosidase inhibitors can offer several advantages and have been recommended by the *Third Asia-Pacific Region Diabetes Treatment Guidelines* as the first-line of treatment for lowering postprandial hyperglycemia.[5]

Several α-glucosidase inhibitors (AGIs), such as Acarbose (Glucobay®), Voglibose (Volix®, Basen®) and Miglitol (Glyset®) (Fig. 1) can reversibly inhibit α-glucosidase consequently delaying the absorption of sugars from the gut and have been used clinically in the treatment of diabetes mellitus.[6] Only a few α-glucosidase inhibitors are commercially available. All of them contain sugar moieties and their synthesis involves tedious multistep procedures like Voglibose (13 steps from (−) shikimic acid)[6] and Miglitol (13 steps from (*R*)-methyl 2-benzamido-3-((*tert*-butyldimethylsilyl)oxy)propanoate).[6] Moreover, clinically they have been associated with serious gastrointestinal side effects such as flatulence and diarrhea. Thus the discovery of small molecules with potent α-glucosidase inhibitory activities have attracted great attention in recent years.[7–10]

Natural products traditionally have played an important role in drug discovery and were the basis of most early medicines.[11–13] In this context, we have chosen two natural products, Deacetyl Sarmentamide **B** and Chaplupyrrolidone **A**, **B** to make semisynthetic/close analogues to evaluate for their glucosidase inhibitory activity. The deacetyl Sarmentamide **B** and Chaplupyrrolidone **A**, **B** (Fig. 2) were isolated from dried leaves of *Piper sarmentosum* Roxb[14]

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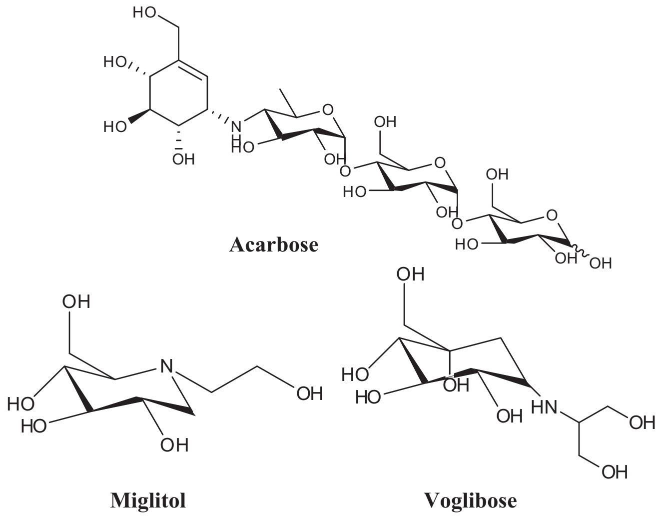
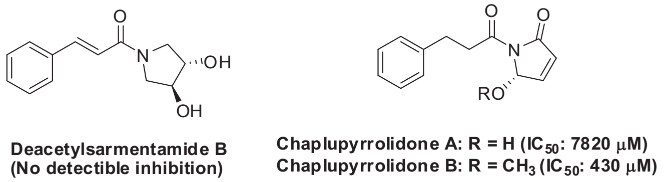


Fig. 1. Structures of some of the available the α-glucosidase inhibitors.



Deacetylsarmentamide B
(No detectible inhibition)

Chaplupyrrolidone A: R = H (IC_{50}: 7820 μM)
Chaplupyrrolidone B: R = CH_3 (IC_{50}: 430 μM)

Fig. 2. Structures of isolated natural products from *Piper sarmentosum* Roxb.[14]

(Piperales: Piperaceae), commonly known in Thai as Chaplu, is a climbing or erect herb with a characteristic pungent odour within the family Piperaceae, which is comprised of over 700 known species worldwide (Parmar et al., 1997). The two compounds, chaplupyrrolidone **A** & **B** were shown negligible α-glucosidase inhibitory activity and the deacetyl Sarmentamide **B** has no potency. The effect of electronics on phenyl ring and double bond of amide derivatives and sulfonamides on the glucosidase inhibitory activity has been studied.

We adopted the literature protocol[15] for the quick access of enantiopure pyrrolidines **4a** and **4b** in which optically pure tartaric acids were converted to *N*-benzyl dihydroxy succinimides **2a** and **2b** (Scheme 1). Reduction of amide was cleanly achieved by using BH_3-THF. Debenzylation under catalytic hydrogenolysis finally afforded the desired 3,4-dihydroxy pyrrolidines **4a** and **4b**. Diverse chemoselective *N*-acylations (**5**/**6** (**a**–**f**), **5**/**6** (**m**–**s**)) were successfully achieved by using HATU / DIPEA. Catalytic hydrogenation was utilized to prepare saturated amides (**5**/**6** **g**–**l**) from their corresponding α, β-unsaturated amides. Same set of reaction sequence is used to synthesize the *meso* analogues (**7a**–**7d**). During the synthesis of 3-(4-aminophenyl)-1-((3*R*,4*R*)-3,4-dihydroxypyrrolidin-1-yl)propan-1-one and 3-(4-aminophenyl)-1-((3*S*,4*S*)-3,4-dihydroxypyrrolidin-1-yl)propan-1-one because of the free NH_2 group, the di-amidatinated by-products (**5m** and **6m**) were formed and were characterized. The α-glucosidase inhibitory activities of **5m** and **6m** analogues were found very encouraging and hence more number of compounds in this series were made by treating 3,4-dihydroxy pyrrolidines **4a**, **4b** with *tert*-butyl 4-(3-amino-3-oxopropyl)phenylcarbamate in presence of HATU/DIPEA, further de-protection of boc group was done by using HCl to afford **5o** and **6o**. Corresponding sulfonamides (**8**/**9** **a**–**c**) were obtained by controlled sulfonation with diverse sulfonyl chlorides and products are tabulated in Table 1. Amides (**10**/**11a**–**g**) and sulfonamides (**12**/**13** **a**–**c**) of 3-(4-aminophenyl)-1-(3,4-dihydroxypyrrolidin-1-yl)propan-1-one were accessed following the earlier reaction sequence (Scheme 2) and products are tabulated in Table 2.

Sixty-seven compounds were made with 3,4-dihydroxy pyrrolidine to evaluate their α-glucosidase inhibitory activity in comparison to acarbose, miglitol and voglibose as reference standards and Baker's yeast α-glucosidase inhibitory activity was assayed using the reported method.[14] The IC_{50} (best fit) were calculated using graph pad prism v 6.0 where n = 3 and results are tabulated in Table 3.

Some of the screened compounds displayed potent α-glucosidase inhibitory activity, with IC_{50} values in the range of 98.47–272.3 μM as compared to standard references acarbose (IC_{50} = 363.3 μM), miglitol (IC_{50} = 465.1 μM) and voglibose (IC_{50} = 320.2 μM). Compound **11f**, bearing –OH group on *para* position of the phenyl ring, represented the most potent α-glucosidase inhibitory activity with IC_{50} values of 98.47 μM which is more active than the standard drugs.

The parent compounds, deacetylsarmentamide **5a** (L) and **6a** (D) were shown very poor or no inhibition against α-glucosidase. Various *trans*-3,4-dyhdroxypyrrolidine cinnamides **5**/**6** **a**–**f** were made with corresponding cinnamic acids. Thiophene acrylic acid was used to make **5f**/**6f** to screen the effect of heteroaryl group on α-glucosidase inhibition. It was observed that there is a visible α-glucosidase inhibitory activity by changing the groups on the phenyl ring of cinnamides. Negligible or no improvement in the activity in case of mono-fluorinated compounds **5b**/**6b**. Minor improvement in the potency was observed by replacing the mono fluoro group with trifluoromethyl group at ortho position in **5c**/**6c** and para in **5d**/**6d**.

The activity was further slightly improved in the case of *p*-hydroxy cinnamide **5e**/**6e**. SAR suggests polar group on the phenyl ring of 3,4-dyhdroxypyrrolidine cinnamide has significant influence on the α-glucosidase inhibitory activity. No encouragement results observed in thiophene analogues, **5f**/**6f**.

Saturated amides **5**/**6** **g**–**l** were synthesized by the reduction of *trans*-3,4-dyhdroxypyrrolidine cinnamides **5**/**6** **a**–**f** and **5**/**6** **m**–**s** were made by the amidation reaction with saturated carboxylic acids. Dramatic change in potency of α-glucosidase inhibitory activity was observed from unsaturated cinnamides **5c**/**6c** to saturated amides **5i**/**6i**. The saturated version of deacetylsarmentamides **5g**/**6g** and the monofluoro analogues **5h**/**6h** has shown no detectible activity. The trifluoromethyl analogues **5i**/**6i** has exhibited excellent activity compared to their unsaturated compounds and more potent than the standard drugs. A 2-fold activity was observed for **6i** when compared to **5i**. Not much improvement in the activity was observed in the case of **5j**/**6j**, **5k**/**6k** and **5l**/**6l** compounds.

Significant α-glucosidase inhibition was observed in a case of by-products **5m**/**6m** with IC_{50} = 258.6 μM for **5m** & 262.2 μM for **6m**. A substantial α-glucosidase inhibitory activity was displayed by **5o**, 3–4-fold potent than the standard drugs with an IC_{50} = 107.6 μM, corresponding enantiomer **6o** also exhibited excellent potency with an IC_{50} value of 184.7 μM whereas corresponding NH-boc-group protected amides **5n**/**6n** has shown zero potency. Polar –NH_2 group on the phenyl ring derivatives **5o**/**6o** showed significant α-glucosidase inhibitory activity. Compounds **5p**/**6p** has no influence on α-glucosidase.

We have prepared the few hetero aryl analogues (**5f**/**6f**, **5l**/**6l**, **5**/**6** **q**–**s**) to screen the effect of heteroaryl group on α-glucosidase inhibition. It is clearly showed that heteroaryl analogues were showed lower potency compared to aromatic systems.

To compare the α-glucosidase inhibition activity of enantiopure pyrrolidine analogues with *meso* pyrrolidine analogues, we have made four *meso* pyrrolidine analogues (**7a**–**d**). There is no much difference in the activity of α-glucosidase inhibition of *meso*