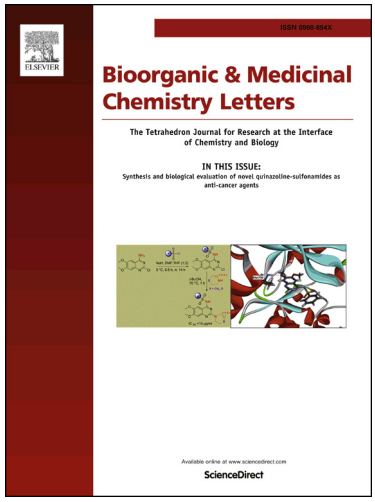
# Accepted Manuscript




Synthesis and α-Glucosidase Inhibition Activity of Dihydroxy Pyrrolidines

Sivaprasad Kasturi, Sujatha Surarapu, Srinivas Uppalanchi, Jaya Shree Anireddy, Shubham Dwivedi, Hasitha Shilpa Anantaraju, Yogeeswari Perumal, Dilep Kumar Sigalapalli, Bathini Nagendra Babu, Krishna S. Ethiraj

PII: S0960-894X(17)30451-1
DOI: http://dx.doi.org/10.1016/j.bmcl.2017.04.078
Reference: BMCL 24931

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 9 December 2016
Revised Date: 22 April 2017
Accepted Date: 25 April 2017

Please cite this article as: Kasturi, S., Surarapu, S., Uppalanchi, S., Anireddy, J.S., Dwivedi, S., Anantaraju, H.S., Perumal, Y., Sigalapalli, D.K., Babu, B.N., Ethiraj, K.S., Synthesis and α-Glucosidase Inhibition Activity of Dihydroxy Pyrrolidines, *Bioorganic & Medicinal Chemistry Letters* (2017), doi: http://dx.doi.org/10.1016/j.bmcl.2017.04.078

## Graphical Abstract

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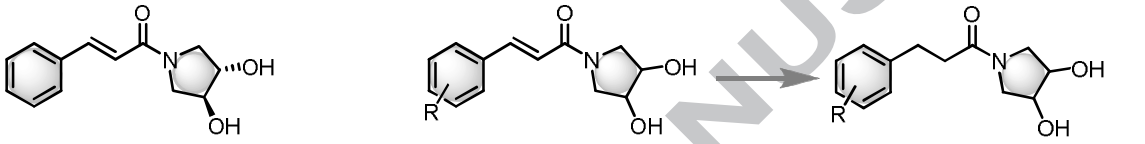
### Synthesis and α-Glucosidase Inhibition Activity of Dihydroxy Pyrrolidines

Sivaprasad Kasturi[a,b], Sujatha Surarapu[a], Srinivas Uppalanchi[a], Jaya Shree Anireddy[b,*], Shubham Dwivedi[c], Hasitha Shilpa Anantaraju[c], Yogeeswari Perumal[c], Dilep Kumar Sigalapalli[d], Bathini Nagendra Babu[d], Krishna S. Ethiraj[a]




Deacetylsarmentamide B
$IC_{50}$= **Not identified**

R=OH: (*3R*, *4R*): *trans;* $IC_{50}$= **545.7** µM
R=OH: (*3S*, *4S*): *trans;* $IC_{50}$= **506.3** µM

R=$NH_2$: (*3R*, *4R*): *trans;* $IC_{50}$= **107.6** µM
R=$NH_2$: (*3S*, *4S*): *trans;* $IC_{50}$= **184.7** µM

**Acarbose** $IC_{50}$= 360.2 µM
**Miglitol** $IC_{50}$= 462.2 µM
**Voglobose** $IC_{50}$= 324.7 µM

Bioorganic & Medicinal Chemistry Letters
journal homepage: www.elsevier.com

# Synthesis and α-Glucosidase Inhibition Activity of Dihydroxy Pyrrolidines

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ARTICLE INFO

*Article history:*
Received
Revised
Accepted
Available online

*Keywords:*
Acarbose
Alpha glucosidase inhibitor (GI)
3,4-Dihydroxypyrrolidine
Tartaric acid

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] (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.

**Figure 1**. Structures of some of the available the *α*-glucosidase inhibitors

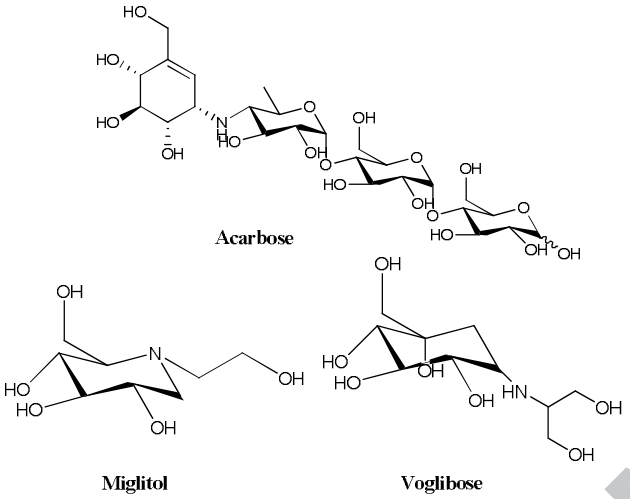
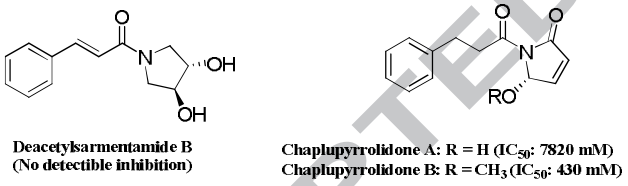



**Figure 2**. Structures of isolated natural products from Piper sarmentosum Roxb[14]




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.




**Scheme 1.** Reagents and conditions: (i) $BnNH_2$, xylene, 190 °C, 6 h, 76-83 %; (ii) $BH_3$ in THF (1.0 M), THF then MeOH, 70 °C, 3 h, 73-88 %; (iii) Pd-C, $H_2$, 100 psi, EtOH, RT, 24 h, 78-83%; (iv) $R^1COOH$ or $R^2COOH$, HATU, DIPEA, DMF, RT, 16 h, 38-87%; (v) $R^3SO_2Cl$, Pyridine, THF, RT, 16 h, 58-86 %; (vi) Pd-C, $H_2$, 50 psi, EtOH, RT, 4 h, 72-90 %; (vii) 4M HCl in dioxane, DCM, 0 °C to RT, 4 h, 71-80%.

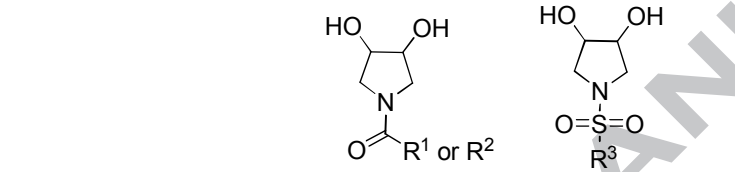
Some of the screened compounds displayed potent α-glucosidase inhibitory activity, with $IC_{50}$ values in the range of 98.47-272.3 μM as compared to standard references acarbose ($IC_{50}$ = 363.3 μM), miglitol ($IC_{50}$ = 465.1 μM) and voglibose ($IC_{50}$ = 320.2 μM). Compound **11f**, bearing –OH 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**.

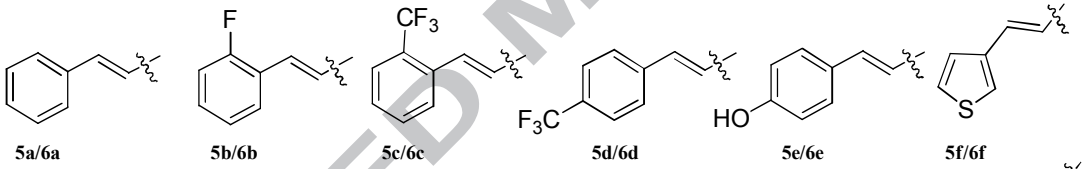
The activity was further slightly improved in the case of p-hydroxy cinnamide **5e/6e**. SAR suggests polar group on the phenyl ring of 3,4-dyhdroxypyrrolidine cinnamide has significant influence on the α-glucosidase inhibitory activity. No encouragement results observed in thiophene analogues, **5f/6f**.

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.

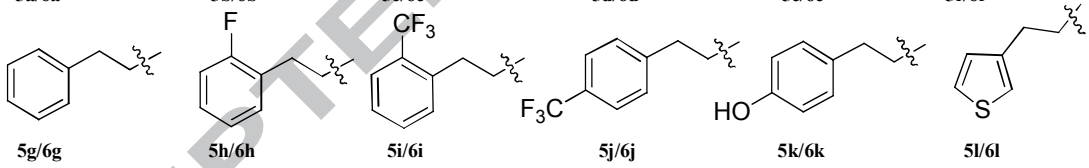
**Table 1**. Synthesized 3,4-dihydroxypyrrolidin derivatives



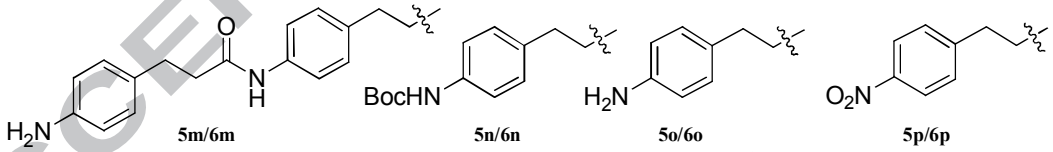

**Amides (5, 6 & 7 series)** **Sulfonamides (8 & 9 series)**



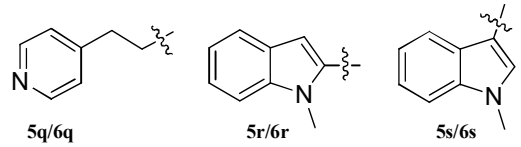
**5a/6a** **5b/6b** **5c/6c** **5d/6d** **5e/6e** **5f/6f**



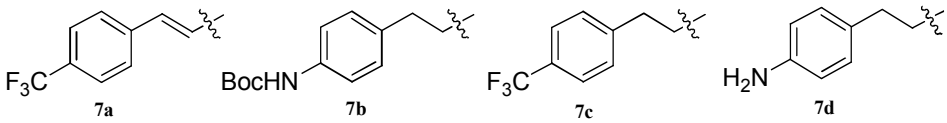
**5g/6g** **5h/6h** **5i/6i** **5j/6j** **5k/6k** **5l/6l**



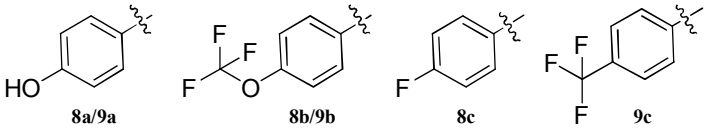
**5m/6m** **5n/6n** **5o/6o** **5p/6p**



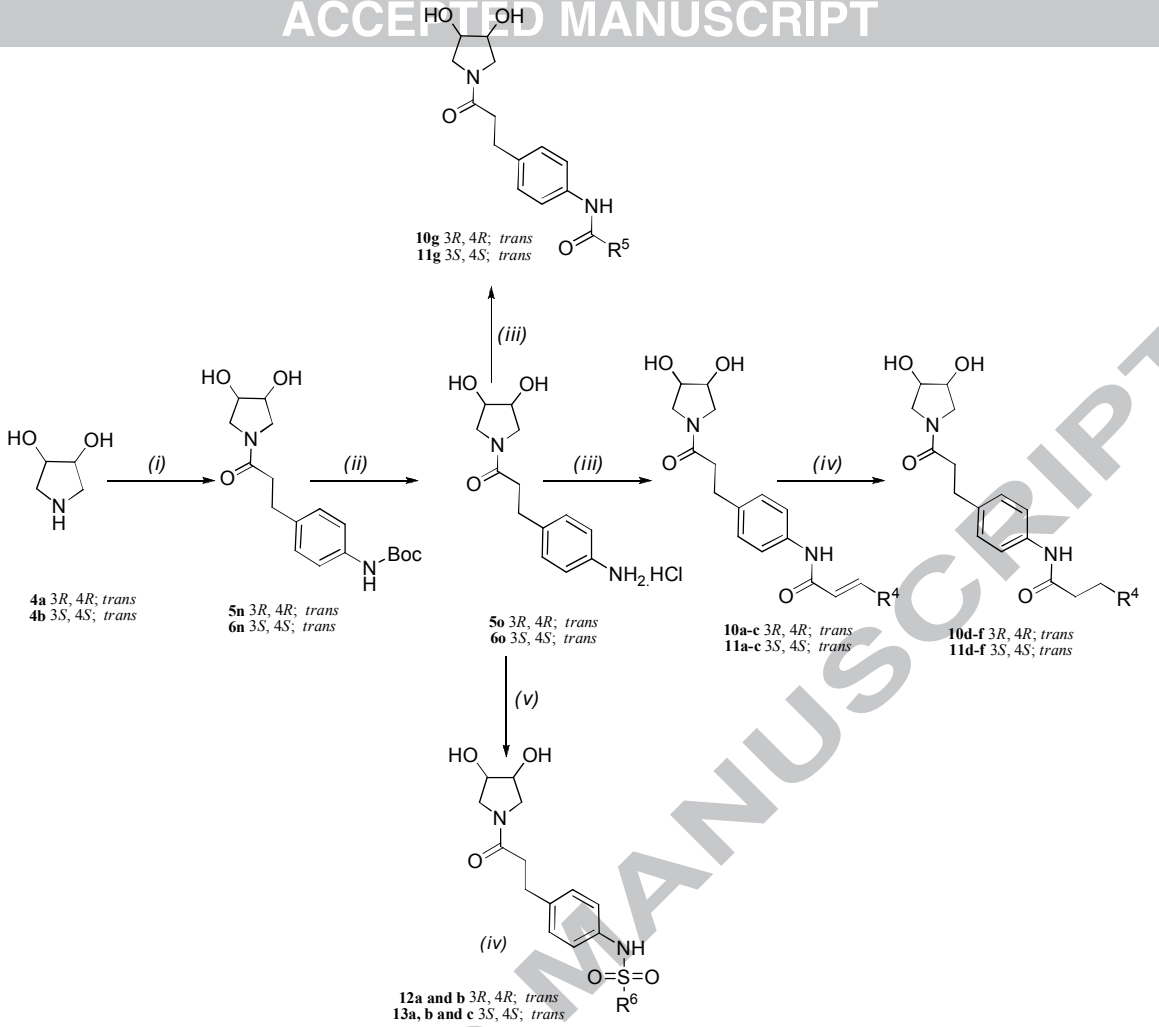
**5q/6q** **5r/6r** **5s/6s**



**7a** **7b** **7c** **7d**

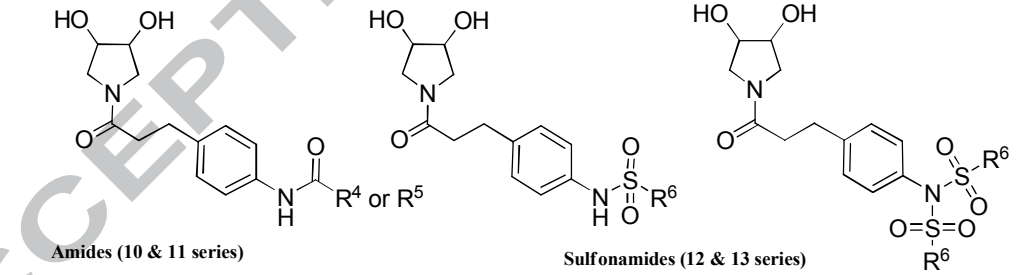


**8a/9a** **8b/9b** **8c** **9c**




**Scheme 2** Reagents and conditions: (i) 3-(4-(*tert*-butoxycarbonylamino)phenyl)propanoic acid, HATU, DIPEA, DMF, 78%; (ii) HCl in 1,4-Dioxane, DCM, 0 °C to RT, 6 h, 91 %; (iii) RCOOH, HATU, DIPEA, DMF, 55-71%; (iv) $H_2$, Pd/C, EtOH, 72-77 %; (v) $RSO_2Cl$, Pyridine, THF, 59-68 %;

**Table 2**. Synthesized 3-(4-aminophenyl)-1-(3,4-dihydroxypyrrolidin-1-yl)propan-1-one derivatives



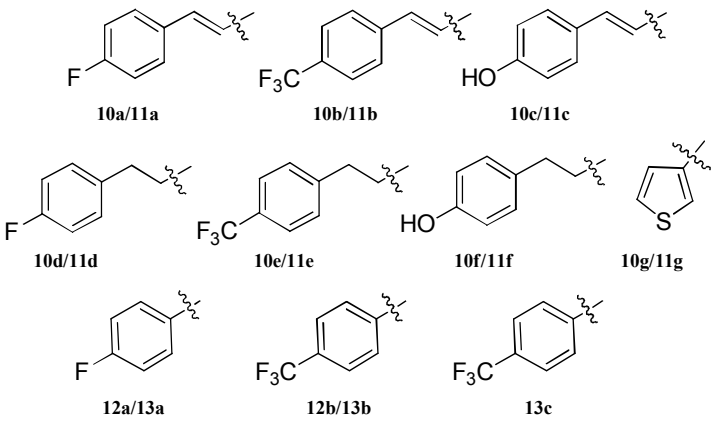
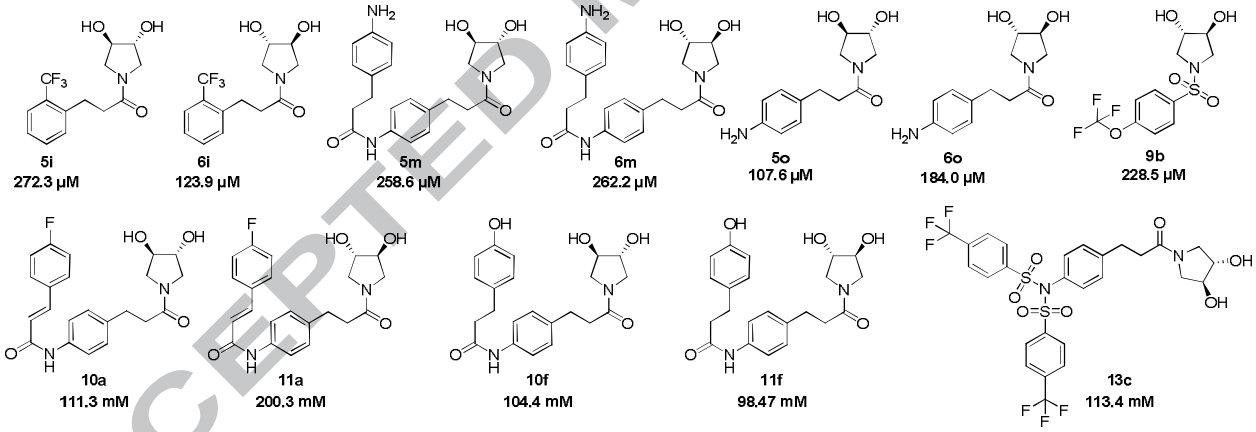



**Table 3**. α-glucosidase enzyme inhibitory effect of derivatives.

| Compound No | α-Glucosidase inhibition IC50 (µM) | Compound No | α-Glucosidase inhibition IC50 (µM) | Compound No | α-Glucosidase inhibition IC50 (µM) |
|---|---|---|---|---|---|
| 5a | 821.7 | 5m | 258.6 | 10a | 111.3 |
| 6a | 747.4 | 6m | 262.2 | 11a | 200.3 |
| 5b | 862.5 | 5n | NI | 10b | NI |
| 6b | 836.9 | 6n | NI | 11b | NI |
| 5c | NI | 5o | 107.6 | 10c | NI |
| 6c | 656.2 | 6o | 184.7 | 11c | NI |
| 5d | 604.6 | 5p | NI | 10d | NI |
| 6d | 652.3 | 6p | 772.2 | 11d | NI |
| 5e | 545.7 | 5q | 966.2 | 10e | NI |
| 6e | 506.3 | 6q | 943.4 | 11e | NI |
| 5f | NI | 5r | 538.8 | 10f | 104.4 |
| 6f | NI | 6r | 556.5 | 11f | 98.47 |
| 5g | NI | 5s | 530.6 | 10g | 474.5 |
| 6g | NI | 6s | 593.6 | 11g | 494.8 |
| 5h | NI | 7a | 637.6 | 12a | NI |
| 6h | NI | 7b | 555.7 | 13a | NI |
| 5i | 272.4 | 7c | 886.1 | 12b | 428.9 |
| 6i | 123.9 | 7d | 302.2 | 13b | 462.6 |
| 5j | 855.6 | 8a | 607.2 | 13c | 113.8 |
| 6j | 862.7 | 9a | 453.3 | **Acarbose** | **360.2** |
| 5k | 656.7 | 8b | NI | **Voglibose** | **324.7** |
| 6k | 602.4 | 9b | 228.5 | **Miglitol** | **462.2** |
| 5l | 722.8 | 8c | NI | | |
| 6l | 796.4 | 9c | 496.8 | | |

*NI: not identified*

**Figure 3**. Promising active compounds identified




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 analogues **7a**, **7b**, **7c** compared to corresponding enantiopure pyrrolidine analogues **5d/6d**, **5n/6n** and **5j/6j**, whereas meso analogue **7d** showed lower potency compared to corresponding enantiopure pyrrolidine analogues **5o/6o**.

To check the α-glucosidase inhibition activity of amides with sulfonamides, we have synthesized six sulfonamide analogues (**8/9 a-c**) in first series. Sulfonamide with -$OCF_3$ group on phenyl ring **7b/8b** has displayed excellent activity.

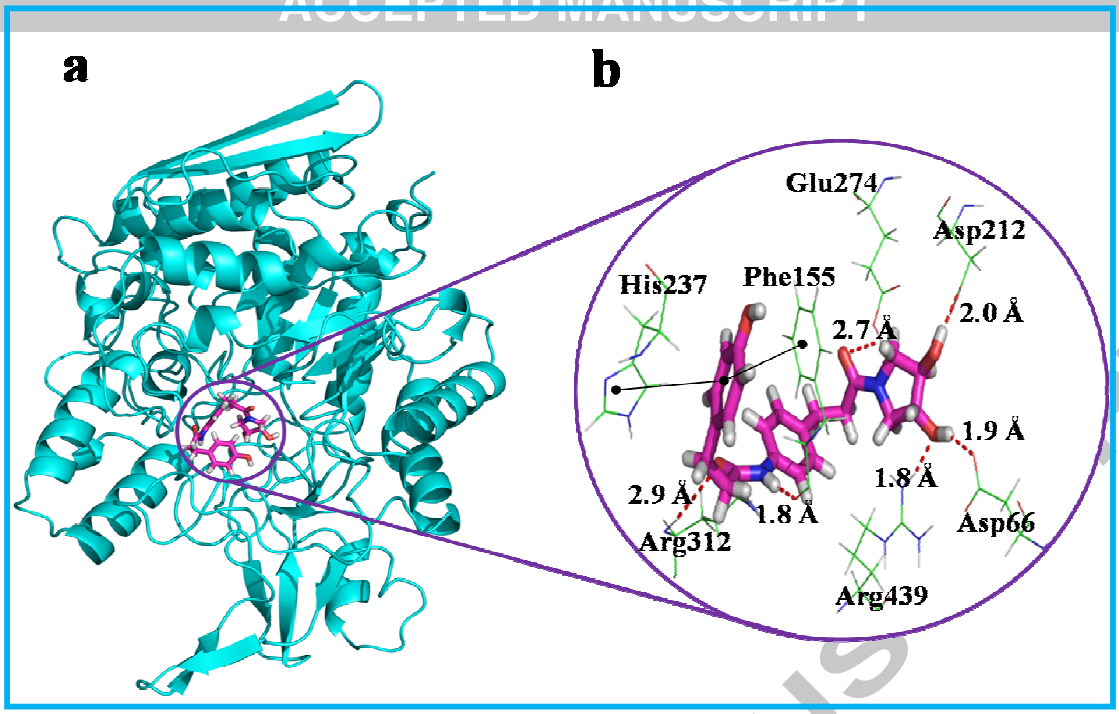



**Figure 4.** a) Binding model of the most active compound **11f** (magenta colour stick) and b) its ligand-protein interactions in the binding site of modeled α-glucosidase. The red dashed lines represent hydrogen bonds. The black lines indicates arene-arene interaction with His 237 and Phe155

As we discussed earlier, by-products **5m/6m** showed significant activity hence we have extended our work and synthesized di-amides (**10/11 a-g**), sulfonamides (**12a/13a** and **12b/13b**) and di-sulfonamide **13c** using **5o/6o.**

In the di-amide series, mono fluoro compound **10a** has exhibited 3-4 fold activity and a 2-fold activity was shown by **11a**. Compounds **10/11b-e** were shown no potency in the activity. Surprisingly, excellent activity was observed in saturated hydroxyl compounds **10f** and **11f**. These two compounds were 3-4 fold active than reference standards ($IC_{50}$ = 104.4 µM for **10f** and 98.47 µM for **11f**. This suggests that the polar groups are necessary for the compounds to be active. Moderate activity was observed in the ase of sulfonamides **12a/13a** and **12b/13b**. Corresponding di-sulfonamide **13c** has shown encouraging results with $IC_{50}$ = 113.8 µM.

Three dimensional (3D) model of yeast α-glucosidase (Fig 5 in supplementary material) was built by comparative modeling using Prime 3.5 in Schrödinger Suite (Schrödinger, LLC, New York, NY)[16] and crystallographic structure of related protein as a template (PDB ID: 3A4A)[17]. Modeled structure was validated by Ramchandran plot analysis. Binding pocket of enzyme and docking simulation were predicted using Schrödinger Suite.

From the docking simulation study, it was observed that the top ranked conformation of all the compounds were nicely accommodated inside the active site of the homology model of α-glucosidase (table 4 in supplementary material). Computationally most of the synthesized compounds showed interaction with the hydroxyl groups attached to pyrrolidine ring of the compounds with the important active site residues. In case of the most active compound **11f** has six hydrogen bond interactions and two π-interactions through arene-arene bond were found with the catalytically active residues Asp66, Phe155, Asp212, Glu274, Arg312, Arg439, Phe155 and His237 as shown in Fig 4. Additionally, several hydrophobic interactions were observed between the compound **11f** and the active site residues, e.g., Tyr69, Val106, Phe155, Phe156, Phe175, Pro238, Phe300, Phe310, Phe311 and Tyr313 are the other residues that stabilized the binding of the compound **11f** in the active site of α-glucosidase. Similar interactions were found in compound **10f** with residues Asp66, Lys153, Phe155, Asp212, Arg439 and His237, these interactions made this compound second active compound in the series. From this docking simulation, we observed that the importance of hydroxyl group at para position of phenyl ring. In general, the hydroxyl group is strong activating group which polarize the molecule and enable it to make several interactions with other residues. The most active compounds **11f** and **10f** have this p-hydroxyl group and this hydroxyl group is responsible for some of the key interactions with active site residues. In case of compound **10f**, the p-hydroxyl group establishing hydrogen bond interaction with Lys153.

In case of compound **5o**, **6i**, **6o**, **10a** and **13c**, the p-hydroxyl group was not exist as in compound **10f** and **11f**, but several interactions was observed with active site residues which made them promising active compounds in this series of synthesized molecules. Similarly, Compound **5i**, **5m**, **6m**, **9b** and **11a** also showing the good docking score and more protein-ligand interactions with the active site residues of α-glucosidase enzyme. On the basis of our molecular docking study, it was found that the biological activity of synthesized dihydroxy pyrrolidines via occupying the active site of α-glucosidase and making favorable interactions with its key residues.

In conclusion, we have synthesized a series of novel 3,4-dihydroxypyrrolidine compounds and studied for their α-glucosidase inhibitory activity. Compounds **5i, 6i, 5m, 6m, 5o, 6o, 9b, 10a, 11a, 10f, 11f** and **13c** were exhibited excellent α-glucosidase inhibitory activity (Fig. 3). Among all these compounds **5o**, **10a, 10f, 11f** and **13c** are considered to be more potent. Polar –OH or -$NH_2$ groups on phenyl ring has a high impact on the potency of the compounds. SAR studies reveal that the further structural modification of these active derivatives may lead to a prospective anti-diabetic candidate molecule and 3,4-dihydroxy piperidine derivatives in this area is in progress.

**Acknowledgments**

Authors wish to sincerely thank GVK Biosciences Pvt. Ltd., for the Higher Education Program, financial support and encouragement. Help from the analytical department for all spectral analysis is highly appreciated. We are thankful to Dr. Sudhir Kumar Singh for his immense support and motivation. We are also thankful to JNTUH, Hyderabad and BITS-Pilani, Hyderabad.

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**Supplementary Material**

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.