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PII: S0223-5234(18)30209-5

DOI: 10.1016/j.ejmech.2018.02.072

Reference: EJMECH 10249

To appear in: *European Journal of Medicinal Chemistry*

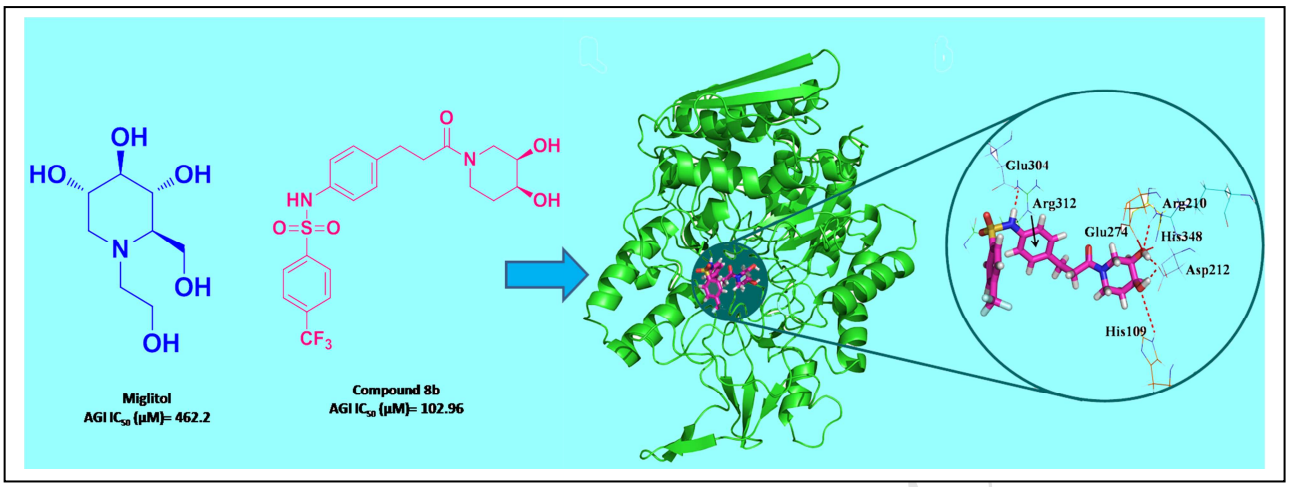
Received Date: 12 December 2017

Revised Date: 19 January 2018

Accepted Date: 21 February 2018

Please cite this article as: S.P. Kasturi, S. Surarapu, S. Uppalanchi, S. Dwivedi, P. Yogeeswari, D.K. Sigalapalli, B.N. Babu, K.S. Ethiraj, J.S. Anireddy, Synthesis, molecular modeling and evaluation of α-glucosidase inhibition activity of 3,4-dihydroxy piperidines, *European Journal of Medicinal Chemistry* (2018), doi: 10.1016/j.ejmech.2018.02.072.

Graphical abstract



Synthesis, molecular modeling and evaluation of α-glucosidase inhibition activity of 3,4-dihydroxy piperidines.

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Abstract: Biological evaluation of 3,4-dihydroxy piperidines as α-glucosidase inhibitors is being reported for the first time. Forty-five derivatives (amides, di-amides and sulfonamides) were made using *cis* and *trans* 3,4-dihydroxy piperidines to evaluate their α-glucosidase inhibition activity. Polar groups (-OH, -NH_2) on phenyl ring having derivatives **5i**, **5l**, **7g**, **7i** & **12j** showed excellent activity compared to standard references. Acarbose, Voglibose and Miglitol were used as standard references. Molecular docking simulations were done for compounds to identify important binding modes responsible for inhibition activity of α-glucosidase.

Key words: Acarbose, Dihydroxy piperidine, α-Glucosidase inhibition, Molecular docking.

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1. Introduction

Diabetes mellitus is a chronic metabolic disorder, it causes various grave health complications such as coronary artery and peripheral vascular diseases, stroke [1-3], diabetic neuropathy [4-7], amputations [8-11], cancer [12-14], renal failure [15-16] and blindness resulting in disability [17-18], reduced life expectancy and enormous health costs. Drastic changes in work patterns, improved transportation, lack of physical activity, prominent modifications in lifestyle and junk foods concomitant with globalization over the last century have resulted in an intense increase in the incidence of diabetes worldwide. According to WHO, it will increase by more than 2.5-fold, in the developing world from 84 million in 1995 to 228 million by 2025 [19]. Type 2 diabetes (T2DM) is the most common form of diabetes. Though, weight control & physical activity improves glucose & lipid metabolism and in turn decreases risk, use of one or more pharmacological agents are must in maximum cases to manage T2DM effectively. Most of the strategies for the treatment of T2DM can be grouped into four categories: 1) Insulin secretagogues [20-22] (trigger insulin exocytosis by increasing intracellular calcium ion concentration) or (stimulate the beta cell to secrete insulin). 2) Decreasing insulin resistance [23-27] (enhance insulin action which reduces hyperglycemia without any increase in plasma insulin levels). 3) Inhibiting hepatic glucose production [28-31]. 4) Inhibiting glucose uptake [32-36] (slowing down the absorption of dietary glucose). As diabetes is a lifelong disorder which requires long-term medical management, extensive studies to explore more effective and safe drugs are essential. In this therapeutic area, we have reported recently the first biological evaluation of aza-flavanones [37] and natural product inspired scaffolds of dihydroxy pyrrolidines as potent α-glucosidase inhibitors [38]. In continuation of our exploration, we envisaged that 3,4-dihydroxy piperidine derivatives will show promising inhibitory activity towards α-glucosidase inhibition like 3,4-dihydroxy pyrrolidine derivatives. Current anti diabetic drugs having piperidine skeleton available in clinical practice are showed in Fig.1.

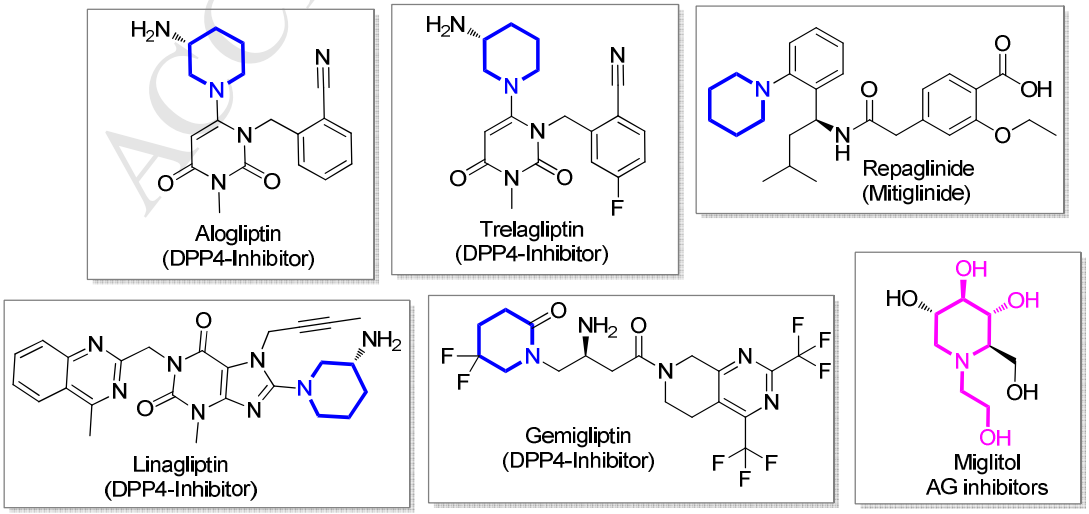
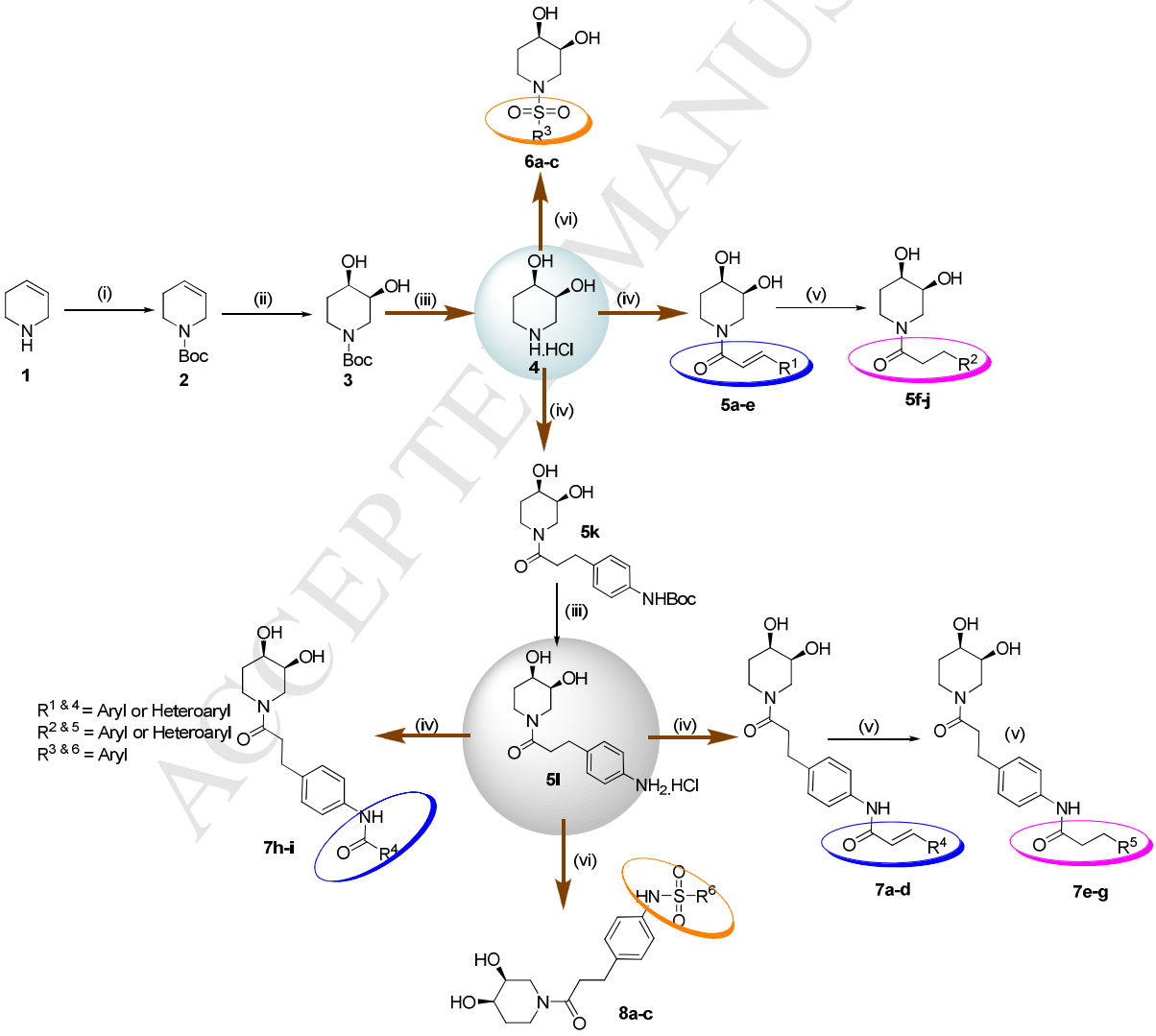


Fig.1. Anti-diabetic drugs having piperidine skeleton

2. Results and discussion

2.1. Chemistry

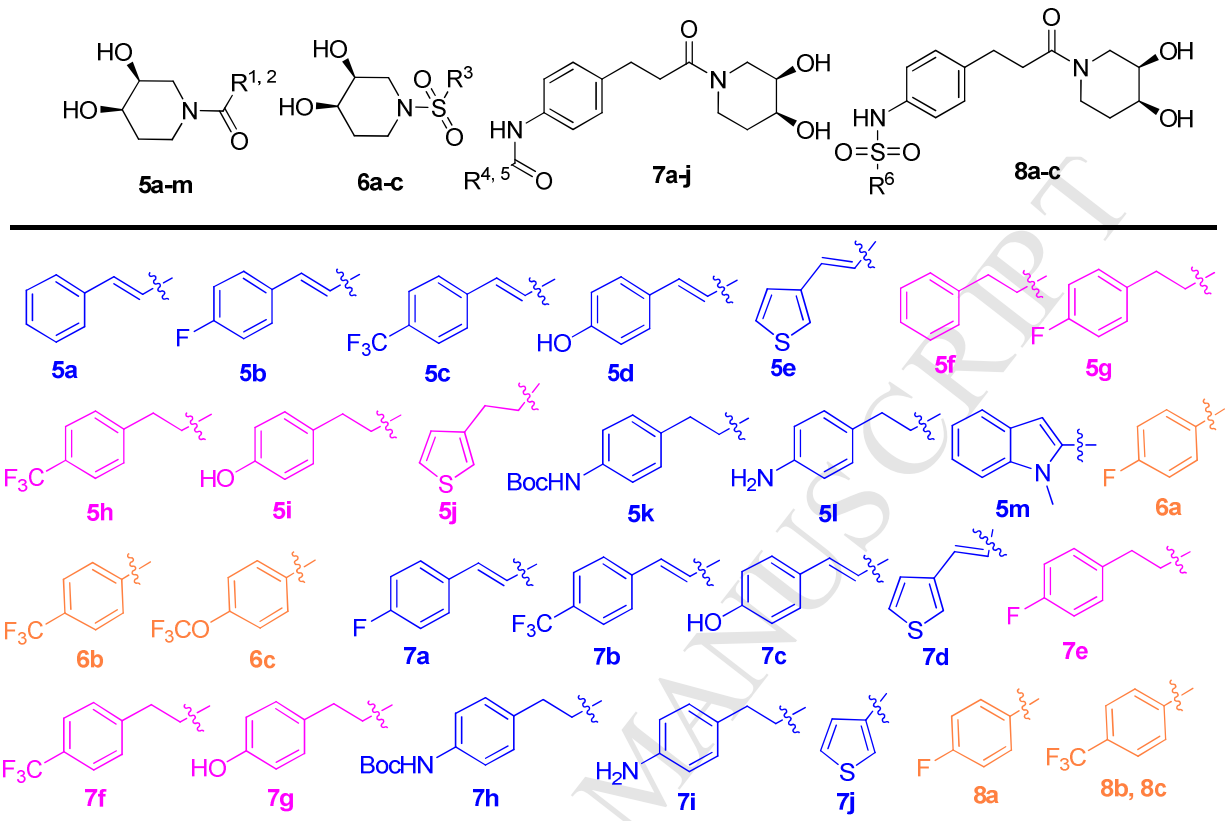
Commercially available *N*-Boc 3,4-dihydro piperidine was subjected for Upjohn dihydroxylation to give the *cis*-diol [39] **3** (Scheme 1) and Prilezhaev reaction to give corresponding epoxide [40] intermediate which was opened under the basic condition to give *trans* diol **10** (Scheme 2). Then Boc deprotection carried out under the acidic condition to afford the required *cis* and *trans* 3,4-dihydroxy piperidines **4** and **11** respectively (Scheme 1 & 2). Diverse chemo selective *N*-acylations were successfully achieved by using uronium coupling agent HATU and the corresponding sulfonamides were obtained by controlled sulfonation with diverse sulfonyl chlorides. Catalytic hydrogenation was utilized to make saturated amides from their corresponding α, β-unsaturated amides. Products were tabulated in Table 1 and 2.

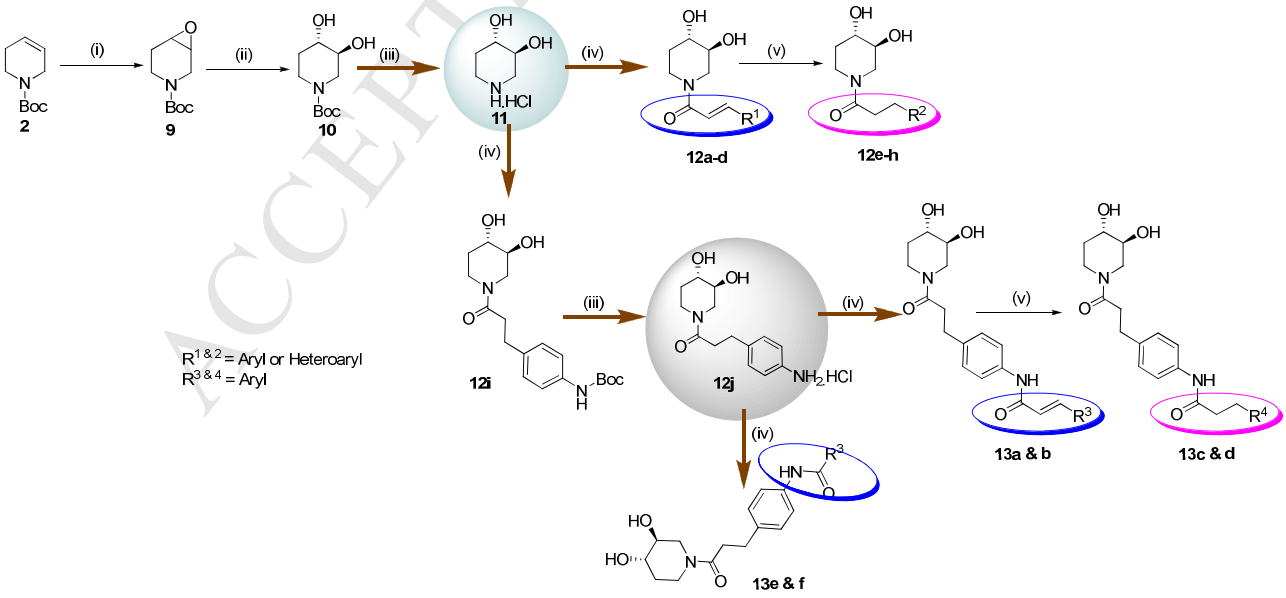


Scheme 1. General synthetic method for *cis* 3,4-dihydroxy piperidines.
Reagents and conditions: (i) $(Boc)_2O$, Na_2CO_3, 1,4-dioxane-water (1:1), 0 °C to RT, 6 h, 92%; (ii) $K_2OsO_4.2H_2O$, NMO, acetone, 16 h, 88%; (iii) 4M HCl in 1,4-dioxane, DCM, 0 °C to RT, 4 h, 90-95%; (iv) RCOOH, HATU, DIPEA, DMF, 0 °C to RT, 16 h, 55-87%; (v) Pd/C, H_2, EtOH, 50 psi, RT, 4 h, 68-94%; (vi) RSO_2Cl, Pyridine, THF, RT, 16 h, 55-72%

Table 1

Synthesized *cis* 3,4-dihydroxy piperidine derivatives

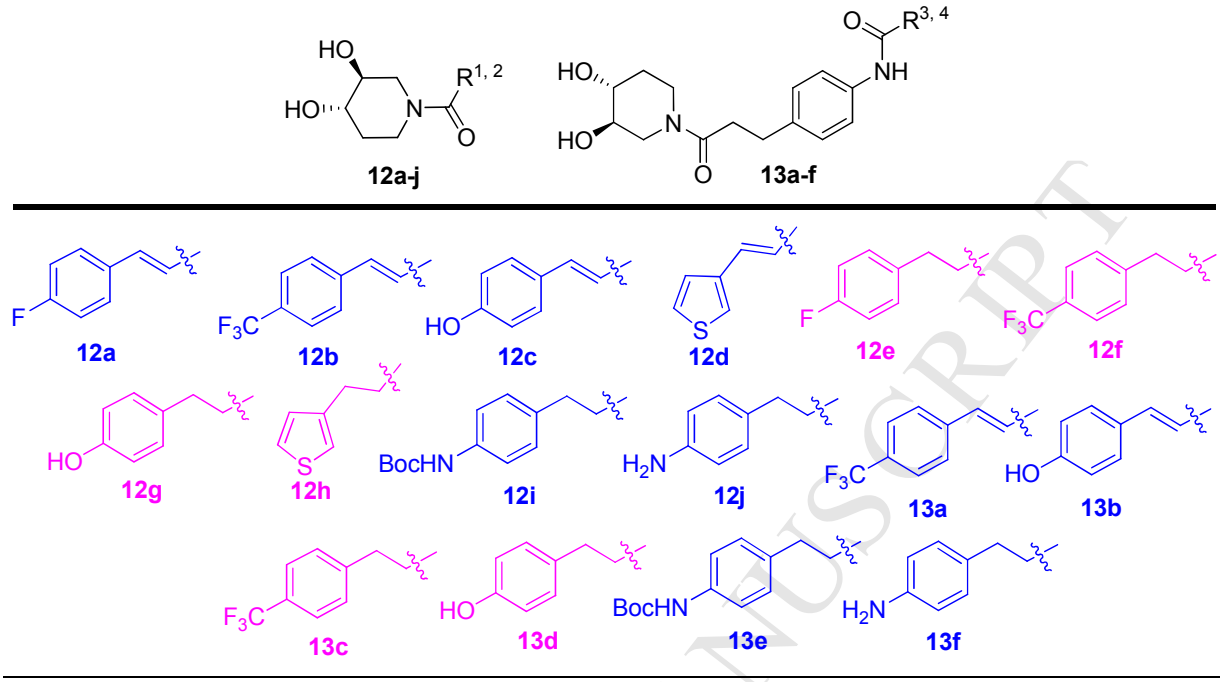




Scheme 2. General synthetic method for *trans* 3,4-dihydroxy piperidines.
Reagents and conditions: (i) *m*CPBA, DCM, 0 °C to RT, 14 h, 88% (ii) KOH, THF-water, 0 °C to RT, 16 h 86%; (iii) (4M) HCl in 1,4-dioxane, DCM, 0 °C to RT, 4 h, 89-96%; (iv) RCOOH, HATU, DIPEA, DMF, 0 °C to RT, 58-82%; (v) Pd/C, H_2, EtOH, 50 psi, RT, 4 h, 72-84%;

Table 2

Synthesized *trans* 3,4-dihydroxy piperidine derivatives



2.2. Biology

Forty-five compounds were made with 3,4-dihydroxy piperidines (Twenty nine from *cis* and sixteen from *trans*) to evaluate their α-glucosidase inhibitory activity in comparison to Acarbose, Miglitol & Voglibose as reference standards and Baker's yeast α-glucosidase inhibitory activity was assayed using the reported method [41-44](Please see the experimental data for method). The IC_{50} (best fit) were calculated using graph pad prism v 6.0 where n = 3 and results are tabulated in Table 3.

Two series of compounds (piperidine-3,4-diol and 3-(4-aminophenyl)-1-3,4-dihydroxypiperidin-1-yl propan-1-one derivatives) were made with *cis*/*trans* 3,4-dihydroxy piperidine to compare the α-glucosidase activities with five-membered 3,4-dihydroxy pyrrolidine series. A similar type of analogues were chosen for comparison. No potency was observed with simple cinnamic acid (**5a**), no improvement in the activity by replacing the phenyl ring either with fluoro phenyl ring (**5b**) or with trifluoro methyl phenyl ring (**5c**). Significant improvement in biological activity was witnessed by replacing with hydroxyl phenyl ring (**5d**) showing an IC_{50} = 442.4 µM which is close to Miglitol. To compare the activity of aromatic compounds with hetero aromatic compounds, thiophene analogue (**5e**) synthesized and tested, showed no potency in the activity.

To compare the activities of α, β-unsaturated amides with saturated amides, eight saturated amides were synthesized by the reduction of unsaturated amides (**5f-j**) or by using saturated acids

(**5k-m**) in the amidation reaction. After reduction, there is no improvement in the case of phenyl (**5f**) and fluoro phenyl (**5g**) derivatives, but a minor improvement was observed in the case of trifluoro methyl phenyl derivative (**5h**).

Table 3

α-Glucosidase enzyme inhibitory effect of 3,4-dihydroxy piperidines.

Compound No	Alpha Glucosidase inhibition IC_{50} (μM)	Compound No	Alpha Glucosidase inhibition IC_{50} (μM)	Compound No	Alpha Glucosidase inhibition IC_{50} (μM)
5a	NI	7a	349.2	12a	NI
5b	NI	7b	889.5	12b	NI
5c	NI	7c	NI	12c	NI
5d	442.4	7d	667.4	12d	NI
5e	887.6	7e	NI	12e	NI
5f	994.4	7f	478.6	12f	NI
5g	NI	**7g**	**284.1**	12g	422.4
5h	742.5	7h	382.6	**12h**	**151.9**
5i	**291.8**	**7i**	**246.8**	12i	NI
5j	NI	**7j**	**267.0**	**12j**	**288.9**
5k	662.7	8a	749.4	13a	709.8
5l	**210.6**	**8b**	**102.96**	13b	NI
5m	388.7	8b	593.6	13c	NI
6a	NI	Acarbose	360.2	13d	488.2
6b	NI	Voglibose	324.7	13e	745.7
6c	464.9	Miglitol	462.2	13f	384.2

NI: not identified

Further improvement in the activity was observed by replacing trifluro methyl group with NHBoc (**5k**), a sharp increase in the activity by replacing Boc group with H atom. The resulting amine (**5l**) showed the highest activity in the first series with an IC_{50} = 210.6 μM, showed 2-3 fold higher activity compared to reference standards. The considerable α-glucosidase activity with an IC_{50} = 291.8 μM was exhibited by phenol derivative (**5i**). To compare the activities of amides with sulfonamides, three sulfonamide analogues prepared using *cis* 3,4-dihydroxy piperidine. Among these sulfonamides trifluoro methoxy derivative (**6c**) showed better activity.

In the second series (*cis*-3-(4-aminophenyl)-1-3,4-dihydroxypiperidin-1-yl propan-1-one derivatives), among unsaturated amides except fluoro amide (**7a**) other amides viz., trifluoro methyl amide (**7b**) and hydroxyl amide (**7c**) have shown negligible or no activity whereas fluoro amide (**7a**) displayed considerable activity with an IC_{50} = 349.2 μM which is comparable to Acarbose and Miglitol, similar pattern of inhibition activity was observed in the case of five-membered pyrrolidines [38].

In saturated amides, fluoro amides (**7e**) showed zero potency, by replacing the fluoro group with trifluoro methyl group (**7f**) minor improvement was observed. By replacing the trifluoro methyl

group with NHBoc (**7h**) activity was further increased, after making the amine free (**7i**) activity was doubled (IC_{50} = 246.8 µM) and also excellent activity was observed in the case of hydroxyl phenyl amide (**7g**) with an IC_{50} = 284.1 µM. SAR studies clearly revealed that polar groups on the phenyl ring are important to exhibit the α-glucosidase activity.

In the second series among all sulfonamides, trifluoromethyl phenyl sulfonamide (**8b**) (IC_{50} = 102.96 µM) showed 3-4 fold higher activity compared to standard references and identified as the most promising active compound in this series.

We have made sixteen *trans* dihydroxy piperidine derivatives to compare the activities with *cis* dihydroxy piperidines. Except for thiophene derivative (**12h**) all other *trans* derivatives showed less inhibition compared to *cis* dihydroxy piperidines. Most active compounds were showcased in Fig.2.

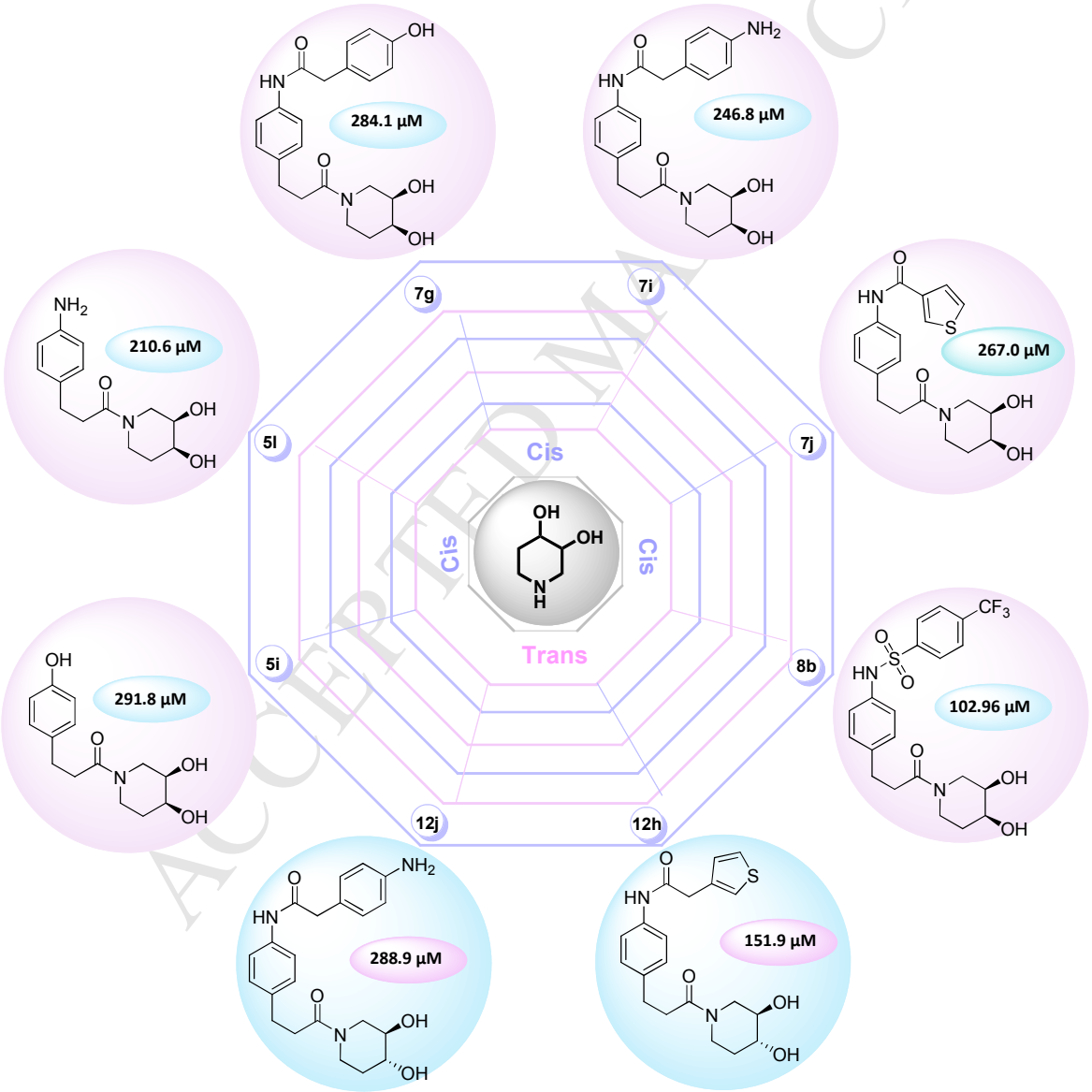


Fig.2. Promising active compounds identified

2.3. Computational methods

Molecular docking studies of corresponding dihydroxy piperidine derivatives, Acarbose, Voglibose and Miglitol were performed by using GLIDE docking module of Schrödinger suite 2014-1. All the 3D structures of molecules were built on Maestro Molecule Builder of Schrödinger. The built molecules were optimized using OPLS_2005 force field in LigPrep module of Schrödinger suite. Docking procedure was followed using the standard protocol implemented in Maestro, version 9.7 and the molecules were docked against binding site of a 3D homology model of α-glucosidase. Each complex of protein-ligand was analyzed for interactions and the 3D pose of the most active compound was taken.

2.3.1. Molecular docking simulation study

The molecular docking simulation study was performed to explore the binding mode of 3, 4-dihydroxy piperidine derivatives within the binding pocket of α-glucosidase and to understand their interaction pattern using Glide 6.2 in Schrödinger software [45]. To perform this molecular docking study, we have used our previously developed homology model of α-glucosidase [39]. The molecular docking was performed by simulation of synthetic compounds into the binding site in α-glucosidase. Table 4 demonstrates the result of the molecular docking along with hydrogen bonding as well as arene-arene and arene-cation interactions of compounds with α-glucosidase enzyme. From this molecular docking study, it was observed that the top-ranked conformation of the most active compound **8b** (Fig. 3) has established six hydrogen bonds with the active site residues (His109, Arg210, Asp212, Glu274, Glu304, His348). Additionally, the oxopropyl phenyl group of the compound formed a π - cation interaction (arene-cation interaction) with the Arg312. Furthermore, several hydrophobic interactions were observed between the compound **8b** and the active site residues, viz., Tyr69, Phe155, Phe156, Phe175, Pro238 and Phe300 stabilizes the binding of the compound **8b** in the active site of α-glucosidase. The binding model of the compound **8b** revealed that they share some of the common interactions with the key residues of the catalytic domain as shown by known inhibitor Acarbose. Fig. 4 shows the superimposition of known inhibitor Acarbose and best-docked pose of compound **8b** in the binding site of α-glucosidase.

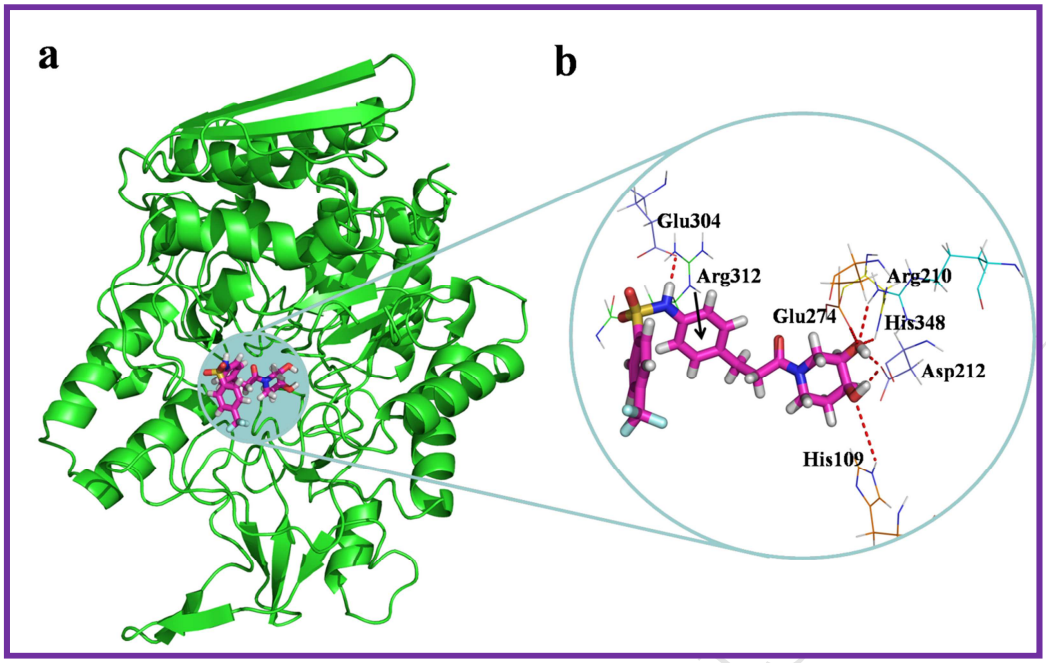


Fig. 3. a) Binding model of the most active compound **8b** (magenta color stick) and b) its ligand-protein interactions in the binding site of modeled α-glucosidase. The red dashed lines represent hydrogen bonds. H-bond distances (in Å) between heteroatoms of ligand and amino acid residues are as follows: His109 (3.7), Arg210 (2.4), Asp212 (1.5 & 1.6), Glu274 (3.7), Glu304 (1.8), His348 (2.5). The black arrow line indicates arene-cation interaction with Arg312.

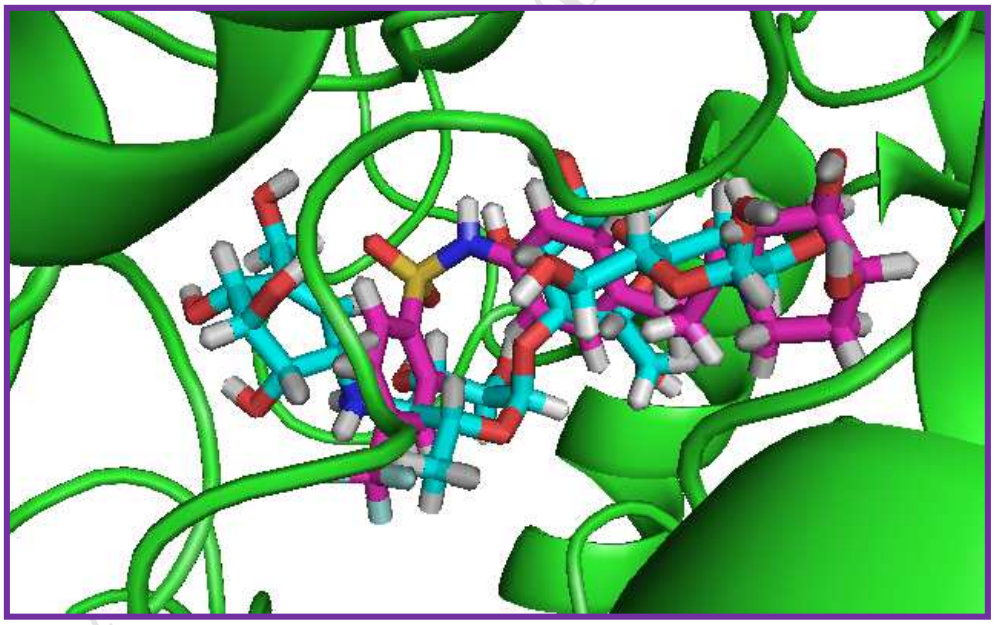


Fig. 4. Superimposition of known inhibitor Acarbose (cyan) and best-docked pose of compound **8b** (magenta) in the binding site of α-glucosidase.

Table 4

GLIDE docking results for Acarbose and some of 3, 4-dihydroxy piperidine derivatives within the binding pocket of α-glucosidase.

S.No	Ligand id	Docking score	Interactions			
			H- bonds	π - π	π - cation	Hydrophobic
1	Acarbose	-8.41	Phe155, Phe156, Glu274, Glu304, Thr307, Ser308, Arg312, Gln350, Asn412	-	-	Phe155, Phe156, Phe175, Ala276, Phe300, Phe309, Phe310, Phe311, Tyr313
2	5i	-6.98	Arg312, Asp408, Asn412	Phe155, His237	-	Phe155, Phe156, Phe175, Pro238, Phe300, Phe311, Tyr313
3	5l	-7.34	Ser154, Phe155, Phe156, Asp349	-	-	Phe 155, Phe 156, Phe 175, Phe 300, Phe 311, Tyr 313
4	7g	-7.02	His109, Glu274, Arg312, His348	His237	Arg312	Tyr69, Phe 155, Phe 156, Phe 175, Pro238, Phe 300, Phe310, Phe311
5	7i	-7.29	Arg210, Asp212, Glu274, Glu304, Arg312, His348	His237	-	Tyr69, Phe155, Phe156, Phe175, Pro238, Phe300, Tyr313
6	7j	-7.24	Arg210, Asp212, Glu274, Arg 312, His348	His237	-	Tyr69, Phe155, Phe156, Phe175, Pro238, Phe300, Phe311
7	8b	-8.28	His109, Arg210, Asp212, Glu274, Glu304, His348	-	Arg312	Tyr69, Phe155, Phe156, Phe175, Pro238, Phe300
8	12h	-7.57	Ser154, Phe155, Arg312	His237, His243	-	Phe155, Pro238, Phe310, Phe311, Tyr313
9	Voglibose	-6.32	Phe155, Phe156, Glu304, Asp349, Gln350, Asp408, Asn412	-	-	Phe155, Phe156, Phe175, Ala276, Phe300, Val303, Tyr313
10	Miglitol	-6.04	Phe155, Arg210, Glu304, Asp349, Gln350, Asp408	-	-	Phe155, Phe156, Phe175, Phe300, Tyr313

In case of compound **12h**, it has shown three hydrogen bond interactions with the binding site residues Ser154, Phe155, Arg312 and also shown some important hydrophobic interactions with Phe155, Pro238, Phe310, Phe311, and Tyr313. Additionally, the thiophene moiety of this compound established two important π - π stacking interactions (arene-arene interaction) with the His237 and His243, respectively (Fig. 5). Similarly, Compounds **5i**, **5l**, **7g**, **7i** and **7j** are also showing good docking score and more protein-ligand interactions with the active site residues of α-glucosidase, which made them promising active compounds in this series of synthesized molecules. Computationally it is worthy to note that the most of the synthesized compounds showed interaction with the hydroxyl

groups attached to piperidine ring of the compounds with the important active site residues. The strong hydrogen bonding network observed for compounds **5i**, **5l**, **7g**, **7i**, **7j**, **8b** and **12h** by the dihydroxy functional group attached to the piperidine ring.

Compounds **5i**, **5l**, **7g**, **7i**, **7j**, **8b** and **12h** have established ~3, 4, 5, 4, 5, 6 and 3 stable hydrogen bonds respectively with the binding site residues of α-glucosidase. The molecular docking simulation study suggests that these compounds are having the good binding affinity towards the binding site of α-glucosidase enzyme. The higher binding affinity for these compounds is presumably attributed to the formation of the higher number of stable hydrogen bonds, arene-arene and arene-cation interactions between the reactive group and several amino acids at the binding site.

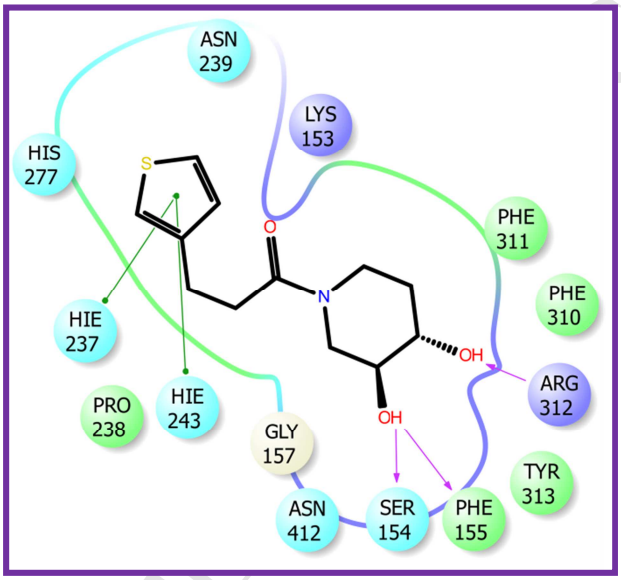


Fig. 5. Receptor-ligand interaction diagram (2D view) of compound **12h** in the binding site of modeled α-glucosidase. Amino acid residues within 4.0Å of the ligand are presented in the two-dimensional interaction diagram. The pink lines represent hydrogen bonding and green lines represent π - π stacking.

2.3.2. Prime MM/GBSA binding energy calculations

MM/GBSA (Molecular mechanics with generalized born surface area) is one of the most frequently employed computational methods to estimate relative binding affinities of target protein-ligand complexes. The MM/GBSA analysis was used to calculate ligand-binding energies based on docking complex, using the MM/GBSA technology available in Prime module of Schrodinger 2014-1. The protein-ligand complexes obtained from the docking studies were subjected to MM/GBSA calculations. The relative binding free energy ΔG_{bind} was estimated according to the following equation:

$$\Delta G_{bind} = E_{complex}\,(\text{minimized}) - [E_{ligand}\,(\text{unbound, minimized}) + E_{receptor}\,(\text{unbound, minimized})]$$

Where ΔG_{bind} is the calculated relative free energy which includes both ligand and receptor strain energy. $E_{complex}$ (minimized) is the MM/GBSA energy of the minimized complex, and E_{ligand} (unbound, minimized) is the MM/GBSA energy of the ligand after removing it from the complex and allowing it to relax. $E_{receptor}$ (unbound, minimized) is the MM/GBSA energy of protein after separating it from the ligand.

Table 5

Binding energies (ΔG_{bind}) obtained for some of synthesized 3, 4-dihydroxy piperidine derivatives and other known α-glucosidase inhibitors.

S.No	Ligand id	Binding energy (kcal/mol)
1	**5i**	-32.204
2	**5l**	-38.046
3	**7g**	-39.096
4	**7i**	-46.439
5	**7j**	-39.299
6	**8b**	-48.947
7	**12h**	-48.017
8	**Voglibose**	-39.342
9	**Miglitol**	-42.027
10	**Acarbose**	-82.208

MM/GBSA calculations were performed for best ranking molecules in **SP** mode of molecular docking. MM/GBSA and docking protocols employed in the present work for assessing ligand affinities to α-glucosidase enzyme, therefore it gives more reliable understanding of enzyme inhibition activity of synthesized 3, 4-dihydroxy piperidine derivatives. The list of some inhibitors along with their ΔG_{bind} energy values from Prime have been tabulated in Table 5. In this study, the analogues showed binding energies comparable to that of known α-glucosidase enzyme inhibitors. However, some of the identified ligands showed more binding energy values than that of the known inhibitors (Miglitol & Voglibose), suggesting stronger binding and the formation of more stable ligand-protein complexes (Table 5).

2.3.3. ADME & Toxicity studies

ADME/T properties were calculated using Qikprop module of Schrodinger 2014-1. It predicts both physicochemically significant descriptors and pharmacokinetically significant properties. QikProp provides comparative ranges of molecule's properties with those of known drugs. Schrodinger software, among which major parameters reported here are required for predicting the ADME/T of molecules, and other *in silico* parameters (carcinogenicity & LogP) were predicted using PreADMET [46] and Molinspiration online property calculation toolkit [47] and the results were presented in Table 6. From these studies, we are able to quickly compare the ADME/T properties of the synthesized 3, 4-dihydroxy piperidine derivatives with that of known α-glucosidase enzyme inhibitors.

The recommended ranges for some of the computed **ADME/T** parameters showed in Table 6 were mentioned below.

1. Predicted central nervous system activity (**CNS**) on a –2 (inactive) to +2 (active) scale
2. Predicted apparent Caco-2 cell permeability (**QPPCaco**) in nm/sec (<25 poor, >500 great)
3. Predicted brain/blood partition coefficient (**QPlogBB**) (–3.0 – 1.2)
4. Predicted skin permeability (**QPlogKp**) (–8.0 – –1.0)
5. PM3 calculated ionization potential (**IP(ev)†**) (7.9 – 10.5)
6. Predicted human oral absorption on 0 to 100% scale (>80% is high <25% is poor)

Some of the synthesized 3, 4-dihydroxy piperidine derivatives showed significant values for the properties analyzed (Table 6) and exhibited drug-like characteristics based on Lipinski's rule. All the ligands have appropriate logP value for biological efficacy and no ligand is showing carcinogenic effect. The other associated factor, such as blood brain permeability also in the acceptable range of all the synthesized molecules. All these *insilico* parameters of synthesized 3, 4-dihydroxy piperidine compounds are within the acceptable range defined for human use. In addition, the marketed drugs such as Acarbose and Voglibose are associated with bioavailability issues such as poor oral absorption, but our synthesized 3, 4-dihydroxy piperidine compounds are showing good percent human oral absorption. Thus, from these studies we observed that the synthesized 3, 4-dihydroxy piperidine derivatives are having good drug likeliness and ADME property.

Table 6
ADME/T Profile of some of the synthesized 3, 4-dihydroxy piperidine compounds and other known α-glucosidase inhibitors.

Ligand Id	Parameters									
	Rule_of_ Five	**LogP**	**Carcino_ Mouse**	**Carcino_ Rat**	**Predicted CNS Activity**	**Predicted apparent Caco-2 cell permeability in nm/sec.**	**Predicted brain/blood partition coefficient**	**Predicted skin permeability**	**Ionization Potential**	**Percent Human Oral Absorption**
5i	Suitable	-0.02	negative	negative	-2	131.924	-1.429	-3.640	9.033	65.750
5l	Suitable	-0.46	negative	negative	-2	113.109	-1.499	-3.783	8.044	63.584
7g	Suitable	1.48	negative	negative	-2	46.939	-2.613	-3.639	8.900	66.111
7i	Suitable	1.04	negative	negative	-2	40.308	-2.705	-3.777	8.124	63.839
7j	Suitable	0.94	negative	negative	-2	153.585	-1.512	-3.047	8.912	75.059
8b	Suitable	2.12	negative	negative	-2	59.429	-1.970	-3.869	9.005	70.172
12h	Suitable	0.05	negative	negative	-1	370.888	-0.763	-2.977	9.561	77.235
Voglibose	Violated	-3.98	negative	negative	-2	8.582	-1.872	-7.209	8.743	14.069 (Slowly and poorly absorbed)
Miglitol	Suitable	-2.79	negative	negative	-2	34.023	-1.005	-6.431	8.537	41.505
Acarbose	Violated	-5.51	negative	negative	-2	0.087	-5.267	-10.093	8.942	0.000 (Extremely low bioavailability)

3. Conclusions

In conclusion, two series of novel 3,4-dihydroxypiperidine compounds were synthesized and evaluated their α-glucosidase inhibitory activity. Compounds **5i**, **5l**, **7g**, **7i**, **7j**, **8b, 12h** and **12j** have exhibited excellent α-glucosidase inhibitory activity. Polar –OH or $–NH_2$ groups on phenyl ring has a high impact on the potency of the compounds and further structural modification of these active derivatives may lead to a potent anti-diabetic candidate molecule and further work in this area is in progress.

4. Experimental section

4.1. Chemistry

Melting points were determined in capillaries, recorded on Buchi Melting Point B-540 and are uncorrected. ^{1}H and ^{13}CNMR spectra were recorded on Varian 400 MHz and 300 MHz spectrometers, using $CDCl_3$ and DMSO-d_6 as solvents. Chemical shifts are given in ppm with TMS as an internal reference. J values are given in Hertz. Reactions were monitored by thin-layer chromatography (TLC) coated with Silica Gel. Column chromatography was performed with 100-200 mesh silica.

***tert*-Butyl 5,6-dihydropyridine-1(2*H*)-carboxylate (2):**

Na_2CO_3 (3.0 mol) and di-*tert*-butyl dicarbonate (1.1 mol) were added sequentially to solution of 1,2,3,6-tetrahydropyridine (1.0 mol) in 1, 4-dioxane and water (1:1, 10 v) at 0 °C. The reaction mixture was slowly allowed to RT, stirred for 6 h. The reaction mixture was diluted with EtOAc (50 v) and washed with water (50 v) and saturated brine solution (50 v), dried over Na_2SO_4 and concentrated in reduced pressure to get the crude compound. The crude compound was purified on a silica gel column using ethyl acetate in hexane yielding title compound as a liquid in 92% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.85-5.78 (br s, 1H), 5.68-5.62 (br s, 1H), 3.87 (s, 2H), 3.48 (t, J = 5.2 Hz, 2H), 2.12 (s, 2H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.96, 125.18, 124.46, 79.37, 43.48, 39.60, 28.17, 25.11; LC-MS (ESI) m/z Calcd. for $C_{10}H_{17}NO_2$: 183.13, Found: 184.17 $[M+H]^+$.

***cis*-*tert*-Butyl 3,4-dihydroxypiperidine-1-carboxylate (3):**

tert-Butyl 5,6-dihydropyridine-1(2*H*)-carboxylate (**2**) (1 mol) was added to a solution of potassium osmate (0.1 mol) and NMO (2 mol) in THF and H_2O (4:1; 10 v). The reaction mixture was stirred at RT for 16 h and a solution of saturated sodium metabisulfite (10 v) was added to quench the excess oxidant. The reaction mixture was diluted with water (40 v) and extracted with EtOAc (2 x 20 v). The combined organic layers were washed with saturated brine solution, dried over Na_2SO_4 and evaporated under *vacuo*. Purification was done by flash column chromatography using EtOAc in hexane, afforded the desired product as a clear liquid in 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.84 (br s, 1H), 3.75 (br s, 1H), 3.56-3.50 (m, 2H), 3.41 (dd, J = 13.2, 3.6 Hz, 1H), 3.28-3.22 (m, 1H), 1.84-

1.76 (m, 1H), 1.70-1.63 (m, 1H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.35, 79.96, 68.43, 67.91, 45.66, 40.17, 29.51, 28.32; LC-MS (ESI) m/z Calcd. for $C_{10}H_{19}NO_4$: 217.13, Found: 216.06 $[M-H]^-$

***tert*-Butyl 7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (9):**

To a solution of *m*-CPBA (2 mmol) in DCM (8 v) was added *tert*-butyl 5,6-dihydropyridine-1(2*H*)-carboxylate (1 mmol) in DCM (2 v) drop-wise at 0 °C. The reaction mixture was stirred at rt for 14 h, then filtered. The filter cake was washed with DCM (10 v x 2) and the combined filtrates were washed with saturated aqueous Na_2CO_3 (300 mL x 2). The solution was dried over anhydrous Na_2S0_4, concentrated in vacuo and purified by a silica gel column chromatography to give the title compound as colorless oil in 93% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.60 (s, 2H), 3.29-3.10 (m, 4H), 1.88-1.81 (m, 2H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 154.02, 78.69, 49.68 & 49.32, 47.27 & 41.67, 37.91, 36.68, 27.96, 23.42; LC-MS (ESI) m/z Calcd. for $C_{10}H_{17}NO_3$: 199.12, Found: 144.32 $[M-tBu]^+$.

***trans*-*tert*-Butyl 3,4-dihydroxypiperidine-1-carboxylate (10):**

2M solution of KOH (2 mmol) was added to a solution of *tert*-butyl 7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (1 mmol) in 1,4-dioxane (10 v), the reaction mixture was stirred at 80 °C for 8 h. The reaction mixture was diluted with water (50 v) and extracted with ethyl acetate (50 v x 2). The combined organic layer was washed with saturated brine solution (30 v), dried over anhydrous sodium sulphate and evaporated under reduced pressure to give crude compound. Purification was done by flash column chromatography using EtOAc in hexane, afforded desired product as a clear liquid in 86% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.17-4.11 (m, 1H), 4.00 (br s, 1H), 3.54-3.48 (m, 1H), 3.45-3.39 (m, 1H), 2.80 (br s, 2H), 2.66-2.61 (m, 1H), 1.97-1.91 (m, 1H), 1.51-1.45 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.85, 80.18, 73.67, 71.93, 47.70, 42.26, 31.53, 28.37; LC-MS (ESI) m/z Calcd. for $C_{10}H_{19}NO_4$: 217.13, Found: 218.12 $[M+H]^+$.

General procedure for the preparation of compounds 4, **5l, 7i, 11, 12j** and **13f**

A solution of 4M HCl in dioxane (3 mol) was added to the solution of Boc-compound (1 mol) in DCM (10 v) under the nitrogen atmosphere at 0 °C. The reaction mixture was slowly warmed to RT & stirred for 4 h. The reaction mixture was evaporated under reduced pressure, diethyl ether (20 v) was added to the residue and stirred for 10 min. The organic layer was decanted and dried to get pure compounds **4**, **5l, 7i, 11, 12j** and **13f** as solids in 89-96% yields.

***cis*-Piperidine-3,4-diol hydrochloride (4):**

Yield: 95.0%; Hygroscopic; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.06 (br s, 2H), 3.81-3.72 (m, 2H), 2.98-2.85 (m, 4H), 1.86-1.69 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 65.68, 65.30, 44.94, 26.61; LC-MS (ESI) m/z Calcd. for $C_5H_{11}NO_2$: 117.08, Found: 118.10 $[M+H]^+$.

3-(4-Aminophenyl)-1-(*cis*-3,4-dihydroxypiperidin-1-yl)propan-1-one hydrochloride (5l):

Yield: 92.0%; Hygroscopic; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.28-7.15 (m, 4H), 4.62-4.46 (m, 2H, OH), 3.70-3.60 (m, 2H), 3.52-3.48 (m, 1H), 3.36-3.30 (m, 1H), 3.21-3.05 (m, 2H), 2.81-2.77 (m, 2H), 2.63-2.59 (m, 2H), 1.64-1.40 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.26 & 169.84, 141.54 & 141.42, 128.30, 128.24 & 128.13, 125.69, 68.07 & 67.74, 67.57 & 67.19, 48.07, 43.13 & 38.11, 34.05 & 33.97, 30.81 & 30.73, 30.35 & 29.05; LC-MS (ESI) m/z Calcd. for $C_{14}H_{20}N_2O_3$: 264.15, Found: 265.10 $[M+H]^+$.

3-(4-Aminophenyl)-*N*-(4-(3-(*cis*-3,4-dihydroxypiperidin-1-yl)-3-oxopropyl)phenyl)propanamide hydrochloride (7i):

Yield: 90%; MR: 181-185 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.23 (br s, 2H, NH_2), 9.93 (s, 1H, NH), 7.46 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 3.71-3.62 (m, 2H), 3.52-3.48 (m, 2H), 3.37-3.30 (m, 1H), 3.21-3.15 (m, 1H), 2.92 (t, *J* = 7.2 Hz, 2H), 2.72 (t, *J* = 7.2 Hz, 2H), 2.63-2.55 (m, 4H), 1.65-1.41 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.35, 169.92, 141.26, 137.04, 136.19, 129.65, 129.52, 128.49 & 128.43, 123.06, 119.07, 68.14 & 67.81, 67.65 & 67.24, 48.14, 43.17, 38.18, 37.62, 34.21 & 34.10, 30.57 & 30.28, 29.09; LC-MS (ESI) m/z Calcd. for $C_{23}H_{29}N_3O_4$: 411.24, Found: 412.22 $[M+H]^+$.

***trans*-Piperidine-3,4-diol hydrochloride (11):**

Yield: 96.0%; Hygroscopic; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.01 (br s, 1H), 8.54 (br s, 1H), 5.50 (br s, 2H), 3.60-3.39 (m, 2H), 3.10-3.01 (m, 2H), 2.89-2.86 (m, 1H), 2.79-2.76 (m, 1H), 2.01-1.94 (m, 1H), 1.58-1.50 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 66.69, 66.55, 45.13, 26.33; LC-MS (ESI) m/z Calcd. for $C_5H_{11}NO_2$: 117.08, Found: 118.06 $[M+H]^+$.

3-(4-Aminophenyl)-1-(*trans*-3,4-dihydroxypiperidin-1-yl)propan-1-one hydrochloride (12j):

Yield: 90.0%; Hygroscopic; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.28 (br s, 3H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 4.04-3.52 (m, 3H), 3.44-3.03 (m, 3H), 2.82 (t, *J* = 7.2 Hz, 2H), 2.68-2.59 (m, 2H), 1.79-1.71 (m, 1H), 1.25-1.20 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.77 & 169.53, 141.70 & 141.59, 129.54, 129.35, 122.95, 71.28 & 70.40, 69.87 & 69.61, 48.01 & 45.19, 42.40 & 37.98, 33.60, 30.09, 29.82; LC-MS (ESI) m/z Calcd. for $C_{14}H_{20}N_2O_3$: 264.15, Found: 265.0 $[M+H]^+$.

3-(4-Aminophenyl)-*N*-(4-(3-(*trans*-3,4-dihydroxypiperidin-1-yl)-3-oxopropyl)phenyl)propanamide hydrochloride (13f):

Yield: 89%; MR: Hygroscopic; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.23 (br s, 2H, NH_2), 9.78 (s, 1H, NH), 7.45 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.47 (d, *J* = 8.4 Hz, 2H), 4.93-4.91 (m, 1H), 4.79 (br s, 3H), 4.04-3.43 (m, 3H), 3.33-3.02 (m, 3H), 2.74-2.49 (m, 8H), 1.77-1.74 (m, 1H), 1.25-1.20 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.39, 170.01 & 169.79, 146.52, 137.10, 136.00 & 135.89, 128.50, 128.36, 128.03, 119.01, 113.91, 71.33 & 70.41, 69.92 & 69.68, 48.19 &

45.20, 42.47 & 38.57, 37.96, 37.03, 31.82, 30.19, 29.88; LC-MS (ESI) m/z Calcd. for $C_{23}H_{29}N_3O_4$: 411.24, Found: 412.36 $[M+H]^+$.

General procedure for the preparation of compounds 5a-e, 5k, 5m, 7a-d, 7h, 7j, 12a-d, 12i, 13a-b and **13e**

DIPEA (3 mol), HATU (1.5 mol) were added sequentially to a stirred solution of acid (1.1 mol) in DMF (10 v). After 5 min, corresponding amine (1.0 mol) was added and stirred at RT under argon atmosphere for 16 h. After completion of the reaction, the reaction mixture was diluted with water (50 v), extracted with EtOAc (50 v X 2) and evaporated the solvent in *vacuo* to get the crude product. The crude product was purified by column chromatography using silica gel to afford **5a-e, 5k, 5m, 7a-d, 7h, 7j, 12a-d, 12i, 13a-b** and **13e** as liquids/solids in 55-87% yield.

(*E*)-1-(*cis*-3,4-Dihydroxypiperidin-1-yl)-3-phenylprop-2-en-1-one (5a):

Yield: 81.0%; MR: 152-154 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.74-7.62 (m, 2H), 7.45-7.34 (m, 4H,), 7.22 (t, *J* = 8.80 Hz, 1H), 4.54-4.48 (br s, 2H, OH), 3.79-3.59 (m, 4H), 3.46-3.19 (m, 2H), 1.76-1.48 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.99 & 164.54, 141.07 & 140.60, 135.22, 129.25, 128.65, 127.85 & 127.76, 118.92 & 118.64, 68.13 & 67.94, 67.71 & 67.35, 48.25, 43.81, 30.95 & 29.18; LC-MS (ESI) m/z Calcd. for $C_{14}H_{17}NO_3$: 247.12, Found: 248.15 $[M+H]^+$.

(*E*)-1-(*cis*-3,4-Dihydroxypiperidin-1-yl)-3-(4-fluorophenyl)prop-2-en-1-one (5b):

Yield: 78.0%; MR: 194-197 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.80-7.75 (m, 2H), 7.43 (dd, *J* = 15.2, 6.8 Hz, 1H), 7.25-7.16 (m, 3H), 4.74-4.58 (m, 2H, OH), 3.80-3.52 (m, 4H), 3.45-3.17 (m, 2H), 1.72-1.48 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.99, 162.36, 138.61, 129.81 & 129.72, 128.55, 119.19, 116.02 & 115.80, 74.63, 73.09, 52.02, 51.32, 29.70; LC-MS (ESI) m/z Calcd. for $C_{14}H_{16}FNO_3$: 265.11, Found: 266.20 $[M+H]^+$.

(*E*)-1-(*cis*-3,4-Dihydroxypiperidin-1-yl)-3-(4-(trifluoromethyl) phenyl)prop-2-en-1-one (5c):

Yield: 67.0%; MR: 148-150 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.92 (t, *J* = 7.2 Hz, 2H), 7.74 (d, *J* = 8.8 Hz, 2H), 7.50 (dd, *J* = 15.6, 4.8 Hz, 1H), 7.38 (t, *J* = 16.4 Hz, 1H), 4.71-4.55 (m, 2H, OH), 3.86-3.60 (m, 4H), 3.47-3.23 (m, 2H), 1.77-1.48 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.62 & 164.13, 139.25, 138.78, 129.17 & 128.85, 128.48 & 128.39, 125.44, 122.73, 121.97 & 121.72, 68.13 & 67.91, 67.69 & 67.33, 48.34, 43.89, 30.91 & 29.11; LC-MS (ESI) m/z Calcd. for $C_{15}H_{16}F_3NO_3$: 315.11, Found: 316.03 $[M+H]^+$.

(*E*)-1-(*cis*-3,4-Dihydroxypiperidin-1-yl)-3-(4-hydroxyphenyl)prop-2-en-1-one (5d):

Yield: 68.0%; MR: 201-204 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 (s, 1H, OH), 7.47 (d, *J* = 7.2 Hz, 2H), 7.34 (d, *J* = 14.4 Hz, 1H), 6.95-6.91 (m, 1H), 6.71 (d, *J* = 8.0 Hz, 2H), 3.73-3.32 (m, 6H), 1.72-1.48 (m, 2H); LC-MS (ESI) m/z Calcd. for $C_{14}H_{17}NO_4$: 263.12, Found: 264.17 $[M+H]^+$.

(*E*)-1-(*cis*-3,4-Dihydroxypiperidin-1-yl)-3-(thiophen-3-yl)prop-2-en-1-one (5e):

Yield: 75.0%; MR: 205-209 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.83 (s, 1H), 7.58 (s, 2H), 7.46 (dd, *J* = 15.2, 6.4 Hz, 1H), 7.06 (t, *J* = 14.4 Hz, 1H), 4.74-4.58 (m, 2H, OH), 3.77-3.57 (m, 4H), 3.45-3.35 (m, 1H), 3.28-3.15 (m, 1H), 1.68-1.45 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.26 & 164.79, 138.49, 135.36, 134.92, 127.52 & 127.23, 126.04 & 125.96, 118.23 & 117.92, 68.19 & 68.01, 67.75 & 67.39, 48.18, 43.85, 31.03 & 29.24; LC-MS (ESI) m/z Calcd. for $C_{12}H_{15}NO_3S$: 253.08, Found: 254.17 $[M+H]^+$.

***tert*-Butyl 4-(3-(*cis*-3,4-dihydroxypiperidin-1-yl)-3-oxopropyl) phenylcarbamate (5k):**

Yield: 76.0%; MR: 70-73 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.16 (s, 1H, NH), 7.32 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 8.4 Hz, 2H), 4.62-4.46 (m, 2H, OH), 3.73-3.04 (m, 6H), 2.71 (t, *J* = 7.2 Hz, 2H), 2.58-2.52 (m, 2H), 1.65-1.39 (m, 11H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.33 & 169.92, 152.74, 137.26, 135.06 & 134.94, 128.38 & 128.33, 118.12, 78.72, 68.07 & 67.74, 67.58 & 67.21, 48.09, 43.13, 38.08, 34.23 & 34.12, 30.08 & 29.06, 28.09; LC-MS (ESI) m/z Calcd. for $C_{19}H_{28}N_2O_5$: 364.20, Found: 365.12 $[M+H]^+$.

(*cis*-3,4-Dihydroxypiperidin-1-yl)(1-methyl-1*H*-indol-2-yl)methanone (5m):

Yield: 72.0%; MR: 118-122 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.58 (d, *J* = 7.60 Hz, 1H), 7.48 (d, *J* = 7.60 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 1H), 7.08 (d, *J* = 7.20 Hz, 1H), 6.61 (s, 1H), 4.72-4.62 (m, 2H, OH), 4.02-3.45 (m, 6H), 3.55-3.42 (m, 2H), 1.78-1.53 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.22, 137.07, 132.92, 126.00, 122.45, 120.96, 119.74, 110.10, 101.86, 67.61, 45.38, 35.70, 30.65, 28.67; LC-MS (ESI) m/z Calcd. for $C_{15}H_{18}N_2O_3$: 274.13, Found: 275.07 $[M+H]^+$.

(*E*)-*N*-(4-(3-(*cis*-3,4-Dihydroxypiperidin-1-yl)-3-oxopropyl)phenyl)-3-(4-fluorophenyl)acrylamide (7a):

Yield: 67.0%; MR: 164-167 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71-7.61 (m, 2H), 7.49 (t, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 7.2 Hz, 1H), 7.17 (t, *J* = 7.6 Hz, 2H), 7.06 (t, *J* = 8.4 Hz, 2H), 6.49 (d, *J* = 15.6 Hz, 1H), 3.84-3.75 (m, 2H), 3.62-3.60 (m, 1H), 3.50-3.47 (m, 1H), 3.27-3.19 (m, 2H), 2.95-2.91 (m, 2H), 2.66-2.62 (m, 2H), 1.75-1.57 (m, 2H); LC-MS (ESI) m/z Calcd. for $C_{23}H_{25}FN_2O_4$: 412.45, Found: 413.09 $[M+H]^+$.

(*E*)-*N*-(4-(3-(*cis*-3,4-Dihydroxypiperidin-1-yl)-3-oxopropyl)phenyl)-3-(4-(trifluoromethyl)phenyl) acrylamide (7b):

Yield: 62.0%; MR: 88-91 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.24 (s, 1H, NH), 7.85-7.79 (m, 4H), 7.66-7.59 (m, 3H), 7.20 (d, *J* = 8.4 Hz, 2H), 6.95 (d, *J* = 15.6 Hz, 1H), 4.68-4.52 (m, 2H, OH), 3.74-3.63 (m, 2H), 3.54-3.49 (m, 1H), 3.34 (s, 1H), 3.22-3.17 (m, 1H), 3.10-3.07 (m, 1H), 2.78-2.75 (m, 2H), 2.62-2.56 (m, 2H), 1.61-1.55 (m, 1H), 1.45-1.40 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.33, 169.90, 162.81, 138.84, 138.16, 136.92, 136.85, 129.02, 128.65, 128.29, 125.85, 125.19, 119.25, 68.13 & 67.79, 67.63 & 67.24, 48.15, 43.18, 38.18, 34.08, 30.25 & 29.06; LC-MS (ESI) m/z Calcd. for $C_{24}H_{25}F_3N_2O_4$: 462.18, Found: 463.21 $[M+H]^+$.

(*E*)-*N*-(4-(3-(*cis*-3,4-Dihydroxypiperidin-1-yl)-3-oxopropyl)phenyl)-3-(4-hydroxyphenyl)acrylamide (7c):

Yield: 55.0%; MR: 228-230 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.00 (s, 1H, NH), 7.57 (d, *J* = 8.4 Hz, 2H), 7.48-7.44 (m, 3H), 7.17 (d, *J* = 8.4 Hz, 2H), 6.82 (d, *J* = 8.0 Hz, 2H), 6.60 (d, *J* = 16.0 Hz, 1H), 4.67-4.51 (m, 2H, OH), 3.74-3.63 (m, 2H), 3.53-3.49 (m, 1H), 3.32-3.17 (m, 2H), 3.09-3.05 (m, 1H), 2.76-2.73 (m, 2H), 2.61-2.59 (m, 2H), 1.64-1.54 (m, 1H), 1.46-1.42 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.36 & 169.93, 163.81, 159.12, 140.09, 137.32, 136.32 & 136.19, 129.45, 128.61 & 128.55, 125.75, 119.08, 118.67, 115.82, 68.13 & 67.79, 67.63 & 67.24, 48.15, 43.18, 38.18, 34.23 & 34.13, 30.25 & 29.10; LC-MS (ESI) m/z Calcd. for $C_{23}H_{26}N_2O_5$: 410.18, Found: 411.21 $[M+H]^+$.

(*E*)-*N*-(4-(3-(*cis*-3,4-Dihydroxypiperidin-1-yl)-3-oxopropyl)phenyl)-3-(thiophen-3-yl)acrylamide (7d):

Yield: 59.0%; MR 215-218 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.06 (s, 1H, NH), 7.86 (s, 1H), 7.64-7.55 (m, 4H), 7.37 (d, *J* = 4.8 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 2H), 6.63 (d, *J* = 16.0 Hz, 1H), 4.67-4.51 (m, 2H, OH), 3.70-3.63 (m, 2H), 3.53-3.50 (m, 1H), 3.41-3.31 (m, 1H), 3.22-3.17 (m, 1H), 3.10-3.09 (m, 1H), 2.75-2.74 (m, 2H), 2.59-2.57 (m, 2H), 1.52-1.42 (m, 2H); LC-MS (ESI) m/z Calcd. for $C_{21}H_{24}N_2O_4S$: 400.15, Found: 411.21 $[M+H]^+$.

***tert*-Butyl 4-(3-(4-(3-(*cis*-3,4-dihydroxypiperidin-1-yl)-3-oxopropyl)phenylamino)-3-oxopropyl) phenylcarbamate (7h):**

Yield: 78.0%; MR: 140-144 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.76 (s, 1H, NH), 9.18 (s, 1H, NH), 7.45 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.11 (t, *J* = 8.8 Hz, 4H), 4.60-4.52 (m, 2H, OH), 3.70-3.52 (m, 3H), 3.32-3.30 (m, 1H), 3.21-3.18 (m, 1H), 3.12-3.06 (m, 1H), 2.81 (t, *J* = 7.2 Hz, 2H), 2.73 (t, *J* = 7.2 Hz, 2H), 2.58-2.49 (m, 4H), 1.65-1.52 (m, 2H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.28, 170.10, 169.86, 152.72, 137.37, 137.01, 136.10, 134.63, 128.35 & 128.25, 119.02, 118.13, 78.74, 68.06 & 67.73, 67.57 & 67.19, 48.07, 43.13, 38.05, 34.16 & 34.05, 30.51, 30.20, 29.05, 28.07; LC-MS (ESI) m/z Calcd. for $C_{28}H_{37}N_3O_6$: 511.27, Found: 512.13 $[M+H]^+$.

***N*-(4-(3-(*cis*-3,4-Dihydroxypiperidin-1-yl)-3-oxopropyl)phenyl) thiophene-3-carboxamide (7j):**

Yield: 87.0%; Thick liquid ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.95 (s, 1H, NH), 8.32-8.31 (m, 1H), 7.65-7.61 (m, 4H), 7.20 (d, *J* = 8.4 Hz, 2H), 4.61-4.54 (m, 2H, OH), 3.72-3.63 (m, 2H), 3.54-3.51 (m, 1H), 3.37-3.32 (m, 1H), 3.23-3.08 (m, 1H), 3.00-2.80 (m, 1H), 2.77-2.63 (m, 2H), 2.61-2.57 (m, 2H), 1.71-1.52 (m, 1H), 1.46-1.42 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.31 & 169.90, 160.64, 137.84, 136.76, 136.62, 129.32, 128.40 & 128.34, 127.11, 126.75, 120.28, 68.08 & 67.76, 67.59 & 67.21, 48.10, 43.16, 34.13 & 34.03, 30.53 & 30.28, 29.05; LC-MS (ESI) m/z Calcd. for $C_{19}H_{22}N_2O_4S$: 374.13, Found: 375.17 $[M+H]^+$.

(*E*)-1-(*trans*-3,4-Dihydroxypiperidin-1-yl)-3-(4-fluorophenyl)prop-2-en-1-one (12a):

Yield: 81.0%; Liquid ^{1}H NMR (400 MHz, D_2O): δ 7.75 (br s, 2H), 7.44 (d, *J* = 14.8 Hz, 1H), 7.25-7.14 (m, 3H), 4.13-3.61 (m, 3H), 3.51-3.19 (m, 3H), 1.99-1.81 (m, 1H), 1.35-1.27 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.70 & 164.39, 163.85 & 161.39, 140.06 & 139.58, 131.84, 130.05, 118.67 & 118.34, 115.68 & 115.47, 71.31 & 70.48, 70.20 & 69.72, 48.33 & 45.79, 42.61 & 38.63, 32.20 & 29.98; LC-MS (ESI) m/z Calcd. for $C_{14}H_{16}FNO_3$: 265.11, Found: 266.23 $[M+H]^+$.

(*E*)-1-(*trans*-3,4-Dihydroxypiperidin-1-yl)-3-(4-(trifluoromethyl) phenyl) prop-2-en-1-one (12b):

Yield: 72.0%; Liquid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.92 (t, *J* = 7.2 Hz, 2H), 7.74 (d, *J* = 8.0 Hz, 2H), 7.50 (dd, *J* = 15.2, 5.2 Hz, 1H), 7.39 (t, *J* = 14.4 Hz, 1H), 4.99-4.96 (m, 1H, OH), 4.87-4.83 (m, 1H, OH), 4.12-3.06 (m, 6H), 1.90-1.82 (m, 1H), 1.33-1.29 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.41 & 164.03, 139.50-139.01 (CF_3), 128.57, 128.47, 125.49, 122.76, 121.82, 121.47, 71.19 & 70.44, 70.05 & 69.47, 48.32 & 45.78, 42.66 & 38.64, 32.15 & 29.83; LC-MS (ESI) m/z Calcd. for $C_{15}H_{16}F_3NO_3$: 315.11, Found: 316.14 $[M+H]^+$.

(*E*)-1-(*trans*-3,4-Dihydroxypiperidin-1-yl)-3-(4-hydroxyphenyl)prop-2-en-1-one (12c):

Yield: 62.0%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.79 (s, 1H, OH), 7.51 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 15.6 Hz, 1H), 6.98 (d, *J* = 15.6 Hz, 1H), 6.77 (d, *J* = 8.8 Hz, 2H), 4.96 (br s, 1H, OH), 4.82 (br s, 1H, OH), 4.18-3.35 (m, 3H), 3.29-3.13 (m, 3H), 1.82 (br s, 1H), 1.76-1.22 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.98 & 164.66, 138.42, 135.47 & 135.06, 127.56 & 127.36, 127.19, 125.97, 118.03 & 117.66, 71.41 & 70.54, 70.33 & 69.91, 48.35 & 45.82, 42.60, 30.09 & 28.96; LC-MS (ESI) m/z Calcd. for $C_{14}H_{17}NO_4$: 263.12, Found: 262.39$[M-H]^-$.

(*E*)-1-(*trans*-3,4-Dihydroxypiperidin-1-yl)-3-(thiophen-3-yl)prop-2-en-1-one (12d):

Yield: 72.0%; MR: 125-130 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.84 (s, 1H), 7.58 (s, 2H), 7.46 (d, *J* = 14.8 Hz, 1H), 7.06 (dd, *J* = 14.8, 8.0 Hz, 1H), 5.00 (br s, 1H, OH), 4.87 (br s, 1H, OH), 4.14-3.60 (m, 3H), 3.46-3.39 (m, 1H), 3.29-3.15 (m, 2H), 1.86-1.82 (m, 1H), 1.29-1.24 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.12, 158.85, 141.72 & 141.23, 129.65, 126.26, 115.53, 114.85, 70.44, 70.01, 45.86, 42.67, 30.22; LC-MS (ESI) m/z Calcd. for $C_{12}H_{15}NO_3S$: 253.08, Found: 254.16 $[M+H]^+$.

***tert*-Butyl 4-(3-(*trans*-3,4-dihydroxypiperidin-1-yl)-3-oxopropyl) phenylcarbamate (12i):**

Yield: 78.0%; Liquid ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.16 (s, 1H, NH), 7.32 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 8.40 Hz, 2H), 4.93-4.91 (m, 1H, OH), 4.81-4.77 (m, 1H, OH), 4.06-3.34 (m, 3H), 3.25-3.04 (m, 3H), 2.71 (t, *J* = 7.2 Hz, 2H), 2.56-2.52 (m, 2H), 1.79-1.72 (m, 1H), 1.46 (9H, s), 1.23-1.21 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.03, 152.74, 137.27, 135.00, 128.33, 118.10, 78.72, 71.33 & 70.41, 69.92 & 69.69, 48.20 & 45.20, 42.49 & 37.95, 34.07, 31.83, 30.69 & 29.89, 28.08; LC-MS (ESI) m/z Calcd. for $C_{19}H_{28}N_2O_5$: 364.20, Found: 365.30 $[M+H]^+$.

(*E*)-*N*-(4-(3-(*trans*-3,4-Dihydroxypiperidin-1-yl)-3-oxopropyl)phenyl)-3-(4-(trifluoromethyl)phenyl) acrylamide (13a):

Yield: 64.0%; MR: 169-176 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.22 (s, 1H, NH), 7.84-7.79 (m, 4H), 7.66-7.58 (m, 3H), 7.20 (d, *J* = 8.4 Hz, 2H), 6.95 (d, *J* = 16.0 Hz, 1H), 4.94 (br s, 1H, OH), 4.82-4.80 (m, 1H, OH), 4.07-3.44 (m, 3H), 3.27-3.01 (m, 3H), 2.77 (t, *J* = 8.0 Hz, 2H), 2.66-2.55 (m, 2H), 1.81-1.73 (m, 1H), 1.27-1.19 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.99 & 169.76, 162.77, 138.82, 138.08, 136.90, 136.74 & 136.62, 129.47, 129.16, 128.59, 128.22, 125.82 & 128.78, 125.20, 119.22, 71.32 & 70.41, 69.92 & 69.68, 48.19 & 45.21, 42.49 & 37.97, 33.97 & 33.92, 31.82, 30.20 & 29.88; LC-MS (ESI) m/z Calcd. for $C_{24}H_{25}F_3N_2O_4$: 462.18, Found: 463.21 $[M+H]^+$.

(*E*)-*N*-(4-(3-(*trans*-3,4-Dihydroxypiperidin-1-yl)-3-oxopropyl)phenyl)-3-(4-hydroxyphenyl)acryl amide (13b):

Yield: 58.0%; MR: 230-234 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.0 (s, 1H, NH), 9.87 (s, 1H, OH), 7.57 (d, *J* = 8.8 Hz, 2H), 7.48-7.43 (m, 3H), 7.17 (d, *J* = 8.4 Hz, 2H), 6.82 (d, *J* = 8.4 Hz, 2H), 6.59 (d, *J* = 15.6 Hz, 1H), 4.94-4.93 (m, 1H, OH), 4.82-4.78 (m, 1H, OH), 4.07-3.36 (m, 3H), 3.10-3.00 (m, 3H), 2.77-2.73 (m, 2H), 2.62-2.56 (m, 2H), 1.78-1.72 (m, 1H), 1.23-1.19 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.01, 163.76, 159.06, 140.02, 137.27, 136.23, 132.15, 129.37, 128.49, 119.06, 118.67, 115.77, 71.33 & 70.41, 69.92 & 69.68, 48.20 & 45.21, 42.49 & 37.97, 34.01, 31.82, 30.20 & 29.89; LC-MS (ESI) m/z Calcd. for $C_{23}H_{26}N_2O_5$: 410.18, Found: 411.08 $[M+H]^+$.

***tert*-Butyl 4-(3-(4-(3-(*trans*-3,4-dihydroxypiperidin-1-yl)-3-oxopropyl) phenylamino)-3-oxopropyl) phenylcarbamate (13e):**

Yield: 82.0%; MR: 190-195 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.73 (s, 1H, NH), 9.15 (s, 1H, NH), 7.41 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.08 (t, *J* = 8.8 Hz, 4H), 4.88 (br s, 1H, OH), 4.76 (d, *J* = 6.4 Hz, 1H, OH), 4.03-3.39 (m, 3H), 3.26-2.96 (m, 3H), 2.78 (t, *J* = 8.0 Hz, 2H), 2.69 (t, *J* = 7.2 Hz, 2H), 2.52-2.46 (m, 4H), 1.73-1.68 (m, 1H), 1.26-1.15 (m, 1H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.13, 170.03, 169.80, 152.75, 137.38, 137.04, 136.08, 134.65, 128.38 & 128.27, 119.04, 118.16, 78.77, 71.33 & 70.41, 69.93 & 69.68, 48.20 & 45.21, 42.90 & 38.05, 37.97, 34.03, 31.82, 30.21, 29.89, 28.09; LC-MS (ESI) m/z Calcd. for $C_{28}H_{37}N_3O_6$: 511.27, Found: 512.41 $[M+H]^+$.

General procedure for the preparation of compounds 5f-j, 7e-g, 12e-h and **13c-d:**

To a solution of α, β-unsaturated amides (1.0 mol) in EtOH (10 v) under the nitrogen atmosphere was added 10% Pd/C (0.2 mol), the reaction mixture was hydrogenated under 60 psi at RT for 4 h. After completion of the reaction, the reaction mixture was filtered through *celite* pad, the filtrate was evaporated in *vacuo* to get the crude material. The crude product was purified by column chromatography to afford **5f-j, 7e-g, 12e-h** and **13c-d** as solids/liquids in 80-94% yield.

1-(*cis*-3,4-Dihydroxypiperidin-1-yl)-3-phenylpropan-1-one (5f):

Yield: 94.0%; MR: 103-106 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.34-7.28 (m, 5H), 3.70-3.58 (m, 2H), 3.54-3.48 (m, 2H), 3.37-3.29 (m, 2H), 2.83-2.78 (m, 2H), 2.64-2.57 (m, 2H), 1.61-1.40 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.18 & 169.75, 141.80 & 141.68, 129.53, 129.35, 123.17, 68.20 & 67.86, 67.71 & 67.32, 48.17, 43.31, 33.88 & 33.73, 30.54 & 30.25, 30.19 & 29.11; LC-MS (ESI) m/z Calcd. for $C_{14}H_{19}NO_3$: 249.14, Found: 250.15 $[M+H]^+$.

1-(*cis*-3,4-Dihydroxypiperidin-1-yl)-3-(4-fluorophenyl)propan-1-one (5g):

Yield: 84.0%; MR: 123-126 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.25 (t, *J* = 8.0 Hz, 2H), 7.07 (t, *J* = 8.80 Hz, 2H), 4.59-4.48 (m, 2H, OH), 3.70-3.62 (m, 2H), 3.52-3.36 (m, 2H), 3.22-3.18 (m, 1H), 3.09-3.05 (m, 1H), 2.79-2.77 (m, 2H), 2.60-2.56 (m, 2H), 1.61-1.42 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.23 & 169.80, 160.61 (d), 137.67 (d), 130.13, 114.82 (d), 68.14 & 67.79, 67.64 & 67.24, 48.12, 43.19, 34.13 & 34.05, 29.97 &, 29.90, 29.09; LC-MS (ESI) m/z Calcd. for $C_{14}H_{18}FNO_3$: 267.13, Found: 268.09 $[M+H]^+$.

1-(*cis*-3,4-Dihydroxypiperidin-1-yl)-3-(4-(trifluoromethyl)phenyl) propan-1-one (5h):

Yield: 85.0%; MR: 103.106 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.62 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 7.6 Hz, 2H), 4.83-4.57 (m, 2H, OH), 3.78-3.54 (m, 3H), 3.36-3.04 (m, 3H), 2.89 (br s, 2H), 2.68-2.54 (m, 2H), 1.67-1.38 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.05 & 169.61, 146.74 & 146.64, 129.30 & 129.23, 126.73 & 125.84, 125.02 & 124.99, 123.14, 68.19 & 67.80, 67.66 & 67.25, 48.15, 43.27, 33.53 & 33.39, 30.55 & 30.46, 29.07;LC-MS (ESI) m/z Calcd. for $C_{15}H_{18}F_3NO_3$: 317.12, Found: 318.23 $[M+H]^+$.

1-(*cis*-3,4-Dihydroxypiperidin-1-yl)-3-(4-hydroxyphenyl)propan-1-one (5i):

Yield: 80.0%; MR: 205-208 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.00-6.93 (t, *J* = 8.0 Hz, 2H), 6.65 (dd, *J* = 8.8, 2.0 Hz, 2H), 3.70-3.43 (m, 3H), 3.30-3.02 (m, 3H), 2.79-2.52 (m, 4H), 1.66-1.41 (m, 2H); LC-MS (ESI) m/z Calcd. for $C_{14}H_{19}NO_4$: 265.13, Found: 266.08 $[M+H]^+$.

1-(*cis*-3,4-Dihydroxypiperidin-1-yl)-3-(thiophen-3-yl)propan-1-one (5j):

Yield: 87.0%; Thick liquid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.41 (dd, *J* = 4.8, 2.8 Hz, 1H), 7.17 (s, 1H), 7.01 (s, 1H), 4.63-4.49 (m, 2H, OH), 3.76-3.04 (m, 6H), 2.81-2.73 (m, 2H), 2.67-2.53 (m, 2H), 1.67-1.42 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.29 & 169.89, 141.86, 128.44, 125.53, 120.48 & 120.35, 68.10 & 67.75, 67.58 & 67.24, 48.06, 43.19, 33.20 & 33.05, 30.51, 29.04; LC-MS (ESI) m/z Calcd. for $C_{12}H_{17}NO_3S$: 255.09, Found: 256.11 $[M+H]^+$.

***N*-(4-(3-(*cis*-3,4-Dihydroxypiperidin-1-yl)-3-oxopropyl)phenyl)-3-(4-fluorophenyl)propanamide (7e):**

Yield: 78%; MR: 127-129 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.81 (s, 1H, NH), 7.45 (d, *J* = 8.4 Hz, 2H), 7.27 (t, *J* = 8.4 Hz, 2H), 7.14-7.07 (m, 4H), 4.67-4.51 (m, 2H, OH), 3.73-3.62 (m, 2H), 3.52-3.47 (m, 1H), 3.34-3.29 (m, 1H), 3.21-3.16 (m, 1H), 3.09-3.03 (m, 1H), 2.88 (t, *J* = 8.4 Hz, 2H), 2.72 (t, *J* = 7.4 Hz,

2H), 2.60-2.53 (m, 4H), 1.63-1.53 (m, 1H), 1.44-1.42 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.34 & 170.0, 169.91, 161.87 & 159.47, 137.33 & 137.02, 136.20 & 136.07, 130.05 & 129.96, 128.52 & 128.45, 119.05, 115.05, 114.83, 68.13 & 67.79, 67.63 & 67.23, 48.13, 43.16, 38.16 & 37.94, 34.20 & 34.11, 30.57 & 30.28, 30.21 & 29.96, 29.08; LC-MS (ESI) m/z Calcd. for $C_{23}H_{27}FN_2O_4$: 414.45, Found: 415.17 $[M+H]^+$.

***N*-(4-(3-(*cis*-3,4-Dihydroxypiperidin-1-yl)-3-oxopropyl)phenyl)-3-(4-(trifluoromethyl)phenyl) propanamide (7f):**

Yield: 71.0%; MR: 94-97 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.82 (s, 1H, NH), 7.64 (d, *J* = 8.4 Hz, 2H), 7.48-7.43 (m, 4H), 7.13 (d, *J* = 8.4 Hz, 2H), 4.59-4.47 (m, 2H, OH), 3.70-3.62 (m, 2H), 3.52-3.47 (m, 1H), 3.37-3.36 (m, 1H), 3.21-3.18 (m, 1H), 3.16-3.07 (m, 1H), 2.99 (t, *J* = 7.6 Hz, 2H), 2.73 (t, *J* = 7.2 Hz, 2H), 2.59-2.53 (m, 4H), 1.61-1.54 (m, 1H), 1.44-1.40 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.29, 169.72, 146.20, 136.94, 136.22, 129.05, 128.39, 126.85 & 126.54, 125.71, 125.05, 119.06, 68.08 & 67.74, 67.58 & 67.20, 48.08, 43.14, 37.20, 34.04, 30.47, 30.15, 29.05; LC-MS (ESI) m/z Calcd. for $C_{24}H_{27}F_3N_2O_4$: 464.19, Found: 465.09 $[M+H]^+$.

***N*-(4-(3-(*cis*-3,4-Dihydroxypiperidin-1-yl)-3-oxopropyl)phenyl)-3-(4-hydroxyphenyl)propanamide (7g):**

Yield: 68.0%; MR: 224-228 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.78 (s, 1H, NH), 9.14 (s, 1H, OH), 7.45 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.01 (d, *J* = 8.4 Hz, 2H), 6.65 (d, *J* = 8.4 Hz, 2H), 4.67-4.51 (m, 2H, OH), 3.71-3.62 (m, 2H), 3.52-3.49 (m, 1H), 3.30-3.28 (m, 1H), 3.21-3.18 (m, 1H), 3.08-3.04 (m, 1H), 2.79-2.71 (m, 4H), 2.59-2.49 (m, 4H), 1.60-1.54 (m, 1H), 1.44-1.39 (m, 1H); LC-MS (ESI) m/z Calcd. for $C_{23}H_{28}N_2O_5$: 412.20, Found: 413.09 $[M+H]^+$.

1-(*trans*-3,4-Dihydroxypiperidin-1-yl)-3-(4-fluorophenyl)propan-1-one (12e):

Yield: 79.0%; Thick gum ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.26 (dd, *J* = 8.4, 5.6 Hz, 2H), 7.08 (t, *J* = 8.0 Hz, 2H), 4.93 (br s, 1H, OH), 4.81 (br s, 1H, OH), 3.57-3.53 (m, 2H), 3.43-3.41 (m, 1H), 3.14-3.01 (m, 3H), 2.78 (t, *J* = 7.6 Hz, 2H), 2.66-2.60 (m, 2H), 1.67-1.66 (m, 1H), 1.23-1.22 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.88 & 169.65, 161.77 & 159.37, 137.59 & 137.51, 130.06 & 129.99, 114.83 & 114.63, 71.30 & 70.40, 69.88 & 69.64, 48.14 & 45.20, 42.45 & 37.95, 33.92 & 33.85, 31.79, 29.86; LC-MS (ESI) m/z Calcd. for $C_{14}H_{18}FNO_3$: 267.13, Found: 268.09 $[M+H]^+$.

1-(*trans*-3,4-Dihydroxypiperidin-1-yl)-3-(4-(trifluoromethyl)phenyl) propan-1-one (12f):

Yield: 81.0%; MR: 89-92 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.62 (d, *J* = 7.6 Hz, 2H), 7.47 (d, *J* = 7.6 Hz, 2H), 4.97 (br s, 1H, OH), 4.85 (dd, *J* = 11.2, 3.2 Hz, 1H, OH), 4.06-3.44 (m, 2H), 4.06-3.44 (m, 1H), 3.32-3.04 (m, 3H), 2.89 (t, *J* = 7.6 Hz, 2H), 2.87-2.63 (m, 2H), 1.78-1.74 (m, 1H), 1.25-1.21 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.73 & 169.49, 146.69 & 146.58, 129.25 & 129.21, 126.75-125.81,

124.99 & 124.95, 123.11, 71.29 & 70.42, 69.83 & 69.55, 40.08 & 45.27, 42.23 & 37.99, 33.34, 31.81, 30.43 & 29.83; LC-MS (ESI) m/z Calcd. for $C_{15}H_{18}F_3NO_3$: 317.12, Found: 318.19 $[M+H]^+$.

1-(*trans*-3,4-Dihydroxypiperidin-1-yl)-3-(4-hydroxyphenyl)propan-1-one (12g):

Yield: 72.0%; Thick gum; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.05 (s, 1H, OH), 6.95 (d, J = 8.4, 2.0 Hz, 2H), 6.60 (d, J = 8.0 Hz, 2H), 4.89-4.86 (m, 1H, OH), 4.78-4.74 (m, 1H, OH), 4.01-3.30 (m, 3H), 3.20-2.93 (m, 3H), 2.62 (d, J = 8.0 Hz, 2H), 2.58-2.49 (m, 2H), 1.73-1.66 (m, 1H), 1.28-1.25 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.64 & 170.42, 155.85, 131.96 & 131.84, 129.56, 115.42, 71.87 & 70.93, 70.47 & 70.25, 48.73 & 45.68, 42.09 & 38.46, 34.91, 32.33, 30.45; LC-MS (ESI) m/z Calcd. for $C_{14}H_{19}NO_4$: 265.13, Found: 266.43 $[M+H]^+$.

1-(*trans*-3,4-Dihydroxypiperidin-1-yl)-3-(thiophen-3-yl)propan-1-one (12h):

Yield: 80.0%; MR: 82-86 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.41 (t, J = 4.0 Hz, 1H), 7.17 (s, 1H), 7.01 (d, J = 4.4 Hz, 1H), 4.94-4.91 (m, 1H, OH), 4.82-4.78 (m, 1H, OH), 4.06-3.56 (m, 2H), 3.44-3.41 (m, 1H), 3.28-3.01 (m, 3H), 2.79 (t, J = 7.2 Hz, 2H), 2.69-2.62 (m, 2H), 1.81-1.72 (m, 1H), 1.25-1.19 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.99 & 169.77, 141.82 & 141.71, 128.45, 125.53, 120.47 & 120.38, 71.31 & 70.40, 69.89 & 69.66, 48.12 & 45.21, 42.43 & 37.97, 33.01, 31.80, 29.86; LC-MS (ESI) m/z Calcd. for $C_{12}H_{17}NO_3S$: 255.09, Found: 256.18 $[M+H]^+$.

***N*-(4-(3-(*trans*-3,4-Dihydroxypiperidin-1-yl)-3-oxopropyl)phenyl)-3-(4-(trifluoromethyl)phenyl) propanamide (13c):**

Yield: 84.0%; MR: 169-174 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.81 (s, 1H, NH), 7.64 (d, J = 8.0 Hz, 2H), 7.48-7.43 (m, 4H), 7.13 (d, J = 8.4 Hz, 2H), 4.93-4.92 (m, 1H, OH), 4.81-4.78 (m, 1H, OH), 4.06-3.42 (m, 3H), 3.25-3.04 (m, 3H), 2.99 (t, J = 7.6 Hz, 2H), 2.73 (t, J = 8.0 Hz, 2H), 2.66 (t, J = 8.0 Hz, 2H), 2.7-2.54 (m, 2H), 1.78-1.74 (m, 1H), 1.24-1.21 (m, 1H); LC-MS (ESI) m/z Calcd. for $C_{24}H_{27}F_3N_2O_4$: 464.19, Found: 465.30 $[M+H]^+$.

***N*-(4-(3-(*trans*-3,4-Dihydroxypiperidin-1-yl)-3-oxopropyl)phenyl)-3-(4-hydroxyphenyl)propanamide (13d):**

Yield: 76.0%; MR: 174-178 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.75 (s, 1H, NH), 9.11 (s, 1H, OH), 7.45 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H), 7.01 (d, J = 8.4 Hz, 2H), 6.65 (d, J = 8.4 Hz, 2H), 4.93-4.91 (m, 1H, OH), 4.82-4.77 (m, 1H, OH), 4.06-3.37 (m, 3H), 3.25-3.00 (m, 3H), 2.78-2.71 (m, 4H), 2.58-2.51 (m, 4H), 1.79-1.72 (m, 1H), 1.24-1.18 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.25, 170.18 & 169.79, 155.40, 137.07, 136.06 & 135.93, 131.18, 129.00, 128.39, 119.03, 115.01, 71.33 & 70.41, 69.92 & 69.68, 48.19 & 45.22, 42.49 & 38.36, 37.96, 34.03, 31.82, 30.15, 30.07 & 29.90; LC-MS (ESI) m/z Calcd. for $C_{23}H_{28}N_2O_5$: 412.20, Found: 413.33 $[M+H]^+$.

General procedure for the preparation of compounds 6a-c and **8a-c:**

To a stirred solution of amine (1.0 mol) in THF (10 v) was added pyridine (5 mol), after 5 min, sulfonyl chloride derivative (1.1 mol) was added at RT under the nitrogen atmosphere stirred for 16 h. After completion of the reaction, the reaction mixture was diluted with water (50 v), extracted with EtOAc (50 v X 2), solvent evaporated under reduced pressure. The crude product was purified by column chromatography to afford **6a-c** and **8a-c** as solids/liquids in 55-72% yield.

***cis*-1-(4-Fluorophenylsulfonyl)piperidine-3,4-diol (6a):**

Yield: 68.0%; Thick liquid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.83-7.79 (m, 2H), 7.48 (t, J = 6.8 Hz, 2H), 3.63-3.53 (m, 2H), 3.10-3.04 (m, 2H), 2.70-2.59 (m, 2H), 1.78-1.52 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.48 (d), 132.09, 130.36 (d), 116.48 (d), 67.33, 65.77, 47.01, 41.01, 29.64; LC-MS (ESI) m/z Calcd. for $C_{11}H_{14}FNO_4S$: 275.06, Found: 276.04 $[M+H]^+$.

***cis*-1-(4-(Trifluoromethyl)phenylsulfonyl)piperidine-3,4-diol (6b):**

Yield: 65.0%; Thick liquid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.04 (d, J = 8.4 Hz, 2H), 7.97 (d, J = 8.0 Hz, 2H), 3.63-3.54 (m, 2H), 3.11 (t, J = 12.0 Hz, 2H), 2.75 (t, J = 9.6 Hz, 2H), 2.67 (t, J = 10.4 Hz, 2H), 1.72-1.68 (m, 1H), 1.63-1.60 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 139.68, 133.15-132.19 (m), 128.39, 126.60 (d), 124.87 (d), 67.31, 65.83, 47.15, 41.21, 29.45; LC-MS (ESI) m/z Calcd. for $C_{12}H_{14}F_3NO_4S$: 325.06, Found: 323.95 $[M-H]^-$.

***cis*-1-(4-(Trifluoromethoxy)phenylsulfonyl)piperidine-3,4-diol (6c):**

Yield: 72.0%; Thick liquid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.86 (d, J = 8.8 Hz, 2H), 7.63 (d, J = 8.0 Hz, 2H), 4.83 (d, J = 5.6 Hz, 1H, OH), 4.51 (d, J = 4.0 Hz, 1H, OH), 3.63-3.54 (m, 2H), 3.17-3.06 (m, 2H), 2.75-2.66 (m, 2H), 1.72-1.59 (m, 2H); LC-MS (ESI) m/z Calcd. for $C_{12}H_{14}F_3NO_5S$: 341.05, Found: 342.21 $[M+H]^+$.

***N*-(4-(3-(*cis*-3,4-Dihydroxypiperidin-1-yl)-3-oxopropyl)phenyl)-4-fluorobenzenesulfonamide (8a):**

Yield: 64.0%; MR: 221-224 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.13 (s, 1H, NH), 7.80-7.77 (m, 2H), 7.38 (d, J = 8.8 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 6.96 (d, J = 8.0 Hz, 2H), 4.70-4.52 (m, 2H, OH), 3.67-3.02 (m, 6H), 2.70-2.42 (m, 4H), 1.56-1.41 (m, 2H); LC-MS (ESI) m/z Calcd. for $C_{20}H_{23}FN_2O_5S$: 422.13, Found: 423.29 $[M+H]^+$.

***N*-(4-(3-(*cis*-3,4-Dihydroxypiperidin-1-yl)-3-oxopropyl)phenyl)-4-(trifluoromethyl)benzene sulfonamide (8b):**

Yield: 62.0%; MR: 194-197; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.39 (m, 1H, NH), 7.94 (t, J = 9.6 Hz, 4H), 7.10 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 8.0 Hz, 2H), 4.65-4.50 (m, 2H, OH), 3.71-3.59 (m, 2H), 3.49-3.44 (m, 1H), 3.28-3.26 (m, 1H), 3.19-3.16 (m, 1H), 3.06-3.02 (m, 1H), 2.69-2.67 (m, 2H), 2.55-2.53 (m, 2H), 1.57-1.52 (m, 1H), 1.45-1.36 (m, 1H); LC-MS (ESI) m/z Calcd. for $C_{21}H_{23}F_3N_2O_5S$: 472.13, Found: 473.14 $[M+H]^+$.

_N_-(4-(3-(_cis_-3,4-Dihydroxypiperidin-1-yl)-3-oxopropyl)phenyl)-4-(trifluoromethyl)-_N_-(4-(trifluoro methyl)phenylsulfonyl)benzene sulfonamide (8c):

Yield: 55.0%; MR: 215-219 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.13-8.08 (m, 8H), 7.36 (d, J = 8.0 Hz, 2H), 7.03 (d, J = 8.0 Hz, 2H), 4.69-4.54 (m, 2H, OH), 3.75-3.50 (m, 3H), 3.38-3.05 (m, 3H), 2.88-2.85 (m, 2H), 2.72-2.64 (m, 2H), 1.65-1.40 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.08 & 169.66, 144.98, 142.12, 134.23 & 133.90, 130.97, 130.57, 129.89 & 129.81, 129.13, 126.97, 124.56, 68.11 & 67.79, 67.64 & 67.19, 48.12, 43.22, 33.27, 30.57 & 30.34, 29.08; LC-MS (ESI) m/z Calcd. for $C_{23}H_{28}N_2O_5$: 412.20, Found: 413.33 $[M+H]^+$; LC-MS (ESI) m/z Calcd. for $C_{28}H_{26}F_6N_2O_7S_2$: 680.11, Found: 681.18 $[M+H]^+$.

4.2. Biology (α-glucosidase enzyme inhibition assay)

4.2.1. Test concentration

The stock solutions (10mM) of standards and each test substances were prepared in 100% Dimethyl Sulfoxide (DMSO, Sigma Chemical Co., St. Louis, MO) and further diluted with PBS to obtain an experimental concentration of 1-0.25 mM (also 0.125 and 0.062 for potent compounds).

4.2.2. Protocol for α-glucosidase enzyme assay

The inhibitory activity assay procedure was performed by optimizing the previously reported method [41-44]. α-Glucosidase enzyme (0.1U/ml) was dissolved in 1mM concentration of phosphate buffer (pH 6.9) and was prepared fresh every time. The initial step was performed by mixing 10 µL of the test sample with 40 µL of prepared enzyme solution and incubated for 15-20 min at 37 °C. Then 40 µL of *p*-nitrophenyl-α-D-glycopyranoside (PNPG) substrate (0.1mM) was added and incubated for 45-60 min. The release of *p*-nitrophenol by quenching effect was determined with the addition of 100 µL of 0.1 M Na_2CO_3. Further, the enzymatic activity was quantified in proportion to the level of *p*-nitrophenol spectrophotometrically with absorbance reading at 415nm. Blank reading was taken without the test compound and with enzyme and substrate. Acarbose, Voglibose and Miglitol were used as positive controls.

4.2.3. Data interpretation

The readings taken at 415nm were further evaluated for their percentage inhibition of test compounds (Table 3). The equation used was:

$$((A_{blank} - A_{sample}) / A_{blank}) * 100$$

The IC_{50} values were calculated plotting graphs with percentage inhibition on the y-axis and log concentrations on x-axis using graph pad prism v 6.0. The IC_{50} values are reported as best fit value after normalization of data (n=3)

Acknowledgements

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 BITS-Pilani and NIPER Hyderabad.

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Highlights:

1. It is the first biological evaluation of 3,4-dihydroxy piperidines as α-glucosidase inhibitors.
2. We have made forty-four final targets (amide, di-amides and sulphonamides) using *cis* and *trans* dihydroxy piperidines to evaluate their α-glucosidase inhibition activities.
3. Eight compounds showed excellent inhibition activity compared to reference standards (Acarbose, Voglibose and Miglitol).