Alpha-glucosidase inhibition and molecular docking studies of 1,2-benzothiazine 1,1-dioxide based carbohydrazides

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Abstract: Diabetes mellitus is a chronic disease in which the infected cells do not have the ability to produce sufficient amount of insulin that results in the abnormality of carbohydrates metabolism and an increase in blood glucose level. Long time exposure to diabetes mellitus results in failure or dysfunction of different organs like kidneys, nerves, heart, eyes, etc. A common practice to cure diabetes is the use of α-glucosidase inhibitors which help in lowering the blood glucose level. We presented 1,2-benzothiazine 1,1-dioxide derivatives as novel and more potent α-glucosidase inhibitors via their *in vitro* and *in silico* screenings. Excellent enzyme inhibitions were observed for compounds 2, 8, 10 and 12 having IC_{50} values of 6.91, 14.0, 4.2, 5.9 and 29.2µM respectively which were found better than the reference acarbose (IC_{50} =38.31µM). Molecular docking studies suggested high binding energies and good binding interactions of these compounds with the active site residues of the receptor protein. A good agreement was found between the results of both modes of evaluation. Moreover, the envisioned candidates have a good potential to treat diabetes.

Keywords: 1,2-benzothiazine, molecular docking, α-glucosidase, hyperglycemia, diabetes.

INTRODUCTION

Diabetes mellitus (DM) is a severe metabolic disorder which is instigated by the diminish insulin sensitivity, disturbance in insulin secretion separately or collectively. Delivery of glucose from blood to cells required insulin but in diabetic patients this function fails, along with retardation of metabolism of many important dietary molecules like lipids, proteins and carbohydrates (Chandran *et al.,* 2016). Major harmful aspect of DM is the raised blood glucose level which leads to various complications, like cardiovascular disorders, retinopathy, neuropathy and coronary artery disease (Cai *et al.,* 2017; Shen *et al.,* 2016). Diabetes is one of the rapidly growing disease and according to a report, 415 million peoples are infected by DM and it is estimated that this fig. will grow to 642 million in 2040 (Ogurtsova *et al.,* 2017).

As dietary carbohydrates like starch are the chief source of blood glucose and these carbohydrates are metabolized by *α*-glucosidase or *α*-amylase, later on, absorbed by small intestine (Balan *et al.,* 2015). One of efficient remedial approach to cure DM is to inhibit the glucose absorption in gastrointestinal tract, by the inhibition of responsible enzymes like *α*-glucosidase (Joshi *et al.,* 2015). *α*-Glucosidase inhibitors are substances which can stop the carbohydrate metabolism and restrain postprandial hyperglycemia and are useful therapeutic agents for diabetes/obesity (Shimabukuro *et al.,* 2017; Saeed *et al.,* 2018; Saeed *et al.,* 2017; Patel *et al.,* 2017)). Use of common *α*-glucosidase inhibitors (AGI) like voglibose, miglitol and acrabose are known therapies for postprandial hyperglycemia. However, many AGIs with *α*-glucoside linkage are associated with some disadvantages such as serious gastrointestinal complications, contain sugar moieties and require multistep synthesis. Similarly, these are also related with some side effects like flatulence, abdominal pain and diarrhea (Ghazanfar *et al.,* 2014). Hence, there is a need to find new drug molecules with good anti-*α*-glucosidase activity and less or almost no side effects.

1,2-benzothiazine 1,1-dioxides is a versatile class of organic compounds in heterocyclic chemistry and have prevailed the field of medicines and drugs for many decades. 1,2-benzothiazine 1,1-dioxides possess a wide range of biological potentials such as anti-HIV (Aslam *et al.,* 2014a; Ahmad *et al.,* 2014; Khalid *et al.,* 2015), anti-inflammatory (Aman *et al.,* 2014; Gannarapu *et al.,* 2015), anti-cancer (Wang *et al.,* 2014), anti-viral (Aslam *et al.,* 2014b; Ahmad *et al.,* 2015), monoamine oxidase inhibitors (Abid *et al.,* 2017), HPPD inhibitors (Lei *et al.,* 2016), cholinesterase inhibitors (Aslam *et al.,* 2014c), etc. To the best of our knowledge, the antidiabetic potential of 1,2-benzothiaziene 1,1-dioxides has not been well explored up till now and there are only a few reports

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available in this regard (Tawada *et al.,* 1990; Pandey and Pathak, 2002; Chen *et al.,* 2011; Parveen *et al.,* 2014a; Parveen *et al,.* 2014b). Keeping in mind the wide biological aspects of this class and unrevealed antidiabetic potential and to fulfill the demand of more potent and novel AGIs, we have screened a number of reported 1,2-benzothiaziene 1,1-dioxide derivatives (Saddique *et al,.* 2018) to assess their *in vitro* α-glucosidase inhibitory activity. In order to check the *in vitro* inhibition mechanism, the detailed *in silico* inhibitory studies were also carried out.

MATERIALS AND METHODS

Enzyme inhibition assay

In vitro enzyme inhibition activity of all the compounds was evaluated spectrophotometrically by using the previously reported assay with slight modifications (Wang *et al*., 2017a). Solutions of all the compounds were made in DMSO while solution of α-glucosidase enzyme (*Saccharomyces cerevisiae*, Sigma-Aldrich) was prepared in phosphate buffer (pH 6.8, 100mM). Test compounds (12.5µL), 0.5 U/mL enzyme (40µL) and 100 mM phosphate buffer (120µL) were added in 96-well microliter plates. Incubation at 37°C for 5 min was executed and then 5 mM of PNPG (*p*-nitrophenyl-α-D-glucopyranoside, Sigma Aldrich) was dropped in each well. After incubation for further 30 mint, 1000mM sodium carbonate solution (30µL) was added and absorbance was found at 405 nm and 37°C. Acarbose (Sigma-Aldrich) and DMSO were used as standard inhibitor and negative control respectively. Experiment was performed in triplicate and finally IC_{50} values were determined.

In silico analysis

Ligand preparation

ChemDraw Ultra 12+Serial was used to design the structures of all the ligands and then saved in MDL file (".sdf") to open these structures in MOE software. From NCBI Pubchem, 2D structure of standard acarbose was downloaded and saved as SDF file. Finally, under default parameters in MOE, structures of all the ligands and acarbose were 3D protonated and energy minimized.

Protein preparation

Protein Data Bank (http://www.rcsb.org/pdb) was used to assess the 3D structure of *Saccharomyces cerevisiae* α-glucosidase (PDB ID: 2QMJ). Ligand (acarbose) showed binding interactions with Asp 203, Asp 542, Asp 327, His 600, Arg 526 residues of protein. After the removal of ligand, solvent molecules and unknown atoms from the receptor protein, the active sites were computed which were consist of Asp 203, Tyr 299, Asp 327, Ile 328, Asp 366, Trp 406, Trp 441, Asp 443, Met 444, Arg 526, Trp 539, Gly 541, Asp 542, Asp 571, Phe 575, Arg 598 and His 600 residues. Dummy atoms were created at these active sites followed by 3D protonation and energy minimization of the protein under default parameters.

Molecular docking

Finally, docking of ten conformations of each ligand and acarbose (standard) was executed using Dock-Module in the MOE under default settings. From the binding energy of top-ranked conformation, binding modes of each ligand with the receptor protein were studied.

RESULTS

In vitro screening

α-Glucosidase inhibitions of all the compounds along with standard acarbose were checked. Significant α-glucosidase inhibitions were observed for some derivatives which showed IC_{50} values even better than the reference acarbose (table 1). Among the screened derivatives, the derivatives 2, 8, 10, 12 and 14 showed excellent inhibitory potential with IC_{50} values of 6.91, 14.0, 4.2, 5.9 and 29.2µM respectively which are less than the reference standard acarbose (IC_{50}=38.31µM).

In silico screening

In molecular docking studies, it was observed that almost all the derivatives (except 11) showed good docking scores and binding interactions with the targeted site residues (His 600, Arg 526, Asp 327, Asp 203, Asp 542) (table 1, fig. 1). The binding energies of most of the ligands were found above -10.0 except for compound 6, 7 and 11. However, compounds 10, 12 and 2 were witnessed with highest binding energy scaffolds and their binding scores were found about nearer to the binding energy of acarbose (-16.1862).

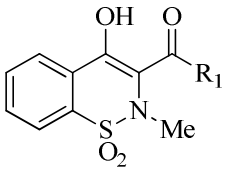
DISCUSSION

In vitro screening

Heterocycles like imidazoles (Yar *et al.,* 2014), halobenzodithiophene derivatives (Abbas *et al.,* 2018) and triazoles (Chinthala *et al.,* 2015) are reported in literature as excellent templates for various α-glucosidase inhibitors, these observations led us for designing benzothiazine derivatives as more potent anti-diabetic agents.

Structure-activity relationship conveyed that compound having polar group like -$NHNH_2$ at position-3 of the thiazine ring showed excellent inhibitory potential which was observed from the low IC_{50} value (6.91µM) of compound 2 and it is 5.5 times more active than the standard acarbose (IC_{50} =38.31µM) and even better than recently reported acetamides (Wang *et al.,* 2017b). Among the compounds 3-14, compounds having phenyl ring and methyl group at the imine carbon were also found much effective against α-glucosidase as illustrated from the low IC_{50} value (4.2µM) of derivative 10. It is the

Table 1: *In vitro* (IC_{50} values) and *in silico* (docking scores) α-glucosidase inhibitory potential of compounds 1-14.



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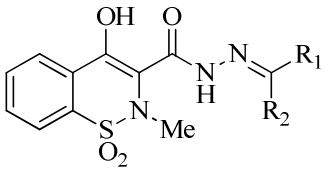

3-14

Compound	R_1	R_2	IC_{50} value	Docking Score
1	OMe	-	>100	-10.4024
2	$NHNH_2$	-	6.91	-12.0285
3	4-ClC_6H_4	H	76.8	-10.4239
4	4-$OMeC_6H_4$	H	>100	-10.3073
5	4-FC_6H_4	CH_3	>100	-10.3599
6	4-MeC_6H_4	H	>100	-9.7754
7	2-OHC_6H_4	H	>100	-9.4289
8	3-ClC_6H_4	H	14.0	-11.3412
9	C_6H_5	H	>100	-10.0809
10	C_6H_5	CH_3	4.2	-12.6818
11	-$CH_2CH_2CH_2CH_2$-		>100	-9.5402
12	4-ClC_6H_4	CH_3	5.9	-12.3327
13	4-$CH(Me)_2C_6H_4$	H	62.5	-10.5013
14	4-$OEtC_6H_4$	H	29.2	-10.5877
Acarbose	-	-	38.31	-16.1862

most active compound among the analyzed series and showed about 9 folds greater inhibition compared to the acarbose. Moreover, this ligand was also proved more effective alpha glucosidase inhibitor compared to the reported tetracyclic oxindole derivatives (Han *et al.*, 2015). Similarly, presence of strong electron donating groups in the phenyl ring also resulted in an increase in the biological activity of the screened compounds which is argued from the low IC_{50} values of derivatives 13 (IC_{50} =62.5μM) and 14 (IC_{50}=29.2μM). However, the bulkiness of the electron donating group also played its role and influenced the potency of compound 13. Among the weak electron donating substituents like F and Cl, the presence of Cl group at any position of the phenyl group was found effective as indicated by the low IC_{50} values of 8 (IC_{50} = 14μM) and 12 (IC_{50} =5.9μM). Compound 8 and 12 were found about 2.7 and 6.5 times more active than acarbose. These compounds were also found better anti-diabetic agents compared to recently reported pyrazolo [3,4-d] pyrimidine derivatives (El-Fal *et al.,* 2017). The presence of methyl group at the imine carbon enhanced the biological activity of compound 12 compared to compound 3 (IC_{50} =76.8μM) which do not have methyl moiety.

***In silico* screening**

Molecular docking is a versatile technique to explore biologically effective scaffolds that eliminates the manual synthetic work. Keeping this aspect of molecular docking we carried out the *in silico* screening of fourteen 1,2-benzothiazine derivatives (table 1 and fig. 1). In order to check the binding interactions between the ligands and the active site residues of the receptor protein (α-glucosidase) MOE software was used. Docking scores and the bindings with active residues helped us to recognize these derivatives.

During molecular docking studies, The most active compound 10 formed two interactions with Asp 203 and Phe 575 residues. A hydrogen bonding was observed between the hydrogen atom of enolic -OH group of the ligand 10 and the active site residue Asp 203 while an arene-arene interaction was found between phenyl moiety of ligand 10 and Phe 575 residue. Due to these strong interactions compound 10 showed the highest binding score (-12.6818). Ligand 12, the second most active compound among the series, showed one interaction with the active site residue, Asp 542. Strong hydrogen bonding was observed between Asp 542 and the hydrogen atom of the enolic -OH group present in the ligand 12. Due to the presence of this strong hydrogen bonding, tight packing and greater number of active site residues resulted in good binding score (-12.3327) of compound 12. In a previously reported *in silico* study, a number of xenthone derivatives also showed alpha glucosidase inhibition by interacting with Asp 203, Asp 542, Arg 526 residues of the receptor enzyme (Lakehal *et al.,* 2016). Two hydrogen bonds were observed between compound 2 and the active site residues, His 600 and Arg 526. His 600 formed a hydrogen bond with the hydrogen atom of $–NH_2$ group

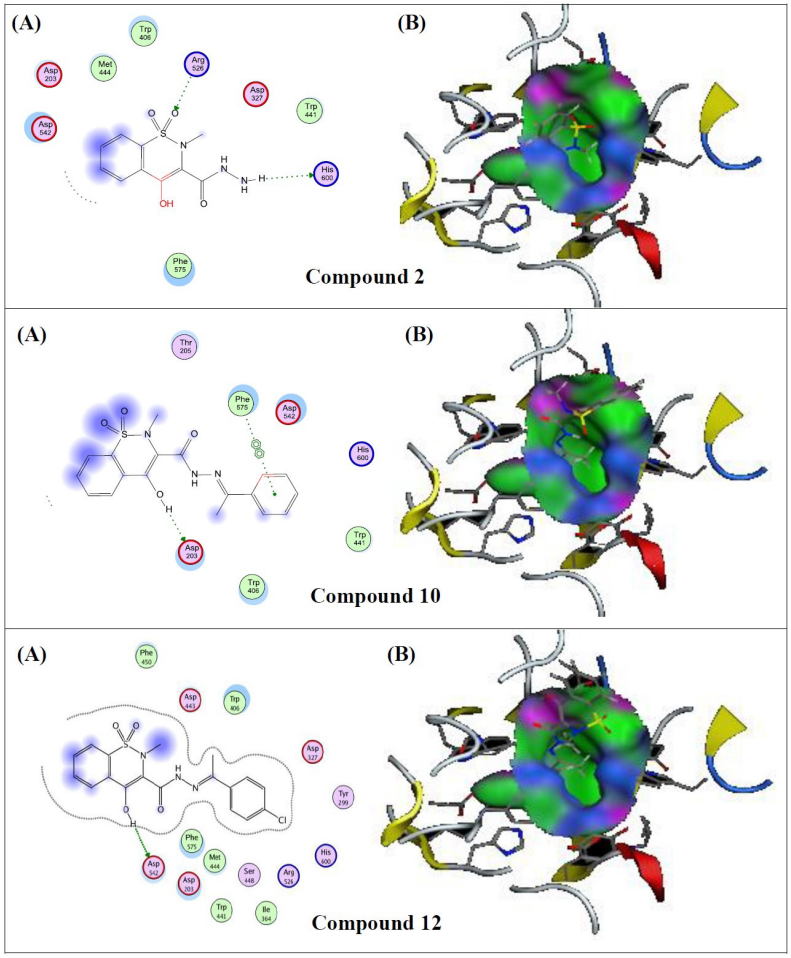

Fig. 1: 2D (A) and 3D (B) interaction modes of most active compounds.

while Arg 526 showed a hydrogen bonding with one of the double bonded oxygen atom of -SO_2 group of the ligand 2. These two strong interactions are responsible for the high docking score (-12.0285) and strong packing of the ligand 2 in the protein active site. Compound 8 showed one hydrogen bond with Arg 526 residue. This hydrogen bond was observed between the residue Arg 526 and the oxygen atom of the carbonyl group of compound 8. Due to the presence of this hydrogen bonding, ligand 8 showed a good binding score (-11.3412). In another report, black tea component, 8-c-ascorbyl-(-)-epigallocatechin was found to inhibit the alpha glucosidase activity by blocking residues Asp 203, Asp 542 and Arg 526 (Mohapatra *et al.,* 2015). Compound 14 formed two interactions with active site residues, Asp 542 and Phe 575. Asp 542 formed a hydrogen bond with the -NH group while Phe 575 showed an arene-arene interaction with the phenyl moiety of the compound 14. Similarly, compound 13 showed a hydrogen bonding with Arg 526 using oxygen atom of its carbonyl group. Similarly, Voglibose inhibited the alpha glucosidase activity *via* bonding with Asp 203, Asp 542, Arg 526 residues (Kulkarni *et al*., 2016). The low docking scores of compounds 13 (-10.5013) and 14 (-10.5877) were attributed to the bulky substituents ($CHMe_2$, OEt) present in the structure of these ligands which resulted in their loose packing in the protein active site. The low binding scores of compounds 1, 3, 4, 5, 6, 7, 9 and 11 showed low binding energy values due to weak attractions with the active site residues and loose packing in the active site of receptor protein.

An analysis of the molecular docking results revealed that polar groups like -NH_2, CO and -OH played a significant role regarding the *in silico* α-glucosidase inhibitory potential of the screened molecules. Moreover, molecules with smaller size substituents were found more effective than the molecules with large size substituents in terms of interactions with active site residues and packing in the active site of protein. The structure-activity relationship was found in good agreement with the *in vitro* inhibitory potential of the compounds.

CONCLUSION

We evaluated 1,2-benzothiazine 1,1-dioxide derivatives for their in vitro and in silico α-glucosidase inhibitory potential. As a result of in vitro evaluation, compounds *2,*

8, 10, 12 and 14 were concluded as best α-glucosidase inhibitors with IC_{50} values of 6.91, 14.0, 4.2, 5.9 and 29.2 μM respectively even better than the reference acarbose (IC_{50}=38.31μM). Regarding the in silico study, compounds 2, 8, 10, 12 and 14 also showed good enzyme inhibition activity as indicated from their high binding energy values and strong interactions with the active site residues. In short, we have presented α-glucosidase inhibition ability of 1,2-benzothiazine based carbohydrazides.

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