Isolation, in vitro antidiabetic, antioxidant activity and molecular docking studies of pentacyclic triterpenoids from Syzygium alternifolium (wt.) Walp bark

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Abstract: Diabetes mellitus type 2 is a metabolic disorder characterized by hyperglycemia including insulin resistance and relative lack of insulin. Type 2 diabetes is expected to reduce ten-year shorter life expectancy. In this research article, we have isolated two terpenoids from the stem bark of Syzygium alternifoliumby column chromatography. The isolated compounds were identified as friedelin and 3β-friedelinol terpenoids by 1H-NMR, 13C-NMR, and Mass spectroscopy. The isolated compounds were screened in vitro enzyme inhibition assays against α-glucosidase & α-amylase; and were found to decrease plasma glucose level significantly showing antidiabetic activity. Isolated compounds also exhibited significant radical scavenging antioxidant activity by DPPH inhibition assay. The results of in vitro experimentation were confirmed by the molecular docking studies of the isolated terpenoids on α-glucosidase and α-amylase enzymes. The present research reveals the antidiabetic and antioxidant activity of isolated terpenoids from stem bark of Syzygium alternifolium against diabetes mellitus type 2 disorders.

Keywords: α-glucosidase, α-amylase, DPPH, Syzygium alternifolium, terpenoids, and docking

1. Introduction

Type 2 diabetes is a public health problem that is characterized by tissue resistance to insulin combined with a relative deficiency in insulin secretion.\cite{2}. On the other hand, diminished glucose-induced insulin secretion with shrinkage in pancreatic cell mass will ultimately lead to postprandial hyperglycemia.\cite{3} Postprandial hyperglycemia is an independent risk factor for cardiovascular disease, stroke, and mortality; it initiates a cascade of pro-atherogenic and pro-thrombotic events.\cite{4} Oxidative stress is also considered to be the major cause in the development of type-II diabetes. In 2011, about 366 million people suffered with diabetes globally and this is expected to increase to 552 million by 2030.\cite{5} One recent study by ICMR-INDIA reported that about 62.4 million type-II diabetic people are from India. This statistics are expected to increase to 101 million by the year 2030.\cite{6}

Currently, the methods used for treating the various types of diabetes can be classified into oral hypoglycemic drugs and insulin injection therapy. However, in taking these hypoglycemic drugs, patients still encounter serious side effects, such as abdominal distention, abdominal pain, diarrhea, gastrointestinal spasmodic pain, constipation, bowel gurgling, nausea, vomiting, anorexia, fatigue, headache, dizziness, skin itching and others. An effective inhibition of α-glucosidase enzyme (preventing postprandial hyperglycemia) and α-amylase (antioxidant activity) is a good strategy for the prevention or treatment of Type 2 diabetes, hypolipoproteinemia and obesity.

Plant-based products have been determined to function in the regulation pathophysiological signaling pathways in diabetes and exhibit anti-diabetic activity.\cite{7, 8} The hypoglycemic effect of some herbal extracts have been established in human and animal models of type-II diabetes and some of the conventional drugs have been derived from the active molecules of these herbs. For example, metformin is a less toxic and potent oral hypoglycemic was developed from plants galgea officinalis.\cite{9} Among natural compounds, pentacyclic triterpenoids (PTs) are a class of pharmacologically active and structurally rich metabolites which are reported to act on glucose metabolism.\cite{10} PTs may exert their glucose-lowering effect through multi-target pathways, including α-amylase, α-glucosidase, glycogen phosphorylase, Akt/protein kinase B, protein tyrosine phosphatase 1B, insulin receptor, the membrane G protein-coupled receptor, glucocorticoid receptor, 11β-hydroxysteroid dehydrogenase, glyceraldehyde-3-phosphate dehydrogenase and glyceraldehyde-3-phosphate dehydrogenase.

Syzygium alternifolium (L.) Walp. (Myrtaceae) is an endemic aromatic tree, distributed in Assam and Andhra Pradesh, states of India. Locally it is known as mogi/mov. The plant parts were used traditionally as a medicine to cure various diseases viz., tender shoots and fruits for dysentery, seeds for diabetes and stem bark was used to treat gastric ulcers.\cite{11} In the present study, we isolated the active constituents from stem bark of Syzygium alternifolium. Isolated compounds were identified as friedelin and 3β-friedelinol pentacyclic terpenoids. Isolated PTs were screened for antioxidant and antidiabetic activities by in vitro DPPH inhibition assay, α-amylase and α-glucosidase enzyme inhibition biochemical assays. Furthermore, the mechanism of action of the isolated PTs was explored by molecular docking analysis.

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II. Materials And Methods

2.1 Plant material

The bark of Syzygium alternifolium was collected in the month of November 2011 from Seshachalam hills of Tirupati, Andhra Pradesh. The botanical identity of the plant was confirmed with the help of botanist, Department of Botany, S. V. University, Tirupati, Andhra Pradesh, India.

2.2 Extraction

The bark of Syzygium alternifolium was chopped into small pieces, cleaned, powdered, air-dried, sieved (mesh size \(\approx 40\)) and stored in an air tight container at room temperature. The powdered plant material (2 kg) was then extracted sequentially with methanol (MeOH) using soxhlet extractor. The extract (329 gm) was concentrated to dryness using rotary evaporator. The yield of methanol extract was found to be 16.45% respectively.

2.3 Isolation

Isolated compounds were identified as terpenoids by positive Liebermann’s Burchardt test and Salkowski test. The stem bark (2 kg) of the Syzygium alternifolium bark was refluxed with methanol of three hours. After refluxing the bark with methanol, the total filtrate was concentrated to dryness in vacuum at 40 °C leaving behind the methanicolic extract (329 gm). The bark methanol extract of Syzygium alternifolium was partitioned with hexane and ethyl acetate. The respective solubles were separated. 310 gm of methanol extract was partitioned with 1:4 ratio of hexane solvent (1200 ml) by refluxing for two hours. The obtained residue was further fractionated with ethyl acetate: hexane (1:4), followed by column chromatography. The column was packed with silica gel (100-120). 5 g of hexane extract was taken and adsorbed with 15 g of silica gel. The column was filled with 50 g of silica gel. The bed volume for the column is 100 ml. The fraction was further chromatographed to give compound 1 (170 mg) and compound 2 (100 mg).

2.4 Biological assays

2.4.1 In vitro inhibition of intestinal \(\alpha\)-glucosidase enzyme

An inhibitory \(\alpha\)-glucosidase activity was performed according to the method by Feng[12]. In this method inhibition of \(\alpha\)-glucosidase enzyme was determined spectrophotometrically in a 96-well microtiter plate which is based on p-nitrophenyl-\(\alpha\)-D-glucopyranoside (PNPG) as the substrate. Everything considered the test samples (Compound 1and 2) 120 \(\mu\)l each was mixed with 20 \(\mu\)l of enzyme solution [0.8 U/ml \(\alpha\)-glucosidase in 0.01 M potassium phosphate buffer]. The whole mixture was preincubated at 37 °C prior to initiation of the reaction by incorporating the substrate. After the preincubation period of 15 min, 20 \(\mu\)l PNPG solutions [5.0 mM PNPG in 0.1 M potassium phosphate buffer (pH 6.8)] was incorporated and then incubated at 37 °C. To terminate the reaction after 15 min of incubation, 80 \(\mu\)l of 0.2 M Na2CO3 in 0.1 M potassium phosphate buffer was added to the microtiter plate. The percentage inhibition of \(\alpha\)-glucosidase activity was determined by measuring the absorbance of the resultant mixture was recorded at 405 nm.

2.4.2 In vitro inhibition of bacterial \(\alpha\)-amylase enzyme

The \(\alpha\)-amylase inhibitory activity of isolated compounds from Syzygium alternifolium bark, was performed according to the method of Wan [13]. Samples acarbose (ALD) were mixed and pre-incubated in 20 mM sodium phosphate buffer (pH 6.7) for 5 min at 37 °C. After that the volume of reaction mixture was made up to 2 ml by incorporation of 1 ml of 2% (v/v) starch dissolved in the buffer, and the whole reaction mixture was incubated for 5 min at 37 °C. After the incubation, 1 ml of di-nitro salicylic acid (DNS) color reagent was incorporated and kept in boiling water bath precisely for 5 min. Then, the temperature of this mixture was decreased to room temperature by cooling it on ice and added another 6 ml of deionized water. \(\alpha\)-Amylase inhibitory activity was determined by measuring the absorbance of the mixture at 540 nm.

2.4.3 Spectrophotometric DPPH inhibition assay

Antioxidant capacities of compounds 1, 2 were assessed by DPPH free radical scavenging assay [14]. This method is based on decline of relatively stable radical DPPH to the development of non-radical form in the presence of hydrogen donating test samples. The test samples depict antioxidant activity by the diminution in purple colored DPPH to the yellow colored diphenylpicryl hydrazine derivatives. In this method, 2 mL of 0.1 mmol/L solution of DPPH in methanol was blended with 1 mL of each compound 1 and 2. The different mixtures were incubated at room temperature in a dark room for 30 min. The absorbance was measured at 517 nm and percentage inhibition of radical scavenging was determined.

2.4.4 Molecular docking analysis

Mode of inhibition of compounds 1 (friedelin) and 2 (3β-friedelinol) on the \(\alpha\)-glucosidase enzyme was further assessed by molecular docking analysis using ligand fit of GLIDE software from Schrodinger Inc.[15]. The protein \(\alpha\)-glucosidase (Pdb Code: 3W37) and \(\alpha\)-amylase (Pdb Code: 2QV4) was downloaded from Protein Data Bank (PDB). These proteins were prepared by filling the missing loops and missing side chains using protein preparation wizard application of Schrodinger drug design software (Maestro 9.1). The proteins were further processed by removing nonreactive water molecules, and ligand molecules other than crystal ligand. The ionized proteins having the lowest penalty were energy minimized using the optimized potential for liquid simulations 2005 force field incorporated in the Impref tool of Glide programme. Then the grid was generated in the processed protein by excluding the crystal ligand in the active site using receptor grid generation tool of Glide programme (van der Waals radius scaling factor was limited to 1.0 with a partial charge cut off of 0.25). The chemical structures of compounds 1 (friedelin) and 2 (3β-friedelinol) and acarbose was drawn using ChemBioDraw software. The ligands (Acarbose, Friedelin and Friedelinol) were subjected to Ligprep simulations to generate energy minimized 3D structures (300 steps) by investigating tautomeric, stereo chemical, and ionization variations. The ligpreptau ligands were docked flexibly in the protein grids using Glide-extra precision (XP) simulations [16]. Energies of...
residues within 12 Å of grid were used for simulations. Poses having coulomb-vdw energy greater than 0.0 kcal/mol and poses having RMS deviation 0.5Å were discarded. Finally the interactions were scored based on non-bonded interactions.

III. Results And Discussion

3.1 Chemistry

The hexane-Et2O (1:1, v/v) extracts of the root barks of stem bark of Syzygium alternifolium was subjected to multiple chromatographic steps, involving vacuum liquid chromatography, medium-pressure liquid chromatography and preparative TLC, on silica gel to yield two friedelane-type triterpenoids. The structures of the new compounds 1-2 (Table 1) were deduced as described below.

3.1.1 Compound 1

The compound 1 was obtained as white crystalline powder with a melting point of 259 °C. Rf(cm) 0.71 (solvent system-hexane: ethyl acetate) (8:2). The molecular formula of compound 1 was shown to be C28H46O4 based on the positive ion LC-MS [m/z 542.5 (M+H)+ and 449.4 (M+Na)+] analysis. The IR spectrum showed bands at 2972, 2945 (CH₃ asymmetric and symmetric stretching); 2895, 2870 (CH₂ asymmetric and symmetric stretching); 1714 (OH stretching), 1454, 1386, 1246 (C=O aromatic skeletal bands). In the 1H-NMR spectrum (CDCl₃, 400 MHz) a quartet signal integrating for one proton at δ 2.40(1H, 4-H). The resonances of eight methyls δ 0.72 (3H, H-24), 0.87 (3H, H-25), 0.97 (3H, H-26) and 1.00 (3H, H-27), 1.005 (3H, H-26) and 1.18 (3H, H-28). Eleven methylene protons showed multiplet signals at δ 0.22 and 2.30 (H-2); δ1.956 and1.75 (H-1'); δ1.70 and 1.58 (H-6'); δ1.58 and1.50 (H-12); δ1.40 and1.39 (H-13); δ1.46 and1.36 (H-14); δ1.35 and1.32 (H-19); δ1.29 and1.28 (H-21); and δ 1.25 and 1.20 (H-22). The remaining three methyl protons were seen as singlets at δ 1.28 (3H, J = 6.5Hz, H-8, H-10 and H-18). The 13C-NMR spectrum of compound 1 indicated the presence of 30 carbon resonances. The DEPT spectrum indicated the presence of carbonyl at δ 213.07 including seven quaternary carbons, four CH₃ carbons, ten CH₂ carbons and eight CH₃ carbons. Since the molecular formula indicated six units of unsaturation, this compound 1 was concluded to be pentacyclic triterpenoids with a ketone group. The presence of signals due to one secondary and seven quaternary methyls in the 1H-NMR spectrum suggested the friedelane skeleton. The 1H and 13C-NMR spectral data of compound 1 indicates that it belongs to identified as Friedelin. The identification of friedelin was confirmed by comparison of the reported spectral data with compound [17].

3.1.2 Compound 2

The compound 2 was obtained as white crystalline powder with a melting point of 294 °C. Rf(cm) 0.71(solvent system-hexane: ethyl acetate) (8:2). The molecular formula of compound 2 was shown to be C28H46O5 based on the positive ion LC-MS [m/z 542.5(M+H)+ and 449.4 (M+Na)+] analysis. The IR spectrum showed bands at 3473 (OH stretching), 3003 (CH stretching), 2978, 2943 (CH₃ asymmetric and symmetric stretch), 2872, 2837 (CH₂ asymmetric and symmetric stretch) and 1477, 1384 (aromatic C=C skeletal bands). The 1H NMR spectrum (CDCl₃, 400 MHz) gave a peak at δ 3.73 which corresponds to H-3. In the HMBC spectrum C-1 showed correlations with H-3 and H-10. H-3 resonated at δ 3.73, dd/J = 10.8, 4.6 Hz, the HMBC correlations and this chemical shift value allowed us to place the hydroxyl functionality at this position (C-3). The resonances of eight methyls δ 0.85 (3H, H-25), 0.93 (3H, H-24), 1.06 (6H, H-29, H-30), 0.99 (d, 3H, H-23), 1.00 (3H, H-27), 1.01 (3H, H-26), 1.16 (3H, H-28). Eleven methylene protons showed multiplet signals at δ1.90 and 1.75 (H-2); δ1.85 and1.70 (H-1'); δ1.53 and 1.50 (H-6'); δ1.51 and1.49 (H-7); δ1.47 and1.39 (H-11); δ1.45 and1.43 (H-12); δ1.43 and1.39 (H-15); δ1.42 and1.38 (H-16); δ1.36 and1.34 (H-19); δ1.35 and1.33 (H-21); and δ 1.24 and 1.19 (H-22). Out of remaining four methine protons, methine proton showed multiplet at δ 1.55 (H-3J = 6.0Hz, H-4), while others were seen at 1.25-1.32 (3H, J = 6.0Hz, H-8, H-10 and H-18). H-10 resonated at δ 1.25, dd/J=6.0 Hz the multiplicity, dd was due to a coupling of this proton with H-1 carbon. C-3 (δ-72.20) showed correlations with H-2 and H-23. These correlations and the chemical shift value supported to phase the hydroxyl functionality at C-3 and methyl a group (C-23) at C-4. Further, in the 1D proton NMR spectrum, the methyl group at C-1 showed split in to a doublets, which was due to the coupling of these methyl protons with H-4 and fits the characteristic of this methyl group (C-23) at C-4. C-4 showed correlation with H-2, H-23 and H-24 and the quaternary carbon C-3 showed correlations with H-1, H-3, H-6 and H-24. These correlations supported the attachment of C-23 methyl group at C-4 and C-24 methyl group at C-5. The methyl protons at H-26 showed correlations with C-12, C-13, C-14 and C-18. These correlations allowed us to place the C-26 methyl group at C-13 and C-27 methyl a group at C-14 respectively. The methyl protons at H-28 showed correlations with C-16, C-17, C-18 and C-22. These correlations allowed us to place C-28 methyl group at C-17. Finally, C-29 showed correlations with H-19, H-21 and H-30; H-30 showed correlations with H-19, H-21 and H-29. C-20 showed correlations with H-19, H-21, H-29 and H-30; C-21 showed correlations with H-22,H-29 and H-30 all these correlations supported the attachment of both C-29 and C-30 (methyl groups) to the same carbon at C-20 and the compound is an oleane type triterpenoid. The β orientation of the hydroxyl group at C-3 was confirmed by comparing the proton coupling between H-3 and H-4 and H-2 confirms the stereochemistry. The 13C-NMR spectrum of 2 indicated the presence of 30 carbon resonances. The DEPT spectrum indicated the presence of six quaternary carbons, five CH₃ carbons, eleven CH₂ carbons and eight CH₃ carbons; one of the carbons resonated at δ72.8 and indicative of presence of hydroxyl group. These data of compound 2 had good agreements with the reported data of Ḟ-bfiedrinol[18].

3.1.3 Biological evaluation

Pentacyclic triterpenoids (PTs) have been reported as naturally occurring active constituents having regulatory action on glucose metabolism by many biochemical mechanisms including inhibition of α-glucosidase and α-amylase. α-glucosidase is membrane bound enzyme integrated in the epithelium of the small intestine and is implicated for the last step of carbohydrate hydrolysis to create absorbable monosaccharide. Starch is the main dietary carbohydrate cause of glucose and

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Isolation, in vitro antidiabetic, antioxidant activity and molecular docking studies of pentacyclic terpenoids from the leaves of Syzygium alternifolium. In this research work, we also sought to give in silico evidence for the binding interaction of isolated compounds 1 (fredeline) and 2 (3β–friedelinol) against α-glucosidase and α-amylase enzymes. The interactions were scored based on non-bonded interactions such as lipophilic pair term, hydrophobic enclosure reward, hydrogen bonding, and electrostatic rewards (Table 4 and Table 5). As expected, compounds 1 and 2 were shown to have efficient antagonism of α-glucosidase and α-amylase enzymes. Acarbose is a tetrasaccharide possessing multiple free hydroxyl groups capable of forming numerous polar interactions with the active site of proteins. While, compounds 1 (fredeline) and 2 (3β–friedelinol) being non polar in nature, exhibited enhanced hydrophobic interactions to inhibit α-glucosidase and α-amylase enzymes (Fig 1 and Fig 2). With α-glucosidase enzyme (Pdbcode: 3W3T), compounds 1 (fredeline) and 2 (3β–friedelinol) possess hydrophilic interactions with Phe476, Trp342, Ile358, Trp329, Phe601, Ala602 aminoacids. The hydrophobic interaction in acarbose were comparatively less (Phe 476, Trp432, Ile 358, Trp329, Phe601 amino acid. The hydrophobic interaction in acarbose were comparatively less (Phe 476, Trp432, Met470, Phe601, Ala602 aminoacids. The hydrophobic interaction in acarbose were comparatively less (Phe 476, Trp432, Met470, Phe601) than polar hydrogen bonding (His626, Asp357(2), Asp568, Arg552, Asp523). With α-amylase protein (Pdb code: 2QV4), the polar interaction are due to the hydroxyl group of 3β–friedelinol with His305 amino acid. The non-polar interactions of compounds 1 and 2 were found to be with Glu60, Trp58, Leu165, Val107, Ala106 aminoacids. Acarbose also possess similar interactions with additional hydrogen bonding with various amino acids (Asp300, Arg195, Glu233, Thr163, and Gln63).

IV. Conclusion

In summary, we report the isolation and characterization of Friedelin and 3β–Friedelinol pentacyclic terpenoids from the stem bark of Syzygium alternifolium. To our knowledge nobody has reported the identification of these two PTs from Syzygium alternifolium. The isolated compounds 1 (fredeline) and 2 (3β–friedelinol) PTs showed a showed significant inhibition of α-glucosidase, α-amylase and DPPH indicating the reduction in high blood glucose level as well as the reduction in the formation of ROS (Reactive Oxygen Species). Inhibition of these enzymes by compounds 1 (fredeline) and 2 (3β–friedelinol) was further supported by the molecular docking analysis. Therefore, these properties would be of therapeutic benefit in insulin resistant states. Future research will be carried out in this direction.

Acknowledgements

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References

[11] Ramesh, B. K. Abdul Nabi, S. Swagna, S. Aparas, C. Cinamic acid as one of the antidiabetic active principle(s) from the seeds of Syzygium alternifolium. Food and Chemical Toxicology, 50,2012, 1425-1431.

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Table 1: Structural details of isolated compounds from the bark of Syzygium alternifolium

<table>
<thead>
<tr>
<th>Compound code</th>
<th>Chemical structure</th>
<th>IUPAC name</th>
<th>Common names</th>
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<tr>
<td>Compound 1</td>
<td>(4R,4aS,6bR,8aR,12bS,14aS)-octadecahydro-4,4a,6b,8a,11,11,12b,14a-octamethylpicen-3(4H,6bH,14bH)-one</td>
<td></td>
<td>Friedelin</td>
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<tr>
<td>Compound 2</td>
<td>(3S,4R,4aS,6bR,8aR,12bS,14aS)-docosahydro-4,4a,6b,8a,11,11,12b,14a-octamethylpicen-3-oil</td>
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<td>3β-Friedelinol</td>
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Table 2: In vitro enzyme inhibition activity against α-glucosidase and α-amylase

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<th>Compound</th>
<th>IC₅₀ value ± SEM</th>
<th>IC₅₀ value ± SEM</th>
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<tr>
<td>Compound 1</td>
<td>10.40 ± 0.12**</td>
<td>23.04 ± 0.34*</td>
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<tr>
<td>Compound 2</td>
<td>15.57 ± 0.23**</td>
<td>36.35 ± 0.21**</td>
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<tr>
<td>Acarbose</td>
<td>09.46 ± 0.02</td>
<td>09.46 ± 0.02</td>
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SEM = Standard Error Mean; **p < 0.001, ***p < 0.0001

Table 3: Inhibition of radical scavenging activity by DPPH assay

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<tr>
<td>Acarbose</td>
<td>30.5*** ± 0.22</td>
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<tr>
<td>Ascorbic acid</td>
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SEM = Standard Error Mean; ***p < 0.0001

Table 4: Scoring Data (kcal/mol) of Glide-XP Docking of Schrodinger (Maestro 9.1) against α-amylase enzyme (PDB Code: 2QV4)

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Docking Score</th>
<th>Lipophilic EvdW</th>
<th>H-Bond</th>
<th>Electro</th>
<th>RotPen</th>
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<tr>
<td>Acarbose</td>
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<tr>
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<td>-0.68</td>
<td>-0.13</td>
<td>0.00</td>
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</table>

* An estimate of ligand-α-amylase binding energy; a Lipophilic van der Walls interactions of ligand-α-amylase complex; b Hydrogen-bonding term; c Electrostatic interactions of ligand-α-amylase complex; d Rotational penalty causing the decreased ligand-protein interactions.

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**Table 5:** Scoring Data (kcal/mol) of Glide-XP Docking of Schrodinger (Maestro 9.1) against α-glucosidase enzyme (PDB Code: 3W37)

<table>
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<th>Lipophilic EvdW (^b)</th>
<th>H-Bond (^c)</th>
<th>Electro (^d)</th>
<th>RotPenal (^e)</th>
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<tbody>
<tr>
<td>Acarbose</td>
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<td>-4.87</td>
<td>-2.00</td>
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<tr>
<td>Compound 1</td>
<td>-3.28</td>
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<tr>
<td>Compound 2</td>
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<td>-0.70</td>
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</tr>
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</table>

\(^a\) An estimate of ligand- α-amylase binding energy; \(^b\) Lipophilic van der Walls interactions of ligand- α-amylase complex; \(^c\) Hydrogen-bonding term; \(^d\) Electrostatic interactions of ligand- α-amylase complex; \(^e\) Rotational penalty causing the decreased ligand-protein interactions.

**Fig. 1** Superimposition of compound 1, compound 2 and acarbose (line forms) in the binding site of α-amylase (PDB Code: 2QV4).

**Fig. 2** Overlay view of compounds 1, 2 and acarbose (stick forms) in α-glucosidase binding pocket surrounded by non-polar amino acids (space fill form) (PDB Code: 3W37).