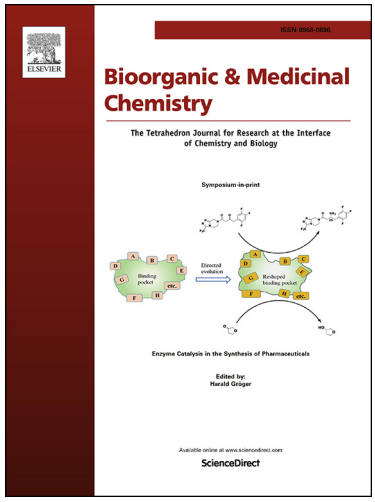

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α-Glucosidase inhibition activity and *in silico* study of 2-(benzo[*d*][1,3]dioxol-5-yl)-4*H*-chromen-4-one, a synthetic derivative of flavone

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Abstract

A synthetic flavone derivative 2-(benzo[*d*][1,3]dioxol-5-yl)-4*H*-chromen-4-one (BDC) was synthesized by the one pot reaction method and assessed for *α*-glucosidase inhibitory activity. The BDC demonstrated dose dependent inhibition of *α*-glucosidase activity. A maximum inhibition (99.3±0.26 %) of *α*-glucosidase was observed at 27.6 µM. The maximum *α*-glucosidase inhibitory activity depicted by BDC 27.6 µM concentration was 22.4 fold over the maximum inhibition observed with acarbose (97.72±0.59 % at 669.57 µM), a standard commercial anti-diabetic drug. In contrast to acarbose that depicted competitive type inhibition, kinetic studies of *α*-glucosidase inhibition by BDC demonstrated non-competitive inhibition with Km of 0.71 mM^{-1} and a Vmax of 0.028 mmol/min. *In silico* studies suggest allosteric interaction of BDC with *α*-glucosidase at a minimum binding energy (ΔG) of -8.64 kcal/mol and Ki of 465.3 nM, whereas, acarbose interacted at the active site of *α*-glucosidase with ΔG of -9.23 kcal/mol and Ki of 172 nM. Thus BDC significantly inhibited *α*-glucosidase in comparison to acarbose. Moreover, BDC has been endorsed for drug likeness by evaluating it as per Lipinski rule of five. Thus, BDC can be a lead compound for the management of type-2 diabetes mellitus.

Keywords: 2-(benzo[*d*][1,3]dioxol-5-yl)-4*H*-chromen-4-one (BDC), *α*-glucosidase, anti-diabetic compounds, non-competitive, acarbose.

1. Introduction

Diabetes mellitus (DM) is a metabolic and heterogeneous disorder causing high blood-glucose level after consumption of carbohydrate-enriched diet, leading to hyperglycemia. According to the world health organization's "Global Report on Diabetes-2014", 422 million adults were

affected with diabetes in 2014, compared to 108 million in 1980. The global prevalence of diabetes in adult population, since 1980 has increased manifolds from 4.7% to 8.5%.[1]

One of the therapeutic approaches to reduce postprandial hyperglycemia is to impede digestion and absorption of dietary carbohydrates by inhibiting carbohydrate digesting enzymes, such as α-glucosidase and α-amylase.[2] The α-glucosidase hydrolyzes the α-(1-4)-linked D-glucose residues from the non-reducing end of α-glucoside,[3] that is the final step in polysaccharides and disaccharides digestion. The α-glucosidase activity is directly related to blood glucose level and directly concern with down regulation of glucose absorption in patients with type 2 diabetes mellitus.

Over the centuries, herbal drugs have been widely employed for the prevention and treatment of diabetes mellitus. Although more than 200 species of medicinal plants have been reported with hypoglycemic potential,[4] purification and identification of anti-diabetic compound from plant crude extract is a major challenge. Several natural products such as picnogenol, acarbose, miglitol, and voglibose reportedly inhibit α-glucosidase and α-amylase enzymes.[5] Acarbose is the first member of α-glucosidase inhibitors that was approved for the treatment of type 2 diabetes.[6,7] Major class of phytochemicals such as alkaloids, phenolics, curcuminoids, terpinoids, and anthocyanins from natural sources have been documented for treatment of diabetes.[8]

Natural flavonoid derivatives like flavones, flavonols, flavanones, isoflavones, catechins and anthocyanidines have been investigated for their broad range of biological activities. Continuous research on these flavonoids and their derivatives has led to the isolation of over 4000 unique flavonoids from plants.[9] Flavones are naturally occurring oxygen containing heterocyclic compounds. Some of the well-known naturally occurring potent bioactive flavones are shown in figure 1.

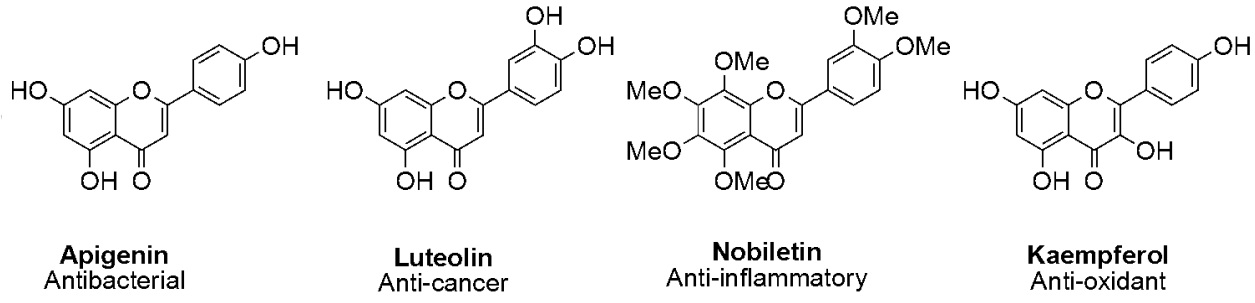


Figure 1: Naturally occurring biologically active flavones.

Other than natural flavones, synthetic flavone derivatives are also reported to demonstrate various pharmaceutical activities such as anti-estrogenic, anti-inflammatory, anti-viral, anticancer, antioxidant, anti-HIV, leishmanicidal, ovipositor stimulant phytoalexins, antimutagenic, antiallergic, etc.[10-13] The naturally occurring sulfonated compounds salaprinol, salacinol, ponkoranol, kotalanol and their corresponding four de-*O*-sulfonated compounds isolated from *Salacia species* inhibited human intestinal *α*-glucosidases, some of which are more strong inhibitors than acarbose and miglitol.[14] Further other synthetic flavone compounds such as 7,8-dihydroxy-4-methyl-2*H*-chromen-2-one, dihydroxynaphthalen-2(1*H*)-one and synthetic peptide RVPSLM purified from egg white protein reportedly inhibit the *α*-glucosidase activity with IC_{50} value of 52, 94 and 23.07 μM respectively.[15]

Without proper knowledge of the actual binding sites on enzyme for inhibitors and close interaction between them, it would be very difficult to identify the potential candidate for future drugs. Consequently, exploring the binding behavior and inhibitory effect of inhibitors with *α*-glucosidase are important for understanding drug-enzyme interactions and therapeutic applications.[16] In recent years, the interaction between inhibitors and *α*-glucosidase (as another important target protein) has attracted much attention.[17, 18] Luteolin, a flavonoid compound is well known inhibitor of *α*-glucosidase.[19-21] Although there are some reports describing the *α*-glucosidase inhibition properties of luteolin, most studies were limited to assay of enzyme activity. The inhibitory mechanism of luteolin on *α*-glucosidase has not been reported.

Hence, based upon the significance of flavones, a synthetic flavone derivative was evaluated for *α*-glucosidase inhibition activity. Further, to understand the mechanism of inhibition mechanism, enzyme kinetic study with flavone derivative followed by *in silico* study was performed. The flavone derivative compound was also evaluated for drug like properties by applying Lipinski rule of five.

2. Results and discussion

2.1. α-glucosidase inhibition activity of BDC

In vitro study using BDC demonstrated remarkable *α*-glucosidase inhibition activity at micro molar concentration. Significant *α*-glucosidase inhibitions were depicted at all the doses of BDC in comparison to their respective controls (t-test) (Fig. 2). Dose dependent *α*-glucosidase

inhibition activity of BDC ranged from 8.4± 0.37% at 3.54 µM to 99.3± 0.26% at 27.62 µM. Further ANOVA of the percentage inhibition of α-glucosidase observed in the control and different doses of BDC depicted significance at $P < 0.0001$ ($F = 345.7$). The α-glucosidase inhibition potential of BDC is 22.4 fold over than the maximum inhibition depicted by acarbose (97.72±0.59 % at 669.57 µM), a standard commercial anti-diabetic drug.[22]

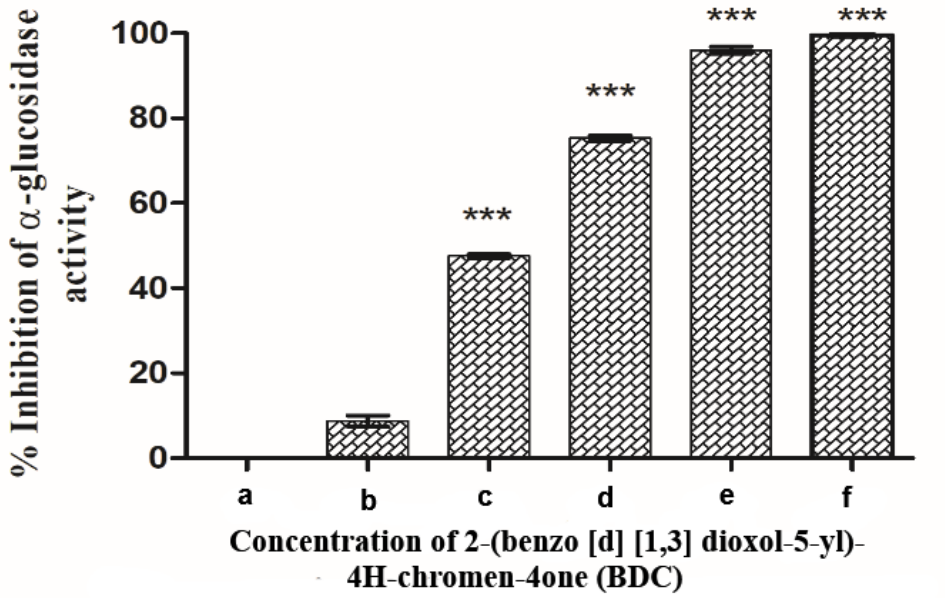


Figure 2: Percentage of α-glucosidase inhibition of in presence of various doses of 2-(benzo[*d*][1,3]dioxol-5-yl)-4*H*-chromen-4-one (a=0; b=3.54; c=9.56; d=15.17; e=21.24; f=27.62 µM). Data are mean ± SD (*P < 0.05, **P < 0.01, ***P < 0.001 denotes statistically significant difference from the test control as determined by student's t-test significance).

2.2. Enzyme Kinetics study

Results of enzyme kinetics study were analyzed using Michaelis–Menten plot and Lineweaver-Burk plot analysis. The type of α-glucosidase inhibition inhibition by BDC was non-competitive type (Fig. 3). In non-competitive type reactions, Michaelli's-Menten constant (Km) remained constant whereas maximum velocity (Vmax) of the enzymatic reaction decreased. In this type of reaction, inhibitor reduces the activity of the enzyme irrespective of substrate binding. The Km and Vmax of α-glucosidase with BDC inhibitor were depicted as 71.42 μM^{-1} and 0.028

μmol/min and without inhibitor (control) as 71.42 μM^{-1} and 0.04 μmol/min respectively. However acarbose, a standard anti-diabetic drug demonstrate a competitive type inhibition with α-glucosidase.[23] However, for the management of type-2 diabetes, drugs depicting non-competitive type inhibition of α-glucosidase are preferred over drugs that depict competitive type inhibition (e.g. acarbose).

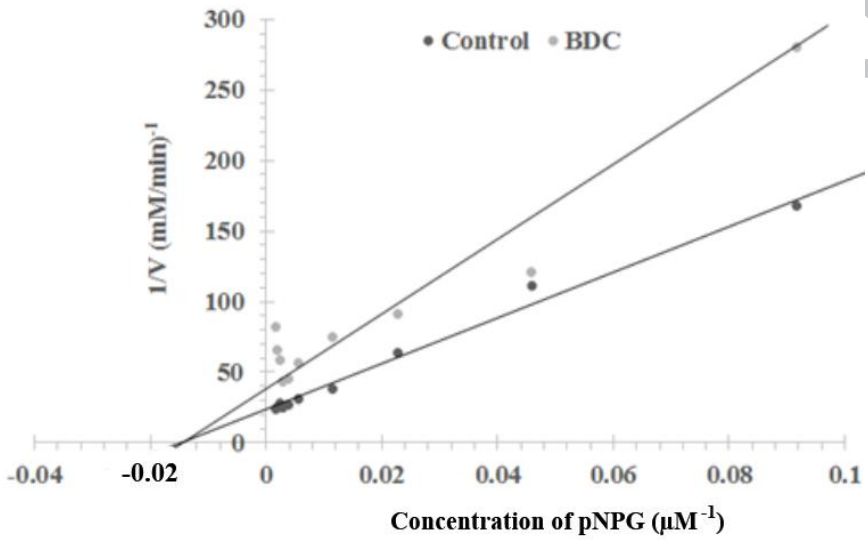


Figure 3: Lineweaver–Burk plots of α-glucosidase inhibition at different concentrations of substrate and 2-(benzo[*d*][1,3]dioxol-5-yl)-4*H*-chromen-4-one.

Competitive type inhibition depends on the substrate concentration and α-glucosidase inhibition potential of these drugs can be easily overcome by increasing the concentration of substrate. If a type-2 diabetes patient is given acarbose tablets and has carbohydrate rich diet than the acarbose effect on enzyme would be overcome by higher concentration of carbohydrates. However, if a patient takes drug that depicts non-competitive type inhibition and simultaneously has high carbohydrate rich diet, the carbohydrates would not affect the enzyme inhibition potential of the drug.

2.3. Molecular docking study

Active sites on the α-glucosidase were determined using online tool CASTp 3.0. Active site of the enzyme was recognized with surface area of 734.22 and volume of 456.22 (Supplementary Fig. 1). The amino acids present in the active site are aspartic acid (Asp), located at 215 and glutamate (Glu) located at position 277 are characterized as nucleophilic and proton donor

respectively. Active site of the enzyme identified as mutagenic site in some amino acids which are present at the positions of 215 (Asp), 216 (VAL), 217 (Gly) and 218 (Ser).

Out of the total 100 docked models, best-fit docked model with lowest minimum binding energy of (ΔG) was chosen to reveal the molecular interaction between acarbose and *α*-glucosidase. Our docking study revealed that Acarbose competes with substrate for active site of *α*-glucosidase enzyme with the minimum binding energy of (ΔG) of -9.23 kcal/mol and minimum inhibition constant (Ki) of 172.23 nM (Fig. 4a,b). Along with the other interactions (electrostatic, vanderwall, cationic etc.) between acarbose and protein molecule, two hydrogen bonds are recognized at LYS156:H23 (2.03Å) and SER 241:HN (2.02Å) (Fig. 4c).

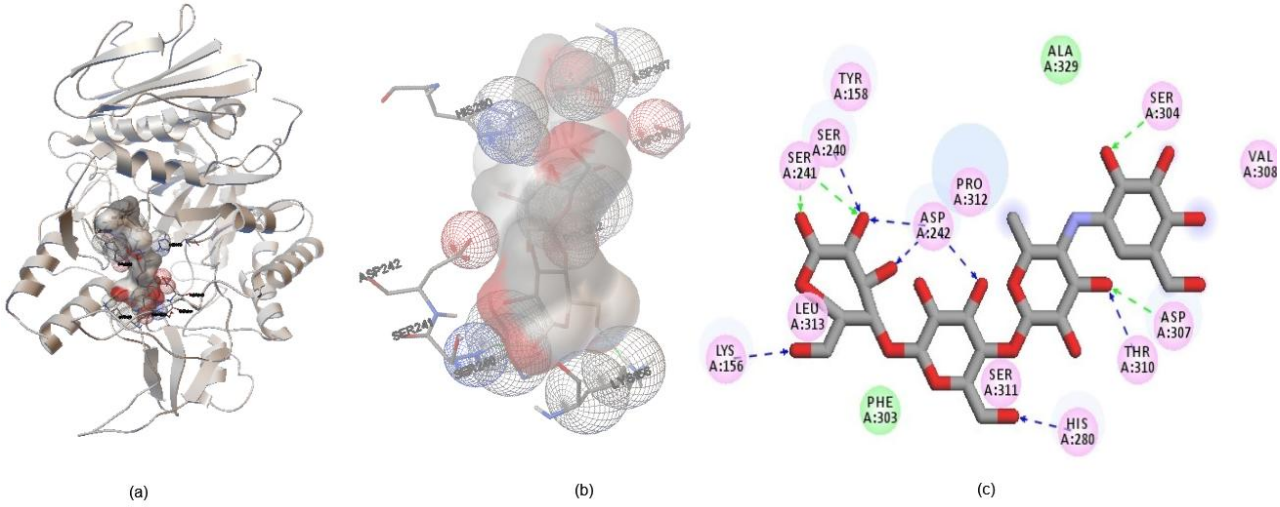


Figure 4: (a) Structural model of the complex between acarbose and *α*-glucosidase, (b) 3D representation of the interaction between acarbose and *α*-glucosidase in the predicted binding site, (c) 2D Representation of the interactions between *α*-glucosidase and acarbose.

In contrary to the acarbose, flavone derivative BDC depicted allosteric interaction with *α*-glucosidase (Fig. 5a). Binding site on *α*-glucosidase for BDC was different than active site of the enzyme (Fig. 5b), Out of total 100 docked model obtained, the best fit model depicted the allosteric interaction of BDC with *α*-glucosidase with ΔG energy of -0.8.64 kcal/mol and Ki of 465.3 nM. The hydrogen bondings were observed between Lys373:H22 (2.077Å) and LYS568:H23 (2.09Å) (Fig. 5c). The other surrounding amino acids depicted hydrophobic and Pi-Pi interaction with BDC inhibitor. Therefore, *in silico* molecular docking results of BDC are in agreement with the results obtained in enzyme kinetic study *in vitro*.

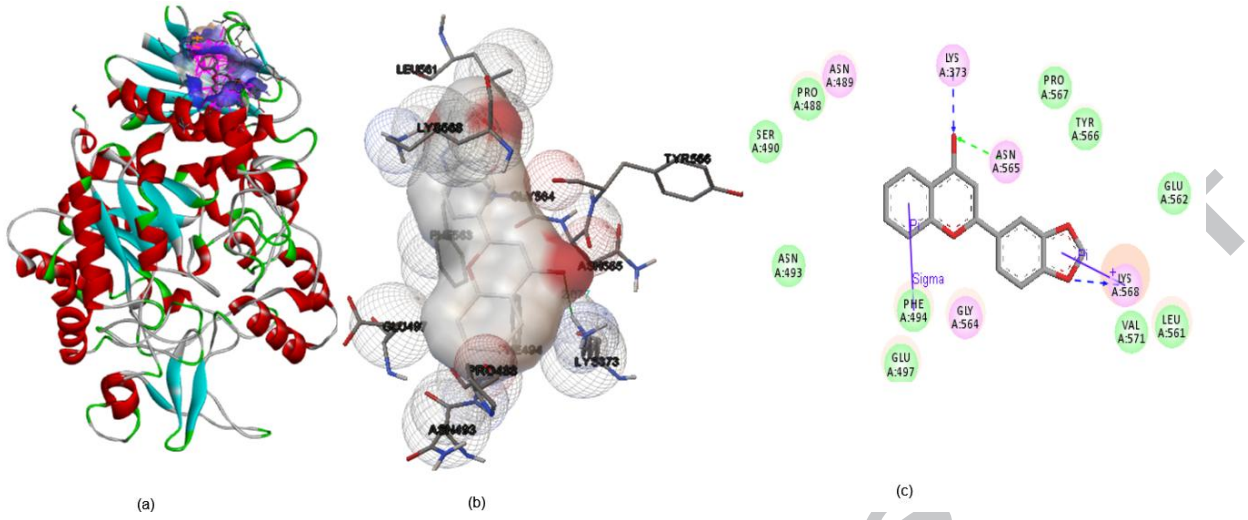


Figure 5: (a) Structural model of the complex between BDC and *α*-glucosidase, (b) 3D Representation of the interaction between BDC and *α*-glucosidase in the predicted binding site, (c) 2D Representation of the interactions between *α*-glucosidase and BDC.

2.4. Drug like/unlike properties of BDC

By following all the five rules, BDC is a lead compound for the inhibition of *α*-glucosidase in management of diabetes type-2 (Table 1). The lead compound need to be further evaluated by SAR studies, wherein various functional group could be added to lead molecule to improve its physiochemical properties (solubility, permeability, chemical stability), Pharmacokinetics & Toxicity (clearance, half-life, bioavailability, drug-drug interactions).

Table 1: Drug like properties of the 2-(benzo[*d*][1,3]dioxol-5-yl)-4*H*-chromen-4-one (BDC) compound evaluated by Lipinski rule of five.

Sl. No.	**Properties**	**Lipinski Rule**	**2-(benzo[*d*][1,3]dioxol-5-yl)-4*H*-chromen-4-one (BDC)**
1	Molecular mass	<500 Dalton	268.00
2	High lipophilicity	Log P< 5	3.45
3	Hydrogen bond donors	< 5	1
4	Hydrogen bond acceptors	< 10	4

5	Molar refractivity	Between 40-130	72.98

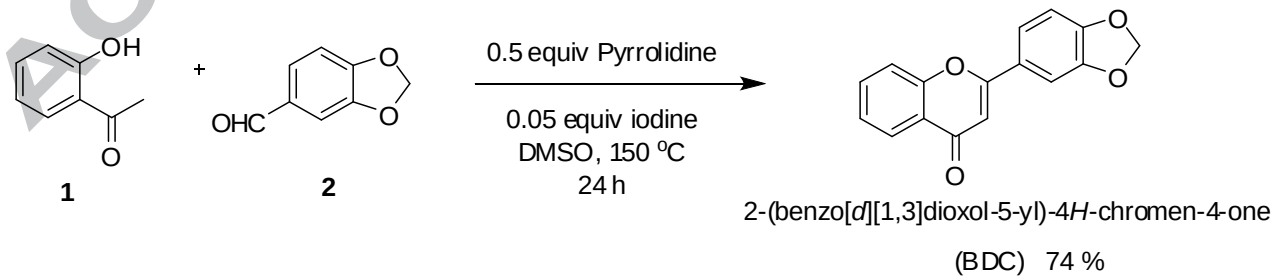
3. Conclusion

In the present study, *α*-glucosidase inhibition potential of flavone derivative BDC was evaluated using both *in vitro* as well as *in silico* approaches. The BDC has identified as a potential anti-diabetic compound and can be a lead compound for future clinical trials because: (1) In comparison to the acarbose, a standard anti-diabetic drug, BDC has demonstrated maximum inhibition of *α*-glucosidase activity at minimum concentration (micromolar) in a dose dependent study. (2) The Mode of *α*-glucosidase inhibition shown by BDC (non-competitive) is also different from acarbose (competitive type). Since, non-competitive inhibition of the enzyme activity is independent on substrate concentration, so during the clinical trials; drugs having non-competitive type of *α*-glucosidase inhibition are more preferable over competitive type inhibiting drugs. (3) BDC has been endorsed successfully for drug likeness as per Lipinski rule of five. Hence, at this stage, BDC has shown a significant *α*-glucosidase inhibition potential, that is more advantageous than acarbose, so, along with the other lead compounds, BDC can also be a future lead compound for the management of type-2 diabetes.

4. Materials and methods

4.1. Synthesis of BDC

BDC was synthesized by a one pot reaction of 2'-hydroxyacetophenone **1** with 3,4-methylenedioxybenzaldehyde **2** in presence of pyrrolidine as a base catalyst and catalytic iodine as an oxidant in DMSO solvent in good yield (scheme 1).[24]



Scheme 1: Synthesis of BDC from 2'-hydroxyacetophenone and 3, 4-methylenedioxybenzaldehyde.

4.2. α-Glucosidase inhibition assay

Chemicals: α-glucosidase (*Saccharomyces cerevisiae*) and P-nitro-phenyl-α-D-glucopyranoside (p-NPG) from SRL Pvt ltd,, sodium carbonate (Na_2CO_3), sodium dihydrogen phosphate, disodium hydrogen phosphate (Himedia Pvt ltd), acarbose from Fluka Chemical (Buchs, Switzerland).

The *α*-glucosidase inhibition potential of BDC was determined spectrophotometrically using *p*-nitrophenol-*α*-D-glucopyranoside (pNPG) as substrate.[25] *α*-Glucosidase (maltase) ex. *Saccharomyces cerevisiae*, 7.5 µL (0.5 U/mL) was mixed with various concentrations of BDC. After incubation of above mixture at 37°C for 30 min, 100 µL of pNPG (3 mM) was added. Reaction mixture was then again incubated for 10 min at 37°C. To stop the reaction, 750 µL of Na_2CO_3 (0.1 M) was added and absorbance was determined at 405 nm in triplicates. Standard anti-diabetic drug acarbose (PHR1253, Fluka) was used as a positive control for *α*-glucosidase inhibition assay. The percentage inhibition of the enzyme activity was calculated using following formula:

Inhibition (%) = Absorbance of test control - Absorbance of sample/ Absorbance of control ×100.

4.3. Kinetic analysis of α-glucosidase inhibition potential of BDC

For kinetic studies, *α*-glucosidase enzyme 7.5 µL (0.5 U/mL) was mixed with BDC (12.5 µg/mL) and incubated for 15 min. Further, various concentrations of pNPG was added at (0.0109-0.612 µM) to individual reactions and the absorbance at 405 nm was recorded at time interval of 3 sec. up to 180 sec. The Km and Vmax values were determined from the Michaelis–Menten equation and mode of inhibition was determined graphically using Lineweaver–Burk plot.

4.4. Molecular docking studies of BDC

PDB structure of *α*-glucosidase was downloaded from PDB (ID: 3A4A) isolated from *Saccharomyces cerevisiae*. Acarbose a standard molecule used for docking studies was downloaded from https://pubchem.ncbi.nlm.nih.gov/. The obtain structure of the protein is made of 589 amino acid and the active site of the enzyme was determined using an online server CASTp http://sts.bioe.uic.edu/castp/index.html?3a4a.[26]

The 3D structure of the BDC was drawn and validated using Marvin sketch (https://www.chemaxon.com /products/marvin/marvinsketch). Windows based automated docking tool Autodock 4.2 was used for docking study. Discovery studio (http://accelrys.com/products/collaborative-science/biovia-discovery-studio/) and LIGPLOT v.5.4.3 (http://www.ebi.ac.uk/thornton-srv/software/LIGPLOT/) were used to analyze the molecular interactions between docked molecules.

Autodock 4.2 tool used for molecular docking study. Docking analysis was initiated with the blind docking followed by site specific docking to find out the best-fit protein-ligand docked model for the acarbose and BDC. Autodock 4.2 tool was run twice for each experiment with the same parameters, to check the reproducibility of the results. All water molecules of *α*-glucosidase were removed and essential hydrogen atoms and Gasteiger charges were assigned. Grid parameter file (GPF) was prepared with the grid spacing of 0.54 Å and ligand dimension 118×100×104 for acarbose and 0.74 Å and ligand dimension 100×102×100 for BDC. Docking parameter file (DPF) was prepared using Lamarckian Genetic Algorithm (LGA) with parameters set to 100 runs, whereas energy evaluation set to 2,500,000 and 27,000 generation. Autogrid4 and autodock4 were run to calculate the lowest energy conformation between ligand and target. Different energy terms including intermolecular energy (vdm + hbond + desolv energy + electrostatic energy), internal energy, torsional energy and binding energy was obtained from the output DLG (Docking Log file) format that was further analyzed by PyMOL and LIG-PLOT.

4.5. Drug-like/unlike properties of BDC

Lipinski's Rule of Five assists screening of lead compounds for properties to support their potential as a drug like. It has been observed commonly that oral administration of the drugs has good absorption and permeation in the body, if the compound in the drug has molecular mass

<500 dalton, low lipophilicity (log P<5), hydrogen bond donor < 5 and hydrogen bond acceptor <10. Thus to evaluate the nature of BDC for its drug like/unlike properties, the synthetic flavone derivative was Lipinski rule of five was investigated for drug like properties using online available tool- http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp.[27]

4.6. Statistical analysis

All samples were evaluated in triplicates and standard deviation was calculated. Sample data were analyzed with student's t-test and One-way ANOVA with tukey's test that was performed using Graph Pad Prism version 5.00 for Windows, Graph Pad Software, San Diego California USA (www.graphpad.com).

Conflict of interest

The authors declare no conflict of interest, financial or otherwise.

Acknowledgments

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Highlights

- BDC, a flavone derivative showed 22.4 fold higher enzyme inhibition than acarbose.
- During the enzyme kinetic study BDC showed non-competitive type inhibition.
- Molecular association between α-glucosidase and BDC revealed by docking study.
- BDC depicted drug-likeness properties by following all the five rules of Lipinski.
- During clinical trials, BDC can be a lead compound for the management of type-2DM.