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Short communication

Evaluation and molecular modelling of bis-Schiff base derivatives as potential leads for management of diabetes mellitus

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Developing a medication to cure and manage diabetes mellitus complications is of interest in medicinal chemistry. Toward this end, six bis-biphenyl-salicylaldehyde Schiff base derivatives have been evaluated for their α-glucosidase inhibition, antiglycation and anti-inflammation potentials. Four compounds (compounds **2**–**5**) showed an excellent α-glucosidase inhibitory effect superior to that produced by acarbose. Additionally, the docking study revealed that these compounds are anchored within the binding pocket of α-glucosidase *via* hydrogen bonding, π-stacking and hydrophobic interactions, comparable to a high number of hydrogen bonding involved in anchoring acarbose. Interestingly, all tested compounds showed varying degrees of antiglycation activity with superior activity for two of them (compound **1** and compound **6**) compared to the standard rutin. Moreover, the results indicated an outstanding anti-inflammatory activity for two compounds (compounds **1** and **6**) compared to ibuprofen.

Keywords: bis-Schiff bases, diabetes mellitus, glycation, postprandial hyperglycemia, α-glucosidase, docking study

Diabetes mellitus (DM) is a chronic disease that is expected to affect 693 million people worldwide by 2045 if no effective preventive measures are adopted (1). It is a leading cause of morbidity and mortality as it increases the risk of developing other disorders and diseases including retinopathy, neuropathy, impaired wound healing, kidney failure, dyslipidemia, strokes and heart attacks (2). Furthermore, hyperglycemic-induced oxidative stress is believed to increase the levels of pro-inflammatory proteins which leads to local and systemic inflammation (3). With an increase in insulin resistance, the possibility of developing inflammation increases too and with more inflammation the body becomes less sensitive to insulin and *vice versa* (4). Several clinical trials demonstrated the beneficial effects of salsalate, a prodrug of salicylate, on glycemia and insulin sensitivity, probably through inhibition of the NF-κB pathway (5). Hence, developing drugs that can target inflammation pathways is still an attractive option for DM treatment.

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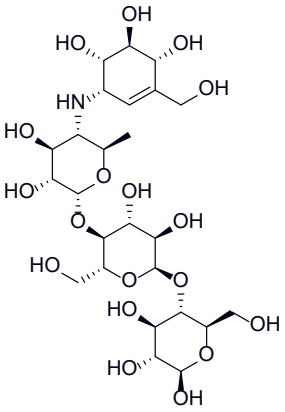
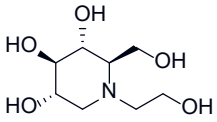
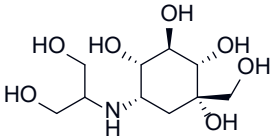
The complications of diabetes are mediated by the glycation reaction that forms stable, heterogeneous adducts called advanced glycation end-products (AGEs). AGEs are formed with persistent high blood glucose levels accelerating non-enzymatic addition of reducing sugar to the biomolecules that got oxidized (6, 7). It has been shown that the formation of AGEs contributes to several pathophysiological conditions associated with ageing and the complications of diabetes mellitus including Alzheimer's disease (7). There is a limited number of effective antiglycation agents with less than satisfactory performance. Therefore, the discovery of new antiglycation agents is still an active area of research (8). Moreover, postprandial hyperglycemia (PPH) is a key contributor to overall glucose control and a predictor of microvascular and macrovascular events (9). α-glucosidase is responsible for the catalytic cleavage of a glycosidic bond in complex molecules of carbohydrates resulting in PPH. α-glucosidase inhibitors (AGIs) were the first drugs developed to control postprandial glucose levels (10). Several AGIs including acarbose, miglitol, and voglibose have been used for the treatment of DM (Fig. 1). However, they are associated with many side effects such as diarrhea, abdominal and flatulence discomfort (11). Hence, developing a safer medication to cure DM is still of interest in medicinal chemistry.



Acarbose



Miglitol



Voglibose

Fig. 1. The chemical structures of α-glucosidase inhibitors used in the clinic for the treatment of DM.

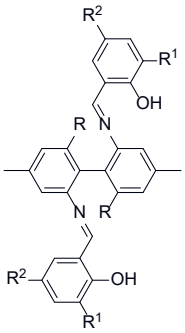
In the present study, α-glucosidase inhibition, antiglycation and anti-inflammatory activity of six bis-biphenyl-salicylaldehyde Schiff base derivatives were evaluated in continuation of our previous synthesis study (12, 13). A molecular docking study of the human α-glucosidase enzyme was also conducted in order to have a good understanding of ligand--enzyme binding interactions.

EXPERIMENTAL

Chemistry

Six bis-Schiff base derivatives (compounds **1**–**6**) which were prepared previously by our team (12, 13) are included in this study, namely, 6,6′-((1*E*,1′*E*)-((6,6′-dibromo-4,4′-dimeth-

Table I. Synthesized bis-biphenyl salicylaldehyde Schiff base derivatives and their bioactivity data



Compd.	R	R^1	R^2	IC_{50} (mmol L^{-1})		
				α-glucosidase inhibition	Antiglycation activity	Anti-inflammatory activity
1	Br	NO_2	NO_2	Inactive	31.0 ± 2.9	19.4 ± 5.3
2	Br	H	*tert*-butyl	257.6 ± 1.2	188.8 ± 5.9	Inactive
3	Br	*tert*-butyl	H	361.1 ± 1.6	141.7 ± 5.4	Inactive
4	Br	Br	Br	342.6 ± 1.7	73.4 ± 2.7	Inactive
5	H	*tert*-butyl	H	192.3 ± 2.0	113.2 ± 3.0	Inactive
6	H	H	*tert*-butyl	Inactive	23.2 ± 1.6	7.9 ± 3.6
Acarbose	–	–	–	875.8 ± 2.1	–	–
Rutin	–	–	–	–	45.5 ± 1.8	–
Ibuprofen	–	–	–	–	–	54.3 ± 9.2

Mean ± SEM, $n = 3$.

yl-[1,1′-biphenyl]-2,2′-diyl)bis(azanylylidene))bis(methanylylidene))bis(2,4-dinitrophenol) (**1**), 2,2′-((1*E*,1′*E*)-((6,6′-dibromo-4,4′-dimethyl-[1,1′-biphenyl]-2,2′-diyl)bis(azanylylidene)) bis(methanylylidene))bis(4-(*tert*-butyl)phenol) (**2**), 6,6′-((1*E*,1′*E*)-((6,6′-dibromo-4,4′-dimethyl-[1,1′-biphenyl]-2,2′-diyl)bis(azanylylidene))bis(methanylylidene))bis(2-(*tert*-butyl)phenol) (**3**), 6,6′-((1*E*,1′*E*)-((6,6′-dibromo-4,4′-dimethyl-[1,1′-biphenyl]-2,2′-diyl)bis(azanylylidene)) bis(methanylylidene))bis(2,4-dibromophenol) (**4**), 6,6′-((1*E*,1′*E*)-((4,4′-dimethyl-[1,1′-biphenyl]-2,2′-diyl)bis(azanylylidene))bis(methanylylidene))bis(2-(*tert*-butyl)phenol) (**5**) and 2,2′-((1*E*, 1′*E*)-((4,4′-dimethyl-[1,1′-biphenyl]-2,2′-diyl)bis(azanylylidene))bis(methanylylidene))bis(4-(*tert*-butyl)phenol)) (**6**) (Table I).

The sketch of the synthetic procedures and identification data for the synthesized compounds are given in Supplementary materials.

Biological evaluation

Alpha-glucosidase inhibition activity. – Bioassays were performed against α-glucosidase recombinant enzyme from *Saccharomyces cerevisiae* (Sigma Aldrich, USA). The α-glucosidase

inhibitory assay was adapted from Taha *et al.* (14). Phosphate saline buffer (50 mmol L^{-1}, pH 6.8, 135 μL) was dispensed in a 96-well plate, followed by the addition of 20 μL of 0.5 mmol L^{-1} of the tested compound (in 7 % DMSO). Then, 20 μL of the enzyme were added into the wells (0.02 U per well), which were then incubated at 37 °C for 15 minutes. After the incubation, the plate was measured by the microplate reader (Spectramax plus 384, Molecular Devices, USA). Following that, 25 μL of the substrate (0.7 mmol L^{-1}, 4-nitrophenyl α-D-glucopyranoside) was added to the reaction mixture and readings were monitored at 400 nm for 30 min. 7 % DMSO was used as a blank. Acarbose was used as a standard with an IC_{50} of 875.8 ± 2.1 μmol L^{-1}. The compounds that showed 50 % inhibition or more, were processed for IC_{50} value calculation by using Ez-fit software (Perrella Scientific, USA).

Antiglycation activity. – In vitro antiglycation assay method (15) was used with slight modifications to determine the antiglycation activity of the test compounds. Human serum albumin (HSA) was employed as the model protein to be glycated at 10 mg mL^{-1} concentration with 0.5 mol L^{-1} fructose as a glycating agent. Tested compounds were dissolved at 1 mmol L^{-1} concentration in absolute DMSO. The test compounds were incubated in triplicates on a 96-well plate at various concentrations with 10 mg mL^{-1} HSA, 0.5 mol L^{-1} fructose, 0.1 mol L^{-1} phosphate buffer (pH 7.4) containing 0.1 mol L^{-1} sodium azide as a bactericidal agent, and incubated for 7 days at 37 °C. In the control experiment HSA, fructose and phosphate buffer were incubated at the same concentrations and conditioned with absolute DMSO. After the 7 days of incubation, fluorescence was measured by using a microtiter plate reader at 330 and 440 nm, excitation and emission, resp. Rutin was used as a standard with IC_{50} of 45.5 ± 1.8 μmol L^{-1}. The percentage of inhibition of test compounds as well as the standard was calculated. EZ-Fit software was used to calculate IC_{50} for the compounds with 50 % or higher inhibition.

Anti-inflammatory activity. – The anti-inflammatory activity of the tested compounds was evaluated using an oxidative burst assay described by Helfand *et al.* (16). Herein, 25 μL of the test compounds were added to 25 μL of diluted, pooled human blood obtained from healthy volunteers (Ethical Approval by Independent Ethics Committee, University of Karachi) in HBSS++ (Hanks balanced salt solution containing calcium chloride and magnesium chloride) and incubated at 37 °C for 15 minutes in the thermostat chamber of the luminometer. Control wells received only HBSS++. After the incubation period, 25 μL of serum opsonized zymosan (SOZ) (Fluka, Switzerland) and 25 μL of intracellular reactive oxygen species (ROS) detecting probe, luminol (Research Organics, USA), were added. Then the level of the ROS was recorded in luminometer in terms of relative light units (RLU) and the percentage of inhibition was calculated by comparison to the negative control. The assay was performed using three different concentrations of the tested compounds (1, 10 and 100 μg mL^{-1}), each in triplicate. The results (% inhibition) were processed using the EZ-Fit software. Ibuprofen was used as a standard with IC_{50} of 54.3 ± 9.2 μmol L^{-1}.

Docking study for human lysosomal acid-alpha-glucosidase

The 3D coordinates of human lysosomal acid-alpha-glucosidase in complex with acarbose were downloaded from the Protein Data (PDB code: 5NN8, 2.45 Å). Hydrogen atoms were added to the proteins utilizing Discovery Studio 2.5.5 templates for protein residues. The protein structure was utilized in subsequent docking experiments without energy

minimization. Explicit water molecules were kept in the binding pocket. Ligands were docked into the binding pocket of the α-glucosidase enzyme using the CDOCKER engine. CDOCKER is a CHARMm-based simulated annealing/molecular dynamics method that uses rigid receptors for docking (17). The CDOCKER parameters implemented in the presented project were adapted from a method reported by Alsalahat *et al.* (18). The resulting top 10 poses were scored using 7 docking-scoring functions: Jain, LigScore1, LigScore2, PLP1, PLP2, PMF and PMF04. Docking/scoring settings that closely reproduced the crystallographic pose of acarbose in α-glucosidase enzyme were chosen to carry docking experiments for the synthesized compounds in the binding pockets of the enzyme.

RESULTS AND DISCUSSION

In the present study, six bis-biphenyl-salicylaldehyde Schiff base derivatives were assessed as an attempt to find a potential multi-target antidiabetic agent.

Alpha-glucosidase inhibition activity and docking study

All six synthesized derivatives were evaluated for α-glucosidase enzyme inhibitory activity. Four compounds (compounds **2**–**5**, Table I) showed superior inhibition (IC_{50} between 192.3 and 361.1 μmol L^{-1}) compared to acarbose (IC_{50} = 875.8 μmol L^{-1}) (19). Although the main skeleton for all these compounds is the same, the difference in their inhibitory potential might be due to the different substitution patterns. As shown in Table I, modifications at position R lead to a paradoxical change in the inhibitory activity of the tested compounds. IC_{50} doesn't change outside uncertainty limits upon switching bromine to hydrogen in the case of compounds **3** and compound **5**, whereas analogous switching converts compound **2** into inactive derivative, compound **6**. Besides, it seems that positions R^1 and R^2 can tolerate non-hydrogen bond-forming groups: hydrogen, bromine and *tert*-butyl; substitution of these sites with H-bond forming group, nitro group, abolish the activity against α-glucosidase.

Before docking the synthesized compounds, the crystallographic pose of acarbose complexed within α-glucosidase enzyme was compared with the docked poses produced by the docking and scoring settings to validate our docking experiment. CDOCKER

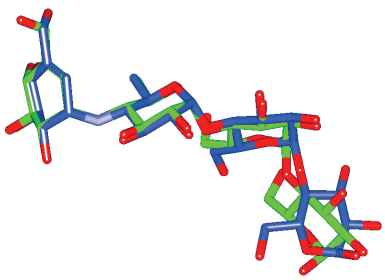


Fig. 2. Comparison between the docked pose of acarbose (blue backbone) as produced by docking simulation and its crystallographic structure (green backbone) within α-glucosidase enzyme binding pocket (PDB code: 5NN8).

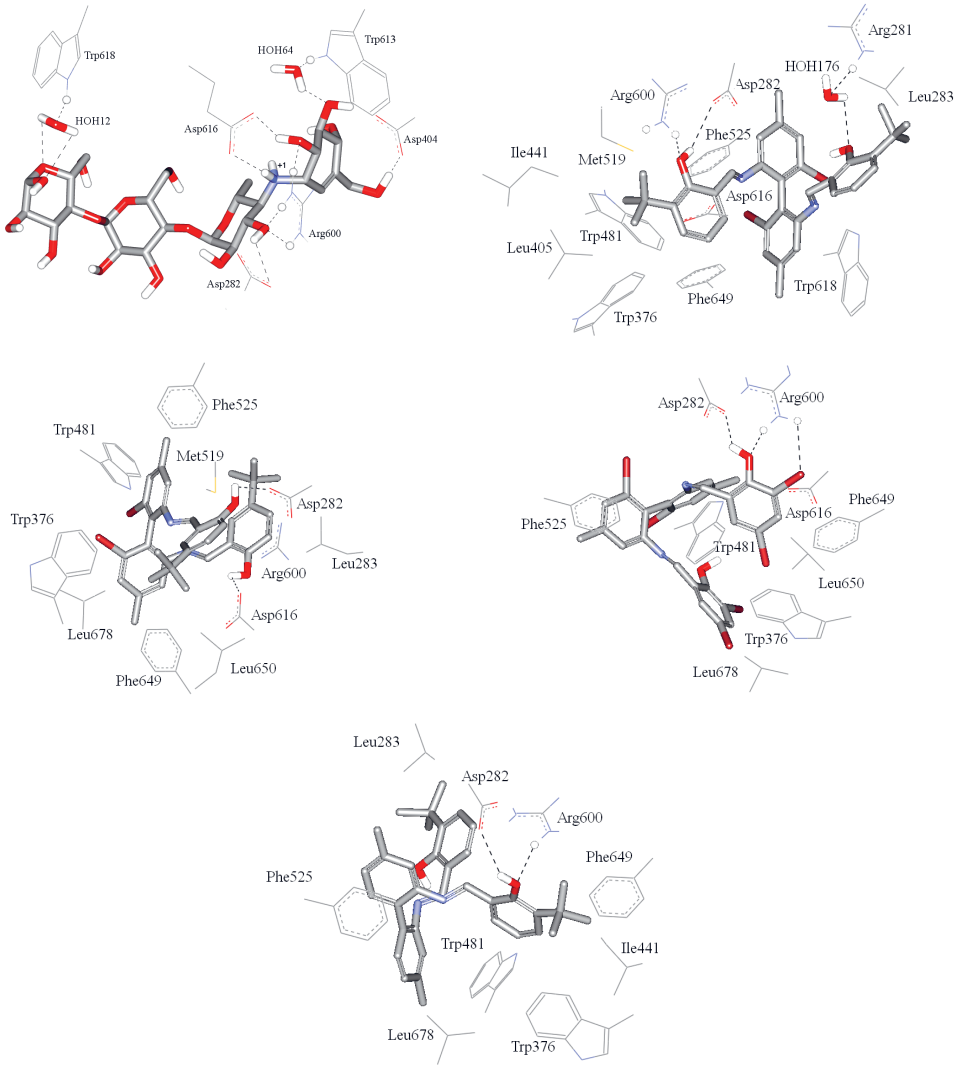


Fig. 3. Detailed view showing the interactions of the different amino acid residues within the binding pocket of the α-glucosidase enzyme with: a) co-crystallized acarbose, b) compound **2**, c) compound **3**, d) compound **4**, e) compound **5**. Atom colors were used according to the CPK system (H white, C grey, O red, N blue, Br dark red), hydrogen bonding interactions are shown as dotted black lines.

engine and Jain scoring function successfully reproduced the crystallographic pose of acarbose with a root mean square difference (RMSD) value of 1.74 Å (Fig. 2). This is providing impetus to dock the active compounds in order to explore their binding interactions with the enzyme, using the same settings, namely, parameters for docking and scoring experiments. Fig. 3 compares the binding interactions anchoring acarbose within α-glucosidase

enzyme binding site with those proposed by the docking study for the active synthesized compounds. Apparently, the docked synthesized compounds bind into the binding site of the α-glucosidase enzyme *via* hydrogen bonding, π-stacking and hydrophobic interactions comparable to binding forces involved when anchoring acarbose.

Acarbose is involved in a high number of hydrogen-bonding interactions (almost ten), either directly with amino acids residues or through bridging water molecules. Furthermore, the cationic nitrogen atom of acarbose forms an electrostatic bond with the carboxylate of Asp616, which enforces the hydrogen bonding interactions (Fig. 3a). The docked poses of active compounds **2**–**5** were involved in a limited number of hydrogen-bonding interactions (only 2–3) and a high number of π–π stacking and the projected backbones of the compounds towards Met519, Leu283, Leu678, Leu650, Leu405, Ile441 suggest the existence of mutual hydrophobic interactions that anchor these ligands within the binding pocket of α-glucosidase (Figs. 3b-e). Clearly, acarbose is a highly polar compound so it is involved in hydrophilic interactions only. On the other hand, the synthesized analogues contain four aromatic rings and hydrophobic substituents: methyl, *tert*-butyl and bromine, which are involved mainly in hydrophobic interactions. This difference in the nature of the binding interactions can explain the superior potency of these derivatives compared to acarbose. Acarbose is rather hydrophilic so that its hydration is expected to be a significant problem for binding. Needless to say that hydrophilic ligands need relatively high dehydration enthalpic costs as they prefer hydration to binding (20).

Furthermore, the careful assessment points to the role of symmetry to the excellent potency of these compounds. Symmetry in a molecule imparts a positive amount of residual entropy (21) and it is well established that ligands that bind with an entropic advantage as a result of high residual mobility can adopt multiple binding modes resulting in less entropic cost and improving their affinity (22).

Antiglycation activity

All the tested compounds showed varying degrees of antiglycation activity (IC_{50} values between 23.20 and 88.82 μmol L^{-1}). Somewhat higher activity was observed with compounds **1** (IC_{50} = 31.03 μmol L^{-1}) and **6** (IC_{50} = 23.20 μmol L^{-1}), compared to the standard antiglycation agent rutin (IC_{50} = 45.48 μmol L^{-1}).

Studies have proven that compounds like rutin that can reduce the plasma concentration of glyoxal and methylglyoxal, which are potent glycating agents formed due to glucose autoxidation, will have a role in glycation prevention (23). Hence, we are inclined to believe that the hydroxyl group in our tested Schiff base derivatives is involved in hemiacetal formation with the aldehyde groups in glyoxal and methylglyoxal, resulting in low plasma concentration of these glycating agents. Moreover, it is expected that the nitro group in compound **1** has formed a zwitter complex with the carbonyl group of methylglyoxal which resulted in high antiglycation activity. On other hand, the remarkable activity of compound **6** can be due to the electron-donating group, *tert*-butyl. Such explanations are possibly supported by the previous study of Khan *et al.* (24) who demonstrated that nitro group or electron-donating groups on bis-Schiff bases of isatin can improve antiglycation activity. Furthermore, it is likely that the metal chelation property of the tested compounds (12, 13) contributes to their antiglycation activity since the metal chelation can inhibit metal-catalyzed oxidative degradation of glucose or various intermediates of glycated protein (25).

Anti-inflammatory activity

The anti-inflammatory activity of compounds **1–6** was determined by oxidative burst assay using the chemiluminescence technique (26). The results indicated that two of the tested compounds exert an excellent anti-inflammatory activity: compound **1** (IC_{50} = 19.4 μmol L^{-1}) and compound **6** (IC_{50} = 7.9 μmol L^{-1}) (Table I) compared to ibuprofen (IC_{50} = 54.3 μmol L^{-1}), which is one of the most widely used drugs against inflammatory diseases.

CONCLUSIONS

Six synthetic bis-biphenyl-salicylaldehyde Schiff base derivatives **1–6** were screened for their α-glucosidase inhibition, antiglycation and anti-inflammation potentials. Four analogues (2,2′-((1*E*,1′*E*)-((6,6′-dibromo-4,4′-dimethyl-[1,1′-biphenyl]-2,2′-diyl)bis(azanylylidene)) bis(methanylylidene))bis(4-(*tert*-butyl)phenol) (**2**), 6,6′-((1*E*,1′*E*)-((6,6′-dibromo-4,4′-dimethyl-[1,1′-biphenyl]-2,2′-diyl)bis(azanylylidene))bis(methanylylidene))bis(2-(*tert*-butyl)phenol) (**3**), 6,6′-((1*E*,1′*E*)-((6,6′-dibromo-4,4′-dimethyl-[1,1′-biphenyl]-2,2′-diyl)bis(azanylylidene)) bis(methanylylidene))bis(2,4-dibromophenol) (**4**) and 6,6′-((1*E*,1′*E*)-((4,4′-dimethyl-[1,1′-biphenyl]-2,2′-diyl)bis(azanylylidene))bis(methanylylidene))bis(2-(*tert*-butyl)phenol) (**5**) exhibited potent α-glucosidase inhibitory activity. Molecular docking study was conducted to understand the ligand-enzyme interactions. Besides, all analogues showed varying degree of antiglycation activity with superior activity of (6,6′-((1*E*,1′*E*)-((6,6′-dibromo-4,4′-dimethyl-[1,1′-biphenyl]-2,2′-diyl)bis(azanylylidene))bis(methanylylidene))bis(2,4-dinitrophenol)) (**1**) and (2,2′-((1*E*,1′*E*)-((4,4′-dimethyl-[1,1′-biphenyl]-2,2′-diyl)bis(azanylylidene))bis(methanylylidene))bis(4-(*tert*-butyl)phenol)) (**6**). The results also demonstrated outstanding anti-inflammatory activity of compounds **1** and **6**. Our findings open the possibility of identifying a multi-target drug for the management of DM.

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Supplementary materials available upon request.

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