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Design, Synthesis, Biological Evaluation and Docking, ADME Studies of Novel Phenylsulfonyl Piperazine Analogues as α-Amylase Inhibitors

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ABSTRACT

Diabetes mellitus (DM) stands as one of the most widespread diseases encountered today. It is primarily characterized by diminished insulin levels and heightened blood glucose concentrations. Inhibition of the α-amylase enzyme plays a pivotal role in the management of diabetes mellitus. Piperazine and sulfonamide groups are recognized for their extensive range of biological effects. The current study involved synthesizing five phenylsulfonyl piperazine derivatives. An evaluation of their α-amylase inhibitory capacities was conducted. Phenylsulfonyl piperazine derivatives (compounds 1-5) exhibited notable α-amylase enzymatic inhibition, with compound 4 showing the most substantial potential for inhibition. The inhibitory percentage of compound 4 (80.61±0.62) surpassed that of the standard drug acarbose (78.81±0.02). The molecular docking studies identified compound 4 as possessing the most substantial inhibitory effect on the α-amylase enzyme, with notable binding energy -8.2 kcal/mol. This compound exhibited specific interactions, including π-π stacking and π-anion interactions with key enzyme residues, solidifying its role as a potent inhibitor.

Keywords: Diabetes mellitus, α-Amylase, Piperazine, Sulfonamide.

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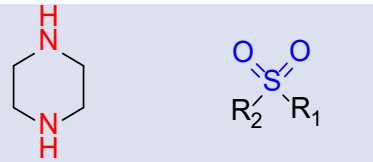
Introduction

Heterocyclics rings are of paramount importance in medicinal chemistry due to their versatility and wide-ranging biological activities that translate into diverse therapeutic applications. Their prevalence in an extensive array of pharmaceuticals underlines this significance. Heterocyclic rings are categorized into several types, each exhibiting a wide range of biological activities — for instance, thiazoles [1–3], thiophenes [4], quinolines [5]. Notably, heterocyclic molecules containing nitrogen, such as the piperazine heterocycle illustrated in Figure 1, have garnered significant attention for their biological efficacy. Piperazine is a non-aromatic heterocycle ring characterized by its two nitrogen atoms. This functional group is present in various FDA-approved medications, including members of the fluoroquinolone family of antibiotics (norfloxacin, ciprofloxacin, lomefloxacin), antihistamines (cyclizine, levocetirizine, cetirizine, hydroxyzine, cinnarizine), and antihypertensive agents (prazosin, terazosin, doxazosin) [6]. Moreover, piperazine derivatives exhibit a multitude of biological activities, functioning as anticonvulsants [7], antianginal [8], anti-inflammatory [9], carbonic anhydrase enzyme inhibitor [10] and antidiabetic [11].

Furthermore, the sulfonyl group stands as another moiety of significant interest due to its contribution to a wide array of biological activities (Fig 1).



Piperazine **Sulfonyl group**

Figure 1. Molecular structures of piperazine and sulfonyl group.

Commonly, the integration of the sulfonyl group into other molecules either augments their biological activity or results in sulfonylated derivatives with unique biological functions. Prominent among the biological efficacies attributed to the sulfonyl group are antidiabetic [11], anticancer [12] and anti-inflammatory [13]. The combination of piperazine and the sulfonyl group, both of which independently display substantial biological activity, often leads to compounds with enhanced biological effects through a synergistic relationship. A prime example of such a compound is sildenafil, which has achieved notable success as a leading pharmaceutical agent, primarily employed in the treatment of erectile dysfunction (Fig 2) [14].

Diabetes mellitus (DM) poses a formidable challenge to global health. This condition is marked by dysregulated blood glucose regulation and impaired insulin secretion, often attributable to malfunction of pancreatic beta-cells, culminating in a state of hyperglycemia.

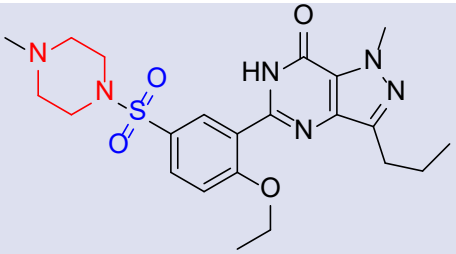


Figure 2. Molecular structure of Sildenafil

Elevated blood glucose levels are critically implicated in the development of major complications affecting vital organs, notably the heart, retina, and vascular system [15]. DM primarily presents as Type 1 and Type 2, with both conditions commonly linked to inadequate insulin production [16]. Beyond compromised insulin function, other physiological processes, including the action of the α-amylase enzyme (E.C. 3.2.1) — responsible for breaking down carbohydrates into monosaccharides — significantly contribute to elevated blood glucose levels [17]. Consequently, inhibition of α-amylase activity is a strategic approach in the management of hyperglycemia, especially in Type 2 DM therapy. Clinically, α-amylase inhibitors such as Acarbose, Voglibose, and Miglitol (Fig 3) are employed to control the postprandial surge in blood glucose typical of Type 2 DM. Nonetheless, these agents are associated with side effects, including gastrointestinal disturbances like flatulence and diarrhea [18,19].

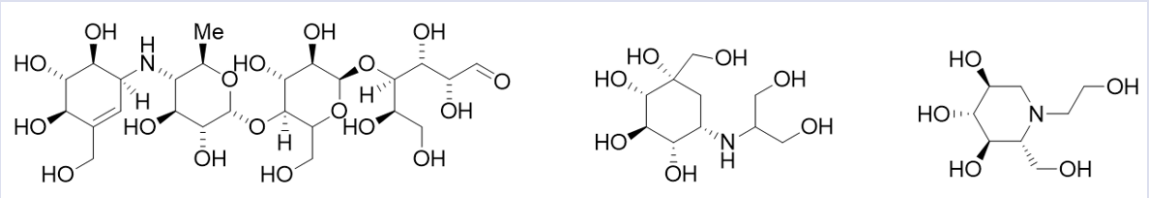
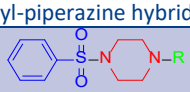
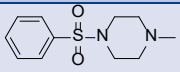
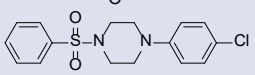
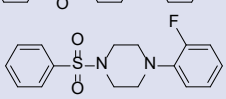
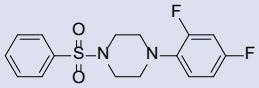
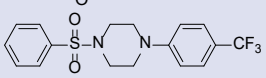


Figure 3. Molecular structure of Acarbose, Viglibose and Miglitol respectively

In a prior investigation [6], a series of piperazine sulfonamide derivatives was crafted and their antidiabetic efficacies were meticulously probed via enzyme inhibition assays. Nonetheless, analyses regarding the influence of substituent groups linked to the piperazine core on enzyme inhibitory action remained unaddressed. In another study, although compounds 1 and 2 were synthesized, their antidiabetic or α-amylase enzyme inhibition potential were not investigated [20]. The current study seeks to bridge this knowledge gap by evaluating the inhibition potency of novel sulfonyl-piperazine hybrids, with a focus on the impact of varying substituents attached to the piperazine scaffold on α-amylase enzyme activity. This was achieved using a combination of in vitro assays and in silico docking simulations. The integration of the sulfonyl group into the molecular architecture was purposeful, leveraging its documented biological activities, while the piperazine segment was chosen for hybridization due to its prevalence in a range of pharmacologically active compounds [6,11].

Table 1. Compounds 1-5, sulfonyl-piperazine hybrid molecules

Compounds	
1	
2	
3	
4	
5	

Within the framework of this research, five distinct derivatives [1-5] cataloged in Table 1 were synthesized for the goal of biological evaluation. To dissect the influence of the substituents on the piperazine ring in terms of enzyme inhibition, a systematic exploration involving both methyl-substituted and phenyl-substituted derivatives was undertaken. It is anticipated that this comparative study will shed light on the structure-activity relationships, thereby facilitating the innovative advancement of antidiabetic therapies.

Material and Methods

Chemicals

Materials and Reagents

All the chemicals were purchased from Fluka Chemie AG Buchs and Sigma Aldrich and used without further purification. Reactions were monitored by thin-layer chromatography (TLC) on silica gel 60 F254 aluminium sheets. The mobile phase was ethyl acetate: *n*-Hexane, and detection was made using UV light. ^{1}H NMR and ^{13}C NMR spectra were registered in $CDCl_3$ on Agilent 400/54 (400 MHz) NMR. The mass spectra were obtained on Agilent 6530 Accurate Mass Q-TOF LC/MS.

General procedure for the synthesis of compounds 1-5

Triethylamine (3.0 eq) was added to a solution of piperazine derivatives (1.0 eq) CH_2Cl_2 at 0 °C, then benzene sulfonyl chloride (1.0 eq) was added and stirred for 2 hours. The completion of reaction was checked with TLC (*n*-hexane and ethyl acetate (1:3)). After the reaction was finished, the solution was quenched with water and extracted with CH_2Cl_2. The combined organic layer was

dried over anhydrous Na_2SO_4 and evaporated to give compounds 1-5 [11].

1-Methyl-4-(phenylsulfonyl)piperazine (1)

Yield: 95%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.7 Hz, 2H), 7.53 (dt, *J* = 26.3, 7.2 Hz, 3H), 3.00 (s, 4H), 2.43 (t, *J* = 4.4 Hz, 4H), 2.22 (s, 3H); ^{13}C NMR (400 MHz, CDCl3) δ 135.2, 132.8, 128.9, 127.7, 53.9, 45.9, 45.6; HRMS (ESI) calcd for $C_{11}H_{16}N_2O_2S$ [M + H]+ m/z: 241.0932, found 241.1004.

1-(4-Cholorophenyl)-4-(phenylsulfonyl)piperazine (2)

Yield: 80%, grey solid.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.9 Hz, 2H), 7.68 – 7.51 (m, 4H), 7.43 – 7.28 (m, 1H), 7.12 (s, 2H), 3.36 (s, 8H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 135.2, 133.3, 130.2, 129.7, 129.3, 128.3, 127.6, 125.7, 44.9; HRMS (ESI) calcd for $C_{16}H_{17}N_2O_2SCl$ [M+H]+ m/z: 336.8502, found 336.8508.

1-(2-Fluorophenyl)-4-(phenylsulfonyl)piperazine (3)

Yield: 42%, white solid ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.7 Hz, 2H), 7.66 – 7.50 (m, 3H), 6.98 (ddd, *J* = 29.3, 15.8, 7.9 Hz, 4H), 3.16 (d, *J* = 17.1 Hz, 8H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 156.8, 154.40 139.16 135.3, 133.0, 129.1, 127.8, 124.5, 123.3, 119.2, 116.2, 49.9, 46.2. HRMS (ESI) calcd for $C_{16}H_{17}N_2O_2FN_2S$ [M+H]+ m/z: 321.1062 found 321.0329.

1-(2,4-Difluorophenyl)-4 (phenylsulfonyl) piperazine (4)

Yield: 73%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.5 Hz, 2H), 7.59 (dt, *J* = 27.0, 7.4 Hz, 3H), 6.94 – 6.69 (m, 3H), 3.13 (dd, *J* = 37.4, 4.3 Hz, 8H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 159.5, 157.0, 154.3, 135.3, 133.0, 129.1, 127.7, 119.9, 110.7, 105.0, 50.3, 46.1; HRMS (ESI) calcd for $C_{16}H_{16}F_2N_2O_2S$ [M+H]+ m/z: 339.0965 found 339.0972.

1-(Phenylsulfonyl)-4-(4-(trifluoromethyl)phenyl) piperazine (5)

Yield: 65%, brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 15.2, 7.5 Hz, 2H), 7.57 (ddd, *J* = 33.6, 20.6, 7.9 Hz, 5H), 7.00 (d, *J* = 8.4 Hz, 2H), 3.37 (d, *J* = 4.6 Hz, 4H), 3.24 (s, 4H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 135.2, 133.2, 129.2, 127.7, 126.5, 125.8, 116.1, 48.6, 45.4; HRMS (ESI) calcd for $C_{17}H_{17}F_3N_2O_2S$ [M+H]+ m/z: 371.1026 found 371.1035.

Biological Activity Assay

α-Amylase Enzyme Inhibition Assay

α-Amylase inhibition activity of samples was calculated by following the method described earlier reference [21]. 3,5-dinitrosalicylic acid (DNS) reagent was used to determine α-amylase inhibition potential of the samples spectrophotometrically. According to the method, maltose is formed from the conversion of the starch and the yellow colour of alkaline DNS is turned into the orange-red colour due to produced maltose from starch. Thus, 96 mM DNS solution was prepared from the mixture of sodium potassium tartrate solution (dissolved in 2 M NaOH) and a certain amount of DNS (dissolved in distilled water). Then, 20 mM sodium phosphate buffer with 6.7 mM NaCl (co-factor of α-amylase enzyme) was prepared at 20°C (pH: 6.9). α-amylase enzyme (1U/mL) and starch (10 mg/mL) were dissolved in this buffer. After that, 50 µL of sodium phosphate buffer and 10 µL of α-amylase enzyme solution were added to 20 µl of the sample solutions. This mixture was incubated at 37°C for 45 minutes. After the incubation period, 20 µL of the starch solution was added to the mixture. Another incubation period was started at 37°C for 45 minutes. The same procedure was applied to the samples without inserting α-amylase enzyme solution called "sample background". The control group was studied with the same procedure in the absence of sample solutions. Absorbance was measured at 540 nm. Acarbose was used as a reference solution at 31.25, 62.5, 125, 250, 500 and 1000 µg/mL concentrations. Results were presented as a percentage of inhibitory activity in 1 mg/mL of samples.

Molecular Docking Study

Ligand Preparation: Data Warrier was utilized to generate SDF files of ligands. In a nutshell, conformers are generated using SMILES codes and the following settings: Random, Low Energy Bias, Energy Minimization Based on MMFF94s+ Forcefield, Torsions Based on Crystallographic Database. 3D atom coordinates from the SD file version 3 have been utilized. Protein Preparation and Docking Parameters: PDB number: 4W93 The structure of the human α-amylase protein in combination with montbretin A has been utilized in docking experiments. In a nutshell, proteins' crystal structures were acquired from https://www.rcsb.org in pdb format. In the PDB ID: 4W93, receptor structures were examined for improper charges and missing atoms. Water molecules, montbretin A, and calcium and chloride ions were eliminated to optimize the structures. 30°A x 24°A x 24°A in a grid box and AutoDockTools 1.5.6 was used to construct the coordinates of x=-11.254, y=0.864, z=-28.914 and spacing of 1°A around the montbretin A binding pocket (for PDB ID: 4W93). With PaDelADV, ligand docking was done automatically. The amino acid interactions between molecules and enzymes were examined using the BIOVIA Discovery studio.

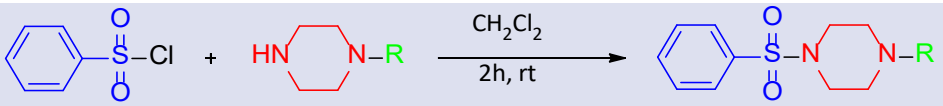
ADME Study

ADME (absorption, distribution, metabolism and excretion) parameters were examined with the help of the publicly available silico SwissADME web tool (http://www.swissadme.ch). This tool offers boiled-egg charts and bioavailability radar. The physicochemical features and drug-likeness properties of compounds are explored using the physicochemical parameters found in bioavailability radar charts.

Results and Discussion

Chemistry

With a few modifications, compounds 1–5 were synthesized in accordance with reference [6]. In short, 1.0 eq of piperazine was dissolved in CH_2Cl_2 (DCM) derivatives, and 3.0 eq of triethylamine was slowly added to the solution at 0 °C. After that, this mixture was added to 1.0 eq of benzene sulfonyl chloride and allowed to stir at room temperature for two hours. TLC was used to ensure that the reaction had finished. Following the completion of the reaction, DCM extraction was carried out and water was added. Compounds 1 through 5 were obtained by evaporating the mixed organic layer over anhydrous Na_2SO_4 (Scheme 1).



Scheme 1. Synthesis pathway of compound 1-5

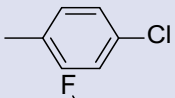
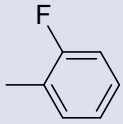
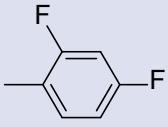
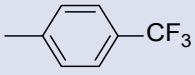
^{1}H-NMR, ^{13}C-NMR and HRMS were used to characterize the compounds. Basic peaks of compounds' aromatic hydrogens have been observed in the ^{1}H-NMR spectra at 7.70 and 7.50 ppm. 3.50 - 2.0 ppm of the piperazine ring's aliphatic hydrogens have been identified. These hydrogens' peaks were identified in two separate ways. Depending on the substituent on the piperazine ring, some of them had only one peak, while others had two peaks.

Biological Activity

α-Amylase Enzyme Inhibition

α-Amylase enzyme inhibition study of synthesized piperazine sulfonamide molecules were performed using acarbose as a reference molecule. As a result of the study, all compounds had variable degree of α-amylase enzyme inhibition percentages between 65.95± 0.41 – 80.61 ± 0.62 (Table 2). Compared to acarbose, the compound 4 showed the best (80.61 ± 0.62) and higher inhibition value than acarbose (78.81 ± 0.02). Compound 4 is composed of two fluorine (F) atoms which are electron withdrawing groups (EWG).

Table 2. α-Amylase enzyme inhibition results of compounds 1-5

Compounds	R	α-Amylase enzyme inhibition (%)
1	-CH_3	65.95±0.41
2		69.17±0.37
3		71.90±0.22
4		80.61±0.62
5		68.84±0.65
Acarbose		78.81±0.02

[a] Results were presented as α- amylase enzyme inhibition experiments were performed independently three different times. [b] standard deviation was symbolized with ±.

Compound 3 has one F atom and showed high enzyme inhibition but not as good as compound 4. The other F contained compound is compound 5 which has three F atoms but showed the lowest inhibition percentage among the substances containing F atoms (3, 4). These results may indicate that, for these molecular structures, optimum F atoms that was located on the piperazine ring was two. Apart from this, we can also conclude that the binding of all three fluorine atoms to the same carbon may have caused a decrease in enzyme inhibition percentage. Investigation of other halogen substituted phenyl ring derivative 2 has good inhibition value but it is lower than acarbose. Compound 2 has chlorine atom at *para* position of phenyl ring. When inhibition value of 2 is compared the other halogenated compounds (3, 5), although it has almost the same inhibition value as other F- containing molecules, it has been found to have a lower value than compound 4. Compound 1 has aliphatic group (methyl) electron donating groups (EDG).

Molecular Docking

Molecular docking is an important tool for elucidating the structural properties of ligands that have biological activity for target enzymes. In this part, the most active compounds were investigated based on their molecular interactions and binding energies for α-amylase enzyme. It was calculated and confirmed with their binding energy which was in the range of -5.9 to -8.2 kcal/mol for α-amylase enzyme. According to binding mode prediction results, the most potent compound for α-amylase enzyme is compound 4 (Fig.4). Compound 4 has π-π stacking between phenyl ring bound to piperazine and TRP59. Moreover, sulfonamide group has π-anion interaction with TRP58 and HIS299. In addition, a phenyl ring bound to sulfonamide interacts with GLU233. There are van der Waals interactions between LEU162, TYR62, LEU165, THR163, GLN63, HIS101, ASP300 and ASP197. According to the results obtained, compound 4 with the highest enzyme inhibition activity is also the molecule with the highest binding energy (-8.2 kcal/mol). When docking results are examined, it is seen that the molecule has strong interactions with the active site of the enzyme.

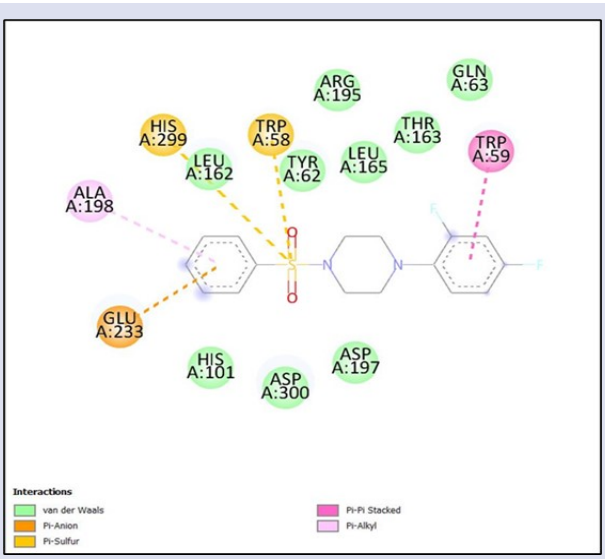


Figure 4. Docking result of compound 4 for α-amylase enzyme

ADME profiling

To investigate the physicochemical properties of the compounds 1-5 SwissADME web tool was used. Using the free SwissADME online program, the physicochemical characteristics of compounds 1–5 were predicted [22]. The bioavailability radar shows a quick predetermination of a drug-likeness properties. Six primary physicochemical properties—lipophilicity, polarity, size, solubility, saturation, and flexibility—are examined in this chart (Fig. 5). The boundary delineating the physicochemical features of the molecules that make them drug-likeness is the portion enclosed by the pink region. Once the red frame of the molecules is in the pink area, it shows that the physicochemical values of the molecule remain within the desired limits. Calculated physicochemical properties of compounds (1 – 5) are in desired limits and in pink area. These charts indicate that lipophilicity, oral bioavailability, and solubility of compounds are suitable for drug-likeness properties.

A technique for predicting ADME parameters like brain penetration (BBB) and passive gastrointestinal absorption (HIA) is the BOILED-Egg method [23]. WLOG and TPSA, two parameters, serve as the basis for these predictions. They serve as indicators of apparent polarity and lipophilicity. The results demonstrate that compounds 1 through 5 were able to enter the yolk and penetrate the BBB (Fig. 6). The substrate of permeability glycoprotein (P-gp) is indicated by red dots. Not every compound is included in the P-gp mechanism for active efflux. The compound's physicochemical properties can help it progress toward becoming a drug-like molecule, even though BBB penetration and not efflux from brain properties may have some negative effects on central nervous systems.

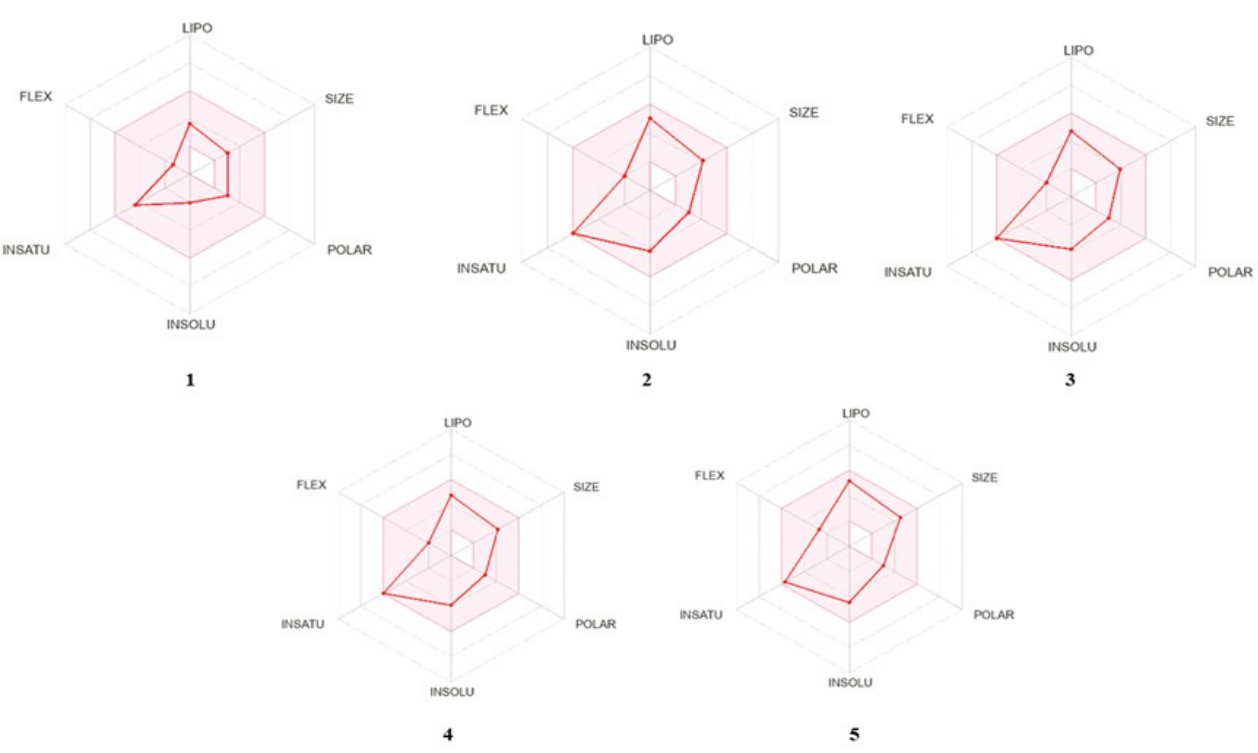


Figure 5. Bioavailability radar chart of compounds 1-5

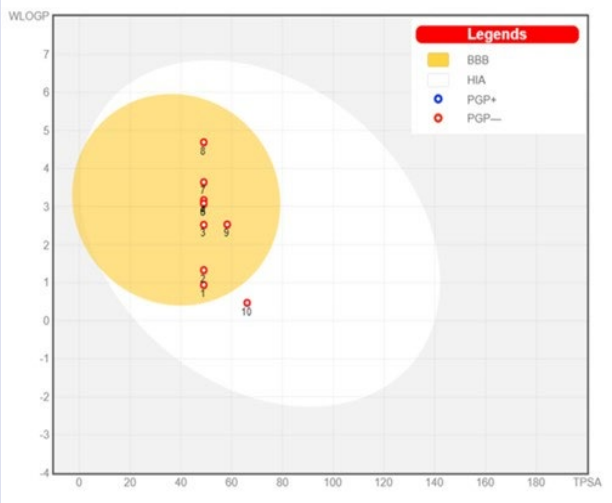


Figure 6. Boiled-egg chart for the compounds 1 -5

Conclusion

In the present study, we synthesized five phenylsulfonyl piperazine derivatives and evaluated their inhibitory effects on the α-amylase enzyme. Notably, compound 4 exhibited an inhibition value that surpassed that of the reference molecule, acarbose, as well as the other derivatives in the series. To assess the physicochemical properties bioavailability radar charts and the boiled-egg model were employed. These analyses predicted favorable drug-like characteristics and pharmacokinetic profiles for the synthesized compounds. Furthermore, molecular docking studies were conducted to elucidate pivotal interactions between the compounds and the enzyme. The promising nature of these findings is supported by binding energies ranging from -5.9 to -8.6 kcal/mol for the α-amylase enzyme, demonstrating strong affinity. Compound 4 possessing the most substantial inhibitory effect on the α-amylase enzyme, with notable

binding energy -8.2 kcal/mol. This compound exhibited specific interactions, including π-π stacking and π-anion interactions with key enzyme residues, solidifying its role as a potent inhibitor.

Conflict of Interest

The authors declare no conflicts of interest.

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