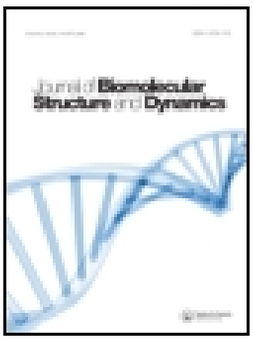

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The Biological Activities, Molecular Docking Studies, and Anticancer Effects of 1-Arylsuphonylpyrazole Derivatives

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ABSTRACT

This work is devoted to definition of the direction of reaction between 1-benzenesulfonylimino pyridinium chloride and α- or β-halo-containing sulfamides, chloroacetic acid, 1-chloro-2,3-dihydroxypropane, etc. The optimal conditions for the synchronous reaction of heterocyclization are determined. Benzenesulfonyliminopyridinium chloride was obtained to form pyrazolopyridines with 1,2-polarophiles, and pyridazine pyridines with 1,3-polarophiles. These novel derivatives were found as effective inhibitors of the α-glycosidase with K_i values in the range of 13.66±2.63-60.63±12.71 nM. The molecules (**II-X**) against enzyme were compared theoretically with the help of molecular docking to compare biological activities. The results were compared with the numerical values of the parameters obtained from molecular docking calculations and found to be in great agreement with the experimental results. However, ADME analysis of molecules was performed. Also, the compounds exhibited significant anticancer effect depending on the doses administered.

Key words: Pyrazolpiridines; pyridazole pyridines; anticancer; enzyme inhibition; molecular docking

1. INTRODUCTION

Creation of the new physiological active compounds with desired biological properties, as well as determination of the link between the chemical structure of synthesized compounds and their biological activity, and expansion of the range of their actions is among the most important problems of organic chemistry today. Among condensed heterocycles, pyrazolo- or pyridazolopyridines, which have a wide spectrum of biological activity, occupy a special place. Condensed pyridines have a pronounced inhibitory effect of cholinesterase and are widely used in pharmacy and medicine. Among them, pyridostigmine bromide, quinotilin, and alloxime are the most known ones. Pyrazolo-pyridines are very strong inhibitors of γ-secretase (Ye et al., 2013) and dihydropyrazolopyridinyl sulfamides have an autoimmune property (Herrey et al., 2004). Pyridazonyl sulfamide derivatives exhibit strong antimicrobial activity. As can be seen from the examples given above, urea and tiourea fragments contain different application areas. New synthesized compounds and active heterocycle rings show that it is necessary to examine their various properties. Moreover, there is no systematic study of the effect of cyclic chains and different functional groups on the chemical properties of the compounds containing the ring in the literature in relation to various side effects with different side effects (Mohamed, 2007). On the basis of the synthesized sulphamides obtain functionally substituted pyrazolin-, pyrazolidone-, -imidazole- and pyrimidine sulfonamides. It is revealed that reaction of arylsulfochlorides with alkyldiamines with high yield give only bis- sulphamides, and with carbamyl guanidine only monosulphamide. Synthesized polyamine sulphamides and their derivatives were tested in different areas. Regularities between structure, composition and properties are defined (Mamedov, 2007; Farzaliev 2010).

Carbohydrate digestive enzymes are found in the brush border of the intestine and break down the long-chain polysaccharides into simple absorbable monosaccharide units including glucose. Indeed, α-glycosidase enzymes play a key role in the lysis of α-glucopyranoside bond in disaccharides and oligosaccharides to release monosaccharide molecules, which then get absorbed in the body and thus regulate glucose availability and the degree of postprandial hyperglycemia. Hence, the inhibition of α-glycosidase is recorded as a prime aim to develop and discover novel potent and less toxic antidiabetic drugs (Demir et al., 2019; Bilgicli et al., 2019; Kaya et al., 2019; Çaglayan et al., 2019). Theoretical calculations have become widespread. One of the main reasons for this is that it is possible to make a clearer comparison of theoretical calculations in less time. The theoretical method used in this study is molecular docking. Molecular docking studies compare biological activities of molecules with enzymes (Tüzün 2020; Tüzün and kaya 2018; Mamedova et al., 2019).

In this study, we performed the design, biological evaluation of some of 1-arylsuphonylpyrazole- or pyridazin [1,5-a]-pyridine (**I-X**) which compounds (**II-X**) were as effective α-glycosidase inhibitors. Also anticancer studies were performed on these compounds. Another goal of this work, is compared their inhibitory results with control compounds like acarbose. Lastly, the biological activity of molecules (**II-X**) against α-glycosidase enzyme, ID 1R47, was compared. ADME (Absorption, Distribution, Metabolism and Excretion) analysis (Mermer et al., 2019; Sari et al., 2019; Şener et al., 2019; Altındağ et al., 2019; Singh and Bast 2014; Sağlık et al., 2019; Tao et al., 2013) of the molecules was carried out so that the molecules can be used as drugs in the future. As a result of this analysis, if the numerical values of the obtained parameters fall within certain ranges, the molecule is said to be a drug.

2. EXPERIMENTAL

2.1. General chemistry

For synthesis of 1-benzenesulfonamide-2-R-3-Z-1,2-dihydropyrazolo[1,5-a]pyridines **(I-III)** 0.001 mol of N-benzenesulfonamidepyridinium chloride and 0.001 mol of dipolar (1,2-dichloro-3-benzenesulfamide, chloroacetic acid, β-bromopropionic acid, 1-chloro-2,3-dihydroxypropane) were dissolved in 50 ml of ethanol. To the solution was added dropwise a solution of NaOH (0.002 mol) in ethanol. It was boiled until complete precipitation of NaCl or NaBr (5.5 - 6.0 hour). It was cooled and filtered, then, the filtrate was evaporated to half the volume, cooled and the precipitated crystals were recrystallized from ethanol.

For synthesis of 6,6-dimethyl-4-oxycyclohexane-2,3-pyrazolo-1-phenylsulfamido [1,5-a] pyridine **(IV)** 4.2 g (0.03 mol) of dimedone and 8.12 g (0.03 mol) of pyridinimine were dissolved in 20 mL of ethanol. With stirring, a 7% alkali solution (1.5 g of NaOH in 40 mL of ethanol) was added dropwise. Then the mixture was heated for 5-6 hours, half the volume of the alcohol was distilled off, cooled, 20 mL of water was added and the crystals obtained were filtered. Then they were recrystallized in ethanol. The method of obtaining is similar to the method of synthesis of compounds **(V-X)**. However, 0.15 mmol of morpholine is taken, instead of alkali. The structure of all substances was confirmed by modern physical and chemical analysis (Tao et al., 2013).

2.2. Enzymes studies

2.2.1. α-Glycosidase enzyme assay

α-Glycosidase inhibitory efficacy of novel 1-arylsuphonylpyrazole- or pyridazin [1,5-a]-pyridine (**II-X**) was performed using p-nitrophenyl-D-glycopyranoside (p-NPG) as the substrate,

according to the procedure of Tao et al. (2013) as described previously (Gulcin et al., 2019; Burmaoglu et al., 2019). The samples were prepared by dissolving 10 mg in 10 mL (EtOH: H_2O). First, 100 µL of phosphate buffer was mixed with 20 µL of the enzyme solution in phosphate buffer (0.15 U/mL, pH 7.4) and 10-100 µL of the sample. Multiple solutions in phosphate buffer were prepared in case of getting full enzyme inhibition. Then, it was pre-incubated at 35 °C for 15 min previous by adding the p-NPG to the initiation of the reaction. Also, after preincubation, 50 µL of p-NPG in phosphate buffer (5 mM, pH 7.4) was added and re-incubated at 37 °C. The absorbances of samples were spectrophotometrically measured at 405 nm (Maharramov et al., 2019; Eruygur et al., 2019; Aktaş et al., 2019). The IC_{50} values were calculated from activity (%) versus novel 1-arylsuphonylpyrazole- or pyridazin [1,5-a]-pyridine (**II-X**) concentration plots. Lineweaver-Burk graphs were used to determine the Ki values (Aktas et al., 2020; Bal et al., 2020;).

2.3. Anticancer studies

2.3.1. Proliferation of cells

Human prostate (PC-3, ATCC) and breast (MCF-7, ATCC) cancer cell lines were used to determine the anticancer properties of the tested compounds. Cells were first extracted from liquid nitrogen and then cultured in 75 cm^2 culture flasks. Cultured PC-3 cells were prepared with RPMI-1640 (Sigma-Aldrich R8758, USA) medium (prepared by adding 10% FBS, 100 U/mL Penicillin and 0.1 mg/mL Streptomycin), and MCF-7 cells were DMEM (Gibco 41965039, UK) medium (prepared by adding 10% FBS, 100 U/mL Penicillin and 0.1 mg/mL Streptomycin, 10 µg/mL insulin). The media of the cells were changed twice a week and the cells were incubated at 37 °C (Thermo Forma II CO_2 Incubator, USA) with CO_2 (5%) in all steps. Cells that were confluent at the base of the flask were removed from the flasks using trypsin-EDTA (Gibco 25300054, UK) and stained with 0.4% trypan blue followed by cell counts under an inverted microscope (Optec BDS400, China). Experimental studies were initiated when cell viability was 90% or more (Koyunoglu et al., 2013).

2.3.2. Cell Viability (MTT assay)

The effect of test compounds on viability in human prostate and breast cancer cells was determined by the 3- (4,5-dimethylthiazol-2-yl)-diphenyltetrazolium bromide (MTT) method, which is widely used in the assessment of cell viability. Cells of which viability levels were determined were cultured in 96-well plates with $15x10^3$ cells per well. The plates were incubated for one day in CO_2 medium and then the test compounds were treated with concentrations of 1,

5, 25, 50 and 100 µM prepared in DMSO for 24 hours. After this time, 0.5 mg/mL MTT (Sigma-Aldrich M2128, USA) working solution was prepared to determine the changes in cell viability and 100 undanL of the prepared MTT solution was added to each well and incubated for 3 hours in a CO_2 incubator. At the end of incubation, the optical densities of the cells in the plates were read in the microplate reader (Thermo MultiskanGo, USA) at a wavelength of 570 nm (Mosmann 1983). Control wells (wells with cells and medium only) were recorded; the obtained mean absorbance values were accepted as 100% viable cells. The absorbance values obtained from the wells treated with vehicle control (DMSO) and test compounds were proportional to the control absorbance value and percent viability values were calculated (Tekin et al., 2015; Koran et al., 2017). The effect of compounds on cell viability was analyzed in comparison to control and solvent. These experiments were repeated 5 times independently on different days.

2.3.3. Statistical Analysis

Statistical analyzes were performed using GraphPad Prism 5 package program. Homogeneity of the variances was evaluated by Bartlett tests test. One-way ANOVA was used to determine the differences between the groups and Bonferroni test was used for multiple comparisons. Quantitative data were expressed as mean ± standard error (mean±SD) and $p<0.05$ was considered significant.

2.4. Docking Study

Bioinformatics chemistry has been greatly influenced by advances in technology and informatics. Bioinformatic chemistry has become widely used in the design of new drugs and active substances (Kaya et al., 2016). Theoretically, there are many programs for the design of new drugs and active substances in bioinformatic chemistry. Molecular docking is one of the methods developed for this. In this study, biological activity value of molecules was calculated by using molecular docking method (Bilgiçli et al., 2019; Günsel et al., 2019; Tüzün and saripinar, 2019). The molecules were first optimized using the Gaussian package program (Frisch et al., 2009). * .pdb extension files were created using optimized structures. The enzyme α-glycosidase file was obtained from the RCSB Protein Data Bank website. The RCSB Protein Data Bank builds upon the data by creating tools and resources for research and education in molecular biology, structural biology, computational biology, and beyond. Maestro Molecular modeling platform (version 12.2) by Schrödinger, LLC was used to calculate biological activity values of 1-Arylsuphonylpyrazole derivatives against enzymes (Schrodinger 2019).

3. RESULTS

3.1. Chemistry

Our research has shown that the reaction of heterocyclization of a dipolarophile with 1-(arylsulfonyl)iminopyridine (comp. A), the nature and content of the electron-withdrawing group in their composition have little effect. For example, the reaction of compound (A) with 1,2-dichloro-3-benzenesulfonamide produces 1-benzenesulfanilamido-3-benzenesulfamidomethyl-pyrazolo [1,5-a] pyridine. Probably, in the presence of alkali, nucleophilic substitution of hydrogen of sulfamide nitrogen by chlorine in secondary carbon occurs, followed by substitution of pyridine hydrogen and closure of the heterocycle. In the interaction of sulfonyliminopyridinium with chloroacetic and α-bromopropionic acid, 1-(benzenesulfonyl)pyrazolo [1,5-a] pyridinones are formed. Compounds **II** and **III** dissolved in 15-20% alkali, which proves the presence of keto-enol tautomerism. Sulfonyliminopyridine with cyclic diketones (Dimedone) in the presence of a base also easily reacts to heterocyclization. It was established that the reaction of sulfonyliminopyridine with chloromethyl- or nitrilaziridine sulfamides and with epichlorohydrin produces 1-(benzenesulfonyl)pyridazino- [1,6-a] pyridines. The outputs of compound **VII** are lower than those of compounds **V** and **VI**. This can be explained by the fact that when using 2-chloroxyrane, the opening of the epoxy group is difficult. Sulfamidopyridinimine in the presence of alkali enters easily into a heterocyclization reaction with diacetone alcohol and with 1-chloro-2,3-hydroxypropane. The yields of compounds **VIII, IX** and **X** are lower than those of other pyridazine pyridines (60-85%). Heterocyclization with benzoin takes place with brief heating (Mamedova et al., 2019). All reactions were shown in the Scheme 1.

3.2. Biochemical Results

3.2.1. Enzymes Results

For the α-glycosidase enzyme, the novel 1-arylsuphonylpyrazole- or pyridazin [1,5-a]-pyridine (**II-X**) compounds had IC_{50} values in the range of 11.73–58.53 nM and K_i values in the range of 13.66±2.63-60.63±12.71 nM (Table 1 and Figure 1). The results obviously showed that all novel 1-arylsuphonylpyrazole- or pyridazin [1,5-a]-pyridines (**II-X**) demonstrated efficient α-glycosidase inhibitory effects than that of acarbose (IC_{50}: 22.80 μM, K_i: 12.60 μM) (Foroumadi et al., 2005) as a standard α-glycosidase inhibitor. However, the most effective K_i values were obtained by compounds **III** and **II,** with K_i values of 13.66±2.63 and 26.93±3.84 nM, respectively.

3.2.2. Anticancer results

The changes in cell viability in human prostate (PC-3) and breast (MCF-7) cancer cell lines after 24 hours of treatment with test compounds are shown in Figures 2 and 3, respectively. Accordingly, concentrations of 5 µM and above of all compounds significantly reduced PC-3 cell viability compared to control groups ($p < 0.05$; Figure 2).

There was no significant change in MCF-7 cell viability after treatment with compound MS72 as compared to control groups. Although all the concentrations of compound MS50 reduced MCF-7 cell viability compared to the control group ($p < 0.05$), no significant difference was found compared to the solvent control. All other compounds were found to reduce MCF-7 cell viability, especially concentrations of 25 µM and above compared to control groups ($p < 0.05$; Figure 3).

3.2.3. Docking result

Many parameters were obtained as a result of docking study of 1-arylsuphonylpyrazole derivatives against enzyme α-glycosidase, which is ID: 1R47. The biological activities of the molecules are compared using the numerical values of these parameters. This parameter provides guidance for experimental studies in designing new drugs and active substances (Mamedova et al., 2019). The interaction of molecules with enzyme α-glycosidase is the most important factor to increase the biological activity values. Interactions between molecules and enzyme are the most important factors affecting the biological activity value of molecules in Figure 4. These interactions have many interactions such as hydrogen bonds, polar and hydrophobic interactions, π-π and halogen bonds (Sayın and Karakaş 2017, 2018, 2018, Sayın and Üngördü 2018, 2019, Üngördü and Sayın 2019, Tüzün and Sayın 2019, Tüzün 2020).

Molecular docking calculations were made at pH 7.0 ± 2.0 ranges. The most important reason for this is that the pH of the enzyme studied is the most active in the human body at pH 7.35, which is the pH of human blood (Friesner et al., 2006). The parameters obtained as a result of the structure calculations are given in Table 2.

To examine the interactions of 1-arylsuphonylpyrazole derivatives with the proteins that make up the enzyme, it was initially prepared using the protein preparation module (Friesner et al., 2006, Schrödinger Release 2019), the α-glycosidase enzyme crystalline, which is ID: 1R47. The water molecules in the enzyme were removed using this module. However, binding methods and protein loads in the enzyme structure were optimized using this module. The most active region of the enzyme was found by evaluating with the proteins that make up the enzyme. Freedom of movement was given during the interaction with 1-arylsuphonylpyrazole derivatives for the proteins in the active region of the enzyme. LigPrep module (Sastry et al., 2013, Schrödinger

Release 2019-4) was used to prepare 1-arylsuphonylpyrazole derivatives for molecular docking calculations. Then, 3D structures of 1-arylsuphonylpyrazole derivatives, correct protonation status at physiological pH and molecular geometries of 1-arylsuphonylpyrazole derivatives were obtained using this module. After the preparation of 1-arylsuphonylpyrazole derivatives, enzymes were interacted with 1-arylsuphonylpyrazole derivatives using the Glide ligand-docking (Du et al., 2019) module.

After interactions of enzymes with 1-arylsuphonylpyrazole derivatives, the possibilities of 1-arylsuphonylpyrazole derivatives to be drugs were investigated. ADME (Absorption, distribution, metabolism, excretion, and toxicity) analysis was used for this examination. The Qik-prop module (Schrödinger Release 2020-1) of Schrödinger was used to perform this analysis. Using this module, drug properties of molecules are examined. Many parameters are obtained at the end of this examination. The most important parameters among these parameters are molecular weight, QP log $P_{o/w}$ donorHB, accptHB, rule of five, and rule of three, etc (Jorgensen and Duffy 2002, Lu et al., 2004, Lipinski et al., 2001).

4. DISCUSSION

It was established that the reactions between arylsulfochlorides and polyamines are always obtained mono-and disulfonamides despite excessive double molar concentration of amine in literature (Gulçin et al., 2018). Type 2 diabetes mellitus is determined by insulin resistance, which may be combined with relatively decreased insulin secretion and lead to hyperglycemia. This disease can cause many disorders or complications, which happen in several organs causing serious health issues, often retinopathy and nephropathy (Boztas et al., 2019). One of the goals for hyperglycemia reduction is to decrease the activity of α-glycosidase responsible for carbohydrates hydrolysis. The α-glycosidase inhibitors delay the absorption of sugars in the intestinal tract, thus limiting the excursions of postprandial plasma glucose. Indeed, acarbose compound is an oral α-glycosidase inhibitor (Taslimi and Gulçin 2017, Song et al., 2019).

Interactions of 1-arylsuphonylpyrazole derivatives with enzymes formed by proteins are examined in Figure 5. When many parameters obtained as a result of the calculations are examined, the docking score parameter is the most important parameter among these parameters (Sağlık et al., 2019, Ertaş et al., 2019, Kecel-Gunduz et al., 2020). The molecule with the most negative numerical value of this parameter has the highest biological activity. Therefore, the biological activity values of the molecules are compared according to the numerical value of this parameter. On the other hand, many parameters are obtained other than this parameter; these other parameters are used to explain the interaction of molecules and enzymes. In molecular

docking calculations, the Glide H-bond parameter is the term residue interaction per hydrogen bond. The total of individual H-bond points for H-bonds between 1-arylsuphonylpyrazole derivatives and a particular residue. If the numerical value of this parameter is more negative, it means stronger H-bond. The types of atoms in the H-bonds and the geometry of the H-bonds influence the numerical value of this parameter. Glide emodel parameter is the energy of the interaction model obtained. This parameter is the combination of the numerical value of many parameters. Glide ligand efficiency parameter is a numerical value that gives information about the effectiveness of ligand molecules. It should be well known that the most important thing affecting the biological activity of molecules is the interaction between the molecule and enzymes (Bıçak et al., 2019, Budama-Kilinc et al., 2019, Mermer et al., 2019). As these interactions increase, the biological activities of the molecules increase.

Since the interactions of molecules with enzymes are examined, it is investigated that molecules can be used as drugs in the future. In order to use a molecule as a drug, ADME analysis of the molecules was done in Table 3. The numerical values of the parameters obtained by this analysis must be within a certain range. If those parameters of the molecule are not in that range, it is thought that the molecule cannot be a drug. Experimental work in the future is not recommended. However, if the numerical values of all parameters provide the conditions, it is said that experiments are appropriate for future medication. However, no value was found in the ADME analysis of molecule V. Because the ADME analysis values of the molecule are very bad, no value could be obtained. As a result of ADME analysis, there are many parameters obtained, among these parameters, Lipinski Rule of 5 and Jorgensen Rule of 3, which are known as the Pfizer 5 rule, are the most important parameters (Bayrak et al., 2019, Karimov et al., 2020, Demir 2020, Shah et al., 2020). In the 5 rules of Lipinski, the number of hydrogen binding atoms in the molecule studied will not be more than 5 (nitrogen and oxygen atoms for one or more hydrogen atoms attached to it). In addition, the number of atoms that accept hydrogen bonds in the studied molecule are 10 (nitrogen and the number of oxygen atoms) will not exceed. In addition, its molecular weight should be under 500 Daltons and the lipophilic coefficient (log p) below 5. Small molecules that follow these rules are thought to have the potential to be medicines. Another parameter is Solute as Donor-Hydrogen Bonds, which is the estimated hydrogen bond sequence to be given to the aqueous solution. Another parameter is Solute as Acceptor-Hydrogen, which is the estimated number of hydrogen bonds to be accepted by the substance dissolved from water molecules in an aqueous solution (Bayindir et al., 2019, Acar et al., 2019, Menteşe et al., 2019, Türkan et al., 2019, Celik et al., 2020).

5. CONCLUSIONS

The effectiveness of the inhibitor action of the synthesized compounds depends not only on the composition of the functional groups, but also on the nature of the heterocycle and the location of the functional groups. Each of the studied drugs has a relatively long latent period of action. This is probably due to the difficulty of transporting the toxophore molecules through the cell walls of microorganisms to the vital centers they suppress. One of the goals of AD therapy is to enhance the level of acetylcholine in the brain by inhibiting AChE. Patients with the neurodegenerative disease treated with these inhibitors present undesirable effects like nausea, diarrhea, gastrointestinal anomalies, and hepatotoxicity. α-Glycosidase inhibition is a logical process in the effective management of type 2 diabetes. Various inhibitors of this enzyme class are in clinical utilize but are riddled with potency, efficacy, and safety challenges. Additionally, novel effective α-glycosidase inhibitors are under evaluation. In molecular docking studies, the parameters obtained from the interaction of molecules with enzyme showed that molecule III has the highest biological activity. The theoretical results were in great agreement with the experimental results.

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Conflicts of interests

The authors declare that no conflicts of interests.

REFERENCES

Acar, M. F., Sari, S., Dalkara, S. (2019). Synthesis, in vivo anticonvulsant testing, and molecular modeling studies of new nafimidone derivatives. Drug Development Research, 80(5), 606-616. https://doi.org/10.1002/ddr.21538

Aktas, A., Barut Celepci, D., Gök, Y., Taslimi, P., Akıncıoğlu, H., Gülçin, İ. (2020). A novel Ag-N-heterocyclic carbene complex bearing the hydroxyethyl ligand: synthesis, characterization, crystal and spectral structures and bioactivity properties. Crystals, 10, 171. https://doi.org/10.3390/cryst10030171.

Aktaş A., Celepci D. B., Kaya R., Taslimi P., Gök Y., Aygün M., Gulcin I. (2019). Novel morpholine liganded Pd-based N-heterocyclic carbene complexes: Synthesis,

characterization, crystal structure, antidiabetic and anticholinergic properties. Polyhedron, 159, 345-354 https://doi.org/10.1016/j.poly.2018.11.048

Altındağ, F. D., Sağlık, B. N., Acar Çevik, U., Işıkdağ, İ., Özkay, Y., Karaca Gençer, H. (2019). Novel imidazole derivatives as antifungal agents: Synthesis, biological evaluation, ADME prediction and molecular docking studies. Phosphorus, Sulfur, and Silicon and the Related Elements, 194(9), 887-894 https://doi.org/10.1080/10426507.2019.1565761

Bal, S., Kaya, R., Taslimi, P., Aktaş, A., Karaman, M., Gulçin, İ. (2020). Novel 2-methylimidazolium salts: synthesis, characterization, molecular docking, and carbonic anhydrase and acetylcholinesterase inhibitory properties. Bioorganic Chemistry, 94, 103468. https://doi.org/10.1016/j.bioorg.2019.103468.

Bayindir, S., Caglayan, C., Karaman, M., Gulcin I. (2019). The green synthesis and molecular docking of novel N-substituted rhodanines as effective inhibitors for carbonic anhydrase and acetylcholinesterase enzymes. Bioorganic Chemistry, 90, 103096. https://doi.org/10.1016/j.bioorg.2019.103096

Bayrak C., Taslimi P., Karaman H.S., Gulcin I., Menzek A., (2019). The first synthesis, carbonic anhydrase inhibition and anticholinergic activities of some bromophenol derivatives with S including natural products, Bioorganic Chemistry, 85, 128–139. https://doi.org/10.1016/j.bioorg.2019.103096

Bıçak, B., Gündüz, S. K., Kökcü, Y., Özel, A. E., Akyüz, S. (2019). Molecular docking and molecular dynamics studies of l-glycyl-l-glutamic acid dipeptide. Bilge International Journal of Science and Technology Research, 3(1), 1-9. https://doi.org/10.30516/bilgesci.476841

Bilgiçli, A.T., Bilgiçli, H.G., Günsel, A., Pişkin, H., Tüzün, B., Yarasir, M. N., Zengin, M. (2020). The new ball-type zinc phthalocyanine with SS bridge; Synthesis, computational and photophysicochemical properties. Journal of Photochemistry and Photobiology A: Chemistry, 389, 112287 https://doi.org/10.1016/j.jphotochem.2019.112287

Bilgicli H.G., Kestane A., Taslimi P., Karabay O., Bytyqi-Damoni A., Zengin M., Gulçin İ., (2019). Novel eugenol bearing oxypropanolamines: Synthesis, characterization, antibacterial, antidiabetic, and anticholinergic potentials. Bioorganic chemistry, 88, 102931 https://doi.org/10.1016/j.bioorg.2019.102931

Boztas, M., Taslimi, P., Yavari, M.A., Gülçin, İ., Sahin, E., Menzek, A. (2019). Synthesis and biological evaluation of bromophenol derivatives with cyclopropyl moiety: Ring opening of cyclopropane with monoester. Bioorganic Chemistry, 89, 103017. https://doi.org/10.1016/j.bioorg.2019.103017.

Budama-Kilinc, Y., Cakir-Koc, R., Kecel-Gunduz, S., Zorlu, T., Kokcu, Y., Bicak, B., Ozel, A. E. (2018). Papain loaded poly (ε-Caprolactone) nanoparticles: In-silico and in vitro studies. Journal of Fluorescence, 28(5), 1127-1142. https://doi.org/10.1007/s10895-018-2276-6

Burmaoglu, S., Yılmaz, A.O., Polat, M.F., Kaya, R., Gulcin, I., Algul, O. (2019). Synthesis of novel tris-chalcones and determination of their inhibition profiles against some metabolic enzymes. Archives of Physiology and Biochemistry, 43(7), e12908. https://doi.org/10.1080/13813455.2019.1623265.

Bursal E., Aras A., Kılıç Ö., Taslimi P., Gören A.C., Gulçin İ., (2019). Phytochemical content, antioxidant activity, and enzyme inhibition effect of Salvia eriophora Boiss. & Kotschy against acetylcholinesterase, α-amylase, butyrylcholinesterase, and α-glycosidase enzymes. Journal of Food Biochemistry, 43(3), e12776 https://doi.org/10.1111/jfbc.12776

Çağlayan C., Demir Y., Küçükler S., Taslimi P., Kandemir F.M., Gulçin İ., (2019). The effects of hesperidin on sodium arsenite-induced different organ toxicity in rats on metabolic enzymes as antidiabetic and anticholinergics potentials: A biochemical approach. Journal of Food Biochemistry, 43(2), e12720 https://doi.org/10.1111/jfbc.12720

Celik, I., Erol, M., Temiz Arpaci, O., Sezer Senol, F., Erdogan Orhan, I. (2020). Evaluation of activity of some 2, 5-disubstituted benzoxazole derivatives against acetylcholinesterase, butyrylcholinesterase and tyrosinase: ADME prediction, DFT and comparative molecular docking studies. Polycyclic Aromatic Compounds, 1-12. https://doi.org/10.1080/10406638.2020.1737827

Demir, Y. (2020). Naphthoquinones, benzoquinones, and anthraquinones: Molecular docking, ADME and inhibition studies on human serum paraoxonase-1 associated with cardiovascular diseases. Drug Development Research. https://doi.org/10.1002/ddr.21667

Demir Y., Duran H.E., Durmaz L., Taslimi P., Beydemir S., Gülçin I., (2019) The influence of some nonsteroidal anti-inflammatory drugs on metabolic enzymes of aldose reductase, sorbitol dehydrogenase, and α-glycosidase: a perspective for metabolic disorders, Applied Biochemistry and Biotechnology, 1-11, https://doi.org/10.1007/s12010-019-03099-7.

Du Q., Qian Y., Yao X., Xue W., Elucidating the tight-binding mechanism of two oral anticoagulants to factor Xa by using induced-fit docking and molecular dynamics simulation. Journal of Biomolecular Structure and Dynamics, (2019) 1-9. https://doi.org/10.1080/07391102.2019.1583605

Eruygur N., Ataş M., Tekin M., Taslimi P., Koçyiğit U.M., Gulçin, İ. (2019). Screening the in vitro antioxidant, antimicrobial, anticholinesterase, antidiabetic activities of endemic Achillea cucullata (Asteraceae) ethanol extract. South African Journal of Botany, 120, 141-145 https://doi.org/10.1016/j.sajb.2018.04.001

Ertas, M., Sahin, Z., Bulbul, E. F., Bender, C., Biltekin, S. N., Berk, B., Yurttas L., Nalbur A.M., Celik H., Demirayak, Ş. (2019). Potent ribonucleotide reductase inhibitors: Thiazole-containing thiosemicarbazone derivatives. Archiv der Pharmazie, 352(11), 1900033. https://doi.org/10.1002/ardp.201900033

Farzaliev V.M., Mamedov S.A., Kuliev F.A., Guseinov I.S., Shakhgeldieva L.M. (2010) Az. Khim. Journal., 4, 19.

Foroumadi, A., Emami, S., Hassanzadeh, A., Rajaee, M., Sokhanvar, K., Moshafi, M. H., & Shafiee, A. (2005). Synthesis and antibacterial activity of N-(5-benzylthio-1, 3, 4-thiadiazol-2-yl) and N-(5-benzylsulfonyl-1, 3, 4-thiadiazol-2-yl) piperazinyl quinolone derivatives. Bioorganic & Medicinal Chemistry Letters, 15(20), 4488-4492 https://doi.org/10.1016/j.bmcl.2005.07.016

Friesner, R.A., Murphy, R.B., Repasky, M.P., Frye, L.L., Greenwood, J.R., Halgren, T.A., Sanschagrin, P.C., Mainz, D.T., Extra Precision Glide: Docking and scoring incorporating a model of hydrophobic enclosure for protein-ligand complexes. Journal of Medicinal Chemistry, 49 (2006) 6177–6196 https://doi.org/10.1021/jm051256o

Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Scalmani G, Barone V, Mennucci B, Petersson GA, Nakatsuji H, Caricato M, Li X, Hratchian HP, Izmaylov AF, Bloino J, Zheng G, Sonnenberg JL, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Vreven T, Montgomery JA, Peralta JE, Ogliaro F, Bearpark M, Heyd JJ, Brothers E, Kudin KN, Staroverov VN, Kobayashi R, Normand J, Raghavachari K, Rendell A, Burant JC, Iyengar SS, Tomasi J, Cossi M, Rega N, Millam JM, Klene M, Knox JE, Cross JB, Bakken V, Adamo C, Jaramillo J, Gomperts R, Stratmann RE, Yazyev O, Austin AJ, Cammi R, Pomelli C, Ochterski JW, Martin RL, Morokuma K, Zakrzewski VG, Voth GA, Salvador P, Dannenberg JJ, Dapprich S, Daniels AD, Farkas O, Foresman JB, Ortiz JV, Cioslowski J, Fox DJ (2009) Gaussian 09, revision D.01. Gaussian Inc, Wallingford CT

Gulcin, İ., Taslimi, P., Aygün, A., Sadeghian, N., Bastem, E., Kufrevioglu, O. I, Turkan F., Şen, F. (2018). Antidiabetic and antiparasitic potentials: inhibition effects of some natural antioxidant compounds on α-glycosidase, α-amylase and human glutathione S-transferase enzymes. International Journal of Biological Macromolecules, 119, 741-746. https://doi.org/10.1016/j.ijbiomac.2018.08.001

Gulcin, I. Tel, A.Z., Goren, A.C., Taslimi, P., Alwasel, S. (2019). Sage (*Salvia pilifera*): Determination its polyphenol contents, anticholinergic, antidiabetic and antioxidant activities. Journal of Food Measurement and Characterization, 13(3), 2062-2074. https://doi.org/10.1007/s11694-019-00127-2.

Günsel, A., Kobyaoğlu, A., Bilgiçli, A. T., Tüzün, B., Tosun, B., Arabaci, G., Yarasir, M. N. (2020). Novel biologically active metallophthalocyanines as promising antioxidant-antibacterial agents: Synthesis, characterization and computational properties. Journal of Molecular Structure, 1200, 127127 https://doi.org/10.1016/j.molstruc.2019.127127

Herrey, G.N., Shaoyun, X.K. & Molina N. (2004). Synthesis of dihydropyrazolo-pyridinyl benzamides and sulfonylamides, Patent 6434190 USA. Claims 07.28.2003. PJChem 04.23 - 19O,139p.

Jayarajan, R., Satheeshkumar, R., Kottha, T., Subbaramanian, S., Sayin, K., Vasuki, G., Water mediated synthesis of 6-amino-5-cyano-2-oxo-N-(pyridin-2-yl)-4-(p-tolyl)-2H-[1, 2′-bipyridine]-3-carboxamide and 6-amino-5-cyano-4-(4-fluorophenyl)-2-oxo-N-(pyridin-2-yl)-2H-[1, 2′-bipyridine]-3-carboxamide–An experimental and computational studies with non-linear optical (NLO) and molecular docking analyses. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 229 (2020) 117861. https://doi.org/10.1016/j.saa.2019.117861

Jorgensen W.L., Duffy E.M., Prediction of drug solubility from structure. Advanced Drug Delivery Reviews, 54(3) (2002) 355-366. https://doi.org/10.1016/S0169-409X(02)00008-X

Karimov, A., Orujova, A., Taslimi, P., Sadeghian, N., Mammadov, B., Karaman, H.S., Farzaliyev V., Sujayev A., Tas R., Alwasel S., Gulçin, İ. (2020). Novel functionally substituted esters based on sodium diethyldithiocarbamate derivatives: synthesis, characterization, biological activity and molecular docking studies. Bioorganic Chemistry, 103762. https://doi.org/10.1016/j.bioorg.2020.103762

Kaya R., Taslimi P., Naldan M.E., Gülçin I. (2019). The impacts of some sedative drugs on α-glycosidase, acetylcholinesterase and butyrylcholinesterase enzymes-potential drugs for some metabolic diseases. Letters in Drug Design & Discovery, 16(5), 592-596 https://doi.org/10.2174/1570180815666180924110023

Kaya S., Tüzün B., Kaya C., Obot I.B., (2016). Determination of corrosion inhibition effects of amino acids: quantum chemical and molecular dynamic simulation study. Journal of the Taiwan Institute of Chemical Engineers, 58, 528-535 https://doi.org/10.1016/j.jtice.2015.06.009

Kecel-Gunduz, S., Budama-Kilinc, Y., Cakir-Koc, R., Zorlu, T., Bicak, B., Kokcu, Y., Ozel A.E., Akyuz, S. (2020). In Silico design of AVP (4–5) peptide and synthesis, characterization and in vitro activity of chitosan nanoparticles. Daru Journal of Pharmaceutical Sciences, 1-19. https://doi.org/10.1007/s40199-019-00325-9

Koran K, Tekin Ç, Çalışkan E, Tekin S, Sandal S, Görgülü AO (2017) Synthesis, structural and thermal characterizations and in vitro cytotoxic activities of new cyclotriphosphazene derivatives. Phosphorus, Sulfur, and Silicon and the Related Elements 192 (9):1002-1011. https://doi:10.1080/10426507.2017.1315420

Koyunoğlu, F., Konar, V., Sandal, S. (2013). İnsan meme kanseri hücre serileri (MCF-7) üzerine apelin-13'ün etkilerinin araştırılması: In vitro bir çalışma. İnönü Üniversitesi Sağlık Bilimleri Dergisi, 1(1), 23-8.

Lipinski C.A., Lombardo F., Dominy B.W., Feeney P.J., (2001). Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings, Adv. Drug Deliv. Rev. 46, 3–26. https://doi.org/10.1016/S0169-409X(00)00129-0

Lu J.J., Crimin K., Goodwin J.T., Crivori P., Orrenius C., Xing L., Tandler P. J., Vidmar T.J., Amore B.M., Wilson A.G.E., Stouten P.F.W., Philip S. Burton Stouten P.F., (2004). Influence of molecular flexibility and polar surface area metrics on oral bioavailability in the rat. Journal of Medicinal Chemistry, 47(24), 6104-6107. https://doi.org/10.1021/jm0306529

Maharramov, A., Kaya, R., Taslimi, P., Kurbanova, M., Sadigova, A., Farzaliyev, V., Sujayev, A., & Gulçin, İ. (2019). Synthesis, crystal structure, and biological evaluation of optically active 2-amino-4-aryl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromen-3-carbonitriles: Antiepileptic, antidiabetic, and anticholinergics potentials. Archiv Der Pharmazie, 352(2), 1800317 https://doi.org/10.1002/ardp.201800317

Mamedova G., Mahmudova A., Mamedov S., Erden Y., Taslimi P., Tüzün B., Taş R., Farzaliyev V., Sujayeva A., Alwasel S.H., Gulçin İ. (2019). Novel tribenzylaminobenzolsulphonylimine based on their pyrazine and pyridazines: Synthesis, characterization, antidiabetic, anticancer, anticholinergic, and molecular docking studies. Bioorganic Chemistry, 93, 103313. https://doi.org/10.1016/j.bioorg.2019.103313

Mamedov S.A., Farzaliev M.F., Shakhgeldiev L.M., Ladokhina N.P., Fatalizade F.A., (2007). 1, 3-dipolar addition of pyridine N-imines to activated alkenes. Synthesis of pyrazolo [1,5-a] pyridines. Azerbaijan Chemical Journal, 3, 19-22.

Menteşe, E., Emirik, M., Sökmen, B. B. (2019). Design, molecular docking and synthesis of novel 5, 6-dichloro-2-methyl-1H-benzimidazole derivatives as potential urease enzyme inhibitors. Bioorganic Chemistry, 86, 151-158 . https://doi.org/10.1016/j.bioorg.2019.01.061

Mermer, A., Demirbas, N., Uslu, H., Demirbas, A., Ceylan, S., Sirin, Y. (2019). Synthesis of novel Schiff bases using green chemistry techniques; antimicrobial, antioxidant, antiurease activity screening and molecular docking studies. Journal of Molecular Structures, 1181, 412-422 https://doi.org/10.1016/j.molstruc.2018.12.114

Mermer, A., Bayrak, H., Şirin, Y., Emirik, M., Demirbaş, N. (2019). Synthesis of novel Azol-β-lactam derivatives starting from phenyl piperazine and investigation of their antiurease activity and antioxidant capacity comparing with their molecular docking studies. Journal of Molecular Structure, 1189, 279-287. https://doi.org/10.1016/j.molstruc.2019.04.039

Mohamed M.J. (2007) Bulg.Chem.Comm. 2, 52-158, *PJChem* 08.23-19O.109.

Mosmann T (1983) Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays. Journal of Immunological Methods 65, 55-63

Sağlık, B.N., Çavuşoğlu, B.K., Osmaniye, D., Levent, S., Çevik, U.A., Ilgın, S., Çevik U.A., Ilgın S., Özkay Y., Kaplancıklı Z.A., Öztürk, Y. (2019). In vitro and in silico evaluation of new thiazole compounds as monoamine oxidase inhibitors. Bioorganic Chemistry, 85, 97-108 https://doi.org/10.1016/j.bioorg.2018.12.019

Sağlık, B. N., Çevik, U. A., Osmaniye, D., Levent, S., Çavuşoğlu, B. K., Demir, Y., Ilgın S., Özkay Y., Koparal A.S., Beydemir Ş., Kaplancıklı, Z. A. (2019). Synthesis, molecular docking analysis and carbonic anhydrase I-II inhibitory evaluation of new sulfonamide derivatives. Bioorganic Chemistry, 91, 103153. https://doi.org/10.1016/j.bioorg.2019.103153

Sari, S., Barut, B., Özel, A., Kuruüzüm-Uz, A., Şöhretoğlu, D. (2019). Tyrosinase and α-glucosidase inhibitory potential of compounds isolated from *Quercus coccifera* bark: In vitro and in silico perspectives. Bioorganic Chemistry, 86, 296-304 https://doi.org/10.1016/j.bioorg.2019.02.015

Sastry, G.M., Adzhigirey, M., Day, T. (2013) Annabhimoju, R.; Sherman, W., Protein and ligand preparation: Parameters, protocols, and influence on virtual screening enrichments. Journal

of Computer-Aided Molecular Design 27(3), 221-234 https://doi.org/10.1007/s10822-013-9644-8

Sayin, K., Karakaş, D. (2018) Investigation of structural, electronic properties and docking calculations of some boron complexes with norfloxacin: A computational research. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 202, 276-283 https://doi.org/10.1016/j.saa.2018.05.055

Sayin, K., Karakaş, D. (2018) Quantum chemical investigation of levofloxacin-boron complexes: a computational approach. Journal of Molecular Structure, 1158, 57-65 https://doi.org/10.1016/j.molstruc.2018.01.016

Sayin, K., Karakaş, D. (2017) Determination of structural, spectral, electronic and biological properties of tosufloxacin boron complexes and investigation of substituent effect. Journal of Molecular Structure, 1146, 191-197. https://doi.org/10.1016/j.molstruc.2017.05.130

Sayin, K., Üngördü, A. (2019) Investigations of structural, spectral and electronic properties of enrofloxacin and boron complexes via quantum chemical calculation and molecular docking. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 220 117102. https://doi.org/10.1016/j.saa.2019.05.007

Sayin, K., Üngördü, A. (2018) Investigation of anticancer properties of caffeinated complexes via computational chemistry methods. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 193, 147-155. https://doi.org/10.1016/j.saa.2017.12.013

Schrodinger, L. (2019). Small-Molecule Drug Discovery Suite 2019-4

Schrödinger Release 2019-4: LigPrep, Schrödinger, LLC, New York, NY, 2019.

Schrödinger Release 2019-4: Protein Preparation Wizard; Epik, Schrödinger, LLC, New York, NY, 2016; Impact, Schrödinger, LLC, New York, NY, 2016; Prime, Schrödinger, LLC, New York, NY, 2019.

Schrödinger Release 2020-1: QikProp, Schrödinger, LLC, New York, NY, 2020.

Shah, U., Patel, S., Patel, M., Gandhi, K., Patel, A. (2020). Identification of chalcone derivatives as putative non-steroidal aromatase inhibitors potentially useful against breast cancer by molecular docking and ADME prediction. Indian Journal of Chemistry 59(B) 2020 283-293.

Singh, P., Bast, F. (2014). In silico molecular docking study of natural compounds on wild and mutated epidermal growth factor receptor. Medicinal Chemistry Research, 23(12), 5074-5085 https://doi.org/10.1007/s00044-014-1090-1

Song, Y. L., Tian, C. P., Wu, Y., Jiang, L. H., Shen, L. Q. (2019). Design, synthesis and antitumor activity of steroidal pyridine derivatives based on molecular docking. Steroids, 143, 53-61. https://doi.org/10.1016/j.steroids.2018.12.007

Şener, L. T., Gündüz, S. K., Şener, A., Bıçak, B., Kökcü, Y., Özel, A. E., Albeniz, I. (2019) Computerised designing of doxorubicin with breast cancer cells. İstanbul Tıp Fakültesi Dergisi, 82, 40-46.

Tao, Y., Zhang, Y., Cheng, Y., Wang, Y. (2013). Rapid screening and identification of α-glucosidase inhibitors from mulberry leaves using enzyme-immobilized magnetic beads coupled with HPLC/MS and NMR. Biomedical Chromatography, 27(2), 148-155 https://doi.org/10.1002/bmc.2761

Taslimi, P., Gulçin, İ. (2017). Antidiabetic potential: In vitro inhibition effects of some natural phenolic compounds on α-glycosidase and α-amylase enzymes. Journal of Biochemical and Molecular Toxicology, 31(10), e21956. https://doi.org/10.1002/jbt.21956

Taslimi, P., Turhan, K., Türkan, F., Karaman, H. S., Turgut, Z., Gulcin, İ. (2020). Cholinesterases, α-glycosidase, and carbonic anhydrase inhibition properties of 1H-pyrazolo [1, 2-b] phthalazine-5, 10-dione derivatives: Synthetic analogues for the treatment

of Alzheimer's disease and diabetes mellitus. Bioorganic Chemistry, 97, 103647 https://doi.org/10.1016/j.bioorg.2020.103647.

Tekin S, Erden Y, Sandal S, Yilmaz B (2015) Is irisin an anticarcinogenic peptide? Med-Science 4(2), 2172-2180. https://doi.org/10.5455/medscience.2014.03.8210.

Turkan, F., Atalar, M.N., Aras, A., Gulçin, İ. Bursal, E. (2020). ICP-MS and HPLC analyses, enzyme inhibition and antioxidant potential of *Achillea schischkinii* Sosn. Bioorganic Chemistry, 94, 103333. https://doi.org/10.1016/j.bioorg.2019.103333.

Turkan, F., Cetin, A., Taslimi, P., Karaman, H. S., GulCin, I. (2019). Synthesis, characterization, molecular docking and biological activities of novel pyrazoline derivatives. Archiv der Pharmazie, 352(6), 1800359. https://doi.org/10.1002/ardp.201800359

Tüzün, B., Investigation of pyrazoly derivatives Schiff base ligands and their metal complexes used as anti-cancer drugs. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 227, 117663 https://doi.org/10.1016/j.saa.2019.117663

Tüzün, B., Saripinar, E. (2019). Molecular docking and 4D-QSAR model of methanone derivatives by electron conformational-genetic algorithm method. Journal of the Iranian Chemical Society, 1-16 https://doi.org/10.1007/s13738-019-01835-8

Tüzün B., Kaya C., (2018). Investigation of DNA–RNA molecules for the efficiency and activity of corrosion inhibition by DFT and molecular docking. Journal of Bio-and Tribo-Corrosion, 4(4), 69 https://doi.org/10.1007/s40735-018-0185-5

Tüzün, B., Sayin, K. (2019) Investigations over optical properties of boron complexes of benzothiazolines. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 208, 48-56. https://doi.org/10.1016/j.saa.2018.09.060

Üngördü, A., Sayin, K. (2019) Quantum chemical calculations on sparfloxacin and boron complexes. Chemical Physics Letters, 733, 136677 https://doi.org/10.1016/j.cplett.2019.136677

Ye X.M., Konradi A.W., Yuan S., Aubele D.L., Dappen M., Dressen D., Garofalo A.W., Jagodzinski J.J., Latimer L., Probst G.D., Sham H.L., Wone D., Xu Y.Z., Ness D., Brigham E., Kwong G.T., Willtis C., Tonn G., Goldbach E., Quinn K.P., Zhang H.H., Sauer J.M., Bova M., Basi G.S. (2013) Bioorganic and Medicinal Chemistry Letters, 23, 996. https://doi.org/10.1016/j.bmcl.2012.12.039.

Scheme 1. The heterocyclization reaction of sulfamidopyridinimine with benzoin **(I-X)**

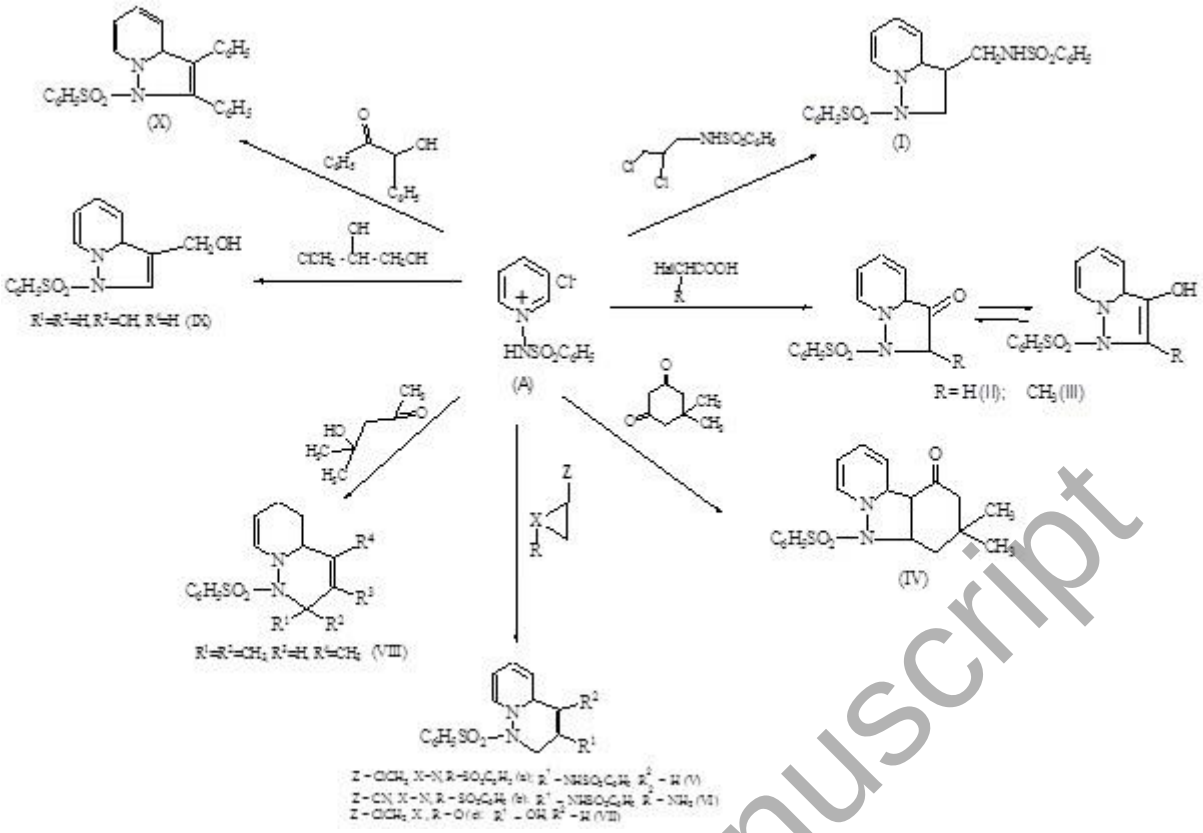

Figure 1. Determination of Ki value from Lineweaver-Burk graphs for excellent inhibitor of α-glycosidase enzyme (III or MS-54)

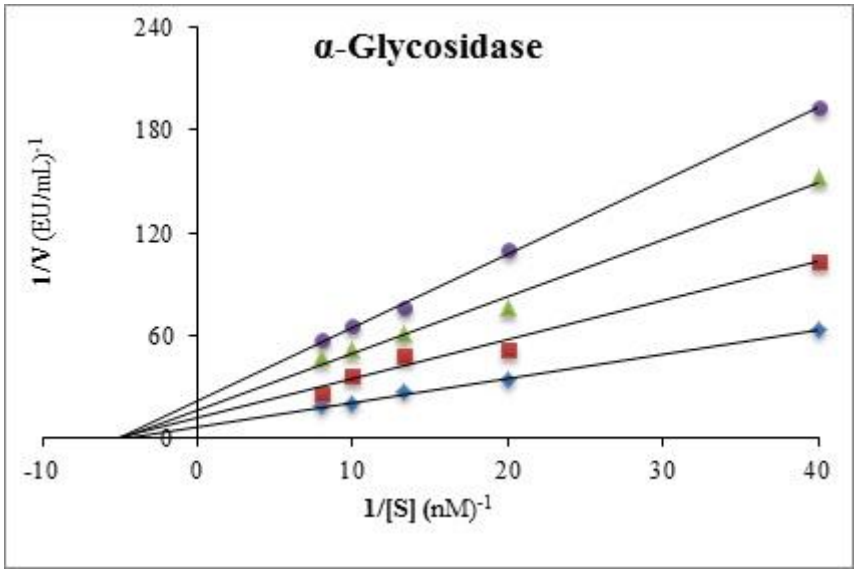

Figure 2. Effects of test compounds on PC-3 cell viability. Different concentrations of the compounds of MS50 (A), MS54 (B), MS56 (C), MS67 (D), MS72 (E), MS82 (F), MS116 (G), MS120 (H) and MS122 (I) for 24 hours PC-3 cells. No application was made to the cells in the control group. Cells in the solvent control group were treated with DMSO, which was used to prepare the same amount of compounds. Values were expressed as mean ± SD. * $p < 0.05$ compared to control group, #$p < 0.05$ compared to vehicle control group.

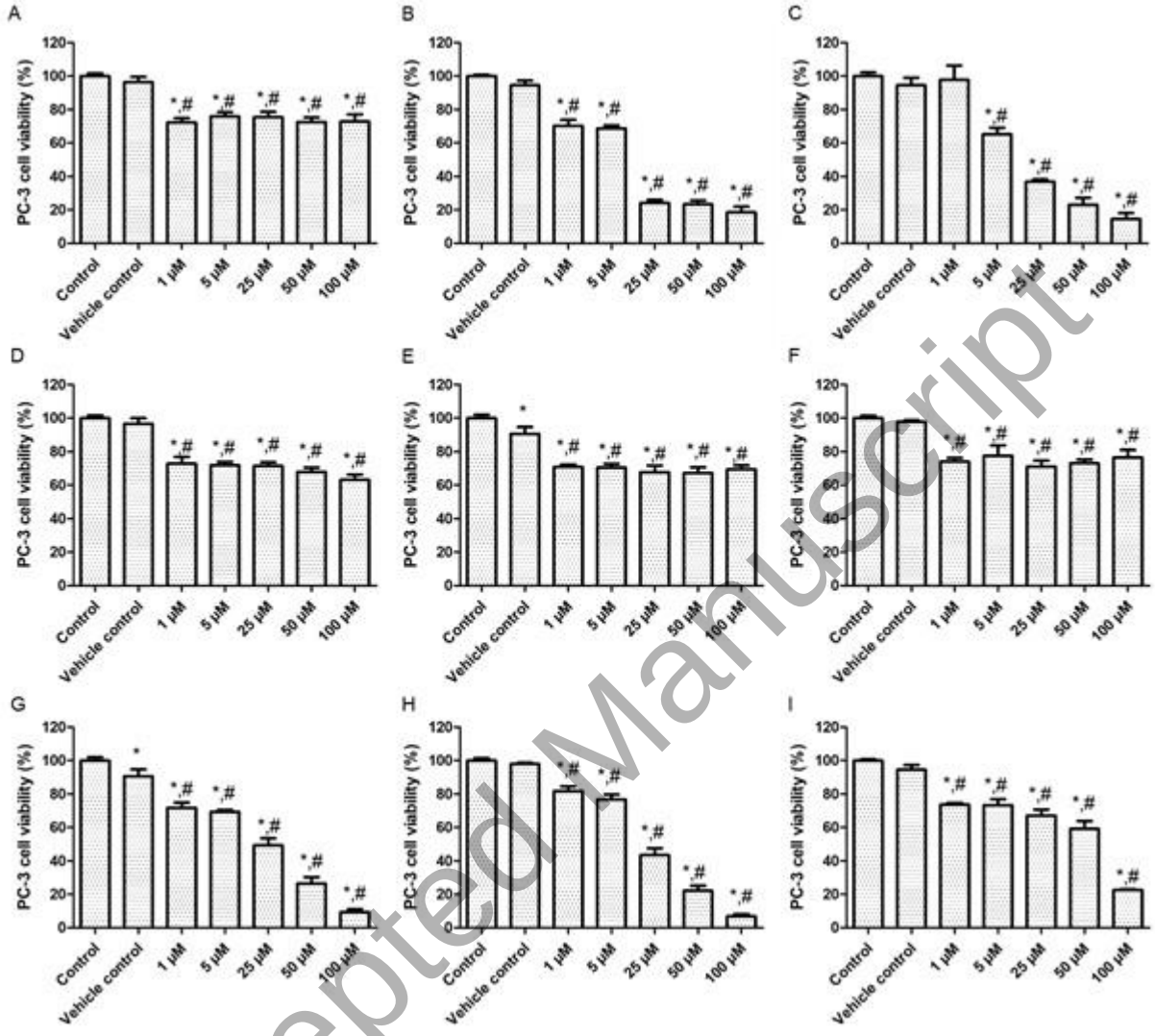

Figure 3. Effects of test compounds on MCF-7 cell viability. Different concentrations of the compounds of MS50 (A), MS54 (B), MS56 (C), MS67 (D), MS72 (E), MS82 (F), MS116 (G), MS120 (H) and MS122 (I) for 24 hours PC-3 cells. No application was made to the cells in the control group. Cells in the solvent control group were treated with DMSO, which was used to prepare the same amount of compounds. Values were expressed as mean ± SD. * p <0.05 compared to control group, #p <0.05 compared to vehicle control group

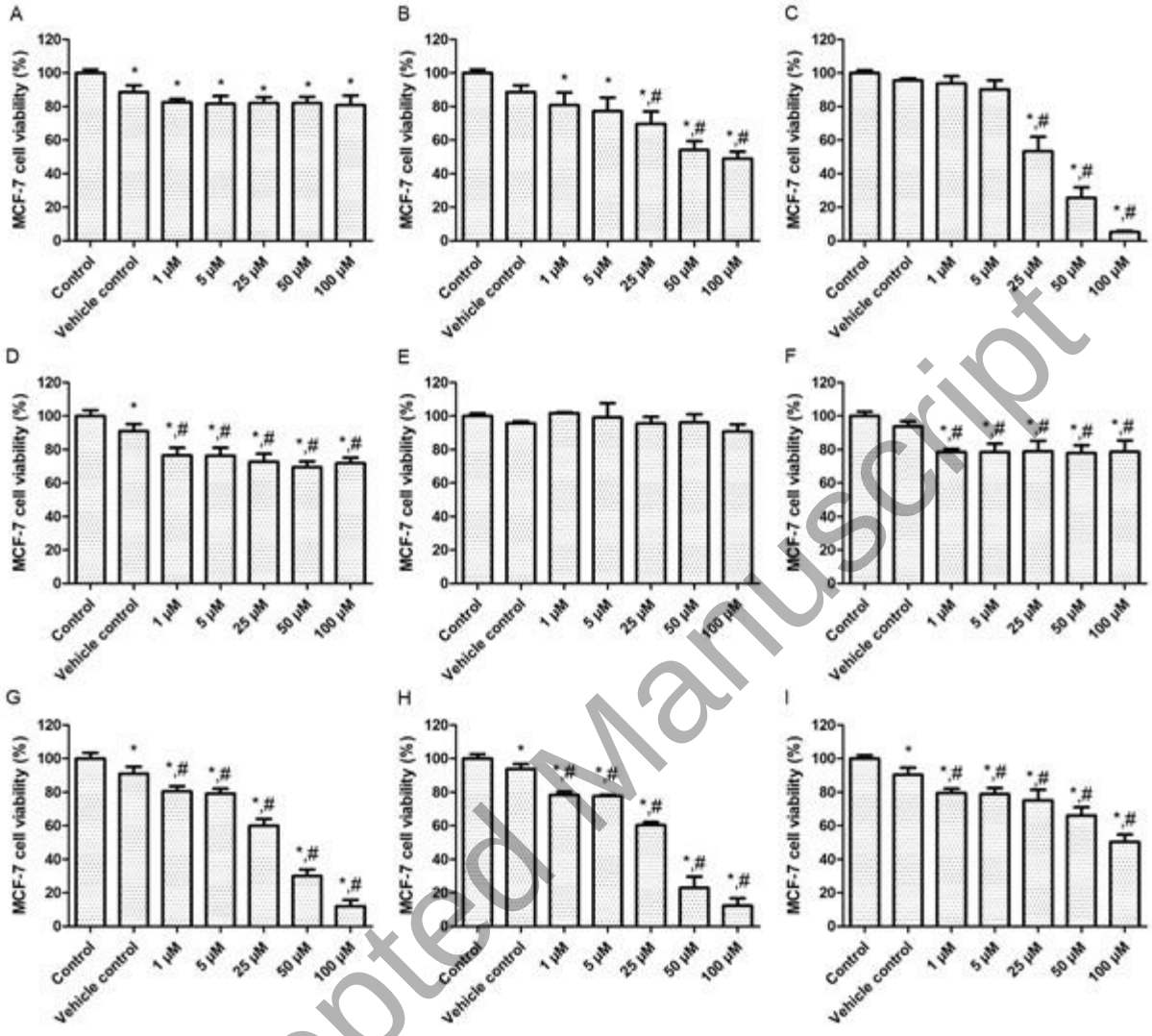

Figure 4. Interaction of molecules against α-glycosidase enzyme

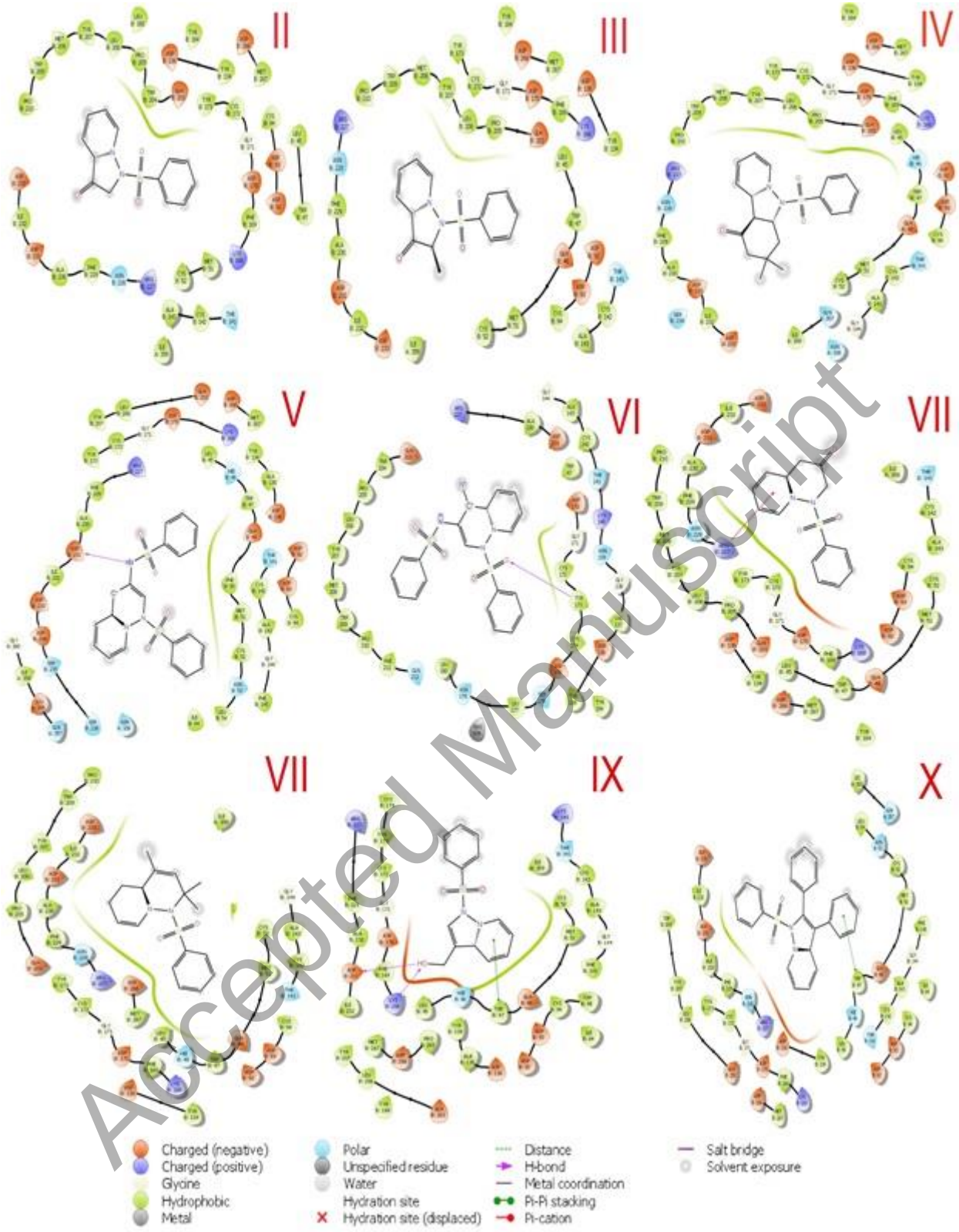

Figure 5. Interaction of molecule III with proteins of α-glycosidase enzyme

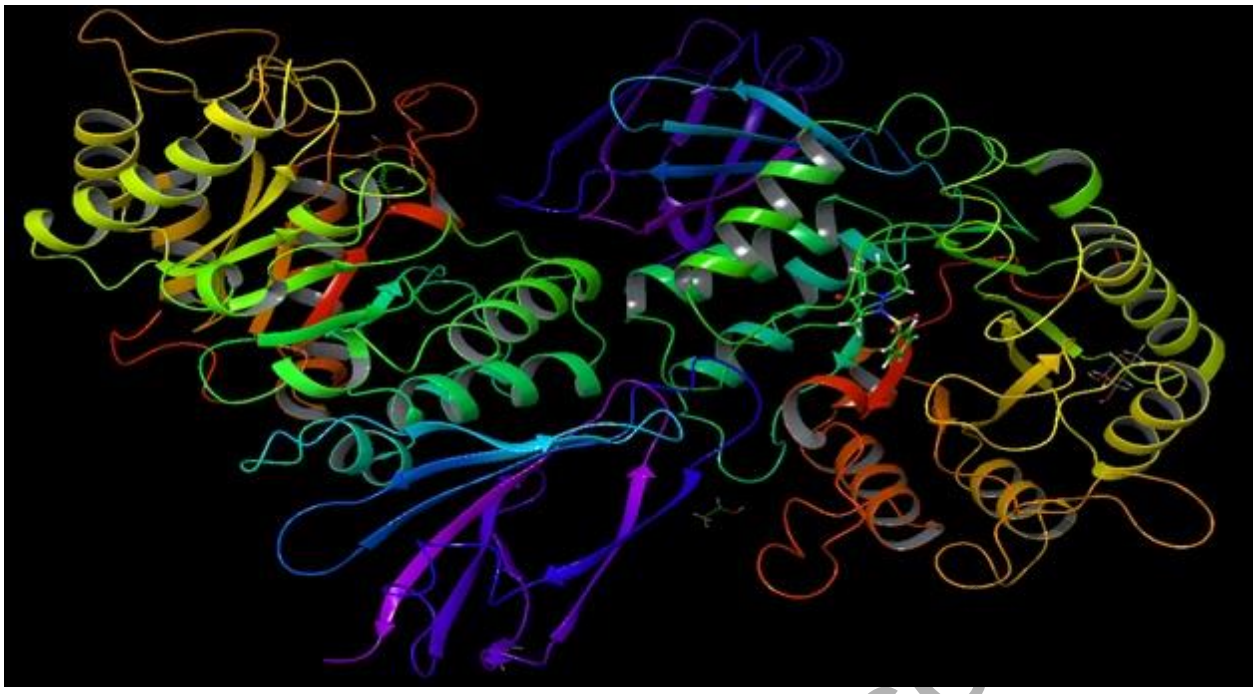

Table 1. Determination of half maximal inhibition concentration (IC_{50}, nM) and inhibition constant values (K_i, nM) of α-Glycosidase enzyme inhibition effects of 1-arylsuphonylpyrazole- or pyridazin [1,5-a]-pyridine (**II-X**) compounds

Compounds	**IC_{50} (nM)**	**r^2**	**K_i (nM)**
(II) MS-50	23.94	0.9843	26.93±3.84
(III) MS-54	11.73	0.9692	13.66±2.63
(IV) MS-56	29.24	0.9904	33.64±6.53
(V) MS-67	58.53	0.9362	60.63±12.71
(VI) MS-72	35.33	0.9599	43.78±9.62
(VII) MS-82	28.41	0.9618	32.88±8.53
(VIII) MS-116	27.04	0.9792	30.92±4.60
(IX) MS-120	40.73	0.9930	46.83±6.05
(X) MS-122	36.95	0.9638	39.68±10.53
ACR*	22800	-	12600±78

*Acarbose (ACR) was used as a control for α-glycosidase enzyme

Table 2. Molecular docking data of studies molecules for α-glycosidase

III	IV	V	VI	VII	VIII	IX	X
-4.68	-3.41	-2.70	-1.10	-3.62	-3.20	-4.14	-2.86
0.00	0.00	-0.08	0.00	0.00	0.00	-0.26	0.00
-31.62	-33.47	-33.63	-23.92	-34.02	-28.66	-34.14	-24.63
-0.16	-0.13	-0.09	-0.03	-0.18	-0.14	-0.20	-0.09

Table 3. ADME properties of molecules

	II	III	IV	V	VI	VII	VIII	IX	X	**Recommended**
Solute Molecular Weight	276	290	358	-	442	290	318	290	412	130-725
Solute Dipole Moment (D)	6.0	6.4	6.3	-	7.5	7.0	6.5	5.4	5.9	1.0-12.5
Solute Total SASA	487	500	582	-	657	495	535	517	637	300.0-1000.0
Solute Hydrophobic SASA	47	80	180	-	2	77	251	59	10	0.0-750.0
Solute Hydrophilic SASA	110	98	101	-	150	123	55	111	58	7.0-330.0
Solute Carbon Pi SASA	32.85	32.20	30.15	-	50.36	29.52	22.86	34.64	57.01	0.0-450.0
Solute Weakly Polar SASA	0.60	0.00	0.00	-	0.43	0.00	0.44	0.42	0.38	0.0-175.0
Solute Molecular Volume (A^3)	837	875	1080	-	1217	878	994	889	1204	500.0-2000.0
Solute CdW Polar SA (PSA)	72	67	71	-	113	71	36	66	42	7.0-200.0
Solute as Donor-Hydrogen Bonds	0.00	0.00	0.00	-	2.00	0.00	0.00	1.00	0.00	0.0-6.0
Solute as Acceptor-Hydrogen	8.5	8.5	8.5	-	11.5	8.0	6.0	8.1	6.5	2.0-20.0
Solute Globularity (Sphere =1)	0.88	0.88	0.87	-	0.83	0.89	0.89	0.86	0.85	0.75-0.95
Solute Ionization Potential (eV)	8.5	8.5	8.3	-	8.4	8.3	8.0	8.2	8.3	7.9-10.5
Solute Electron Affinity (eV)	1.0	0.9	0.9	-	1.3	1.1	0.8	0.8	0.8	-0.9-1.7
Predictions for Properties										
QP Polarizability (Angtroms ^3)	29	30	38	-	43	30	34	30	46	13.0-70.0
QP log p for hexadecane/gas	9.1	9.4	11.1	-	14.5	9.4	9.6	9.9	13.8	4.0-18.0
QP log p for octanol/gas	14.8	15.3	17.9	-	24.6	15.2	14.9	16.2	19.6	8.0-35.0
QP log p for water/gas	11.8	11.7	11.7	-	18.6	11.1	8.4	12.7	11.4	4.0-45.0
QP log p for octanol/water	0.24	0.56	1.85	-	1.68	0.62	2.75	1.20	4.25	-2.0-6.5
QP log S aqueous solubility	-0.67	-0.92	-2.48	-	-3.34	-1.09	-2.90	-2.26	-4.59	-6.5-0.5
QP log S-conformation independent	-1.7	-2.0	-3.4	-	-4.8	-2.2	-3.7	-2.7	-6.3	-6.5-0.5
QP log K has Serum protein Binding	-1.3	-1.1	-0.6	-	-0.4	-1.0	-0.1	-0.6	-0.2	-1.5-1.5
QP log BB for brain/blood	-0.5	-0.3	-0.4	-	-1.2	-0.5	-0.0	-0.6	-0.0	-3.0-1.2
No. of Primary Metabolites	2	2	3	-	2	3	3	2	1	1.0-8.0
Predicted CNS Activity (-- to ++)										
HERG K+ Channel blockage: log IC_{50}	-5.0	-4.9	-5.0	-	-6.5	-4.6	-4.2	-5.3	-6.5	(corcern below -5)
Apparent Caco-2 Permeability (nm/sec)	891	1157	1087	-	369	670	2968	870	2783	*
Apparent MDCK Permeability (nm/sec)	440	579	541	-	169	321	1611	427	1502	*

QP log Kp for skin Permeability Jm	-2.2	-2.0	-2.1	-	-1.9	-2.5	-1.5	-1.9	-0.3	Kp in cm/hr
Lipinski Rule of 5 Violations	0	0	0	-	0	0	0	0	0	Maximum is 4
Jorgensen Rule of 3 Violations	0	0	0	-	0	0	0	0	0	Maximum is 3
% Human Oral Absorption in GI (+-20%)	3	3	3	-	3	3	3	3	3	<25% is poor
Qual. Model for Human Oral Absorption	81	85	92	-	82	81	100	86	100	>80% is high