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In silico investigation of novel 5-benzylidene-2-(arylsulfonylhydrazono)thiazolidine-4-ones as potential inhibitors of mPGES-1 and COX-2

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ABSTRACT: Studies on the development of safe anti-inflammatory agents targeting the inhibition of the mPGES-1 enzyme responsible for PGE_2 production are increasing day by day. Moreover, selective inhibition of the mPGES-1 enzyme which modulates the tumor microenvironment and inhibits tumor growth, making the mPGES-1 enzyme one of the important macromolecular targets in cancer therapy. The aim of our study was to develop selective mPGES-1 inhibitors and to determine their *in silico* mPGES-1 enzyme inhibition potential. In this study, the binding affinities of 14 novel designed 5-benzylidene-2-(arylsulfonylhydrazono)thiazolidine-4-one derivatives were investigated against mPGES-1 and COX-2 enzymes by computer-aided molecular modeling studies. Among the designed compounds **1-14**, it was presented with *in silico* data that compound **8-14**, which does not interact with the active site of the COX-2 enzyme, exhibited selective binding with mPGES-1 enzyme. Moreover, compounds **10-13** have been suggested as selective mPGES-1 inhibitors with a better *in silico* binding energy than the first discovered mPGES-1 inhibitor MK886. Finally, ADMET profiles of compounds **1-14** were calculated. None of these compounds violated the Lipinski and Veber rules.

KEYWORDS: 4-Thiazolidinone; mPGES-1; COX-2; *in silico*; ADMET.

1. INTRODUCTION

The mechanism of action of NSAIDs has been revealed as controlling inflammatory reactions in which prostacyclin and prostaglandins play a role by inhibiting cyclooxygenase [1]. The cardiovascular and gastrointestinal side effects associated with the use of NSAIDs restrict the use of these drugs in the treatment of inflammation. Therefore, the medical need for alternative drugs continues. Prostaglandins (PG), members of the eicosanoid family, are lipid mediators that are not stored by cells. Because they are produced by almost all cells in the body, they play a role in many biological events. Two important pathways that play a role in the synthesis of prostaglandins primarily from arachidonic acid occur via cyclooxygenase (COX) and lipoxygenase (LOX) enzymes [2]. Although the COX-1 and COX-2 enzymes in human cells perform basically the same catalytic reaction, they differ in terms of their location of release, function and structure [3]. Synthesis of prostaglandins occurs structurally or in response to trauma, stimulus or signaling molecules in cells, by the action of COX enzymes.

PGE_2 is the most abundant prostanoid in the human body and acts as an important bioactive mediator for physiological and pathological events such as inflammation, pain, fever, cancer and neurological diseases by activating prostanoid receptors, which are effective in the modulation of various pathways that conduct cellular proliferation, apoptosis and inflammation [4,5]. There are three isoforms of PGE_2 synthases: microsomal PGES-1 (mPGES-1), microsomal PGES-2 (mPGES-2) and cytosolic PGES (cPGES). Excess PGE_2 synthesized by COX-2 and mPGES-1 enzymes has a role in the development of vascular inflammatory diseases [6]. However, while selective COX-2 inhibitors (coccibs) provide a potent anti-inflammatory and analgesic effect without the side effects caused by non-selective COX inhibitors, long-term use of these agents can lead to cardiovascular side effects [7]. Since inhibition of the mPGES-1 enzyme does not block PGI_2 production, selective mPGES-1 inhibitors are not expected to cause cardiovascular side effects [8–10].

mPGES-1 is a membrane-bound, 16 kDa microsomal enzyme from the MAPEG family, consisting of 152 amino acids [11]. Although many potent inhibitors from various chemotypes have been developed

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following the discovery of the mPGES-1 enzyme in 1999, most of them have only SAR analyzes reported, whereas in vivo inhibition studies of the mPGES-1 enzyme are limited to a small number of molecules [12]. Although the first discovered mPGES-1 inhibitor MK-886 (1-[(4-chlorophenyl)methyl]-3-[(1,1-dimethylethyl)thio]-α,α-dimethyl-5-(1-methylethyl)-1*H*-indole-2-propanoic acid) [13] is used as a reference molecule in enzyme inhibition studies, it has not found a place in the clinic. The development of selective, potent and orally administered inhibitors has been continuing for many years [14–20]. There is no mPGES-1 inhibitor approved by the FDA yet. Expression of mPGES-1 enzyme is increased in the presence of inflammation. The design of selective new mPGES-1 inhibitors as anticancer [21–23] and anti-inflammatory [24] agents aiming to block PGE_2 production by inhibiting the mPGES-1 enzyme remains up-to-date [25].

Many methods are given in the literature for synthetic access to 4-thiazolidinone compounds. Some of the prominent methods are as follows:

- Treatment of thiosemicarbazides [26,27] or thiosemicarbazone [28] derivatives in ethanol with ethyl bromoacetate in the presence of sodium acetate.
- Treatment of 2-chloroacetamides with ammonium thiocyanate in a suitable solvent [29,30].
- Treatment of thioureas with chloroacetylchloride or chloroacetic acid in suitable solvent in the presence of TEA or sodium acetate [31,32].

According to the previous reports in the literature, reaction of 2-imino-1,3-thiazolidin-4-ones with substituted arylaldehydes could give their corresponding 5-arylmethylene derivatives in several catalyst and solvent combinations, such as ethanol-piperidine [31], sodium acetate-anhydrous acetic acid [33], sodium acetate-ethanol [34], and sodium methoxide-ethanol [35–38].

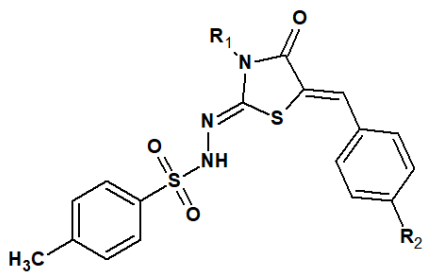
So far, antiviral [39], antibacterial [40], antimycobacterial [26,27], anticancer [41], anti-inflammatory [42], antihypertensive-antiarrhythmic [34], HCV-NS5B inhibitory [36] and mPGES-1 inhibitory [43,44] effects have been reported for 5-arylidene-1,3-thiazolidin-4-one derivatives, which are target structures.

2. RESULTS and DISCUSSION

2.1. Molecular docking studies

To prevent the overexpression of PGE_2, which causes by COX-2 and mPGES-1 enzymes is among the current strategies in the treatment of cancer and inflammation. However, many studies have been reported for the development of selective mPGES-1 inhibitors in recent years due to the cardiovascular side effects of long-term use of COX-2 inhibitors. In this study, the interactions of the designed compounds with the both the mPGES-1 and COX-2 enzymes were evaluated with *in silico* studies to examined their selectivity profiles. The binding energies of 14 new 5-(arylmethylene)-2-imino-1,3-thiazolidinone derivatives against mPGES-1 and COX-2 enzymes are given in Table 1. MK886 and celecoxib were used as reference compounds.

Table 1. Binding energies of compounds **1-14** to active site of both mPGES-1 and COX-2.

Designed structure	Compound	R_1	R_2	mPGES-1	COX-2
	1	-H	-H	-5.3	-11.3
	2	-H	-OH	-6.1	-12.2
	3	-H	-F	-6.3	-12.7
	4	-H	-Cl	-6.4	-12.5
	5	-H	$-OCH_3$	-6.4	-11.6
	6	-H	$-OCF_3$	-6.6	-11.8
	7	-H	$-N(CH_3)_2$	-6.1	-9.9
	8	$-CH_3$	-H	-6.1	n.i[b].
	9	$-CH_3$	-OH	-6.2	n.i.
	10	$-CH_3$	-F	-6.4	n.i.
	11	$-CH_3$	-Cl	-6.5	n.i.
	12	$-CH_3$	$-OCH_3$	-6.4	n.i.
	13	$-CH_3$	$-OCF_3$	-6.3	n.i.
	14	$-CH_3$	$-N(CH_3)_2$	-5.9	n.i.
	MK886[a]			-6.2	
	Celecoxib				-12.0

[a] First discovered mPGES-1 inhibitor [13].
[b] n.i.: no interaction observed.

mPGES-1, which is responsible for the conversion of PGH_2 to PGE_2, uses glutathione as a cofactor for this conversion. Glutathione exhibits hydrogen bonding interactions with ARG 38, ARG73, ASN74,

GLU77, HIS113, TYR117, ARG126 and SER127 residues besides hydrophobic interaction with TYR130. In molecular modeling studies, a grid box containing both substrate and cofactor binding site was chosen. Previously reported studies indicate that the U-shaped structure of a potential inhibitor is important for the binding to the enzyme [45]. Therefore, compounds **1-14** containing two exocyclic double bonds were prepared in (2Z,5Z) conformation for docking studies. This conformation also has similar to conformation of the selective COX-2 inhibitor celecoxib. These designed compounds have exhibited similar and even higher (-5.3 kcal/mol to -6.5 kcal/mol) binding energies than the reference compound MK886 (ΔG= -6.2 kcal/mol) against mPGES-1 enzyme. As seen in Figure 1a, all of the designed compounds were located at the glutathione binding site. Therefore, it has been thought that our compounds inhibited the mPGES-1 enzyme competitively with the cofactor.

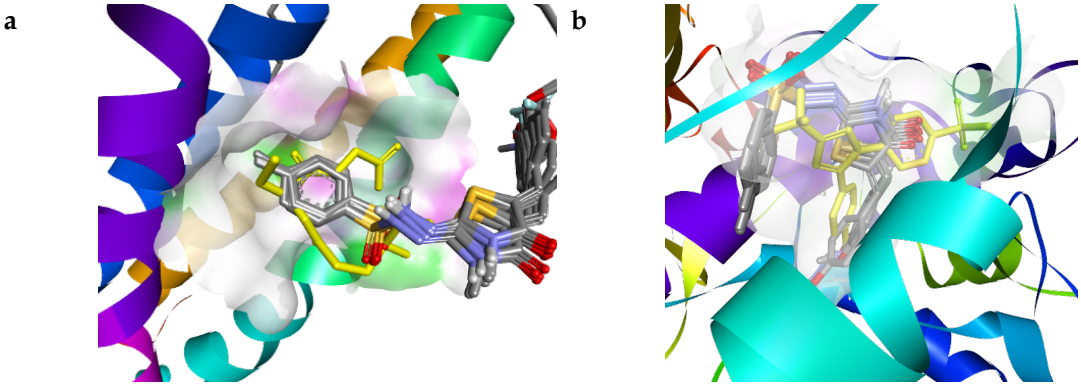


Figure 1. a) Binding poses of compounds **1-14** in mPGES-1 active site, b) Binding poses of compounds **1-7** in COX-2 active site.

As seen in Figure 1b, compounds **1-7** have located as like as the celecoxib in the active site of the COX-2 enzyme. However, no interaction was found between the active site of the COX-2 enzyme and the compounds **8-14** bearing the methyl group at the 3rd position of the thiazolidinone ring. Compound **3** (ΔG= -12.7 kcal/mol) was observed to have a higher binding energy than the reference compound celecoxib (ΔG= -12.07 kcal/mol). The active site interactions of compound **3** were given Figure 2. There are two hydrogen bonds interaction that the hydrozono nitrogen (-N=) in the 2nd position of the thiazolidinone ring with TYR341 residue and the sulfonyl group (SO_2) with ARG106 residue, besides various hydrophobic interactions. It is noteworthy that the substitution of the 3rd position of the thiazolidinone ring with the methyl group sterically prevents the hydrozono (-N=) group in the 2nd position of the ring from approaching the active site. Therefore, compounds **8-14** could not enter the active site of COX-2 enzyme. These data have shown that compounds **8-14** might be selective inhibitors of mPGES-1.

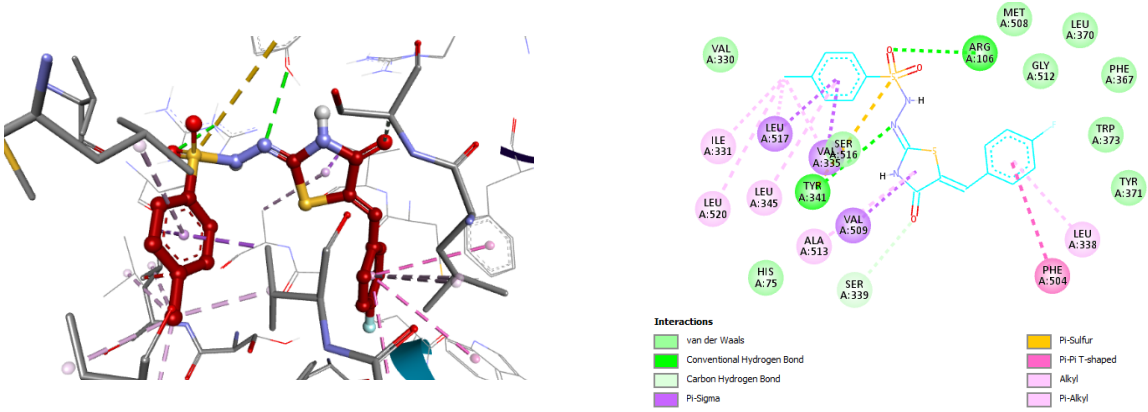


Figure 2. Interactions of compound **3** with COX-2 enzyme as 3D and 2D diagrams

The 3D diagram of the interactions of compounds **8-14** with the active site of the mPGES-1 enzyme is given in Figure 3. As all designed compounds, it was observed that compound **8-14** which

exhibited selective mPGES-1 enzyme inhibition, provides a U-shape location in the active site of the relevant enzyme.

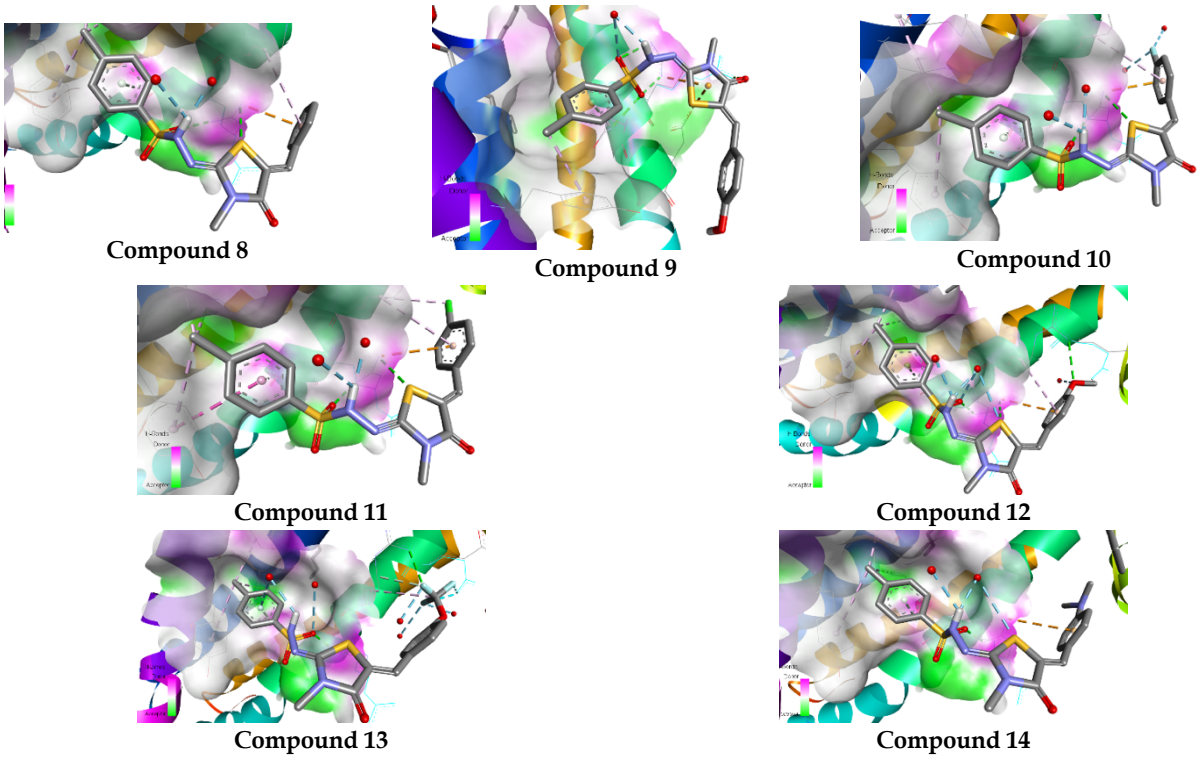
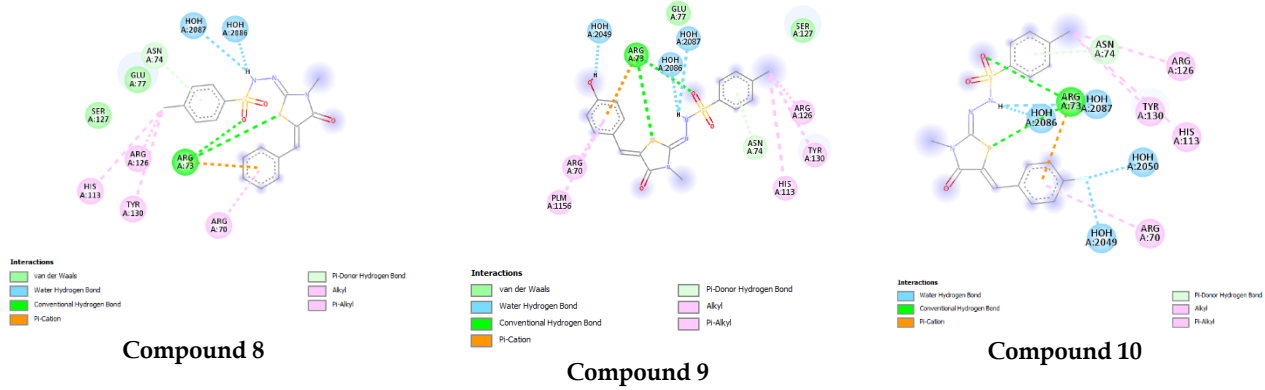
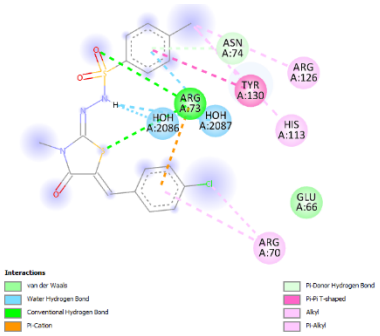


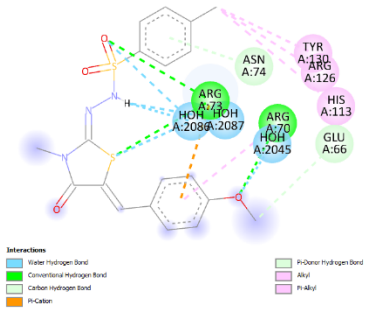
Figure 3. 3D Diagram of interactions of compounds **8-14** with mPGES-1 enzyme.

The hydrogen bond interactions of both the thiazolidinone ring and the sulfahydrozono group of the compounds **8-14** with the ARG73 were given in Figure 4. In addition, pi-cation interactions were observed between the ARG73 and the phenyl ring of the aryl methylidene group. It was also determined that the p-toluenesulfonyl group increases the affinity by exhibiting hydrophobic interaction between methyl moiety and HIS113, ARG126, TYR130 residues.

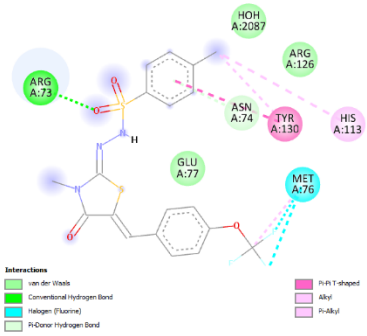




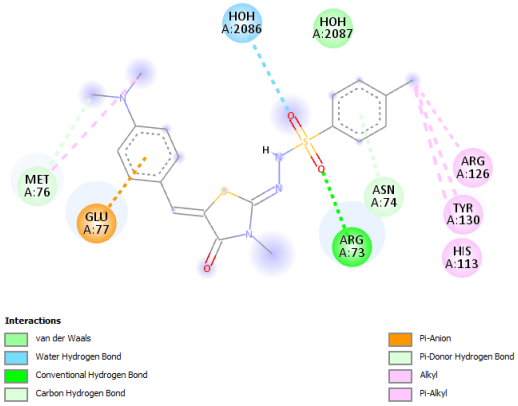
Compound 11



Compound 12



Compound 13



Compound 14

Figure 4. 2D Diagram of interactions of compounds **8-14** with mPGES-1 enzyme.

For the designed compounds, the substitution of the 3rd position of the thiazolidinone ring reveals the selectivity against the mPGES-1 enzyme, while the substitution of the benzylidene ring is a modification that determines the affinity for the mPGES-1 enzyme. Active site interactions of compounds **10-12** with the highest mPGES-1 binding energy are given in Table 2.

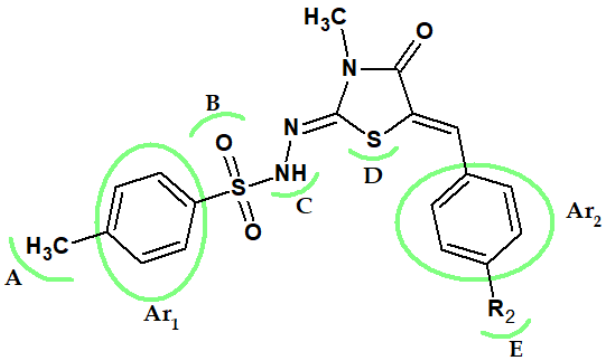


Table 2. Interactions of compounds **10-12** with mPGES-1 active site.

Compound	Binding enery (kcal/mol)	R_2	H-Bond Interactions			Other Interactions		
			Group	Residue	Distance (Å)	Group	Residue (Interaction)	Distance (Å)
10	*-6.4*	*-F*	*B*	*ARG73*	*2.83*	*A*	*His113 (pi-alkyl)*	*4,77*
			D	*ARG73*	*3.63*	*A*	*Arg126 (alkyl)*	*4,40*
			R_2	*HOH2049*	*3.39*	*A*	*Tyr130 (pi-alkyl)*	*4,58*
			R_2	*HOH2050*	*2.65*	*Ar_2*	*Arg70 (pi-alkyl)*	*5.10*
			C	*HOH2086*	*2.02*	*Ar_2*	*Arg73 (pi-cation)*	*3.84*
			C	*HOH2087*	*2.62*			
11	*-6.5*	*-Cl*	*B*	*ARG73*	*2.83*	*A*	*His113 (pi-alkyl)*	*4,74*
			D	*ARG73*	*3.63*	*A*	*Arg126 (alkyl)*	*4,40*
			C	*HOH2086*	*2.02*	*A*	*Tyr130 (pi-alkyl)*	*4,56*
			C	*HOH2087*	*2.62*	*Ar_2*	*Arg70 (pi-alkyl)*	*5.04*
						Ar_2	*Arg73 (pi-cation)*	*4.21*
12	*-6.4*	*-OCH_3*	*R_2*	*ARG70*	*3.17*	*A*	*His113 (pi-alkyl)*	*4,93*
			B	*ARG73*	*2.80*	*A*	*Arg126 (alkyl)*	*4,55*
			D	*ARG73*	*3.78*	*A*	*Tyr130 (pi-alkyl)*	*4,45*
			R_2	*HOH2045*	*2.77*	*Ar_2*	*Arg70 (pi-alkyl)*	*5.07*
			B	*HOH2086*	*3.36*	*Ar_2*	*Arg73 (pi-cation)*	*4.21*
			D	*HOH2086*	*3.41*			
			C	*HOH2086*	*2.11*			
			C	*HOH2087*	*2.36*			

2.2. *In silico* ADMET predictions

Because the physicochemical properties of a drug affect the pharmacokinetic and metabolic profile of that drug in the body, the predicted physicochemical properties of compounds **1-14** were calculated using SwissADME (http://www.swissadme.ch/) (Table 3). In this study, we used consensus LogP, which is an average of the predictions of five different methods which atomistic, knowledge-based, topological, in-house physics-based, hybrid piecemeal methods. Our designed compounds **1-14** exhibited moderate water solubility according to LogS calculated by estimating aqueous solubility from the molecular structure. We determined that all designed compounds had LogP values less than 5. Additionally, it was observed that number of hydrogen acceptors≤8, number of hydrogen donors≤3, number of rotatable bonds≤6 for these compounds. As result of this, it was found that compounds **1-14** do not violate any of the rule by Lipinski [2] and Veber [3]. Finally, % ABS of our designed compounds were calculated in the range of 60.17-70.13%.

Tablo 3. Solubility and molecular descriptors of compounds **1-14** from SwissADME.

Compound	MW (g/mol)	$LogP_{o/w}$	LogS (ESOL)	nON	nOHN	nRot	TPSA	%ABS	Lipinski Rule nviol	Veber's Rule nviol
1	373.45	2.66	-4.58	4	2	4	121.31	67.15	0	0
2	389.45	2.66	-4.58	5	3	4	141.54	60.17	0	0
3	391.44	2.66	-4.58	5	2	4	121.31	67.15	0	0
4	407.89	2.66	-4.58	4	2	4	121.31	67.15	0	0
5	403.48	2.66	-4.58	5	2	5	130.54	63.96	0	0
6	457.45	3.60	-5.65	8	2	6	130.54	63.96	0	0
7	416.52	2.72	-4.82	4	2	5	124.55	66.03	0	0
8	387.48	2.72	-4.82	4	1	4	112.52	70.18	0	0
9	403.48	2.72	-4.82	5	2	4	132.75	63.20	0	0
10	405.47	2.72	-4.82	5	1	4	112.52	70.18	0	0
11	421.92	2.72	-4.82	4	1	4	112.52	70.18	0	0
12	417.50	2.72	-4.82	5	1	5	121.75	67.00	0	0
13	471.47	2.72	-4.82	8	1	6	121.75	67.00	0	0
14	430.54	2.72	-4.82	4	1	5	115.76	69.06	0	0

MW: Molecular weight; LogPo/w: Consensus; LogS (ESOL): Estimating aqueous solubility from molecular structure; nON: Number of hydrogen acceptors; nOHN: Number of hydrogen donors; nRot: Number of rotatable bonds; TPSA:Topological polar surface area; %ABS: Percentage of absorption was estimated using the equation: %ABS=109-(0.345xTPSA), according to Zhao et al.

In this study, we used SwissADME web server for boiled egg plot denotes shown in Figure 5. As none of the compounds **1-14** are located in the yellow region, which indicates effective brain penetration with positive intestinal absorption, it is predicted that these compounds will not cross the blood-brain barrier. While most of the designed compounds exhibited good intestinal absorption by being located in the white region, compounds **2**, **6** and **13** have exhibited poor intestinal absorption (located in the gray region). Finally, none of these compounds are potential substrates of P-glycoprotein according to prediction studies.

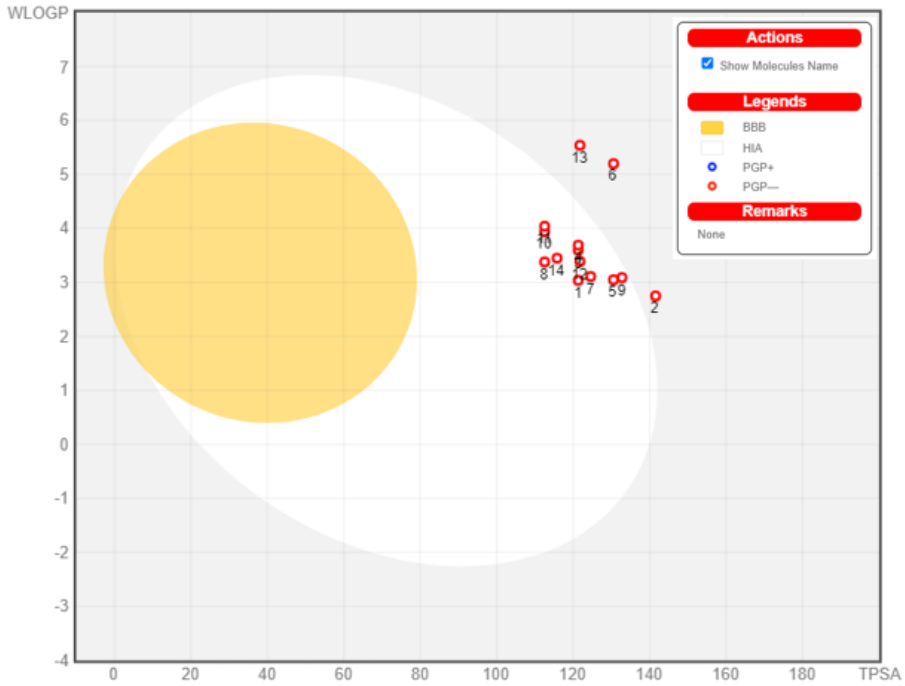


Figure 5. Graphical distribution of compounds **1-14** according to the boiled egg predictive model.

3. CONCLUSION

This study includes the design of safer and selective mPGES-1 enzyme inhibitors, the evaluation of their *in silico* enzyme inhibition potentials and ADMET profiles. The affinities of 14 novel 5-benzylidene-2-(arylsulfonylhydrazono)thiazolidine-4-ones (**1-14**) against both mPGES-1 and COX-2 enzymes were investigated using AutodockVina program. It has been determined that all of these compounds are located

in the cofactor binding site of the mPGES-1 enzyme and can competitively inhibit the enzyme with glutathione. However, it was determined that compounds **8-14** were not located at the binding site of the COX-2 enzyme. Compounds **8-14** have a methyl substitution at the 3rd position of the thiazolidinone ring. It was concluded that the aforementioned methyl group obstructed the observed interaction between the sulfonylhydrozono structure and the TYR341 amino acid for compounds **1-7** at the active site of the COX-2 enzyme, thus causing selective mPGES-1 enzyme inhibition. The substitution of the benzylidene group in the 5th position of the thiazolidinone ring was decisive in the binding energy values of the designed compounds to the active site of the mPGES-1 enzyme. Compounds **10-13** were identified as selective mPGES-1 inhibitors by exhibiting better binding energy than reference compound MK885. Finally, drug-like properties were calculated for all the designed compounds and it was observed that they were in compliance with the Lipinski and Veber rules. The synthesis of the compounds determined by *in silico* studies and the investigation of their *in vitro* effects are suggested as the subject of future research.

4. MATERIALS AND METHODS

4.1. Molecular docking studies

AutodockVina [46], an open-license soft-ware developed by Scripps Research Institute, was used in molecular modeling studies of the designed compounds with mPGES-1 and COX-2 enzymes.

4.1.1. Preparation of the 3D structure of the mPGES-1 enzyme

The crystal structure of the mPGES-1 enzyme (pdb code: 4AL0) [5] was obtained from the protein database. The water molecules in the crystal structure whose interaction with the active site was not detected were removed. Octyl beta-*D*-glucopyranoside and palmitic acid that entered the structure during crystallization were removed, too. After removing glutathione, which is the cofactor of the enzyme, the enzyme was protonated using the AutoDock Tools [47] program and made ready for docking studies by making energy minimization.

4.1.2. Preparation of the 3D structure of the COX-2 enzyme

The structure of COX-2 (PDB code:3LN1, resolution:2.4 Å) [48] were obtained from the protein data bank. The target enzyme was cleaned by removing the water molecules and cocrystallized inhibitors celecoxib. The charge of the Fe atom in each enzyme was set to +2 manually. Then, this enzyme was protonated using the AutoDock Tools [47] program and made ready for docking studies by making energy minimization.

*4.1.3. Preparation of 3D structures of compounds **1-14** (for docking studies)*

The conformations of target 5-arylidene-1,3-thiazolidin-4-ones were scanned by the semi-experimental PM3 method using the Spartan4 quantum chemistry program (SPARTAN 04, Wavefunction, Inc., Irvine, USA). The most stable (*2Z,5Z*) conformation each compound was selected and their structures were saved in pdb format. Subsequently, compounds **1-14** were converted to pdbqt format by using AutodockTools program [47].

4.1.4. Molecular docking studies and analysis of results

During the docking studies, AutoDock Vina soft-ware (http://autodock.scripps.edu) was used for flexible ligand in rigid protein. The Vina parameter "exhaustiveness" was set to the value of 10, besides a grid spacing of 0.375 Å was employed for the calculation of the energetic map of both enzymes. The grid box size was determined as 24 Å × 20 Å × 18 Å and center_x= 10.304, center_y= -11.033, center_z= -8.384 dimensions were used in mPGES-1 enzyme (4AL0) docking studies. The grid box size of COX-2 (3LN1) was determined as 40 Å × 40 Å × 40 Å center_x (30.518), center_y (-21.298), and center_z (-16.69), appropriate to the position of co-crystallized ligand. The docking results files were analyzed using BIOVIA Discovery Studio Visualizer program (https://discover.3ds.com/).

4.2. *In silico* ADMET studies

SwissADME web server [49] were used for evoluation of the solubility properties and structural descriptors of the novel 5-(aryl methylene)-2-imino-1,3-thiazolidin-4-ones, compounds **1-14**. To evaluate the compliance of the target compounds to the Lipinski rule, their LogP's, molecular weights, and the number of hydrogen bond acceptors/transmitters were determined, while their compliance with Veber's rule was determined by calculating the number of rotatable bonds and the topological polar surface areas of compounds **1-14**. Moreover, %ABS and water solubility profiles of these compounds were examined, too.

Author contributions: Concept – N.K.; Design – N.K.; Analysis and Interpretation – N.K; Literature Search – N.K; Writing – N.K.

Conflict of interest statement: The author declared no conflict of interest.

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