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Investigation of the Usability of Some Triazole Derivative Compounds as Drug Active Ingredients by ADME and Molecular Docking Properties

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Abstract

In this study, some important ADME parameters such as physicochemical properties, lipophilicity, water solubility, pharmacokinetics, medicinal chemistry and drug-likeness properties of ten triazole derivative compounds, which may be drug active ingredients, were performed on the SwissADME a web tool worked on-line. Bioavailability radar plotted for each molecule for rapid assessment of drug-likeness. The BOILED-Egg graph was plotted for each molecule to assess passive gastrointestinal absorption (HIA) and brain penetration (BBB) relative to the position of the molecules. SwissTargetPrediction a web tool worked on-line was used to predict the most likely protein targets of molecules. Docking programs have a wide range of applications ranging from computer aided to drug design. Molecules were docked with the determined target protein using the SwissDock a web tool worked on-line.

Keywords: *SwissADME, Physicochemical properties, Docking, Triazole derivatives.*

1. Introduction

Heterocyclic chemistry is a very interesting and valuable area, and heterocycles are by far the most common kind of organic chemistry. Synthetic organic chemists, in particular, have made significant progress in identifying and producing a diverse spectrum of heterocyclic molecules for the benefit of mankind. Triazole is a five-membered heterocyclic ring with three nitrogen atoms at positions 1,2, and 4. It's a lot more basic aromatic chemical that'll dissolve in any organic solvent [1]. More than 0.2 million triazole derivatives, particularly 1,2,4-triazole derivatives, have been described in the literature, and this class of organic compounds has grown in importance due to its diverse chemical and biological characteristics [2-4].The 1,2,4-triazole derivatives have very important pharmacological activities such as antiviral and antifungal properties [5]. The examples of drug for antifungal are fluconazole [6, 7], itraconazole [8], ravuconazole [9], voriconazole [10-12] and posaconazole [13]. Also, diverse 1,2,4-triazole derivatives are reported as insecticides [14], antiasthmatics [15], anticonvulsants [16], antidepressants [17], anti-inflammatory [18], insecticidal [19] and plant growth regulators [20]. Furthermore, molecules having triazole fragments, such as vorozole, letrozole, and anastrozole are found to be very effective aromatase inhibitors, which could prevent nipple cancer [21-23]. Actually, there are a number of drugs, which contain 1,2,4-triazole nucleus viz., triazolam [24], alprazolam [25], etizolam [26] and furacylin [27]. Numerous sulfur containing heterocycles are pretty encouraging with a few practical applications. Besides, the thione and mercapto substituted 1,2,4-triazole derivatives have antibacterial [28-31], antifungal [32-34], antitubercular [35], antimycobacterial [36], anticancer [37, 38], diuretic [39, 40] and hypoglycemic [41] properties. Computational chemistry is a rapidly growing field of study that touches on everything from tiny molecules to macromolecules and nanostructures, the gas phase to the solid state, and stationary points to molecular dynamics. Many studies have shown that computational approaches may be used to investigate the processes and structures of organic, inorganic, and biological systems [42-47]. We break it down into five main directions that describe the different steps involved in solving chemical problems with computational tools. These five main items are the choice of computational method, structure calculation, descriptor calculation, analysis and visualization. These are shown in Fig. 1.

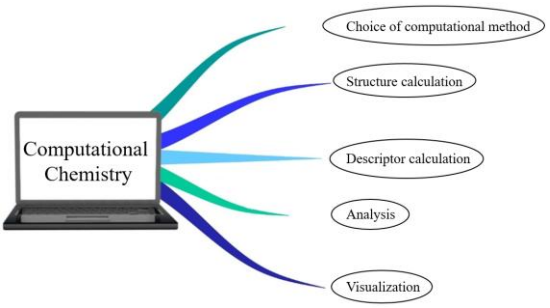


Figure 1. Figurative representation of the five main section involving computational chemistry [48].

SwissADME is a free web application that may be used to assess pharmacokinetics based on several drug-likeness factors such as physicochemical qualities, solubility, and pharmacokinetics [49]. SwissTargetPrediction is an online tool that has been available on the internet since 2014 and seeks to forecast the most likely protein targets for small compounds. Reverse screening is used to make predictions based on the similarity principle [50]. SwissDock is a web server dedicated to doing straightforward and elegant protein-ligand docking simulations. SwissDock is based on the EADock DSS (dihedral space sampling) protein-ligand docking technology and features a simple and integrated interface [51].

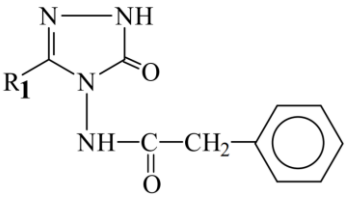
2. Materials and methods

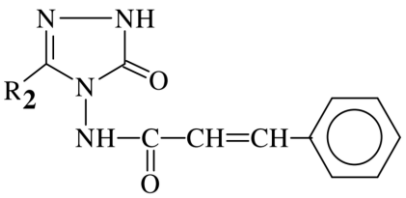
2.1. Studied molecules

Ten different triazole derivative compounds (**(1)** 3-methyl-4-phenylacetylamino-4,5-dihydro-1H-1,2,4-triazol-5-one, **(2)** 3-ethyl-4-phenylacetylamino-4,5-dihydro-1H-1,2,4-triazol-5-one, **(3)** 3-benzyl-4-phenyl acetylamino-4,5-dihydro-1H-1,2,4-triazol-5-one, **(4)** 3-(p-methylbenzyl) -4-phenylacetylamino-4,5-dihydro-1H-1,2,4-triazol-5-one, **(5)** 3-(p-chlorobenzyl)-4-phenyl acetylamino-4,5-dihydro-1H-1,2,4-triazol-5-one, **(6)** 3-methyl-4-cinnamoylamino-4,5-dihydro-1H-1,2,4-triazol-5-one, **(7)** 3-ethyl-4-cinnamoylamino-4,5-dihydro-1H-1,2,4-triazol-5-one, **(8)** 3-benzyl-4-cinnamoylamino-4,5-dihydro-1H-1,2,4-triazol-5-one, **(9)** 3-(p-methylbenzyl)-4-cinnamoylamino-4,5-dihydro-1H-1,2,4-triazol5-one, **(10)** 3-(p-chlorobenzyl)-4-cinnamoylamino-4,5-dihydro-1H-1,2,4-triazol5-one), which we synthesized before and registered in the literatüre [52, 53], were selected for this study. The molecular formulas of these ten different triazole derivative compounds that we examined in this study are given in Table 1.

Table 1. Molecular formulas of studied triazole derivative compounds

Group		**Molecule**
R_1	R_2	
1	6	$-CH_3$
2	7	$-CH_2CH_3$
3	8	$-CH_2C_6H_5$
4	9	$-CH_2C_6H_4CH_3$ *(-p)*
5	10	$-CH_2C_6H_4Cl$ *(-p)*





Pharmacokinetics is a branch of science that studies the movement of drugs in the body over time. The effects of drugs on biological systems are defined as ADME through four basic mechanisms, namely absorption, distribution, metabolism (biotransformation) and elimination. These mechanisms cover the time from the moment substances taken into the body are taken into the body to the moment they are removed from the body. First, the drug is absorbed from the application lacation and transferred to the plasma. Secondly, the drug leaves the blood circulation reversibly and passes into the intercellular and intracellular fluid, In other words, it is the distribution of the substance taken into the body to other parts of the body. The third mechanism is the metabolism of the drug by the liver, kidneys and other tissues. In this process, it involves the transformation of the chemical substance taken into the body into new chemical substances (metabolites). In the fourth mechanism, drugs or metabolites are excreted by the body in various ways. In this process, many parameters of the active molecule can be determined by physicochemical calculations. These parameters help determine the properties of the drug, such as route of administration, dose and dose intervals. The fact that physicochemical calculations for ADME studies can be done electronically constitutes the starting point for laboratory studies. With ADME studies in electronic environment, parameters such as molecular weight, lipophilicity and degree of ionization of the molecule can be determined. These determined properties allow us to better understand the behavior of the molecule in the cell membrane. By performing ADME studies in electronic environment, many parameters can be reached about a molecule in the pharmacokinetic phase.

2.1. Brain or intestinal estimated permeation

In this study, the BOILED-Egg (Brain or Intestinal Estimated permeation) graph was first created for ten molecules using the SwissADME a web tool. The BOILED-Egg allows for intuitive evaluation of passive gastrointestinal

absorption (HIA) and blood-brain penetration (BBB) in function of the position of the molecules in the WLOGP (a purely atomistic method based on Wildman and Crippen's [54] piecewise system of the octanol-water distribution coefficient (log P) used as a measure of lipophilicity)-versus-TPSA (topological polar surface area) referential in the SwissADME a web tool [49]. The white region is for high possibility of passive absorption by the gastrointestinal tract, and the yellow region is for high possibility of brain diffusion. Yellow and white regions are not mutually exclusive. In this graph drawn the points are painted in blue if foreboded as actively effluxed by P-gp (PGP+) and in red if foreboded as non-substrate of P-gp (PGP−). The BOILED-Egg graph for the ten molecules studied is given in Fig. 2.

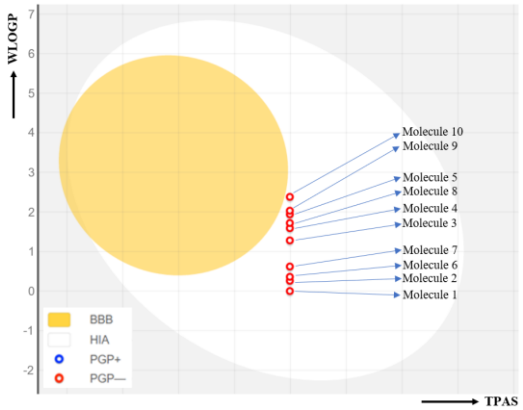
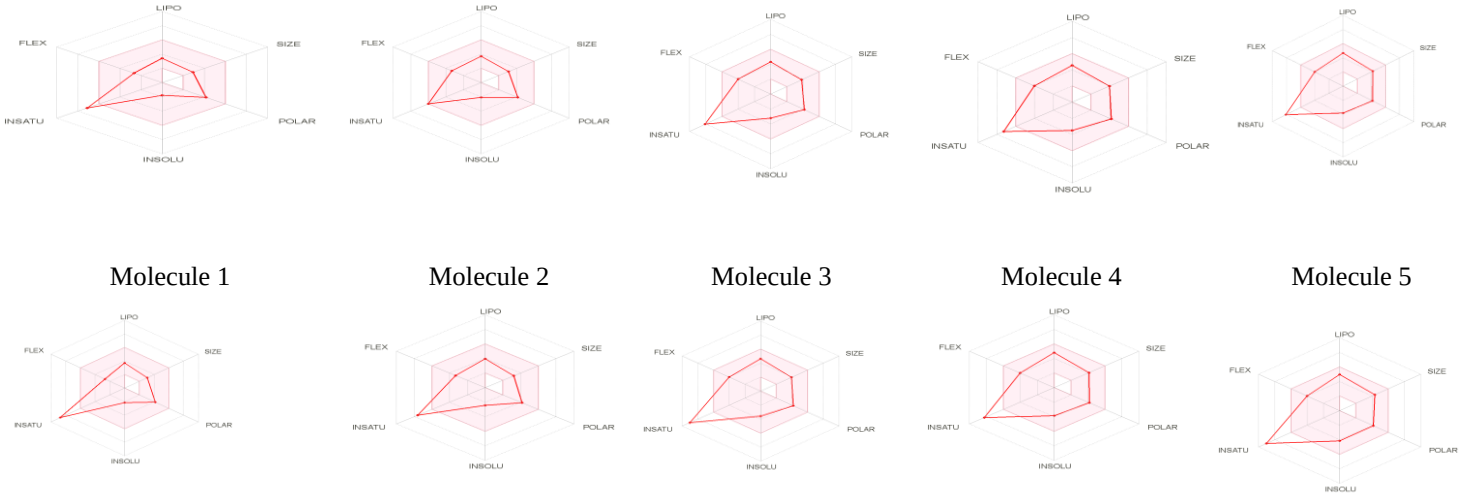


Figure 2. The BOILED-Egg graph for molecules

2.2. Bioavailability radar

Bioavailability Radar is displayed for a rapid evaluation of drug-likeness. Six hysicochemical properties are considered in the Bioavailability Radar. These properties are lipophilicity, size, polarity, solubility, flexibility and saturation. For the molecule to be a drug-like compound, the Bioavailability Radar graph must be contained within a pink area. If the graph is in this pink area, it can be defined as a drug-like compound for the molecule. Bioavailability Radar graphs of molecules drawn with the help of the SwissADME a web tool are given in Fig. 3.



Molecule 1 Molecule 2 Molecule 3 Molecule 4 Molecule 5

Molecule 6 Molecule 7 Molecule 8 Molecule 9 Molecule 10

Figure 3. Bioavailability Radar graphs of molecules

2.3. Physicochemical properties

Simple molecular and physicochemical descriptors like molecular weight (MW, g/mol), molecular refractivity (MR), number of heavy atoms, number of aromatic heavy atoms, fraction Csp3, number of rotatable bonds, number of H-bond acceptors, number of H-bond donors, topological polar surface area, (TPSA, Å2) are collected in this section. The polar surface area is calculated using the fragmental technique called topological polar surface area (TPSA), thinking sulfur and phosphorus as polar atoms [55]. This has approved a useful descriptor in many models and rules to quickly prediction some ADME properties, exclusively with regards to biological barrier crossing such as absorption and brain access [56]. The Physicochemical Properties of the molecules are given in Table 2.

Physicochemical	**Molecule**									
Properties	1	2	3	4	5	6	7	8	9	10
Formula	$C_{11}H_{12}N_4O_2$	$C_{12}H_{14}N_4O_2$	$C_{17}H_{16}N_4O_2$	$C_{18}H_{18}N_4O_2$	$C_{17}H_{15}ClN_4O_2$	$C_{12}H_{12}N_4O_2$	$C_{13}H_{14}N_4O_2$	$C_{18}H_{16}N_4O_2$	$C_{19}H_{18}N_4O_2$	$C_{18}H_{15}ClN_4O_2$
Molecular weight (g/mol)	232.24	246.27	308.33	322.36	342.78	244.25	258.28	320.35	334.37	354.79
Number of heavy atoms	17	18	23	24	24	18	19	24	25	25
Number of aromatic heavy atoms	11	11	17	17	17	11	11	17	17	17
Fraction Csp3	0.18	0.25	0.12	0.17	0.12	0.08	0.15	0.06	0.11	0.06
Number of rotatable bonds	4	5	6	6	6	4	5	6	6	6
Number of H-bond acceptors	3	3	3	3	3	3	3	3	3	3
Number of H-bond donors	2	2	2	2	2	2	2	2	2	2
Molar refractivity	62.35	67.16	86.84	91.80	91.85	67.48	72.28	91.96	96.93	96.97
TPSA ($Å^2$)	79.78	79.78	79.78	79.78	79.78	79.78	79.78	79.78	79.78	79.78

Table 2. Physicochemical properties of the molecules

2.4. Lipophilicity

Lipophilicity is defined as the partition coefficient (log Po/w) between n-octanol and water. Pharmacokinetics has a special section in SwissADME due to the critical importance of the Lipophilicity physicochemical property for drug discovery. Many computational techniques for log Po/w prediction were developed with various performance on diffrerent chemical sets. In general, it is the use of multiple estimators to choose the most accurate methods for a particular batch of chemicals or to generate a consensus estimate. Consensus models should be as diverse as possible to increase the prediction accuracy of logPo/w. SwissADME allows access to five predictive models that are used free of charge. These are iLOGP [57], XLOGP3 [58], WLOGP [54], MLOGP [59, 60] and SILICOS-IT (version 1.0.2, 2013, http://silicos-it.be.s3-website-eu-west-1.amazonaws.com/software/filter-it/1.0.2/filter-it.html). Finally, the arithmetic average of these five different values is taken and given as Consensus log Po/w. The Lipophilicity of the molecules are given in Table 3.

Table 3. Lipophilicity properties of the molecules

Lipophilicity	**Molecule**

	1	2	3	4	5	6	7	8	9	10
Log $P_{o/w}$ (iLOGP)	1.25	1.39	1.57	1.92	2.00	1.44	1.55	2.04	2.34	2.21
Log $P_{o/w}$ (XLOGP3)	0.48	0.95	2.08	2.44	2.70	0.97	1.44	2.57	2.93	3.19
Log $P_{o/w}$ (WLOGP)	0.00	0.26	1.28	1.59	1.94	0.36	0.62	1.65	1.95	2.30
Log $P_{o/w}$ (MLOGP)	1.23	1.92	2.97	3.21	3.48	1.43	2.11	3.14	3.37	3.64
Log $P_{o/w}$ (SILICOS-IT)	0.99	1.35	2.44	2.95	3.08	1.17	1.53	2.64	3.15	3.28
Consensus Log $P_{o/w}$	0.79	1.17	2.07	2.42	2.64	1.07	1.45	2.41	2.75	2.92

2.5. Water solubility

The water solubility of the molecule facilitates usability, formulation and many drug development activities. If the drug is to be taken orally, water solubility is a very important property that affects absorption.

Table 4. Water solubility of the molecules

Water	**Molecule**									
Solubility	1	2	3	4	5	6	7	8	9	10
Log *S* (ESOL)	-1.80	-2.09	-3.21	-3.50	-3.79	-2.15	-2.45	-3.57	-3.87	-4.16
Solubility (mg/mL)	3.71	2.01	$1.89.10^{-1}$	$1.01.10^{-1}$	$5.50.10^{-2}$	1.71	$9.23.10^{-1}$	$8.55.10^{-2}$	$4.55.10^{-2}$	$2.47.10^{-2}$
Solubility (mol/L)	$1.60.10^{-2}$	$8.17.10^{-3}$	$6.12.10^{-4}$	$3.13.10^{-4}$	$1.61.10^{-4}$	$7.02.10^{-3}$	$3.57.10^{-3}$	$2.67.10^{-4}$	$1.36.10^{-4}$	$6.97.10^{-5}$
Class	Very soluble	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble	Moderately soluble
Log *S* (Ali)	-1.72	-2.21	-3.38	-3.76	-4.03	-2.23	-2.72	-3.89	-4.27	-4.54
Solubility (mg/mL)	4.38	1.51	$1.27.10^{-1}$	$5.62.10^{-2}$	$3.21.10^{-2}$	1.43	$4.91.10^{-1}$	$4.09.10^{-2}$	$1.81.10^{-2}$	$1.03.10^{-2}$
Solubility (mol/L)	$1.89.10^{-2}$	$6.13.10^{-3}$	$4.12.10^{-4}$	$1.74.10^{-4}$	$9.37.10^{-5}$	$5.85.10^{-3}$	$1.90.10^{-3}$	$1.28.10^{-4}$	$5.41.10^{-5}$	$2.91.10^{-5}$
Class	Very soluble	Soluble	Soluble	Soluble	Moderately soluble	Soluble	Soluble	Soluble	Moderately soluble	Moderately soluble
Log *S* (SILICOS-IT)	-3.26	-3.67	-5.77	-6.15	-6.37	-2.95	-3.35	-5.45	-5.83	-6.05
Solubility (mg/mL)	$1.27.10^{-1}$	$5.33.10^{-2}$	$5.19.10^{-4}$	$2.26.10^{-4}$	$1.46.10^{-4}$	$2.77.10^{-1}$	$1.16.10^{-1}$	$1.13.10^{-3}$	$4.92.10^{-4}$	$3.18.10^{-4}$
Solubility (mol/L)	$5.47.10^{-4}$	$2.16.10^{-4}$	$1.68.10^{-6}$	$7.01.10^{-7}$	$4.27.10^{-7}$	$1.13.10^{-3}$	$4.49.10^{-4}$	$3.52.10^{-6}$	$1.47.10^{-6}$	$8.97.10^{-7}$
Class	Soluble	Soluble	Moderately soluble	Poorly soluble	Poorly soluble	Soluble	Soluble	Moderately soluble	Moderately soluble	Poorly soluble

The dosage of a drug intended for parenteral use must be highly soluble in water to provide an adequate amount of the active ingredient in its small volume. Water Solubility is examined according to three different methods in

SwissADME. The first one is an implementation of the ESOL model [61], the second one is adapted from Ali et al. [62] and third predictor was developed by SILICOS-IT. Water solubility of the molecules are given in Table 4. In the table, water solubility is given in three different classes (solubility (mg/mL), solubility (mol/L) and class).

2.6. Pharmacokinetics

Pharmacokinetics is a sub-branch of pharmacology that examines processes such as absorption, distribution, transformation and excretion of drugs into the body by establishing mathematical models. Pharmacokinetics generally consists of four main parts: absorption, distribution metabolism and elimination. Here, it is aimed to estimate the skin permeability coefficient (Kp) as a multiple linear regression model. Kp has a linear relationship with molecular size and lipophilicity. A negative value of Log Kp means that the molecule has less skin permeability. Predictions of passive human gastrointestinal absorption (HIA) and blood-brain barrier (BBB) permeation are both included in this section. The information about compounds being substrate or non-substrate of the permeability glycoprotein is key to evaluate active efflux through biological membranes. It has been proposed that cytochrome P450 (CYP is a protein superfamily consisting of enzymes that function as monooxygenases and contain hemes as cofactors) and glycoprotein (P-gp, the general definition used for organic molecules composed of sugars and amino acids. Many molecules found in living organisms are glycoproteins. In addition, proteins and carbohydrates form glycoproteins) can process small molecules synergistically to develop conservation of organisms and tissues. It is estimated that 50% to 90% of therapeutic molecules are substrates of five major isoforms (CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4) [63, 64]. Data on gastrointestinal absorption, BBB permeant, p-glycoprotein substrate, CYP1A2 inhibitor, CYP2C19 inhibitor, CYP2C9 inhibitor, CYP2D6 inhibitor, CYP3A4 inhibitor and Log Kp (skin permeation, cm/s) evaluated within pharmacokinetics properties are given in Table 5.

Table 5. Pharmacokinetics properties of the molecules

Pharmacokinetics properties	**Molecule**									
	1	2	3	4	5	6	7	8	9	10
Gatrointestinal absorption	High	High	High	High	High	High	High	High	High	High
BBB permeant	No	No	No	No	No	No	No	No	No	No
P-glycoprotein substrate	No	No	No	No	No	No	No	No	No	No
CYP1A2 inhibitor	No	No	No	No	Yes	No	No	No	No	No
CYP2C19 inhibitor	Yes	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes
CYP2C9 inhibitor	No	No	No	No	No	No	No	No	No	No
CYP2D6 inhibitor	No	No	No	No	No	No	No	No	No	No
CYP3A4 inhibitor	No	No	No	No	No	No	No	No	No	No
Log *Kp* (skin permeation, cm/s)	-6.20	-7.13	-6.70	-6.53	-6.47	-7.10	-6.85	-6.43	-6.26	-6.20

2.7. Drug-likeness

Drug similarity qualitatively evaluates the chance of a molecule becoming an oral drug in terms of bioavailability. Drug-likeness consists of structural or physicochemical examinations of compounds advanced enough to be

considered oral drug candidates. The SwissADME web tool provides access to five different rule-based filters with various property ranges where the molecule is defined as drug-like. These filters usually consist of analyzes of major pharmaceutical companies aimed at improving the quality of their range of proprietary chemicals. The Lipinski (Pfizer), Ghose (Amgen), Veber (GlaxoSmithKline), Egan (Pharmacia) and Muegge (Bayer) methods were adapted from refs [65-69] respectively. The Bioavailability score, predicts the percentage of drug molecule that might reach the systemic circulation. The Bioavailability score, predicts the percentage of drug molecule that might reach the systemic circulation and Druglikeness data of the studied molecules are given in Table 6.

Table 6. Druglikeness properties of the molecules

Druglikeness properties	**Molecule**									
	1	2	3	4	5	6	7	8	9	10
Lipinski	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ghose	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Veber	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Egan	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Muegge	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bioavailability score	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55

2.8. Medicinal chemistry

Two complementary pattern recognition methods allow for the detection of potentially hazardous parts. PAINS (Pan Assay Interference Structures) are substructured chemicals that respond strongly in tests independent of the protein target. PAINS are chemicals that frequently provide false positive findings in high-throughput screening. PAINS have a tendency to respond nonspecifically with a variety of biological targets rather than impacting a single target. Many PAINS have a number of disruptive functional groupings in common. Furthermore, Structural Alert is used, which is a list of 105 fragments recognized by Brenk et al. [70] as potentially hazardous, chemically reactive, metabolically unstable, or possessing characteristics that cause poor pharmacokinetics.

Table 7. Medicinal chemistry properties of the molecules

Medicinal chemistry properties	**Molecule**									
	1	2	3	4	5	6	7	8	9	10
PAINS (Pan Assay Interference Structures)	0	0	0	0	0	0	0	0	0	0
Structural Alert (Brenk)	0	0	0	0	0	1	1	1	1	1
Leadlikeness	No	No	Yes	Yes	Yes	No	Yes	Yes	Yes	No
Synthetic accessibility score	2.22	2.55	2.96	3.07	2.96	2.57	2.81	3.18	3.29	3.16

2.9. Molecular docking studies

One of the most often utilized computational methodologies in computer-aided drug creation is protein-ligand docking simulations. Protein-ligand docking simulations offer the ability to identify ligands for a particular protein target. Because thousands of candidate ligands can be docked against a protein target, such data could speed up drug design and development. This process is known as virtual screening. We used the SwissDock program in this study. Firstly,

we predicted which target protein (homo sapiens) the molecule would interact with using the SwissTargetPrediction program. We have done docking work with the target we determined from here. Then, we calculated the full fitness (kcal/mol) and estimated ΔG (kcal/mol) values. All the values we found are given in Table 8.

Table 8. Docking results for studied molecules

Molecule	Protein	Gene	Full Fitness (kcal/mol)	Estimated ΔG (kcal/mol)
1	Threonine-protein kinase 2	LRRK2	-2054.47	-7.54
2	Hepatocyte growth factor receptor	MET	-1034,33	-6,85
3	Muscarinic acetylchlorine receptor M1	CHRM1	-1769,92	-8,56
4	Proteinase-activated receptor 2	F2RL1	-2973,94	-8,13
5	Melatonin receptor type 1A	MTNR1A	-1648,47	-8,45
6	Serine/threonine-protein kinase CHK1	CHEK1	-1906,69	-7,51
7	Hepatocyte growth factor receptor	MET	-1038,51	-6,77
8	Adenosine receptor A1	ADORA1	-1938,20	-8,30
9	Glycogen synthase kinase-3 beta	GSK3B	-3759,90	-8,59
10	Poly [ADP-ribose] polymerase 1	PARP1	-1718,33	-8,42

3. Result and Discussion

3.1. BOILED-Egg

In the Brain or Intestinal Estimated Permeation (BOILED-Egg) graph, TPSA (topological polar surface area) values found in x coordinate and the WLOGP values used to compare the lipophilicity in the y coordinate. The WLOGP used here is the calculated form of the logarithm of the partition coefficient of the molecule between octanol and water, and TPSA is the calculated area of the surface covered by polar groups. BOILED-Egg graph, the yellow area represents the transition to the blood-brain barrier, and the white area represents the absorption in the gastrointestinal system. The red dot represents the molecule when interpreting the BOILED-Egg graph. If the red dot remains in the outermost gray area, this molecule is not absorbed by the gastrointestinal system and therefore it cannot cross the blood-brain barrier. The presence of the red dot in the white area indicates that its absorption in the gastrointestinal system is high, but it means that the molecule cannot pass through the blood-brain barrier. If the red dot is in the yellow region, it means that the absorption of this molecule in the gastrointestinal system is high and it can easily pass through the blood-brain barrier. Accordingly, when the graph given in Fig. 2 is examined, it is seen that all molecules are absorbed by the gastrointestinal system, but not all molecules can pass through the blood-brain barrier. Especially molecules 10, 9 and 5 seem to be getting very close to passing through the brain barrier. The addition of various functional groups to the structures of these molecules can be accomplished by synthesis and these molecules can be allowed to pass through the blood-brain barrier. In this way, new active drug molecules can be introduced.

3.2. Bioavailability radar

Bioavailability Radar was created using six different features. These properties are LIPO-lipophilicity, SIZE-molecular weight, POLAR-polarity, INSOLU-solubility, INSATU-saturation and FLEX-flexibility. In order for the molecule to be a drug candidate, it is interpreted by looking at whether the graph line falls within the pink area or not.

If the graph line is completely within the pink area, it means that it can be considered as a drug candidate. When the Bioavailability Radars given in Fig. 3 for ten molecules are examined, it is seen that molecule 2 fits the description and the entire graphic line is in the pink area. We can consider this molecule as a drug candidate. Molecules 1, 4 and 7 are close to being considered as drug candidates, but there is a slight deviation from the red area at the point of insaturation feature. By adding new functional groups to the structures of these molecules, the graph line can be completely drawn into the pink area.

3.3. Physicochemical properties

In this case, nine different parameters were examined. These are molecular weight (g/mol), number of heavy atoms, number of aromatic heavy atoms, fraction Csp3, number of rotatable bonds, number of H-bond acceptors, number of H-bond donors, molar refractivity and TPSA ($Å^2$). We made the evaluation according to the Lipinski rule-of-five. Accordingly, when we examine the data in Table 2, it is seen that the molecular weights are in the range of 150 – 500 g/mol in all compounds. Number of heavy atoms is found in at least molecule 1 with 17 atoms, and at most molecule 9 and molecule 10 with 25 atoms. Number of aromatic heavy atoms is found in the molecule 1, 2, 6 and 7 with at least with 11 atoms, and at the most in the molecule 3, 4, 5, 8, 9 and 10 with 17 atoms. Fraction Csp3 should be at least 0.25 and only molecule 2 provides this value. Number of rotatable bonds should be no more than 9. All of the molecules appear to have a value below this number (4 - 6). Number of H-bond acceptors must be ≤ 5 and number of H-bond donors must be ≤ 10. All of the molecules have the number of H-bond acceptors and H-bond donors below these values. It is seen that the molar refractivity value takes values between 62.35 – 96.97 in all molecules. Finally, TPSA ($Å^2$) values are required to be between 20 and 130 $Å^2$. All molecules appear to be within this range. Graphs related to Physicochemical properties are given in Fig. 4-5.

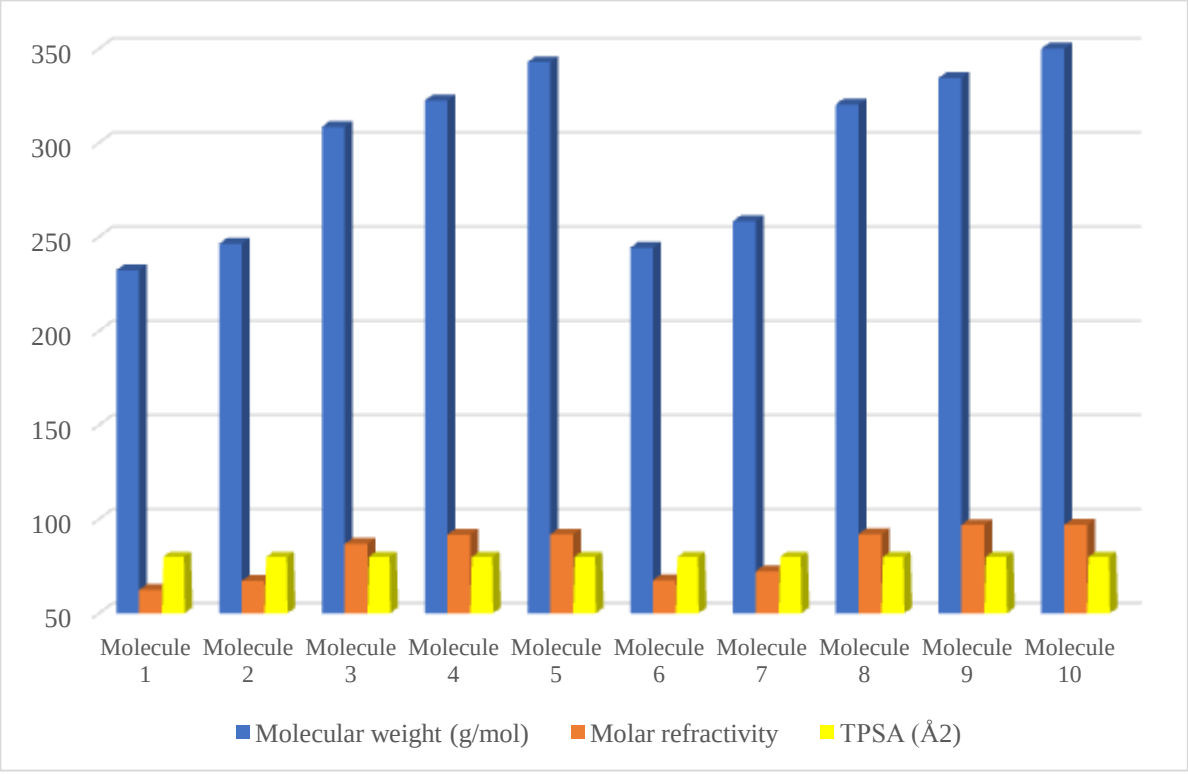


Figure 4. Graphical comparison of molecular weight (g/mol), molar refractivity and TPSA ($Å^2$) values in studied molecules

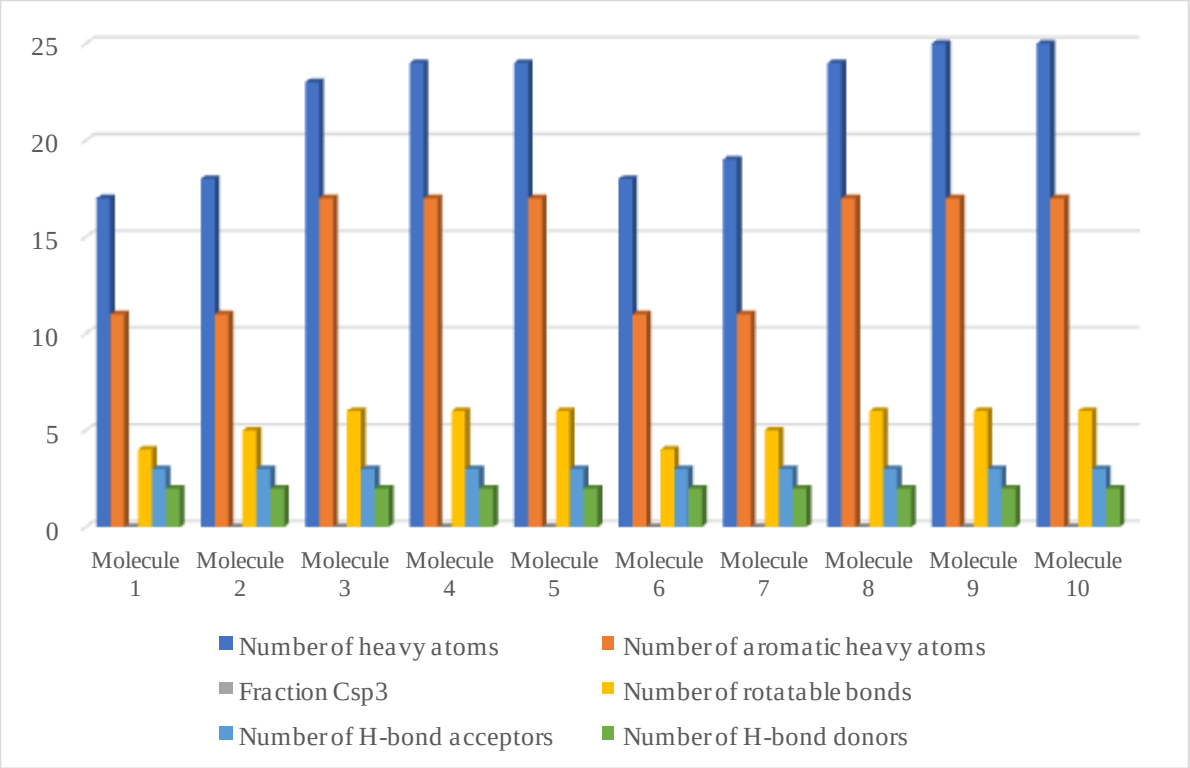


Figure 5. Graphical comparison of number of heavy atoms, number of aromatic heavy atoms, fraction Csp3, number of rotatable bonds, number of H-bond acceptors and number of H-bond donors values in studied molecules

3.4. Lipophilicity

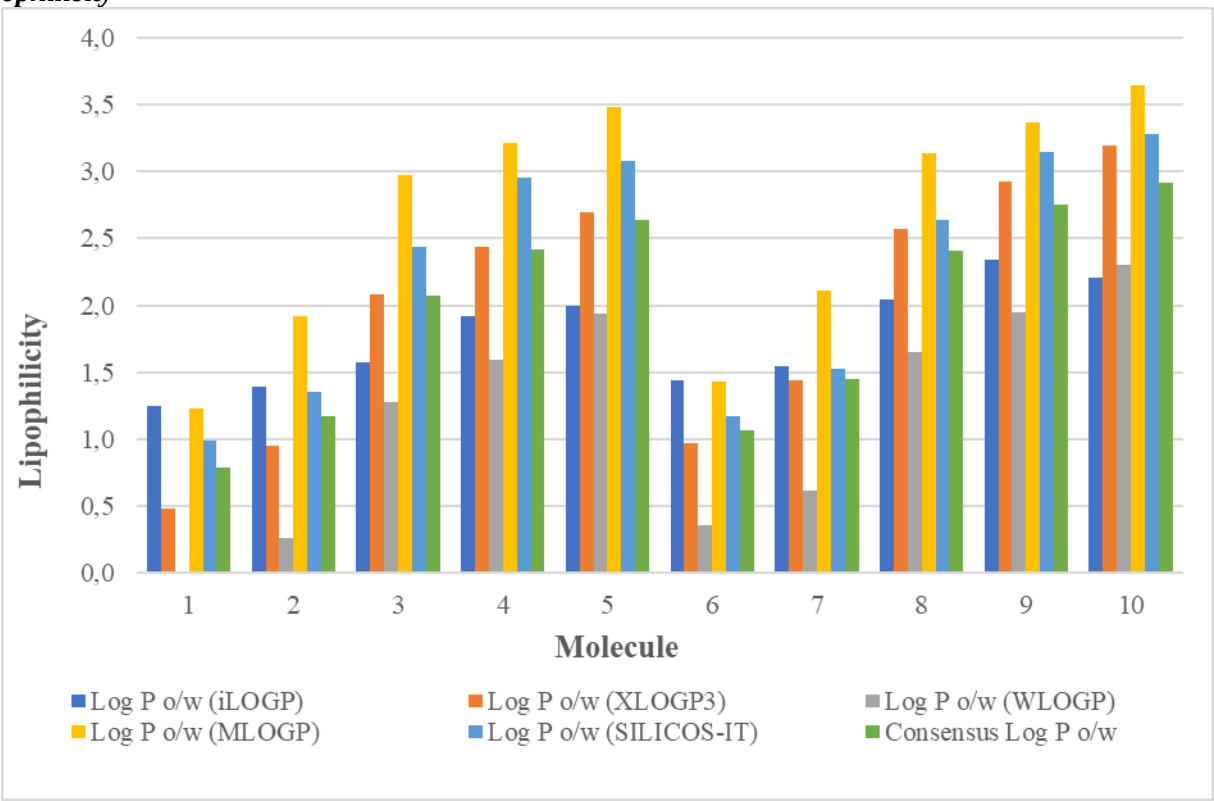


Figure 6. Lipophilicity value of studied molecules

Lipophilicity refers to the ability of a chemical compound to dissolve in oils, lipids. Here, the logarithm of the partition coefficient of molecules between octanol and water was calculated according to five different methods (iLOGP, XLOGP3, WLOGP, MLOGP, SILICOS-IT). Then, the average of these five different values (Consensus Log P o/w) is given. The lipophilicity value should be between (-0.7 - +5.0). When the values given in Table 3 are examined, it is seen that all the molecules studied are in this range. The graphical representation of the values given in this table is given in Fig. 6.

3.5. Water Solubility

Water Solubility, negative logarithm of solubility was calculated according to three different methods (ESOL, Ali, SILICOS-IT). Log S value should not be less than -6. The relationship between resolution and Log S value; insoluble < -10 < poorly soluble < -6 < moderately soluble < -4 < soluble < -2 < very soluble < 0 < highly soluble. When the values given for the studied molecules are examined in Table 4, it is seen that the molecule 1 is evaluated as very soluble according to the ESOL and Ali methods. On the other hand, the molecule 4, 5 and 10 was evaluated as poorly soluble according to the SILICOS-IT method. It is seen that the Log S value of these molecules is less than -6. Therefore, these molecules cannot be considered as drug candidates. The graphical representation of the values of water solubility in studied molecules is given in Fig. 7.

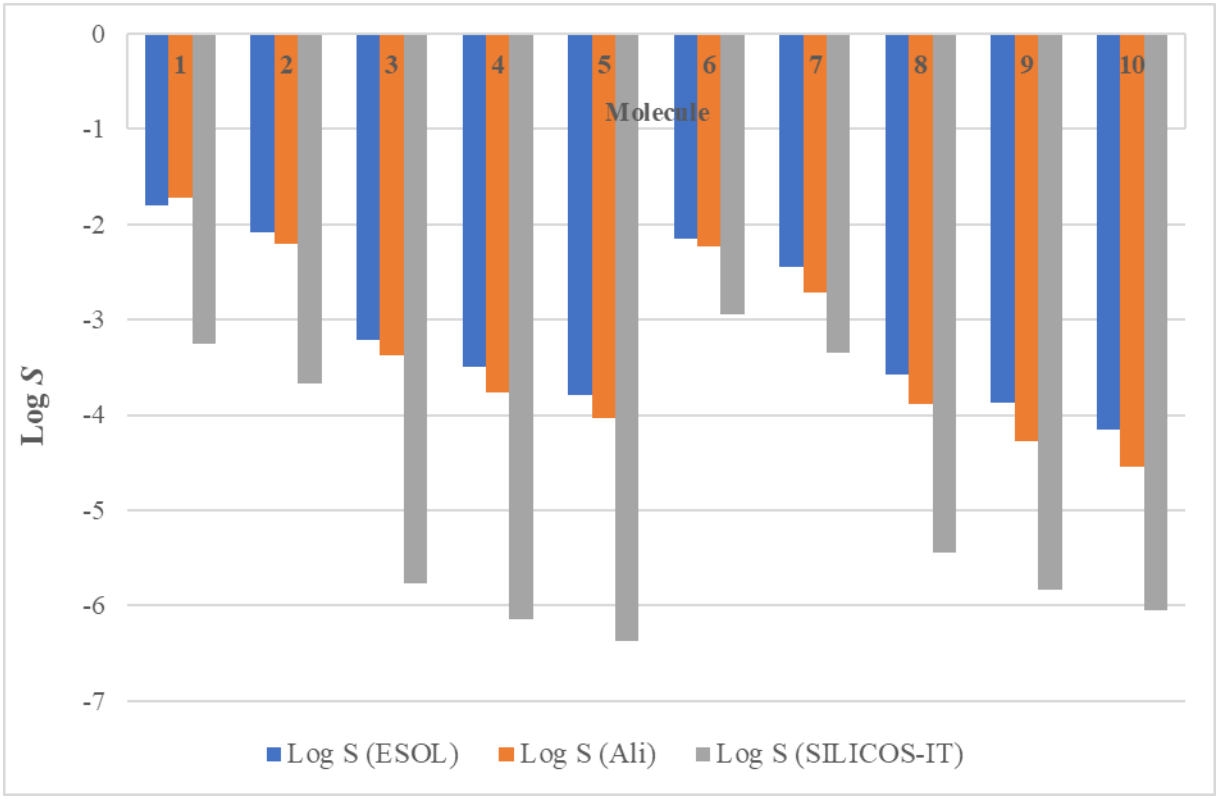


Figure 7. Water solubility value of studied molecules

3.6. Pharmacokinetics

The most important pharmacokinetics properties are Gastrointestinal absorption, BBB permeant, P-glycoprotein substrate and skin permeation (Log Kp, cm/s). When the data given in Table 5 are examined, it has been observed that all molecules are highly absorbed in the gastrointestinal system, but not all molecules can cross the blood-brain barrier. Cytochrome 450 is a protein superfamily of enzymes that function as monooxygenases and contain hemes as

cofactors. It has been observed that Cytochrome 450 1A2, Cytochrome 450 2C19, Cytochrome 450 2C9, Cytochrome 450 2D6, Cytochrome 450 3A4 have different inhibitory interactions with all compounds. As the skin permeation value decreases, the skin permeability of the molecule decreases. According to this definition, the compounds with the highest skin permeation value are molecule 1 and molecule 10. The compound with the weakest skin permeation value is molecule 2. The graph showing the skin permeation value of the molecules is given in Fig. 8.

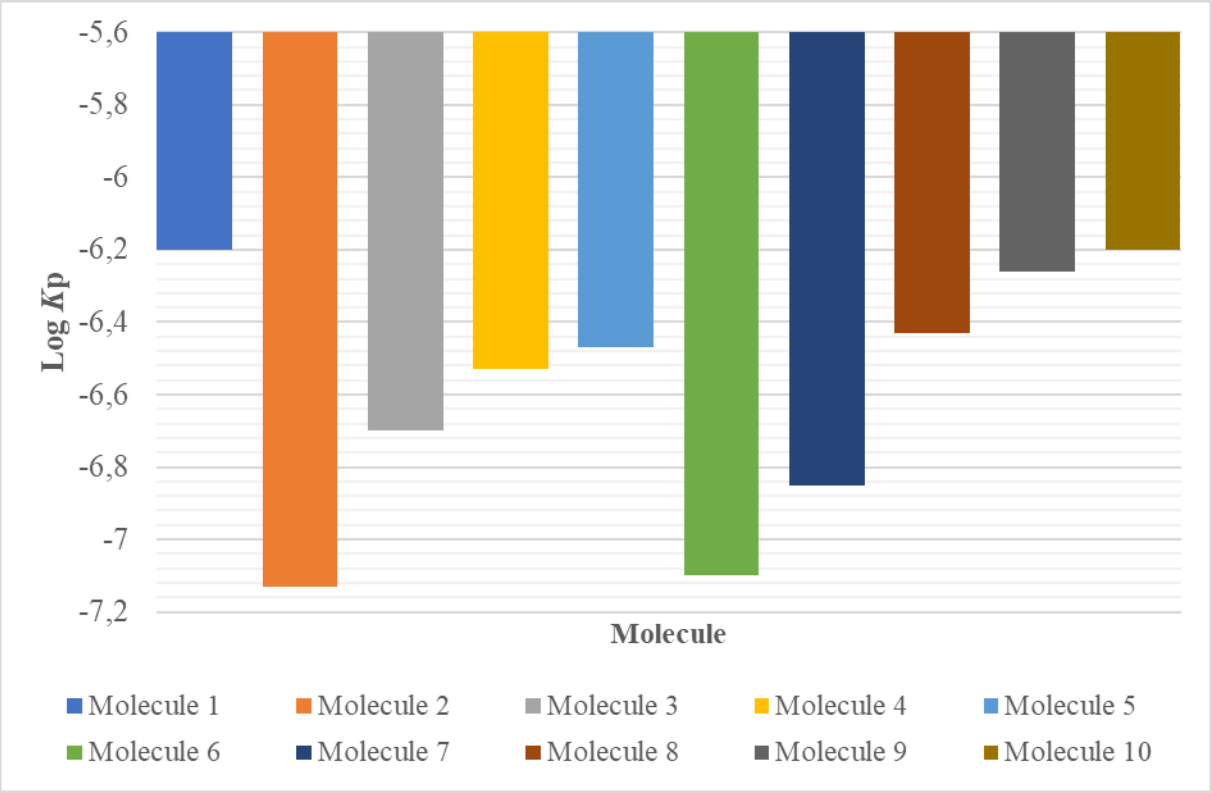


Figure 8. Skin permeation value of studied molecules

3.7. Druglikeness

When the Druglikeness properties given in Table 6 are examined, it is seen that the molecules have Druglikeness properties in all of the applied the Lipinski (Pfizer, MW ≤ 500, MLOGP ≤ 4.15, N or O ≤ 10, NH or OH ≤ 5), Ghose (Amgen, 160 ≤ MW ≤ 480, -0.4 ≤ WLOGP ≤ 5.6, 40 ≤ MR ≤ 130, 20 ≤ atoms ≤ 70), Veber (GlaxoSmithKline, rotatable bonds ≤ 10, TPSA ≤ 140), Egan (Pharmacia, WLOGP ≤ 5.88, TPSA ≤ 131.6) and Muegge (Bayer, 200 ≤ MW ≤ 600, -2 ≤ XLOGP ≤ 5, TPSA ≤ 150, num. rings ≤ 7, num. carbon > 4, num. heteroatoms > 1, num. rotatable bonds ≤ 15, H-bond acc. ≤ 10, H-bond don. ≤ 5) methods. Bioavailability in pharmacology, one of the main pharmacokinetic properties of a drug, acting on the circulatory system and that is defined as a function of the dose of the drug. By definition, the bioavailability is 100% when the drug is administered intravenously. However, the bioavailability is reduced when administered by other routes (orally). This is due to the lack of absorption in the first pass of the drug to metabolism. Therefore, it is seen that the bioavailability for all the molecules we studied remains at 55%.

3.8. Medicinal Chemistry

Chemical substances known as pan-assay interference compounds (PAINS) frequently produce false positive results in high-throughput screens. PAINS have a tendency to respond nonspecifically with a variety of biological targets rather

than impacting a single target. When the data in Table 7 are examined, it is seen that the PAINS value is zero in all studied molecules. In chemical toxicology and regulatory decision support, structural alerts are widely acknowledged as a simple and transparent way to highlight potential chemical dangers or group chemicals into categories for read-across. However, there is growing criticism that toxicity alerts incorrectly label too many substances as harmful, casting doubt on their validity as toxicity markers. While the structural alerts value is zero for the first five molecules of the studied molecules, molecule 6 – molecule 10 has a value of one. The pharmaceutical industry's high program failure rates inspired the creation of predictive software that can classify compound libraries as "druglike" (similar to existing medications) or "leadlike" (possessing the structural and physicochemical profile of a quality lead). It has been determined that molecules 3, 4, 5, 7, 8 and 9 among the studied molecules have leadlikeness ($250 \leq MW \leq 350$, $XLOGP \leq 3.5$, num. rotatable bonds ≤ 7) property, while the remaining molecules 1, 2, 6 and 10 do not have leadlikeness property. Synthetic accessibility score (1 very easy - 10 very diffucult), synthetic accessibility assessment is a process for evaluating the ease of synthesis of compounds. A rapid method for assessing synthetic accessibility for a large number of chemical compounds is an important step in drug discovery. When the studied molecules are examined, the synthetic accessibility score is low, which indicates that they can be easily synthesized by the synthetic method. Synthetic accessibility score change graph in molecules is given in Fig. 9. It is seen that molecule 1 can be synthesized most easily among ten molecules.

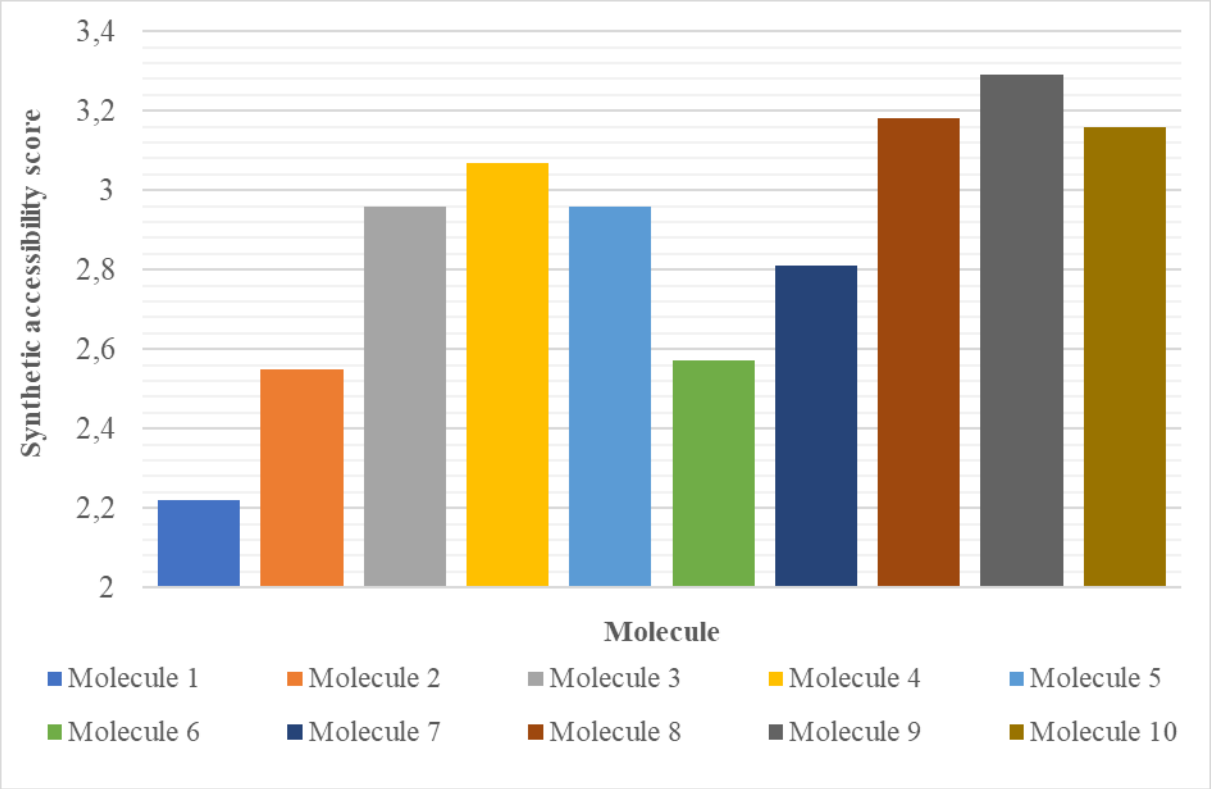


Figure 9. Synthetic accessibility score change graph in molecules

3.9. Molecular docking studies

When the Docking results for the studied molecules given in Table 8 are examined, it is seen that the values of full Fitness (-3759.90 kcal/mol) and estimated ΔG (-8.59 kcal/mol) are in the highest molecule 9. After that, molecule 3 estimated ΔG (-8.56 kcal/mol) and molecule 5 estimated ΔG (-8.45 kcal/mol) come respectively. Molecule 9 had the strongest interaction with the target protein. All interactions of the studied ten molecule are given in Fig. 10. In

addition, the graphical representation of full fitness (kcal/mol) and estimated ΔG (kcal/mol) values are given in Fig. 11 and Fig. 12.

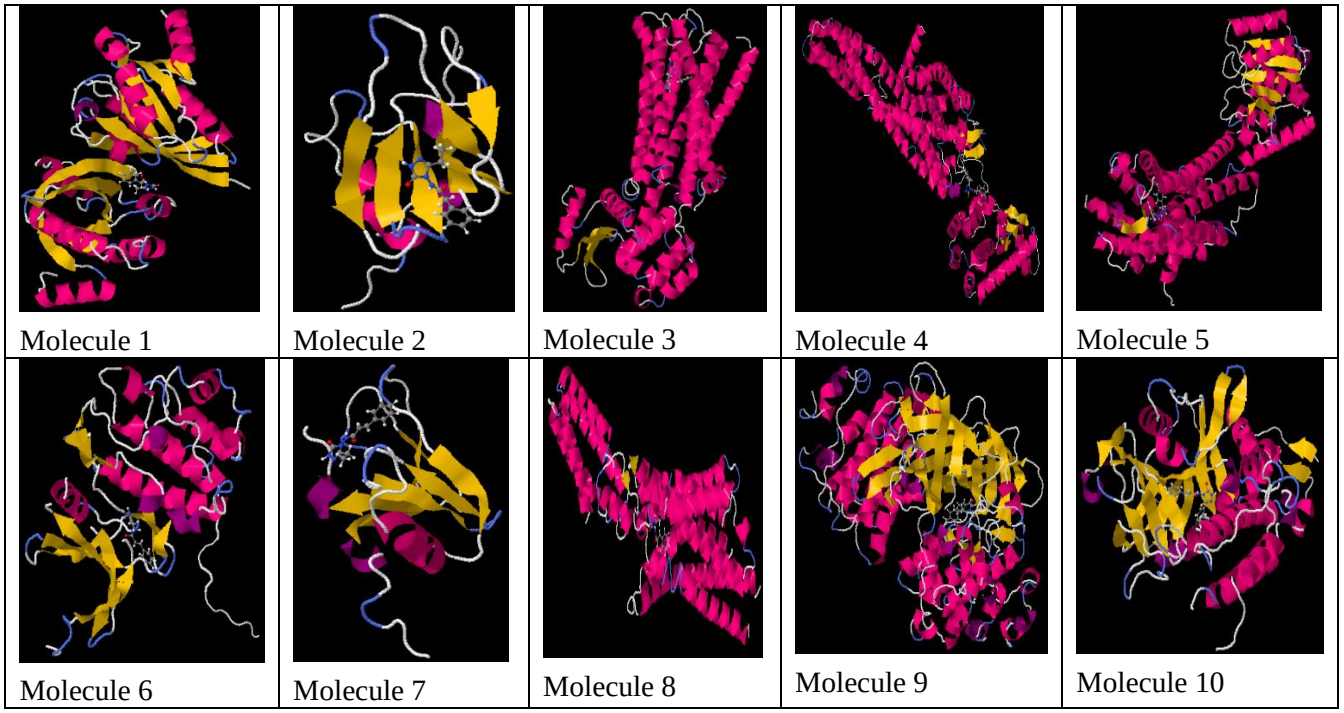


Figure 10. Protein-ligand interactions of the ten studied molecules

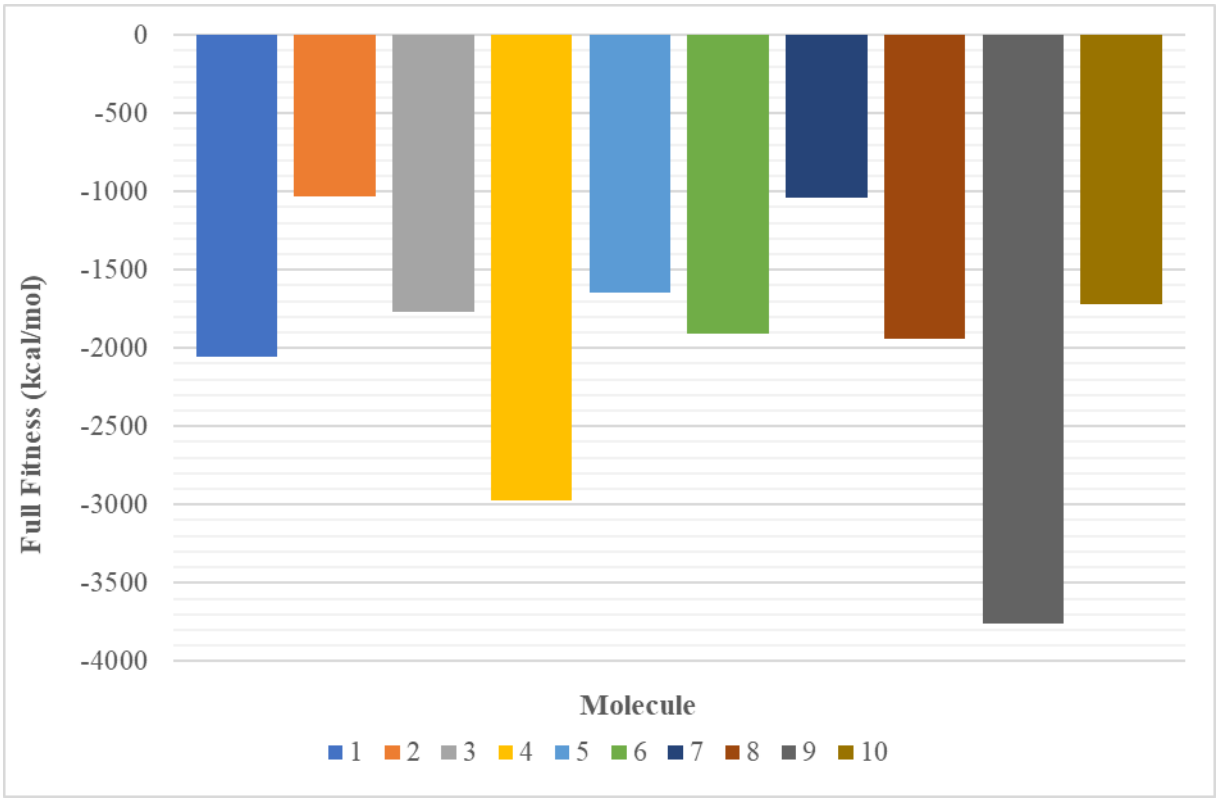


Figure 11. Full Fitness (kcal/mol) values for studied molecules

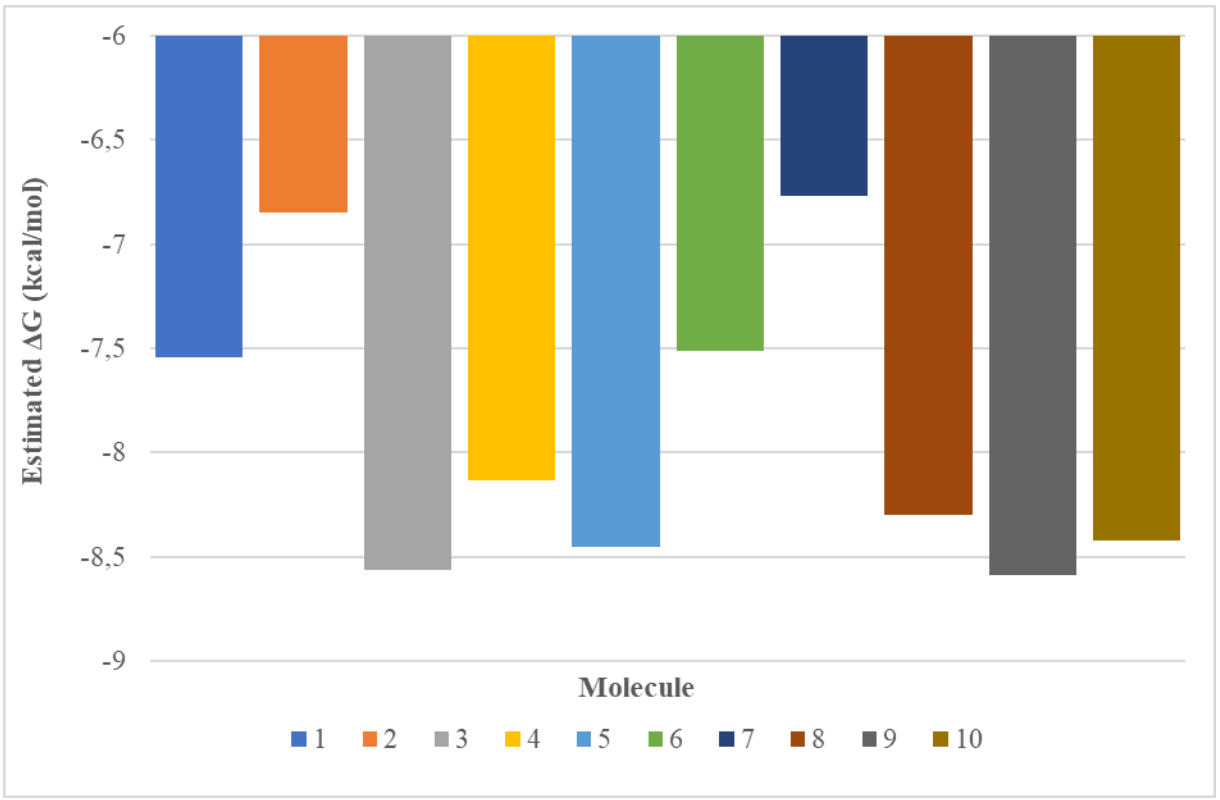


Figure 12. Estimated ΔG (kcal/mol) values for studied molecules

4. Conclusion

Consequently, it is seen that all molecules are absorbed by the gastrointestinal system, but not all molecules can pass through the blood-brain barrier. Especially molecules 10, 9 and 5 seem to be getting very close to passing through the brain barrier. Bioavailability Radar is seen that molecule 2 fits the description and the entire graphic line is in the pink area. We can consider this molecule as a drug candidate. Molecules 1, 4 and 7 are close to being considered as drug candidates, but there is a slight deviation from the red area at the point of insaturation feature. When we look at it as physicochemical properties, molecular weights are in the range of 150 – 500 g/mol in all compounds. Fraction Csp3 should be at least 0.25 and only molecule 2 provides this value. Number of rotatable bonds should be no more than 9. All of the molecules appear to have a value below this number (4 - 6). Molar refractivity value takes values between 62.35 – 96.97 and TPSA (Å2) values are between 20 and 130 Å2 in all molecules. Lipophilicity values are between -0.7 - +5.0 all the studied molecules. When the values given for the studied molecules are examined for water solubility, it is seen that the molecule 1 is evaluated as very soluble according to the ESOL and Ali methods. On the other hand, the molecule 4, 5 and 10 was evaluated as poorly soluble according to the SILICOS-IT method. It is seen that the Log S value of these molecules is less than -6. Therefore, these molecules cannot be considered as drug candidates. It has been observed that all molecules are highly absorbed in the gastrointestinal system, but not all molecules can cross the blood-brain barrier and the compounds with the highest skin permeation value are molecule 1 and molecule 10, the compound with the weakest skin permeation value is molecule 2 as pharmacokinetics properties. The bioavailability for all the molecules we studied remains at 55% as druglikeness. When we look at medicinal chemistry, structural alerts value is zero for the first five molecules and molecule 6 – molecule 10 has a value of one. It has been determined that molecules 3, 4, 5, 7, 8 and 9 among the studied molecules have leadlikeness property, while the remaining molecules 1, 2, 6 and 10 do not have leadlikeness property. When the studied molecules are examined, the synthetic accessibility score is low, which indicates that they can be easily synthesized by the synthetic

method. When the Docking results for the studied molecules are examined, it is seen that the values of full Fitness (-3759.90 kcal/mol) and estimated ΔG (-8.59 kcal/mol) are in the highest molecule 9. After that, molecule 3 estimated ΔG (-8.56 kcal/mol) and molecule 5 estimated ΔG (-8.45 kcal/mol) come respectively. Molecule 9 had the strongest interaction with the target protein.

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