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Determination of ADMET properties of substituted-piperidine-3-carboxamide derivatives with potential use in the treatment of Crohn's disease

Abstract. In this study, ADME studies were carried out on seven different substituted-piperidine-3-carboxamide derivatives compounds, which were considered as drug active ingredients that can be used in the treatment of Chron's disease with docking studies that were done in our previous studies. In this context, these molecules were examined in terms of physicochemical properties, lipophilicity, water solubility, absorption property, distribution property, metabolism property, toxicity property, environmental toxicity property, tox21 pathway property, and medicinal chemistry property. According to the results obtained, it was concluded that (E)-4-((4-(((4-bromopyridin-1(2H)-yl)methylene)amino)-3-(4-methoxy phenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)methyl) piperazine-1-carboxylic acid molecule is the most ideal molecule that can be used in the treatment of Chron's disease in terms of ADME properties among the molecules studied.
Keywords: Crohn's disease, piperidine-3-carboxamide derivatives, ADME properties, physicochemical properties, toxicity property, medicinal chemistry property.

Introduction

A chronic inflammatory disease of the digestive tract, Crohn's disease is a member of the inflammatory bowel disease (IBD) group [1]. Although it can occur anywhere in the digestive tract, it most frequently occurs in the ileum, the end of the small intestine, and the colon, the beginning of the large intestine [2]. Crohn's disease can lead to ulcers by thickening the intestinal wall. Crohn's disease symptoms can range from minor to severe and differ from person to person. Anal fissures or fistulas, fever, weariness, diarrhea, cramping and soreness in the abdomen, and loss of appetite are common symptoms [3]. Although the precise origin of Crohn's disease is unknown, environmental factors, immune system issues, and genetic predisposition are believed to be involved [4]. A number of tests and procedures are used to diagnose Crohn's disease. These include MRI, CT scans, or x-rays with barium, stool tests to screen for infection or bleeding, colonoscopy or upper endoscopy to image the digestive tract, and blood tests to check for inflammation and diseases like anemia [5]. Crohn's disease has no known cure, although a number of therapeutic approaches are employed to manage symptoms and bring the condition into remission. Anti-inflammatory medications, immunosuppressants, antibiotics, and biological therapies are the most crucial ones. Other measures include limiting particular meals and providing nutritional assistance, and treating intestinal obstruction or fistulas when medicine is ineffective [6]. Serious side effects include intestinal blockage, deep ulcers throughout the digestive tract, aberrant connections between the intestines and other organs, malnourishment, arthritis, skin issues, and inflammation of the eyes can result from Crohn's disease if it is not treated or is not treated well enough [7]. A balanced diet, stress management, regular checkups with the doctor, and following the treatment plan are just a few of the lifestyle adjustments needed to control Crohn's disease symptoms and enhance quality of life [8].

When developing a new medication, the ADMET concept is essential for assessing its pharmacological characteristics. It establishes a drug's safety, effectiveness, and physiological behavior. Before moving on to clinical trials, choosing a successful therapeutic candidate and reducing any risks requires evaluating ADMET characteristics during the drug development process [9]. Potential drug candidates' ADMET characteristics are assessed both *in vitro*, or in a lab setting, and *in silico*, or through computer modeling.

At this point, molecules with favorable metabolism, low toxicity, favorable distribution, and high absorption are chosen [10]. Selected medication candidates are examined for ADMET characteristics in animal models during preclinical research. Important information about the drug's safety can be found in toxicological studies [11]. Regulatory bodies (such as the FDA and EMA) submit ADMET data for the medicine's approval. These statistics are used to evaluate the medication's safety and effectiveness [12].

Materials and Methods

Studied molecules. In this study seven different piperidine-3-carboxamide derivative molecules:

- (E)-4-((3-(4-chlorophenyl)-5-oxo-4-((pyridin-1(2H)-ylmethylene)amino)-4,5-dihydro-1H-1,2,4-tri- azol-1-yl)methyl)piperazine-1-carboxylic acid (1);
- (E)-4-((5-oxo-4-((pyridin-1(2H)-ylmethylene) amino)-3-(p-tolyl)-4,5-dihydro-1H-1,2,4-triazol-1-yl)methyl)piperazine-1-carbo xylic acid (2);
- (E)-4-((3-(4-fluorophenyl)-4-(((4-methylpyridin-1(2H)-yl)methylene)amino)-5-oxo-4,5-di hydro-1H-1,2,4-triazol-1-yl)methyl)piperazine-1-carboxylic acid (3);
- (E)-4-((4-(((4-chloro pyridin-1(2H)-yl)methylene)amino)-3-(4-hydroxyphenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)methyl)piperaz ine-1-carboxylic acid (4);
- (E)-4-((4-(((4-bromopyridin-1(2H)-yl) methylene)amino)-3-(4-methoxy phenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)methyl) piperazine-1-carboxylic acid (5);
- (E)-4-((4-(((4-bromopyridin-1(2H)-yl)methylene)amino)-3-(4-fluorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)methyl)piperazine-1-carboxylic acid (6);
- (E)-4-((4-(((4-bromopyridin-1(2H)-yl)methylene)amino)-3-(4-hydroxyphenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)methyl)piperaz ine-1-carboxylic acid (7)

that have not yet been synthesized and not yet registered in the literature have been selected. The aim of this study is not only to propose a new active ingredient for Crohn's disease A visual showing the molecular structures of the compounds studied is given in Figure 1.

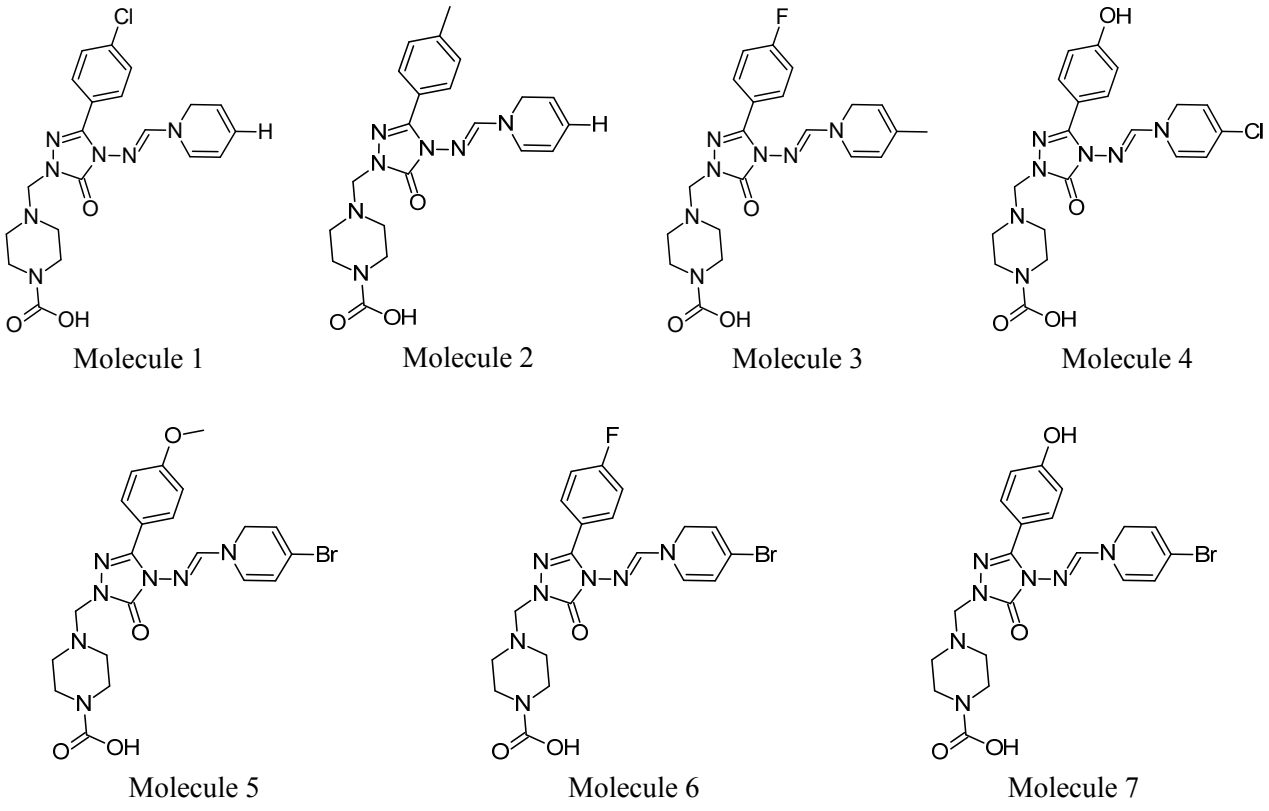

Figure 1 – Molecular formulas of studied piperidine-3-carboxamide derivatives

Computer program used. In this study, the ADMETlab 3.0 and SwissADME computer programs were used for all calculations. ADMETlab 3.0 is an *in silico* (computer-based) tool used in drug discovery and development processes to predict the ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties of molecules. This platform provides great convenience to researchers in the evaluation of pharmacokinetic and toxicological properties and has been widely used in studies in the literature [13-16]. Among the main features of ADMETlab 3.0, we can say that it has a comprehensive database, uses multiple prediction models, has a user-friendly interface, provides fast and reliable results, and has advanced features. SwissADME is a web-based tool for predicting pharmacokinetic and pharmacodynamic properties of molecules used in drug discovery and development processes. This platform is widely used to assess ADME properties and drug similarity, especially for drug candidate molecules.

Physicochemical properties. In the process of discovering a new drug, the physicochemical properties of molecules are critical to the efficacy, safety and pharmacokinetic behavior of the drug candidate. These properties determine how the molecule behaves in the body, how it interacts with the target protein and its potential toxicological risks [17]. From this point, physicochemical properties molecular weight, volume, density, number of heavy atom, number of aromatic heavy atom, number of hydrogen bond acceptors (nHA), number of hydrogen bond donors (nHD), number of rotable bonds (nRot), number of rings (nRing), number of atoms in the biggest ring (MaxRing), number of heteroatoms (nHet), formal charge (fChar), number of rigid bonds (nRig), flexibility, number of stereo centers, topological polar surface area (TPSA), molar recractivity, sp^3 hybridization rate (fraction Csp^3), the logarithm of aqueous solubility (logS), the logarithm of the n-octanol/water distribution coefficient (logD), acid dissociation constant (pKa), melting point, and boiling point were calculated for all studied molecules. The results obtained (together with the optimal values) are given in Table 1. All data are colored for a better visual understanding of the results. Here, the data obtained are colored green if they are good (in the range of optimal values), orange if they are moderate, and red if they are poor.

Lipophilicity. Lipophilicity properties of the molecules were analyzed in detail according to iLOGP (a physics-based technique that uses the generalized-born and solvent accessible surface area (GB/SA) model created by Daina and colleagues to compute the free energies of solvation in n-octanol and water) [18], WLOGP (an atomistic approach based on topological descriptors and fragments) [19], MLOGP (based on topological indices and the linear relationship between structure and logP) [20], XLOGP3 (an atomistic approach that incorporates corrective factors and a knowledge-based library) [21], and SILICOS-IT (a hybrid fragment/topological method that uses seven topological descriptors and 27 fragments) [22]. The data obtained were averaged, and the results were given as consensus log Po/w. The data obtained regarding the lipophilicity property are given in Table 2.

Water solubility. Water solubility is examined according to three different methods in SwissADME. These are ESOL [23], Ali [24], and SILICOS-IT [22], respectively. The water solubility of our candidate molecules through these three models were examined. Molecules with high water solubility are generally better absorbed from the gastrointestinal tract and have higher bioavailability, facilitating passive diffusion of molecules across the cell membrane. Water solubility affects the rate of binding of molecules to plasma proteins, the distribution of molecules to different tissues, and the interaction of molecules with metabolic enzymes. Molecules with high water solubility are more easily excreted by the kidneys. Molecules with low water solubility can accumulate in the body and cause toxic effects [25]. The data obtained as a result of the calculations are given in Table 3.

Absorption properties. Caco-2 Permeability (Caco-2 permeability is an *in vitro* assay widely used in drug discovery to predict the absorption of drugs from the gut), MDCK Permeability (MDCK permeability refers to an *in vitro* assay used to assess the permeability of drug candidates across cell membranes), PAMPA (Parallel Artificial Membrane Permeability Assay is an *in vitro* assay used to assess the permeability of drug candidates across a synthetic membrane that simulates passive diffusion through biological membranes) [26], Pgp-inhibitor (understanding the role of P-gp inhibitors is crucial

for predicting drug absorption, bioavailability and distribution), Pgp-substrat (A P-glycoprotein (P-gp) substrate refers to a drug or compound transported by P-glycoprotein (P-gp), an efflux carrier protein that plays a role in limiting the absorption and bioavailability of certain drugs), human intestinal absorption (HIA, refers to the percentage of an orally administered drug that is absorbed from the human intestine and enters the systemic circulation), $F_{20\%}$ (an F_{20} of 20% means that 20% of the orally administered drug dose is absorbed and enters the bloodstream), $F_{30\%}$ (an F_{30} of 30% means that 30% of the orally administered drug dose is absorbed and enters the bloodstream), and $F_{50\%}$ (an F_{50} of 50% means that 20% of the orally administered drug dose is absorbed and enters the bloodstream) parameters from absorption property were analyzed. The data obtained for absorption properties are given in Table 4.

Distribution property. Distribution features plasma protein binding (PPB, describes how much a drug binds to plasma proteins (such as albumin or α1-acid glycoprotein) [27] while in the bloodstream), steady-state volume of distribution (VDss, refers to the theoretical volume that must be evenly distributed for the total amount of drug to result in the same concentration as in steady-state plasma), blood-brain barrier penetration (BBB, refers to the ability of a drug to cross the blood-brain barrier and reach the central nervous system) [28], the fraction unbound in plasms (Fu, refers to the fraction of a drug in the bloodstream that remains unbound to plasma proteins), organic anion transporting polypeptide 1B1 (OATP1B1) inhibitor (it refers to a compound that inhibits the activity of the OATP1B1 transporter), organic anion transporting polypeptide 1B3 (OATP1B3) inhibitor (it refers to a compound that inhibits the activity of the OATP1B3 transporter), breast cancer resistance protein (BCRP) inhibitor (refers to a compound that inhibits the activity of the breast cancer resistance protein transporter) [29], and finally multidrug pesistance protein 1 (MRP1) inhibitor (refers to a compound that inhibits the activity of the protein 1 transporter associated with multidrug resistance) were analyzed. The data obtained for distribution properties are given in Table 5.

Metabolism property. As metabolism properties, CYP1A2 inhibitor (refers to a compound that inhibits the activity of the enzyme cytochrome P450 1A2), CYP1A2 substrate (refers to a compound (such as a drug) that is metabolized by the enzyme cytochrome P450 1A2), CYP2C19 inhibitor (refers to a compound that inhibits the activity of the enzyme CYP2C19, which is part of the cytochrome P450 (CYP) enzyme family), CYP2C19 substrate (refers to a drug or compound metabolized by the enzyme CYP2C19, which is part of the cytochrome P450 enzyme family), CYP2C9 inhibitor (refers to a compound that inhibits the activity of the enzyme CYP2C9, which is part of the cytochrome P450 family of enzymes involved in the metabolism of many drugs), CYP2C9 substrate (refers to a compound or drug that is metabolized primarily by the enzyme CYP2C9, a member of the cytochrome P450 enzyme family), CYP2D6 inhibitor (means a compound or drug that inhibits the activity of the enzyme CYP2D6, a member of the cytochrome P450 enzyme family), CYP2D6 substrate (refers to a compound or drug metabolized by the enzyme CYP2D6, which is part of the cytochrome P450 enzyme family), CYP3A4 inhibitor (a substance that slows down or blocks the activity of the enzyme CYP3A4, one of the most important enzymes in the cytochrome P450 family), CYP3A4 substrate (a drug or compound metabolized by the enzyme CYP3A4, one of the most important enzymes in the cytochrome P450 family), CYP2B6 inhibitor (a compound that reduces or blocks the activity of the CYP2B6 enzyme, part of the cytochrome P450 family involved in drug metabolism), CYP2B6 substrate (a compound metabolized by the enzyme CYP2B6, which belongs to the cytochrome P450 family), CYP2C8 inhibitor (is a substance that interferes with the activity of the CYP2C8 enzyme, part of the Cytochrome P450 family involved in drug metabolism), and human liver microsome stability (HLM) stability (an important parameter for assessing metabolic stability) were analyzed. CLplasma, meaning plasma clearance, which is an important parameter in the excretion phase of ADMET studies, and $T_{1/2}$ (half-life), which refers to the time it takes for the concentration of a drug in plasma to decrease by half, were examined within the scope of excretion properties. The data obtained for metabolism and excretion properties are given in Table 6.

Table 1 – Physicochemical properties (together with the optimal values) of molecules

Physicochemical Property	**Molecule 1**	**Molecule 2**	**Molecule 3**	**Molecule 4**	**Molecule 5**	**Molecule 6**	**Molecule 7**
Formula	$C_{20}H_{22}ClN_7O_3$	$C_{21}H_{25}N_7O_3$	$C_{21}H_{24}FN_7O_3$	$C_{20}H_{22}ClN_7O_4$	$C_{21}H_{24}BrN_7O_4$	$C_{20}H_{21}BrFN_7O_3$	$C_{20}H_{22}BrN_7O_4$
Molecular Weight (g/mol, Optimal:100~600)	443.150	423.200	441.19	459.14	517.11	505.09	503.09
Volume (Å^3, Optimal:200 ~ 600)	415.081	417.166	423.234	423.871	445.24	425.221	427.944
Density (g/cm^3, Optimal:1.0 ~ 1.5)	1.068	1.014	1.042	1.083	1.161	1.188	1.176
N. Heavy Atom (Optimal:20 ~ 70)	31	31	32	32	33	32	32
N. Aromatic Heavy Atom (Optimal:0 ~ 15)	11	11	11	11	11	11	11
nHA (Optimal:0 ~ 12)	10.0	10.0	10.0	11.0	11.0	10.0	11.0
nHD (Optimal:0 ~ 7)	1.0	1.0	1.0	2.0	1.0	1.0	2.0
nRot (Optimal:0 ~ 11)	6.0	6.0	6.0	6.0	7.0	6.0	6.0
nRing (Optimal:0 ~ 6)	4.0	4.0	4.0	4.0	4.0	4.0	4.0
MaxRing (Optimal:0 ~ 18)	6.0	6.0	6.0	6.0	6.0	6.0	6.0
nHet (Optimal:1 ~ 15)	11.0	10.0	11.0	12.0	12.0	12.0	12.0
fChar (Optimal:-4 ~ 4)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
nRig (Optimal:0 ~ 30)	26.0	26.0	26.0	26.0	26.0	26.0	26.0
Flexibility (nRot /nRig, Optimal:0.1 ~ 0.4)	0.231	0.231	0.231	0.231	0.269	0.231	0.231
Stereo Centers (Optimal: ≤ 2)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
TPSA (Å^2, Optimal:0 ~ 140)	99.2	99.2	99.2	119.43	108.43	99.2	119.43
Molar Recractivity (cm^3/mol, Optimal:40 ~ 130)	128.63	128.59	128.38	130.44	137.98	131.45	133.51
Fraction Csp^3 (Optimal:0.25 ~ 0.65)	0.30	0.33	0.33	0.30	0.33	0.30	0.30
logS (Optimal -4 ≤ LogS ≤ 0)	-1.773	-1.928	-1.966	-2.278	-2.137	-1.824	-2.378
logD (0 < LogP < 3)	1.379	1.360	1.29	1.062	1.337	1.289	1.092
pKa (Acid) (Optimal:3 ~ 7)	3.051	3.463	3.896	3.919	4.345	3.423	4.019
Melting point (^{o}C, Optimal 50 ~ 250)	192.617	189.594	199.294	201.583	193.899	199.123	201.001
Boiling point (^{o}C, Optimal 150 ~ 400)	261.529	266.401	261.321	288.841	270.879	266.124	289.524

Table 2 – Lipophilicity properties of molecules

Lipophilicity Properties*	Molecule						
	1	2	3	4	5	6	7
Log Po/w (iLOGP)	3.55	3.64	3.84	3.20	3.95	3.76	2.56
Log Po/w (XLOGP3)	-0.17	-0.44	-0.79	-0.81	-0.42	-0.29	-0.75
Log Po/w (WLOGP)	0.50	0.16	0.80	0.12	0.58	1.13	0.28
Log Po/w (MLOGP)	3.33	3.06	3.44	2.56	2.89	3.54	2.67
Log Po/w (SILICOS-IT)	-0.47	-0.59	-0.19	-0.96	-0.39	-0.02	-0.93
Consensus Log Po/w	1.35	1.16	1.42	0.82	1.32	1.62	0.77
Note: *Log Po/w <0: hydrophilic; 0<Log Po/w <3: balanced lipophilicity; 3<Log Po/w <5: high lipophilicity; Log Po/w >5: extremely lipophilic							

Table 3 – Water solubility properties of molecules

Molecule	Water Solubility								
	Log S_1	Solubility	Class	Log S_2	Solubility	Class	Log S_3	Solubility	Class
1	-2.35	1.98 mg/mL $4.45.10^{-3}$ mol/L	Soluble	-1.46	$1.55.10^{1}$ mg/mL $3.48.10^{-2}$ mol/L	Very Soluble	-1.58	$1.18.10^{1}$ mg/mL $2.65.10^{-2}$ mol/L	Soluble
2	-2.05	3.73 mg/mL $8.81.10^{-3}$ mol/L	Soluble	-1.18	$2.81.10^{1}$ mg/mL $6.64.10^{-2}$ mol/L	Very Soluble	-1.37	$1.82.10^{1}$ mg/mL $4.30.10^{-2}$ mol/l	Soluble
3	1.94	5.10 mg/mL $1.15.10^{-2}$ mol/L	Very Soluble	-0.81	$6.67.10^{1}$ mg/mL $1.53.10^{-1}$ mol/L	Very Soluble	-1.85	6.26 mg/mL $1.42.10^{-2}$ mol/L	Soluble
4	-2.04	4.20 mg/mL $9.13.10^{-3}$ mol/L	Soluble	-1.22	$2.78.10^{1}$ mg/mL $6.04.10^{-2}$ mol/L	Very Soluble	-1.20	$2.88.10^{1}$ mg/mL $6.25.10^{-2}$ mol/L	Soluble
5	-2.57	1.38 mg/mL $2.67.10^{-3}$ mol/L	Soluble	-1.39	$2.10.10^{1}$ mg/mL $4.05.10^{-2}$ mol/L	Very Soluble	-2.80	4.33 mg/mL $8.36.10^{-3}$ mol/L	Soluble
6	-2.65	1.12 mg/mL $2.21.10^{-3}$ mol/L	Soluble	-1.33	$2.35.10^{1}$ mg/mL $4.64.10^{-2}$ mol/L	Very Soluble	-2.24	2.89 mg/mL $5.70.10^{-3}$ mol/L	Soluble
7	-2.35	2.24 mg/mL $4.44.10^{-3}$ mol/L	Soluble	-1.28	$2.64.10^{1}$ mg/mL $5.24.10^{-2}$ mol/L	Very Soluble	-1.39	$2.05.10^{1}$ mg/mL $4.06.10^{-2}$ mol/L	Soluble

Table 4 – Absorption properties of molecules

Absorption Property	Molecule 1	Molecule 2	Molecule 3	Molecule 4	Molecule 5	Molecule 6	Molecule 7
Caco-2 Permeability (Optimal: higher than Log -5.15)	-5.156	-5.095	-5.264	-5.374	-5.303	-5.221	-5.331
MDCK Permeability (low permeability: <2.10^{-6} cm/s, medium permeability: 2-20.10^{-6} cm/s, high passive permeability: >20.10^{-6} cm/s)	-4.600	-4.733	-4.759	-4.951	-4.788	-4.834	-4.905
PAMPA (log Peff <0, Category 0, low-permeability log Peff >2.5, Category 1, high-permeability)	0.728	0.856	0.758	0.957	0.614	0.612	0.945
Pgp-inhibitor (Category 1: Inhibitor, Category 0: Non-inhibitor)	0.003	0.003	0.004	0.000	0.001	0.007	0.000
Pgp-substrate	0.006	0.017	0.021	0.030	0.008	0.005	0.015
HIA	0.395	0.638	0.371	0.637	0.841	0.156	0.555
$F_{20\%}$	0.600	0.920	0.732	0.953	0.767	0.244	0.897
$F_{30\%}$	0.998	0.999	0.997	0.999	0.997	0.983	0.999
$F_{50\%}$	0.905	0.948	0.850	0.991	0.933	0.460	0.977

Table 5 – Distribution properties of molecules

Distribution Property	Molecule 1	Molecule 2	Molecule 3	Molecule 4	Molecule 5	Molecule 6	Molecule 7
PPB	94.576	91.356	74.509	85.82	93.535	93.563	89.665
VDss	-0.124	-0.185	-0.060	-0.244	-0.133	-0.066	-0.065
BBB	0.001	0.000	0.000	0.000	0.000	0.003	0.000
Fu	4.301	6.835	18.001	12.456	6.395	6.252	8.200
OATP1B1 inhibitor	0.111	0.168	0.089	0.155	0.125	0.079	0.137
OATP1B3 inhibitor	0.615	0.546	0.557	0.839	0.892	0.690	0.845
BCRP inhibitor	0.000	0.000	0.000	0.000	0.000	0.000	0.000
MRP1inhibitor	0.181	0.283	0.416	0.456	0.438	0.514	0.604

Table 6 – Metabolism and excretion properties of molecules

Metabolism Property	Molecule 1	Molecule 2	Molecule 3	Molecule 4	Molecule 5	Molecule 6	Molecule 7
CYP1A2 inhibitor	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CYP1A2 substrate	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CYP2C19 inhibitor	0.335	0.391	0.392	0.037	0.021	0.065	0.015
CYP2C19 substrate	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CYP2C9 inhibitor	0.900	0.961	0.955	0.934	0.993	0.992	0.976
CYP2C9 substrate	0.188	0.032	0.016	0.001	0.002	0.001	0.000
CYP2D6 inhibitor	0.000	0.000	0.004	0.000	0.000	0.001	0.001
CYP2D6 substrate	0.000	0.002	0.003	0.000	0.002	0.000	0.000
CYP3A4 inhibitor	0.000	0.000	0.000	0.005	0.000	0.000	0.001
CYP3A4 substrate	0.002	0.002	0.007	0.000	0.000	0.000	0.000
CYP2B6 inhibitor	0.031	0.014	0.066	0.093	0.122	0.155	0.062
CYP2B6 substrate	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CYP2C8 inhibitor	0.985	0.793	0.950	0.946	0.996	0.992	0.996
HLM Stability	0.064	0.116	0.681	0.171	0.258	0.061	0.080
Excretion Property							
CL_{plasma}	2.944	3.367	3.170	3.391	3.498	2.516	3.366
$T_{1/2}$	0.965	0.931	0.929	1.146	0.966	1.071	1.259

Toxicity property. Toxicity properties, hERG blockers (the hERG gene encoding a potassium ion channel that plays a critical role in the electrical activity of the heart, particularly in the repolarization of the cardiac action potential) [30], hERG Blockers (10 μM), drug-induced liver injury (DILI), AMES mutagenicity (AMES mutagenicity testing helps identify compounds that can cause genetic mutations) [31], rat oral acute toxicity, FDA maximum recommended daily dose [32] (FDAMDD), skin sensitization, Log Kp (cm/s, skin permeation), carcinogenicity (assesses the potential of a compound to cause cancer after long-term exposure), eye corrosion, eye irritation, respiratory, human hep atotoxicity (refers to the toxic effects of a substance on the human liver), drug-induced nephrotoxicity (nephrotoxicity refers to the adverse effects of drugs or their metabolites on kidney function, which can lead to conditions such as acute kidney injury, chronic kidney disease, and even kidney failure in severe cases), ototoxicity (refers to the potential for medicines or chemicals to cause damage to the inner ear, resulting in hearing loss, tinnitus or balance problems), hematotoxicity (refers to the adverse effects of a drug or compound on blood and its components, including red blood cells, white blood cells, platelets and bone marrow cells), genotoxicity, RPMI-8226 immunitoxicity, A549 cytotoxicity, Hek293 cytotoxicity, and drug-induced neurotoxicity were examined. The data obtained for toxicity properties are given in Table 7.

Environmental toxicity property. Environmental toxicity properties, bioconcentration factors (it is a critical metric for assessing the potential for a compound to accumulate in biological organisms), inhibition growth concentration 50 (IGC_{50}) [33], lethal concentration 50% for freshwater microorganisms ($LC_{50}FM$), and lethal concentration 50% for daphnia magna ($LC_{50}DM$) were analyzed. The data obtained for environmental toxicity properties are given in Table 8.

Tox21 pathway property. Tox21 pathway property, NR-AhR (provides valuable information on potential metabolic, immune, endocrine and carcinogenic toxicity), NR-AR (important for assessing endocrine toxicity, reproductive risks and cancer potential), NR-AR-LBD (refers to a specific assay targeting the nuclear receptor pathway for the androgen receptor ligand-binding domain), NR-aromatase (help us detect and understand the interactions between compounds and the aromatase enzyme), NR-ER (helps us understand endocrine disruption and its implications for human health and safety), NR-ER-LBD (interaction of compounds with the ligand binding domain of the estrogen receptor, which plays a crucial role in mediating hormonal responses and signaling pathways helps us understand), NR-PPAR-gamma (identify compounds that interact with the receptor and help predict their effects on metabolism, toxicity and therapeutic potential), SR-ARE (helps to understand how compounds affect cellular oxidative stress and activation of detoxification pathways), SR-ATAD5 (a valuable tool for assessing DNA damage response and repair mechanisms), SR-HSE (helps assess how compounds interact with the cellular heat shock response, a fundamental stress adaptation mechanism), SR-MMP (helps to evaluate the interaction of compounds with matrix metalloproteinases), and SR-p53 (assess how compounds affect the p53 pathway, which plays a central role in regulating the cellular response to DNA damage [34], oxidative stress and other genotoxic insults) were analyzed. The data obtained for Tox21 pathway properties are given in Table 9.

Medicinal chemistry property. Lastly, medicinal chemistry properties, quantitative estimate of drug-likeness (QED), globally accessible surface area (GASA), synthetic accessibility score (Synth), the proportion of sp^3-hybridized carbon atoms (Fsp3), molecular complexity estimation – 18 (MCE-18), natural product similarity score (NPscore), Lipinski Rule, Ghose Rule, Veber Rule, Egan Rule, Muegge Rule, Pfizer Rule, Glaxo Smith Kline (GSK) Rule, Golden Triangle, pan-assay interference compounds (PAINS), Brenk Rule, antibiotic-like activity related to mechanism nuclear magnetic resonance (ALARM NMR), Bristol-Myers Squibb (BMS), Chelator Rule, colloidal aggregators, firefly luciferase (FLuc) inhibitors, blue fluorescence, green fluorescence, reactive compounds, promiscuous compounds, synthetic accessibility (SA), and leadlikeness were examined in ADMET properties [35,36]. The data obtained for medicinal chemistry properties are given in Table 10.

Table 7 – Toxicity properties of molecules

Toxicity Property	Molecule 1	Molecule 2	Molecule 3	Molecule 4	Molecule 5	Molecule 6	Molecule 7
hERG Blockers	0.099	0.058	0.066	0.030	0.053	0.050	0.036
hERG Blockers (10 μM)	0.210	0.140	0.113	0.113	0.087	0.102	0.094
DILI	0.995	0.987	0.988	0.948	0.998	0.995	0.994
AMES Mutagenicity	0.131	0.218	0.495	0.612	0.725	0.710	0.641
Rat Oral Acute Toxicity	0.336	0.263	0.353	0.395	0.457	0.693	0.513
FDAMDD	0.425	0.402	0.645	0.772	0.874	0.932	0.904
Skin Sensitization	0.204	0.186	0.261	0.685	0.599	0.576	0.795
Log Kp (cm/s, Skin Permeation)	-9.130	-9.200	-9.550	-9.680	-9.760	-9.590	-9.910
Carcinogenicity	0.528	0.596	0.888	0.813	0.961	0.959	0.945
Eye Corrosion	0.001	0.001	0.001	0.056	0.137	0.271	0.171
Eye Irritation	0.146	0.357	0.295	0.755	0.867	0.893	0.938
Respiratory	0.640	0.717	0.611	0.991	0.985	0.980	0.975
Human Hep atotoxicity	0.782	0.791	0.826	0.707	0.535	0.588	0.534
Drug-induced Nephrotoxicity	0.988	0.972	0.991	0.873	0.919	0.982	0.801
Ototoxicity	0.237	0.200	0.182	0.247	0.132	0.137	0.112
Hematotoxicity	0.206	0.192	0.357	0.188	0.198	0.175	0.091
Genotoxicity	1.000	1.000	1.000	1.000	1.000	1.000	1.000
RPMI-8226 Immunitoxicity	0.018	0.021	0.023	0.028	0.039	0.029	0.024
A549 Cytotoxicity	0.002	0.001	0.002	0.003	0.001	0.002	0.001
Hek293 Cytotoxicity	0.072	0.024	0.059	0.114	0.060	0.072	0.121
Drug-induced Neurotoxicity	0.807	0.783	0.831	0.749	0.877	0.923	0.837

Table 8 – Environmental toxicity properties of molecules

Environmental Toxicity Property	Molecule 1	Molecule 2	Molecule 3	Molecule 4	Molecule 5	Molecule 6	Molecule 7
Bioconcentration Factors	0.439	0.291	0.194	0.497	0.579	0.452	0.547
IGC_{50}	3.134	2.946	2.862	3.200	3.294	3.128	3.267
$LC_{50}FM$	3.929	3.561	3.467	3.959	4.172	3.928	4.057
$LC_{50}DM$	4.531	4.255	4.229	4.613	4.699	4.524	4.680

Table 9 – Tox21 pathway properties of molecules

Tox21 Pathway Property	Molecule 1	Molecule 2	Molecule 3	Molecule 4	Molecule 5	Molecule 6	Molecule 7
NR-AhR	0.011	0.010	0.004	0.010	0.007	0.003	0.009
NR-AR	0.027	0.027	0.035	0.052	0.051	0.040	0.065
NR-AR-LBD	0.001	0.000	0.001	0.000	0.001	0.001	0.000
NR-Aromatase	0.003	0.001	0.002	0.015	0.001	0.001	0.005
NR-ER	0.025	0.029	0.011	0.427	0.009	0.004	0.180
NR-ER-LBD	0.001	0.000	0.000	0.018	0.000	0.000	0.004
NR-PPAR-gamma	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SR-ARE	0.920	0.779	0.672	0.962	0.786	0.822	0.971
SR-ATAD5	0.001	0.001	0.000	0.002	0.000	0.000	0.001
SR-HSE	0.157	0.097	0.102	0.080	0.131	0.156	0.131
SR-MMP	0.023	0.004	0.006	0.242	0.006	0.013	0.150
SR-p53	0.032	0.006	0.008	0.068	0.016	0.013	0.100

Table 10 – Medicinal chemistry properties of molecules

Medicinal Chemistry Property	**Molecule 1**	**Molecule 2**	**Molecule 3**	**Molecule 4**	**Molecule 5**	**Molecule 6**	**Molecule 7**
QED	0.558	0.577	0.560	0.512	0.460	0.492	0.469
GASA	1.000	1.000	1.000	1.000	1.000	1.000	1.000
Synth	3.000	3.000	3.000	3.000	3.000	3.000	3.000
Fsp^3	0.300	0.333	0.333	0.300	0.333	0.300	0.300
MCE-18	52.462	51.857	54.214	54.846	54.214	54.846	54.846
NPscore	-1.065	-0.975	-1.032	-0.827	-0.906	-1.170	-0.756
Lipinski Rule	0.000	0.000	0.000	0.000	1.000	0.000	1.000
Ghose Rule	0.000	0.000	0.000	1.000	1.000	1.000	1.000
Veber Rule	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Egan Rule	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Muegge Rule	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Pfizer Rule	0.000	0.000	0.000	0.000	0.000	0.000	0.000
GSK Rule	1.000	1.000	1.000	1.000	1.000	1.000	1.000
Golden Triangle	0.000	0.000	0.000	0.000	1.000	1.000	1.000
PAINS	0 alerts	0 alerts	0 alerts	0 alerts	0 alerts	0 alerts	0 alerts
Brenk	2 alerts	2 alerts	2 alerts	2 alerts	2 alerts	2 alerts	2 alerts
ALARM NMR	0 alerts	0 alerts	0 alerts	2 alerts	2 alerts	1 alerts	2 alerts
BMS	0 alerts	0 alerts	0 alerts	0 alerts	0 alerts	0 alerts	0 alerts
Chelator Rule	0 alerts	0 alerts	0 alerts	0 alerts	0 alerts	0 alerts	0 alerts
Colloidal aggregators	0.133	0.057	0.155	0.434	0.443	0.496	0.495
FLuc inhibitors	0.290	0.435	0.341	0.316	0.538	0.307	0.387
Blue fluorescence	0.194	0.137	0.207	0.137	0.213	0.117	0.092
Green fluorescence	0.672	0.546	0.604	0.622	0.631	0.629	0.636
Reactive compounds	0.004	0.002	0.001	0.005	0.004	0.004	0.007
Promiscuous compounds	0.039	0.028	0.004	0.025	0.001	0.001	0.006
SA (Synthetic Accessibility)	4.190	4.320	4.310	4.260	4.330	4.230	4.260
Leadlikeness	1.000	1.000	1.000	1.000	1.000	1.000	1.000

Result and Discussion

When the physicochemical properties were examined for the seven molecules studied, it was determined that the molar refractivity (MR) values for molecules 4, 5, 6, and 7 were slightly higher than the ideal values and that the molecules met the desired conditions in all other parameters. MR is a measure that reflects the polarizability of a molecule, the volume of the electron cloud, and its steric properties (volumetric size). The hydrophobic interaction potential of the molecule also influences molar refractivity at the point of binding with the target protein. This in turn affects the binding affinity. It also provides indirect information on how far the molecule can diffuse into tissues. For good oral bioavailability, an ideal molar refractivity value in the range $40 \leq MR \leq 130$ is desirable. Since the deviation observed in the MR values for molecules 4, 5, 6, and 7 was very small, all values were considered acceptable. Molar refractivity values of molecules were given Figure 2.

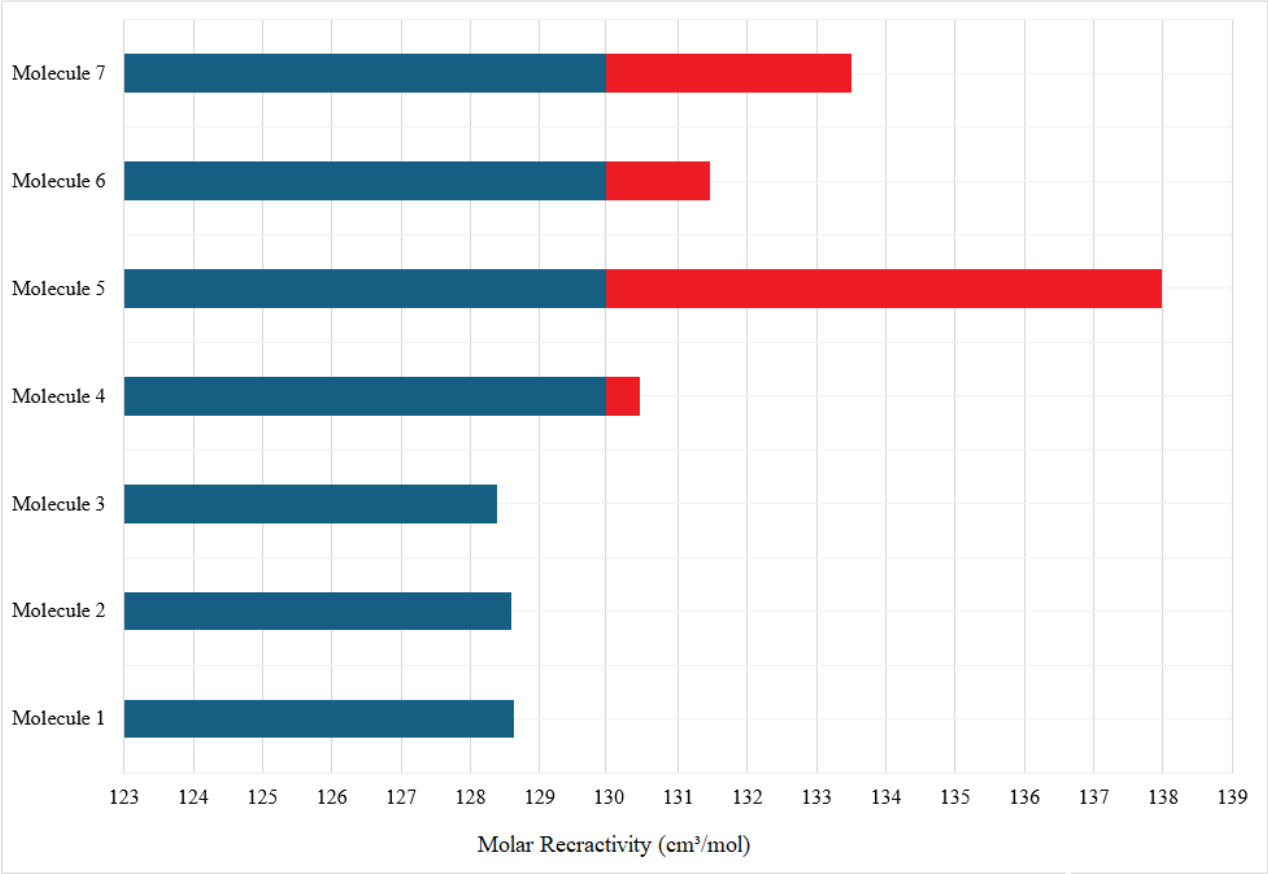

Figure 2 – Molar refractivity values of molecules

In order for the molecules to show good absorption and solubility potential, a lipophilicity (Log Po/w) value between 0 and 3 is desired. This range is considered the ideal range. This range is especially important for a good oral bioavailability and solubility balance. When the lipophilicity values of our molecules are examined, it is seen that the consensus Log Po/w values of all the molecules studied are within this ideal range. This shows us that all of our molecules can be characterized as suitable molecules in terms of lipophilicity. Lipophilicity values of molecules were given Figure 3.

When the water solubility values calculated according to ESOL, Ali, and SILICOS-IT methods and given in Table 3 were analyzed, it was found that all molecules were soluble. Water solubility plays a critical role in terms of ADME properties. Because water solubility directly affects the absorption, distribution, metabolism, and excretion of a drug candidate molecule in the body. Such that the molecule

must be dissolved in water to be absorbed through the digestive tract (GI tract), and highly soluble molecules show rapid and complete absorption. For passage through the cell membrane, molecules must first be dissolved in aqueous media. Even lipophilic compounds cannot be absorbed unless they are slightly dissolved in water. Water-soluble molecules can reach the target tissues by circulating freely in the plasma. The balance of solubility and lipophilicity is critical for central nervous system drugs. Enzymes in the liver (CYP450) have easier access to water-soluble molecules. It determines the half-life of the drug by affecting metabolic stability. High-solubility molecules are more suitable for excretion in urine. The visual representation of these data obtained is given in Figure 4.

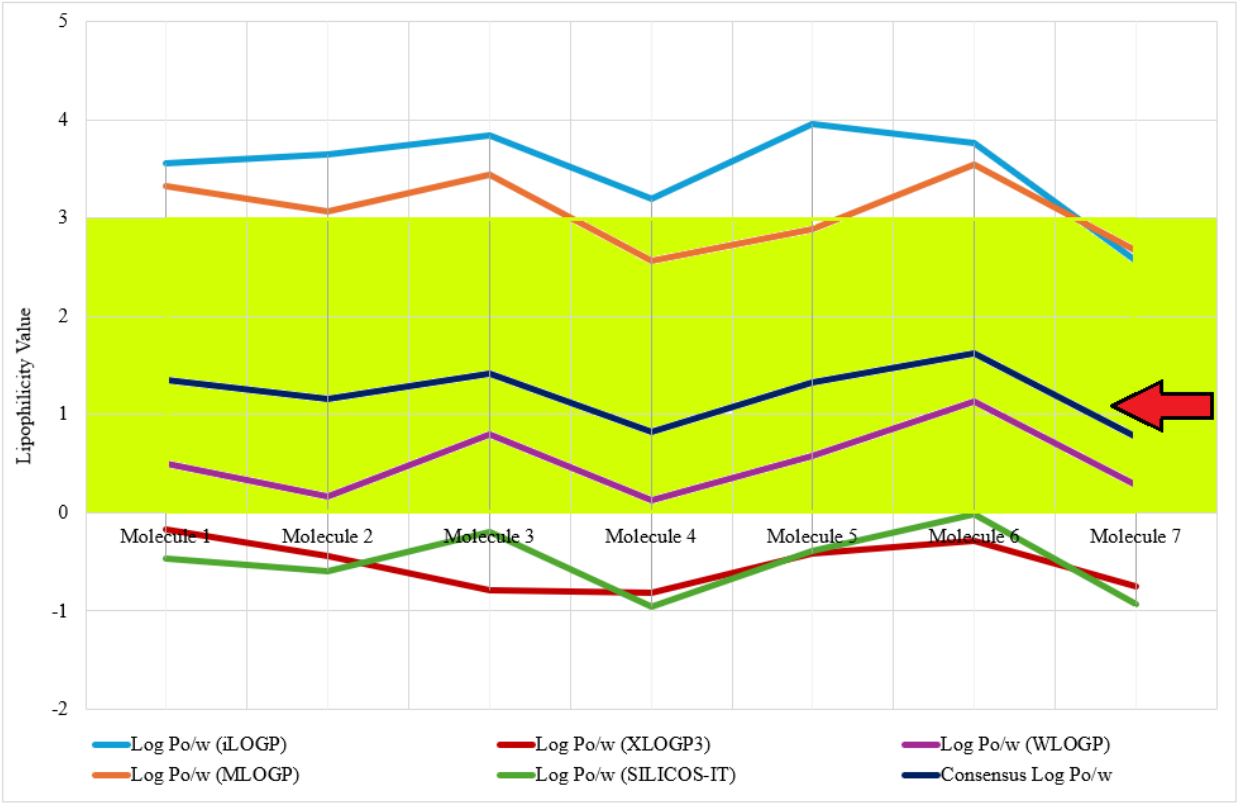

Figure 3 – Lipophilicity values of molecules

When the absorption properties values of the molecules given in Table 4 were analyzed, it was found that only molecule 2 was ideal in terms of Caco-2 Permeability, no molecule was ideal in terms of MDCK Permeability, and molecule 5 and molecule 6 were found to be evaluable in terms of PAMPA. It was observed that all molecules were ideal in terms of Pgp-inhibitor and Pgp-substrate. In terms of HIA, $F_{20\%}$, $F_{30\%}$, and $F_{50\%}$, the values obtained from molecule 6 were found to have better values compared to other molecules. When the molecules were analyzed in terms of distribution properties, generally good results were obtained in terms of other properties except for VDss property. In terms of metabolism and excretion properties, it was observed that all data except CYP2C9 inhibitor and CYP2C8 inhibitor values were suitable for all molecules studied, and in terms of excretion property, it was observed that the values for CLplasma were very good and $T_{1/2}$ values were partially ideal. In terms of toxicity properties, very good values were obtained for all molecules for hERG Blockers, hERG Blockers (10 μM), rat oral acute toxicity, ototoxicity, hematotoxicity, RPMI-8226 immunotoxicity, skin sensitization, A549 Cytotoxicity, and Hek293 Cytotoxicity. In terms of environmental toxicity properties, ideal results were obtained for all the substances studied. The visual graph of these data is given in Figure 5. In terms of Tox21 pathway properties, good results were obtained for all molecules except SR-ARE.

Figure 4 – Water solubility values of molecules

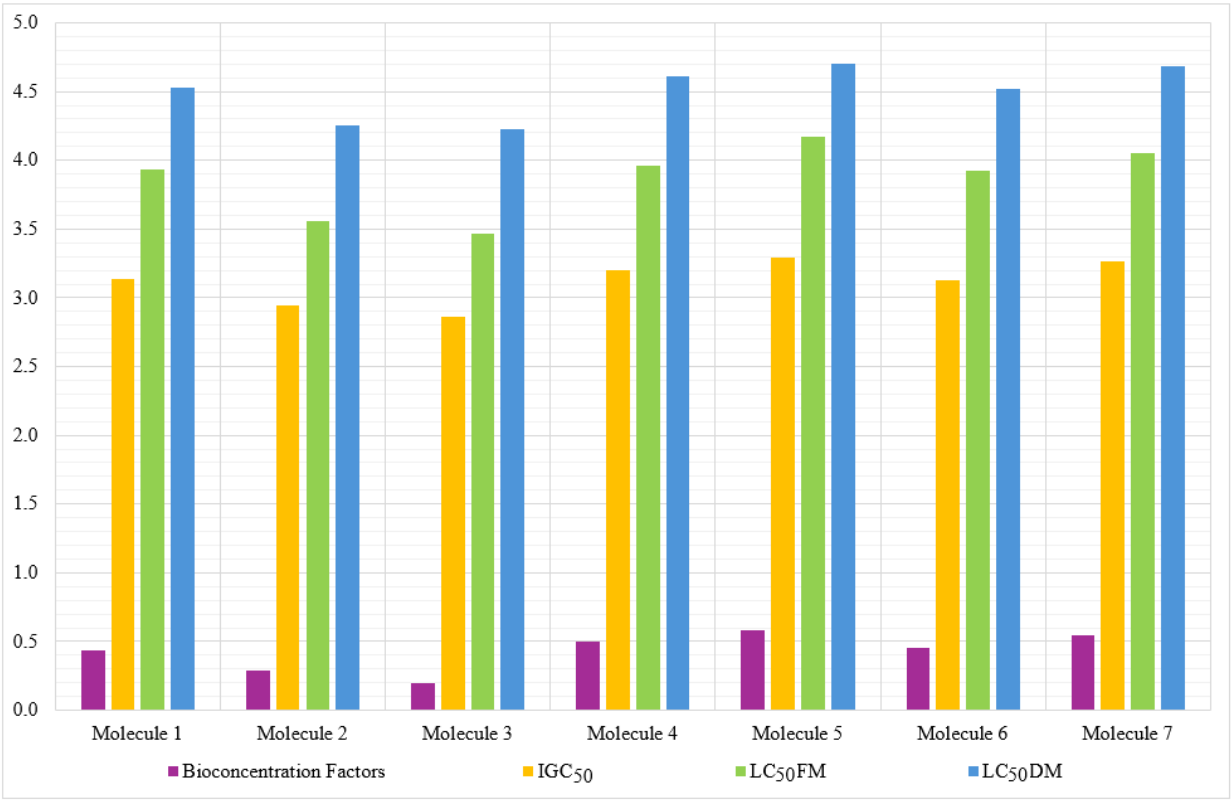

Figure 5 – Environmental toxicity properties of molecules

Finally, when the medicinal chemistry property values were examined, it was observed that the results obtained for all molecules in terms of Synth, MCE-18, Veber Rule, Egan Rule, Muegge Rule, Pfizer Rule, PAINS, BMS, Chelator Rule, Colloidal Aggregators, FLuc Inhibitors, Blue Fluorescence, Reactive Compounds, Promiscuous Compounds, and SA (Synthetic Accessibility) were very good.

Conclusion

In this study, it was concluded that molecule 5 ((E)-4-((4-(((4-bromopyridin-1(2H)-yl) methylene) amino)-3-(4-methoxyphenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)methyl)piperazi-ne-1-carboxylic acid) can be considered as a drug candidate to be used in the treatment of this disease and advanced studies can be carried out when the physicochemical properties, lipophilicity, water solubility, absorption property, distribution property, metabolism property, toxicity property, environmental toxicity property, tox21 pathway property, and medicinal chemistry properties of seven different substituted-piperidine-3-carboxamide derivatives compounds that can be used in the treatment of Crohn's disease are examined.

Conflict of interest

The authors declare that they have no conflicts of interest.

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