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BIOLOGICAL NEW TARGETS PREDICTION & *ADME* PROFILING OF 1,1 - DICHLORDIAZODIENES ON THE BASIS OF O-NITROBENZOIC ALDEHYDE

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Abstract. As we know, aromatic compounds with nitro group have high antimicrobial properties. Considering this, the study of the biological targets and molecular docking of the synthesized compounds was planned using the Swiss Targeted Prediction and Swiss ADME programs. New Biological Targets Prediction by using SWISS Target Prediction covers Biological Activities, Mapping of Bioavailability Radar of Newly Synthesized Products, Brain Or Intestina L Estimate D permeation (Egan BOILED-Egg), *ADME* Profiling by using Swiss ADME, Lipinski ROF Drug ability criteria. Based on the obtained results, it can be said that compounds can show biological activity.

Keywords: *dichlorodiazadiene, Swiss target prediction, Swiss ADME, BOIELD-Egg, Pharmacokinetics properties, Blood Brain Barrier (BBB), Human Intestinal Absorption (HIA).*

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1. Introduction

The synthesis of new drugs become the reason of interest of researches for many years (Yousuf *et al.*, 2022). Thus, in order to synthesize the corresponding compounds, it is necessary to conduct various experiments by taking into account their specific parameters, numerous research works were carried out to determine to be the effective drugs for patients. At the same time, the synthesized pharmaceuticals must meet a number of obligations, such as the low toxicity of the molecules, at the same time one of the important issues is showing high biological activity.

Even if corresponding pharmaceuticals are synthesized, a number of problems still remain relevant. Because infections grow rapidly, become stronger and more resistant to drugs, and in this case, the demand for the synthesis of new drugs is increasing day by day.

In addition, there are certain molecular targets for compounds to show biological activity, which are time-consuming to identify by researchers. To overcome a number of

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difficulties like this, have been created a number of computational programs related to the design and development of drugs.

The use of calculation-based programs specificate a large number of potential targets, at the same time prevent additional time loss for researchers.

For the identification of biological targets have been developed a number of softwares, one of them is Swiss Targeted Prediction and Swiss ADME programs (Willett, 2011; Ballester *et al.,* 2007; Sastry *et al.,* 2011; Liu *et al.,* 2011; Armstrong *et al.,* 2011; Perez-Nueno *et al.,* 2012; Armstrong *et al.,* 2010).

By means of this software, it is possible to calculate physicochemical descriptors, as well as predict compounds' ADME (absorption, distribution, metabolism, and excretion) parameters, pharmacokinetic properties, drug-like nature, and medicinal chemistry compatibility.

As is known from the literature, aromatic compounds with nitro group have high antimicrobial properties. Thus, aromatic nitro compounds found in plants and mushrooms are also used in folk medicine as biologically active metabolites.

For example can be showed, the use of 1-Nitroacnadine (an alkaloid of the Chinese plant Stepanin) (Xian-kai *et al.,* 1993) in the treatment of cardiovascular and throat pain (Bukhalid *et al.,* 2002; Isolde *et al.,* 2008) Aristolox used as a dietary supplement for weight loss (Johnson *et al.,* 2000)

It has also been determined that nitro group-bearing compounds play an important role in cell signaling (Uppal *et al.,* 2011). 2-Nitrophenol is used to prevent the accumulation of ticks on mammals.

Nitration of aromatic amino acids leads to changes in the functions of proteins in mammals.

2. Materials and Methods

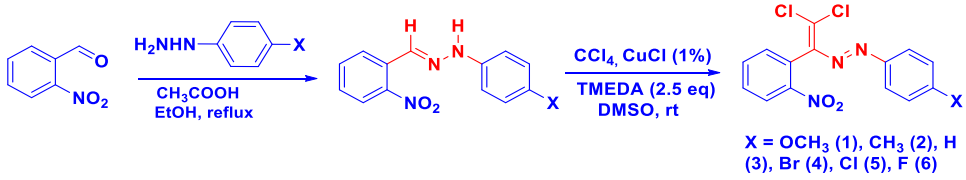
Taking into account that aromatic compounds with a nitro group which show high biological activity, it is planned to study the biological targets and molecular docking of the synthesized compounds (Maharramov *et al.,* 2018) 1-6 using Swiss Targeted Prediction and Swiss ADME software.

The SwissADME software for molecular docking and prediction of biological targets of synthesized dichlorodiazadienes is freely available at http://www.swissadme.ch

New Biological Targets Prediction by using SWISS Target Prediction covers Mapping of Bioavailability Radar of Newly Synthesized Products (3.1), Biological Activities (3.2), Brain Or IntestinaL EstimateD permeation (Egan BOILED-Egg) (3.3), ADME Profiling by using Swiss ADME (3.4), Lipinski ROF Drug ability criteria (3.5).

3. Results and Discussion

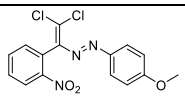
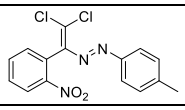
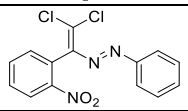
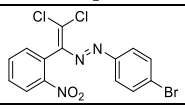
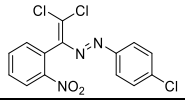
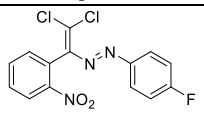
Taking all this into account, we synthesized 1,1-dichlorodiazadienes based on the corresponding nitrobenzoic aldehyde (Scheme 1).



Scheme 1. General scheme for the synthesis of 1,1-dichlorodiazadienes

First, we present an overview of synthesized dichlorodiazadienes.

Table 1. Overview of presented dichlorodiazadienes

N	Structure	Name of the substance	Molecular formula	Molecular weight	Smile notation
1		(E)-1-(2,2-dichloro-1-(2-nitrophenyl)vinyl)-2-(4-methoxyphenyl)diazene	C15H11Cl2N3O3	352.17 g/mole	COC1=CC=C(C=C1)\N=N\C(=C(Cl)Cl)C1=C(C=CC=C1)N(=O)=O
2		(E)-1-(2,2-dichloro-1-(2-nitrophenyl)vinyl)-2-(p-tolyl)diazene	C15H11Cl2N3O2	336.17 g/mole	CC1=CC=C(C=C1)\N=N\C(=C(Cl)Cl)C1=C(C=CC=C1)N(=O)=O
3		(E)-1-(2,2-dichloro-1-(2-nitrophenyl)vinyl)-2-phenyldiazene	C14H9Cl2N3O2	322.15 g/mole	ClC(Cl)=C(\N=N\C1=CC=CC=C1)C1=C(C=CC=C1)N(=O)=O
4		(E)-1-(4-bromophenyl)-2-(2,2-dichloro-1-(2-nitrophenyl)vinyl)diazene	C14H8BrCl2N3O2	401.04 g/mole	ClC(Cl)=C(\N=N\C1=CC=C(Br)C=C1)C1=C(C=CC=C1)N(=O)=O
5		(E)-1-(4-chlorophenyl)-2-(2,2-dichloro-1-(2-nitrophenyl)vinyl)diazene	C14H8Cl3N3O2	356.59 g/mole	ClC(Cl)=C(\N=N\C1=CC=C(Cl)C=C1)C1=C(C=CC=C1)N(=O)=O
6		(E)-1-(2,2-dichloro-1-(2-nitrophenyl)vinyl)-2-(4-fluorophenyl)diazene	C14H8Cl2FN3O2	340.14 g/mole	FC1=CC=C(C=C1)\N=N\C(=C(Cl)Cl)C1=C(C=CC=C1)N(=O)=O

3.1. Mapping of Bioavailability Radar of the Products

First, were studied the pharmacokinetic properties of compounds.

It should be noted that the most convenient way to study pharmacokinetics, that is, the result of a therapeutic combination in the human body, is to divide the various effects directed at the specified target into individual parameters.

By using Swiss ADME software, are performed pharmokinetics, physico-chemical, bio-chemical such as membrane permeability calculations and studied properties such as lipophilicity, volume, polarity, insolubility, unsaturation and flexibility (Pastewska *et al.*, 2021).

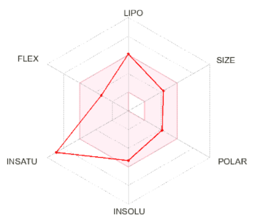
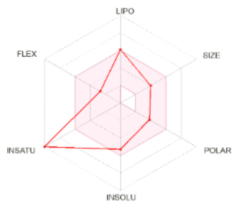
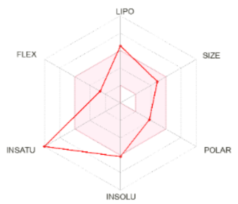
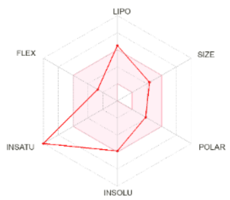
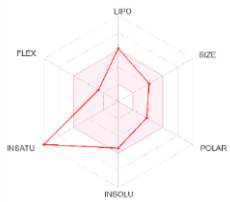
The six descriptors (LIPO, SIZE, POLAR, INSOLU, INSATU, FLEX), show us that those molecules which exist within the pink region of radar are considered to possess good bioavailability property in the body.

The table below shows the bioavailability radar and results of the synthesized compounds.

It was found from the results obtained by the program, that the unsaturation property of the synthesized compound 1-6. at the same time, the insolubility property of compound 4, the lipophilic property of compounds 2 and 5 slightly deviated from the pink zone.

In general all the compounds are showing excellent bioavailability radar properties for the descriptors LIPO, SIZE, POLAR, INSOLU & FLEX.

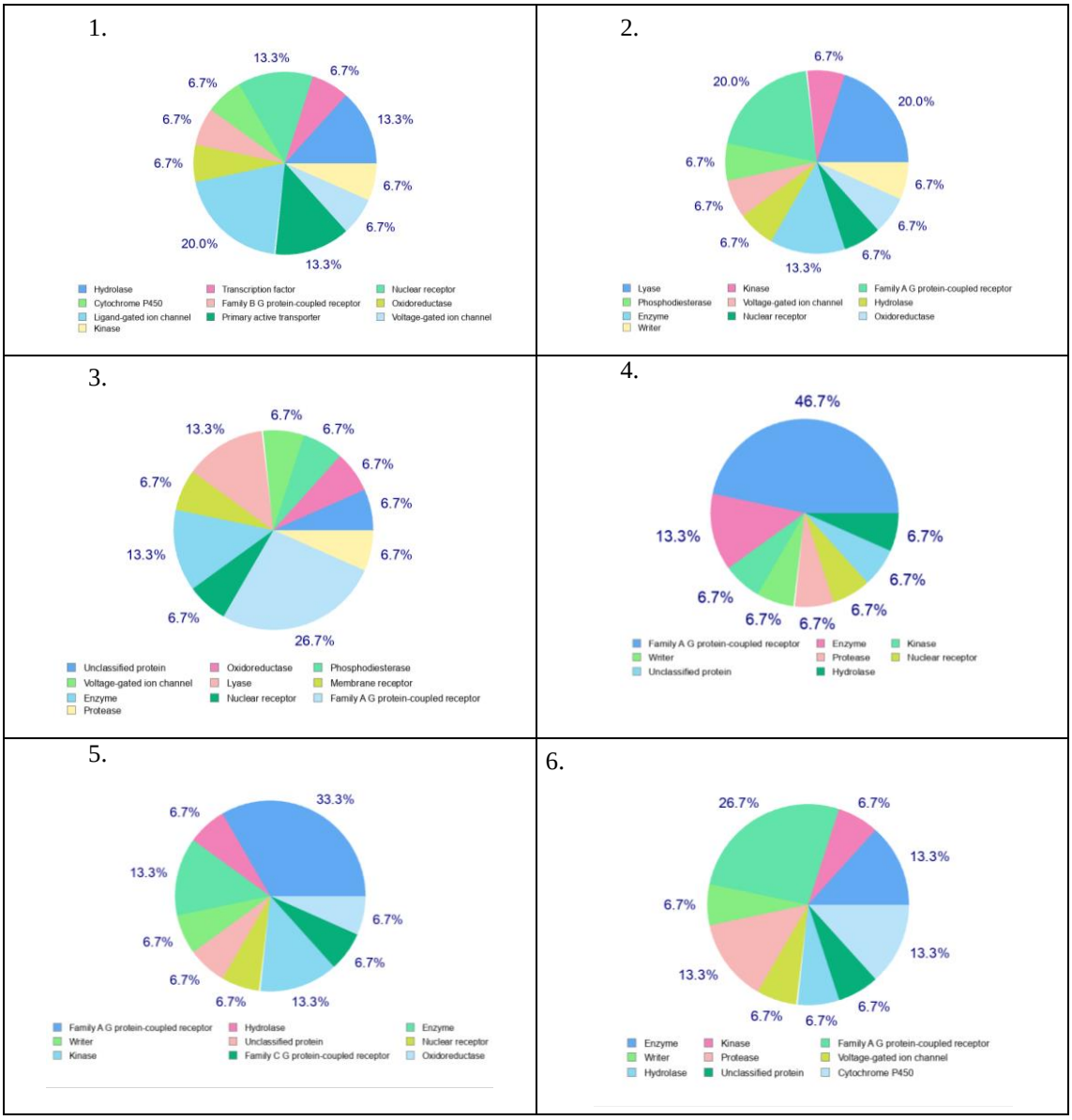
Table 2. Bioavailability radar and obtained results

Bioavailability radar	Lipophilicity	size	polarity	insolubility	insaturation	flexibiliti
	Lying in pink zone	Lying in pink zone	Lying in pink zone	Lying in pink zone	Slightly exceeding the pink zone	Lying in pink zone
	Lying in pink zone	Lying in pink zone	Lying in pink zone	Lying in pink zone	Slightly exceeding the pink zone	Lying in pink zone
	Lying in pink zone	Lying in pink zone	Lying in pink zone	Lying in pink zone	Slightly exceeding the pink zone	Lying in pink zone
	Lying in pink zone	Lying in pink zone	Lying in pink zone	Lying in pink zone	Slightly exceeding the pink zone	Lying in pink zone
	Lying in pink zone	Lying in pink zone	Lying in pink zone	Lying in pink zone	Slightly exceeding the pink zone	Lying in pink zone
	Lying in pink zone	Lying in pink zone	Lying in pink zone	Lying in pink zone	Slightly exceeding the pink zone	Lying in pink zone

3.2. Biological Activities

At the same time by using the Swiss Targeted Prediction software , was compared the similarity some of the molecules with biological activity and enzymes (Table 3)

Table 3. Biological activities of compounds



The synthesized dichlorodiazadienes were screened (both 2D and 3D) to find similar molecules among compounds known to be experimentally active on one or more of the 3068 proteins (Daina *et al.*, 2019).

In the given diagram, the ligand-gated ion channel in (E)-1-(2,2-dichloro-1-(2-nitrophenyl)vinyl)-2-(4-methoxyphenyl)diazene (1) compound has 20% percent similarity compared to (E)-1-(2,2-dichloro-1-(2-nitrophenyl)vinyl)-2-(p-tolyl)diazene (2) Phosphodiesterase enzyme and enzyme.

Other (E)-1-(2,2-dichloro-1-(2-nitrophenyl)vinyl)-2-phenyldiazene (3), (E)-1-(4-bromophenyl)-2-(2,2- dichloro-1-(2-nitrophenyl)vinyl)diazene (4), (E)-1-(4-chlorophenyl)-2-(2,2-dichloro-1-(2-nitrophenyl)vinyl)diazene (5) , (E)-1-(2,2-dichloro-1-(2-nitrophenyl)vinyl)-2-(4-fluorophenyl)diazene (6) substances Family A.G protein-coupled receptor enzyme similarity in properties exceeds compared to others .

3.3. Brain Or Intestina L Estimate D permeation (Egan BOILED-Egg)

By using the SWISS ADME prediction program at the same time was used Brain or Gut permeability method (BOILED-Egg).

The Brain or Gut Permeability Method (BOILED-Egg) is an efficient and accurate predictive computer program that calculates the lipophilicity and polarity properties of small organic molecules.

At this time, a graph of dependence is drawn between the total area of the polar surface of WLOGP and TPSA-. Here, a fragmental technique called topological polar surface area calculated using (TPSA), WLOGP , representation of a purely atomistic method based on the fragmental system of Wildman and Crippen.

It is believed that compounds with a high probability of passive absorption of the gastrointestinal tract are located in the form of dots in the egg white (white ellipse). The dots in the egg yolk (in the yellow ellipse) are for compounds that are more likely to be absorbed through the BBB (Blood-Brain-Barrier) to enter the central nervous system. Compounds with a poor absorption or lack of BBB permeability are in the gray zone.

If a given molecule is a blue colored dot, it is predicted to be a substrate of P-glycoprotein (PGP+) and is actively absorbed from the brain or into the gastrointestinal lumen. If a non-substrate of P-glycoprotein (PGP-) is predicted, the corresponding dot is red color (picture 1).

It is noted that all compounds are observed in egg white (white ellipse), that is, they are likely to be absorbed from the gastrointestinal tract. At the same time, all compounds are listed as red dots, which predicts that they are non-substrates of P-glycoprotein (PGP-).

It should be noted that the presence of electron-donor groups in the compound has a positive impact on their biological activity. Thus, compared compound 1 containing a methoxy group to compound 6 containing a fluorine atom showed less activity.

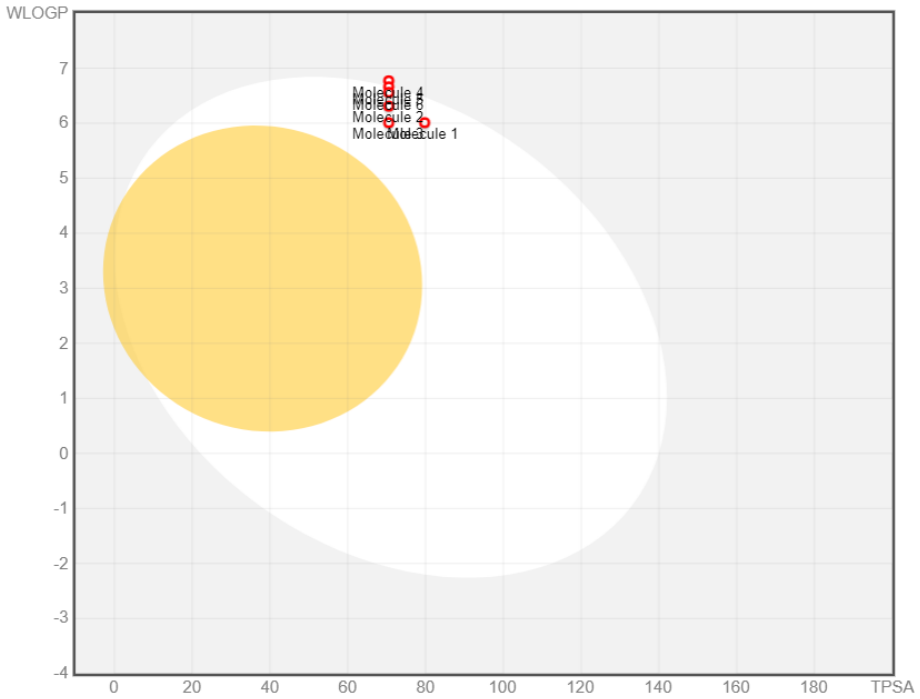


Fig 1. BBB (Blood-Brain-Barrier) method

3.4. ADME Profiling by using Swiss ADME

With another program, pharmacokinetic computation of P-glucoprotein and cytochrome P450 proteins is possible. Pharmacokinetics (PK) studies the trajectory of drug action in the body and provides important information about how drugs affect the body.

The synthesized compound was also screened on P-glucoprotein and Cytochrome P 450 isoenzymes by means of Swiss ADME.

This method allows us to effectively predict in advance how well the synthesized compound can be an affordable substrate or inhibitor for p-glucoprotein and various cytochrome P450 isozymes.

During the study of the compounds, it was known that this compound is not a substrate for P-glucoprotein. But it has shown good results as an inhibitor for cytochrome P450. Gastrointestinal absorption of the compound is high. Blood-brain barrier permeability is also good (Table 4).

Table 4. Farmokinetic properties of the compound

Compound	GI absorbtion	BBBermeant	P-gp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Log Kp (skin permeation) cm/s
1	High	-	-	+	+	+	-	-	-4.77
2	High	-	-	+	+	+	-	-	-4.40
3	High	-	-	+	+	+	-	-	-4.57
4	Low	-	-	+	+	+	-	-	-4.56
5	High	-	-	+	+	+	-	-	-4.33
6	High	-	-	+	+	+	-	-	-4.60

3.5. Lipinski ROF Drug ability criteria

The Lipinski's five rules, or it called in another way as Pfizer's five rules, is the basic rule for studying the drug-likeness of compounds, for determining whether a chemical compound with a certain pharmacological activity has chemical properties and physical features.

The rule was put forward by Christopher A. Lipinski in 1997.

According to this rule, the molecular weight of the compound should not be greater than 500 a.m.u (atomic mass unit), the octanol/water ratio (Clog P) should be less than 5, the number of rotating bonds in the molecule should not exceed 9, the total polar surface area (TPSA, 20- 130 A^2) should be in the appropriate range, the number of donor-acceptor bonds should be less than 5, and the number of hydrogen acceptor bonds should be less than 10.

This rule also has some drawbacks. Thus, it cannot provide information about whether the compound is pharmacologically active or not. The physical and chemical properties of the substances are given below (Table 5).

Table 5. Physico-chemical properties of compounds

Presented data	1	2	3	4	5	6
Molecular weight	352.17 g/mole	336.17 g/mole	322.15 g/mole	401.04 g/mole	356.59 g/mole	340.14 g/mole
Num. heavy atoms	23	22	21	22	22	22
Num. arom. heavy atoms	12	12	12	12	12	12
Fraction Csp3	0.07	0.07	0.00	0.00	0.00	0.00
Num. rotatable bonds	5	4	4	4	4	4
Num. H-bond acceptors	5	4	4	4	4	5
Num. H-bond donors	0	0	0	0	0	0
Molar Refractivity	91.34	89.81	84.85	92.55	89.86	84.81
TPSA	79.77 Å²	70.54 Å²	70.54 Å²	70.54 Å²	70.54 Å²	70.54 Å²

It is clear from the table that these compounds follow Lipinski's five rules.

4. Conclusion

As a result of studying biological targets and molecular docking by means of Swiss Targeted Prediction and Swiss ADME software, were obtained the following results for the corresponding dichlorodiazadiens.

1. In general compounds show excellent bioavailability radar properties for LIPO, SIZE, POLAR, INSOLU & FLEX descriptors.

2. All compounds are observed in egg white (white ellipse), that is, they are supposed to be absorbed from the gastrointestinal tract.

3. The presence of an electron donor group in compounds has a positive impact on their biological activity.

4. During the study of compounds it had become clear that this compound is not a substrate for P-glucoprotein. But it has shown good results as an inhibitor for cytochrome P450

5. It allows to predict in advance that compounds which follow Lipinski's 5 rules have properties as pharmaceauticals.

Based on these results, it is possible to predict that the compounds may show biological activity.

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