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1,3,5-TRIAZINE DERIVATIVES SYNTHESIS AND POTENTIAL BIOLOGICAL TARGETS PREDICTION AND ADME PROFILING

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Abstract. In order to synthesize TAP complexes, the reactions of metal-activated nitriles obtained from their reactions with metals were carried out with ammonia. The reaction of N,N-dimethylsianamide with $Zn(CH_3COO)_2$ resulted in the formation of the corresponding bis-(2,4-bis-(N,N-dimethylamino)-1,3,5-triazapentadienato Zn(II)) complex, which was confirmed by mass spectrometry analysis. Continuing the research in this direction, reactions were carried out with other derivatives of acetonitrile, $CHBr_2CN$ and CCl_3CN, leading to the formation of a new product. Specifically, dissolving the reaction product in acetone resulted in the formation of 2,6-bis(dibromomethyl and dichloromethyl)-4,4-dimethyl-1,4-dihydro-1,3,5-triazines. The structure of the synthesized compounds was confirmed using the RQA method. As we know, 1.3.5-triazine compounds have high biological properties. Taking all this into account, Swiss ADME and Swiss Targeted Prediction software was used to study biological targets of the 2,6-bis(dibromo and dichloro methyl)-4,4-dimethyl-1,4-dihydro-1,3,5-triazines and to create their ADME profiles. New biological targets for 1.3.5-triazine compounds include Mapping of Bioavailability Radar of substances, ADME Profiling, Egan BOILED EGG, Lipinski Drug ability (ROF) criteria and biological activities based on the obtained results. Thus, obtained results allow us to say that synthesized compounds are able to show biological activity.

Keywords: *TAP complex, 1.3.5 triazine Swiss target prediction, Swiss ADME, BOIELD-Egg, pharmacokinetics properties, Blood Brain Barrier (BBB), Human Intestinal Absorption (HIA).*

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1. Introduction

1,3,5-Triazines are also called as s-triazines, i.e. symmetrical triazines, so that the three nitrogen atoms are arranged alternately with carbon atoms to form a six-membered ring (Cascioferro *et al*., 2017). Compounds with 1,3,5-triazine structure have found wide application in pharmacological and biochemical research, for example as, anti-microbial

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(Bahar *et al*., 2015), anti-viral (Mibu *et al*., 2015), anti-fungal (Singla *et al*., 2015) are a class of compounds with a wide range of applications due to their activity. Along with this, it has antitumor activity (Liu *et al*., 2015). Considering all of it, these types of compounds offer new potential molecular targets in drug design and development.

Drug design is a field that involves the process of synthesis new drugs and developing currently existing drugs. It's based on a computer-based modeling system in another ways called *in silico*. When we say *In silico* approach, experiments are conducted using computer programs and algorithms instead of real experimental studies and as a result, it provides an opportunity to rapidly evaluate the intended compounds, saving time and resources. The main stages involving design are as follows (Mandal *et al*., 2009; Anderson *et al*., 2003).

The first stage is target selection. It's the first step of drug design. Here, identified as the molecular targets that can interact with the drug. Second, is to find out the "Leader" compound. Third, design based on structure. Fourth, development of the structure and functional groups. Fifth is the synthesis and testing: This is where selected compounds are synthesized in the laboratory and biological researches conducted over them. And the final stage is Clinical tests: Compounds are sent for clinical tests assessing their safety and effectiveness (Makhouri *et al*., 2018; Aziz *et al*., 2018).

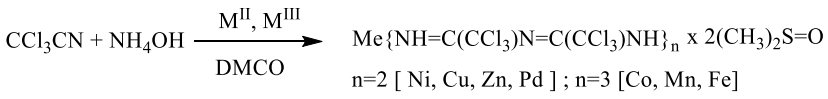
Recently, one of the most widely used insilico studies is SwissADME and SwissTargetPrediction, which are used in drug design and pharmacology research and let us to investigate molecular and pharmacokinetic properties (Bakchi *et al*., 2022). They are used to determine the effects and hazards of pharmaceuticals on the body. However, they differ from each other in their fields of application. So, SwissADME assesses the pharmacokinetic properties of drugs and predicts how they affect the body (Sączewski *et al*., 2024; Daina *et al*., 2019; Kar & Leszczynski, 2020). On the other hand, Swiss Target Prediction determines the potential effect of synthesized compounds on biological targets (Mathai *et al*., 2020; Patil *et al*., 2024). Both play an important role in drug design (Atakishiyeva *et al*., 2023).

In the presented article the structures of synthesized compounds were determined by means of RA and were investigated intermolecular non-covalent bonds. A non-covalent bond is seen as an interaction between atoms or molecules that occurs without direct electron sharing. Compared to covalent interactions, such bonds are not considered as strong ones. Nevertheless, they play an important role in a number of chemical and biological processes (Mati *et al*., 2010, Müller-Dethlefs & Hobza, 2000).

2. Result and Discussion

2.1. Synthesis of Triazapentadiene Complexes

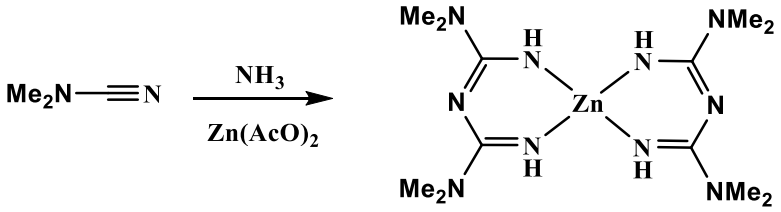
In our previous studies, were synthesized complexes of bis and tris-(2,4-bis-trichloromethyl-1,3,5-triazapentadienate (MeII,III) (TAP) as templates from the reaction of trichlorasetonitrile with transition metals (Me = Cu, Ni, Zn, Pd, Fe, Co, Mn) in the presence of NH_3 (Shixaliyev *et al*., 2012, 2013a, 2013b, 2014).



Scheme 1. Synthesis of triazapentadiene complexes

It should be noted that the synthesis of TAP complexes with high yield and solubility in organic solvents, enable apply them as catalysts in organic synthesis. Along with this, it was determined by us that TAP complexes show high biological activity (Lehnert & Tampe, 2017). Taking into account the application of TAP complexes as catalysts and that they showphysiological activity, obtaining TAP complexes compatible with other derivatives of acetonitrile (CH_3CN, $ClCH_2CN$, $BrCH_2CN$, $(CH_3)_2NCN$-) in the templating form, is an urgent issue in terms of organic synthesis. Studies have shown that the corresponding TAP complexes are not obtained by the conducting reactions with acetonitrile and other derivatives (CH_3CN, $ClCH_2CN$, $BrCH_2CN$,$(CH_3)_2NCN$) under these conditions.

Therefore, in order to synthesize TAP complexes of these types of nitriles, initially on our part were carried out corresponding reactions of metal-activated nitriles along with ammonia obtained from their reaction with metals. Thus, it was determined by mass spectral analysis that in this condition, the corresponding bis-(2,4-bis-N-dimethylamine)-1,3,5-triazapentadienate Zn-II) complex is obtained in the reaction of N,N-dimethylamine amide with $Zn(CH3COO)_2$.



Scheme 2. Synthesis of the complex of bis-(2,4-bis-(*N*,*N*-dimetilamin)-1,3,5-triazapentadienato Zn(II)

The structure of the synthesized complex was determined by the mass spectrum analysis. So, in the spectrum, the masses M/z = 493.2056 and m/z=297.1017, m/z = 237.0884 correspond to the molecular ion of the complex (4) $[C_{16}H_{34}N_{10}O_4Zn\text{-}(H)]^+$ and $[C_6H_{18}N_6Zn\text{-}(H)AcO]^+$, (2) 1,1-dimethylquanidine $[C_6H_{18}N_6Zn\text{-}(H)]^+$, respectively.

Unlike trichloroacetonitrile, N,N-dimethylcyanamide does not react with ammonia under normal conditions because the carbonyl activity of the carbon atom in the nitrile group is weak. It is in this regard that the pre-interaction of N,N-dimethylcianamide with metal Zn allows the formation of metal-activated nitrile (1). At this time, the interaction of the nitrogen atoms with the positively charged Zn atom facilitates the attack of the ammonia molecule which is a weak nucleophilic particle to the carbon atom, leading to the getting of 1,1-dimethylquanidine (2). Then, 1,1-dimethylquanidine as a nucleophile particle reacts with the second molecule of N,N-dimethylcianamide to synthesize 2,4-bis(dimethylamine)-1,3,5-triazopentadiene ligand (3) and from the reaction of the NH_2 amine group formed in the latter with the anion of the salt, is synthesized the corresponding complex (4) by releasing two molecules of acetic acid. It is clear that while N,N-dimethyl cyanamide interacts with “hard” acids, they will readily react with nucleophilic reagents as the (1) - activation increases the polarity of the CN bond and the positive charge of the carbon atom bound to the nitrogen, as is the case with CCl_3CN in trichloroacetonitrile.

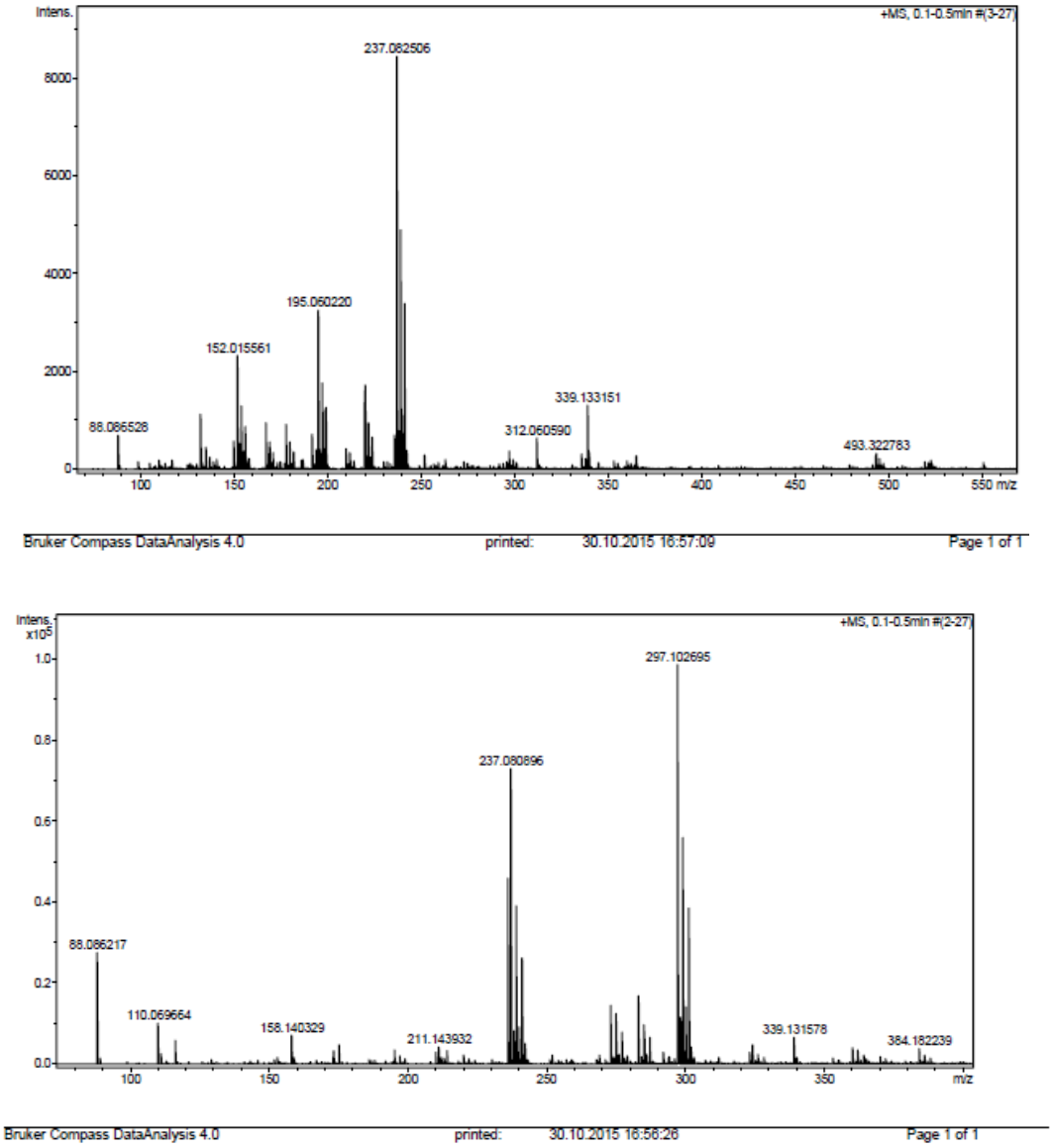
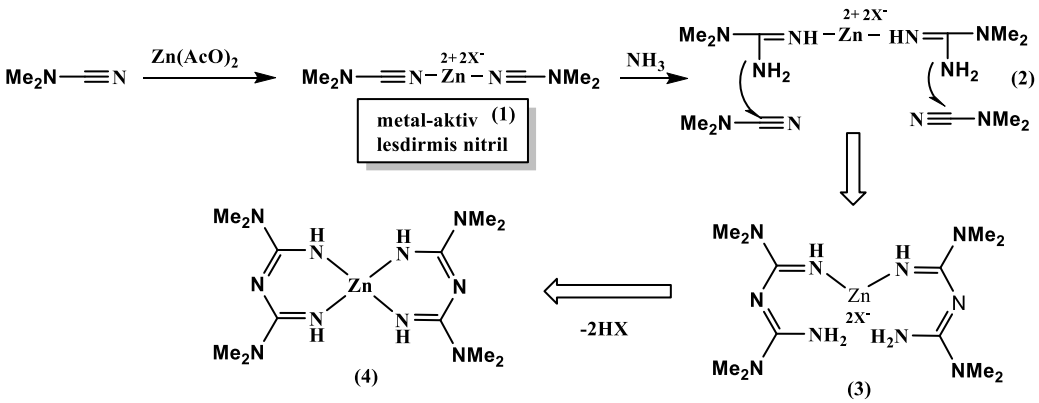


Figure 1. Analysis of the mass spectrum of the synthesized complex

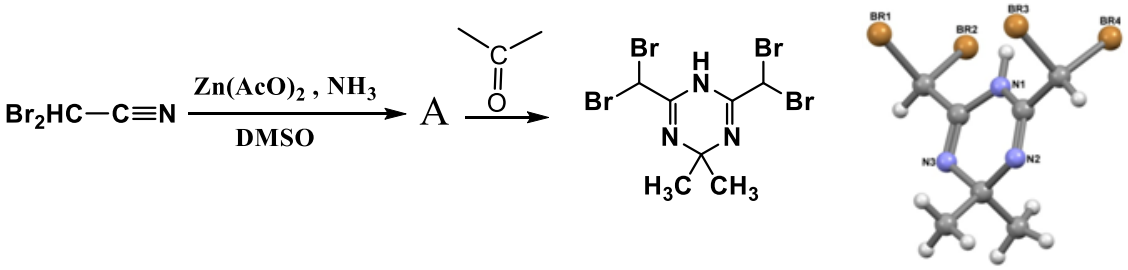


Scheme 3. Mechanism of obtaining of the bis-(2,4-bis-(*N*,*N*-dimetilamin)-1,3,5-triazapentadienato Zn(II) complex

Thus, it was possible to obtain the Zn(II) complex on the basis of 1,3,5-triazapentadiene ligand from the reaction of the [N,N-dimethylcianamide] Zn(II) (metal-active nitrile) complex with ammonia, obtained from the reaction of Zn acetate with N,N-dimethylcianamide.

2.2. Synthesis of 1,3,5-triazine derivatives

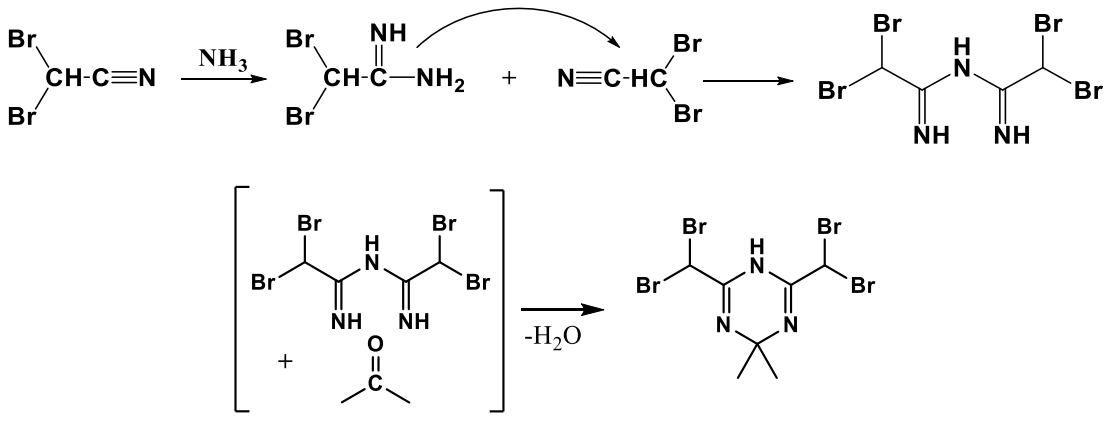
While continuing research in this direction, another derivative of acetonitrile was reacted with CHBr2CN and a new product was determined to be obtained. So, the dissolution of the obtained reaction product (A) in acetone resulted in the formation of the 2,6-bis(dibrommethyl)-4,4-dimethyl-1,4-dihydro-1,3,5-triazine (5) (Scheme 4) compound.



Scheme 4. Obtaining of 2,6-bis(dibromethyl)-4,4-dimethyl-1,4-dihydro-1,3,5-triazine

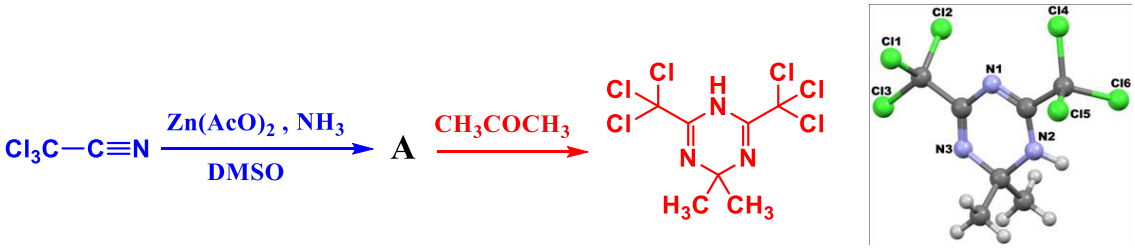
The presence of a heminal dimethyl fragment in the 4,4 position of the compound 2,6-bis(dibromomethyl)-4,4-dimethyl-1,4-dihydro-1,3,5-triazine 5 (as can be seen from its molecular structure) suggests that the structure of the compound A corresponds to 2,2-dibrom-N-(2,2-dibrom-1-aminoethyl) acetamid 6 in the simplest case (without taking into account Zn for simplicity). Thus, the presence of the heminal dimethyl fragment in compound 5 can be obtained only in one case, from the reaction of the imine groups in compound 6 with acetone.

The synthesis of the compound 2,2-dibromo-N-((2,2-dibromo-1-iminoethyl) acetamidamide can be represented by the following simple conversions in the reaction of dibromasetonitrile CHBr2CN with ammonia NH3.



Scheme 5. Mechanism of the obtaining of 2,6-bis(dibrommethyl)-4,4-dimethyl-1,4-dihydro-1,3,5-triazine

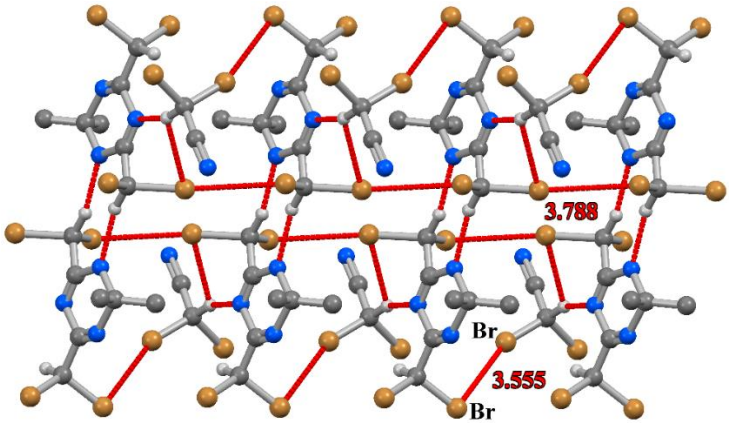
By the same way, triazine was obtained on the basis of trichlorasetonitrile and its structure was confirmed by the RQA method.



Scheme 6. The reaction for the obtaining of 4,4-dimethyl-2,6-bis ((trichloromethyl)-1,4-dihydro-1,3,5-triazine

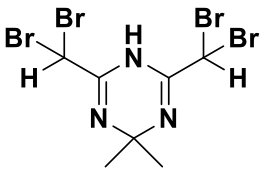
2.3. The study of non-covalent compounds in the molecule of 2,6-bis (dibromide)-4,4-dimethyl-1,4-dihydro-1,3,5-triazine

In recent years, with the aim of studying non-covalent interactions of interest in synthetic compounds, the crystal of the 2,6-bis(dibromide)-4,4-dimethyl-1,4-dihydro-1,3,5-triazine molecule has been grown and the non-covalent interactions present in the molecule have been investigated. As seen in the Figure 2 below, there are two types of non-covalent interactions in the molecule: Br···Br [3.555 Å] and H···Br [3.788 Å]. Considering the halogen bond formed between the intermolecular heminal Br atoms, as well as the intramolecular hydrogen bond, it can be concluded that the nature of the halogen atom significantly influences the crystal design in the formation of both interactions.



2.4. Potential biological targets prediction and ADME profiling of 1,3,5-triazine derivatives

Recently, planned synthesis has allowed the prediction of the biological properties of synthesized compounds based on their structures. Considering that many natural compounds and pharmaceuticals contain the 1,3,5-triazine fragment, our synthesized 2,6-bis ((dibromine and dichloromethyl)-4,4-dimethyl-1,4-dihydro-1,3,5-triazines (conditionally referred to as compounds 1 and 2) are pre-calculated in the Swiss Targed Prediction and Swiss ADME biological activities. For this, the formula of the compound is written in Swiss in SMILE format and then in a few seconds all the calculations are given, i.e. pharmacokinetic, physicochemical, biochemical calculations, membrane conductivity and similar properties that are possible with drug substances.



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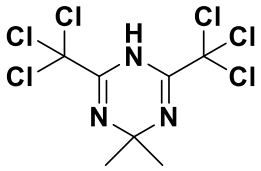

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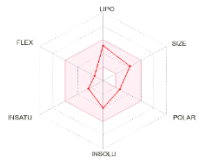
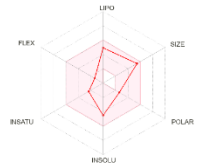
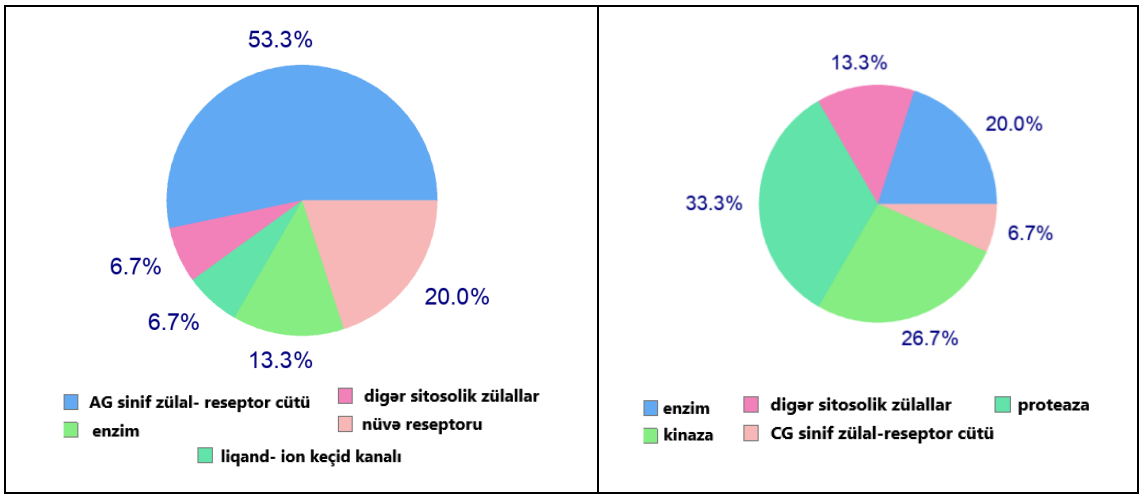
Table 1. Mapping of bioavailability radar of the products 1 and 2

	Biological activity	Lipophilicity	Volume	Polarity	Insolubility	Saturation	Elasticity
1		Lying in pink zone	Lying in pink zone	Lying in pink zone	Lying in pink zone	Lying in pink zone	Lying in pink zone
2		Lying in pink zone	Lying in pink zone	Lying in pink zone	Lying in pink zone	Lying in pink zone	Lying in pink zone

In the Table, 6 properties are calculated to determine the similarity of the compound to the drug substances. The fact that the given properties of compounds (lipophilicity, volume, polarity, insoluble, saturation elasticity) are from the pink zone of the diagram allows to assume that they exhibit high biological activity.

Table 2. Biological activities of compounds



Another method of analysis of the synthesized compounds suggested that they possessed new biologically active properties. Therefore, there have been given different classes of studies based on the diagram shown. Here is a graph of the percentage of specific similarity of the compounds with the receptors of enzyme inhibitors, the AG-

class proteins, the inhibitor of the enzymes lyase, kinase, phosphodiesterase and protease. Based on the colored areas, we can assume that the molecule has a greater affinity (53.3%) for AG class proteins than for property 1. For molecule 2, the property similarity to the enzyme kinase is 33.3%, which suggests that the synthesized compounds can be studied as bioactive compounds.

The brain or intestinal permeability method (BOILED - Egg) is an effectively working accurate predictive model that calculates the lipophilicity and polyarity properties of small organic molecules. In this case, the dependence graph is drawn between WLOGP and TPSA (total area of the polar surface). It is assumed that if the synthesized compound is located in the egg yolk, this compound passively passes through the blood-brain barrier if the synthesized compound is located in the egg white, then that compound can be absorbed in the gastrointestinal tract. This makes it possible to assume that the synthesized compound can be separated from the central nervous system due to p-glucoprotein.

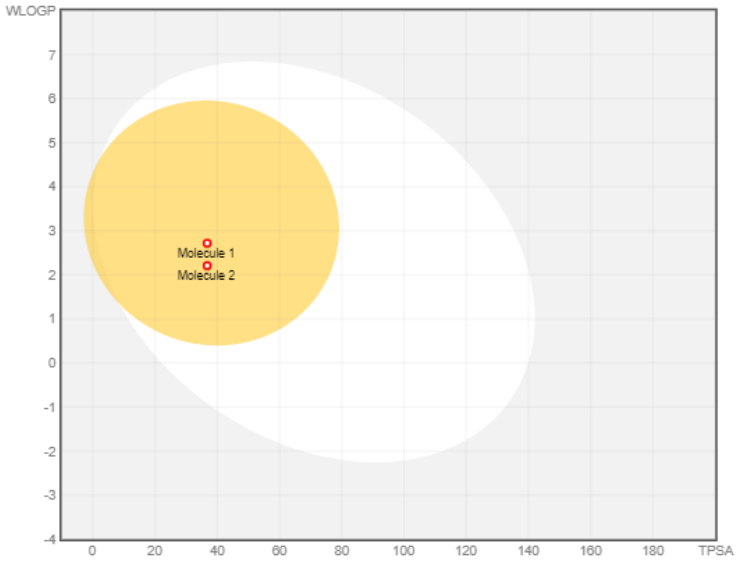


Figure 3. Combinations 1 and 2 are located in the egg yolk. This passively passes the combination 1 and 2 through the blood-brain barrier

In our example, in the course of research, it turns out that compounds 1 and 2 are most likely to be active as transcription factors for the androgen receptor. By means of Swiss ADME also performed screening of synthesized compounds on P-glucoprotein and cytochrome P450 isoferments. . This method allows to effectively predict in advance how favorable a substrate or inhibitor the synthesized compounds may be for p-glucoprotein and various cytochrome P450 isoferments. Our thematic study further revealed that neither of the two compounds is a substrate for P-glycoprotein. One compound has shown good results as an inhibitor for cytochrome P450. Gastrointestinal adsorption of both compounds is high. It also has good blood-brain barrier transmission.

Table 3. ADME properties of compounds

Substance	Gastrointestinal adsorption	blood-brain barrier conductance	P-glycoprotein	CytochromeP1A2 Inhibitor	CytochromeP2C19 Inhibitor	CytochromeP2C9 Inhibitor	CytochromeP2D6 Inhibitor	CytochromeP3A4 Inhibitor	Log *Kp* cm/s (Skin permeability)
1	High	+	-	+	+	+	-	-	-5.94
2	High	+	-	-	+	-	-	-	-6.85

ADME - absorption, distribution, metabolism and excretion

The study of such various physicochemical properties of the molecule with descriptors is based on Lipinsky's 5 rules. According to this rule, the mass of the molecule should not exceed 500 a.m.n (atomic mass number), the number of donor acceptor bonds should be less than 5, the number of acceptor hydrogen bonds should be less than 10, the number of acceptor hydrogen communications should be less than 10, the octanol/water ratio (log P) should be less than 5, the number of rotating bonds should not be more than 9, the number of specific type atoms and the total area of the polar surface (TPSA, 20-130 A2) should be in the appropriate range. This is also associated with the presence of polar atoms in the molecule, mainly nitrogen “N” and sulfur “S”.

Table 4. Both combinations copmly with Lipinsky's 5 Rule

Sunstance	Formula Of The Molecule	Molecule mass g/mol	Number of heavy atoms	The number of heavy atoms of the atom in the nucleus	Fraction Csp^3	Number of rotating communications	H-number of acceptor bonds	H-number of donor bonds	Log *Po/w* *(iLOGP) (octanol to water ratio)	TPSA Polyarsəthinsahəsi) Å²
1	$C_7H_7Cl_6N_3$	345.87	16	0	0.71	2	2	1	2.56	36.75
2	$C_7H_9Br_6N_3$	454.78	14	0	0.71	2	2	1	1.84	36.75

3. Conclusion

As a result, the study suggests that the biotransformed products of all newly obtained fungi may be active, which means that all compounds can be used as drug preparations according to Lipinski's ?? 5 rule. These compounds may be active against transcription factors, mainly androgen and glucocorticoid receptors. Molecular docking studies have also been conducted. Thus, all compounds exhibited high pharmacokinetic properties without the possibility of Drug-Drug Interactions (DDIs) with any cytochrome P450 isoferment. It is thought that the compounds 1 and 2 have blood-brain barrier permeability. The results obtained during the prediction of the biological network pathways indicate that the new metabolites are likely to be active as a transcription factor against AR (androgen receptor) and GR (glucocorticoid receptor) receptors. Associated genes of compounds (AR and NR3C1 - nuclear receptor subfamily 3 group C member

1)1. Nuclear receptor transcription is related to two biological pathways, such as the Chaperone cycle of HSP90 (heat shock protein 90 - heat shock protein 90) for steroid hormone receptors. It's also possible that the corresponding genes will be linked to 25 other biological networks.

4. Experimental Part

4.1. Method of synthesis of TAP-Zn complex

A solution of 1.6 ml of N,N-dimethyl cyanamide and 2.5 ml of NH_3 and 5 ml of DMSO is prepared. Then 1.1 mmol of Zn $((CH_3COO)_2$ salt dissolved in C_2H_5OH or DMSO was added to the mixture. The reaction is instantaneous, lasting seconds and precipitation forms. The sediment is then filtered and air-dried. Analysis of the mass spectrum of the structure of the synthesized complex, m/z = 493.2056 and m/z = 297.1017, m/z = 237.0884 corresponds to the molecular ion of the complex (4) $[C_{16}H_{34}N_{10}O_4Zn.(H)]_+$ and $[C_6H_{18}N_6Zn.(H)\ AcO]_+$, (2) 1,1-dimethylquanidine $[C_6H_{18}N_6Zn.(H)]_+$ respectively.

4.2. Method of synthesis of 4,4-dimethyl-1,4-dihydro-1,3,5-triazines

TAP complexes were synthesized with CHBr2CN and CCl3CN. The resulting TAP complexes were dissolved in 5 ml of acetone. Red crystals deposited in the solution were filtered and 2,6-bis ((dibromethyl) -4,4-dimethyl-1,4-dihydro-1,3,5-triazine and 4,4-dimethyl-2,6-bis ((trichloromethyl) -1,4-dihydro-1,3,5-triazine compounds were obtained.

Author Contributions

Conceptualization, GTA, NEA software, GTA, NRZ; writing-original draft preparation, GTA, SHM, SAI; writing-review and editing, GTA, AMM, visualization NEA, NRZ, IJA; project administration, NQS, GTA. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

Original data supporting the findings of this study are available. These data are available upon request from the corresponding author.

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