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N. A. Kopak
Lviv Polytechnic National University,
Department of Technology of Biologically Active Substances, Pharmacy and Biotechnology
nazarii.a.kopak@lpnu.ua

SEARCHING OF BIOLOGICAL ACTIVITY OF S-ESTERS 4-ACETYLAMINOBENZENETHIOSULFOACID USING METHODS OF CHEMOINFORMATICS

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The biological activity screening of thiosulfonoesters was carried out using the SuperPred, SwissTargetPrediction, and molecular docking programs. Based on the obtained data from virtual screening, promising directions for experimental biological investigations of S-esters 4-acetylaminobenzenethiosulfoacid were identified. Molecular docking demonstrated the feasibility of searching for new antiviral agents among the investigated thiosulfonoesters and selected a lead compound for these studies, namely thiosulfonoesters.

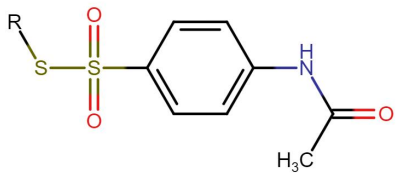
Key words: virtual screening; biological activity; molecular docking; Lipinski's rule.

Introduction

With each passing day, humanity faces novel challenges that arouse significant concern and increasingly command attention. Among such challenges is the rapidly growing prevalence of diseases caused by various viruses, necessitating the quest for new effective and safe antiviral agents. The task of addressing this issue is substantially complicated by the high probability of developing a wide range of bacterial and fungal infections as a result of weakened immunity caused by viruses. In particular, there have been instances of COVID-19 patients developing mucormycosis, aspergillosis, and other opportunistic bacterial and fungal infections, which in turn have complicated the disease's progression [1].

Advancements in treating viral infections are not making significant headway due to the complex nature of viral biology and how it differs from bacterial infections. At present, antiviral medications fail to eradicate viruses effectively and often provide limited relief in treating viral diseases, merely decreasing symptoms and mortality rates. The task becomes exponentially difficult due to co-existing microbial infections that thrive in an immunity-compromised environment. For instance, COVID-19 patients are frequently afflicted with bacterial and fungal infections such as mucormycosis and aspergillosis, which further challenge the treatment of the viral disease itself. Consequently, the urgent necessity is to discover novel, non-toxic drugs boasting both potent antiviral and antimicrobial properties. In recent times, extensive research focus has been placed on the investigation of organosulfur compounds. These compounds, especially those encompassing -S-S-disulfide bonds, have extensive applications in numerous fields [2], [3].

In the course of this article, we are set to explore the biological activities of certain specific compounds, as depicted in Scheme 1. They have been selected for their potential antimicrobial properties. However, it's not only the antimicrobial characteristics of these compounds that make them so promising. It is known that other synthetic thiosulfoesters have a wide range of biological activity, in particular antiparasitic [4], antithrombotic [5], antioxidant [6], antimicrobial [7] and antitumor [8] properties.



Scheme 1. S-esters 4-acetylaminobenzenethiosulfoacid

a $R = CH_3$
b $R = C_2H_5$
c $R = C_3H_5$
d $R = C_3H_7$
e $R = i\text{-}C_3H_7$

f $R = C_4H_9$
g $R = i\text{-}C_4H_9$
h $R = CH_2COOCH_3$
I $R = CH_2\text{-}CH(OH)\text{-}CH_2Cl$
j $R =$ 

k $R =$ 
l $R = C_6H_5$
m $R =$ 
n $R =$ 
o $R =$ 

Taking into account the prospects of these compounds as biologically active substances, it is advisable to carefully screen their biological activity, which in many cases can be both long-term and expensive. Avoiding such a situation can help the performance of primary biological screening using in silico methods. In particular, prediction of biological activity using the SuperPred, SwissTargetPrediction, MolliInspiration applications and molecular docking using the AutoDockTools software.

To plan directions for experimental studies of biological activity, we used SuperPred, SwissTargetPrediction and molecular docking applications. SuperPred is an online tool for predicting the metabolism and toxicity of chemicals. It employs various computational models to predict the potential metabolic fate of a chemical compound within an organism. It uses machine learning algorithms trained on a large dataset of known metabolism information to estimate the likelihood of different metabolic reactions occurring, such as oxidation, reduction, and hydrolysis.

Among the various methods utilized in computational chemistry, molecular docking stands out as one of the most informative and reliable. This technique is becoming increasingly important, especially considering recent advancements in the field. The database of protein structures, a crucial resource for molecular docking, has seen significant growth. It has recently surpassed the notable milestone of 100.000 structures cataloged. When we consider that the human body potentially has up to 500.000 such structures, the scale and relevance of this database become apparent. With this extensive repository at hand, the use of docking to determine the extent of ligand binding with the receptor has become progressively more accurate and dependable.

Molecular docking has a fundamental role in the journey of a drug compound in the body, serving as the final stage before a drug can elicit its intended effects. This process is instrumental in estimating how a ligand, or a drug molecule, interacts with its target, the receptor. Accurate predictions of these interactions are crucial for the development of effective drugs.

It is important to note, however, that molecular docking does not account for other crucial phases of a drug's lifecycle within the body. It doesn't consider aspects such as the drug's absorption into the bloodstream, its metabolism or transformation within the body, its subsequent excretion, or its potential toxicity. Despite not covering these stages, molecular docking remains indispensable.

The reason for this lies in its decisive role. While the aforementioned processes are all critical parts of a drug's journey, it is the actual binding of the ligand with the receptor that triggers the physiological reaction – the ultimate purpose of administering the drug. By accurately predicting this binding, molecular docking contributes significantly to our understanding of how and why a drug works. Therefore, the role of molecular docking in the development and testing of new drugs is becoming increasingly crucial in the world of medicinal chemistry [9].

Aim of the research – the virtual screening of the biological activity of S-esters 4-acetylaminobenzenethiosulfoacid using the computer programs SuperPred, SwissTargetPrediction, and molecular docking using AutoDockTools software to identify substances effective against COVID-19 disease.

Materials and research methods

S-esters of 4-acetylaminobenzenethiosulfoacid were chosen as objects of research received at the Department of Technologies of Biologically Active Compounds of Pharmacy and Production Biotechnology, the physicochemical and some antimicrobial properties of which are described in the work [10].

The predictions provided by SuperPred can assist researchers and scientists in understanding how a particular compound may be metabolized in the body, which is important for drug development, toxicology studies, and assessing the potential risks associated with exposure to chemicals [11].

SwissTargetPrediction serves as a valuable online resource for forecasting the macromolecular targets of bioactive small molecules, specifically proteins found in human, mouse, and rat organisms. This tool facilitates the comprehension of molecular mechanisms associated with specific phenotypes or bioactivities, enables the identification of potential side-effects, aids in the prediction of off-target interactions, and assesses the potential for repurposing therapeutically-relevant compounds. By leveraging this platform, researchers and scientists can gain deeper insights into the interplay between small molecules and their protein targets, leading to enhanced understanding and informed decision-making in drug discovery and development endeavors. Furthermore, SwissTargetPrediction provides a valuable resource for exploring novel therapeutic applications and improving the safety and efficacy profiles of potential drug candidates [12].

The Molinspiration program was used to calculate the parameters of compounds according to Lipinski's rules [13].

The Biovia program was used to present the 3D structure of compounds and targets, as well as to model bonds in the process of molecular docking [14].

The Autodock program was used for molecular docking [15].

Results and discussion

Before predicting activities of selected research objects in applications we will confirm that given compounds meet the requirements of the Lipinski rules (Table 1). The calculations were done using Molinspiration Cheminformatics Software [16].

Table 1

Compounds properties calculations results

Compound	Log P	Molecular polar surface, Å^2	The number of non-hydrogen atoms	Molecular weight	Number of hydrogen bond acceptors (O and N atoms)	Number of hydrogen bond donors (NH and OH groups)	The number of rotating connections	Molecular volume, Å^3
a	0.96	63.24	15	245.32	4	1	3	198.11
b	1.34	63.24	16	259.35	4	1	4	214.91
c	1.52	63.24	17	271.36	4	1	4	225.53
d	1.84	63.24	17	273.38	4	1	5	231.72
e	1.70	63.24	17	273.38	4	1	4	231.50
f	2.40	63.24	18	287.41	4	1	6	248.52
g	2.21	63.24	18	287.41	4	1	5	248.30
h	0.83	89.55	19	303.36	6	1	6	242.88
i	0.93	83.47	19	323.82	5	2	6	253.53
j	2.36	63.24	19	299.42	4	1	4	254.74
k	2.87	63.24	20	313.44	4	1	4	271.55
l	2.50	63.24	20	307.40	4	1	4	252.96
m	3.18	63.24	21	341.84	4	1	4	266.50
n	2.46	109.06	23	352.39	7	1	5	276.29
o	2.41	109.06	23	352.39	7	1	5	276.29

Requirements for the compounds by Lipinski [13]:

- No more than 5 hydrogen bond donors.
- No more than 10 hydrogen bond acceptors (all nitrogen or oxygen atoms).
- Molecular mass is less than 500 daltons.
- Calculated lipophilicity (log *P*) is less than 5.
- No more than 10 rotational bonds.

After the analysis of the obtained results, which are presented in the table, all the studied compounds meet the requirements prescribed in Lipinski's rules. These rules, also known as the Rule of Five, are essential guidelines in the field of drug discovery. Therefore, our compounds have a higher likelihood of good absorption, distribution, metabolism, and excretion (ADME) properties, which can contribute to their suitability as drug candidates [13].

The SuperPred web server establishes a connection between the chemical similarity of drug-like compounds and their molecular targets, enabling a therapeutic approach based on the principle of similar properties. Since its initial release, the server has witnessed a remarkable increase in the number of known compound-target interactions, soaring from 7.000 to 665.000. This expanded dataset not only enhances prediction quality but also allows for the estimation of confidence levels. To further enhance target prediction, the server has introduced new methodologies. These include considering 3D similarity, fragment occurrence, and the concordance of physical chemical properties. Additionally, the impact of different fingerprints on prediction accuracy has been thoroughly examined.

Significant improvements have been made to the dataset used for target prediction. It is no longer limited to confirmed binders but now includes non-binding substances as well, aiming to reduce false positives. With the latest version, SuperPred 3, the accuracy for ATC prediction has increased by nearly 5 % to reach 80.5 % compared to previous versions. By utilizing query compounds with sufficient structural similarity, the web server enables the prediction of potential medical indication areas for novel compounds and facilitates the discovery of new leads for known targets [17].

In the course of our research, we predicted the biological activity of thiosulfoesters a-o with the help of the program. The results of the screening are presented in Table 2.

Table 2

Prediction of biological activities using SuperPred resource

Compound	Target name	Indication	Probability, %	Model accuracy, %
1	2	3	4	5
a	CDK2/Cyclin A	Lymphoma [ICD-11:2A80-2A86]	89.23	91.38
	PI3-kinase p110-alpha/p85-alpha	Breast cancer [ICD-11: 2C60-2C65]	88.41	94.33
	Sodium channel protein type III alpha subunit	Angina pectoris [ICD-11: BA40]	86.79	96.9
	Adaptor-associated kinase	Coronavirus Disease 2019 (COVID-19) [ICD-11: 1D6Y]	73.96	83.1
b	Cyclin-dependent kinase 1/cyclin B1	Breast cancer [ICD-11: 2C60-2C65]	91.61	91.24
	PI3-kinase p110-alpha/p85-alpha	Follicular lymphoma [ICD-11: 2A80]	90.65	94.33
	Sodium channel protein type III alpha subunit	Angina pectoris [ICD-11: BA40]	87.86	96.9
	Adenosine A2b receptor	Herpes simplex virus infection [ICD-11: 1F00]	85.26	98.59
c	CDK2/Cyclin A	Acute lymphoblastic leukemia [ICD-11: 2A85]	88.95	91.38
	PI3-kinase p110-alpha/p85-alpha	Breast cancer [ICD-11: 2C60-2C65]	88.37	94.33
	Cyclin-dependent kinase 1/cyclin B1	Acute lymphoblastic leukemia [ICD-11: 2A85]	88.03	91.24

Continuation of Table 2

1	2	3	4	5
	Adenosine A2b receptor	Herpes simplex virus infection [ICD-11: 1F00]	79.3	98.59
d	Cyclin-dependent kinase 1/cyclin B1	Solid tumor/cancer [ICD-11: 2A00-2F9Z]	92.91	91.24
	PI3-kinase p110-alpha/p85-alpha	Breast cancer [ICD-11: 2C60-2C65]	91.09	94.33
	Adenosine A2b receptor	Solid tumor/cancer [ICD-11: 2A00-2F9Z]	88.72	98.59
	Adenosine A2b receptor	Herpes simplex virus infection [ICD-11: 1F00]	88.72	98.59
e	PI3-kinase p110-alpha/p85-alpha	Breast cancer [ICD-11: 2C60-2C65]	88.14	94.33
	Cyclin-dependent kinase 1/cyclin B1	Acute lymphoblastic leukemia [ICD-11: 2A85]	87.65	91.24
	G-protein coupled receptor 55	Attention deficit hyperactivity disorder [ICD-11: 6A05.Z]	87.41	78.15
	Adaptor-associated kinase	Coronavirus Disease 2019 (COVID-19) [ICD-11: 1D6Y]	79.85	83.1
f	Cyclin-dependent kinase 1/cyclin B1	Breast cancer [ICD-11: 2C60-2C65]	93.85	91.24
	PI3-kinase p110-alpha/p85-alpha	Breast cancer [ICD-11: 2C60-2C65]	91.38	94.33
	Sodium channel protein type III alpha subunit	Angina pectoris [ICD-11: BA40]	90.71	96.9
	Adenosine A2b receptor	Herpes simplex virus infection [ICD-11: 1F00]	87.68	98.59
g	Indoleamine 2,3-dioxygenase	Brain cancer [ICD-11: 2A00]	91.44	96.38
	Sodium channel protein type III alpha subunit	Angina pectoris [ICD-11: BA40]	89.14	96.9
	PI3-kinase p110-alpha/p85-alpha	Breast cancer [ICD-11: 2C60-2C65]	88.99	94.33
	Adenosine A2b receptor	Herpes simplex virus infection [ICD-11: 1F00]	88.36	98.59
h	PI3-kinase p110-alpha/p85-alpha	Breast cancer [ICD-11: 2C60-2C65]	93.03	94.33
	Adenosine A2b receptor	Herpes simplex virus infection [ICD-11: 1F00]	91.55	98.59
	Cyclin-dependent kinase 1/cyclin B1	Breast cancer [ICD-11: 2C60-2C65]	91.23	91.24
	Sodium channel protein type III alpha subunit	Angina pectoris [ICD-11: BA40]	87.4	96.9
i	Cyclin-dependent kinase 1/cyclin B1	Breast cancer [ICD-11: 2C60-2C65]	93.14	91.24
	Sodium channel protein type III alpha subunit	Angina pectoris [ICD-11: BA40]	89.89	96.9
	PI3-kinase p110-alpha/p85-alpha	Breast cancer [ICD-11: 2C60-2C65]	89.67	94.33
	Adaptor-associated kinase	Coronavirus Disease 2019 (COVID-19) [ICD-11: 1D6Y]	77.54	83.1
j	Indoleamine 2,3-dioxygenase	Brain cancer [ICD-11: 2A00]	96.2	96.38
	PI3-kinase p110-alpha/p85-alpha	Breast cancer [ICD-11: 2C60-2C6	90.42	94.33
	Cyclin-dependent kinase 1/cyclin B1	Breast cancer [ICD-11: 2C60-2C65]	89	91.24
	Adaptor-associated kinase	Coronavirus Disease 2019 (COVID-19) [ICD-11: 1D6Y]	72.59	83.1
k	Indoleamine 2,3-dioxygenase	Brain cancer [ICD-11: 2A00]	97.22	96.38
	PI3-kinase p110-alpha/p85-alpha	Breast cancer [ICD-11: 2C60-2C65]	90.42	94.33
	Cytochrome P450 3A4	Atopic dermatitis [ICD-11: EA80]	89.78	91.19
	Adaptor-associated kinase	Coronavirus Disease 2019 (COVID-19) [ICD-11: 1D6Y]	73.48	83.1

End of the Table 2

1	2	3	4	5
l	Casein kinase II alpha/beta	Cholangiocarcinoma [ICD-11: 2C12.10]	82.67	99.23
	Cyclin-dependent kinase 5/CDK5 activator 1	Obesity [ICD-11: 5B81]	81.73	93.03
	Cytochrome P450 3A4	Atopic dermatitis [ICD-11: EA80]	80.61	91.19
	Adenosine A2b receptor	Herpes simplex virus infection [ICD-11: 1F00]	58.59	98.59
m	Epoxide hydratase	Hypertension [ICD-11: BA00-BA04]	93.45	94.09
	Sodium channel protein type III alpha subunit	Angina pectoris [ICD-11: BA40]	91.22	96.9
	Cytochrome P450 3A4	Atopic dermatitis [ICD-11: EA80]	87.31	91.19
	Adenosine A2b receptor	Herpes simplex virus infection [ICD-11: 1F00]	72.95	98.59
n	G-protein coupled receptor 55	Attention deficit hyperactivity disorder	92.85	78.15
	Cyclin-dependent kinase 1/cyclin B1	Breast cancer [ICD-11: 2C60-2C65]	92.4	91.24
	Thromboxane A2 receptor	Allergic asthma [ICD-11: CA23.0]	91.67	92.62
	Adenosine A2b receptor	Herpes simplex virus infection [ICD-11: 1F00]	72.09	98.59
o	Glutathione S-transferase Pi	Solid tumor/cancer [ICD-11: 2A00-2F9Z]	90.01	93.81
	CDK2/Cyclin A	Lymphoma [ICD-11: 2A80-2A86]	89.38	91.38
	Cyclin-dependent kinase 1/cyclin B1	Breast cancer [ICD-11: 2C60-2C65]	88.28	91.24
	Adaptor-associated kinase	Coronavirus Disease 2019 (COVID-19) [ICD-11: 1D6Y]	60.78	83.1

Results of screening are showing that from the studied library of 4-acetylaminobenzenethiosulfoacid S-esters, the most promising for the search for drugs effective against the covid virus are the following: **e –** S-(1-Methylethyl)4-(acetylamino)benzenesulfonothioate with 79.85 % potential activity, **i** – S-(3-Chloro-2-hydroxypropyl) 4-(acetylamino)benzenesulfonothioate with 77.54 % potential activity and **a –** S-Methyl 4-(acetylamino)benzenesulfonothioate with 73.95 % potential activity.

It is worth noting that in the process of our screening promising compounds with anticancer properties were revealed. For example, compounds **f** – S-butyl 4-(acetylamino) benzenesulfonothioate, **h** - Methyl 4-(acetylamino) phenyl-sulfonyl-sulfanylacetate and **i** – S-(3-Chloro-2-hydroxypropyl) 4-(acetylamino)benzenesulfonothioate showed potential activity against targets responsible for breast cancer. Compounds **k** – S-Cyclohexyl 4-(acetylamino) benzenesulfonothioate, **j** – S-Cyclopentyl 4-(acetylamino) benzenesulfonothioate and **g** – S-(2-Methylpropyl) 4-(acetylamino)benzenesulfonothioate showed potential activity against targets responsible for brain cancer.

The results of the prediction of the biological activity of compounds a-o are presented in Table 3.

In Table 3 probability column indicate the estimated probability of a given protein to be a true target given its score [12]. На жаль, результати скринінгу сполук у SwissTargetPreditction дали неочікувано низькі ймовірності зв'язування з білками-таргетами. Найкращими були результати у сполук h, j, o, k, l, n.

Так наприклад сполука **j** показала високу ймовірність зв'язування до наступних таргетів Phosphodiesterase 7A, Androgen Receptor, Monoamine oxidase B. Inhibitors of Phosphodiesterase 7A have displayed efficiency in the treatment of diseases, such central nervous system disorders and asthma [18]. Androgen receptor (AR) plays a significant role in breast cancer pathogenesis, influencing both estrogen receptor-positive and negative breast cancer cells, and targeting AR along with other signaling pathways shows promise for the development of new treatment strategies, including combinations with standard-of-care therapies [19]. Monoamine oxidase B inhibition has shown an anti-depressant activity [20].

Table 3

Prediction of biological activities using SwissTargetPrediction resource

Compound	Target name	Target class	Probability, %
a	Carbonic anhydrase XII	Lyase	4.66
	Carbonic anhydrase IX	Lyase	4.66
	Tyrosine-protein kinase JAK1	Kinase	4
b	Tyrosine-protein kinase ABL	Kinase	6
	Adenosine A2b receptor	Family A G protein-coupled receptor	6
	Leukocyte common antigen	Enzyme	6
c	Monoamine oxidase B	Oxidoreductase	4.66
	Tyrosine-protein kinase JAK1	Kinase	4.66
	Tyrosine-protein kinase JAK2	Kinase	4.66
d	Phosphodiesterase 4B	Phosphodiesterase	4.66
	Epidermal growth factor receptor erbB1	Kinase	4.66
	Tyrosine-protein kinase JAK2	Kinase	4.66
e	Cyclin-dependent kinase 5/CDK5 activator 1	Kinase	4.66
	Tyrosine-protein kinase ABL	Kinase	4.66
	Tyrosine-protein kinase JAK1	Kinase	4.66
f	Arachidonate 5-lipoxygenase	Oxidoreductase	5.33
	Adenosine A1 receptor	Family A G protein-coupled receptor	5.33
	Adenosine A2a receptor	Family A G protein-coupled receptor	5.33
g	Vitamin D receptor	Nuclear receptor	5.33
	Aryl hydrocarbon receptor	Transcription factor	5.33
	Pregnane X receptor	Nuclear receptor	5.33
h	Metabotropic glutamate receptor 1	Family C G protein-coupled receptor	10.66
	Glutathione S-transferase Pi	Enzyme	10.66
	Adenosine A3 receptor	Family A G protein-coupled receptor	10.66
i	–	–	–
	–	–	–
	–	–	–
j	Phosphodiesterase 7A	Phosphodiesterase	10.66
	Androgen Receptor	Nuclear receptor	10.66
	Monoamine oxidase B	Oxidoreductase	10.66
k	Tyrosine-protein kinase JAK2	Kinase	10
	Nicotinamide phosphoribosyl transferase	Enzyme	10
	Protein kinase C gamma	Kinase	10
l	Monoamine oxidase A	Oxidoreductase	10
	Monoamine oxidase B	Oxidoreductase	10
	Bromodomain-containing protein 4	Reader	10
m	Monoamine oxidase A	Oxidoreductase	9.33
	Monoamine oxidase B	Oxidoreductase	9.33
	Glycogen synthase kinase-3 beta	Kinase	9.33
n	Cannabinoid receptor 1	Family A G protein-coupled receptor	10
	Monoamine oxidase A	Oxidoreductase	10
	Monoamine oxidase B	Oxidoreductase	10
o	Cannabinoid receptor 1	Family A G protein-coupled receptor	10
	Monoamine oxidase A	Oxidoreductase	10
	Monoamine oxidase B	Oxidoreductase	10

As we can see, the results obtained by the program (SwissTargetPrediction) are further different from the previous program (SuperPred). According to her, the studied compounds can be classified as compounds with low activity, but despite this, SwissTargetPrediction still made it possible to single out some potential biological activities that were not detected by SuperPred.

Another stage of virtual screening of the biological activity of the studied library of S-esters of 4-acetylaminobenzenethiosulfonic acid was the use of molecular docking.

The process of preparing the protein target was carried out using the Autodock Tools program [15]. The protein structure was optimized by adding polar water molecules, removing water molecules and adding of Kollman charges. Kollman charges, named after Allinger's colleague Paul Kollman, are often added to atoms in a molecule to account for the molecule's electrostatic potential. This is important because in biochemical interactions, such as those between a drug and its target receptor, the electrostatic potential can greatly influence the likelihood and strength of the interaction. The establishment of the active zones of the protein receptor as well as final results visualization was carried out using the BIOVIA Discovery Studio program [14].

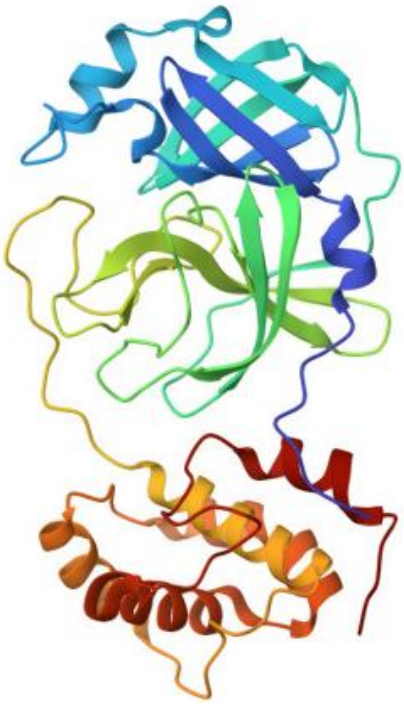


Fig. 1. The structure of the 6lu7 protein is obtained from the RCSBProtein Data Bank

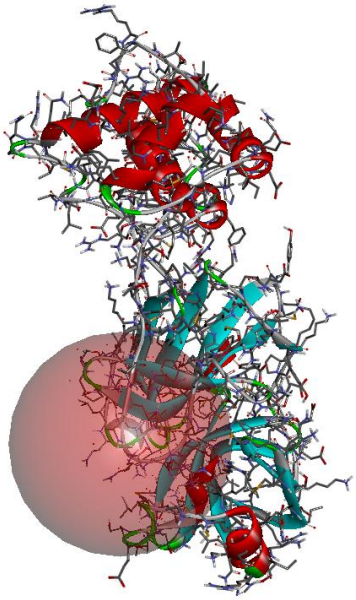


Fig. 2. Binding regions of 6lu7 protein

Docking studies were performed on a COVID-19 main protease in complex with an inhibitor N3 – 6lu7. The 6LU7 is a specific structure of the SARS-CoV-2 main protease (Mpro) which plays a crucial role in the life cycle of the virus. As such, it has become a key target for potential drug design efforts against COVID-19. This protease is essential for processing the polyproteins that are translated from the viral RNA.

The protein structure consists of three domains. Domains I and II are both comprised of six-stranded antiparallel beta-barrels. The Cys-His catalytic dyad is located in the cleft between these two domains. Domain III, which is made up of five alpha-helices, is connected to Domain II by a loop region. This domain is responsible for dimerization, a crucial process for the protease's function.

The active site, where inhibitor binding takes place, is located in a cleft between domains I and II and contains the catalytic dyad (His41 and Cys145). The substrate-binding pocket is rather shallow and solvent-accessible, and it displays a preference for substrates with a small residue, like a glycine, at the P1' position.

In the 6LU7 structure, a covalent inhibitor (N3) is found in the active site, making key interactions with the protease. The N3 inhibitor forms a covalent bond with the sulfur atom of Cys145. It also forms important hydrogen bonds with the catalytic residue His41, as well as with Gly143, Ser144, and Cys145,

providing an excellent example of the potential key interactions for the design of protease inhibitors [21].

From the series of compounds studied, the compound "**o**" S-(2-Nitrophenyl) 4-(acetylamino)benzenesulfonothioate exhibited the best binding level with the active site of the main protease 6lu7. According to the affinity, this is -7.0 kcal/mol, which corresponds to a high level of binding, even higher than that with the described ligand (Inhibitor N3) [21]. This definitely indicates the prospect of conducting further experimental studies of this thiosulfoester on the possibility of using it as an effective drug for the treatment of Covid-19 disease.

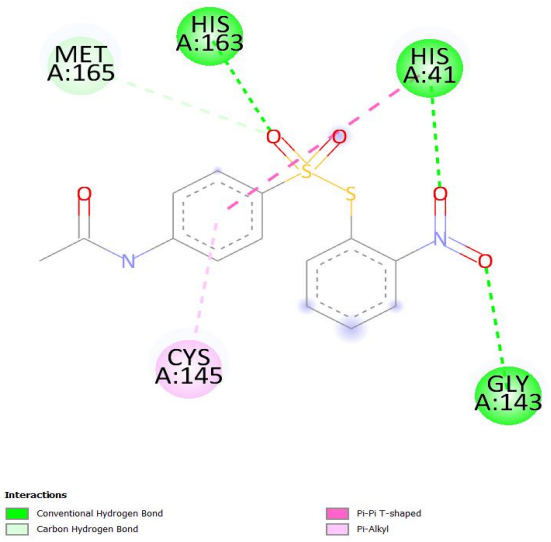


Fig. 3. Compound hit S-(2-Nitrophenyl) 4-(acetylamino)benzenesulfonothioate in the binding region 2. Visualization of retention of the hit compound

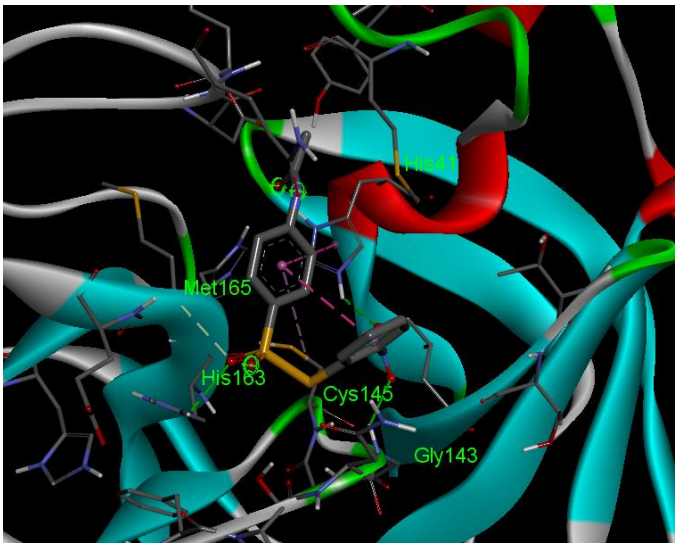


Fig. 4. S-(2-Nitrophenyl) 4-(acetylamino)benzenesulfonothioate in the active zone of protein 6lu7

Table 4

The results of the Gscore summary function of the conducted docking studies

Compound / Affinity, kcal/mol	Described ligand (Inhibitor N3)	a	b	c	d	e	f	g	h	i	j	k	l	m	n	**o**
Affinity, kcal/mol	6.8	5.4	5.2	5.8	5.6	5.5	5.5	5.2	5.8	6.0	6.0	6.5	6.0	6.3	6.6	**7.0**

Therefore, the results of the screening of the biological activity of thiosulfoesters **a–o** using molecular docking indicate the high feasibility of searching for new antivirus drugs among the investigated thiosulfoesters. The most promising in this plan of research may be the hit compound "**o**" – S-(2-Nitrophenyl) 4-(acetylamino)benzenesulfonothioate. Affinity value was calculated at level of 7.0 kcal/mol. The nitrophenyl fragment is held in the active site by the conventional hydrogen bonds GLY A:143, HIS A:41. The sulfo group is established bond with HIS A:163 via conventional hydrogen bond and bond with MET A:165 via Carbon hydrogen bond as shown on Fig. 3 and on Fig. 4. Benzen fragment of benzenesulfonothioate is held in an active site of a 6lu7 protein via Pi-Pi T-shaped bond and Pi-Alkyl bond.

Conclusions

The virtual screening of the biological activity of S-esters of 4-acetylaminobenzenethiosulfonic acid was conducted using computer programs such as SuperPred and SwissTargetPrediction. Additionally, molecular docking studies were performed using AutoDockTools software to identify potential substances with efficacy against COVID-19 disease.

In the course of the conducted virtual screening, a lead compound was identified for conducting experimental research on the search for an effective medicinal substance for the treatment of covid. The most promising is S-(2-nitrophenyl) 4-(acetylamino)benzenesulfonothioate (compound **o**), which proved to be the best in docking studies and showed a high level of affinity with the 6lu7 protein.

According to the prediction of the SuperPred resource, compound **o** also showed the probability of binding to the targets responsible for COVID-19 (around 60 %), and according to SwissTargetPrediction, unfortunately, it did not show activity against covid-19, but the indicated compound showed one of the best results among the studied substances in relation to other activities (antidepressant).

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Н. А. Копак
Національний університет “Львівська політехніка”,
кафедра технології біологічно активних сполук, фармації та біотехнології

ПОШУК БІОЛОГІЧНОЇ АКТИВНОСТІ S-ЕФІРІВ 4-АЦЕТИЛАМІНОБЕНЗЕТІОСУЛЬФОКИСЛОТИ МЕТОДАМИ ХІМІОІНФОРМАТИКИ

Скринінг біологічної активності тіосульфоефірів здійснювали за допомогою програм SuperPred, SwissTargetPrediction та molecular docking. На основі отриманих даних віртуального скринінгу визначено перспективні напрями експериментальних біологічних досліджень s-ефірів 4-ацетиламінобензолтіосульфокислоти. Молекулярний докінг продемонстрував доцільність пошуку нових антивірусних агентів серед досліджуваних тіосульфоефірів і дав змогу вибрати провідну сполуку для цих досліджень, а саме тіосульфоефіри.

Ключові слова: віртуальний скринінг; біологічна активність; молекулярний докінг; правило Ліпінського.