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COMPUTER MODELS FOR THE PREDICTION OF ANTIMICROBIAL ACTIVITY OF 4-((5-(DECYLTHIO)-4-METHYL-4H-1,2,4-TRIAZOL-3-YL)METHYL)MORPHOLINE AS A POTENTIAL MEDICINE

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The article is devoted to the polypharmacological profiling of 4-((5-(decylthio)-4-methyl-4H-1,2,4-triazole-3-yl)methyl)morpholine, which has potential as an antimicrobial agent. The study was conducted using 15,148 electronic pharmacophore models of organisms, ranked according to the Tversky index. A detailed analysis of the compound’s interactions with selected enzymes showed that 4-((5-(decylthio)-4-methyl-4H-1,2,4-triazole-3-yl)methyl)morpholine forms classical types of bonds with chosen biotargets. The key amino acid residues involved in the formation of complexes were also identified. Based on the binding profiles observed for selected complexes with the active centers of thymidine kinase (4IVR), phosphate synthase (1G6C), and biotin carboxylase (2W6O), it can be concluded that this bioactive ligand is likely to exhibit antibacterial and antiviral effects by inhibiting molecular and biological processes in pathogenic organisms. The chosen targets had acceptable binding modes with 4-((5-(decylthio)-4-methyl-4H-1,2,4-triazole-3-yl)methyl)morpholine, did not form unwanted contacts, and interacted with some critically important amino acid residues. This suggests the potential for further use in virtual screening, computer modeling, and more in-depth in vitro and in vivo studies. The results of the multitarget analysis could contribute to the development of new antimicrobial drugs effective against various types of infectious agents.

Keywords: 1,2,4-triazole, antifungal activity, biologically active compounds, computer models, molecular docking.

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Introduction

Creation of new original medicines is a long and multi-level process. It covers the knowledge of various areas of pharmaceutical science and the scientists’ experience in different fields of cognition. A special role in this process belongs to synthetic organic chemistry, which currently has turned into the most powerful and promising component of this process. The heterocyclic 1,2,4-triazole system deserves special attention, the derivatives of which are known as biologically active compounds, some of them exhibit the properties of anti-corrosion agents, plasticizers of plastics, plant growth regulators, etc. [1,2]. It is well known that 1,2,4-triazole derivatives are low-toxic compounds which properties depend on the presence of various functional substituents [2]. Chemical modification of 1,2,4-triazole by adding various fragments to its structure is popular and necessary to expand the arsenal of new promising molecules [3].

In our opinion, the use of computer modeling and forecasting tools on the way of researching the properties of the 1,2,4-triazole derivatives is innovative

and modern. In 2022, «Vetmikoderm», a modern original domestic veterinary drug in the form of a 10% liniment, appeared on the Ukraine's veterinary drug market (RP No. AB-09522-01-21 dated 02.14.2022). The active substance of the drug belongs to the derivatives of the 1,2,4-triazole (4-((5-(decylthio)-4-methyl-4H-1,2,4-triazole-3-yl)-methyl)morpholine). Antifungal effect of «Vetmikoderm» is caused by violation of the cell membrane's integrity of the fungus, the active substance disrupts the ergosterol's synthesis as the main structural component of the fungi' cell membrane [4]. The effect is associated with the inhibition of cytochrome P450-dependent enzymes, including 14-α-demethylase (sterol-14-demethylase), which catalyzes the reaction of converting lanosterol into ergosterol, which leads to the violation of the ergosterol's synthesis in the cell membrane of fungi.

The bacteriostatic activity of the 4-((5-(decylthio)-4-methyl-4H-1,2,4-triazole-3-yl)-methyl) morpholine consists in disrupting the normal flow of biochemical processes in microbes due to inhibition of the individual enzyme systems' activity. At the same time, unfavorable conditions are created for the development and reproduction of the microorganisms. The bactericidal action of the 4-((5-(decylthio)-4-methyl-4H-1,2,4-triazole-3-yl)-methyl)morpholine causes irreversible changes in the cell's protoplasm (protein denaturation) and thus they lead to the rapid death of the microbes [5]. The drug is recommended in the treatment of animals for various skin diseases, especially of fungal etiology (microsporia, trichophytia, favus), as an additional remedy in the therapy of demodicosis, because it has desensitizing properties and has a wound-healing, anti-inflammatory, and anti-itching effects thanks to milk thistle oil (*Silybum marianum*).

Currently, the problem of fungi and bacteria resistance to existing antimicrobial and antifungal agents is quite relevant [6,7]. This is an extremely important and urgent challenge in the field of medicine and pharmacy. Looking for new antimicrobial drugs, scientists turn to a polypharmacological approach, using compounds that have the ability to fight with several types of pathogenic organisms simultaneously [8]. This approach opens wide prospects for the development of effective medicines.

Biologically active compounds often interact with different target proteins, exhibiting polypharmacology. However, experimental determination of these interactions is a rather time-consuming process. Structural virtual screening of biologically active compounds is used to accelerate drug discovery and establish priorities for experimental testing. One of the recently registered datasets is ePharmaLib [8], it is a library containing of 15,148 electronic pharmacophores modeled on the basis of the active protein-ligand complex structures from the protein data bank [9]. ePharmaLib can be used for targeted search of phenotypic interactions, prediction of side effects, drug repurposing and new drug development. The aim of our further work was to investigate the properties of the 4-((5-(decylthio)-4-methyl-4H-1,2,4-triazole-3-yl)-methyl)morpholine using molecular descriptors and in silico studies. This scientific research is based on the use of computer methods for the targeted search of phenotypic interactions, prediction of side effects, repurposing of drugs and development of new drugs.

The experiment is aimed at investigating the 4-((5-(decylthio)-4-methyl-4H-1,2,4-triazole-3-yl)-methyl)morpholine properties, using molecular descriptors and *in silico* studies (Fig. 1).

Materials and methods

Prediction of protein targets

The structure of the 4-((5-(decylthio)-4-methyl-4H-1,2,4-triazole-3-yl) methyl) morpholine was drawn and transfered in SMILES format using the freely available MarvinSketch. A concatenated ePharmaLib [9] subset representing different protein targets was obtained through the Zenodo database [10]. The prediction of protein targets of the bioactive ligand was carried out based on the Galaxy web service and included several stages as follows:

– creation of a ligand structure file in SMILES format and its subsequent hydration;

– creation of 46 minimized energy conformers' set for the requested ligand;

– uploading the ePharmaLib data set in phar format to the web service;

– the ePharmaLib division into separate pharmacophores, to speed up the analysis by performing several parallel measurements;

– pharmacophore alignment, where the data set of the 4-((5-(decylthio)-4-methyl-4H-1,2,4-triazole-3-yl)methyl) morpholine conformer is converted into a pharmacophore data set and simultaneously aligned by individual pharmacophores ePharmaLib data one;

– concatenation of pharmacophore alignment scores and ranking of predicted protein targets according to the Tversky index. The higher the Tversky index, the higher the probability of the predicted protein–ligand interaction. For simplification, the one-stage Zauberkugel algorithm was used (Fig. 2).

Docking protocol

The structure of the 4-((5-(decylthio)-4-methyl-4H-1,2,4-triazole-3-yl) methyl) morpholine ligand was converted to SDF format by means of OpenBabel

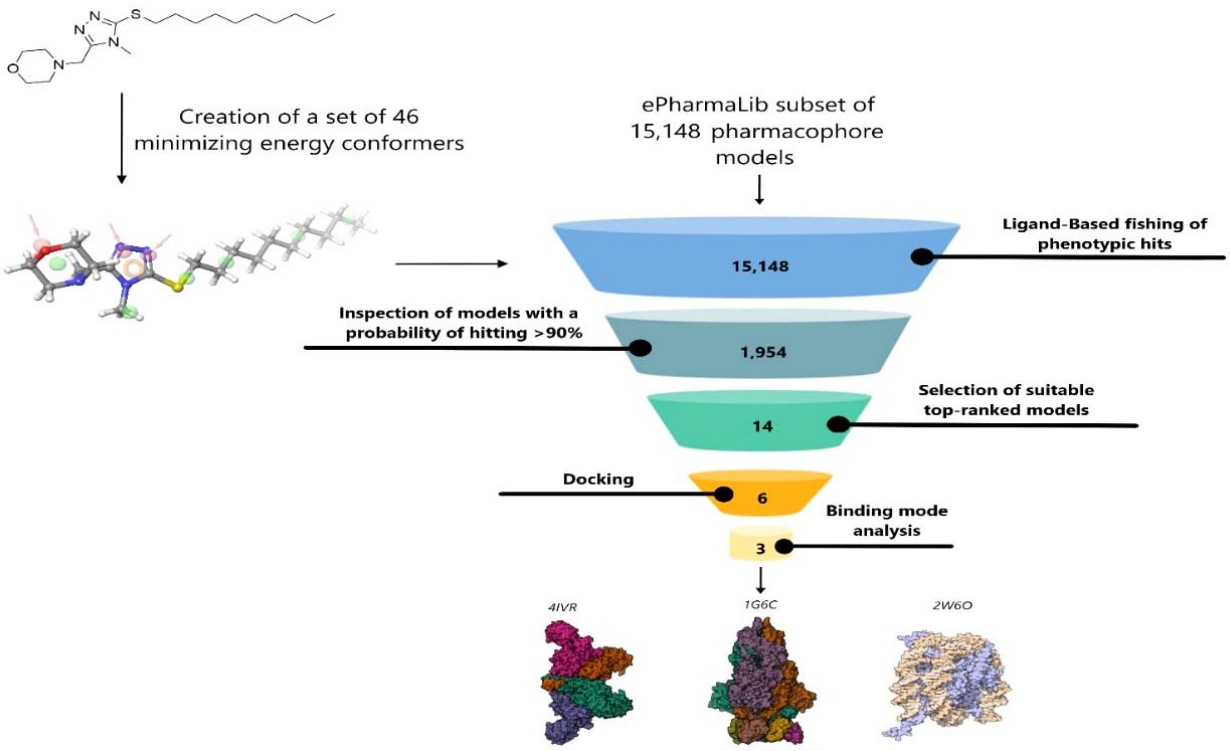

Fig. 1. General scheme summarizing the methodological steps

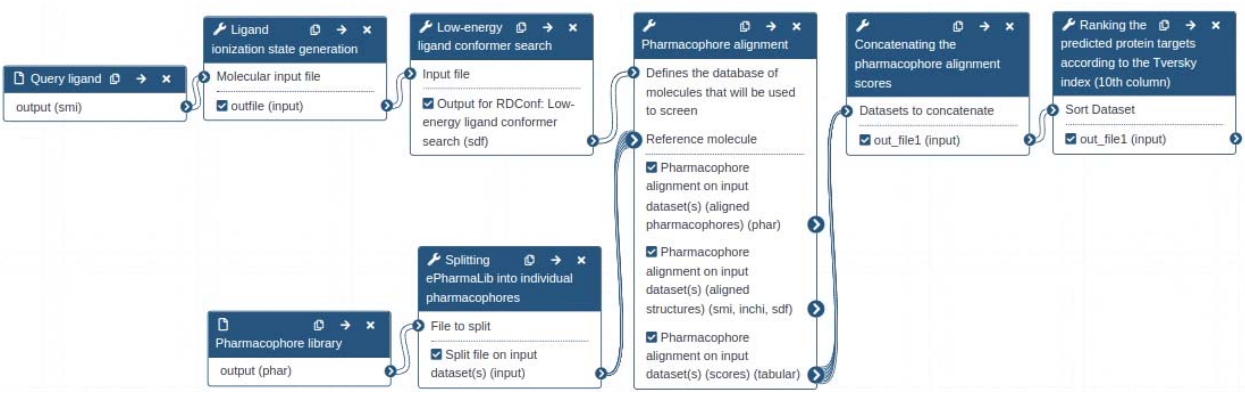

Fig. 2. Zauberkugel workflow algorithm

[11]. The ligand was additionally subjected to energy minimization using Chimera [12]. X-ray crystal structures of proteins with co-crystallized ligands were obtained from the Protein Data Bank (PDB). To prepare the protein structure, co-crystallized ligand and water molecules were removed, and polar hydrogen atoms and combined charges of Kolman atoms were added. The DockingPie Vina plugin in PyMOL was used to perform protein-ligand docking studies and their conversion to pdbqt format [13]. To confirm the docking protocol, a validation was carried out (Table 1).

It is known from previous studies that the value of root mean square deviation of atomic positions (RMSD), which reflects the difference between the calculated and crystallographic conformation of the ligand complex, should not exceed 2.0 Å. After re-docking, similarity in the overlap between crystallographic (orientation+conformation, blue) and calculated (yellow) positions was achieved, which confirms the low value of RMSD (Fig. 3).

Table 1

Data to verify molecular docking

Biotarget	Ligand comparison	Center coordinates Grid Box	Size Grid Box	RMSD
Thiamin phosphate synthase (PDB:1G6C)	2-Trifluoromethyl-5-methylene-5*H*-pyrimidin-4-ylideneamine	15.99 x	16 x	0.149
		42.80 y	16 y	
		16.08 z	16 z	
Biotin carboxylase (PDB:2W6O)	4-Amino-7,7-dimethyl-7,8-dihydroquinazolin-5(6*H*)-one	18,30 x	16 x	0.767
		9.41 y	18 y	
		–1.19 z	16 z	
Heterodimer mutant reaction center (PDB:3G7F)	Ubiquinone-1	112.25 x	20 x	1.648
		47.58 y	20 y	
		–5.60 z	20 z	
Ketosteroid Isomerase (PDB:3OWU)	Equilenin	7.88 x	17 x	1.555
		1.85 y	18 y	
		1.24 z	18 z	
Thymidine kinase (PDB:4IVR)	2-[(2,6-Dimethoxy-5-methylpyrimidin-4-yl)methylidene]propane-1,3-diol	20.67 x	16 x	0.123
		22.01 y	20 y	
		64.15 z	20 z	
Enoyl reductase (PDB:4TZT)	(3S)-N-(3-chloro-2-methylphenyl)-1-cyclohexyl-5-oxopyrrolidine-3-carboxamide	39.84 x	18 x	1.305
		52.06 y	22 y	
		60.69 z	20 z	

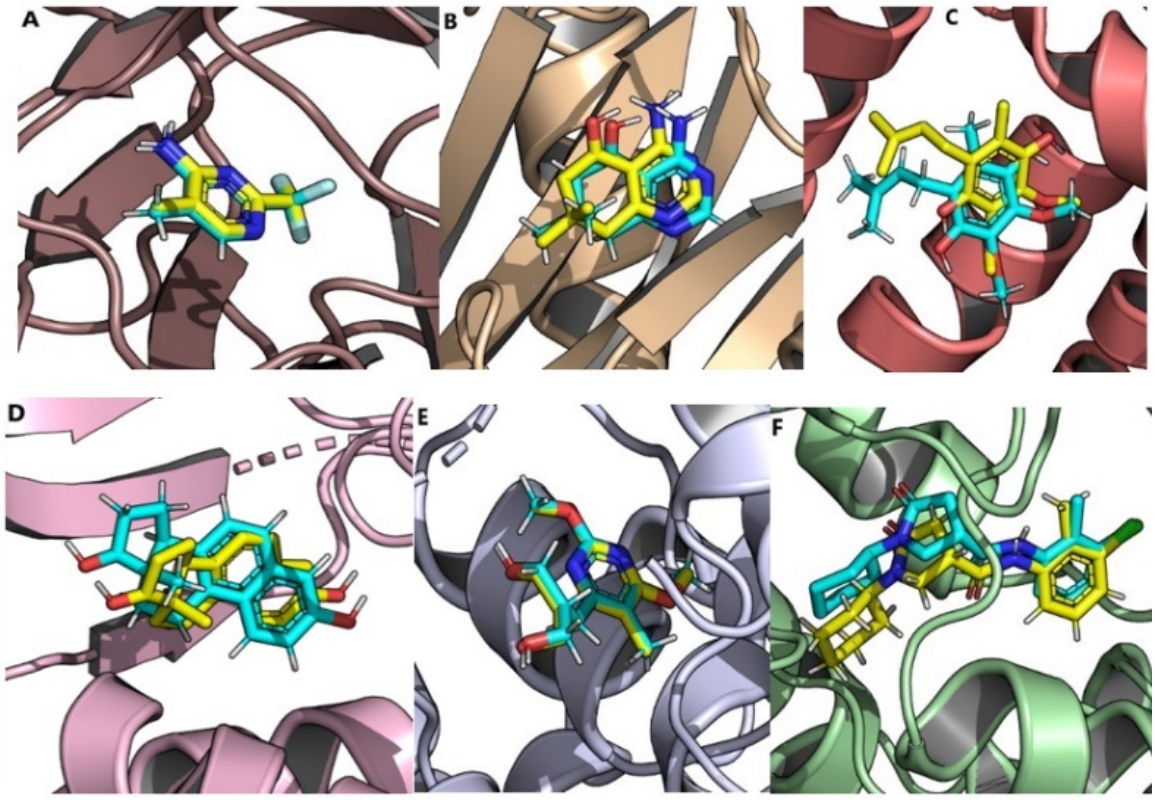

Fig. 3. Proteins in complexes with calculated and experimental ligand conformations: 1G6C (A); 2W6O (B); 3G7F (C); 3OWU (D); 4IVR (E); and 4TZT (F)

PyMOL v.2.5 and Discovery Studio Visualizer programs were used to generate images of receptor-ligand complexes. Estimated inhibitory constant (pKi) was carried out using the following standardized equation:

$$pKi = 10^{\left[\frac{\text{bond energy estimate}}{1.336}\right]}.$$

Results and discussion

Polypharmacological profiling of a bioactive compound using 15,148 pharmacophores generated a collection of 1,954 source files, from which the best 14 models were selected, whose matching index (Tversky index) exceeded the value of 0.900 and corresponded to a probability of >90% (Table 2). The TANIMOTO measure is used to compare bit vectors and is widely used to assess similarity between pharmacophores. On the other hand, the TVERSKY_DB measure is taken to identify compounds in the database that have a pharmacophore that is a subset of the reference pharmacophore.

Based on the prediction results, it is possible to distinguish 5 biotargets that are responsible for specific molecular functions and biological processes in bacterial organisms: thiamin phosphate synthase (PDB:1G6C) of *Bacillus subtilis*, inhibition of which causes a violation of the vitamin B1 balance; biotin carboxylase (PDB:2W6O) of the *Escherichia coli* organism, which catalyzes the first relevant step in the path of fatty acid biosynthesis; the photosynthetic reaction center (PDB:3G7F) of *Blastochloris viridis*, which carries out the light transport of electrons through the photosynthetic membrane; ketosteroid isomerase (PDB:3OWU) *Pseudomonas putida*; and enoyl reductase (PDB: 4TZT) of the bacterium *Mycobacterium Tuberculosis*, which is involved in the elongation cycle of mycobacterial fatty acids, and is an effective antimicrobial target. In addition, one biotarget of the virus was present, thymidine kinase (PDB:4IVR) of *Human alphaherpesvirus* (strain 17), which catalyzes the phosphorylation of thymidine (dT) to thymidylate (dTMP).

The next stage was the study of the 4-((5-(decylthio)-4-methyl-4H-1,2,4-triazole-3-yl)methyl)morpholine on six enzymes. Intermolecular interactions between the reference/test ligand and the target receptor were assessed to determine and compare docking profiles. The results of the study, including binding affinity and inhibition constants (pKi), are presented in Table 3.

According to the results of docking study, the best three structural complexes were selected for which the evaluation of the binding affinity of the experimental ligand exceeded than the comparison ones. Docking has showed that the compound has the potential to bind to thymidine kinase (PDB:4IVR) with a binding energy of −7.292 kcal/mol (0.348 μM), and to thiamine phosphate synthase (PDB:1G6C) and biotin carboxylase (PDB:2W6O) with a binding energy of −7.221 and −6.074 kcal/mol, respectively. In addition, the predicted values of target inhibition concentration for the studied ligand were twice smaller than for the comparison ligands.

Creation of the 4-((5-(decylthio)-4-methyl-4H-1,2,4-triazole-3-yl)methyl)morpholine with thymidine kinase 4IVR model

The location of the compound in the active site of the protein is due to interaction with key residues in the pocket of the active center (Fig. 3): AGR163, GLU83, and TYR172. For the compound 4-((5-(decylthio)-4-methyl-4H-1,2,4-triazole-3-yl)methyl)morpholine, the binding profile with thymidine kinase was somewhat similar to the interaction of 2-[(2,6-dimethoxy-5-methylpyrimidin-4-yl)methylidene]propane-1,3-diol with the target protein, namely π−π stacking with TYR172, and hydrogen contacts with amino acid AGR163 (1.8−2.4 Å). However, unlike the reference ligand, the studied compound forms a weak H-bond with GLU83

Table 2

Predicted protein targets

Id of the reference structure	TVERSKY_REF score	TANIMOTO score	TVERSKY_DB score
1r8q-AFB-ARF1_BOVIN	0.9933	0.3259	0.3266
4ivr-N50-KITH_HHV11	0.9684	0.3914	0.3964
2jsd-NGH-MMP20_HUMAN	0.9537	0.3303	0.3357
3i58-7NA-NCSB1_STRCZ	0.9331	0.3745	0.3848
3i5u-5NA-NCSB1_STRCZ	0.9295	0.3653	0.3757
5jr3-4MU-DNRK_STRPE	0.9286	0.3826	0.3942
1g6c-IFP-THIE_BACSU	0.9256	0.3761	0.3878
3ofm-4B0-CSK22_HUMAN	0.9246	0.3718	0.3835
3nya-JTZ-ADRB2_HUMAN	0.9228	0.3752	0.3873
3g7f-UQ1-CYCR_BLAVI	0.9137	0.3053	0.3144
1y2k-7DE-PDE4D_HUMAN	0.9112	0.3146	0.3245
3owu-EQU-SDIS_PSEPU	0.9102	0.3501	0.3661
2w6o-OA3-ACCC_ECOLI	0.9083	0.3466	0.3632
4tzt-468-INHA_MYCTU	0.9026	0.3901	0.4193

Table 3

Results of the docking study and determination of binding affinity and inhibition constants

PDB id of the reference structure	Tversky index	Affinity for reference ligand, kcal/mol	Affinity the investigated ligand, kcal/mol	Predicted value of pKi (μM) for reference ligand	Predicted value of pKi (μM) for the investigated ligand
4IVR	0.9684	–6.887	**–7.292**	0.700	0.348
1G6C	0.9256	–6.753	**–7.221**	0.882	0.394
3G7F	0.9137	–4.748	–4.683	27.932	31.244
3OWU	0.9102	–9.422	–6.048	0.009	2.972
2W6O	0.9083	–5.804	**–6.074**	4.526	2.842
4TZT	0.9026	–8.255	–6.641	0.066	1.070

(3.8 Å). π-Hydrophobic bonds were observed for many other amino acid residues:

– TYR172 was bound by π-sulfur contact with the thiomethylene group.

– The aromatic 1,2,4-triazole heterocycle formed π–π stacking with HIS58, and π–π T-stacking with TPR88.

– The decyl residue of the bioactive compound interacted with the aromatic hydroxyphenyl of TYR172 and TYR101 through a π-alkyl bond.

Amino acid residues MET128, ALA168, ILE100 and ILE97 formed an intermolecular alkyl bond with a decyl radical (Fig. 4).

Creation of the 4-((5-(decylthio)-4-methyl-4H-1,2,4-triazole-3-yl)methyl)morpholine model with phosphate synthase (1G6C)

The next complex used for virtual screening was 1G6C. To stabilize the conformation, the traditional hydrogen bond between the oxygen of morpholine and GLU111 (2.4 Å) is involved, as well as the carbon hydrogen bond between the nitrogen of 1,2,4-triazole and PRO152 (2.5 Å), the methylene linker and ASP161 (3.4 Å) (Fig. 5).

A π-alkyl bond with the aromatic π-system of 1,2,4-triazole and a conventional alkyl bond with the decyl radical were characterized to the amino acid residue PRO152. In addition, the decyl radical formed a large number of hydrophobic alkyl bonds with ILE186, ILE208, LYS159, and AGR163.

Creation of the 4-((5-(decylthio)-4-methyl-4H-1,2,4-triazole-3-yl) methyl) morpholine model with biotin carboxylase (2W6O)

The interaction of the 4-((5-(decylthio)-4-methyl-4H-1,2,4-triazole-3-yl)methyl) morpholine with protease has demonstrated a high binding affinity, because critically important amino acid residues were involved in the formation of the bond: HIS209, GLN233, LEU278, LEU204, and ILE157. The docking profile is characterized by three carbon-hydrogen bonds: the methyl radical in the fourth position of 1,2,4-triazole forms an H-bond with HIS209 and GLN233, the nitrogen of 1,2,4-triazole

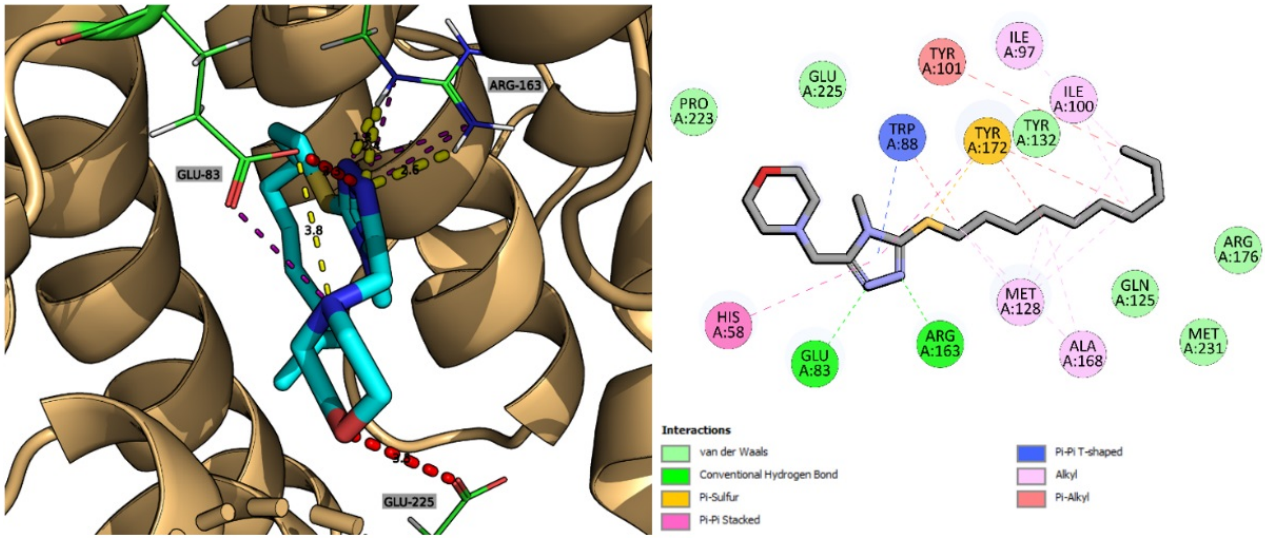

Fig. 4. Two-dimensional and three-dimensional binding interaction models of the compound after docking calculations in the thymidine kinase binding pocket

has a contact with the GLY165 residue. The polarizing π-electron cloud of the 1,2,4-triazole aromatic ring interacted with GLU through π-anion bond and with HIS209 through π—π stacking (Fig. 6). In turn, the decyl radical formed alkyl interactions with the LEU204, LEU278, ILE287 and ILE157 residues and also formed the π-alkyl bond with the aromatic TYR203.

Conclusions

Based on the binding profiles observed for selected complexes with the active centers of thymidine kinase (4IVR), with phosphate synthase (1G6C), biotin carboxylase (2W6O), it can be concluded that the bioactive ligand can probably show antibacterial and antiviral effects through molecular and biological inhibition of pathogenic organisms. The selected targets had acceptable binding modes with the 4-((5-(decylthio)-4-methyl-4H-1,2,4-triazole-3-yl)methyl)morpholine, did not form unwanted contacts, and interacted with some critically important amino acid residues, which gives reason to use them in further virtual screening, computer modeling and more in-depth *in vitro* and *in vivo* studies. The results of the multitarget analysis can contribute to the further development of new antimicrobial drugs that have the potential to be effective against various types of infectious agents.

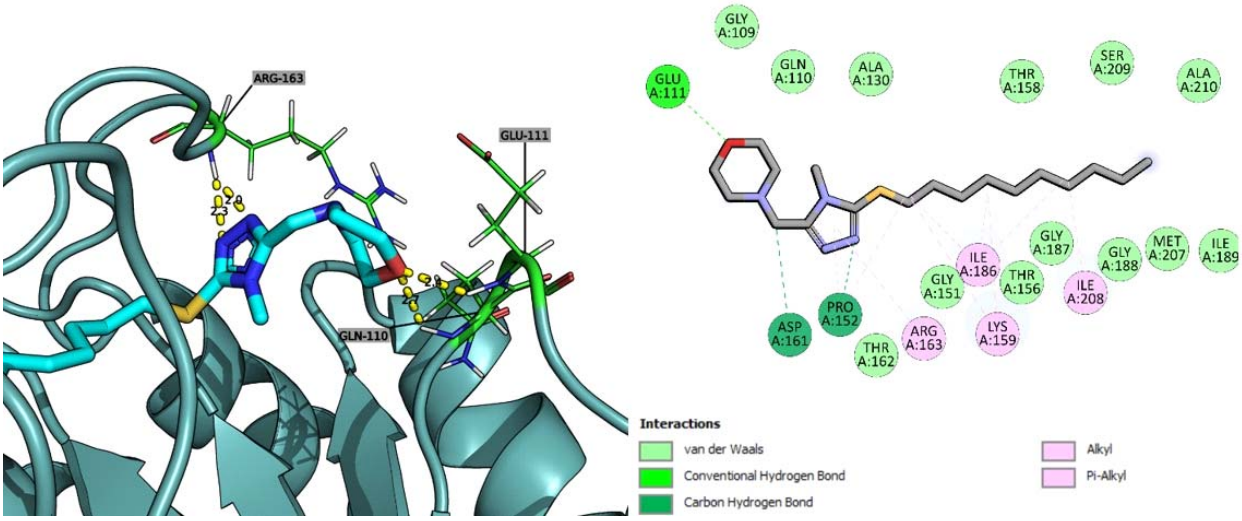

Fig. 5. Graphic representation of the binding position and interaction of the 4-((5-(decylthio)-4-methyl-4H-1,2,4-triazole-3-yl)methyl)morpholine with thiamine phosphate synthase

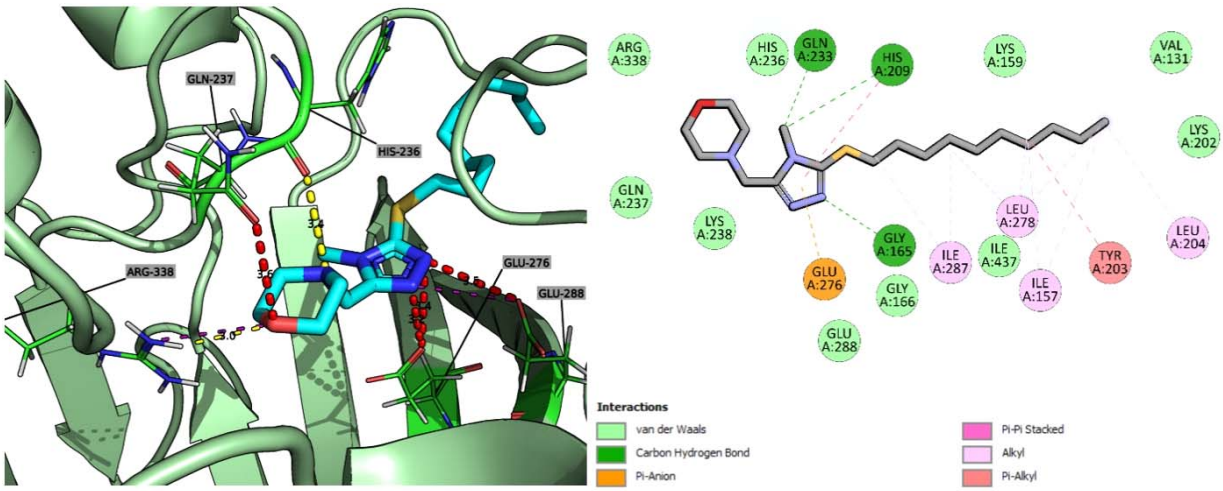

Fig. 6. 2D and 3D interaction surface of hydrophobic and H-bonds for the 4-((5-(decylthio)-4-methyl-4H-1,2,4-triazole-3-yl)methyl)morpholine ligand and biotin carboxylase

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КОМП'ЮТЕРНІ МОДЕЛІ ДЛЯ ПЕРЕДБАЧЕННЯ АНТИМІКРОБНОЇ АКТИВНОСТІ 4-((5-(ДЕЦИЛТІО)-4-МЕТИЛ-4Н-1,2,4-ТРІАЗОЛ-3-ІЛ)МЕТИЛ)МОРФОЛІНУ ЯК ПОТЕНЦІЙНОГО ЛІКАРСЬКОГО ПРЕПАРАТУ

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Стаття присвячена поліфармакологічному профілюванню 4-((5-(децилтіо)-4-метил-4Н-1,2,4-тріазол-3-іл)метил)морфоліну, який має потенціал як антимікробний засіб. Дослідження здійснювали з використанням 15148 електронних фармакофорних моделей організмів, які були ранжовані за значенням індексу Тверського. Детальний аналіз взаємодії сполуки з вибраними ферментами показав, що 4-((5-(децилтіо)-4-метил-4Н-1,2,4-тріазол-3-іл)метил) морфолін утворює класичні типи зв'язків на вибрані біоцілі. Також визначено ключові амінокислотні залишки, що беруть участь в утворенні комплексів. На основі профілів зв'язування, що спостерігаються для вибраних комплексів з активними центрами тимідинкінази (4IVR), з фосфатсинтазою (1G6C), біотинкарбоксилазою (2W6O), можна зробити висновок, що біоактивний ліганд, ймовірно, виявлятиме антибактеріальну та противірусну дію через гальмування молекулярно-біологічних процесів патогенних організмів. Вибрані мішені мали прийнятні режими зв'язування з 4-((5-(децилтіо)-4-метил-4Н-1,2,4-тріазол-3-іл)метил)морфоліном, не утворювали небажаних контактів і взаємодіяли з деякими критично важливими амінокислотними залишками, що дає підстави використовувати їх у подальшому віртуальному скринінгу, комп'ютерному моделюванні та більш поглиблених дослідженнях in vitro та in vivo. Результати багатоцільового аналізу можуть сприяти подальшій розробці нових протимікробних препаратів, які можуть бути ефективними проти різних типів інфекційних агентів.

Ключові слова: 1,2,4-триазол, протигрибкова активність, біологічно активні сполуки, комп'ютерні моделі, молекулярний докінг.

COMPUTER MODELS FOR THE PREDICTION OF ANTIMICROBIAL ACTIVITY OF 4-((5-(DECYLTHIO)-4-METHYL-4H-1,2,4-TRIAZOL-3-YL)METHYL)MORPHOLINE AS A POTENTIAL MEDICINE

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The article is devoted to the polypharmacological profiling of 4-((5-(decylthio)-4-methyl-4H-1,2,4-triazole-3-yl)methyl)morpholine, which has potential as an antimicrobial agent. The study was conducted using 15,148 electronic pharmacophore models of organisms, ranked according to the Tversky index. A detailed analysis of the compound's interactions with selected enzymes showed that 4-((5-(decylthio)-4-methyl-4H-1,2,4-triazole-3-yl)methyl)morpholine forms classical types of bonds with chosen biotargets. The key amino acid residues involved in the formation of complexes were also identified. Based on the binding profiles observed for selected complexes with the active centers of thymidine kinase (4IVR), phosphate synthase (1G6C), and biotin carboxylase (2W6O), it can be concluded that this bioactive ligand is likely to exhibit antibacterial and antiviral effects by inhibiting molecular and biological processes in pathogenic organisms. The chosen targets had acceptable binding modes with 4-((5-(decylthio)-4-methyl-4H-1,2,4-triazole-3-yl)methyl)morpholine, did not form unwanted contacts, and interacted with some critically important amino acid residues. This suggests the potential for further use in virtual screening, computer modeling, and more in-depth in vitro and in vivo studies. The results of the multitarget analysis could contribute to the development of new antimicrobial drugs effective against various types of infectious agents.

Keywords: 1,2,4-triazole; antifungal activity; biologically active compounds; computer models; molecular docking.

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