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RESEARCH ARTICLE

In vitro and *in silico* study of 1,3-oxazol-4-yltriphenylphosphonium salts as potential inhibitors of *Candida albicans* transglycosylase

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Abstract: The previously established *in vitro* high antimicrobial activity of triphenylphosphonium salts (TPPs) against bacterial (*Staphylococcus aureus* ATCC 25923 and multi-drug resistant (MDR)) and fungal (*Candida albicans* ATCC 10231 and MDR) strains made it possible to propose a molecular mechanism of action of these compounds associated with transglycosylase (TG) activity. The hypothesis was based on the well-known literature data on TPPs as inhibitors of *S. aureus* TG. The created homology model of TG *C. albicans* is optimal in terms of quality indicators such as GMQE (0.61), ERRAT (overall quality factor 95.904) and Ramachandran plot analysis (90% amino acid residues in the favored regions). The modeling of molecular docking of the most active ligands **1a-d**, **3c** into the active center of the created homology *C. albicans* TG model demonstrated the formation of stable ligand-protein complexes with calculated binding energies from -8.9 to -9.7 kcal/mol due to the various types of interactions. An important role in complex formation belongs to amino acid residues TYR307, TYR107, GLU275, ALA108 and PRO136. The presented qualitative homologous model of *C. albicans* TG can be used to search and create new agents with a dual mechanism of antimicrobial action. 1,3-oxazol-4-yltriphenylphosphonium salts **1a-d**, **3c** are the perspective objects for further study as antimicrobials against infectious MDR pathogens.

Keywords: transglycosylase; triphenylphosphonium salts; 1,3-oxazole; *Candida albicans; Staphylococcus aureus.*

Introduction

Hospital infections, which often lead to systemic damage and mortality in patients with various types of diseases, are an important problem in the modern healthcare system [1]. The increase in the number of hospital infections is directly related to patients with reduced immunity of various etiologies. The rapid development of multidrug resistance in most microbial pathogens is the main motivation for the rapid development and creation of drugs with new alternative molecular mechanisms of action [2]. It is known that bacterial TG are used as a promising target for the development of new antimicrobial drugs [3-4]. On the other hand, such antifungal agents as caspofungin, anidulafungin and micafungin are inhibitors of 1,3-beta-glucan synthase (EC 2.4.1.34) from the transglycosylase family and participate in the formation of the main component of the fungal cell wall - beta-1,3-glucan polymer [5-6].

Many transglycosylases inhibitors are known as drugs or antibiotics. There is evidence about echinocandins as inhibitors of fungal β-1,3-glucan synthases [6], ethambutol as an inhibitor of mycobacterial arabinotransferases [7], moenomycin as an inhibitor of peptidoglycan glycosyltransferases [8] and niccomycins as inhibitors of chitin synthases [9]. Phosphonium salts have also demonstrated transglycosylase activity as antimicrobial agents against methicillin-resistant *S. aureus* [10]. Analysis of the structure-activity relationship of salts in the online chemical database ChEMBL confirmed this fact as well [11]. As pharmacological agents, a number of phosphonium salts have shown high activity against parasites of the genus *Leishmania* [12], *Trypanosoma brucei* [13], *Trypanosoma cruzi* [14] and *Schistosoma mansoni* [15]. Particular interest in the TPPs is due to a number of other unique properties. They can act as intracellular antioxidants [16], acetylcholinesterase inhibitors [17], chemotherapeutic

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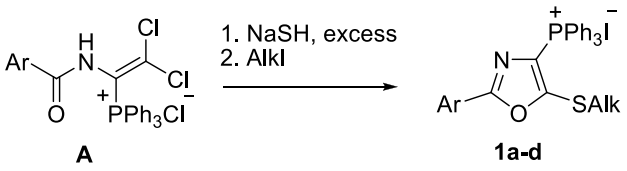
agents [18], some studies have demonstrated the antiglycemic properties and antiproliferative activity of phosphonium salts [19, 20].

In our work, the results of *in silico* and *in vitro* studies of a number of 1,3-oxazol-4-yltriphenylphosphonium salts are presented as effective antimicrobial agents with a high activity potential against bacterial and fungal strains with a special type of molecular action.

Results and discussion

The synthesis of 5-amino- and 5-sulfanyl-1,3-oxazol-4-yl(triphenyl)phosphonium salts **1-4** was based on convenient approaches developed by B. S. Drach and coworkers [21-23]. 5-Alkylsulfanyl-1,3-oxazol-4-yl(triphenyl)phosphonium iodides **1a-d** were synthesized from available 1-acylamino-2,2-dichloroethenyl (triphenyl)phosphonium chlorides **A** of the general formula $Cl_2C{=}C(NHC(O)Ar)P^+Ph_3Cl^-$ [21] by the reaction with sodium hydrosulfide followed by alkyl iodide treatment [21] (Scheme 1).

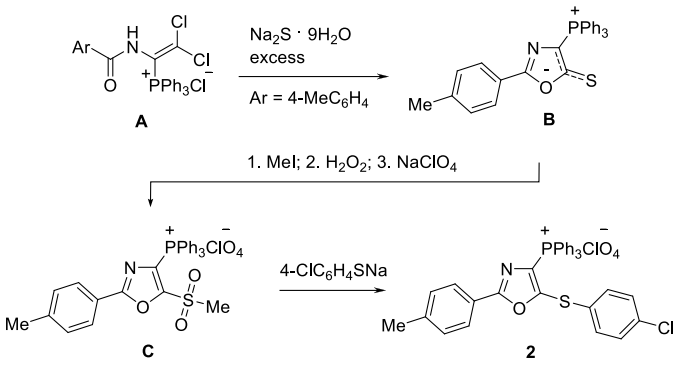


	Ar	Alk
1a	4-MeC_6H_4	Et
1b	4-ClC_6H_4	Et
1c	4-MeC_6H_4	$CH_2CH{=}CH_2$
1d	C_6H_5	$CH_2CH{=}CH_2$

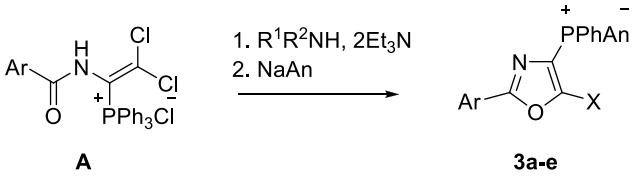
Scheme 1. Synthesis of 5-alkylsulfanyl-1,3-oxazol-4-yl(triphenyl)phosphonium iodides **1a-d.**

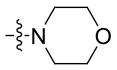
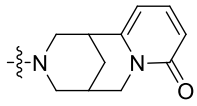
For the synthesis of 5-(4-chlorophenylsulfanyl)-2-(4-methylphenyl)-1,3-oxazol-4-yl(triphenyl)phosphonium perchlorate (**2**) 2,2-dichloro-1-((4-methylbenzoyl)amino) ethenyl(triphenyl)phosphonium chloride **A** was converted into the corresponding ylide betaine **B.** The reaction of compound **B** with methyl iodide with subsequent hydrogen peroxide oxidation and sodium perchlorate treatment leads to 5-mesyl-substituted 1,3-oxazol-4-yl(triphenyl)-phosphonium chloride **C.** By the substitution of mesyl group with sodium 4-chlorobenzenethiolate we obtained compound **2** [22] (Scheme 2).

Interaction of the 1-acylamino-2,2-dichloroethenyl-(triphenyl)phosphonium chlorides **A** with amines leads to formation of 5-amino-1,3-oxazol-4-yl(triphenyl)-phosphonium chlorides converted to the corresponding phosphonium iodides or perchlorates **3a-e** [21, 24] (Scheme 3). Cyclization of urea derivatives **D** with morpholine leads to 2-anilino-5-morpholino-1,3-oxazol-4-yl(triphenyl) phosphornium perchlorate (**4**) [23] (Scheme 4).

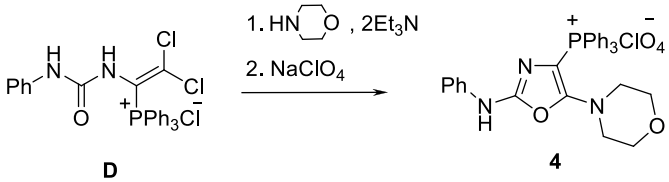


Scheme 2. Synthesis of 5-(4-chlorophenylsulfanyl)-2-(4-methylphenyl)-1,3-oxazol-4-yl(triphenyl)phosphonium perchlorate (**2**).



	Ar	X	An
3a	Ph		
3b	Ph	4-MeC_6H_4NH	I^-
3c	Ph	Me_2N	I^-
3d	4-MeC_6H_4	PhNH	ClO_4^-
3e	4-MeC_6H_4		ClO_4^-

Scheme 3. Synthesis of 5-aminosubstituted 2-aryl-1,3-oxazol-4-yl(triphenyl)phosphonium iodides or perchlorates **3a-e.**



Scheme 4. Synthesis of 2-anilino-5-morpholino-1,3-oxazol-4-yl(triphenyl)phosphonium perchlorate (**4**).

Earlier, we have obtained and published the results of *in silico* and *in vitro* studies of a number of TPPs as effective antimicrobial agents against *S. aureus* and *C. albicans*, including against their clinical drug-resistant isolates [25, 26], presented in Table 1.

Table 1 demonstrates that salts **1a-d, 3c** are the most active against both bacterial *S. aureus* and fungal *C. albicans* strains. It is important to note the high antimicrobial potential of these compounds against clinical drug-resistant strains. Many authors associate the anti-staphylococcal potential of TPPs with their transglycosylase activity [10]. A similarly high potential was noted in our

Table 1. Antimicrobial activity of TPPs.

Compound	Antibacterial activity*		Antifungal activity*	
	S. aureus ATCC 25923	*S. aureus* MDR	*C. albicans* ATCC 10231	*C. albicans* MDR
1	38,7±0,3	32,3±0,3	36,0 ± 0,3	30,3 ± 0,3
2	34,3±0,9	31,0±0,9	35,3 ± 0,9	30,0 ± 0,6
3	34,7±0,6	34,7±0,6	36,7 ± 0,3	37,3 ± 0,6
4	37,3±0,6	34,7±0,6	29,3 ± 0,6	31,3 ± 0,3
5	20,3 ± 0,3	34,3±0,6	22,0 ± 0,3	17,0 ± 0,6
6	32,3±0,6	24,3±0,3	14,3 ± 0,3	15,3 ± 0,3
7	30.3±0.6	28.3±0.3	22,3 ± 0,3	21,0 ± 0,3
8	35.0±0.6	31.3±0.3	38,0 ± 0,9	34,7 ± 0,3
9	36.3±0.9	32.0±0.3	25,7 ± 0,3	27,0 ± 0,6
10	20,7±0,3	19,3±0,3	21,3 ± 0,3	16,0 ± 0,3
11	27,5±0,3	22,0±0,6	18,0 ± 0,3	14,0 ± 0,6
Fluconazole	-	-	21,6±0,3	n/a
Ampicillin	29,0±0,6	n/a	-	-
Oxacillin	30,3±0,3	n/a	-	-
Ceftriaxone	11,3±0,6	n/a	-	-

work against the fungi (Table 1). Hence, it was possible to assume a similar target-oriented molecular mechanism of TPPs action. Based on this hypothesis, we conducted *in silico* studies including the creation of a homology model *C. albicans* TG.

A preliminary search of amino acid sequences associated with *C. albicans* TGs was conducted by the SWISS-MODEL template library. 1726 templates were created, from which the 5oa6.1.A template with 48.65% sequence identity was selected and a homology model was built. The created model (Figure 1) is the most optimal considering the resolution (1.94Å) and the estimation quality QMEAN (-1.75), GMQE (0.61).

At the next stage, the quality of the homology model was assessed using the online resources ERRAT and PROCHECK-web server data analysis has been also confirmed the 3D model structure TG good quality using Ramachandran plot analysis (Figure 2). Ramachandran plot results indicated that 90.0 % of the amino acid residues were distributed in the favored regions, 9.5 % – in the additionally allowed regions, 0.3 % – in the generously allowed regions and only 0.3 % – in the disallowed regions.

Thus, the created 3D structure of TG *C. albicans* has good stereochemically quality and was used for molecular docking. Molecular docking of ligands **1a-d** and **3c**, as the most active antimicrobials, was carried out into the active site of the created homology *C. albicans* TG model (Figure 3, 4). Ligand-protein complex formation of the studied TPPs was provided by various types of interactions (Table 2).

Thus, the formation of ligand-protein complexes is accompanied by estimated binding energies in a certain range from -8.9 to -9.7 kcal/mol (Table 2). The ligand-protein complexes were stabilized through strong hydrogen bonds (2.59-2.75 Å), electrostatic (3.38-4.55 Å) and hydrophobic (3.94-5.26 Å) interactions. The amino acid residues TYR307, TYR107, GLU275, ALA108 and PRO136 play a key role in this complexation.

Conclusions

Thus, we have experimentally established the presence of high antibacterial and antifungal activity of TPPs **1a-d**, **3c**, including the activity against drug-resistant clinical isolates obtained from biomaterial. The formation of stable ligand-protein complexes is provided by strong hydrogen bonds between amino acid residues and the oxazole ring of the ligands. The triphenylphosphonium group also plays a special role in the stabilization of the complexes. Other substituents in the structure of salts also form a number of electrostatic (3.38-4.55 Å) and hydrophobic interactions (3.94-5.26 Å).

Thus, a qualitative homology model of *C. albicans* TG can be used as a tool for the successful construction of new agents with the double antimicrobial action mechanism.

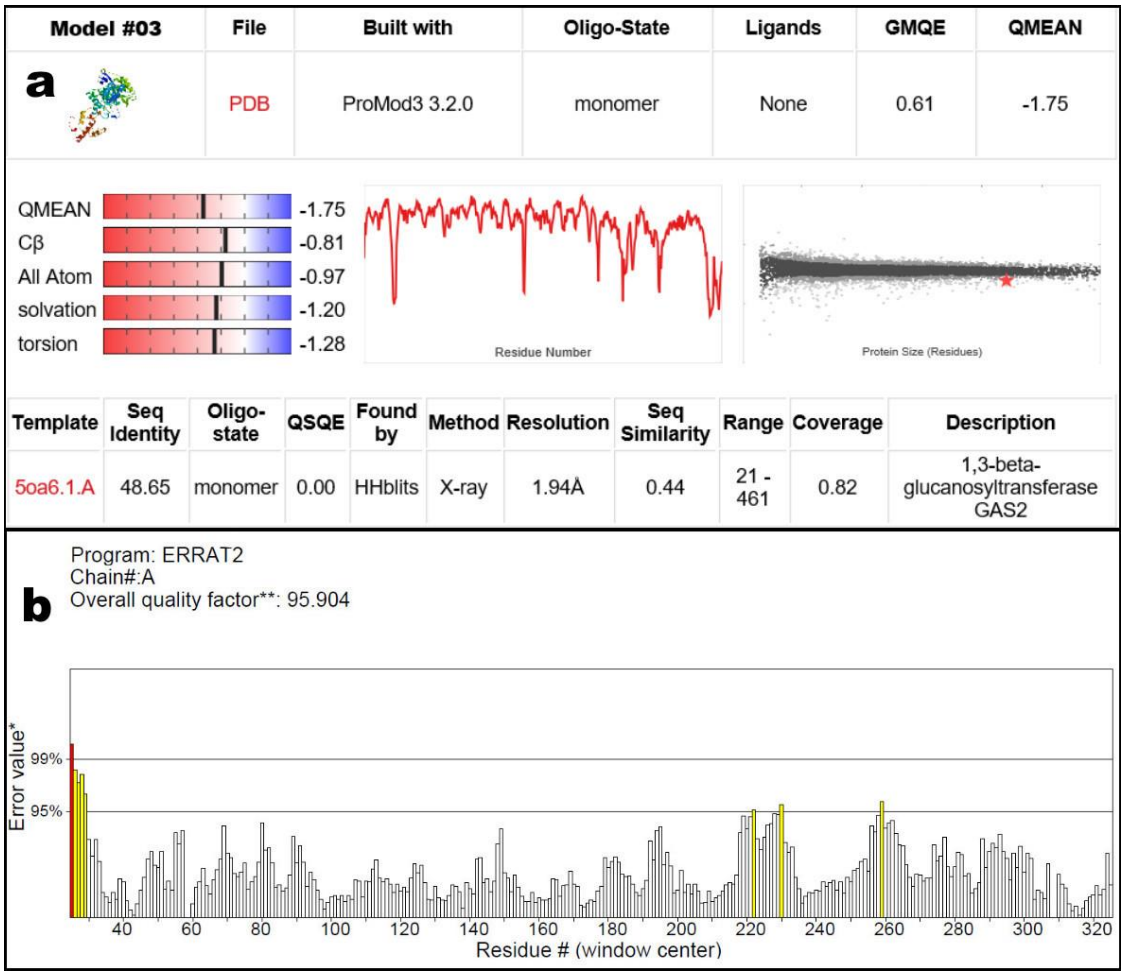


Figure 1. Quality assessment of the created homology model TG *C. albicans*. a) QMEAN quality plot of the homology model; b) the 3D profile of subunit A TG verified by using ERRAT server.

Table 2. Docking results of ligands **1a-d, 3c** into TG *C. albicans* active sites.

Compound	ΔG, kcal/mol	Hydrogen bonds	Electrostatic interaction	Hydrophobic interactions
1a	−9.2	TYR307 (2.59Å)	GLU275 (3.61Å), GLU275 (3.38Å), GLU176 (4.12Å)	TYR307 (5.20Å), TYR107 (4.41Å), TYR244 (4.92Å), TYR307 (5.18Å), TYR107 (5.18Å), TYR107 (3.94Å), ALA108 (5.27Å), PRO136 (4.45Å), PRO136 (4.60Å)
1b	−9.3	TYR307 (2.65Å)	TYR307 (3.60Å), TYR307 (3.38Å), GLU275 (4.12Å), TYR107 (4.08Å)	GLU275 (5.20Å), TYR107 (4.41Å), TYR107 (3.96Å), ALA108 (5.22Å), PRO136 (4.35Å), PRO136 (4.53Å)
1c	−8.9	TYR307 (2.75Å)	GLU275 (3.64Å), TYR107 (3.94Å)	TYR244 (4.89Å), TYR307 (5.26Å), TYR107 (4.41Å), TYR107 (3.97Å), ALA108 (5.26Å), PRO136 (4.32Å), PRO136 (4.55Å)
1d	−9.1	TYR307 (2.76Å)	GLU275 (3.58Å), TYR107 (4.00Å)	TYR307 (5.25Å), TYR107 (4.39Å), ALA108 (5.22Å), PRO136 (4.29Å), PRO136 (4.54Å)
3c	−9.7	TYR307 (2.74Å)	GLU275 (3.70Å), GLU275 (4.99Å), ARG142 (4.55Å)	TYR307 (5.05Å), TYR107 (4.88Å), TYR107 (5.10Å), PRO136 (5.21Å), PRO136 (5.16Å)

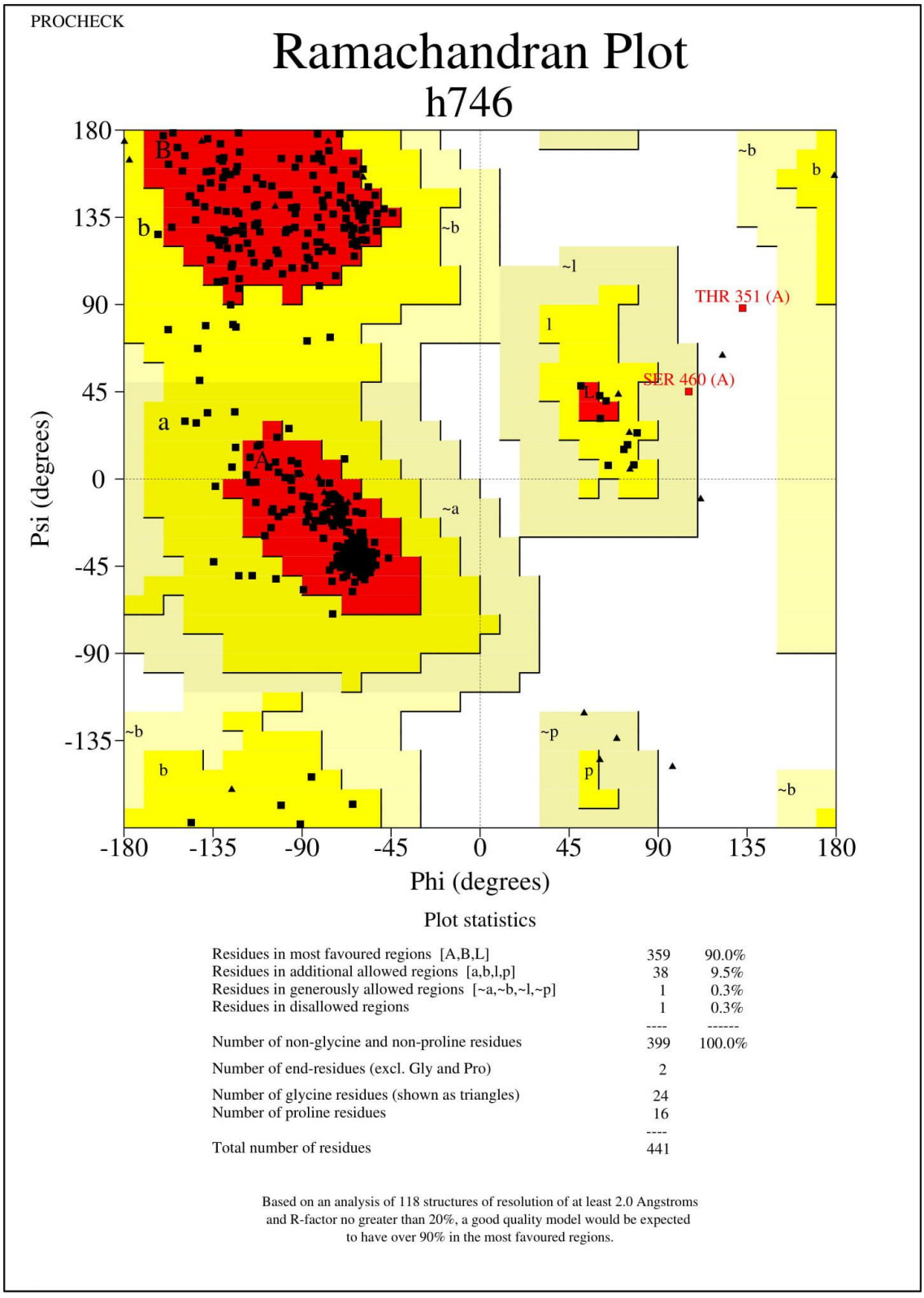


Figure 2. Quality assessment of the created homology model TG *C. albicans*. Ramachandran plot analysis of the stereochemical quality of TG model generated by PROCHECK validation server.

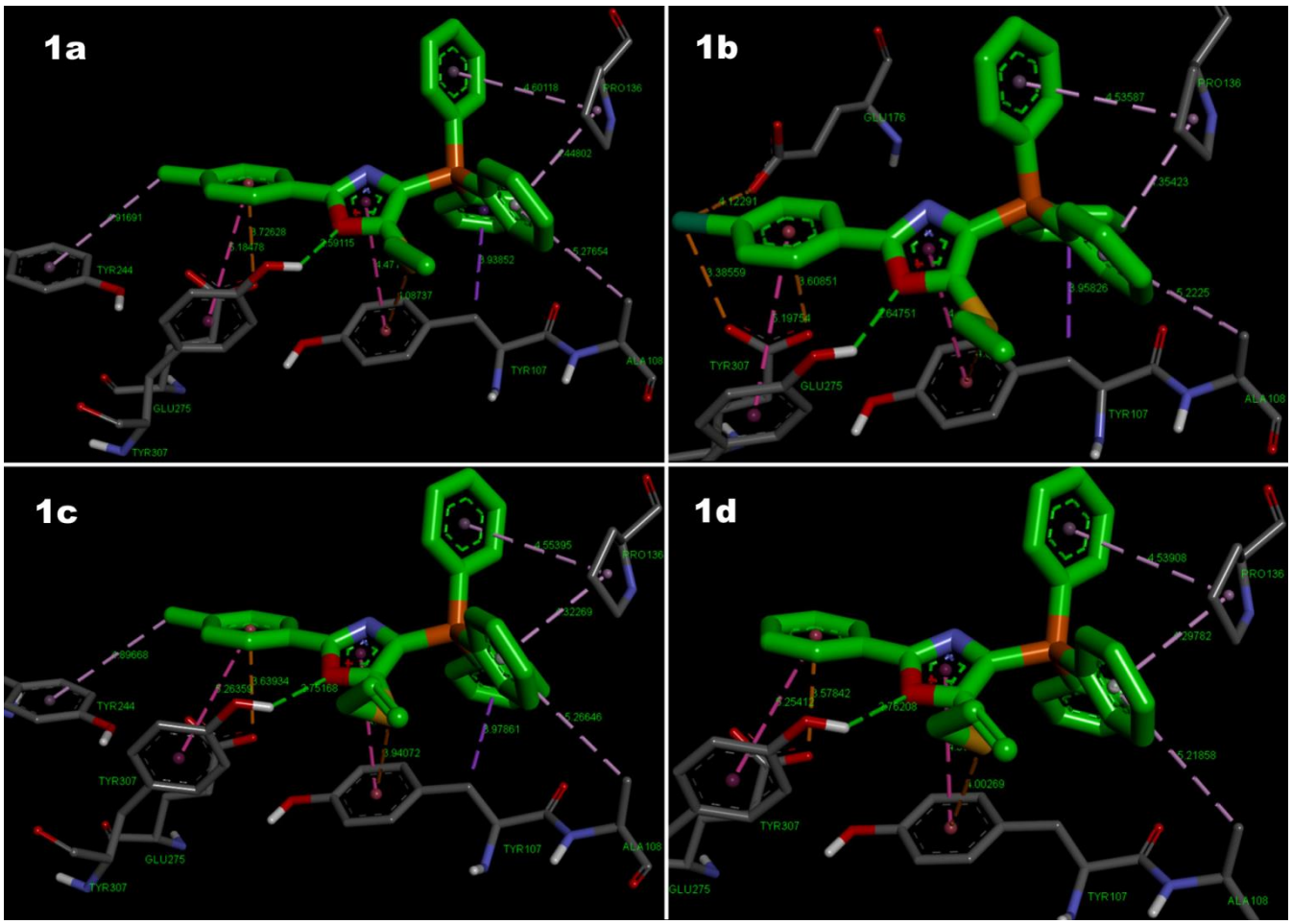


Figure 3. Molecular docking of the ligands **1a-d** into the active site of TG *C. albicans*.

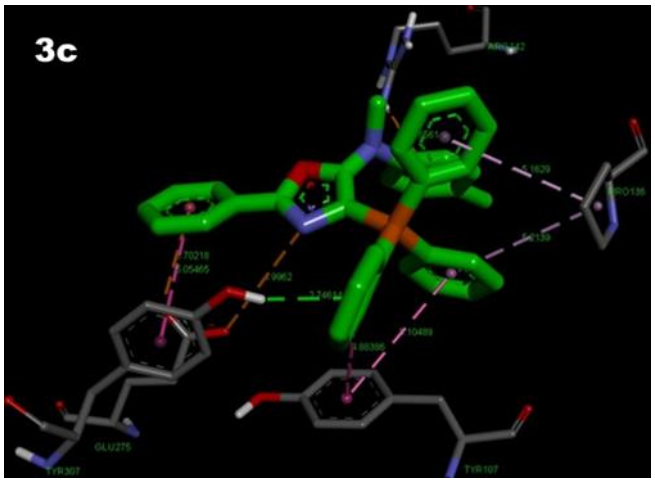


Figure 4. Molecular docking of the ligand **3c** into the active site of TG *C. albicans*.

1,3-oxazol-4-yltriphenylphosphonium salts **1a-d**, **3c** are promising candidates for the development of new antimicrobials against infectious pathogens MDR *S. aureus* and *C. albicans*.

Experimental section

General chemistry methods

Melting points were determined on a Fisher-Johns apparatus. IR spectra were recorded on a Vertex-70 spectrometer from KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury 400 (400 MHz) and Bruker Avance DRX 500 (500 and 125 MHz, respectively) spectrometers in $(CD_3)_2SO$ or $CDCl_3$ taking its residual protons signal as a standard. LCMS analysis was performed on an Agilent 1200 Series system equipped with a diode array and a G6130A mass-spectrometer (atmospheric pressure electrospray ionization). Combustion elemental analysis was performed in the V.P. Kukhar Institute of Bioorganic Chemistry and Petrochemistry of the NAS of Ukraine analytical laboratory.

The structure of investigated 1,3-oxazole derivatives **1a-d** [26, 27], **2** [27, 22], **4** [28], **3a** [29, 30], **3b,c** [21], **3d** [26] and **3e** [24] have been confirmed by NMR (1H and 13C NMR), IR spectroscopy, chromato-mass and elemental analysis and corresponded to previously described.

Biology

The antimicrobial activity of the studied triphenylphosphonium salts (TPPs) was estimated against *C. albicans* (ATCC 10231 and fluconazole-resistant clinical isolate) and *S. aureus* (ATCC 25923 and multi-drug (MDR) resistant clinical isolate) received from the Museum of Microbial Culture Collection of the P.L. Shupyk National Medical Academy of Postgraduate Education.

Antimicrobial properties were determined by the disc diffusion method in Mueller-Hinton and Sabouraud agar [31]. A final inoculum concentration of $1 \cdot 10^5$ colony-forming unit (CFU) per mL was established using a 0.5 McFarland turbidity standard and subsequent dilution of 0.02 ml of the tested compounds was applied on standard paper disks (6 mm) which were placed on the agar plate. The compound content on a disk was 0.3 µM. The known antifungal Fluconazole and antibacterial Ampicilline, Oxacilline and Ceftriaxone were used as positive controls.

The activity of tested compounds was identified by measuring the zone diameter of the growth inhibition, which indicates the degree of susceptibility or resistance of all microbial pathogens against the test compounds. The compounds, which formed zones > 15 mm of growth inhibition of microorganisms, were selected as active.

Homology modeling

Homology modeling of the aminoacid sequence of *C. albicans* TG (UniProt: C4YFM5) [32] was performed using web server SWISS-MODEL [33]. First, a preliminary search for evolutionarily related aminoacids sequences was performed using the SWISS-MODEL template library. Search and analysis of structures homologous to *C. albicans* TG were performed using the methods of BLAST [34] and HHBlits [35]. Templates for building a homology model were selected based on the overall rating of the created templates. The quality of the created homology model of *C. albicans* TG was estimated using internal methods of testing the web server SWISS-MODEL [36] and web servers ERRAT [37] and PROCHECK [38].

Molecular docking

The created homology model of *C. albicans* TG was used for docking studies. AutoDock Tools (ADT) 1.5.6 [39] was used to prepare the protein and ligands. All polar hydrogens were added to the protein molecules by ADT. The renumbering of all atoms with included new hydrogen atoms were performed by the noBondOrder method. The Gasteiger method was applied for the calculation and addition of partial charges. The made protein and ligands were saved in PDBQT format. The ChemAxon Marvin Sketch 5.3.735 program [40] was used to create, optimize and save the ligand structures in Mol2 format. The ligands optimization and energy minimization were performed by Avogadro v1.1.1 [41] using an auto-optimization tool by applying MMFF94s force field with the steepest descent algorithm. The partial charges and torsion angles of the ligands were altered by ADT and saved in PDBQT format. Docking was performed by AutoDock Vina 1.1.2 program [42]. The grid map (30*30*30 points) with a grid spacing of 1Å was used. The analysis and visualization of protein-ligand interactions were conducted by Accelrys DS 4.0 [43].

Notes

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The authors declare no conflict of interest.

Author contributions. **I. V. S**: molecular docking, homology modeling, analysis results, conceptualization, writing and editing. **M. M. T., D. M. H.** the investigation of bioactivity. **M. V. K**: synthesis of compounds, writing experimental section. **V. S. B**: synthesis of compounds, conceptualization. **L. O. M**: the investigation of bioactivity, conceptualization, results analysis, writing and editing.

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In vitro та *in silico* дослідження 1,3-оксазол-4- ілтрифенілфосфонієвих солей як потенційних інгібіторів трансглікозилази *Candida albicans*

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Резюме: У роботі запропоновано новий потенційний молекулярний механізм дії 1,3-оксазол-4-ілтрифенілфосфонієвих солей як інгібіторів трансглікозилази. За результатами біологічних досліджень встановлено високий антимікробний потенціал досліджених солей трифенілфосфонію як проти бактеріальних (*Staphylococcus aureus* ATCC 25923 та мультирезистентний), так і проти грибкових (*Candida albicans* ATCC 10231 та мультирезистентний) штамів. Отримані експериментальні дані щодо їх антимікробної активності дозволили запропонувати молекулярний механізм дії цих сполук, пов'язаний з трансглікозилазною активністю. В основу гіпотези було покладено результати аналізу «структура-активність» солей трифосфонію в онлайн хімічній базі ChEMBL, а також за відомими літературниими джерелами щодо антимікробної активності солей як інгібіторів трансглікозилази *S. aureus*. Створена гомологічна модель трансглікозилази *C. albicans* продемонструвала високі показники якості та була використана для молекулярного докінгу. Молекулярний докінг найбільш активних лігандів **1a-d**, **3c** в активний центр створеної гомологічної моделі *C. albicans* засвідчив утворення стабільних ліганд-білкових комплексів з ΔG в діапазоні від -8,9 до -9,7 ккал/моль шляхом формування різних типів взаємодій. Представлена якісна гомологічна модель трансглікозилази *C. albicans* може бути використана для пошуку та створення нових агентів з подвійним механізмом антимікробної дії. Солі 1,3-оксазол-4-ілтріфенілфосфонію **1a-d**, **3c** є перспективними об’єктами для подальшого вивчення в якості антимікробних засобів проти мультирезистентних інфекційних збудників.

Ключові слова: трансглікозилаза; трифенілфосфонієві солі; 1,3-оксазол; *Candida albicans*; *Staphylococcus aureus*.