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Coumarin structure as a lead scaffold for antibacterial agents - molecular docking study

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***Abstract*:**

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Coumarins owe their class name to "Coumarou", the vernacular name of the tonka bean (*Dipteryx odorata* Willd, Fabaceae), from which coumarin was isolated in 1820. Many molecules based on the coumarin structure have been synthesized utilizing innovative synthetic techniques. Various synthetic routes have led to interesting derivatives including the furanocoumarins, pyranocoumarins and coumarinsulfamates which have been found to be useful in photochemotherapy, antitumor and anti-HIV therapy, as stimulants for central nervous system, antiinflammatory therapy, as anti-coagulants, etc. One of important pharmacological activity of coumarin molecules is their potential as antibacterial agents since they show inhibitory activity toward isoleucyl-transfer RNA (tRNA) synthetase. In the presented research molecular docking studies of selected coumarin compounds inside isoleucyltransfer RNA (tRNA) synthetase active site were performed. Molecular docking scores of all studied compounds were obtained through score functions. Presented results indicate that from all studied coumarin compounds the strongest interactions with studied enzyme has 7,8-dihydroxy-4-phenyl coumarin followed by 5,7-dihydroxy-4-phenyl coumarin. Presented results are in accordance with *in vitro* obtained results for their antibacterial activity. Presented findings suggest that 4-phenyl hydroxycoumarins may be considered as good molecular templates for potential antibacterial agents and can be used for further chemical modifications for improving their antibacterial activity.

Key words: *Verbascum davidoffii*, endemic species, genetic diversity, conservation

***Apstrakt*:**

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Kumarini su dobili ime od reči "Coumarou", narodnom nazivu za tonku (*Dipterix odorata* Willd, Fabaceae) iz koje je kumarin izolovan 1820. godine. Mnogi molekuli bazirani na kumarinskoj strukturi su sintetisani primenom inovativnih hemijskih tehnika. Različiti putevi sinteze su doveli do interesantnih derivata koji uključuju furanokumarine, piranokumarine i kumarinsulfamate koji imaju primenu u fitohemoterapiji, antitumorskoj i anti-HIV terapiji, kao stimulanti za centralni nervni sistem, kao antinflamatorni i antikoagulativni agensi, itd. Jedna od važnih farmakoloških aktivnosti kumarinskih jedinjenja je njihov potencijal kao antibakterijskih agenasa, jer pokazuju inhibitornu aktivnost prema izoleucil-transfer RNK sintetazi (tRNK). U predstavljenom istraživanju studija molekularnog dokinga unutar aktivnog mesta izoleucil-

transfer RNK sintetaze (tRNK) je primenjena za odabrana kumarinska jedinjena. Vrednosti molekularnog dokinga za sva ispitivana jedinjenja su dobijene primenom odgovarajućih skoring funkcija. Predstavljeni rezultati ukazuju da od svih ispitivanih kumarinskih jedinjenja najviše interakcija sa ispitivanim enzimom ima 7,8-dihidroksi-4-fenil kumarin, a zatim 5,7-dihidroksi-4-fenil kumarin. Predstavljeni rezultati su u skladu sa *in vitro* dobijenim rezultima za njihovu antibakterijsku aktivnost. Prikazani rezultati ukazuju da se 4-fenil hidroksikumarini mogu smatrati dobrim molekuskim osnovama za potencijalne antibakterijske agense i da se mogu koristiti za dalje hemijske modifikacije u cilju poboljšanja antibakterijske aktivnosti.

Key words: 4-fenil hidroksikumarini, antibakterijska aktivnost, molekularni doking

Introduction

Great hopes that the discovery and the application of penicillin and other antibiotics would forever solve the problem of bacterial infections lasted for a relatively short time period. Seven decades after antibiotics were introduced, infectious diseases as a cause of mortality are in third place in Europe. In the European Union (EU) around 2 million people are hospitalized and around 200,000 die from some infectious diseases annually. As a gloom example in South Asia in every 2 minutes one infant dies due to resistance to existing antibiotics. It is considered that the main reason for this "failure" of the treatment is a large percentage of drug-resistant and multidrug-resistant bacteria. Today, antibacterial resistance is a growing public health threat of major concern around the world. A post-antibiotic era (in which common infections and minor injuries can kill), far from being an apocalyptic fantasy, is instead a very real possibility for the 21st century (WHO, 2014).

Bacterial resistance is a natural biological phenomenon that can be associated with their fight for survival. Mechanisms of bacterial resistance to antibiotics are very different and complex and depend both on the bacteria and the structure of antibiotics. Also, it involves a range of resistance mechanisms acting an ever-widening range of bacteria, most of which can cause a wide spectrum of diseases in humans and animals. Factors that favor the development of bacterial resistance are: overusing prescribing antibiotics, improper use - the compliance, inadvertent application of antibiotics and slow development of new effective antibiotics. Of all identified bacterial strains resistant to antibiotics of particular concern are methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae*, vancomycin-resistant *Enterococcus*, and *Mycobacterium tuberculosis*, since many of these organisms are resistant to several classes of established antibiotics and they can cause infections which are very difficult to treat. Above stated facts are forcing the search for novel antibacterial agents which affect targets that are essential to bacteria (Payne et al., 2007; Bollenbach, 2015). In this regard, the aminoacyl-tRNA synthetase (AaRS) enzymes have been a focus of recent antibacterial drug research. Inhibition of these enzymes halts protein biosynthesis which in turn results in the attenuation of bacterial growth under both *in vitro* and infectious conditions and for this reason bacterial AaRSs present a vast number of opportunities for the identification of novel inhibitors that can be considered as candidates for development as antibiotics (Ochsner et al., 2007).

Today resistant bacterial strains occur significantly faster than the synthesis and the release of new effective antibiotics. It is well known fact that the development of new drugs in recent decades has become extremely expensive and time-consuming process. For this reason novel computational methods like molecular docking are used to speed up the process of drug design and development. The main aim of molecular docking is the determination of a suitable geometry and binding affinity of the tested molecule (ligand) to the active site of the target macromolecules (receptors) with the application of the "scoring" functions (Kroemer, 2007).

Coumarins are a group of molecules found extensively in plants and they show various biological and pharmacological activities including anticoagulant, estrogenic, vasodilator, hypothermic, anthelmintic, sedative, analgesic, anti-inflammatory and antiulcer. Further, coumarin derivates have a wide range of structural modifications (Borges et al., 2005) and they can serve as molecular templates for new drugs. Coumarin derivates are also considered as potential antibacterial agents (Veselinović et al., 2015).

Main goal of presented research was to establish the influence of 4-phenyl group addition and the number and position of hydroxyl groups within main coumarine structure on the interaction with isoleucyl-transfer RNA (tRNA) synthetase using molecular docking study. Studied interactions are considered as main influence on enzyme inhibition which can lead to antibacterial activity.

Material and methods

Molecular docking. In order to gain insight into the plausible mechanism of antibacterial action docking simulations were performed. The crystal structure of isoleucyl-transfer RNA (tRNA) synthetase (IleRS)

was obtained from the Brookhaven Protein Data Bank http://www.rcsb.org/pdb (PDB entry: 1QU3). The compounds were docked into enzyme binding sites using the MolegroVirtual Docker (MVD) and published methodology [7]. Three dimensional structures of compounds (7-hydroxy-4-phenyl coumarin (7C), B) 5,7-dihydroxy-4-phenyl coumarin (57C) and C) 7,8-dihydroxy-4-phenyl coumarin (78C)) used for docking simulation were constructed using MarvinSketch 6.1.0, 2013, ChemAxon (http://www. chemaxon.com). Geometry optimization was carried out by employing MMFF94 molecular force field.

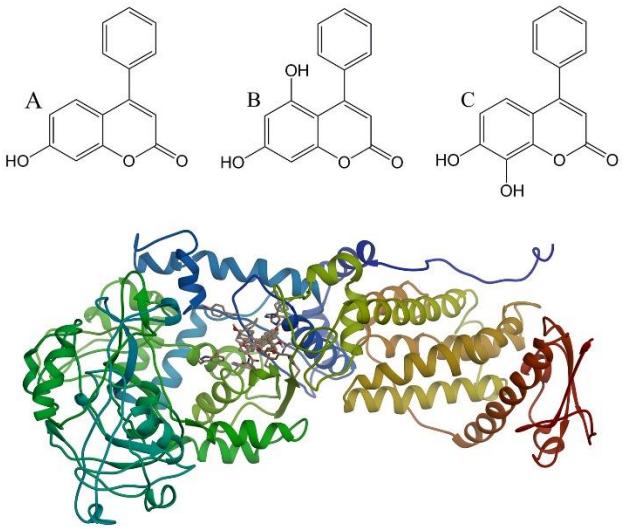

Fig. 1. Above: Chemical structures of investigated compounds: A) 7-hydroxy-4-phenyl coumarin (7C), B) 5,7-dihydroxy-4-phenyl coumarin (57C) and C) 7,8-dihydroxy-4-phenyl coumarin (78C). Bellow: The structure of IleRS with best docking poses for all investigated coumarins inside enzyme binding pocket.

Results and discussion

Chemical structures of investigated coumarines are presented in **Fig. 1**.

The least energy binding mode of compounds has been studied and best docking poses for all investigated coumarins inside enzyme binding pocket is presented in **Fig. 1**. Binding affinity of a ligand to the active site of the enzyme can be estimated based on the score values obtained using scoring functions form the molecular docking method. **Table 1** presents score values for all studied compounds.

Presented results indicate that of all studied compounds the highest interactions with enzyme has 78C followed by 57C. According to presented results the difference between their interaction energies is not as big as difference between their interaction energies and 7C interaction energy. It is of great importance that presented results are in accordance with *in vitro* obtained results for antibacterial activity. Interesting result was obtained with molecular docking study – that 7C don't form any hydrogen bond with the active site of studied enzyme. This can be one of the reasons why 7C show the lowest antibacterial activity, because number, bond length, and bond energy of hydrogen bonds formed between ligand and enzyme have an important role in ligand effect on investigated activity. Two dimensional representations of formed hydrogen bonds for 57C and 78C are presented in **Fig. 2**.

It was observed from *in silico* studies that 57C forms one hydrogen bond - oxygen atom from carbonyl group from the lacton part of molecule with Lys-71 (2.80 Å). 78C forms four hydrogen bonds. Oxygen atom from carbonyl group from the lacton part of molecule forms one hydrogen bond with Lys71 (2.79 Å). Hydroxyl group at position 7 forms

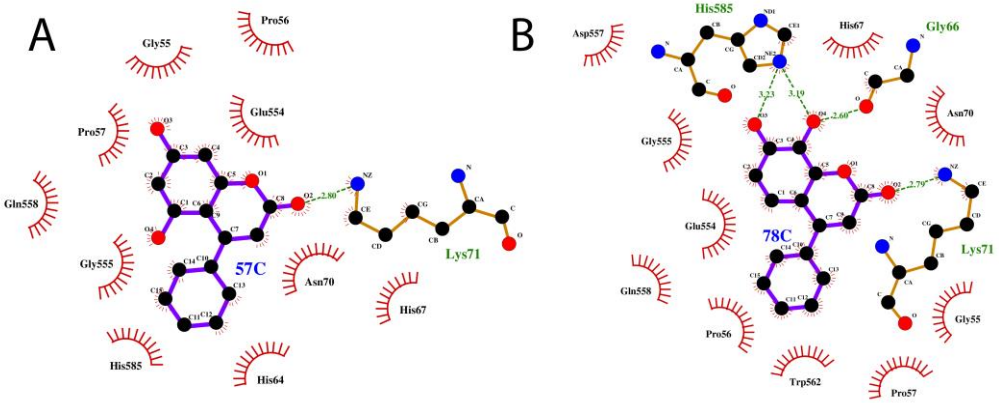

Fig. 2. Two dimensional representations of the best docking pose for A) 5,7-dihydroxy-4-phenyl coumarin, and B) 7,8-dihydroxy-4-phenyl coumarin inside isoleucyl-transfer RNA (tRNA) synthetase active site.

Table 1. Score values (kcal/mol) for all studied coumarin compounds.

	MolDock	ReRank	Interaction	Inter.	HBond	Docking Score
78C	-125.476	-108.328	-138.994	13.517	-6.0007	-127.625
57C	-118.820	-101.209	-130.653	11.832	-3.8847	-124.704
7C	-106.467	-88.612	-116.639	10.172	0	-104.336

one hydrogen bond with His585 (3.23 Å). Hydroxyl group at position 8 forms two hydrogen bonds with His585 (3.19 Å) and Gly66 (2.60 Å).

Conclusion

Molecular docking simulations against IleRS were performed and correlation between the observed inhibitory activity and the *in silico* molecular docking scores of the compounds was obtained through hydrogen bonding interactions. These findings suggest that 4-phenyl hydroxycoumarins may be considered as good molecular templates for potential antibacterial agents and can be used for further chemical modifications for improving antibacterial activity what will be the main goal of our further research.

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