APPLICATION OF ARTIFICIAL INTELLIGENCE IN THE DESIGN OF WARFARIN DERIVATIVES TO OVERCOME VKOR1 MUTATION-INDUCED WARFARIN RESISTANCE

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Abstract:

Artificial Intelligence (AI) has become embedded in different areas of everyday life, especially in different branches of industry and science. At the same time, *in silico* drug discovery and development have progressed rapidly over the last few decades. In comparison to experimental techniques, *in silico* methods have an advantage in a number of areas. Molecule design, synthesis planning, ADMET analysis, drug targeting, pharmacokinetic and pharmacodynamic properties, and mechanism of action studies are just a few of the aspects that are frequently investigated *in silico* prior to the compounds being synthesized and tested *in vitro* and *in vivo*. One important example is the development of substitute drugs for application in preventing drug-specific resistance. In this paper, a range of different *in silico* techniques quenched with AI were employed in order to predict a modification of warfarin that would circumvent organism resistance caused by vitamin K epoxide reductase mutation (*VKOR1*). It was found that one compound from the series of investigated compounds has shown promising inhibitory potential towards the tested enzyme. Additionally, it was found that the investigated warfarin derivate is water-soluble, with high gastrointestinal absorption, and no ability of blood-brain barrier permeability. It satisfies all five rules of the drug-likeness test and does not interact with the cytochrome P450 family, which potentially raises its efficiency as a coagulant.

Keywords: drug discovery, artificial intelligence, warfarin, drug resistance

1. Introduction

Artificial Intelligence (AI) has been ingrained in our daily lives, with applications ranging from product suggestions to data analysis in medicine, science, radiology, etc. Many tools established for other industries, such as language translation and computer vision, are also being used in the drug discovery process. The analysis of high-content screening data, as well as the design and prediction of the possibility to synthesize novel compounds, have all been made a part of the scope of AI [1]. The processes of *in silico* drug discovery and development have advanced rapidly in the last 50 years. The possibility of simulating different systems, and the drugs in them, has led to a significant shift in the methodology of drug development and to some of the most important discoveries of the 21st century so far.

There is a number of areas where *in silico* methods have the advantage compared to experimental techniques. For example, molecule design, synthesis planning, ADMET analysis, drug targeting, pharmacokinetic and pharmacodynamic properties, and study of the mechanism of action are only some of the aspects which are often investigated *in silico* before the compounds are synthesized and tested *in vitro* and *in vivo*. The possibility of screening large sets of molecules for certain properties has allowed for easier and more precise drug development.

When AI algorithms are applied to the methodologies mentioned in the previous paragraph, they will be able to achieve higher degrees of accuracy and efficiency. An interesting application of these techniques will be in the modification of drugs to circumvent drug resistance. For example, warfarin (figure 1) is a widely used drug with proven anticoagulant activity [2]. However, warfarin prevents blood coagulation by inhibiting the vitamin K epoxide reductase multiprotein complex (VKOR), which in organisms resistant to warfarin was found to have a certain mutation in the genetic sequence that generates this enzyme [3-5]. In this paper, techniques and methods which implement AI will be used to find the derivates of warfarin suitable as a potential replacement anticoagulative drug.

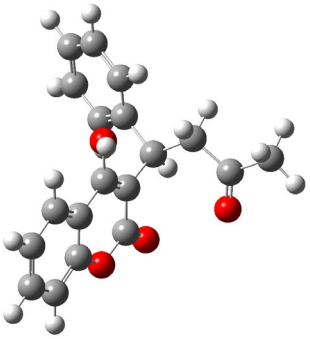

Figure 1. Geometry of warfarin

2. Methodology

A series of warfarin derivatives was generated using a Chemically Reasonable Mutations (CReM) webserver. CReM is an open-source Python framework that generates chemical structures using a fragment-based approach [6-7]. The mode of generating new derivatives was set to "scaffold mode", for a server to add substituents on an already existing structure. The fragment database was set on the strictest synthetic availability score SA≤2, and the rest of the parameters were left on default. SMILES structures generated by CReM are then subjected to the SwissADME webserver [8] and, from there, selected derivatives are further investigated for inhibitory potency by the PlayMolecule server. This server implements machine learning and artificial intelligence algorithms in drug discovery processes. Molecular docking was performed by ACEdock, which is a part of the PlayMolecule web server, where the active site was determined by the existing (template) ligand from the protein's crystal structure [9-12]. The docking mode was set on a "scaffold" in order for warfarin derivates to find a position that will occupy the active site in such a way that vitamin K cannot be bonded next to it, so it does not activate the enzyme. The "Pharmacophoric rescoring" function was used in order to introduce a series of corrections which lead to more realistic docking scores. The crystal structure of the mutated *VKOR1* enzyme was downloaded from RCSB Protein Data Bank (PDB ID:6VW5) [13].

3. Results and discussion

A series of warfarin derivates generated by the CReM server were subjected to SwissADME in order to investigate their ADME properties. From there, derivates fulfilling two main criteria were selected. The first criterion was high-to-moderate water solubility. The second was inhibitory potential towards Cytochrome P450 2C9 because binding to this enzyme lowers the activity of warfarin and its derivates. Six derivates met these criteria and their structures are presented in Figure 2.

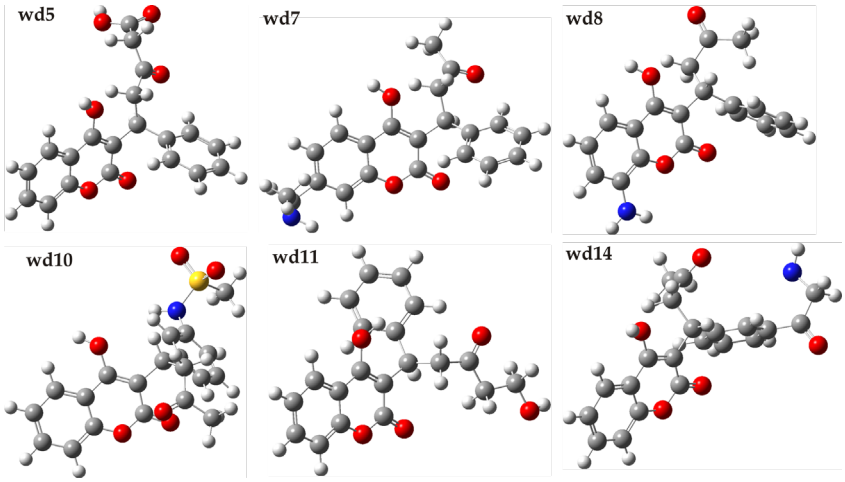

Figure 2. Geometries of compounds selected for the docking investigation

The docking investigation of six selected derivates was performed as described in the methodology section. The results are presented in Table 1. As standard ligands for this binding site, warfarin and vitamin K were used.

	Warfarin	**Vitamin K**	**wd5**	**wd7**	**wd8**	**wd10**	**wd11**	**wd14**
R-dock score	11.56	-3.63	-4.95	96.38	166.91	120.09	106.64	62.82
PP score	0.28	0.31	0.29	0.28	0.23	0.30	0.24	0.28

Table 1. Docking scores obtained for investigated compounds

As can be seen from the obtained data, the binding of warfarin is not favourable, especially in regard to Vitamin K, which is to be expected since *VKOR1* is a protein with a mutation that is found in warfarin resistant organisms. Additionally, R-dock scores suggest that wd7-wd14 show even lower activity when it comes to *VKOR1* inhibition, in comparison to warfarin. However, it was found that compound wd5 shows promising inhibitory potential with an R-dock score lower than the score of Vitamin K. This indicates that in presence of the wd5, Vitamin K would not bind to *VKOR1,* and thus *VKOR1* would not express its physiological function. In addition, examining the results obtained by screening performed on the SwissADME webserver, compound wd5 fulfils all five rules of drug-likeness, which indicates that it possesses all structural elements of a potential drug., It was discovered by the same server that, in comparison to warfarin, wd5 does not express blood-brain-barrier permeability.Additionally, even though it is soluble in water and skin permeable it is not a P-gp substrate and it is easily absorbed through the gastro-intestinal organ system, so it probably undergoes a passive transport system. Overall, this indicates that it is likely that wd5 may become a potential substitute for warfarin.

4. Conclusions

Implementation of AI in *in silico* methods of drug discovery and development have allowed easier screening and more accurate results. The application of AI enables the screening of a large series of warfarin derivates and, coupled with other methods, it can be of significant help in the investigation process. In this paper, a series of fifteen new derivates of warfarin was generated and screened for ADME properties by CReM and SwissADME webservers. Derivates that satisfied certain criteria mentioned in the previous paragraph, were subjected to docking studies, and it was found that one of the derivates shows good potential inhibitory activity against the tested enzyme. Additionally, it was found that wd5 is water-soluble, with high gastrointestinal absorption, and no ability of blood-brain barrier

permeability. It satisfied all five rules of drug-likeness and does not interact with the cytochrome P450 family, which potentially raises its efficiency as a coagulant. Consequently, this compound should be considered for further investigation and regarded as a possible substitution for warfarin in warfarin resistant organisms.

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