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Sar-Based Design of Protease Inhibitors Novel Scarfold

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Abstract

To design new antimalarial agents from both active synthetic and natural products fragments using *in silico* software to determine their pharmacokinetics and pharmacodynamics profiles as therapeutic molecules against the deadly malaria causing parasite biological targets.

In this study, active fragments from prenylated and quinolinyl chalcones with known antimalarial activities were hybridized through molecular hybridization. Four enzymes which have been reported to be involved in malaria transmission are used as the biological targets for the ligands (prenylated-quinolinyl chalcones hybrids) during docking simulation. Receptor-ligand complexes were viewed using Chimera and Discovery Studio Visualizer 2017. Web-based softwares (Moftsoft, SwissADME, AdmetSAR 1 and 2) were employed in drug-likeness and ADMET prediction.

Hybridization of the active fragments resulted to a novel scarfold including 126 novel prenylated-quinolinyl chalcones. Post-docking analysis revealed strong interactions of the compounds with the targets used. At least 25 of the compounds have high affinities for the targets (-9.4 to -7.5 kcal/gmol^{-1}). The selected compounds demonstrated good drug-likeness and ADMET properties.

The compounds exhibited plausible pharmacokinetics and pharmacodynamics properties in conjunction to their promising antimalarial activities which ranked them as potential antimalarial agent.

Keywords: Prenylated chalcones; Quinolinyl chalcones; SAR; Docking simulation; Molecular hybridization

Description

Malaria remain one of the most prevalent diseases claiming more than 400,000 lives annually across the globe. Children and pregnant women are most vulnerable to this disease [1]. *Plasmodium falciparum* remain the most dreadful malaria parasite which poses resistance with the current first-line antimalarial drugs [2]. Scientists across the world are constantly searching for new principles to combat the emerging parasite strain. Several years of drug discovery and development of novel antimalarial drugs has led to increasing focus on elimination and eradication of malaria [1-6]. In the papain-family cysteine proteases falcipain-2 (FP-2) and falcipain-3 (FP-3) are known to catalyze the proteolysis of host hemoglobin, a process that is essential for the development of erythrocytic parasites [7].

Hemoglobin is degraded by a series of proteases in an acidic digestive vacuole of the parasite. The aspartic proteases found in the vacuole, named plasmepsin, make an initial attack on the hemoglobin molecule, followed by proteolysis of the large fragments into small peptides by a cysteine protease named falcipain [8]. The initial cleavage by plasmepsin is critical to hemoglobin degradation because intact hemoglobin cannot be cleaved by falcipain unless it is first denatured. It is believed that this cleavage results in the unraveling of the hemoglobin molecule, allowing

further proteolysis to proceed efficiently [8,9].

Subtilisin-like serine protease called SUB1 is an enzyme which have been reported to promote egress [10]. Minutes before egress, a calcium and cGMP-dependent signal triggers the discharge of a SUB1 from specialized secretory organelles of the still intracellular merozoite, called exonemes [10]. On its release into the Basilophorous Vacuole lumen, SUB1 proteolytically modifies a number of abundant merozoite surface and Basilophorous Vacuole resident soluble proteins including SERA6, a putative cysteine protease involved in egress and invasion. Pharmacological inhibition of SUB1 discharge or catalytic activity blocks egress and/or reduces the invasive capacity of released merozoites. Drugs that target SUB1 activity should prevent disease progression and so have potential as a new class of antimalarial therapeutics, urgently needed in response to increasing drug resistance of the parasite.

Discussion

Rule of Three (RO3) has been useful in ensuring that fragment libraries really do consist of compounds with active fragment-like properties . The parameters of 'Rule of Three' are such that a molecule with molecular weight ≤ 300, the number of hydrogen bond donors is ≤ 3, the number of hydrogen bond acceptors is ≤ 3, ClogP is ≤ 3, NROT (≤ 3) and PSA (≤ 60) would be an active fragment. Any fragment that passes these rules on the average could be useful when constructing fragment libraries for efficient lead discovery. The RO3 was applied to the fragment library to assess whether our derived active fragments possess the parameters to exhibit active fragment-like properties.

Six series of a novel scaffold comprising of 126 hybrids resulted from the hybridization of the screened fragments as listed above. The best twenty-five hybrids with high affinity for at least two biological targets were selected from the docking score ranking (unpublished). Nineteen of these compounds have higher affinities for three receptors (Falcipain 2, Falcipain 3, and SUB1) compared to the respective receptors' natural inhibitors.

The drug-likeness score depicts the structural similarity features of the compounds with the existing marketed drugs using Molsoft's chemical fingerprints. The training set for this model consisted of five thousand of marketed drugs from WDI (positives) ten thousand of carefully selected non-drug compounds (negatives). All the compounds exhibit good drug-likeness score except for compounds 10e and 21a with -0.58 and 0.10, respectively.

During the time and resource-consuming processes of drug discovery and development, enormous number of molecular compounds are evaluated using diverse parameters in order to determine the selection of which chemicals to synthetize, test and promote, with the sole aim of identifying those with the best likelihood of becoming an effective medicine for the patients. The molecules must show high biological activity together with low toxicity. Chemical absorption, distribution, metabolism, excretion, and toxicity (ADMET) play key roles in drug discovery and development. A good drug candidate should not only have

effective efficacy against the therapeutic target, but also show teeming ADMET properties at a therapeutic dose.

In silico ADMET analysis was conducted to further predict the pharmacokinetics and physico-dynamic profile of the selected compounds. The permeability glycoprotein P-gp is essential to allowing active efflux through biological membranes, for instance from the gastrointestinal wall to the lumen or from the brain. Specifically, P-gp functions to protect the central nervous system (CNS) from xenobiotics. Therefore, it is important to determine whether a molecule is an agonist or antagonist of this glycoprotein. Cytochromes P450 (CYP) is a group of isoenzymes responsible for drug elimination through metabolic biotransformation. It has been reported that CYP and P-gp can transform small molecules synergistically to increase protection of tissues and organisms. It has been estimated that 50% to 90% of drug molecules are agonist of five major isoforms (depending on the author) (CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4). Inhibition of these isoenzymes majorly results to pharmacokinetics-related drug-drug interactions posing major toxicity or other unwanted adverse effects due to the non-efficient expulsion and accumulation of the drug or its metabolites. Several antagonists of the CYP isoforms have been discovered. A handful of compounds affects different CYP isoforms, while other compounds are selective for certain isoenzymes. It is therefore of great importance during drug discovery stage to determine the tendency with which the molecules might cause an expressive drug-drug interaction by inhibition of CYPs, and also to predict those isoforms that could be affected.

The two most important parameters for toxicity prediction are chemical carcinogenicity and acute oral toxicity, others are models for binary classification. Based on acute oral toxicity models, compounds have been grouped into different categories. Category I and II comprises of compounds with LD50 ≤ 50 mg, and kg^{-1} 50 mg kg^{-1} < LD50 ≤ 500 mg kg^{-1} respectively and are considered as toxic. Category III comprises of compounds with 500 mg kg^{-1} < LD50 ≤ 5000 mg kg, while category IV comprises of compounds with 5000 mg kg < LD50 and are considered to be non-toxic.

It shows results of *in silico* absorption and distribution of the selected compounds. This indicated good absorption of the compounds in human intestine and CaCo$_2$. These compounds also have good distribution profile being able to pass through the two barriers namely; plasma protein barrier and blood brain barrier.

From all the compounds are agonist to P-gp. Also compounds 4b, 4d, 7c, 15d, 19, and 21a, are substrates to all the five major CYP isoenzymes. The results showed that compounds 2a, 4a, 4e, 8d, 10e, 11d, 11e, 13b, 13d, 13e, 13f, 16b, 19a, and 21d are agonists to four major CYP isoforms. Most of these compounds inhibited 2C19 isoform while compounds 8d and 19a inhibited 2C9 isoform, and compound 21d inhibited 1A2 isoform. All the compounds are considered as non-toxic and non-carcinogenic as indicated by their *in silico* acute oral toxicity and carcinogenesis evaluation.

Conclusion

Overall results have proven that selected compounds with the best affinities for the selected malaria biological targets (PlmII, Falcipain 2 and 3, and SUB1) exhibited plausible drug-able properties which raise them to be possible antimalarial drug candidates.

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