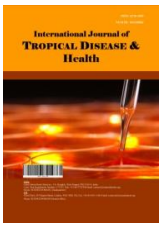

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In Silico ADME/T Properties of Quinine Derivatives using SwissADME and pkCSM Webservers

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Aim: Malaria is among the most devastating and widespread tropical parasitic diseases. To overcome antimalarial drug resistance, new drugs need to be developed. This study is designed to establish the pharmacokinetic profile and toxicity of nine quinine derivatives as potential antimalarial drugs using *in silico* approaches by SwissADME and pkCSM.
Methodology: The structures of investigated compounds were translated into canonical SMILES format and then submitted to SwissADME web tool that gives free access to physicochemical properties, pharmacokinetics, drug-likeness and medicinal chemistry friendliness of compounds, and pkCSM webserver for predicting and optimizing pharmacokinetic and toxicity properties.
Results: SwissADME mainly used to predict the physicochemical properties of compounds and their drug-likeness revealed that all quinine derivatives have good bioavailability and satisfied the Lipinski's rule of five. The pkCSM results on the absorption, distribution, metabolism, excretion and toxicity show that all investigated compounds have a good pharmacokinetic profile and they are

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safe since they belong to class 4 of the Globally Harmonized System (300 < Category 4 ≤ 2000 mg/kg/day).
Conclusion: Drug-likeness and ADME/T predictions of nine investigated quinine derivatives revealed that they are good candidates to oral drug formulation and thus they can be used in a broader context of overcoming the development of resistance by *Plasmodium* protozoans against most of the drugs currently used to treat malaria. As future prospects, further studies on bioevaluation of compounds are needed to elucidate their potential pharmacological activities.

Keywords: Quinine derivatives; malaria; pharmacokinetic profile; SwissADME; pkCSM.

1. INTRODUCTION

Quinine (QB, Fig. 1) is an alkaloid with powerful antimalarial activity isolated from the bark of Peru's cinchona trees. Its usage is currently reserved for particularly severe cases in order to prevent the development of resistance by the plasmodium parasites [1]. Resistance to antimalarial drugs challenges the ability to save lives threatened by malaria, and to eliminate the burden that malaria places on individuals and societies. This burden is substantial, with malaria having caused an estimated 228 million cases and 405 000 deaths in 2018 [2].

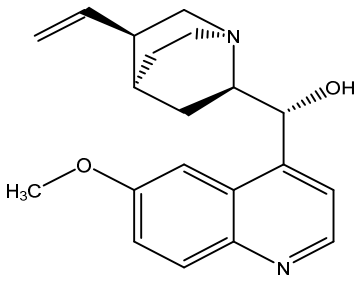

Fig. 1. Structure of quinine

Malaria is an endemic disease in most tropical countries (Africa, Asia, and Latin America), with about half of the world's population at risk of infection according to the World Health Organization (WHO) [2].

The causative agents for malaria infections are *Plasmodium* protozoans: *Plasmodium falciparum*, *Plasmodium malariae*, *Plasmodium ovale*, and *Plasmodium vivax,* although most severe infections are caused by *P. falciparum* [3]. Africa is the most affected continent where most deaths are recorded among children below the age of 5 years [2-3].

The malaria life cycle is very complex which requires two organisms as host, mosquito, and human being [4]. The most common symptoms of malaria (chills, high fever, sweating, malaise, headache, and muscle aches) manifest usually one to four weeks after infection with the parasite; in relapsing *Plasmodium* parasites it ranges from five to eight years, but these signs and symptoms may also have seen in other diseases [5].

Beside quinine, the disease was mainly treated by chloroquine, mefloquine, and artemisin. However, due to high level of resistance, chloroquine is no longer used to treat falciparum malaria, although it remains the first-line treatment in combination with primaquine for vivax malaria in some African countries, such as Ethiopia, South Africa and Sudan; in American countries, such as Brazil, Colombia, Nicaragua and Venezuela; in Eastern Mediterranean countries, such as Afghanistan and Pakistan; in south east Asian countries, such as India and Myanmar [6]. In 2002, WHO recommended the use of artemisinin-based combination therapies (ACTs) as first- and second-line treatment for uncomplicated malaria caused by *P. falciparum* in Asia, South America and Africa. For example, the combination artesunate-amodiaquine is currently used in Democratic Republic of Congo, Burundi, Cameroon, Gabon and Ivory Coast, or artemether-lumefantrine in Benin, Central African Republic, Malawi and South Africa. Countries such as Brazil and Cambodia prefer using the combination artesunate-mefloquine, while countries such as Vietnam and Thailand are using the association dihydroartemisinin-piperaquine.

The strategy which consists of combining two or more drugs with the aim to enhance their pharmacological activity is widely used and is one of the effective strategies to tackle the resistance problem by the synergistic effect [7-10]. The development of resistance by *Plasmodium* protozoans against most of the drugs currently used to treat malaria remains a serious global public health problem since it requires either the introduction of newer drugs or

the structural modifications for the existing drugs.

Since it is a challenging process to develop new molecules to be used for the treatment of diseases, we report in this paper a cheminformatic analysis of a series of nine synthesized quinine derivatives, among which five acetyl derivatives 1-5 (Fig. 2) and four benzoyl derivatives 1'-4' (Fig. 3). Their structures have been characterized by ^{1}H- and ^{13}C-NMR, and the synthesis part and other considerations are the subject of another publication.

This paper aims to perform an *in silico* analysis of nine quinine derivatives to predict their physicochemical properties, drug-likeness properties, ADME (absorption, distribution, metabolism and excretion) and toxicity in order to understand their pharmacokinetic behavior, using SwissADME [11] and pkCSM [12] webservers. In fact, many *in silico* webservers for predicting pharmacokinetic and toxicity properties of compounds have been developed, but several of these are unfortunately not free available, which limits their utility for the scientific community. The webservers used in this study, in addition to be free, a series of comparative experiments have been conducted that indicate that pkCSM and SwissADME perform as well as or better than several other widely used methods [11-12,13-16].

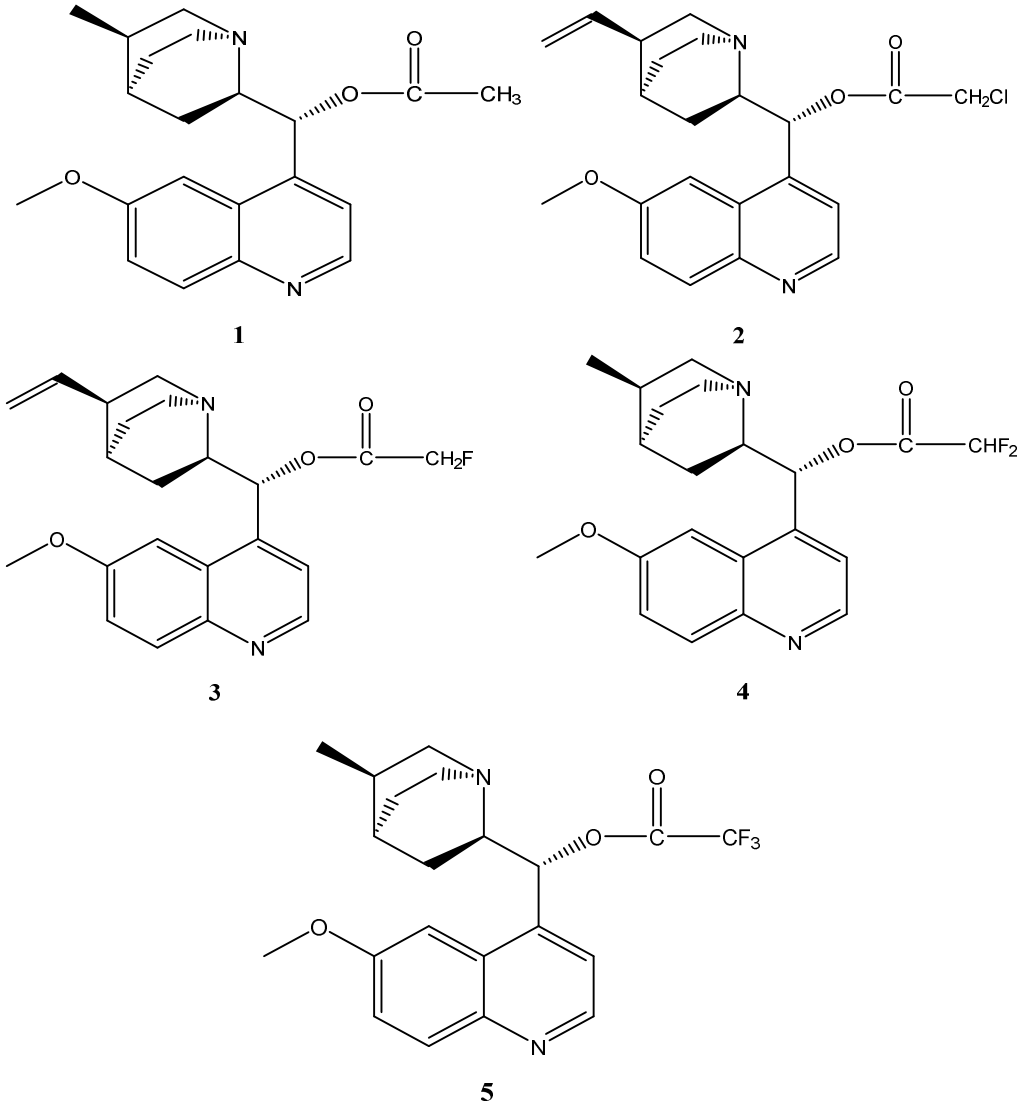

Fig. 2. Structure of acetyl quinine derivatives

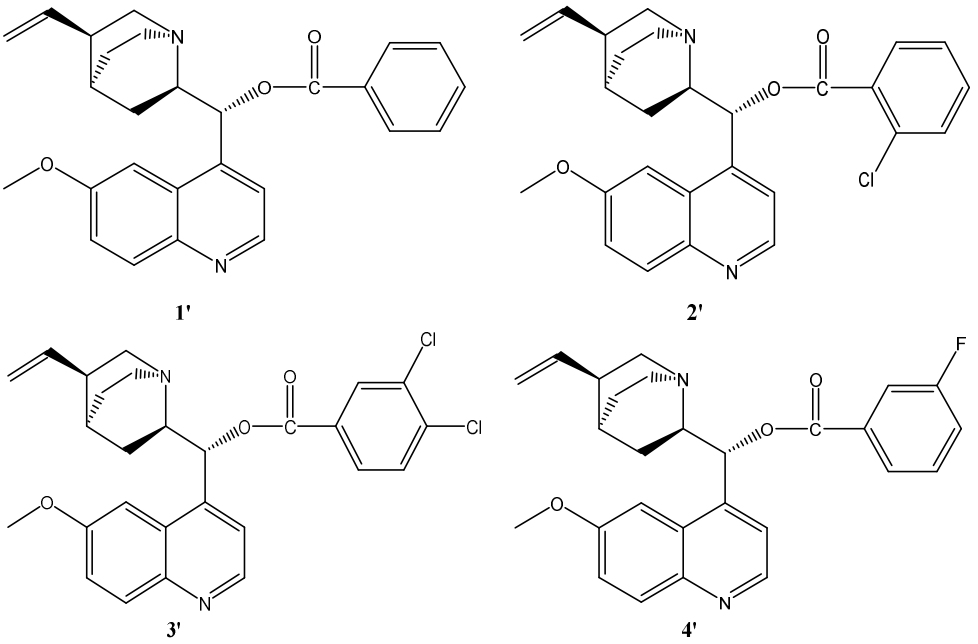

Fig. 3. Structure of benzoyl quinine derivatives

For comparison purposes with quinine, as a starting structure on which structural modifications were made, we also performed the same *in silico* analysis on the compound.

Information about the properties of ADME/T from a compound is mainly needed in the development of a new drug compound [13-16].

2. MATERIALS AND METHODS

2.1 Materials

The software used for sketching structures is ChemDraw Professional 16.0 from CambridgeSoft and then copied into the Chem3D Professional 16.0 software application to create the 3D structures.

The ADMET prediction servers used are SwissADME (http://swissadme.ch/) from the Swiss Institute of Bioinformatics and pkCSM (http://biosig.unimelb.edu.au/pkcsm/) from the Biosig Lab University of Melbourne.

SwissADME is a free web tool to evaluate physicochemical properties, pharmacokinetics, drug-likeness and medicinal chemistry friendliness of molecules. It is widely used because of its simplicity to establish the drug-likeness profile of compounds by integrating the rule of Lipinski, who examined orally active compounds to define physicochemical ranges for high probability to be an oral drug.

pkCSM (Predicting Small-Molecule Pharmacokinetic and Toxicity Properties Using Graph-Based Signatures) is a method for predicting and optimizing pharmacokinetic properties and toxicity properties. It uses graph-based signatures approach. Graph modeling is an intuitive and well established mathematical representation of chemical entities, from which different descriptors encompassing both molecule structure and chemistry can be extracted. An intuitive graph representation of a compound can be achieved by representing atoms as nodes and their covalent bonds as edges. pkCSM adapted the cut off scanning concept to develop a predictive model of ADME/T properties for drug development. The performance of pkCSM software in the external validation dataset showed an accuracy of 83.8% in the mutagenicity test. There are several endpoints of pkCSM, i.e. LD_{50}, Ames test, maximum daily dose and hepatotoxic.

2.2 Methods

As stated above, structures of quinine derivatives were drawn as 2D molecular structures with ChemDraw Professional 16.0 and then copied into the Chem3D Professional 16.0 software application to create the 3D structures,

and then stored as .sdf file or .pdb files. Further, the investigated compounds were translated into canonical SMILES (simplified molecular-input line-entry system) format using SMILES Translator Online Help [17], and then submitted to SwissADME and pkCSM for the ADMET analysis, the prediction of physicochemical parameters and the drug-likeness using the Lipinski rule of five. The so-called *Rule-of-five* of Lipinski delineated the relationship between pharmacokinetic and physicochemical parameters [18].

The IUPAC name and the code of the SMILES of all compounds are presented in Table 1.

3. RESULTS AND DISCUSSION

Computational methods in chemistry and biology are of paramount importance in several areas affecting life, particularly in the field of drug design (computer-aided drug design) [19-23]. For a hit molecule to be developed and used as drug, the next step to deal with in the pipeline of computer-aided drug design is the pre-clinical optimization that concerns the physicochemical properties, the prediction of absorption, distribution, metabolism and excretion (ADME), as well the *in silico* evaluation of toxicity. A large variety of *in silico* methods (e.g. pkCSM, preADMET [24], admetSAR [25] share the objective of predicting ADMET parameters from molecular structure but differ in their computational approaches.

3.1 Physicochemical Parameters

Physicochemical property is an important parameter of a molecule that influences efficacy, safety or metabolism which could be predicted by using Lipinski's rule of five, Veber's rule or Muegge's rule. In this paper, we used the Lipinski's rule that defines an orally active drug, which confirms to the number of hydrogen bonds acceptor (HBA) ≤ 10, hydrogen bonds donor (HBD) ≤ 5, molecular weight (MW) < 500 Da and Log P (the logarithm of octanol water partition coefficient) ≤ 5 [18]. Quinine, as a reference compound and its synthesized derivatives are submitted one by one in the canonical SMILES format to the SwissADME webserver.

The physicochemical properties include molecular weight, number of the rotatable bonds (NRB), HBA, HBD, molar refractivity (MR, in $m^3.mol^{-1}$) and polar surface area (PSA, in Å). The other two significant determinant are lipophilicity and solubility that are monitored for favorable drug development. Predicted physicochemical parameters of QB and its derivatives by SwissADME are summarized in Table 2.

The scrutiny of Table 2 reveals that all compounds meet every single criterion of Lipinski's rule of five and thus fully obey the rule. Consequently, all the investigated compounds present a good drug-likeness profile, since they are predicted to be easily absorbed and have good permeability and bioavailability.

Further, the molecular refractivity is a ubiquitous parameter for a drug molecule that cannot exceed 130 $m^3.mol^{-1}$ and not to be under 40 $m^3.mol^{-1}$ [26]. It can be seen that compounds 1' and 2' have molecular refractivity values more than 130 $m^3.mol^{-1}$. With regards to the polar surface area (PSA), according to Cerqueira and co-workers, for optimal drug absorption and distribution, the PSA values cannot be higher than 140 Å and lower than 20 Å [27], that means a compound with PSA more than 140 Å or lower than 20 Å is not a (good) drug candidate. The PSA values of all quinine derivatives ranging from 71.16 to 104.41 Å are an indication of a good therapeutic profile of druggability. Compound 2' has the highest PSA value (104.41 Å) among the other derivatives, enabling greater interaction with the receptor.

The number of rotatable bonds (NRB) is another indication of the flexibility of a compound. A drug candidate is predicted not orally bioavailable when its rotatable bonds are more than 9 (too flexible) [18]. Accordingly, quinine derivatives are good flexibility and are predicted to have good bioavailability.

Turning next to solubility, this is one major property influencing absorption. Having a soluble molecule greatly facilitates many drug development activities, primarily the ease of handling and formulation [28]. The solubility characteristic of the compounds is defined as insoluble if more negative than -10. It ranges from poorly soluble to highly soluble corresponding to the value of -10 to greater than zero, respectively. The values of the poorly soluble compounds lie in between -10 and - 6. The higher than -6 and less than -4 is classified as moderately soluble.

The soluble compounds are in between -4 and -2. The values between -2 and 0 are very soluble, while higher than zero are highly soluble.

The solubility values reveal that only two compounds are soluble: QB and compound **1**; five compounds are moderately soluble: compounds **2**, **3**, **4**, **5**, and **4'**; and remaining compounds (**1'**, **2'** and **3'**) are poorly soluble.

3.2 Prediction of ADMET Properties

Since the design and development of new drugs is both a time-consuming process and expensive, especially when it comes to experimentally evaluate the compounds pharmacokinetic profile, computational approaches to optimize pharmacokinetic and toxicity properties enables the progression of discovery leads effectively and swiftly to drug candidates molecule. Indeed, a good computational method is not necessarily the one that gives the same results as experimentation, but the one that can give the same information as an experimental result.

The pharmacokinetic profile of a compound defines its absorption, distribution, metabolism, and excretion (ADME) properties.

During the early stages of drug discovery, the compound to be selected as a hit must be non-carcinogenic and non-hepatotoxic [29]. The toxicity assessment (ADMET, T for Toxicity) allows one to predict the mutagenicity and carcinogenicity among others. The selected endpoints for toxicity are Ames toxicity, hepatotoxicity and oral rat acute toxicity (LD_{50}). The lethal dose (LD50) was chosen since its value and the classification of compound toxicity based on the Globally Harmonized System (GSH) allow to predict the toxicity degree of a compound.

These ADMET parameters are gathered in Tables 3 and 4.

Table 1. The IUPAC name and the SMILES code of all quinine derivatives

No	IUPAC NAME	CANONICAL SMILES
QB	6-Methoxy-quinolin-4-yl)-(5-vinyl-1-aza-bicyclo [2.2.2] octyl-2-yl)-methanol	COC1=CC2=C(C=CN=C2C=C1)C(C3CC4CCN3CC4C=C)O
1	Acetic acid (6-Methoxy-quinolin-4-yl)-(5-vinyl-1-aza-bicyclo [2.2.2] octyl-2-yl)-methyl ester.	CC(=O)OCOC1=CC2=C(C=CN=C2C=C1)C(C3CC4CCN3CC4C=C)O
2	Chloro-acetic acid (6-Methoxy-quinolin-4-yl)-(5-vinyl-1-aza-bicyclo [2.2.2] octyl-2-yl)-methyl ester	COC1=CC=C2N=CC=C([C@@H](OC(=O)CCl)[C@H]3C[C@@H]4CC[N@]3C[C@@H]4C=C)C2=C1
3	Fluoro-acetic acid (6-Methoxy-quinolin-4-yl)-(5-vinyl-1-aza-bicyclo [2.2.2] octyl-2-yl)-methyl ester.	COC1=CC=C2N=CC=C([C@@H](OC(=O)CF)[C@H]3C[C@@H]4CC[N@]3C[C@@H]4C=C)C2=C1
4	Difluoro-acetic acid (6-Methoxy-quinolin-4-yl)-(5-vinyl-1-aza-bicyclo [2.2.2] octyl-2-yl)-methyl ester	COC1=CC=C2N=CC=C([C@@H](OC(=O)C(F)F)[C@H]3C[C@@H]4CC[N@]3C[C@@H]4C)C2=C1
5	Trifluoro-acetic acid (6-Methoxy-quinolin-4-yl)-(5-vinyl-1-aza-bicyclo [2.2.2] octyl-2-yl)-methyl ester	COC1=CC=C2N=CC=C([C@@H](OC(=O)C3=C(Cl)C=CC=C3)[C@H]3C[C@@H]4CC[N@]3C[C@@H]4C=C)C2=C1
1'	2-Chloro-benzoic acid (6-Methoxy-quinolin-4-yl)-(5-vinyl-1-aza-bicyclo [2.2.2] octyl-2-yl)-methyl ester	COC1=CC=C2N=CC=C([C@@H](OC(=O)C3=C(Cl)C=CC=C3)[C@H]3C[C@@H]4CC[N@]3C[C@@H]4C=C)C2=C1
2'	3,4-Dichloro-benzoic acid (6-Methoxy-quinolin-4-yl)-(5-vinyl-1-aza-bicyclo [2.2.2] octyl-2-yl)-methyl ester	COC1=CC=C2N=CC=C([C@@H](OC(=O)C3=CC=C(Cl)C(Cl)=C3)[C@H]3C[C@@H]4CC[N@]3C[C@@H]4C=C)C2=C1
3'	3-Fluoro-benzoic acid (6-Methoxy-quinolin-4-yl)-(5-vinyl-1-aza-bicyclo [2.2.2] octyl-2-yl)-methyl ester.	COC1=CC=C2N=CC=C([C@@H](OC(=O)C3=CC=CC(F)=C3)[C@H]3C[C@@H]4CC[N@]3C[C@@H]4C=C)C2=C1
4'	Benzoic acid (6-Methoxy-quinolin-4-yl)-(5-vinyl-1-aza-bicyclo [2.2.2] octyl-2-yl)-methyl ester.	COC1=CC=C2N=CC=C([C@@H](OC(=O)C3=CC=CC=C3)[C@H]3C[C@@H]4CC[N@]3C[C@@H]4C=C)C2=C1

Table 2. *In silico* predicted physicochemical parameters of QB and its derivatives

No	Formula	MW	HBD	HBA	Log P	NRB	PSA	MR	Log S	Violations
QB	$C_{20}H_{24}N_2O_4$	324.42	1	4	3.36	4	71.16	99.73	-3.71	0
1	$C_{22}H_{28}N_2O_4$	384.47	2	6	3.62	4	82.50	113.23	-2.47	0
2	$C_{22}H_{25}ClN_2O_3$	400.90	0	5	3.81	7	84.91	114.27	-4.70	0
3	$C_{22}H_{25}FN_2O_3$	384.44	0	6	3.57	7	81.85	109.52	-4.44	0
4	$C_{22}H_{24}F_2N_2O_3$	390.42	0	7	3.34	6	83.93	105.24	-4.77	0
5	$C_{21}H_{23}F_3N_2O_3$	408.41	0	8	3.60	6	86.01	105.33	-5.05	0
1'	$C_{27}H_{27}ClN_2O_3$	462.97	0	5	3.89	7	99.26	134.38	-6.22	0
2'	$C_{27}H_{26}Cl_2N_2O_3$	497.41	0	5	4.42	7	104.41	139.39	-6.82	0
3'	$C_{27}H_{27}FN_2O_3$	446.51	0	6	4.26	7	96.19	129.33	-5.79	0
4'	$C_{27}H_{28}N_2O_3$	428.52	0	5	4.06	7	94.11	129.37	-5.62	0

Table 3. Pharmacokinetic profile and toxicity prediction of quinine and its acetyl derivatives

Parameter	QB	Compound 1	Compound 2	Compound 3	Compound 4	Compound 5
Absorption						
Water solubility (log mol/L)	-2.605	-2.804	-3.649	-3.403	-3.665	-4.073
Caco-2 permeability (log Papp, cm/s)	1.320	0.828	1.299	1.274	1.290	1.302
HIA (%)	93.232	89.790	93.100	93.010	91.802	90.671
Skin permeability (log K_p)	-3.024	-2.727	-2.835	-3.060	-3.088	-3.105
BioS (from SwissADME)	0.55	0.55	0.55	0.55	0.55	0.55
Distribution						
VDss (human) (log L/kg)	1.393	0.672	1.107	0.979	0.998	0.900
BBB permeability (log BB)	0.124 Yes	-0.899 No	-0.207 Yes	-0.116 Yes	-0.149 Yes	-0.121 Yes
BBB perm. (SwissADME)						
Metabolism						
CYP2D6	Yes	No	No	No	No	No
CYP3A4	No	No	Yes	No	No	No
Excretion						
Total clearance	1.052	0.714	1.136	0.969	0.842	0.611
Renal OCT2 substrate	Yes	No	Yes	Yes	Yes	Yes
Toxicity						
Ames test	Yes	No	No	No	No	No
Hepatotoxicity	Yes	Yes	Yes	Yes	No	Yes
Oral rat acute toxicity (LD_{50}, in mol/kg)	2.728	2.778	2.715	3.082	3.130	3.236
	1364	**1389**	**1358**	**1541**	**1565**	**1618**

Table 4. Pharmacokinetic profile and toxicity prediction of quinine benzoyl derivatives

Parameter	Compound 1'	Compound 2'	Compound 3'	Compound 4'
Absorption				
Water solubility (log mol/L)	-5.177	-4.929	-5.469	-4.609
Caco-2 permeability (log Papp, cm/s)	1.001	1.004	1.019	1.583
HIA (%)	92.077	91.242	92.991	95.089
Skin permeability (log K_p)	-2.687	-2.711	-2.725	-2.742
Bioavailability score (SwissADME)	0.55	0.55	0.55	0.55
Distribution				
VDss (human) (log L/kg)	1.317	1.325	1.128	0.532
BBB permeability (log BB)	-0.114	-0.160	0.025	0.053
BBB perm. (SwissADME)	Yes	Yes	Yes	Yes
Metabolism				
CYP2D6	No	No	No	No
CYP3A4	Yes	Yes	Yes	Yes
Excretion				
Total clearance	0.899	0.972	0.874	0.995
Renal OCT2 substrate	Yes	Yes	Yes	Yes
Toxicity				
Ames test	No	No	No	No
Hepatotoxicity	Yes	Yes	Yes	No
Oral rat acute toxicity (LD_{50}, in mol/kg)	2.913	3.039	2.921	2.383
	1457	**1520**	**1461**	**1192**

The ADMET properties of quinine and its derivatives reveal that quinine and its acetyl derivatives have good solubility which reflects their good absorption and better elimination by the urinary tract, compared to benzoyl derivatives. This is not surprising because the properties of the benzoyl groups are relatively nonpolar, so the addition of the benzoyl group has been predicted to reduce the solubility in water from the derivatives of these compounds [30].

However, one of the advantages of benzoyl groups is the formation of the moiety of esters which is known to be able to increase the solubility of a compound in water, so it is expected that a decrease in the solubility parameters in the water can be compensated by the formation of the ester compound.

These results on solubility from pkCSM are somewhat consistent with those stemming from SwissADME. Further, both acetyl and benzoyl derivatives have good profile of absorption rate in the intestine. In fact, the values of the human intestine absorption (HIA) are too high, and reveal that quinine and its all derivatives have more than 90 % of probability of being absorbed by human intestine, with compound 4' (benzoic acid (6-Methoxy-quinolin-4-yl)-(5-vinyl-1-aza-bicyclo [2.2.2] octyl-2-yl)-methyl ester) having the highest probability (95.089), and compound 1 (acetic acid (6-Methoxy-quinolin-4-yl)-(5-vinyl-1-aza-bicyclo [2.2.2] octyl-2-yl)-methyl ester) the lowest. The Caco-2 cell line is composed of human epithelial colorectal adenocarcinoma cells, which is widely used as an *in vitro* model of the human intestinal mucosa to predict the absorption of orally administered drugs by measuring the log of the evident permeability coefficient (log Papp; log cm/s). For the pkCSM webserver, a compound is considered to have a high Caco-2 permeability if it has log Papp value > 0.90 cm/s [12]. It can be seen from tables 3 and 4 that all quinine derivatives have high Caco-2 permeability, except compound 1 (0.8 cm/s). It is worthy to point out that quinine and its acetyl derivatives have almost the same Caco-2 permeability value, predicted to be 1.3 cm/s, higher than the Caco-2 permeability values of benzoyl derivatives that also have the same value (1.0 cm/s) except for compound 9 (1.6 cm/s).

The recommended value of the skin permeability (log K_p) for a drug-molecule, which is an important consideration for improving drug efficacy that is particularly of interest in the development of transdermal drug delivery is set at more than -2.5 cm/h [27]. The computed log K_p values of all compounds range from -2.7 to -3.1 cm/h. Accordingly, all quinine derivatives are predicted to have good skin penetrability, but better for quinine acetyl derivatives (all between -2.7 and -3.1 cm/h) than quinine benzoyl ones (-2.7 cm/h). The bioavailability score which is evaluated to 0.55 confirms that all investigated derivatives have good absorption since they may have more than 10% of bioavailability in rat [31].

The volume of distribution at steady state (VDss) and the blood−brain barrier (BBB) are amongst the important parameters to take into account to evaluate the drug ability to be distributed in the body. The higher the VD is, the larger the amount of a drug is distributed to tissue rather than plasma. This model is established from the estimation of the steady-state volume of distribution (VDss). Pires *et al*. reported that a compound have good distribution if its VDss value is higher than 0.45 [17]. It can be seen that almost all quinine derivatives have VDss value twice larger than the recommended value. With regards to the BBB that defines the drug ability to cross into the brain while improving the efficacy of drugs (less side effects), a compound is capable to pass through the blood brain barrier promptly when log BB is higher than 0.3. Consequently, since log BB values of the all investigated derivatives are not higher than 0.3, they are able to penetrate the blood-brain barrier moderately [15,32]. BBB permeability results from SwissADME webserver are also listed in tables 3 and 4, and one sees that there are substantial discrepancies between pkCSM results and SwissADME results. The latter webserver reveals that quinine and its derivatives can highly cross the BBB immediately except for compound 1. The difference in results is due to differences in approaches and modules used on each webserver, so the discrepancies in results obtained are not astonishing.

Turning next to metabolism of xenobiotics which is made possible due to certain enzymes including cytochromes P450 which play a central role in the biotransformation, metabolism and/or detoxification of these foreign compounds in the body, it was reported that only CYP2D6 and CYP3A4 are responsible for drug metabolism. The outcomes on metabolism prediction are encouraging for acetyl derivatives since they are found to be non-inhibitors of CYP2D6 and

CYP3A4 except for compound 2 that affects the CYP3A4. This latter is also affected by all benzoyl derivatives while CYP2D6 is not. However, it is should be noted that drug metabolism is essentially hepatic, where the liver is the key organ in the metabolism and detoxification of xenobiotic compounds [33-34].

Excretion (also called elimination) parameters which consisted of total clearance and OCT2 (organic cation transporter 2) substrate are listed in lower part of tables 3 and 4. The OCT2 is a protein transporter that has a vital contribution in the renal uptake, disposition, and clearance of drugs compounds. This means that the total clearance is directly linked to the renal OCT2.

Evaluating the transfer of a candidate compound by OCT2 offers useful information regarding not only its clearance but also its potential contraindications [32]. Surprisingly, all quinine derivatives (except for compound 1) and even quinine itself are predicted by pKCSM to be OCT2 substrates. This implies that they may undergo a renal uptake process and stay longer in the body.

To close definitively with toxicities predictions, essential parameters for toxicity include oral rat acute toxicity LD50 and thus toxicity class, and in some extent the mutagenicity and hepatotoxicity. The toxicity results reveal that all quinine derivatives did not confer mutagenic, but they are predicted to be hepatotoxic. However, their LD_{50} values that are in the range of 1192-1618 mg/kg/day (values on bold) are classified in category or class 4 of the Globally Harmonized System (300 < Category 4 ≤ 2000 mg/kg/day), meaning that they are slightly toxic if swallowed and can thus be considered as safe.

4. CONCLUSION

The main objective of this study was to establish the pharmacokinetic profile and toxicity of nine quinine derivatives, among them five acetyl derivatives and four benzoyl counterparts, using *in silico* or computational methods by SwissADME and pkCSM. The ADME/T properties of a compound are strongly needed for future research, especially in the stage of evaluating its pharmacological activities.

The results obtained from this study provide excellent guidelines and reveal that chemical modifications on quinine as reference compound can improve its ADMET properties since overall all investigated derivatives are predicted to have a good therapeutic profile of druggability in addition of being safe, despite some minor drawbacks. These encouraging results can be placed in a broader context of overcoming the development of resistance by *Plasmodium* protozoans against most of the drugs currently used to treat malaria.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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