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SwissADME and pkCSM Webservers Predictors: an integrated Online Platform for Accurate and Comprehensive Predictions for In Silico ADME/T Properties of Artemisinin and its Derivatives

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ABSTRACT

In vivo ADME analysis is costly, laborious and puts animal lives at danger, whereas in silico ADME analysis is not dangerous, simpler, and quicker. This study will use *in silico* methodologies from SwissADME and pkCSM as an integrated online platform for precise and complete predictions to determine In Silico ADME/T Properties of Artemisinin and its Derivatives. The studied compounds' structures were converted to canonical SMILES files and then sent to the SwissADME and pkCSM webserver tools, which provide free access to different properties of compounds. A compound's ADME/T characteristics are critical for future study and the results obtained will be of beneficial use for researchers. Additionally, the results of this study give great guidance and show that chemical alterations to the reference molecule artemisinin can enhance its ADMET capabilities. The webservers used in this work are free, and several comparison trials show that pkCSM and SwissADME performed are better than a number of other frequently used methods. The designing or engineering of a novel drug molecule primarily requires knowledge of the features of ADME/T of the new drug compound.

Keywords: SwissADME, artemisinin derivatives, ChemDraw, silico prediction, pkCSM.

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Introduction

Artemisinin is a sesquiterpene based lactone along with a peroxide component [[1], [2]]. It is obtained from the leafy sections of artemisia annua, which is a herb and medicinal plant herb that has been used for ages to cure fever and chills [3]. Artemisinin, also known identified as Qinghaosu, was the first to be isolated. Dihydroartemisinin (DHA) was the main derivative to be created by converting the carbonyl groups to hydroxyl groups [2]. Others, for instance the more water-soluble artesunate and the further oil-soluble artemether and arteether, followed [4]. These compounds were ten times more effective than artemisinin [2], with artesunate getting a more beneficial pharmacokinetic-pharmacodynamic profile [5].

Artemisinins and their derivatives are preferentially taken up by parasite-infected erythrocytes and then localized in parasite membranes such as the mitochondrial, digesting vacuole, and parasite limiting membrane [[2], [4]]. All versions of medicine have an endoperoxide bridge (C-O-O-C) that is vital for its anti-malarial impact, where the molecule itself is stimulated by iron or heme to create free radicals. The latter free radicals subsequently alkylate malaria membrane-associated proteins, killing the parasite [4]. They have been discovered to be useful versus various strains of malaria, particularly those resistant to established gold standard medications. They are very effective, needing just nanomolar doses in vitro [4]. They are also fast-acting, with therapeutic ability as early as 20 hours following treatment. Furthermore, artemisinins have a comparatively low-profile toxicity, with the LD_{50} of 4223 mg/kg. Furthermore, despite the widespread use of the medicine, there was no indication of neurotoxicity in neuronal cells or animals at high-level doses [[2], [4]].

Artemisinin and its derivatives revealed further characteristics in illnesses other than malaria. Artesunate, for example, demonstrated anti-cancer effects as evidenced by its cytotoxic action versus 55

cancer cell lines via the control of numerous processes such as the damage of DNA and repair, apoptosis, as well as proliferation [[6], [7]]. Artesunate inhibited the creation of interleukin (IL)-1, IL-6, and IL-8 in TNF-stimulated rheumatoid arthritis fibroblast-like synoviocytes (RA FLS) via the NF-B and phosphoinositide 3 kinases (PI3K) pathways [8]. It also has antiviral characteristics, since artemisinin suppressed the duplication of human cytomegalovirus (HCMV) [9]. Several of these pathophysiological routes are also marked in respiratory illnesses. Hence, artemisinin and its derivatives might be used to treat respiratory illnesses as well. Because developing novel molecules for disease therapy is a difficult procedure, we provide in the current study a cheminformatic examination of a sequence of five artemisinin derivatives (Fig. 2).

The goal of this study is to use SwissADME [10] and pkCSM [11] webservers to forecast the physicochemical qualities, drug-likeness properties, ADME (absorption, distribution, metabolism, and excretion), and toxicity of five artemisinin derivatives to understand their pharmacokinetic behaviour. In addition to being free, the webservers utilized in this work have undergone several comparison trials that show that SwissADME and pkCSM present as well as or improved than numerous other frequently used techniques [[10], [11], [12], [13], [14], [15], [16]].

We did the same *in silico* investigation on the molecule for comparative reasons with artemisinin derivatives on which structural alterations were done. Information on a molecule's ADME/T characteristics is mostly required in the development of a novel medicinal compound [[12], [14], [15]].

Materials and Methods

1.1 Materials

ChemDraw software Professional 16.0 from Cambridge was used to drwa structures.. SwissADME from the Swiss Institute of Bioinformatics and pkCSM from the Biosig Lab University of Melbourne were utilized as ADMET prediction servers. SwissADME is a free of charge web tool for assessing compounds' physicochemical qualities, pharmacokinetics, drug-likeness, and medicinal chemistry easiness. It is extensively utilized due to its simplicity in determining the drug-likeness profile of compounds by including Lipinski's rule, which evaluated orally active substances to determine physicochemical parameters for the high chance of becoming an oral drug. The pkCSM technique predicts and optimizes pharmacokinetic and toxicity properties. The cut-off scanning idea was extended by pkCSM to create a prediction simulation of ADME/T characteristics for drug advance. The pkCSM program performed well in the outer validation dataset, with an accuracy of a value of 83.8% in the mutagenicity check. pkCSM has numerous endpoints, including LD_{50}, Ames test, highest daily dosage, and hepatotoxic.

1.2 Methods

Structures of artemisinin derivatives were generated with ChemDraw Professional 16.0. The derivatives were subsequently converted into canonical SMILES (simple molecular-input line-entry system) format [17] and run using SwissADME and pkCSM for ADMET Lipinski's so-termed Rule-of-Five established a link between pharmacokinetic and physicochemical characteristics [18]. Table 1 shows the code of each compound's SMILES.

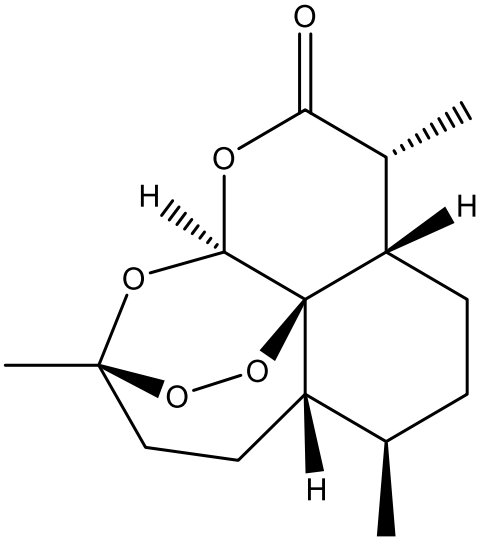

Figure 1 – The chemical structures of artemisinin.

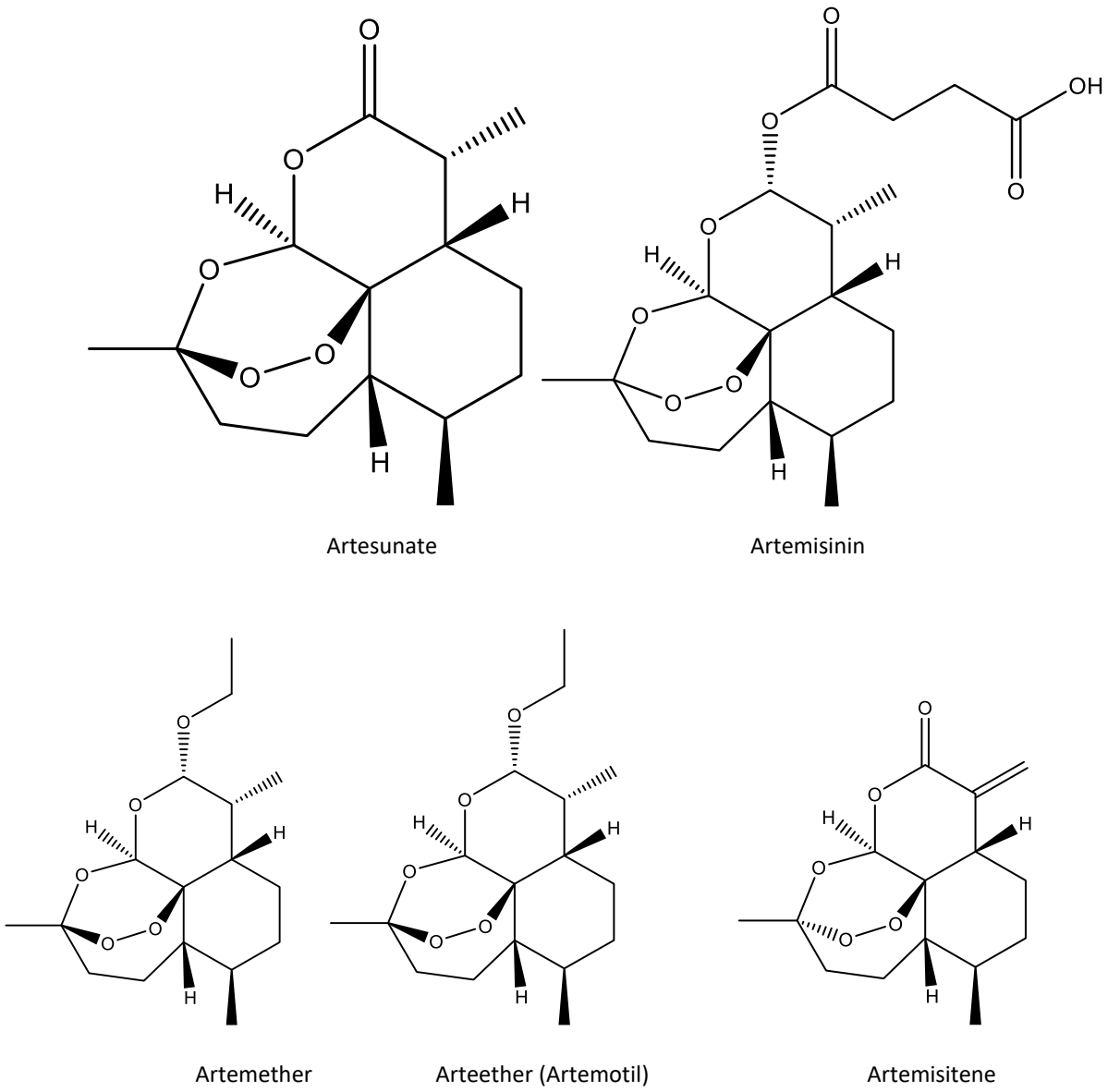

Figure 2 – The chemical structures of artemisinin and its derivatives

Table 1. The SMILES code of all artemisinin derivatives

No.	Derivatives	CANONICAL SMILES
1	Artemisinin	CC1CCC2C(C(=O)OC3C24C1CCC(O3)(OO4)C)C
2	Artesunate	CC1CCC2C(C(OC3C24C1CCC(O3)(OO4)C)OC(=O)CCC(=O)O)C
3	Artemether	CC1CCC2C(C(OC3C24C1CCC(O3)(OO4)C)OC)C
4	Arteether (Artemotil)	CCOC1C(C2CCC(C3C24C(O1)OC(CC3)(OO4)C)C)C
5	Artemisitene	CC1CCC2C(=C)C(=O)OC3C24C1CCC(O3)(OO4)C

Results and Discussion

Computational approaches in biology and chemistry are crucial in many fields impacting life, notably drug design (computer-aided drug design) [[16], [19], [20], [21], [22], [23]]. For the desired molecule to be established and used as a drug, the subsequent step in the computer-aided drug model pipeline to deal with is the pre-clinical optimization. A wide range of *in silico* techniques (e.g., pkCSM, preADMET [24], admetSAR [25]) contribute to the

Table 2. *In silico* calculated physicochemical properties of artemisinin and its derivatives

No.	Derivatives	Formula	MW	HBD	HBA	Log P	NRB	PSA	MR	Log S	Violations
1	Artemisinin	$C_{15}H_{22}O_5$	282.336	0	5	2.75	0	53.99	70.38	-3.42	0
2	Artesunate	$C_{19}H_{28}O_8$	384.425	1	8	2.62	0	100.52	92.46	-3.08	0
3	Artemether	$C_{16}H_{26}O_5$	298.379	0	5	3.19	1	46.15	76.07	-3.85	0
4	Arteether (Artemotil)	$C_{17}H_{28}O_5$	312.406	0	5	3.50	2	46.15	80.88	-4.10	0
5	Artemisitene	$C_{15}H_{20}O_5$	280.320	0	5	2.62	0	53.99	69.90	-3.27	0

goal of calculating ADMET parameters from the molecular structure but change in their computational methodology.

Physicochemical Parameters

The physicochemical property is a molecular attribute which affects efficacy, safety, or metabolism and can be anticipated utilizing Lipinski's rule of five, Veber's rule, or Muegge's rule. In this research, we employed Lipinski's rule to create an orally active medication, which proves the number of hydrogen bonds acceptor (HBA) of less or equal to 10, hydrogen bonds donor (HBD) of less or equal to 5, molecular weight (MW) of less than 500 Da, and Log P of less or equal to 5 [16]. Artemisinin, as a reference chemical, and its synthesized variants are uploaded to the SwissADME website one by one in the standard SMILES format..

Lipophilicity and solubility are the other two major determinants that are examined for optimal medication development. Table 2 summarizes the physicochemical properties of artemisinin and its derivatives predicted by SwissADME. Table 2 indicates that all compounds match each single condition of Lipinski's rule of five and hence totally conform the rule. As a result, all the examined compounds exhibit a favourable drug-likeness profile, as they are predicted to be rapidly absorbed and to have great permeability and bioavailability.

Furthermore, the molecular refractivity of a drug molecule must not exceed 130 $m^3.mol^{-1}$ and must not be less than 40 $m^3.mol^{-1}$ [16]. All derivatives have a $m^3.mol^{-1}$ range of 69.90 - 92.46 $m^3.mol^{-1}$. According to the work of Cerqueira and colleagues, for optimal medication distribution and absorption, PSA readings must be greater than 140 and less than 20 Å, implying that a molecule with PSA larger than 140 Å or less than 20 Å is not a (good) therapeutic candidate. The PSA values of the complete artemisinin derivatives range from 46.15 to 100.52 Å, indicating an excellent therapeutic profile of druggability. Artesunate has the maximum PSA value (100.52 Å) of the further derivatives, allowing for stronger interaction with the receptor.

The sum of rotatable bonds (NRB) in a molecule is a further indicator of its flexibility. When a medication candidate has more than 9 rotatable bonds (too flexible), it is projected that it would not be orally accessible [16]. As a result, artemisinin derivatives are versatile and are expected to be bioavailable. Solubility is another important factor regulating absorption. Many drug development tasks are substantially facilitated by having a soluble molecule, particularly the simplicity of handling and formulation. The compound's solubility is described as insoluble if it is more negative than -10. It varies from weakly soluble to very soluble, with a value ranging from -10 to higher than zero. The weakly soluble chemicals have values between -10 and -6. A value more than -6 and less than -4 is considered somewhat soluble.

The solubility of the compounds varies between -4 and -2. Values between -2 and 0 are extremely soluble, whereas values greater than zero are extremely soluble. Because their solubility values range between -4 and -2, all artemisinin derivatives are soluble.

Prediction of ADMET Properties

Because the design and advancement of new drugs is both laborious and expensive, particularly when it comes to through an experiment assessing the compound's pharmacokinetic outline. In fact, a good computational method can provide the same information as an experimental result rather than one that produces the same outcomes as experimentation. A compound's pharmacokinetic

Table 3. The pharmacokinetic profile and toxicity prediction of artemisinin and its derivatives

Parameter	Artemisinin	Artesunate	Artemether	Arteether (Artemotil)	Artemisitene
Absorption Water solubility (log mol/L)	-3.678	-3.097	-3.927	-3.908	-3.643
Caco-2 permeability (log Papp, cm/s)	1.295	0.863	1.311	1.332	1.291
HIA (%)	97.543	72.19	96.855	96.488	97.69
Skin permeability (log K_p) (cm/s)	-3.158	-2.735	-2.929	-3.345	-3.161
BioS (from SwissADME) (Bioavailability Score)	0.55	0.56	0.55	0.55	0.55
Distribution VDss (human) (log L/kg)	0.457	0.172	0.611	0.448	0.453
BBB permeability (log BB)	0.235	-0.954	0.861	0.253	0.235
BBB perm. (SwissADME)	Yes	No	Yes	Yes	Yes
Metabolism CYP2D6	No	No	No	No	No
CYP3A4	Yes	Yes	Yes	Yes	Yes
Excretion Total clearance	0.98	0.969	1.031	1.068	1.082
Renal OCT2 substrate	No	No	No	No	No
Toxicity AMES test	Yes	No	No	No	Yes
Hepatotoxicity	No	No	No	No	No
Oral rat acute toxicity (LD_{50}, in mol/kg)	2.459	3.112	2.429	2.32	2.449

profile describes its absorption, distribution, metabolism, and excretion (ADME) characteristics.

Through the early phases of drug study, the chemical chosen as a hit must be noncarcinogenic and non-hepatotoxic [[16], [26]]. Toxicity assessment (ADMET, T for Toxicity) predicts mutagenicity and carcinogenicity, among other things. The toxicity endpoints used include Ames toxicity, hepatotoxicity, and oral rat acute toxicity (LD_{50}). The lethal dosage (LD_{50}) was selected since its value and the Globally Harmonized System (GSH) categorization of chemical toxicity allow for the prediction of a substance's toxicity degree. Table 3 contains a list of these ADMET options. The ADMET characteristics of artemisinin and its derivatives demonstrate that they have strong solubility, which indicates their good absorption and enhanced elimination through the urinary system.

The values of human intestinal absorption (HIA) are extremely high-level, indicating that artemisinin and all derivatives except artesunate (72.19) have a more than 95% chance of being absorbed by the human intestine. The Caco-2 cell line is generally utilized as an *in vitro* example of the human intestinal mucosa to calculate drug absorption by assessing the log of the apparent permeability coefficient (log Papp; log cm/s). A chemical is considered to have high-level Caco-2 permeability for the pkCSM webserver if its log Papp value is more than 0.90 cm/s. Table 3 shows that all artemisinin and its derivatives have high Caco-2 permeability, except for artesunate (0.863 cm/s).

The recommended value of skin permeability (log Kp), which is a significant factor for enhancing drug effectiveness and is especially relevant in the creation of transdermal drug administration, is more than -2.5 cm/h [27]. The calculated log Kp values for all compounds differ from -2.735 to -3.345 cm/h. As a result, all artemisinin derivatives are expected to have high skin penetration. The bioavailability score of 0.55 shows that all examined compounds have excellent absorption because they may have greater than 10% bioavailability in rats [28].

The volume of supply at steady state (VDss) and the blood-brain barrier (BBB) are two significant factors to consider when evaluating a drug's capacity to be

dispersed in the body. The higher the VD, the more medication is delivered to tissue rather than plasma. This type is based on the estimate of the steady-state volume of distribution (VDss). Pires et al. observed that a chemical has good dispersion if its VDss value is greater than 0.45 [16]. Except for artesunate, practically all artemisinin derivatives have VDss values of 0.45 or greater (0.172).

In terms of the BBB, which determines a drug's capacity to enter the brain while boosting effectiveness (fewer adverse effects), a molecule is capable of moving across the blood-brain barrier quickly when log BB is greater than 0.3. As a result, because the log BB values of all examined derivatives are less than 0.3, they can only cross the blood - brain barrier marginally [[16], [29]]. Table 3 also includes BBB permeability findings from the SwissADME website, revealing significant differences between pkCSM and SwissADME results.

The parameters of excretion (also known as elimination) consisting of total clearance and OCT2 (organic cation transporter 2) substrate are supplied in the lower portion of table 3. The OCT2 protein transporter plays an important role in the renal uptake, disposition, and clearance of pharmacological molecules. This suggests that overall clearance is directly proportional to renal OCT2.

Assessing a suggested compound's transfer by OCT2 provides significant information about not just its clearance but also its possible contraindications [29]. Amazingly, pKCSM predicts that all artemisinin derivatives are not OCT2 substrates. The toxicity studies show that all artemisinin derivatives are not mutagenic, however, they are hepatotoxic.

Conclusions

The major goal of the current study was to determine the pharmacokinetic profile and toxicity of five artemisinin derivatives utilizing SwissADME and pkCSM *in silico* or computational approaches. A compound's ADME/T characteristics are critical for future study, particularly when assessing its pharmacological actions. The findings of this study offer outstanding guidelines and determine that chemical modifications to artemisinin as a reference compound can enhance its ADMET chracteristics, as all examined derivatives are expected to have a good therapeutic profile of druggability as well as being safe, regardless of some slight weaknesses.

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SwissADME және pkCSM болжау веб-серверлері: Артемизинин және оның туындыларының in Silico ADME/T қасиеттерін дәл және жан-жақты болжауға арналған интеграцияланған онлайн-платформа

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ТҮЙІНДЕМЕ

In vivo ADME сынағы қымбат, уақытты қажет етеді және жануарлардың өміріне қауіп төндіреді, ал silico ADME сынағы қауіпсіз, қарапайым және жылдамырақ. Бұл зерттеу SwissADME және pkCSM силико әдістемелерінде Artemisinin және оның туындыларының Silico ADME/T қасиеттерін анықтау үшін дәл және жан-жақты болжамдарға арналған біріктірілген онлайн платформа ретінде пайдаланылады. Зерттелген қосылыстардың құрылымдары канондық SMILES пішіміне аударылды, содан кейін қосылыстардың әртүрлі қасиеттеріне еркін қол жеткізуді қамтамасыз ететін SwissADME және pkCSM веб-сервер құралдарына жіберілді. Қосылыстың ADME/T сипаттамалары болашақ зерттеу үшін өте маңызды және алынған нәтижелер зерттеушілер үшін пайдалы болады. Сонымен қатар, бұл зерттеудің нәтижелері үлкен нұсқаулық береді және артемизинин сілтеме молекуласының

химиялық өзгерістері оның ADMET мүмкіндіктерін жақсарта алатынын көрсетеді. Бұл жұмыста пайдаланылатын веб-серверлер ақысыз және бірнеше салыстыру сынақтары орындалған pkCSM және SwissADME басқа жиі қолданылатын әдістер қатарынан жақсырақ екенін көрсетеді. Жаңа дәрілік молекуланы жобалау немесе жобалау, ең алдымен, жаңа дәрілік қосылыстың ADME/T ерекшеліктерін білуді талап етеді.

Түйін сөздер: SwissADME, artemisinin туындылары, ChemDraw, кремнийді болжау, pkcs.

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Веб-серверы SwissADME и pkCSM прогнозирования: интегрированная онлайн-платформа для точного и всестороннего прогнозирования свойств In Silico ADME/T артемизинина и его производных

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АННОТАЦИЯ

Тестирование ADME in vivo является дорогостоящим, трудоемким и подвергает риску жизнь животных, тогда как тестирование ADME in silico безопаснее, проще и быстрее. В этом исследовании будут использоваться методологии in silico от SwissADME и pkCSM в качестве интегрированной онлайн-платформы для точных и всесторонних прогнозов для определения свойств артемизинина и его производных In Silico ADME/T. Структуры исследуемых соединений были переведены в канонический формат SMILES, а затем переданы в инструменты веб-сервера SwissADME и pkCSM, которые обеспечивают свободный доступ к различным свойствам соединений. Характеристики ADME/T соединения имеют решающее значение для будущих исследований, и полученные результаты будут полезны исследователям. Кроме того, результаты этого исследования дают отличные рекомендации и показывают, что химические изменения в эталонной молекуле артемизинина могут улучшить его возможности ADMET. Веб-серверы, используемые в этой работе, бесплатны, и несколько сравнительных испытаний показывают, что pkCSM и SwissADME работают лучше, чем ряд других часто используемых методов. Проектирование или создание новой молекулы лекарственного средства в первую очередь требует знания особенностей ADME/T нового лекарственного соединения.

Ключевые слова: SwissADME, производные артемизинина, ChemDraw, силиконовое предсказание, pkcs.

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