Computational Molecular Bioscience, 2014, 4, 47-57
Published Online December 2014 in SciRes. http://www.scirp.org/journal/cmb
http://dx.doi.org/10.4236/cmb.2014.44006

Scientific Research

Computational Analysis of Physicochemical, Pharmacokinetic and Toxicological Properties of Deoxyhypusine Synthase Inhibitors with Antimalarial Activity

Nayara S. R. Silva[1], Luana K. S. Gonçalves[1], Jonatas L. Duarte[1], Juliane S. Silva[1], César F. Santos[1], Francinaldo S. Braga[1], Raí C. Silva[1], Josivan S. Costa[1], Lorane I. S. Hage-Melim[1,2], Cleydson B. R. dos Santos[1,2*]

[1]Laboratory of Modeling and Computational Chemistry, Federal University of Amapá, Campus Universitário Marco Zero, Macapá, Brazil
[2]Postgraduate Program in Pharmaceutical Sciences, Federal University of Amapá, Macapá, Brazil
Email: *breno@unifap.br

Received 25 October 2014; revised 22 November 2014; accepted 8 December 2014

Abstract

Malaria is a parasitic disease which has as etiological agents protozoa of the genus *Plasmodium* prevalent in tropical countries. The appearance of *Plasmodium* strains resistant to artemisinin has become necessary the development of new drugs using computational tools to combat this epidemic. Diverse transporter proteins can act as antimalarials targets, thereby being the enzyme deoxyhypusine synthase a promising antimalarial target. The present study aimed to investigate 15 most active inhibitors of deoxyhypusine synthase target, deposited in databases Binding DB, in order to trace a pattern of physicochemical, pharmacokinetic and toxicological properties of the inhibitors for this enzyme and propose new inhibitors of deoxyhypusine synthase target. The physicochemical properties were obtained according to the Lipinski parameters to evaluate oral absorption. Based on the certain properties were proposed three new inhibitors (A, B and C). The ADME/Tox properties were calculated for new inhibitors compared with results of the selected compounds. The fifteen inhibitors for oral administration showed satisfactory results, because they have adapted to the Lipinski parameters. In relation to the penetration of the blood-brain barrier the inhibitors analyzed showed penetration values less than 1, and ranged from 0.0411815 to 0.481764, being that the compound 1 showed value of C_{Brain}/C_{Blood} = 0.135467. Compound B showed a higher strength in plasma protein binding in relation to the compound 1, having a variation be-

*Corresponding author.

How to cite this paper: Silva, N.S.R., *et al*. (2014) Computational Analysis of Physicochemical, Pharmacokinetic and Toxicological Properties of Deoxyhypusine Synthase Inhibitors with Antimalarial Activity. *Computational Molecular Bioscience*, **4**, 47-57. http://dx.doi.org/10.4236/cmb.2014.44006

tween them of ±1.489344. Therefore, the compound B would present a longer half-life compared with compound 1. The proposed compounds showed positive and satisfactory results, being able to reach less adverse effects related to the central nervous system depending of administered dose.

Keywords

Antimalarial Activity, Deoxyhypusine Synthase Inhibitors, Physicochemical Property, Pharmacokinetic and Toxicological Properties

1. Introduction

Malaria is a disease prevalent in tropical climate countries regarded as a major social and economic problems in the world, being considered one of the oldest diseases, affecting a quarter of the world population. Malaria is inserted mainly in third world countries, concentrating on the Americas, Southeast Asia and Central Africa, with the highest death rate in Africa, caused by public health problem in the region [1]. In Brazil there three species responsible for the causes of malaria in humans that are: *P. vivax*, *P. falciparum* and *P. malariae*. A fourth species known as *P. ovale*, is only found in restricted areas of the African continent, and may occasionally be diagnosed in Brazil [1].

Many studies on the rational design of new antimalarial drugs have been performed using molecular modeling. However, complex molecular systems containing external and internal transition atoms, proteins, polymers, or compounds with a higher molecular weight overestimate the ability of computational chemistry to obtain molecular properties, which can lead to inaccurate results when compared with experimental data [2] [3].

The appearance of *Plasmodium* strains resistant to artemisinin has become necessary to search and development of new targets and drugs using computational tools to combat malaria. The description and identification performed by genome sequencing of several species provides the search for new pharmacological targets. In this context, diverse transporter proteins can act as antimalarial targets [4]. Therefore, eukaryotic initiation factor (eIF-5A), whose activation involves deoxyhypusine synthase that has already been suggested to be antimalarial drugs target [5].

In this work, a computational investigation of 15 inhibitors of deoxyhypusine synthase target existing in databases such as the BindingDB was carried out [6] (www.bindindb.org/bind/index.jsp) to trace a pattern for the physicochemical properties, pharmacokinetic properties: human intestinal absorption (HIA), cellular permeability (P_{CaCO_2}), cell permeability Maden Darby Canine Kidney (P_{MDCK}), skin permeability (P_{Skin}), plasma protein binding (PPB) and penetration of the blood-brain barrier ($C_{Brain/Blood}$), and toxicological: mutagenicity and carcinogenicity to the existing inhibitors of this enzyme. Therefore, increase knowledge in this area, and develop new proposals for inhibitors that may be more active and selective, besides to optimizing the investigated properties and decrease side effects.

2. Experimental

2.1. Selection of Molecules and Derivation of the Pharmacophore

Inhibitors of deoxyhypusine synthase target were selected in the database BindingDB, being chosen 15 most active inhibitors, based in Ki value (constant enzyme inhibition), see **Figure 1**. After this selection process, inhibitors were optimized in Discovery Studio Visualizer 4.0 software (http://accelrys.com) [7].

The derivation of the pharmacophore was generated with the help of PharmaGist server [8] utilizing 15 inhibitors selected from BindingDB, in order to calculate the pharmacophore group present with the crystallographic inhibitor as a reference (compound 1, **Figure 1**). The pharmacophore hypothesis is given by the alignment of the most active inhibitors, thereby identifying the regions wherein these are shared [8]. From the identification of each inhibitor (CID) were analyzed in the database BindingDB their respective physicochemical properties related to five rule in accordance with Lipinski parameters [9].

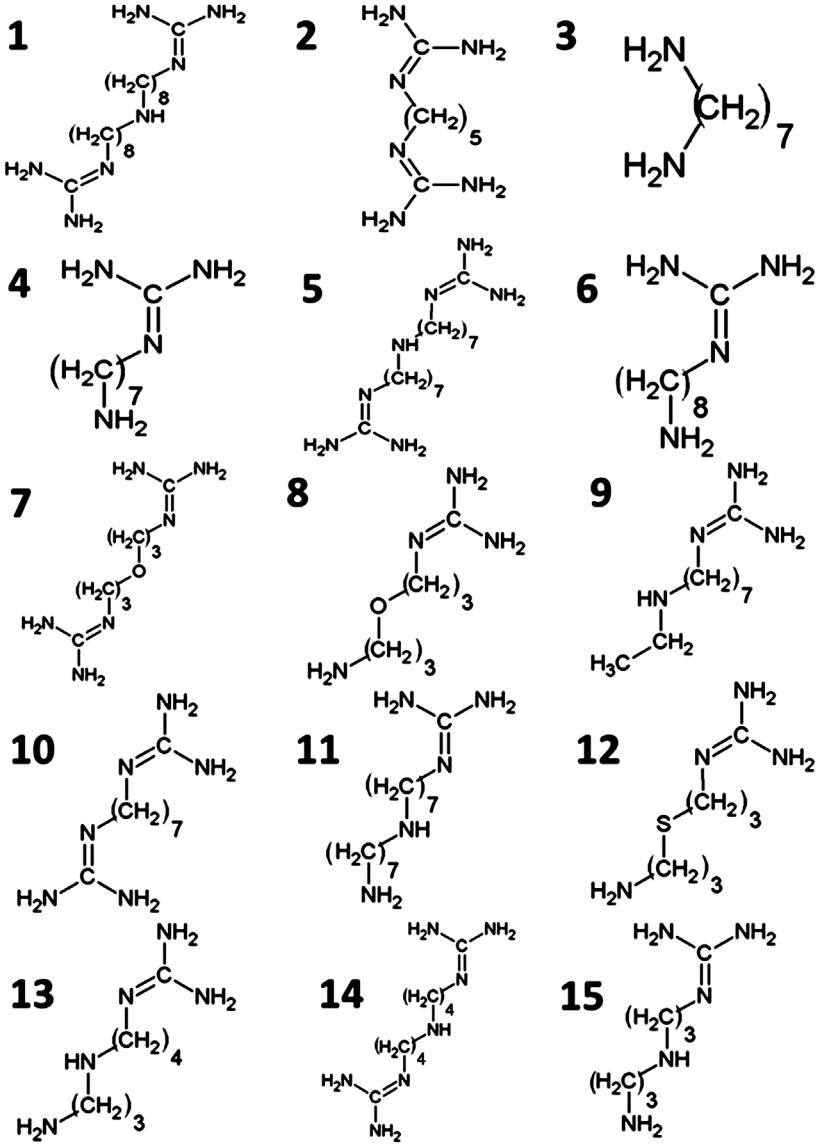

Figure 1. Inhibitors of deoxyhypusine synthase target.

2.2. Prediction of Pharmacokinetic and Toxicological Properties of the Inhibitors (ADME/Tox)

The absorption, distribution, metabolism, excretion (ADME) and toxic (Tox) properties were calculated with the aid of online server preADMET [10]. The server calculates parameters such as human intestinal absorption, cellular permeability Caco-2 *in vitro*, cell permeability Maden Darby Canine Kidney (MDCK), skin permeability, plasma protein binding, penetration of the blood-brain barrier, mutagenicity and carcinogenicity.

2.3. Modeling of New Inhibitors of Deoxyhypusine Synthase Target

Modeling of new inhibitors was performed with the aid of ChemSketch software [11], from the structural modifications in more active molecule, compound (1) of **Figure 1**, with the aim of analyze the pharmacokinetic and toxicological properties in an attempt to improve the pharmacological activity with antimalarial activity, being that were proposed three structural modifications, see **Figure 2**.

In the first modification (compound A) were removed three carbons of the side chain on each side of the molecule from molecule of compound 1 (**Figure 1**). This modification had the objective of decrease the hydrophobic

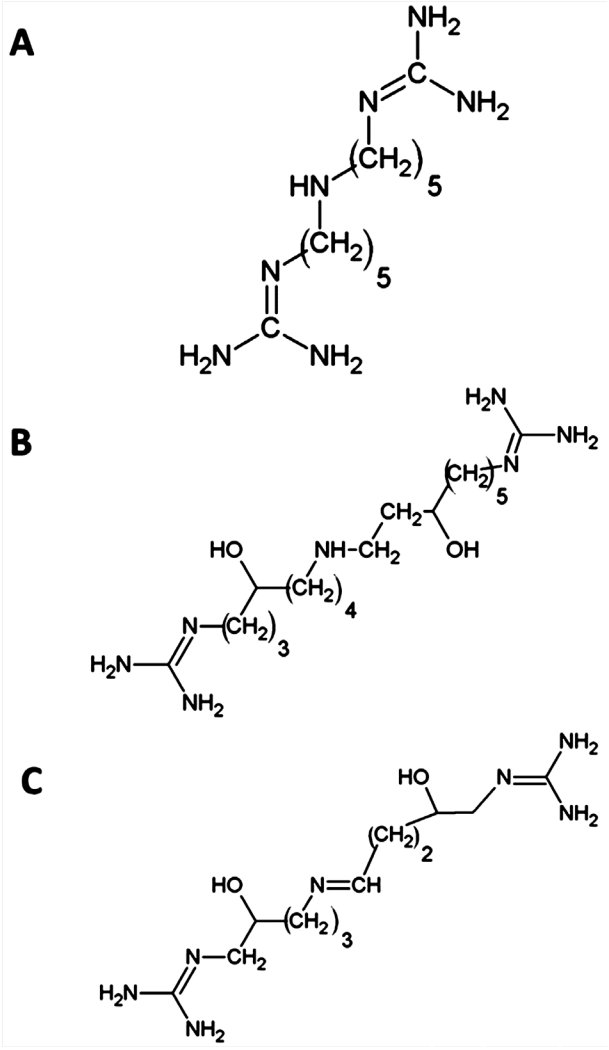

Figure 2. Inhibitors proposed for deoxyhypusine synthase target.

region, providing greater solubility of drug candidate. In the second modification (compound B) was added a hydroxyl (OH^-) on carbon atoms 5 and 5', starting from of most active compound (compound 1). Such modification has the aim to increase solubility, because the hydroxyl group (OH^-) is classified as a hydrogen acceptor, enabling the formation of hydrogen bond. In the third amendment (compound C) were removed three carbon atoms from each side of the molecule (carbon 3 and carbon 3'), being replaced by two hydroxyl (OH^-) and a double bond in the central nitrogen. The removal of carbon atoms and substitution of hydrogens by hydroxyl had as objective decrease the hydrophobic region creating a higher molecular solubility. Such modifications can alter hydration energy of the molecule.

Hydration energy is released when water molecules are separated from each other and are attracted by molecules or ions of a solute that is dissociating in water, *i.e.*, replacement of the hydrogen atom by the hydroxyl may result in decreased hydration energy resulting in increased solubility of the proposed inhibitors [12].

The proposed new inhibitors A, B and C were submitted to the ADME/Tox tests and compared with inhibitors selected by database BindingDB.

3. Results and Discussion

3.1. Derivation of the Pharmacophore

The identification of the pharmacophoric groups are defined as essential structural basis for molecular recogni-

tion and biological activity. These being important features to propose new drugs [13].

The derivation of the pharmacophore of deoxyhypusine synthase target was obtained by alignment of 15 molecules, having a score of 22.677, see **Figure 3**. Compounds aligned share the following characteristics: 3 donor groups and one positive group. Compound 1 (CID3526) is classified as the most active and characteristics are presented inhibitor: 10 hydrophobic groups, 7 donor groups, 1 acceptor group and 2 positive groups, see **Figure 4**.

3.2. Physicochemical Properties—Lipinski Parameters

A drug to have good oral absorption must satisfy of the parameters following: molecular weight of less than 500 Da, logP (lipophilicity) less than five (5); maximum of five (5) hydrogen donor groups and maximum of ten (10) groups acceptors binding intestinal permeability and comprise the first steps to good oral bioavailability. In analyzing the parameters of the selected compounds was observed that all had values within Lipinski parameters, as shown in **Table 1**.

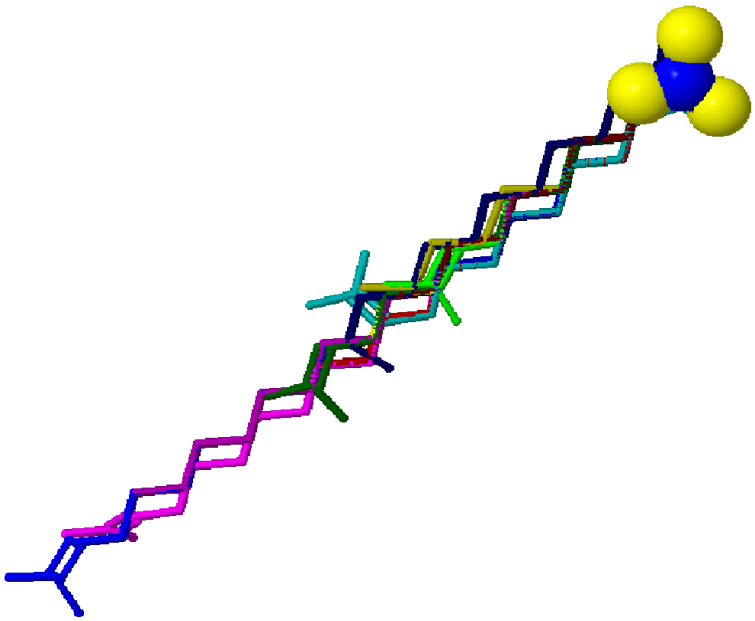

Figure 3. Pharmacophore—alignment of the 15 inhibitors of deoxyhypusine synthase target.

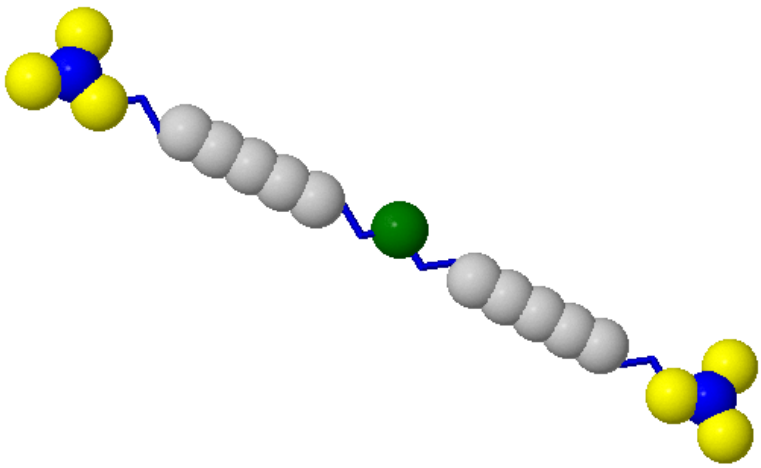

Figure 4. Pharmacophoric groups of compound 1 (CID3526).

Table 1. Physicochemical properties for inhibitors of deoxyhypusine synthase target selected in database BindingDB.

Compounds	CID	Molecular Weight (g/mol)	Donor	Acceptor	logP
1	CID3526	353.56504	5	3	1.7
2	CID42788	186.25802	4	2	−1.8
3	CID 69533	130.23112	2	2	0.3
4	CID448393	172.2712	3	2	−0.3
5	CID10019366	327.51188	5	3	0.6
6	CID10035350	186.29778	3	2	0.3
7	CID10059175	216.284	4	3	−2.3
8	CID10103656	174.24402	3	3	−1.7
9	CID10104259	200.32436	3	2	0.6
10	CID10104702	214.31118	4	2	−0.9
11	CID10334149	285.4719	4	3	1.2
12	CID10352523	190.30926	3	3	−0.9
13	CID10397928	201.31242	4	3	−1.3
14	CID10444474	243.3524	5	3	−1.9
15	CID44334124	173.25296	4	3	−2

3.3. Pharmacokinetic and Toxicological Properties

The results of ADME tests (absorption, distribution, metabolism and excretion) are shown in **Table 2**. These properties are presented as a determinant for drug development factors, being the biggest target objectives: good absorption, distribution, metabolism and excretion. Mainly, human intestinal absorption properties, because it is determinant for the drug development that purport to be administered orally [13] [14].

Analyzing the ADME tests of inhibitors shown in **Table 2**, it was observed that the compounds presented human intestinal absorption values (HIA) in the range of $27.402177 \leq \text{HIA}\% < 89.0000$. Being that compounds 2 (HIA = 39.555199%), 7 (HIA = 30.912700%) and 14 (HIA = 27.402172%) showed an absorption low with respect to compound 3 (HIA = 88.386566), having a variation of ±48.831367 (compound 2), ±57.473866 (compound 7) and ±60.984394, respectively. While six compounds (1, 5, 8, 10, 13 and 15) have absorption values in the range of $42.946999 \leq \text{HIA}\% < 60.871844$. In relation to compounds (3, 4, 6, 9, 11 and 12) showed the highest human intestinal absorption values, being $\text{HIA}\% \geq 71.643096$, highlighted for compound 3 that showed highest degree of HIA with value of 88.386566%, having a variation of ±38.824496% in relation to the compound 1. The absorption processes are related to the permeation of compounds through biological membranes under the influence of physicochemical characteristics [15].

The cell permeability *in vitro* Caco-2 is an important test to assess intestinal absorption of drugs. Since, Caco-2 cells derived from human colon adenocarcinoma, having various transport via in the intestinal epithelium [16]. The results of the compounds in **Table 2** showed an average permeability of 18.1458. In inhibitor calculated, it was found that the P_{CaCO_2} (nm/s) was moderate, ranging from 7.1205 nm/s to 21.1135 nm/s.

The cell permeability *in vitro* in MDCK system utilizes canine kidney cells and has a shorter growth that the Caco-2 cells. Thus, this system is used as a tool for the rapid analysis of permeability [17]. Analyzing the data in this MDCK system in the inhibitors shown in **Table 2**, it is verified that the permeability can be classified into low (25 nm/s) and mean (25 to 500 nm/s). Being mean in the compounds (1, 5, 6, 9 and 11) varying between 27.1622 nm/s to 45.4108 nm/s, and low in the other compounds varying between 0.59622 nm/s to 10.4543 nm/s.

The skin permeability is an important factor for the use of the drug transdermal administration via. This parameter is used in the pharmaceutical industry to assess the risk chemical products in case there is accidental contact with skin [18]. All studied and proposed inhibitors showed negative permeability values, not showing importance of use of the drug by this administration via, as shown in **Table 2**.

Table 2. Absorption properties of the 15 compounds selected in BindingDB.

Compounds	CID	Absorption			
		HIA (%)[a]	P_{CaCO_2} (nm/s)[b]	P_{MDCK} (nm/s)[c]	P_{skin}[d]
1	CID3526	49.562070	20.5758	34.8444	−1.76146
2	CID42788	39.555199	21.1000	0.861217	−4.24338
3	CID 69533	88.386566	21.1135	10.4543	−3.06874
4	CID448393	72.494187	20.8667	4.84472	−3.8169
5	CID10019366	42.946999	21.0601	27.2364	−2.29245
6	CID 10035350	74.230056	14.2796	27.1622	−3.53211
7	CID10059175	30.912700	17.4583	0.643974	−4.80094
8	CID10103656	60.871844	14.8764	0.667039	−4.81275
9	CID 10104259	79.507480	21.0662	34.4223	−3.47067
10	CID10104702	43.165636	19.7541	4.5730	−3.81426
11	CID10334149	71.981855	21.1009	45.4108	−2.44189
12	CID10352523	71.643096	7.1205	0.639253	−4.17547
13	CID10397928	56.184461	15.2704	1.54586	−4.41581
14	CID10444474	27.402177	16.5338	1.14559	−4.36115
15	CID44334124	51.725148	20.0113	0.59622	−4.70716

[a]percentage of human intestinal absorption; [b]cell permeability (Caco-2 in nm/s); [c]cell permeability Maden Darby Canine Kidney in nm/s; [d]skin permeability.

In **Table 3**, is shown the human intestinal absorption values for modified compounds. When evaluating the values of HIA was observed that decreased mainly in the compounds B and C which showed a HIA low of 12.505273% and 9.981487%, respectively. However, compound A obtained an absorption classified as mean, presenting equal value to 31.686200% with a range of ±17.875870 in relative to compound 1. The cell permeability in vitro Caco-2 was classified as moderate, but improved relative to compound 1 which had equal value 20.5758 nm/s, while compound A showed a permeability of 21.0928 nm/s. The permeability in MDCK system was considered less than 25 nm/s, mainly in the compound C which showed a permeability of 0.532287 nm/s, demonstrating that the modifications decreased the probability of pharmacokinetic success in the oral administration of possible proposed antimalarial compound.

The drug has two forms in the blood, the plasma protein bond form and non-bond form, although that bond directly depends on their affinity for such bond portion and the free portion. The binding to these proteins can alter the half-life of the drug in the body of the individual [19] [20].

According to **Table 4** of the distribution properties of plasma protein binding (PPB) and penetration of the blood-brain barrier, it is verified that all calculated inhibitors bind poorly to plasma proteins, being this variation of 0.00% to 76.277691%. Compounds 7 and 8 have no force in the bond these proteins by presenting equal value 0.00%, *i.e.*, such inhibitors have a large amount of free drug to interact with their receptors, triggering the form of this pharmacological response. In addition to changing the pharmacological response of molecules the PPB, also modifies the renal excretion, because only unbound drug is available for glomerular filtration, thus increasing its excretion and decreasing the half-life [21].

The blood-brain barrier (BBB) is an important component of a communication network that connects the central nervous system and peripheral tissues, limiting and regulating the exchange of substances between blood and the central nervous system [22]. Therefore has an importance in the pharmacology of drugs, because the compounds are classified as inactive (if not surpass the barrier) and active (if it exceeds the barrier), *i.e.*, inactive compounds avoid the side effects [23]. In **Table 4** are shown the penetration values of blood-brain barrier, and classified according to Ma *et al.* [24], compounds which exhibit higher values of 1 ($C_{Brain}/C_{Blood} > 1$) are considered

Table 3. Absorption properties of the modified compounds.

Compounds	Absorption			
	HIA (%)[a]	P_{CaCO_2} (nm/s)[b]	P_{MDCK} (nm/s)[c]	P_{skin}[d]
A	31.686200	21.0928	2.73356	−3.83239
B	12.505273	14.1505	1.09384	−4.11687
C	9.981487	16.654	0.532287	−4.99943

[a]percentage of human intestinal absorption; [b]cell permeability (Caco-2 in nm/s); [c]cell permeability Maden Darby Canine Kidney in nm/s; [d]skin permeability.

Table 4. Distribution properties in percentages of PPB and penetration of the blood brain barrier for 15 compounds selected from the BindingDB.

Compounds	CID	Distribution	
		PPB (%)	C_{Brain}/C_{blood}
1	CID3526	71.225137	0.135467
2	CID42788	7.733322	0.481764
3	CID 69533	24.425873	0.41683
4	CID448393	37.065502	0.342364
5	CID10019366	64.301410	0.102047
6	CID 10035350	61.718219	0.0659145
7	CID10059175	0.000000	0.0758001
8	CID10103656	0.00000	0.145835
9	CID 10104259	76.277691	0.147121
10	CID10104702	27.453272	0.0485379
11	CID10334149	68.587812	0.214323
12	CID10352523	10.045292	0.141524
13	CID10397928	54.874665	0.0504752
14	CID10444474	49.749746	0.0411815
15	CID44334124	26.490951	0.275474

active in the CNS may cause collateral effects, and compounds that have values below 1 ($C_{Brain}/C_{Blood} < 1$) are classified as inactive in the CNS. Therefore, inhibitors analyzed showed that all the compounds have less penetration values than 1, and ranged from 0.0411815 to 0.481764, being that compound 1 showed a value of $C_{Brain}/C_{Blood} = 0.135467$.

In **Table 5** are shown the results of distribution properties for the proposed inhibitors, and these modified compounds (A, B and C) were considered poor plasma proteins binding with values of 42.041932%, 72.714481% and 25.975504%, respectively. Compound B showed a higher strength in plasma protein binding relative to compound 1, having a variation between them ±1.489344. However, compound B presented higher half-life than that compound 1, according to Godin (1995), because the connected portion acts as a reservoir where the drug is released slowly so that it remains in equilibrium with unbound fraction that is being metabolized and excreted [19] [20]. The proposed inhibitors, **Table 5**, showed penetration values less than 1, *i.e.*, they are classified as inactive in the CNS by presenting low absorption in comparing its precursor compound (compound 1, **Figure 1**) that presented an absorption of 0.135467.

The Ames test assesses mutagenicity of the compounds, and this test uses *Salmonella typhimurium* strains

with modifications in genes responsible for the histidine synthesis, because this histidine is important for growth. The test assesses the ability of the mutagenic agent to cause growth inhibition in medium without histidine [25]. Inhibitors (1 - 15) submitted to this test showed positive prediction, *i.e.*, were predicted as a mutagen, and only compound 3 showed a negative prediction, being predicted as non-mutagenic.

The carcinogenicity test has the objective of identifying the tumorigenic potential in animals and risk assessment in humans. Such test requires much study time (>2 years) and the preADMET online server predicts the results from data NTP (National Toxicology Program) and EUA/FDA, because they are data made *in vivo* in rats and mice for 2 years [26]. Study performed by Vieira *et al*. (2014), used computational methods to classify the degree of anticancer activity against a cell line of human hepatocellular carcinoma (HepG2) of artemisinin derivatives, based on their molecular structure it is concluded that such derivatives have anticancer effects, showing satisfactory results in predicting of pharmacokinetic and toxicological properties using preADMET server [27]. When analyzing carcinogenicity in mice the compounds 1 - 12, 14 and 15 were predicted as negative, *i.e.*, have carcinogenic evidence and compound 13 has positive prediction, *i.e.*, show non-carcinogenic evidence for mice.

By analyzing rat carcinogenicity the compounds 1 - 6 and 9 - 15 were predicted positive showing non-carcinogenic evidence, and compounds 7 and 8, presented negative predictions showing strong carcinogenic evidence, according **Table 6**. To the proposed compounds A, B and C were predicted as mutagenic and presented negative predictions, *i.e.*, carcinogenic both to rats and mice, as shown in **Table 7**.

Table 5. Distribution properties of the modified compounds.

Compounds	Distribution	
	PPB (%)	C_{Brain}/C_{blood}
A	42.041932	0.0376156
B	72.714481	0.0384155
C	25.975504	0.0290816

Table 6. Toxicological properties of mutagenicity (Ames test) and carcinogenicity (mouse and rat) of selected compounds from the BindingDB.

Compounds	CID	Ames Test	Carcinogenicity	
		Mutagenicity	Mouse	Rat
1	CID3526	Mutagenic	Negative	Positive
2	CID42788	Mutagenic	Negative	Positive
3	CID 69533	Non-mutagenic	Negative	Positive
4	CID448393	Mutagenic	Negative	Positive
5	CID10019366	Mutagenic	Negative	Positive
6	CID 10035350	Mutagenic	Negative	Positive
7	CID10059175	Mutagenic	Negative	Negative
8	CID10103656	Mutagenic	Negative	Negative
9	CID 10104259	Mutagenic	Negative	Positive
10	CID10104702	Mutagenic	Negative	Positive
11	CID10334149	Mutagenic	Negative	Positive
12	CID10352523	Mutagenic	Negative	Positive
13	CID10397928	Mutagenic	Positive	Positive
14	CID10444474	Mutagenic	Negative	Positive
15	CID44334124	Mutagenic	Negative	Positive

Table 7. Toxicological properties of mutagenicity (Ames test) and carcinogenicity (mouse and rat) of the modified compounds.

Compounds	Ames Test	Carcinogenicity	
	Mutagenicity	Mouse	Rat
A	Mutagenic	Negative	Negative
B	Mutagenic	Negative	Negative
C	Mutagenic	Negative	Negative

4. Conclusions

Pharmacokinetic and toxicological properties (ADME/Tox) of the 15 most active inhibitors of deoxyhypusine synthase target selected database BindingDB showed satisfactory results for oral administration, because it have been adequate to the Lipinski parameters. However, the modifications performed from the most active compound, compound 1, not obtained results that enabled administration by the same via, because HIA these decreased having less values than 31.686200%. Being that human intestinal absorption is the sum of absorption and bioavailability, assessed from the proportion of excretion or cumulative excretion in urine, bile and feces.

In relation to the penetration of the blood-brain barrier (C_{Brain}/C_{Blood}) inhibitors exhibited penetration values less than 1, being classified as inactive in the CNS. The modified compounds have decreased penetration C_{Brain}/C_{Blood}, and showed lower values when compared to compound 1 which had value of C_{Brain}/C_{Blood} = 0.135467, thus being able to have less side effects. However, the same drug did not present an absorption level equal to or higher when compared to the precursor compound, modifications showed positive and satisfactory results and depending on the administered did it will produce the same effects with degree of adverse effects on the CNS.

Acknowledgements

We gratefully acknowledge the support provided by the Brazilian Agency National Council of Scientific and Technological Development (CNPq-Brazil). The authors would like to thank the Scientific Initiation Program (IC/CNPq/UNIFAP), and the Laboratory of Modeling and Computational Chemistry of Federal University of Amapá for computational support.

References

[1] Santos, C.B.R. (2014) Desenvolvimento Racional de Fármacos Antimaláricos Derivados da Artemisinina usando Métodos Computacionais SAR e QSAR. Dr. Thesis, Federal University of Amazonas, Brazil.

[2] Santos, C.B.R., Lobato, C.C., Vieira, J.B., Brasil, D.S.B., Brito, A.U., Macêdo, W.J.C., Carvalho, J.C.T. and Pinheiro, J.C. (2013) Evaluation of Quantum Chemical Methods and Basis Sets Applied in the Molecular Modeling of Artemisinin. *Computational Molecular Bioscience*, **3**, 66-79. http://dx.doi.org/10.4236/cmb.2013.33009

[3] Santos, C.B.R., Lobato, C.C., Braga, F.S., Morais, S.S.S., Santos, C.F., Fernandes, C.P., Brasil, D.S.B., Hage-Melim, L.I.S., Macêdo, W.J.C. and Carvalho, J.C.T. (2014) Application of Hartree-Fock Method for Modeling of Bioactive Molecules Using SAR and QSPR. *Computational Molecular Bioscience*, **4**, 1-24. http://dx.doi.org/10.4236/cmb.2014.41001

[4] Guiguemde, W.A., Shelat, A.A., Bouck, D., Duffy, S., Crowther, G.J., Davis, P.H., Smithson, D.C., Connelly, M., Clark, J., Zhu, F., Jiménez-díaz, M.B., Martinez, M.S., Wilson, E.B., Tripathi, A.K., Gut, J., Sharlow, E.R., Bathurst, I., Mazouni, F.E., Fowble, J.W., Forquer, I., Mcginley, P.L., Castro, S., Angulo-Barturen, I., Ferrer, S., Rosenthal, P.J., Derisi, J.L., Sullivan, D.J., Lazo, J.S., Roos, D.S., Riscoe, M.K., Phillips, M.A., Rathod, P.K., Van Voorhis, W.C., Avery, V.M. and Guy, R.K. (2010) Chemical Genetics of *Plasmodium falciparum*. *Nature*, **465**, 311-315. http://dx.doi.org/10.1038/nature09099

[5] Kaiser, A., Ulmer, D., Goebel, T., Holzgrabe, U., Saeftel, M. and Hoerauf, A. (2006) Inhibition of Hypusine Biosynthesis in Plasmodium: A Possible, New Strategy in Prevention and Therapy of Malaria. *Mini-Reviews in Medicinal Chemistry*, **6**, 1231-1241. http://dx.doi.org/10.2174/138955706778742795

[6] Inbar, Y., Schneidman-duhovny, D., Dror, O., Nussinov, R. and Wolfson, H.J. (2007) Deterministic Pharmacophore Detection via Multiple Flexible Alignment of Drug-Like Molecules. *Lecture Notes in Computer Science*, **3692**, 423-434.

[7] (2012) Discovery Studio Visualizer Software, Version 4.0. http://www.accelrys.com

[8] Schneidman-Duhovny, D., Dror, O., Inbar, Y., Nussinov, R. and Wolfson, H.J. (2008) PharmaGist: A Webserver for Ligand-Based Pharmacophore Detection. *Nucleic Acids Research*, **36**, 223-228. http://dx.doi.org/10.1093/nar/gkn187

[9] Lipinski, C.A., Lombardo, F., Dominy, B.W. and Feeney, P.J. (2001) Experimental and Computational Approaches to Estimate Solubility and Permeability in Drug Discovery and Development Settings. *Advanced Drug Delivery Reviews*, **23**, 3-26. http://dx.doi.org/10.1016/S0169-409X(96)00423-1

[10] Yamashita, S., Furubayashi, T., Kataoka, M., Sakane, T., Sezaki, H. and Tokuda, H. (2000) Optimized Conditions for Prediction of Intestinal Drug Permeability Using Caco-2 Cells. *European Journal of Pharmacology*, **10**, 195-204. http://dx.doi.org/10.1016/S0928-0987(00)00076-2

[11] Advanced Chemistry Development, Inc. (2010) ACD/Chemsketch Freware, Version 12.00. Toronto.

[12] Wulfsberg, G. (1987) Principles of Descritive Chemistry. Broks/Cole Publishing, Monterey, 23.

[13] Postigo, M.P., Guido, R.V.C., Castilho, M.S., Pitta, I.R., Albuquerque, J.F.C., Oliva, G. and Andricopulo, A.D. (2010) Discovery of New Inhibitors of *Schistosoma mansoni* PNP by Pharmacophore-Based Virtual Screening. *Journal of Chemical Information and Modeling*, **50**, 1693-1705. http://dx.doi.org/10.1021/ci100128k

[14] Zhao, Y.H., Le, J., Abraham, M.H., Hersey, A., Eddershaw, P.J., Luscombe, C.N., Butina, D., Beck, G., Sherborne, B., Cooper, I. and Platts, J.A. (2001) Evaluation of Human Intestinal Absorption Data and Subsequent Derivation of a Quantitative Structure-Activity Relationship (QSAR) with the Abraham Descriptors. *Journal of Pharmaceutical Sciences*, **90**, 749-784. http://dx.doi.org/10.1002/jps.1031

[15] Balimane, P.V., Chong, S. and Morrison, R.A. (2000) Current Methodologies Used for Evaluation of Intestinal Permeability and Absorption. *Journal of Pharmacological and Toxicological Methods*, **44**, 301-312. http://dx.doi.org/10.1016/S1056-8719(00)00113-1

[16] Yazdanian, M., Glynn, S.L., Wright, J.L. and Hawi, A. (1998) Correlating Partitioning and Caco-2 Cell Permeability of Structurally Diverse Small Molecular Weight Compounds. *Pharmaceutical Research*, **15**, 1490-1494. http://dx.doi.org/10.1023/A:1011930411574

[17] Irvine, J.D., Takahashi, L., Lockhart, K., Cheong, J., Tolan, J.W., Selick, H.E. and Grove, J.R. (1999) MDCK (Madin-Darby Canine Kidney) Cells: A Tool for Membrane Permeability Screening. *Journal of Pharmaceutical Sciences*, **88**, 28-33. http://dx.doi.org/10.1021/js9803205

[18] Singh, S. and Singh, J. (1993) Transdermal Drug Delivery by Passive Diffusion and Iontophoresis: A Review. *Medicinal Research Reviews*, **13**, 569-621. http://dx.doi.org/10.1002/med.2610130504

[19] Godin, D.V. (1995) Pharmacokinetics: Disposition and Metabolism of Drugs. In: Munson, P.L., Mueller, R.A. and Breese, G.R., Eds., *Principles of Pharmacology*: *Basic Concepts and Clinical Applications*, Chapman & Hall, New York, 39-84.

[20] Pratt, W.B. and Taylor, P. (1990) Principles of Drug Action: The Basis of Pharmacology. 3th Edition, Churchill Livingstone, New York.

[21] Brunton, L.L. (2012) Goodman & Gilman: As Bases Farmacológicas da Terapêutica. 12th Edition, McGraw-Hill, Rio de Janeiro.

[22] Banks, W.A. (2010) Blood-Brain Barrier as a Regulatory Interface. *Forum of Nutrition*, **63**, 102-110. http://dx.doi.org/10.1159/000264398

[23] Bemis, G.W. and Murcko, M.A. (1999) Designing Libraries with CNS Activity. *Journal of Medicinal Chemistry*, **42**, 4942-4951. http://dx.doi.org/10.1021/jm990017w

[24] Ma, X., Chen, C. and Yang, J. (2005) Predictive Model of Blood-Brain Barrier Penetration of Organic Compounds. *Acta Pharmacologica Sinica*, **26**, 500-512. http://dx.doi.org/10.1111/j.1745-7254.2005.00068.x

[25] Ames, B.N., Gurney, E.G., Miller, J.A. and Bartsch, H. (1972) Carcinogens as Frameshift Mutagens: Metabolites and Derivatives of 2-Acetylaminofluorene and Other Aromatic Amine Carcinogens. *Proceedings of the National Academy of Sciences of the United States of America*, **69**, 3128-3132. http://dx.doi.org/10.1073/pnas.69.11.3128

[26] Woo, Y.T. (2003) Mechanisms of Action of Chemical Carcinogens, and Their Role in Structure-Activity Relationships (SAR) Analysis and Risk Assessment. In: Benigni, R., Ed., *Quantitative Structure-Activity Relationship* (*QSAR*) *Models of Mutagens and Carcinogens*, CRC Press, Boca Raton, 41-80.

[27] Vieira, J.B., Braga, F.S., Lobato, C.C., Santos, C.F., Costa, J.S., Bittencourt, J.A.H.M., Brasil, D.S.B., Hage-Melim, L.I.S., Macêdo, W.J.C., Carvalho, J.C.T. and Santos, C.B.R. (2014) A QSAR, Pharmacokinetic and Toxicological Study of New Artemisinin Compounds with Anticancer Activity. *Molecules*, **19**, 10670-10697. http://dx.doi.org/10.3390/molecules190810670

Scientific Research Publishing (SCIRP) is one of the largest Open Access journal publishers. It is currently publishing more than 200 open access, online, peer-reviewed journals covering a wide range of academic disciplines. SCIRP serves the worldwide academic communities and contributes to the progress and application of science with its publication.

Other selected journals from SCIRP are listed as below. Submit your manuscript to us via either submit@scirp.org or Online Submission Portal.