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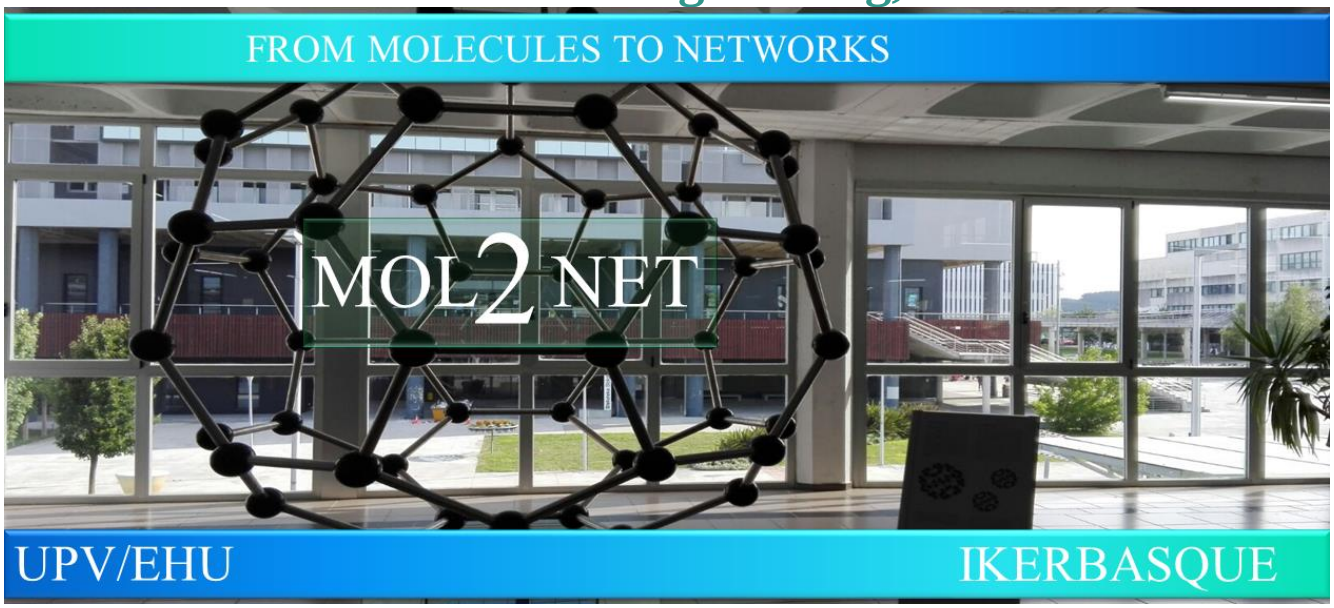

Prediction of antiviral activity, cytotoxicity risks and molecular docking against HIV of constituents from marine algae

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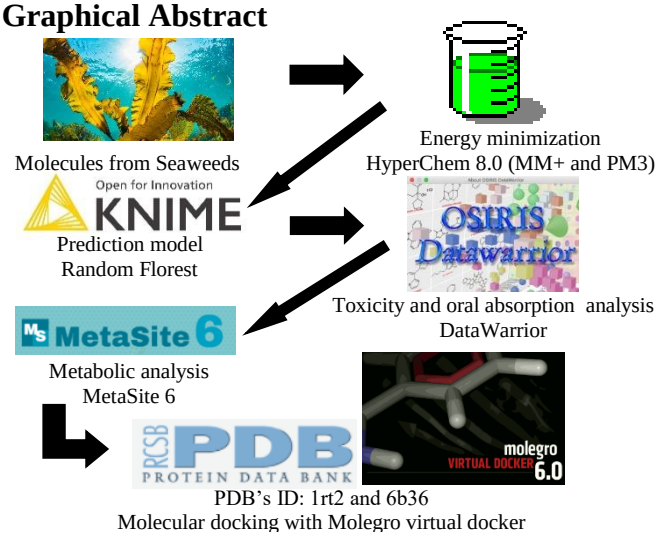
Graphical Abstract



Abstract.

The Human Immunodeficiency Virus has been affecting people for years. Leading patients to acquire several other diseases due to weakening of the immune system. The use of metabolites from marine algae have antiviral activities. Therefore, this work analyzed among 40 molecules, originating from algae, through in silico techniques, with the objective of proposing a promising molecule with possible HIV inhibitory activity.

Introduction

The disease caused by the Human Immunodeficiency Virus (HIV) has infected people for over 50 years [1]. Currently, 37.7 million people live with the virus, among these 150,000 people were infected with the HIV virus only in the year 2020, in addition 73% of people use drug therapy with retrovirals [2]. Therefore, it is important to investigate new possible drugs, one of these ways is through computational techniques.

The oceans have an enormous biodiversity, with biological sources rich in bioactive molecules, since the pharmaceutical and cosmetic industries seek technological innovations, numerous marine sources have been the object of study. [3].

Among these are marine algae that are divided into macroscopic and microscopic. Both are rich in secondary metabolites that have great pharmacological potential. [4]. Seaweeds already have several studies on their broad biological activities such as: antimicrobial, anticancer, antiallergic, antioxidant, anticoagulant, antidiabetic, antiparasitic, anti-inflammatory and antiviral. [5], [6].

Thus, this work aimed to analyze the possible inhibitory activity of molecules present in seaweeds in proteins present in HIV.

Materials and Methods

40 chemical structures of marine algae were obtained from articles. Molecules and control drugs were designed in Marvin Marvin Sketch 21.13 and optimized in HyperChem 8.0.6 software (RMS 0.1 kcal/mol/Å) in standard configuration, using the force field method of molecular mechanics MM+ and semi-quantum method. empirical PM3 [7], [8].

For the prediction model, molecular descriptors were generated in Dragon 7 software, they will be imported into a workflow developed for drug delivery in KNIME Analytics Platform 4.4.0 software. [9]. For the construction of the model, algorithms will be used through a classification method, such as: RandomFlorest, which is based on the formation of forests, random decisions and the model provided by Weka 7.0. Models that present statistical values ≥0.7 will be discarded, as they do not have prediction quality [10]–[12].

The oral absorption analyzes were based on the total topological surface area (TPSA) using the equation: $\%ABS = \left(109 - (\mathrm{TPSA} \times 0.345)\right) \times 100/maximum\ value$ and were performed using the Osiris Data Warrior 5.0 software [13], as well as toxicity risks were predicted according to mutagenicity, carcinogenicity, tissue irritability and toxic effect on the reproductive system. In addition, the toxicity of the metabolites of the selected molecules were analyzed. [14]

For molecular docking, the best molecules and the control drugs were used: darunavir for protease and doravirine for reverse transcriptase. The crystal structures of HIV-1 reverse transcriptase with TNK-651 and of HIV protease with CKD ((S)-N-(3-fluoro-2-(2-(1-(phenylsulfonyl)piperazin-2-yl))ethyl)phenyl)-3,3-bis(4-fluorophenyl)propanamide)) were obtained from the RCSB Protein Data Bank (PDB) (http://www.rcsb.org/pdb/home/home.do) under the 1RT2 codes for the 6B36, respectively. Molecular docking was performed in Molegro Virtual Docker (MVD) software.[15]. For validation, redocking was performed, as an evaluation parameter analyzed for values of root mean square deviation (RMSD - Root Mean Square Deviation) < 2 Å [16]. Other parameters evaluated will be the anchoring energy and the types of interactions with the target binding site.

Results and Discussion

After the treatment of the 40 molecules, these were analyzed in the prediction model, which presents several chemical and biological parameters for drugs with activity against the HIV. The prediction model showed that only 8 molecules showed possible biological activity and reliable domain. In addition, other parameters were analyzed in order to minimize the error (Table 1).

Table 1. Statistical analysis from the prediction model.

Statistical parameters	Cross validation	Teste
Precision	0.85	0.89
Sensitivity	0.84	0.87
Specifity	0.80	0.85
Accuracy	0.83	0.86
Matthews Correlation Coefficient	0.65	0.72
ROC curve	0.8895	0.9330

Subsequently, the analyzes of oral absorption and cytotoxicity of the molecules that passed through the prediction model and their metabolites were performed, thus only 2 molecules presented acceptable parameters, of which they had values for the oral absorption of M1 and M4 (Figure 1), 100% and 72.6%, respectively. In addition, both substances did not present any toxic risk for the analyzed parameters, only 1 of the possible metabolites of both molecules presented a risk of mucosal irritability. In this way, both compounds were submitted to the molecular docking test.

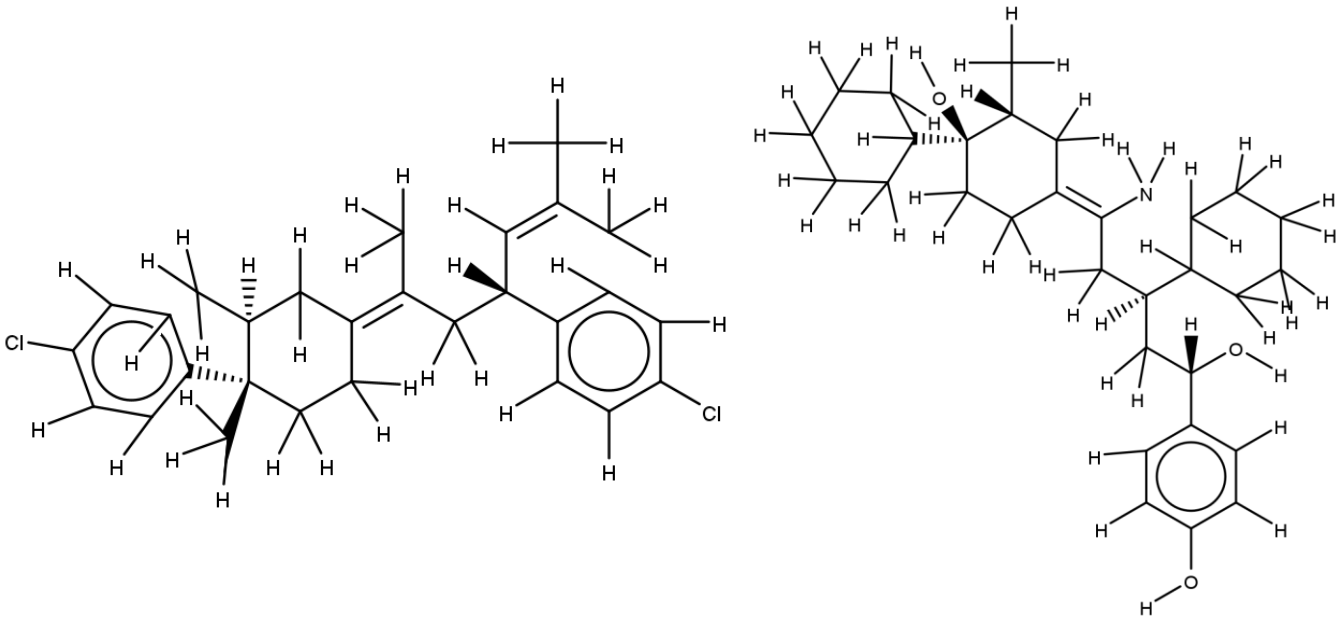


Figura 1. A) M1 e B) M4

After performing the molecular docking, it was observed that the M4 molecule presented the best results for both proteins. When analyzing the inhibitory activity of the molecules in the protease (6B36), the M4 molecule presented binding energy (-138.71 kcal.mol-1) higher than M1 (-125.09 kcal.mol-1), but lower than the standard drug darunavir (-179.34 kcal.mol-1) and the co-crystallized inhibitor (-221.32 kcal.mol-1). The redocking with the already crystallized ligand showed a significant result for RMSD of 0.195 Å. The interactions between structure-ligand are expressed in Table 2

Table 2. Molecular docking results for protease inhibitory activity

Protein (PDB ID)	Name	Energy [kcal.mol^{-1}]	Interactions	
			Types	Residues
6B36	M1	0	H-bond	None
			Steric	2(Gly48), Ile47, Ile50(A), Gly49(A), Gly49(B), Leu76, Asp25(B) and Asp30
	M4	-3.22	H-bond	2(Gly48), Gly27 and Asp25(B)
			Steric	2(Ile47), 2(Gly48), Ile84, Ile50(A), Ile50(B), Gly27, Asp29, Ala28 and Asp25
	Darunavir	-10.29	H-bond	2(Ile50(A)), Ile50(B), Asp29, Gly27 and Gly48
			Steric	2(Asp30), Asp29, Ala28, Ile84, Ile50(B) and Gly49
	CKD	-12.00	H-bond	Ile50(A), Ile50(B), Asp25, Asp29 and Gly48
			Steric	2(Asp25(A)), 2(Asp50(B)), Asp30, Asp29, Ile50 and Gly49

However, when analyzing the results of the inhibitory activity of molecules in reverse transcriptase (1RT2) the chemical structure M4(-181.19 kcal.mol-1) showed the best binding energy when compared to doravirine (-177.84 kcal.mol-1), M1 itself (-160.71 kcal.mol-1) and the co-crystallized ligand (-173.91 kcal.mol-1). Redocking with the already crystallized ligand showed a significant result for RMSD of 0.298 Å.

Table 3. Molecular docking results for reverse transcriptase inhibitory activity

Protein (PDB ID)	Name	Energy [kcal.mol^{-1}]	Interactions	
			Types	Residues
1RT2	M1	0	H-bond	None
			Steric	3(Tyr181), 2(Tyr188),2(Lys103), Lys101, Tyr318, Leu100, Val179, Val106, His235, Pro236, Phe227 and Trp229
	M4	-1.84	H-bond	His235, Tyr318 and Lys101
			Steric	3(Val106), 3(Leu100), 3(Phe227), 2(Val179), 2(Tyr101), 2(Tyr188), 2(Gly190), Lys103, Pro236, Ty318
	Doravirine	-0.61	H-bond	Val106
			Steric	3(Tyr188), Phe227, Trp229, Lys101, Lys103, Tyr318 and His235
	CKD	-4.13	H-bond	2(Lys101) and Tyr318
			Steric	His235 and Tyr188

When comparing the molecular interactions at the protease binding site of darunavir with M4, both showed the same hydrogen bonds at the amino acid residues Gly48 and Gly27, in addition to steric interactions with Ile50, Ile84, Asp29 and Ala28. In the reverse transcriptase binding site, it was possible to see that M4 and doravirine showed steric interactions with the amino acid residues Tyr188, Phe227, Lys103 and Tyr318.

VonRanke and collaborators [17] in an *in silico* study with diterpenes from seaweeds, they also showed possible inhibitory activity of reverse transcriptase, corroborating the above results. Furthermore, Besednova *et al.* [18] under review lists several metabolites from seaweed with activity on various HIV targets.

Conclusions

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Several studies demonstrate the activity of molecules from marine algae with human immunodeficiency virus inhibitory activity. The present study analyzed 40 molecules of which only the M4 structure was shown not to cause cytotoxicity risks, good absorption and optimal interaction with the binding site of both proteins. However, it showed more promise when analyzed in reverse transcriptase. Thus, it is concluded that M4 may have a possible inhibitory activity on the HIV reverse transcriptase target.

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