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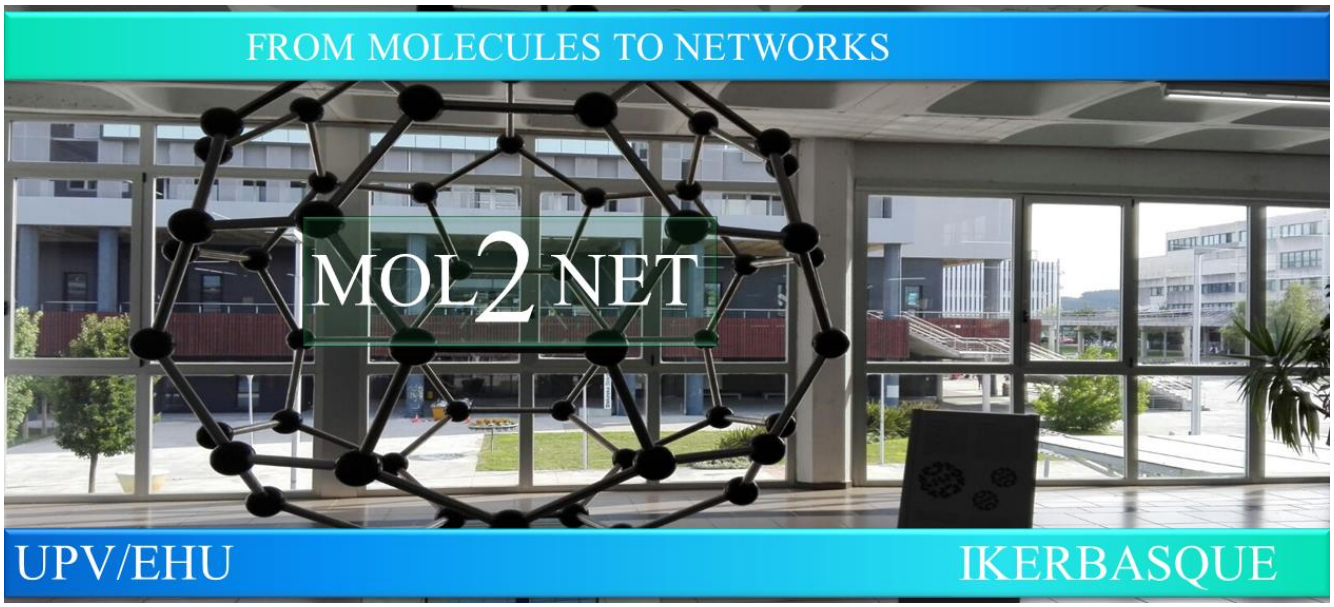
MOL2NET'21, Conference on Molecular, Biomedical & Computational Sciences and Engineering, 7th ed.



Computational study by molecular docking of structures from algae predicting activity against the protozoan *Leishmaniasis donovani* and toxicity parameters

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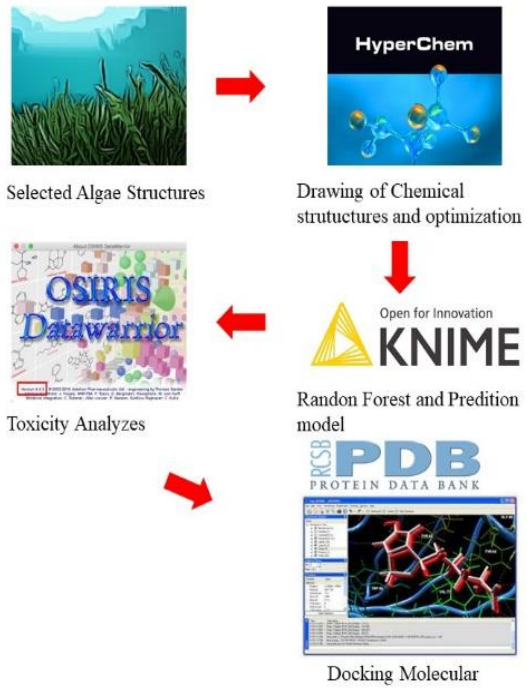
Graphical Abstract



Abstract.

Leishmaniasis is a neglected disease that accounts for approximately 30,000 deaths annually. Studies demonstrate drug resistance in the treatment of this pathology, thus making it necessary to search for new bioactive molecules for the treatment of this disease. Due to this, the objective of the following study is to verify through a molecular doking the most promising structures from algae selected through a bibliographic search. Presenting two promising molecules through computational data.

Introduction

Leishmaniasis is a neglected disease that occurs mainly in tropical regions of the world, being found endemically in about 98 countries, where it totals approximately 30,000 deaths annually. Often appearing in its most lethal form as visceral leishmaniasis (VL), caused by the dimorphic parasite *Leishmaniasis donovani*. Currently, it is known that drugs are losing their effectiveness against this pathology, due to the development of resistance [1]. Therefore, it is essential to search for molecules that may be promising for the manufacture of future drugs that help in the treatment of this pathology [1].

Natural products of aquatic origin such as those derived from algae, has been gaining prominence in the pharmaceutical and biomedicine industry, due to its rich diversity of bioactive molecules with antioxidant, anti-inflammatory, antifungal, antibacterial and neuroprotective activities, Also due to the interaction with the most diverse diseases [2]. Among them those caused by Leishmaniasis, due to the amount of structures coming from living organisms, studies that have a rapid molecular verification capability are needed.

The development of chemoinformatics facilitated the choice of future candidates for medicament, due to the ability to verify a large number of molecules with biological activity, through molecular docking, and thus perform a low-cost analysis selecting the most promising drug candidates [1]. Due to this, the objective of the following study is to verify the possibility through molecular doking to find possible promising bioactive molecules from algae, that may be future candidates for studies that help in the treatment of Leishmaniasis caused by the parasite *Leishmaniasis donovani*.

Materials and Methods

To carry out the following study, 10 molecules were selected from marine algae considered promising for the development of bioactive products, these being the 2,4,6-tribromophenol; Chromene; Colpol; Fucodiphlorethol; Phlorofucofuroeckol A; Phloroglucinol ; Tetrafucol A; Tetrafuhalol A; Tetrafuhalol B e Tichocarpol A [2]. These molecules were designed and optimized in the software HyperChem 7.5 TM (RMS 0.1 kcal.$Å^{-1}$.mol^{-1} em cycles [6], using molecular mechanics (MM+), soon after these molecules were tested in the biological activity model of free software KNIME Analytics Platform 3.7 [7,1], being used the RandomForest as classifier and Weka 3.7 as a predictor, at the end of the analysis they were considered active or inactive.

The molecules considered active were transferred to free software OSIRIS DataWarrior 5.0 [3] for the assessment of its total toxicity through parameters such as mutagenicity, carcinogenicity, toxic effect on the reproductive system and irritability, as well as verification of oral absorption. The molecules considered toxic were those that showed some toxicity in the parameters studied.

Molecular docking was performed in the software Molegro Virtual Docker 6.0 (MVD) using two proteins directly related to the disease *Leishmaniose donovani* [8,10], deposited in PDB with the codes 2kvk and 2haq. The structure used as a reference for an already known drug was Paromomycin [5].

Results and Discussion

Ten molecules were tested for the *Leishmaniasis donovani* model, its statistical basis is shown in Table 1. The sensitivity for this model was 79%, meaning that it has a 79% chance of considering a molecule that actually has the activity active. In terms of accuracy, this value ranged from 68% to 75%, indicating a good margin of total hits in the predictions, as well as a variation from 0.38 to 0.50 in the Matthews correlation (MCC) that generates a global assessment of the model.

Table 1. Statistical result for the model of *leishmaniose donovani*

Row ID	Teste	Cross
VP	237	438
FP	78	236
VN	196	349
FN	63	124
Precision	0,752381	0,649852
Sensitivity	0,79	0,779359
Specificity	0,715328	0,596581
MCC	0,50723	0,381773
Accuracy	0,754355	0,686138
ROC curve	83,05109	76,78636

The ROC graph (Figure 1) showed that the model used presented a good predictive performance and, therefore, a good reliability of the results presented in this study.

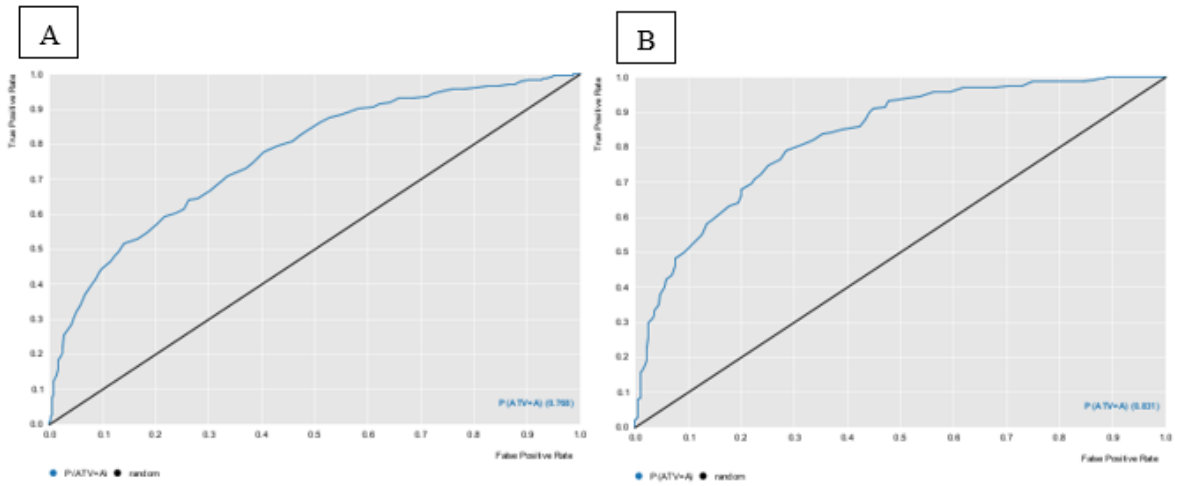


Figure 1. Graph characteristic curve (ROC), A-Cross Validation, B-Test.

After submitting the structures to the model, five molecules were considered active and reliable (Table 2), namely 2,4,6-Tribromophenol (58%), Fucodiphlorethol (60%), Phlorofucofuroeckol A (59%), Phloroglucinol (64 %), Tetrafucol A (60%). Two were active but unreliable and three were inactive. Only molecules considered active and reliable passed the cytotoxic and pharmacokinetic test.

Table 2. Results corresponding to the domain, activity and percentage of activity of the molecules tested in the model for *Leishmania donovani.*

Molecules	Domain	Active	% Active
2,4,6-Tribromophenol	Reliable	Active	58
Chromene	Reliable	Inativo	47
Colpol	Reliable	Inativo	45
Fucodiphlorethol	Reliable	Active	60
Phlorofucofuroeckol A	Reliable	Active	59
Phloroglucinol	Reliable	Active	64
Tetrafucol A	Reliable	Active	60
Tetrafuhalol A	Unreliable	Active	54
Tetrafuhalol B	Unreliable	Active	51
Tichocarpol A	Reliable	Inativo	24

Among these molecules, only two passed the toxicity test, which is Fucodiphlorethol and Tetrafucol A (Table 3) where they were considered non-toxic in the parameters tested. In oral absorption both had low values of 32 and 25% respectively.

Table 3. Results of cytotoxic and pharmacokinetic parameters.

Results of cytotoxic and pharmacokinetic parameters	Structure	
	Fucodiphlorethol	**Tetrafucol A**
% Abs	32,8378	25,2478
Mutagenic	None	None
Tumorigenic	None	None
Reproductive Effective	None	None
Irritant	None	None
Toxicidade Total	No	No

Molecular docking was performed with the two proteins shown in Figure 2 at 2kvk and 2haq for the drug already known in the literature (Paromomycin) and the two new structures.

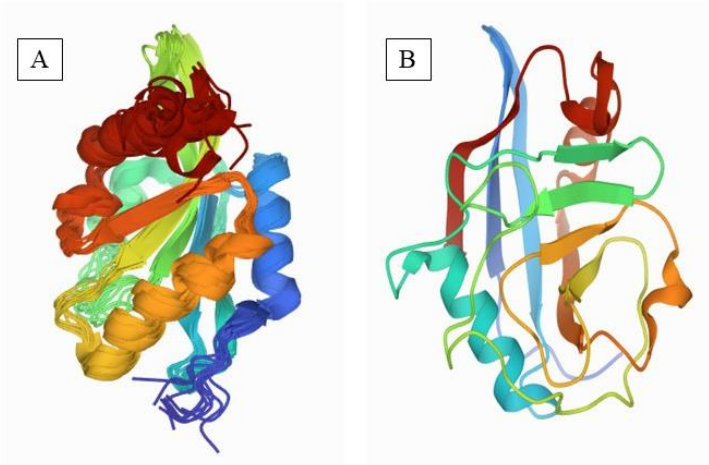
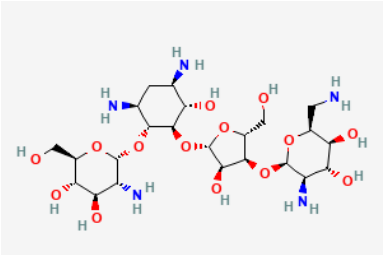
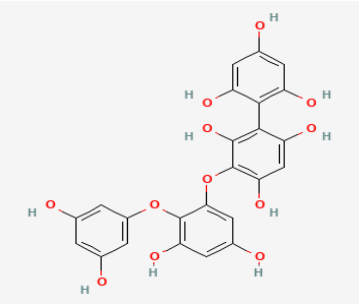
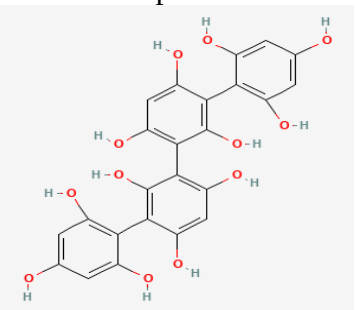


Figure 2. Proteins used. A- 2kvk B -2haq.

The value of molecular docking is shown in Table 4. In which the interaction of these molecules with related proteins is perceptible, Fucodiphlorethol having a better performance with the 2kvk protein having a better interaction than the known drug (Paromomycin).

Table 4. Result of the molecular docking of the tested structures.

Structure	Mol Dock (kJ mol $^{-1}$)	
	2kvk	2haq
 Paromomycin	-320.662	-174.918
 Fucodiphlorethol	-612.383	-130.089
 Tetrafucol A	-351.532	-107.564

The relationships between the tested structures and the amino acids of the proteins are shown in Figure 3 and Table 5. The figure shows the interactions per cavity, occurring mainly by hydrogen highlighted in blue and steric in red.

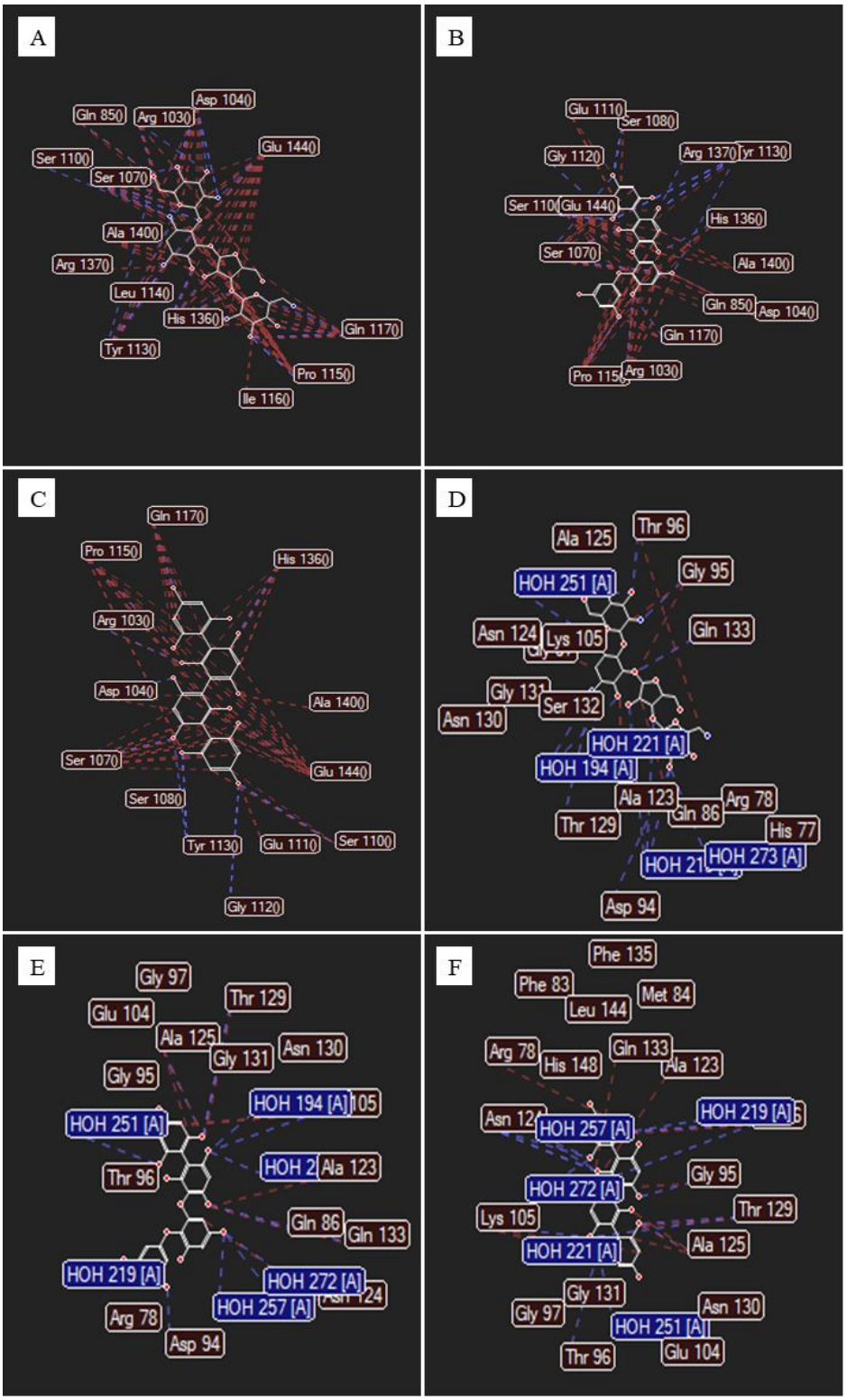


Figure 3. Interaction of molecular structures with protein amino acids 2kvk: A. Paromomycin B. Fucodiphlorethol C. Tetrafucol A. Interaction with protein amino acids 2haq D. Paromomycin E. Fucodiphlorethol F Tetrafucol A.

Table 5 . Interactions between the structures tested with the selected proteins

Proteins	Molecule	Amino acid	Hydrogen interactions	Steric interactions
2kvk	Paromomycin	Gin 85	1	2
		Gin 117	> 3	> 3
		Arg 103	2	2
		Arg 137	0	1
		Asp 104	3	> 3
		Ser 110	1	0
		Ser 107	3	> 3
		Ala 140	0	3
		Leu 114	0	1
		Tyr 113	3	2
		His 136	3	> 3
		Lhe 116	0	1
		Pro 115	1	> 3
		Glu 144	1	> 3
	Fucodiphlorethol	Glu 111	0	2
		Glu 114	0	> 3
		Ser 110	1	0
		Ser 107	3	> 3
		Ser 108	1	1
		Gly 112	1	0
		Gln 117	1	2
		Gin 85	0	2
		Asp 104	1	2
		Arg 137	3	0
		Tyr 113	1	1
		His 136	1	2
		Ala 149	0	3
		Arg 103	1	> 3
		Pro 115	1	> 3
	Tetrafucol A	Pro 115	1	> 3
		Gln 117	1	> 3
		His 136	1	> 3
		Arg 103	1	1
		Asp 104	1	2
		Ala 140	0	1

		Ser 107	1	> 3
		Glu 144	1	> 3
		Ser 108	1	0
		Tyr 110	1	0
		Gly 112	1	0
		Glu 111	0	1
		Ser 110	1	3
		Thr 96	1	1
2haq	Paromomycin	Ala 125	0	0
		Gly 95	1	2
		Gin 133	1	0
		Asn 124	0	0
		Lys 105	0	0
		Gyl 01	0	1
		Asn 130	0	0
		Gly 131	0	0
		Ser 132	0	1
		Ala 123	1	0
		Thr 129	1	0
		Asp 94	1	0
		Gin 86	1	0
		Arg 78	0	0
		His	0	0
	Fucodiphlorethol	Gly 97	0	0
		Glu 104	0	0
		Thr 129	1	1
		Ala 125	1	2
		Asn 130	0	0
		Gly 131	0	0
		Gly 95	0	0
		Thr 96	1	0
		Ala 123	0	1
		Gin 86	1	0
		Gin 133	1	1
		Arg 78	0	0
		Asp 94	1	0
		Asp 124	1	1
	Tetrafucol A	Phe 135	0	0
		Phe 83	0	0
		Met 84	0	0

Gin 133	0	1
His148	0	0
Lev 144	0	0
Arg 78	0	1
Gin 133	0	1
Ala 123	0	1
Asn 124	3	0
Gly 95	1	1
Lys 105	1	2
Thr 125	2	1
Ala 125	1	3
Gly 131	1	0
Gly 97	0	0
Thr 96	1	0
Glu 104	0	0
Asn 130	0	0

Conclusions

Leishmaniasis is a disease that is experiencing difficulties in its treatment, mainly due to the mechanisms of resistance to drugs already known, and with this, studies are necessary to find molecules that can be used as drugs or associated with those already known. These structures can be found in aquatic organisms as presented in the study.

The structures Fucodiphlorethol and Tetrafucol A, presented good performances as possible drugs, having only a low absorption by the oral route, therefore being necessary more systematic studies of molecular modification if the use of these molecules by this route is required. However, these structures were considered promising for future studies.

References

1. Carlo, R., Renato, C., Giuseppe, C., Lorenzo, U., Giovanni, I., Domenico, S., Valeria, R., Elia, G., Maria, C.L. and Mario, C. (2019). Distinguishing Functional from Non-functional Pituitary Macroadenomas with a Machine Learning Analysis. *IFMBE Proceedings*, pp.1822–1829.

2. Cotas, J., Leandro, A., Monteiro, P., Pacheco, D., Figueirinha, A., Gonçalves, A.M.M., da Silva, G.J. and Pereira, L. (2020). Seaweed Phenolics: From Extraction to Applications. *Marine Drugs*, 18(8), p.384.

3. S. J., R.D. and Kumar B., P. (2020). In Silico Screening for Anti-inflammatory Bioactive Molecules from Ayurvedic Decoction, Balaguluchyadi kashayam. *Current Computer-Aided Drug Design*, 16(4), pp.435–450.

4. Dumetz, F., Cuypers, B., Imamura, H., Zander, D., D'Haenens, E., Maes, I., Domagalska, M.A., Clos, J., Dujardin, J.-C. . and De Muylder, G. (2018). Molecular Preadaptation to Antimony Resistance in Leishmania donovani on the Indian Subcontinent. *mSphere*, 3(2).

5. Jhingran, A., Chawla, B., Saxena, S., Barrett, M.P. and Madhubala, R. (2009). Paromomycin: Uptake and resistance in Leishmania donovani. *Molecular and Biochemical Parasitology*, 164(2), pp.111–117.

6. Laxmi K. Structural Elucidation of Drug Aspirin by Using Various Software Tools Like HyperChem, Argus Lab, ChemSketch, Avogrado and Chemeo Database. J Theor Comput Sci. 2019;5(163):2.

7. Lieder B, Hans J, Hentschel F, Geissler K, Ley J. Biological Evaluation of Natural and Synthesized Homovanillic Acid Esters as Inhibitors of Intestinal Fatty Acid Uptake in Differentiated Caco-2 Cells. Molecules. 2019;24(19):3599.

8. Pathak, P.P., Pulavarti, S.V.S.R.K., Jain, A., Sahasrabuddhe, A.A., Gupta, C.M. and Arora, A. (2010). Solution structure and dynamics of ADF/cofilin from Leishmania donovani. *Journal of Structural Biology*, 172(3), pp.219–224.

9. Pinzi, L. and Rastelli, G. (2019). Molecular Docking: Shifting Paradigms in Drug Discovery. *International Journal of Molecular Sciences*, 20(18), p.4331.

10. Venugopal, V., Sen, B., Datta, A.K. and Banerjee, R. (2007). Structure of cyclophilin fromLeishmania donovaniat 1.97 Å resolution. *Acta Crystallographica Section F Structural Biology and Crystallization Communications*, 63(2), pp.60–64.