International Journal of Recent Research and Review, Vol. XI, Issue 2, June 2018
ISSN 2277 – 8322

Comparative Study of Molecular Docking Between the Carotenoid Bixin and HIV Inhibitor Protease Indinavir

Jacilene Silva[1], Márcia Machado Marinho[2], Emmanuel Silva Marinho[3]
[1]*Department of Chemistry, University State of Ceará, Brazil.*
[2]*Departamento of Pharmacy, Federal University of Ceará.*
[3]*Department of Chemistry, University State of Ceará, Brazil.*
Email: [1]jacilenesilva1000@gmail.com,[2]marinho.marcia@gmail.com.br,[3]emmanuel.marinho@uece.br

Abstract -From 2007 to June 2017, 194.217 cases of HIV infection in Brazil were reported in the Sinan (Notification of Injury Information System), of which 131.969 (67.9%) were men and 62.198 (32.1%) cases were women. By July 2017, there were around 20.9 million people living with HIV on antiretroviral treatment. Given this, people with HIV / AIDS need access to preventive care and treatment of HIV-related infections. It is of fundamental importance that they obtain the best services and care possible. Since the introduction of antiretroviral therapy in Brazil in 1996, a reduction in the estimate of AIDS deaths has been observed, in which this therapy is extended to all those that have an indication of use and is provided free of charge in the national territory. Indinavir is a protease inhibitor with activity against human immunodeficiency virus type 1 (HIV-1). However, Bixaorellana L. (Urucum) is a plant that is characterized by the production of a reddish pigment extracted from its seeds, used for various purposes, including medicinal purposes, in which Bixin is the carotenoid found in the seeds of plant in greater quantity. In this perspective, the objective of this study is focused on the analysis of the inhibitory potential of the Bixin ligand in comparison to the Indinavir ligand (MK1) complexed in the HIV-1 Protease 1HSG protein, through molecular coupling. This study was developed in four stages, (1) obtaining the ligand and the protein; (2) Preparation of the binder; (3) Protein preparation and (4) Molecular docking. From the AutoDockTools, AutoDockVina: Vina command prompt software, the molecular docking between the Bixin ligand and the HIV-1 Protease 1HSG protein was performed. After the completion of the molecular coupling, the deviation between the ligand and the protein was analyzed, where the RMSD values found were RMSD l.b. 1320 Å and RMSD u.b. 2,029 Å, Affinity Energy of -3.3 kcal / mol and 21 active kinks. From semi-empirical molecular optimization simulations using the Mopac software and molecular docking through the AutoDockTools, AutoDockVina: Vina command prompt, it was possible to determine the spatial orientation of the Bixin ligand and the HIV-1 Protease protein in than the lowest distances found in comparison with indinavir, thus evidencing the potential of bixin as a new inhibitor against HIV-1 Protease.

Keywords –Bixa Orellana. Computational simulation. Docking molecular.HIV proteaseinhibitor.

I. INTRODUCTION

From 2007 to June 2017, 194.217 cases of HIV infection were reported in Sinan (Brazil), 96.439 (49.7%) in the Southeast region 40.275 (20.7%) in the South, 30.297 (15.6%) in the Northeast, 14.27 (7.4%) in the North and 12.931 (6.7%) in the Central-West region, of which 131.969 (67.9%) were men and 62.198 (32,1%) cases in women [1]. As of July 2017, there were around 20.9 million people living with HIV in antiretroviral treatment [2].
HIV is the acronym in English related to the human immunodeficiency virus. It is the cause of AIDS, a disease that attacks the immune system, responsible for defending the body from diseases, the T lymphocytes with CD4 + receptors are the most affected cells, in which the virus changes the DNA of that cell to produce copies of itself, in which after if it multiplies, it breaks the lymphocytes in search of others to continue the infection [3]. An HIV-infected person does not necessarily mean that she has AIDS, since there are many HIV-positive people who live years without symptoms and without developing the disease. However, they may transmit the virus to others for

unprotected sex, sharing contaminated syringes, or mother to child during pregnancy and breastfeeding, when proper prevention measures are not followed. Therefore, it is always important to take the test and protect yourself in all situations [3]. Acquired Immune Deficiency Syndrome (AIDS) is caused by HIV, "S" is a syndrome, a combination of signs and symptoms that form a different clinical picture of a dysfunction; "I" and "D" are of Immunodeficiency: fall of the immune system of a person making it vulnerable to infections. "A" is from Acquired, which means that the disease is neither hereditary nor congenital, although the use of the term AIDS is widespread for medical purposes, this has been replaced by phase-by-stage classifications of HIV infection; in which AIDS refers only to the last stages of immune suppression [4]. It was first described in 1981 after a succession of cases of people developing uncommon infections and rare neoplasms found only in advanced immunodeficiency states, where it was later discovered that this syndrome occurs at a late stage of HIV infection [5]. Given this, people with HIV / AIDS need access to preventive care and treatment of HIV-related infections. It is of fundamental importance that they obtain the best possible and non-discriminatory services and care [3-4]. Since the introduction of antiretroviral therapy in Brazil in 1996, a reduction in the estimate of AIDS deaths has been observed, in which this therapy is extended to all those that have an indication of use and is provided free of charge in the national territory [6]. The treatment inhibits HIV replication, thereby reducing viral RNA and thus elevating CD4 + lymphocytes, HIV target cells. Recovery of immunity in these individuals provides greater survival, since they reduce the risk of infection from infections [7]. Currently, early antiretroviral therapy is recommended, to reduce the transmissibility of the virus [8].Indinavir is a potent specific inhibitor of HIV protease that has good oral bioavailability. Identified by its CAS number 150378-17-9, chemical formula C36H47N5O4 and IUPAC name (2S) -4-benzyl-2-hydroxy-4 - {[(1S, 2R) -2-hydroxy-2,3- dihydro-1H-inden-1-yl] carbamoyl} butyl] -N-tert-butyl-4- (pyridin-3-ylmethyl) piperazine-2-carboxamide. It is a protease inhibitor with activity against human immunodeficiency virus type 1 (HIV-1). In which protease inhibitors block the part of HIV called protease. HIV-1 protease is an enzyme necessary for the proteolytic cleavage of viral cleavage cleavage precursors resulting in the formation of non-infectious immature viral particles [9-11].

The *Bixaorellana* L. (Urucum) belonging to the family Bixaceae, genus Bixa, is a plant that is characterized by the production of a reddish pigment, extracted from its seeds, used for various purposes, including medicinal, in which Bixin is the carotenoid found in the seeds of the plant in greater quantity [12]. In this perspective, the aim of this study is focused on the analysis of the inhibitory potential of the Bixin ligand compared to the Indinavir ligand complexed on the HIV-1 Protease 1HSG protein, through molecular coupling.

II. METHODOLOGY

Computational Resources

To perform this work, we used the Molecular Orbital Package (Mopac)[13][14], AutoDockTools[15][16], Vina[17] and the UCSFChimera[18], free access, based on the Operating System Windows 7 Ultimate 64 Bits. The hardware used has an Intel® Core ™ i3-5005U CPU @ 2.0 GHz processor, 4 GB of RAM and 1000 GB of HD.

Obtaining the molecular structure of the ligand Bixin and the protein of HIV-1 Protease

In the first step, a search of the Bixin ligand structure was performed in the ChemSpider repository (http://www.chemspider.com/), where it was obtained by identification code ID 4444638 [19]. At the second moment, the protein structure of HIV-1 Protease was obtained from the Protein Data Bank repository (http://www.rcsb.org/pdb/home/home.do)[20], where it was deposited with the 1HSG code, which was generated $\gamma = 0.766$ Å, c = 46,710 Å, b = 87,070 Å, c = 46,710 Å, b = 87,070 Å, c = 46,710 Å, b = 87,070 Å, $\alpha = 90.00$ °, $\beta = 90.00$ °, $\gamma = 90.00$ °, being classified as Escherichia coli HIV-1 protease consisting of two chains (A and B), complexed with the ligandIndinavir (MK1) [21].

Ligand Preparation, Protein Preparation and Molecular Docking

The Mopac (Molecular Orbital Package)[14-15] is a semiempirical quantum chemistry software for the prediction of chemical properties and chemical reaction modeling, used by chemists and biochemists for research and teaching, running on Windows®, Linux and Macintosh platforms. In the present study, the binder molecule was optimized in the Mopac software, Version 16.111W [15], configured to use the semi-empirical PM7 (Parametric Method 7) [22] using the Hartree- Fock (HF) (self-consistent field method), for wave function, considering the molecule in the ground state and in the vacuum [23]. Later, both the binder and the protein were prepared in the AutoDockTools software, aiming to obtain the files in PDBQT format, in which the residues (MK1 and HOH) were removed from the protein and added the polar hydrogens, essential for the formation of H After the preparation of the HIV-1 Protease ligand and protein, the molecular docking was performed using the AutoDockTools software, AutoDockVina: Vina command prompt.

III. RESULTS AND DISCUSSIONS

Using the AutoDockTools software, it was possible to visualize the three-dimensional structure of the HIV-1 Protease 1HSG Protease (Fig. 1), as well as visualize the added polar hydrogen atoms.

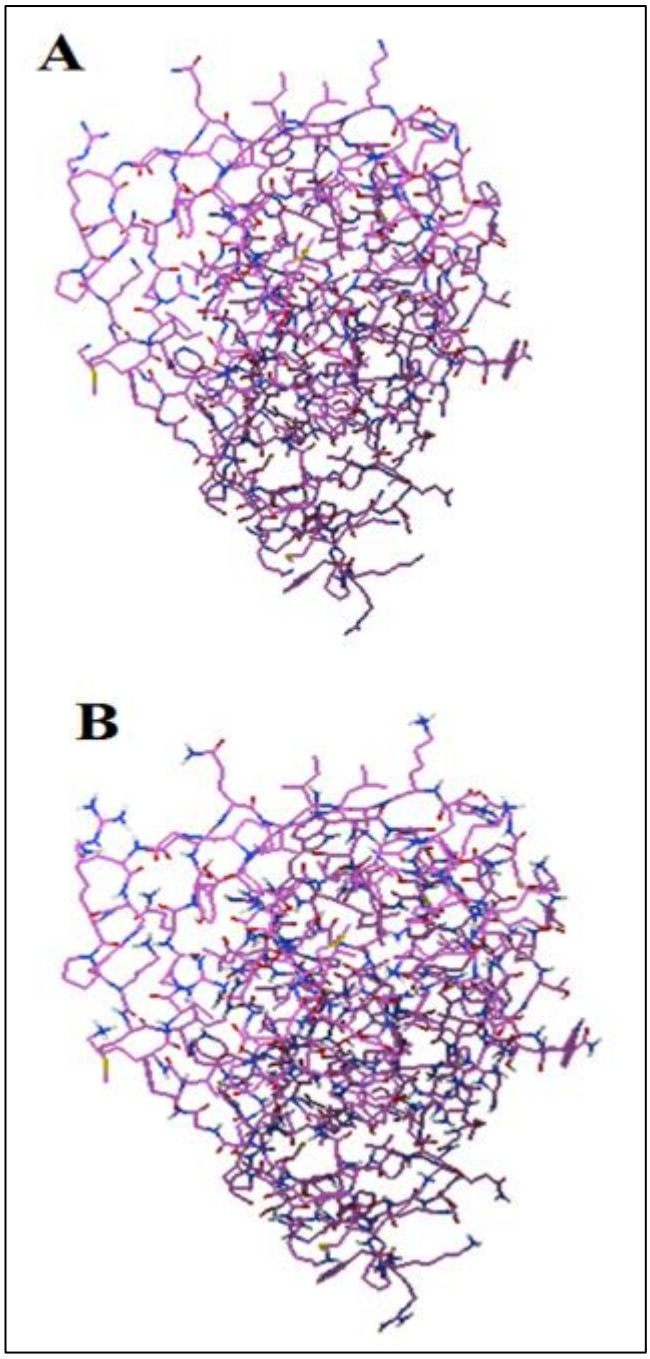

Fig.1 Visualization of the three-dimensional structure of the HIV-1 Protease 1HSG Protease(A). Visualization of the added polar hydrogen atoms(B)

The protein obtained directly from the Protein Data Bank repository comes with the complexed MK1 linker (Fig. 2), which is a drug used to treat HIV-1 Protease.

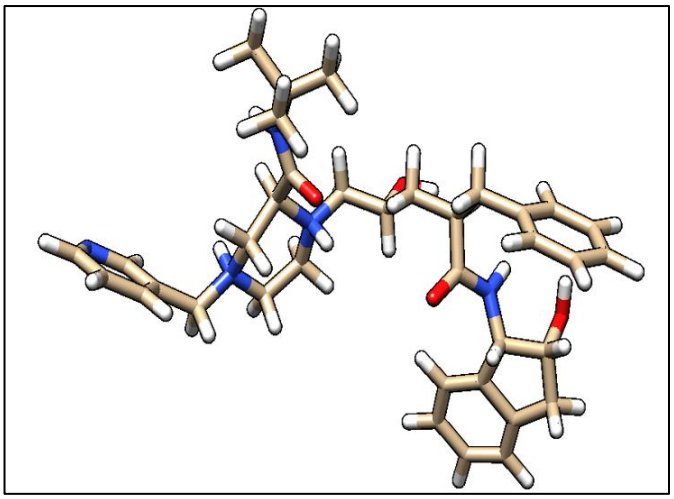

Fig. 2Ligand structure indinavir

This study focuses on the analysis of the inhibitory potential of the Bixin ligand (Fig. 3) compared to the ligand Indinavir (MK1) with the 1HSG protein through molecular docking.

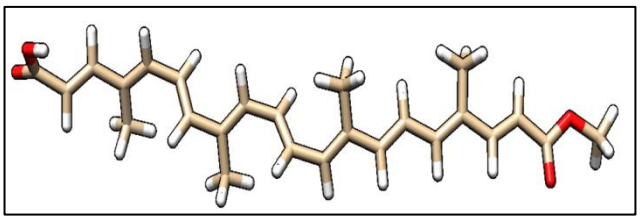

Fig. 3Ligand structure Bixin

In the molecular coupling, it is necessary to use the Grid Box (Fig. 4), which has the function of highlighting (delimiting) the region where the docking can be performed. For this, the grid box should involve all the protein.

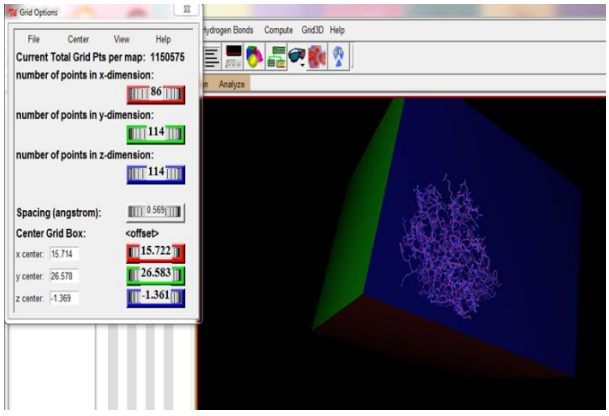

Fig. 4 View of the Grid Box involving HIV-1 Protease 1HSG Protease through AutoDockTools software.

From the UCSFChimera® software [18] it was possible to visualize the HIV-1 Protease 1HSG protein (Fig. 5), where it has only two amino acid chains, being the A chain (represented by blue color) and B chain (shown in red), it is also possible to observe MK1 (Indinavir) complexed at the center of the protein.

Fig. 5Visualization of the structure of the HIV-1 Protease 1HSG protein, visualized using UCSFChimera® software.

Fig. 6 shows the molecular docking between the Bixin ligand and the HIV-1 Protease 1HSG protein performed using the AutoDockTools, AutoDockVina: Vina command prompt. After the termination of the molecular coupling, the deviation between the ligand and the protein was analyzed, where RMSD values were calculated between the structures [24]. following values: RMSD lb 1320 Å and RMSD u.b. 2,029 Å, Affinity Energy of -3.3 kcal / mol and 21 active torsions.

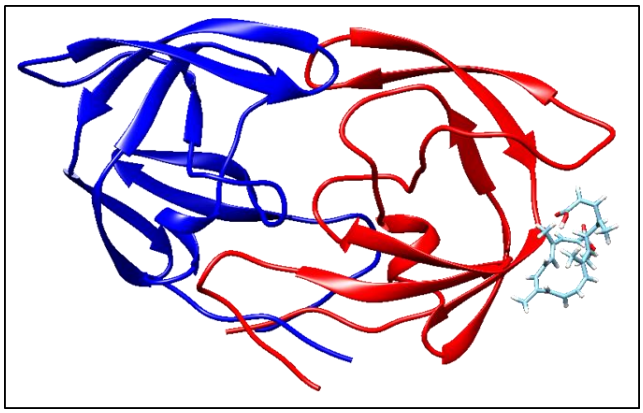

Fig. 6.Molecular docking between Bixin binder and HIV-1 Protease 1HSG Protease, visualized in Chimera software

Although bixin does not bind to the same region of the drug Indinavir (MK1), shown in Fig. 7, its RMSD and affinity energy values are consistent, evidencing bixin as a possible drug coupled with the treatment of HIV-1.

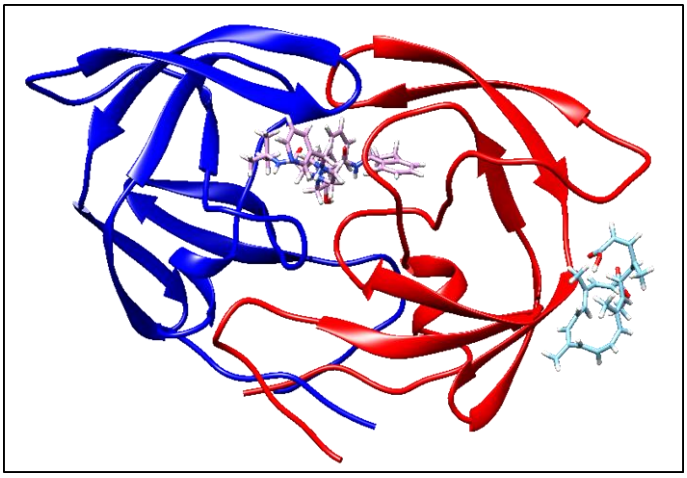

Fig. 7Visualization of the molecular coupling between the Bixin ligand and the HIV-1 Protease 1HSG Protease with complexed indinavir (MK1).

In the literature, an RMSD with value less than 2.0 Å indicates that the mode of binding of the protein-binding complex was correctly predicted. RMSD values of less than 2.5 Å are also considered good results [25]. Therefore, the Bixin-1HSG complex is within the standard proposed in the literature, presenting RMSD values l.b. 1320 Å and RMSD u.b. 2,029 Å (Fig. 8).

mode	affinity (kcal/mol)	dist from best mode rmsd l.b.	rmsd u.b.
1	-3.8	0.000	0.000
2	-3.3	1.320	2.029
3	-3.2	21.794	25.450
4	-3.0	3.617	5.869
5	-3.0	34.711	37.328
6	-2.9	50.938	53.529
7	-2.9	39.861	42.794
8	-2.9	21.589	25.961
9	-2.8	35.882	39.212

Fig. 8Affinity Energy Values and RMSDs of the coupling between the Bixin Binder and the 1HSG protein.

Fig. 9 demonstrates the molecular coupling between the Bixin binder and the 1HSG protein performed through the AutoDockTools, AutoDockVina [15-17]: Vina command prompt software. In that by means of the software Chimera it was possible to visualize the three smaller distances between the complex 1HSG-Bixin.

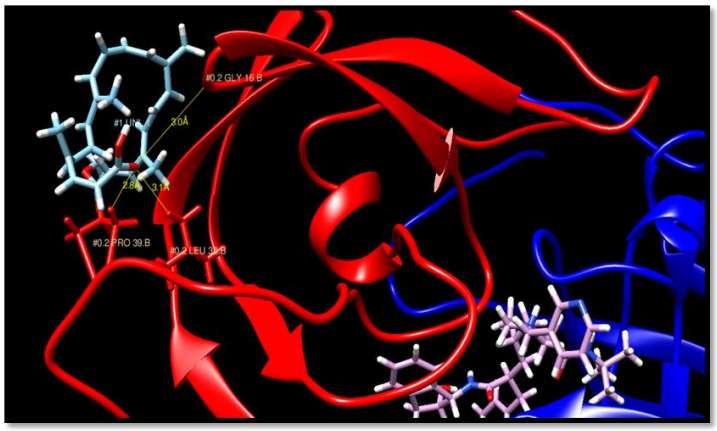

Fig.9 Molecular docking between the Bixin ligand and the HIV-1 Protease 1HSG Protein.

In Fig. 10 it is possible to observe that the oxygen atom of the Bixin ligand is closer to the amino acid PRO 39 (Proline), located in the B chain of the HIV-1 Protease protein at 2.8 Å of distance, being also a hydrogen bond , since the O atom is bonded to the hydrogen atom 2HD of amino acid PRO 39.B.

Atom 1	Atom 2	Distance
#1 UNL 1 O	#0.2 GLY 16.B 1HA	3.0Å
#1 UNL 1 O	#0.2 LEU 38.B 2HD2	3.1Å
#1 UNL 1 O	#0.2 PRO 39.B 2HD	2.8Å

Fig. 10 Distances found between the bixin binder and the 1HSG protein, making use of the Chimera software.

However, fig. 11 shows the hydrophobicity surface of the Bixin-1HSG molecular coupling.

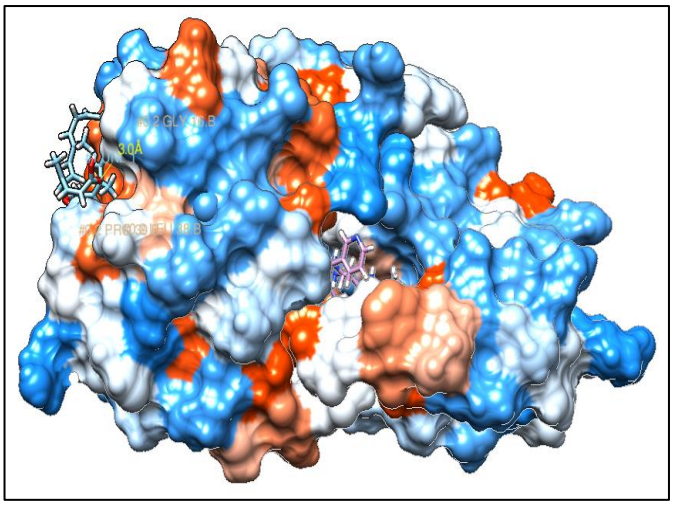

Fig.11 Visualization of the hydrophobicity surface of the ligand-protein complex.

In Figure 12, the lower H binding between the O atom and the Bixin ligand of 2.8 Å is interacting with the hydrophilic region of the protein, which is represented by the blue color.After the analysis of the obtained results, the ligand-protein interactions, demonstrated that the smaller distances obtained in the molecular docking of 2.8 Å and 3.0 Å between the protein and the Bixin ligand, indicate that the complex (receptor-binder) studied has potential to development of a new drug against HIV-1 Protease.

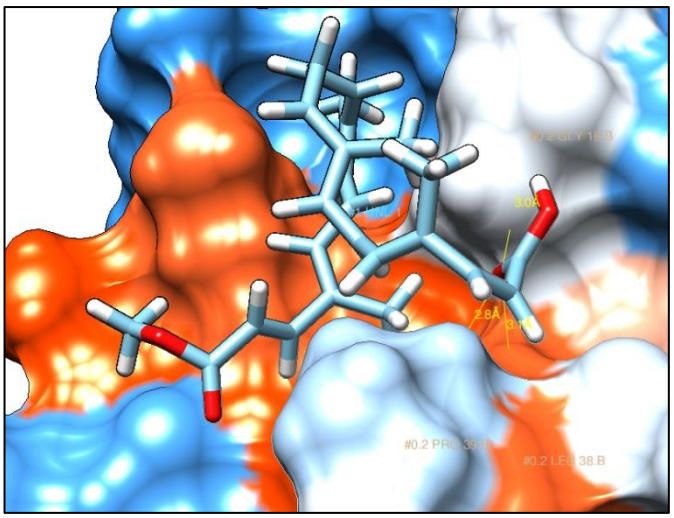

Fig 12 Bixin binding to the hydrophilic region of the HIV-Protease protein.

IV. CONCLUSIONS

From semi-empirical molecular optimization simulations using the Mopac software and molecular docking through the AutoDockTools, AutoDockVina: Vina command prompt, it was possible to determine the spatial orientation of the Bixin ligand and the HIV-1 Protease protein in than the lowest distances found in comparison with indinavir, thus evidencing the potential of bixin as a new inhibitor against HIV-1 Protease.

V. ACKNOWLEDGMENT

The State University of Ceará (PROPGPQ / UECE) for the support. This work was partly supported by the Cearense Foundation in Support of Scientific and Technology (FUNCAP), Coordination of Improvement of Higher Level Personnel (CAPES).

VI. REFERENCES

[1] MINISTÉRIO DA SAÚDE (2018). Departamento de Vigilância, Prevenção e Controle das IST, do HIV/Aids e das HepatitesVirais. Disponívelem: <http://www.aids.gov.br/pt-br/publico-geral/o-que-e-hiv>. Acesso: 07 mai. 2018.

[2] UNAIDS (Programa Conjunto das NaçõesUnidassobre HIV/AIDS) (2018). Ponhafim à epidemia de AIDS até 2030. Disponívelem: < http://www.unaids.org/es>. Acesso: 07 mai. 2018.

[3] Ministériodа Saúde, SecretariaemVigilânciaemSaúde, Departamento de DST, AIDS e HepatitesVirais. Protocoloclínico e diretrizesterapêuticas para manejo da infecçãopelo HIV emadultos. Brasília, 2013. Disponívelem: <http://www.aids.gov.br/pt-br/pub/2013/protocolo-clinico-e-diretrizes-terapeuticas-para-manejo-da-infeccao-pelo-hiv-em-adultos>. Acesso: 07 mai. 2018.

[4] UNICEF.; WHO.; UNAIDS. HIV/AIDS: Prevenção, tratamento, cuidado. Promovendo a UtilizaçãoRacional de Medicamentos e aAdministraçãoCorreta de CasosnosServiçosBásicos de Saúde (1998). Disponívelem: <https://www.unicef.org/prescriber/port_p16.pdf>. Acesso: 07 mai. 2018.

[5] Secretaria Municipal de Saudedo Rio de Janeiro (SMS/RJ). Guia de ReferênciaRápida, Infecçãopelo HIV e AIDS. Prevenção, Diagnóstico e TratamentonaAtençãoPrimária. 1ª Ed. Rio de

Janeiro, 2016. Disponívelem: < http://www.rio.rj.gov.br/dlstatic/10112/6552790/4176326/GuiadeReferenciaRepidaemHIV_AIDS_pagsimples_web.pdf>. Acesso: 07 mai. 2018.

[6] A. C. S., Vieira et al. "Aepidemia de HIV/Aids e a ação do Estado. Diferenças entre Brasil, África do Sul e Moçambique". R. Katál., Florianópolis, v. 17, n. 2, p. 196-206, jul./dez. 2014. Disponível: < http://www.scielo.br/pdf/rk/v17n2/1414-4980-rk-17-02-0196.pdf>. Acesso: 21 mar. 2018.

[7] K. A., Sepkowitz."AIDS - The first 20 years". The New England Journal of Medicine. v. 344, n. 23, p. 1764-1772, 2001. Disponívelem: < https://www.nejm.org/doi/full/10.1056/NEJM200106073442306#article_citing_articles>. Acesso: 07 mai. 2018.

[8] Ministérioda Saúde. Secretaria de VigilânciaemSaúde - Departamento de Vigilância, Prevenção e Controle das InfecçõesSexualmenteTransmissíveis, do HIV/Aids e das HepatitesVirais. BoletimEpidemiológico HIV AIDS 2017. ISSN: 1517-1159. Disponívelem: < http://www.aids.gov.br/pt-br/pub/2017/boletim-epidemiologico-hivaids-2017>. Acesso 07 mai. 2018.

[9] D. S.Wishart,C.Knox, A. C.Guo, S.Shrivastava, M.Hassanali, P.Stothard, &J.Woolsey."DrugBank: a comprehensive resource for in silico drug discovery and exploration". Nucleic acids research, 34(suppl_1), D668-D672, 2006.

[10] Drug, D. O. D. (2015). Drug Target Database. DrugBank database, version, 2.

[11] DRUGBANK (2018). Indinavir Identification. Disponívelem: < https://www.drugbank.ca/drugs/DB00224>. Acesso: 19 mar. 2018.

[12] J. M. Barbosa-Filho. "Bixaorellana: Retrospectiva de usospopulares, atividadesbiológicas, fitoquímica e empregonafitocosmética, no continente americano". SimpósioBrasileiro do Urucum—SIMBRAU, Joao Pessoa, 2006.

[13] J. J. Stewart."MOPAC: a semiempirical molecular orbital program". Journal of computer-aided molecular design, 4(1), 1-103, 1990.

[14] J. J. P. Stewart. MOPAC2016, version: 16.175 W. Stewart Computational Chemistry. Colorado Springs, CO, USA http://OpenMOPAC. net.

[15] M. F.Sanner, R.Huey, S.Dallakyan, S.Karnati, W.Lindstrom,G. M.Morris, ... &G.Vareille. AutoDockTools, version 1.4. 5. The Scripps Research Institute, La Jolla, 2007.

[16] R.Huey &G. M. Morris. Using AutoDock 4 with AutoDocktools: a tutorial. The Scripps Research Institute, USA, 54-56, 2008.

[17] O.Trott&A. J.Olson.AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. Journal of computational chemistry, 31(2), 455-461, 2010.

[18] E. F.Pettersen, T. D.Goddard, C. C.Huang,G. S.Couch, D. M.Greenblatt, E. C.Meng &T. E.Ferrin. UCSF Chimera—a visualization system for exploratory research and analysis. Journal of computational chemistry, 25(13), 1605-1612, 2004.

[19] J. Silva,A. R. Lima, L. L. Bezerra, M. M.Marinho, E. S.Marinho. "Bixinoids potentially active against dengue virus: a molecular docking study". International Journal of Scientific Research & Engineering, Volume 8, Issue 4, ISSN 2229-5518, April 2017.

[20] Bank, P. D. Protein Data Bank. Nature New Biol, 233, 1971.

[21] Z. Chen, Y. Li, E. Chen, D. L. Hall, P. L. Darke, C. Culberson & L. C. Kuo."Crystal structure at 1.9-A resolution of human immunodeficiency virus (HIV) II protease complexed with L-735,524, an orally bioavailable inhibitor of the HIV proteases". Journal of Biological Chemistry, 269(42), 26344-26348, 1994.

[22] P. O. Dral, X. Wu, L.Spörkel, A. Koslowski, W. Weber, R. Steiger& W. Thiel. "Semiempirical quantum-chemical orthogonalization-corrected methods: theory, implementation, and parameters". Journal of chemical theory and computation, 12(3), 1082-1096, 2016.

[23] A. R. Lima, E. M. Marinho, J. Silva, M. M. Marinho, M. M., &E. S. Marinho.Estudo in silico do flavonoideantitrombóticoternatin, presentenoscapítulosflorais de egletesviscosa less"macela-da-terra". RevistaExpressãoCatólicaSaúde, 2(1), 23-31. Acesso: 08 mai. 2018.

[24] J. Silva, A. R.Lima, L. L. Bezerra, M. M. Marinho, E. S.Marinho. "Molecular coupling study between the potential inhibitor of dengue fever, Annatto and Protein E (DENV-4)". International Journal of Scientific Research & Engineering, Volume 8, Issue 7, ISSN 2229-5518, July – 2017.

[25] E. A. Philot. “Desenvolvimento de um método/software (PL-DOCK) para o Docking Proteína-LiganteusandoAlgoritmosGenéticos e Biblioteca de Rotâmeros. SistemasAlvos: protease do HIV-1 e DiidrofolatoRedutase”. [Dissertação] Universidade Federal do ABC; Santo André – SP, 2010.