International Journal of Research in Engineering and Innovation (IJREI)
journal home page: http://www.ijrei.com
ISSN (Online): 2456-6934

Structure-activity relationship and virtual screening of monosubstituted lamivudine with HIV-1 reverse transcriptase

Ifeanyi Edozie Otuokere[1], Victor Okezie Ikpeazu[2], Kalu Kalu Igwe[3]

[1]*Department of Chemistry, Michael Okpara University of Agriculture, Umudike, Nigeria*
[2]*Department of Biochemistry, Abia State University, Uturu, Nigeria*
[3]*Dept of Vet Biochemistry, Animal Health and Production, Michael Okpara University of Agriculture, Umudike, Nigeria*

Abstract

Lamivudine, commonly referred to as nucleoside reverse transcriptase inhibitor (NRTI), is an antiretroviral medication used in the treatment of HIV/AIDS. We carried out molecular docking for five structurally diverse lamivudine analogues with HIV-1 reverse transcriptase using Patchdock and Firedock software servers. Extensive structure activity relationship work was carried out with these molecules. Lipinski drug likeness of lamivudine and its analogues were evaluated. These molecules were designed by substituting NH_2 with $CONH_2$, COPh, COOH and $COCH_3$ functional groups. The empirical binding free energy was used to estimate the inhibitory activity of protein-ligand complex. The binding energy for lamivudine- HIV-1 reverse transcriptase complex was -34.25 kcal/mol. The empirical free binding energies for $CONH_2$, COPh, COOH, $COCH_3$ analogues of lamivudine with HIV-1 reverse transcriptase complex were -41.57, -49.61, -39.55, and -40.44 Kcal/mol respectively. All the monosubstituted analogues of lamivudine, showed lower values than lamivudine. These lower values (more negative values), means that they show better inhibitory activity than lamivudine. All the compounds obeyed Lipinski rule of five. These results clearly indicated that the new substituents may be better antiretroviral medications. Synthesis and pre-clinical studies of these monosubstituted derivatives with HIV-1 reverse transcriptase complex is recommended in order to confirm their new potentials as better antiretroviral agent than the unsubstituted analogue.

Keywords: Lamivudine, Antiretroviral, Docking, Binding energy.

1. Introduction

Lamivudine, commonly referred to as nucleoside reverse transcriptase inhibitor (NRTI), is an antiretroviral medication used in the treatment of HIV/AIDS [1]. It is conjointly used to treat chronic viral hepatitis once other choices are not successful. It is effective against HIV-1 and HIV-2. It is generally employed in combination with other antiretrovirals nucleoside reverse transcriptase inhibitor and abacavir. NRTI is also enclosed as a part of post-exposure hindrance in those that are doubtless exposed to HIV. NRTI is taken orally as a liquid or pill [1]. Common side effects are cough, nausea, tiredness, diarrhea and headaches. Serious side effects are dairy product pathology and worsening viral hepatitis among those already infected. It is safe for folks over 3 months aged and may be used throughout physiological condition. The medication should be taken after meal. NRTI is a glycoside polymerase inhibitor and works by inhibiting the HIV polymerase and viral hepatitis enzyme [1]. Lamivudine was initially approved to be used within the United States in 1995 [2]. It is on the World Health Organization's List of Essential Medicines, the foremost effective and safe medicines required during a health system [3]. It is accessible as a generic medication [1]. In developing countries, the wholesale price is 0.06 USD per day [3]. As of 2015, in the United States the value for a typical month of medication rose above 200 USD [4]. Lamivudine has been used for treatment of chronic viral hepatitis at a lower dose than for treatment of HIV/AIDS. It improves the seroconversion of

Corresponding author: Ifeanyi Edozie Otuokere
Email Id: ifeanyiotuokere@gmail.com

e-antigen positive viral hepatitis and conjointly improves microscopic anatomy staging of the liver. Semi-permanent use of NRTI ends up in emergence of a resistant viral hepatitis virus. Despite this, NRTI continues to be used worldwide because it is well tolerated. Lamivudine is a structural derivative of cytidine. It can block (1 and 2) of HIV polymerase and additionally the polymerase of serum hepatitis virus. It is phosphorylated to active metabolites that vie for incorporation into deoxyribonucleic acid of the virus. They inhibit the HIV polymerase accelerator competitively and act as a series slayer of deoxyribonucleic acid synthesis. The dearth of a 3'-OH cluster within the incorporated glycoside analogue prevents the formation of the 5' to 3' phosphodiester linkage essential for deoxyribonucleic acid chain elongation, and thus, the infective agent deoxyribonucleic acid growth is terminated. Lamivudine is taken orally, and it is quickly absorbed with a bio-availability of over 80%. Some analysis suggests that NRTI will cross the blood–brain barrier [5]. NRTI is usually given together with azidothymidine (AZT), because it is extremely synergistic. NRTI treatment has been shown to revive AZT sensitivity of antecedently resistant HIV. There is no proof of carcinogenicity or mutagenicity of lamivudine in mice and rats at doses from ten to fifty eight times those utilized in humans [5]. The half-life of lamivudine in adults is 5 - 7 hours. In HIV-infected children the half-life is 2 hours [5].

2. Materials and Methods

2.1 Protein preparation

The three dimensional structure of HIV-1 reverse transcriptase was obtained from the Protein Data Bank, PDB ID – 1REV. The protein structure was subjected to a refinement protocol using Molegro Molecular Viewer [6].

2.2 Designing of structural analogues of lamivudine

The structure of lamivudine was drawn with ACD/ChemSketch software [7]. The structural analogues of lamivudine were developed with structural modifications with different substituents. The NH_2 group at position 4 in lamivudine was replaced with $CONH_2$, COPh, COOH and $COCH_3$ functional groups. The structures were built with ACD/ChemSketch software [7] and minimized with ArgusLab software [8].

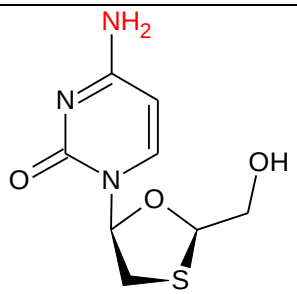
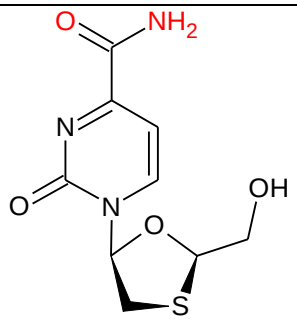
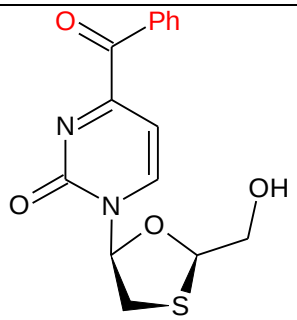
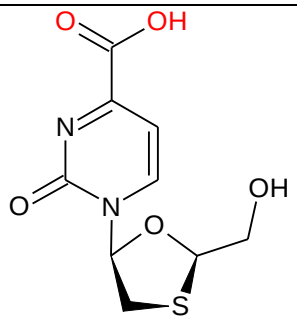
2.3 Molecular docking

Molecular docking was performed using Patchdock software [9]. Patchdock is a molecular docking algorithm based on shape complementary principles. The docking job was refined in Firedock software [10, 11] and processed with Molegro Molecular Viewer [6]. Lipinski rule of 5 was evaluated using molinspiration software [12]

3. Result and Discussion

Estimated free energy of binding (FEB) of lamivudine and its analogues are shown in Table 1. Assessments of drug-likeness of the pre-screened ligands are presented in Table 2. Crystal structure of HIV-1 reverse transcriptase is shown in Figure 1, while the docked lamivudine analogues with HIV-1 reverse transcriptase are presented in Figures 2a – 6a. The Hydrogen bonding and steric interactions are depicted in Figures 2b -6b.

Table 1: Estimated free energy of binding (FEB) of lamivudine and its analogues against HIV-1 reverse transcriptase

Substituents	Structure	Binding Energy (Kcal/mol)
NH_2 (Lamivudine)		-34.25
$CONH_2$		-41.57
COPh		-49.61
COOH		-39.55

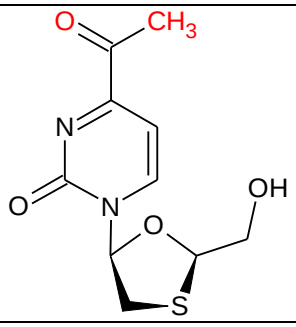
$COCH_3$		-40.44

Table 2: Lipinski rule of 5 and assessment of drug-likeness of lamivudine and its analogues

Property	Lamivudine derivatives				
	NH_2	$CONH_2$	COPh	COOH	$COCH_3$
LogP	-1.09	-1.64	1.00	-0.88	-0.56
TPSA	90.38	107.45	81.43	-0.88	81.43
No of atoms	15	17	22	17	17
Mol. Weight	229.26	257.27	318.35	258.25	256.28
No of H bond acceptors	6	7	6	7	6
No of H bond donors	3	3	1	2	1
No of violations	0	0	0	0	0
No of Rotatable bonds	2	3	4	3	3
volume	187.07	206.06	266.18	202.79	211.33

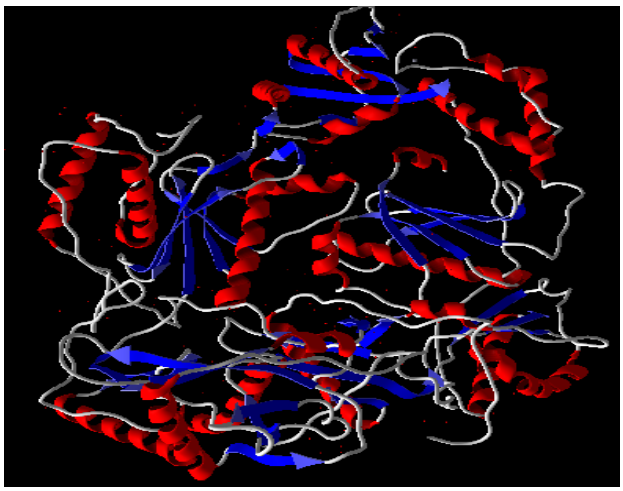


Figure 1: Crystal structure of HIV-1 reverse transcriptase, PDB ID – 1REV

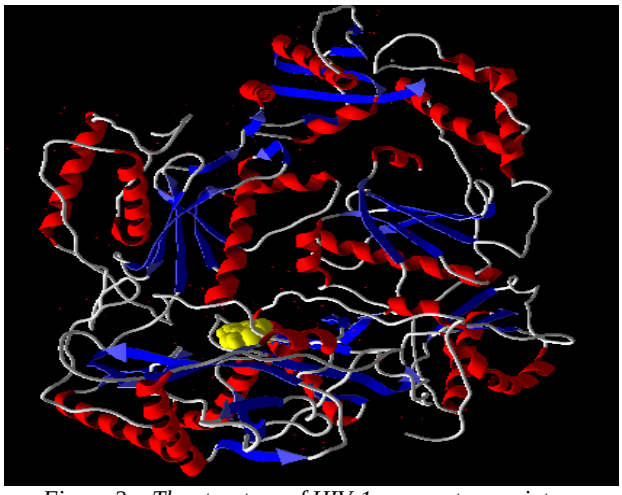


Figure 2a: The structure of HIV-1 reverse transcriptase complexed with lamivudine

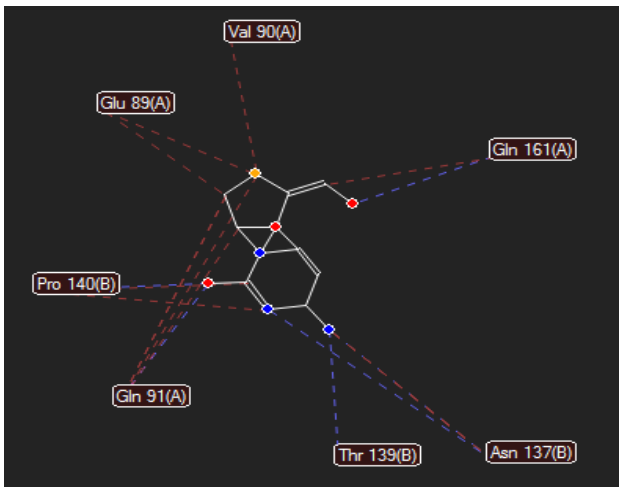


Figure 2b: Interactions of HIV-1 reverse transcriptase with lamivudine

Figure 3a: The structure of HIV-1 reverse transcriptase complexed with $CONH_2$ modified lamivudine analogue.

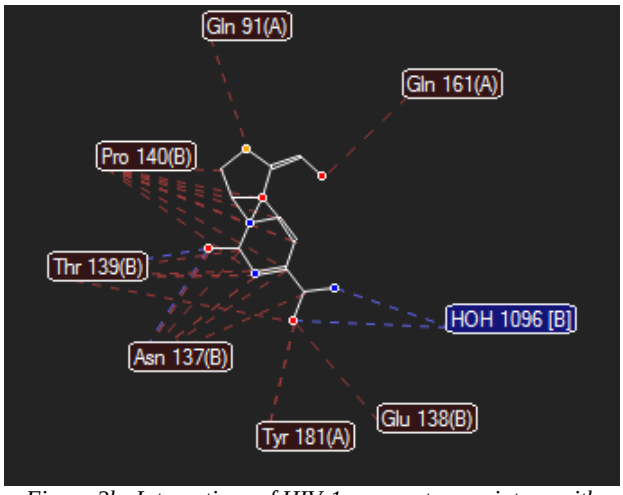


Figure 3b: Interactions of HIV-1 reverse transcriptase with $CONH_2$ modified lamivudine analogue.

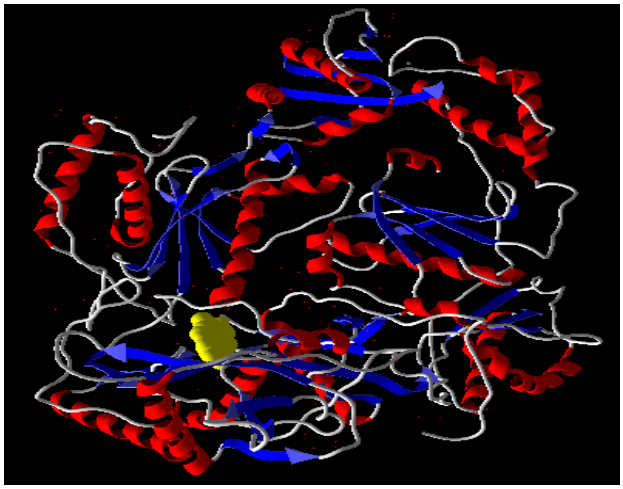


Figure 4a: The structure of HIV-1 reverse transcriptase complexed with COPh modified lamivudine analogue.

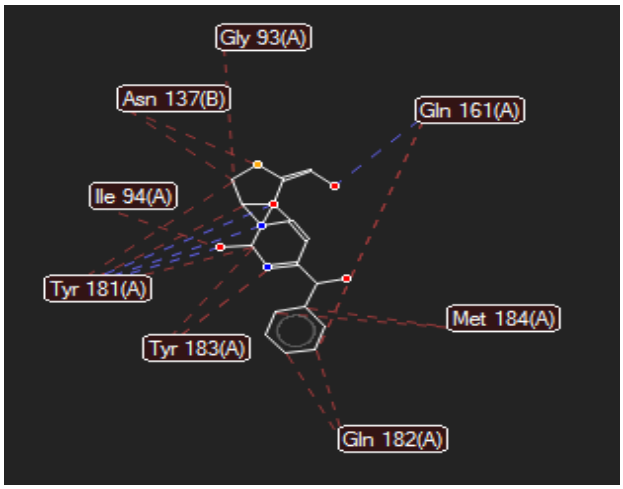


Figure 4b: Interactions of HIV-1 reverse transcriptase with COPh modified lamivudine analogue.

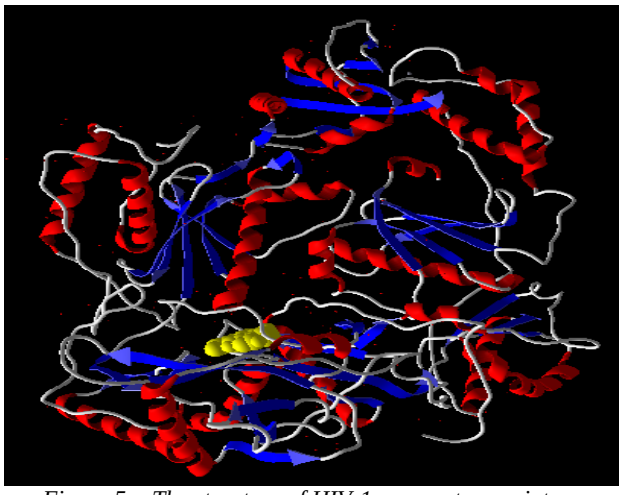


Figure 5a: The structure of HIV-1 reverse transcriptase complexed with COOH modified lamivudine analogue.

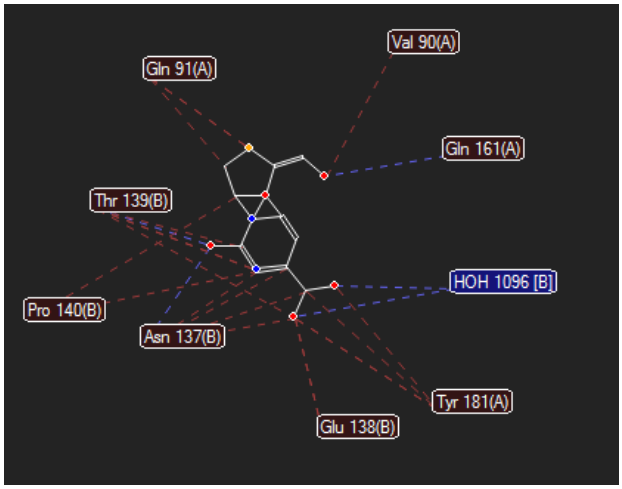


Figure 5b: Interactions of HIV-1 reverse transcriptase with COOH modified lamivudine analogue.

Figure 6a: The structure of HIV-1 reverse transcriptase complexed with $COCH_3$ modified lamivudine analogue.

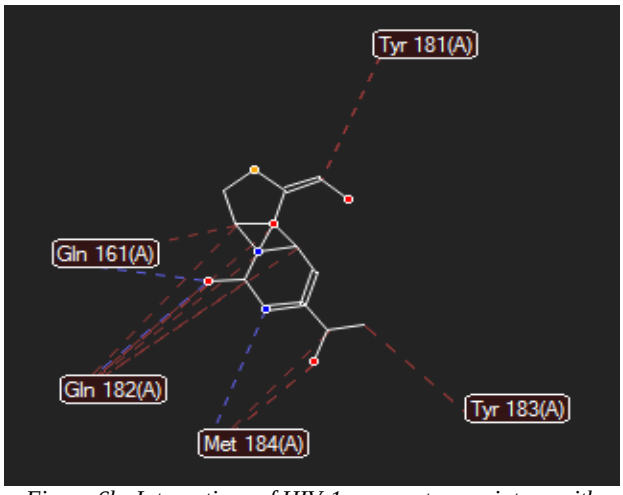


Figure 6b: Interactions of HIV-1 reverse transcriptase with $COCH_3$ lamivudine modified lamivudine analogue.

Estimated free energy of binding (FEB) of lamivudine and its analogues against HIV-1 reverse transcriptase are shown in Table 1. The negative values of the binding energy suggest that lamivudine and its analogues works by blocking HIV-1 reverse transcriptase. The lower values of the binding energy of lamivudine ($CONH_2$, COPh, COOH, $COCH_3$) analogues implies that they can block HIV-1 reverse transcriptase better than lamivudine. This confirms that the structural modification implemented in this study is significantly related to their activity. Also, this proved the reasonability and reliability of the docking results. It can be seen that substitution of NH_2 functional group of lamivudine with $CONH_2$, COPh, COOH, $COCH_3$ analogues at positions 4 lead to a decrease in the binding affinity. These results clearly indicated that before synthesis and biochemical testing of new analogues one can use molecular docking based methods for qualitative assessment of relative binding affinities for speeding up drug discovery process by eliminating less potent compounds from synthesis.

The Lipinski rule of 5 [13] for lamivudine and its analogues are shown in Table 2. Lipinski rule of 5 [13] helps in distinguishing between drug like and non-drug like molecules. It predicts high probability of success or failure due to drug likeness for molecules complying with 2 or more of the following rules: Molecular mass less than 500 Dalton; High lipophilicity (expressed as LogP less than 5);Less than 5 hydrogen bond donors ;Less than 10 hydrogen bond acceptors ;Molar refractivity should be between 40-130. Lamivudine and its modified analogues obeyed the Lipinski rule of 5 (Table 2). These filters help in early preclinical development and could help avoid costly late-stage preclinical and clinical failures.

The docking structures of all the compounds showed that they bind in a very similar pattern with the active site of HIV-1 reverse transcriptase, as is evident from the superposition of all the five analogues in Figures 2a – 6a.

Hydrogen bonding and steric interactions were observed in lamivudine and its modified analogues. Interactions of lamivudine with HIV-1 reverse transcriptase showed the involvement of Thr 139(B), Asn 137(B), Pro 140(B), Gln 91(A), Glu 91(A), Glu 89(A), Val 90(A) and Gln 161(A) (Figure 2b). Their binding energies are -5.0226, -3.7803, -15.5055, -15.5213, 3.3271, -10.7649, -2.7110 Kcal/mol respectively. Interactions of $CONH_2$ modified lamivudine analogue with HIV-1 reverse transcriptase showed the involvement of Gln 91(A), Glu 161(A), HOH 1096(B), Glu 138(B), Tyr 181(A), Asn 173(B), Thr 139(B) and Pro 140(B) (Figure 3b). Their binding energies are -10.9433, -3.7360, -5.6089, -0.3804, -3.6203, 3.7900, -0.4184 and -13.7121 Kcal/mol respectively. Interactions of COPh modified lamivudine analogue with HIV-1 reverse transcriptase showed the involvement of Gly 93(A), Glu 161(A), Met 184(A), Gln 182(A), Tyr 183(A), Tyr 181(A), Ile 94(A) and Asn 137(B) (Figure 4b). Their binding energies are -2.8213, -9.4943, -9.3011, -8.766, -20.9048, -11.6055, -3.6671 and 3.0917 Kcal/mol respectively. Interactions of COOH modified lamivudine analogue with HIV-1 reverse transcriptase showed the involvement of Gln 91(A), Val 90(A), Gln 161(A), HOH 1096(B), Tyr 181(A), Glu 138(B), Asn 137(B), Pro 140(B) and Thr 139(B) (Figure 5b). Their binding energies are -10.2148, -6.9242, -8.0095, -2.7793, 0.3825, 5.2814, -1.0330, -22.0068 and -3.8598 Kcal/mol respectively. Interactions of $COCH_3$ modified lamivudine analogue with HIV-1 reverse transcriptase showed the involvement of Gln 161(A), Gln 182(A), Met 184(A), Tyr 183(A) and Tyr 181 (A) (Figure 6b). Their binding energies are – 7.6782, -3.3739, -3.4671, -23.3384 and -12.3125 Kcal/mol respectively. These interactions were quite favorable due to negative free binding energy.

4. Conclusion

We carried out molecular docking for five analogous structurally diverse lamivudine analogues with HIV-1 reverse transcriptase using Patchdock and Firedock software servers. The empirical binding energy of lamivudine and its structurally diverse analogues were negative. The empirical binding energy of the structural analogues were found to be lower (more negative) compared to lamivudine. These lower values, means that they have better inhibitory activity. All the compounds obeyed Lipinski rule of five. These results indicated that the new drugs have very good binding affinity towards HIV-1 reverse transcriptase. Synthesis and pre-clinical studies of these monosubstituted derivatives with HIV-1 reverse transcriptase is recommended.

References

[1] "Lamivudine". The American Society of Health-System Pharmacists. Retrieved 31 July 2016.

[2] Therapy of Viral Infections, Topics in Medicinal Chemistry, Springer, vol. 15 2015, pp. 6.

[3] "Lamivudine". International Drug Price Indicator Guide. Retrieved 23 July 2016.
[4] H. Richart, Tarascon Pocket Pharmacopoeia, Deluxe Lab-Coat Edition. Jones & Bartlett Learning. 2015, pp. 65.
[5] "Epivir package insert" , GlaxoSmithKline. Retrieved January 20, 2011.
[6] Molegro Molecular Viewer 2.5, CLC Bio Company, 2012, http://www.clcbio.com.
[7] ACDLab ChemSketch, Advanced Chemistry Development, 2008, http://www.acdlabs.com
[8] M. A. Thompson , ArgusLab 4.0, Planaria Software LLC, Seattle, WA. http://www.arguslab.com.
[9] D. Duhovny , R. Nussinov and H.J. Wolfson, " Efficient Unbound Docking of Rigid Molecules", International Workshop on Algorithms in Bioinformatics vol. 2452 2002, pp. 185-200.
[10] E. Mashiach, D. Schneidman-Duhovny, N. Andrusier, R. Nussinov and H.J. Wolfson, "FireDock a webserver for fast interaction refinement in molecular docking", Nucleic Acids Res., vol. 36 2008, pp. 229 -292.
[11] N. Andrusier, R. Nussinov and H.J. Wolfson (2007) FireDock: fast interaction refinement in molecular docking. Proteins vol. 69 issue1 2007, pp. 139-159.
[12] Molinspiration Cheminformatics Nova Ulica SK-900 26 Slovensky Grob Slovak Republic.
[13] C.A. Lipinski, "Lead- and drug-like compounds: the rule-of-five revolution. Drug Discovery Today: Technologies, vol. 1 issue 4 2004, pp. 337-341.