Computational Studies of 1,2,3-Triazoles Derivatives against Yellow Fever Virus: DFT Based

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Abstract. Yellow fever virus belongs to a family called *Flaviviridae*. It is transmitted by some species of mosquitoes such as Sabethes, Haemagogus or Aedes mosquitoes. In this work, computational method was employed to study the cytotoxicity effect, drug potentials and inhibitory activities of some eight different triazoles derivatives against yellow fever virus protein receptor (1yks). All the compounds bind to the receptor with exceptional binding affinity of -9.7kcal/mol and -9.6kcal/mol from ligand 1b and 2a respectively. The two ligands also show high inhibition with the receptors as compared to the other ligands. In addition, all the ligands pass the Lipinski rule of five (RO5) and the quantum chemical calculations shows that all the ligands are of high stability with the receptor under investigation. Hence, the ligands are of good drug candidate towards any form of Yellow fever virus.

Keywords: DFT, Yellow fever, Docking, Triazoles, Descriptors

Introduction

Triazoles and some other heterocyclic compounds have been confirmed to have a good biological activity such as antibiotics (Mallikarjuna, et. al., 2012), antifungal (Yassin, 2010), anticancer (Jonathan, et. al., 2010), antimicrobial (Yogesh, et. al., 2019), anti-antitubercular (Luisa, 2002) e.t.c. hence; they are used in the synthesis of new drugs. Vicinal triazoles also known as 1,2,3- triazoles, are five membered and unsaturated heterocyclic compounds, the ring consists of three linked nitrogen atoms sequentially arranged with two carbon atoms. It molecular formula is $C_3H_3N_3$ (Xia, et. al., 2012). Triazoles derivative provides a very high stability even under strong oxidative and reductive environment and their ability to form hydrogen bonding improves their solubility which favors strong binding towards a protein receptor, through various mechanism like receptor-mediated mechanism and enzymatic action. Also 1,2,3- trizoles derivatives possess a very wide range of biological activities (Dalvie, et. al., 2002). It has been used as inhibitor against various enzymes such as histone deacetylase, cysteine protease and alkalinephosphatase.

Apart from it inhibitory activities towards various enzymes, it has also been used in the preparation of glycoconjugates and even in DNA modifications such as deoxynojirimycin based imino sugars and nucleoprotein inhibitors (Divya, et. al., 2017). Some 1,2,3-triazoles derivatives also serve as a good synthetic intermediates in many industrial process such as corrosion inhibitors, agrochemicals, additives, pigments, metal chelators e.t.c which shows it application has a very broad spectrum (Rostovtsev, et. al., 2002).

Infectious diseases have been a serious threat to humans and these are caused by pathogenic microorganisms, such as bacteria, viruses, parasites or fungi; the diseases can be transferred from one person to another either directly or indirectly. Bacteria such as gram-positive pathogens (*S.aureus and S.pneumonia*) and gram negative pathogens (*E. coli, P. aeruginosa and S. typhi*) causes serious infection and are also responsible for most hospital workers, patients and community infections (Waggoner, et. al., 2018). It has been statistically established that more than 700,000 drug resistant pathogens related death occur annually and

as a result urgent attention is required in proffering solutions to various antibiotic resistant organisms by designing new drugs that will be more potent and effective on such organisms (Xu, et. al., 2019). Flavivirus result in to yellow fever, a disease which is transmitted when infected mosquito from human with the virus bites another human. The disease as a non-contagious one is caused by arthropod-borne virus which belongs to a family called *Flaviviridae*. It symptoms includes fever, myalgia, headache, lack of appetite, bradycardia, vomit, abdominal pain, jaundice, bleeding etc (Vasconcelos, 2003). It is on this note, this research work is structured towards investigating quantum chemical and molecular descriptors responsible for the biological activity of some eight different 1,2,3-triazoles derivatives and also study their interactions with yellow fever virus protein receptor with PDB code 1yks using DFT and docking method.

Materials

The eight compounds used in this work were obtained from the literature (Rajesh, et. al., 2019). ChemDraw Ultra 12.0 version was used to model the 2D structures and to give the IUPAC nomenclature of these compounds. The compounds are listed in the Figure 1.

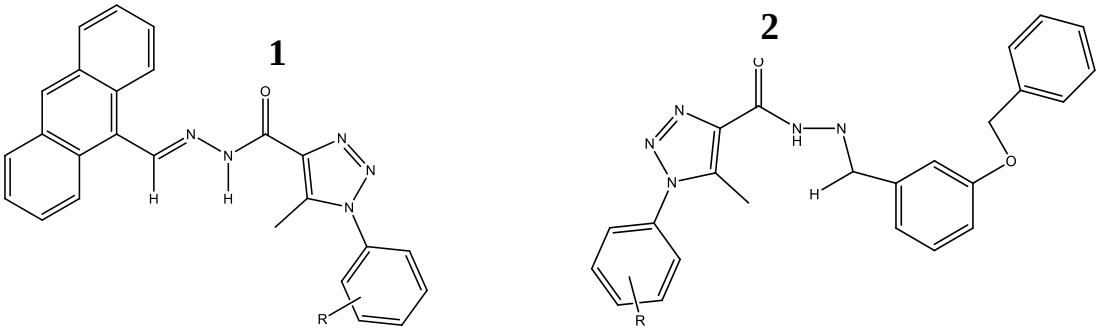


Figure 1. The 2D Model

1a;R = 4-Cl
1b; R= 4-F
1c; R = 2, 4-di Cl
1d; R = 2, 3 di Cl

2a;R = 4-Cl
2b; R= 4-F
2c; R = 2, 4-di Cl
2d; R = 2, 3 di Cl

The eight compound used in the study **1a** (N'-(anthracen-9-ylmethylene)-1-(4-chlorophenyl)-5-methyl-1H-1,2,3-triazole-4-carbohydrazide), **1b** (N'-(anthracen-9-ylmethylene)-1-(4-fluorophenyl)-5-methyl-1H-1,2,3-triazole-4-carbohydrazide), **1c** (N'-(anthracen-9-ylmethylene)-1-(2,4-dichlorophenyl)-5-methyl-1H-1,2,3-triazole-4-carbohydrazide), **1d** (N'-(anthracen-9-ylmethylene)-1-(2,4-dichlorophenyl)-5-methyl-1H-1,2,3-triazole-4-carbohydrazide), **2a** (N'-(3-(benzyloxy)benzyl)-1-(4-chlorophenyl)-5-methyl-1H-1,2,3-triazole-4-carbohydrazide), **2b** (N'-(3-(benzyloxy)benzyl)-1-(4-fluorophenyl)-5-methyl-1H-1,2,3-triazole-4-carbohydrazide), **2c** (N'-(3-(benzyloxy)benzyl)-1-(2,4-dichlorophenyl)-5-methyl-1H-1,2,3-triazole-4-carbohydrazide) and **2d** (N'-(3-(benzyloxy)benzyl)-1-(2,3-dichlorophenyl)-5-methyl-1H-1,2,3-triazole-4 carbohydrazide) were shown above. The 3D optimized models were shown in Figure 2.

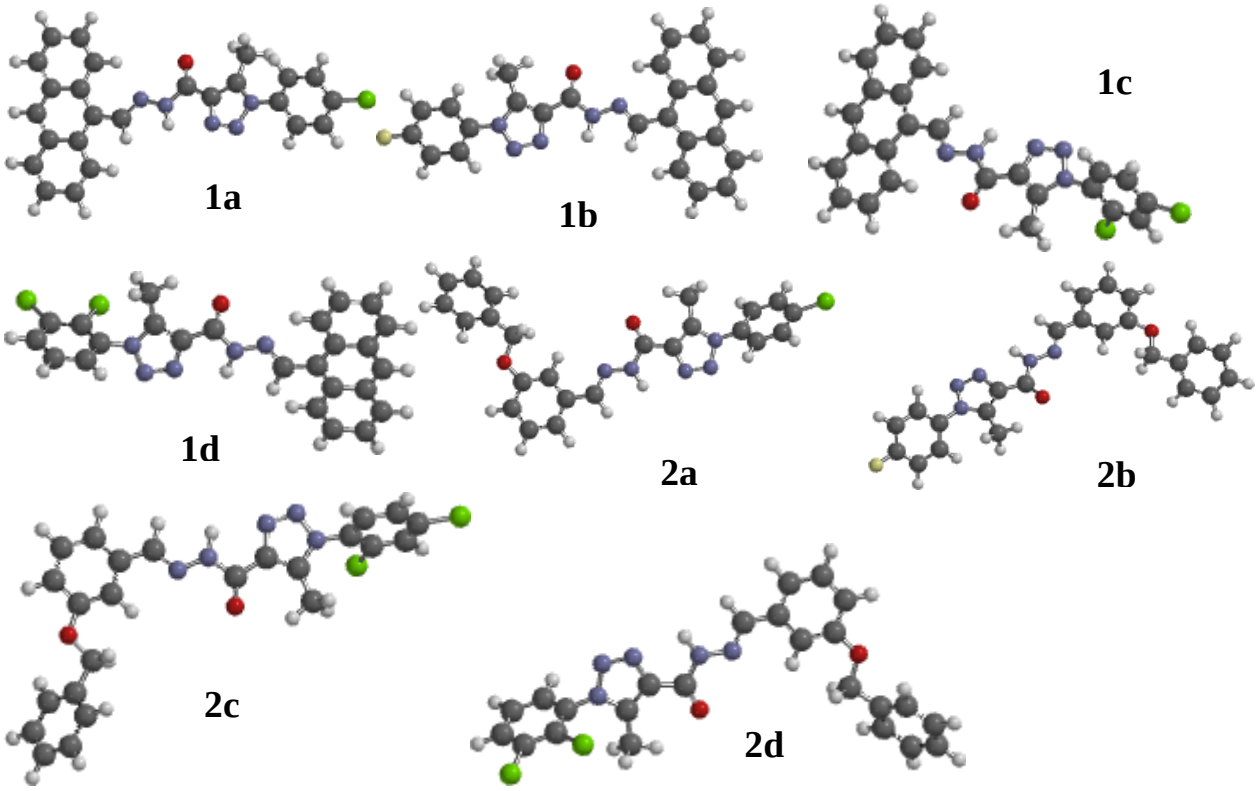


Figure 2. The 3D optimized model

Computational Procedure

Molecular modeling and descriptors. The eight 3D models (Figure 2) were built and all the calculations were performed using Spartan 14 by wave function Inc (Parr and Yang, 1989) on a personal computer Intel(R) Core i5 at 2.5GHz CPU. The 3D ball and spoke model of the eight compounds in the ground state (in vacuum) was then minimized and the best stable conformer of each compounds were obtained using Molecular mechanics. The compounds were then optimized using density functional theory (DFT) with 6-31G* basis set with algorithm hybrid B3LYP model (Becke's three parameter hybrid exchange functional with the Lee-Yang-Parr correlation functional) (Lee, et. al., 1989 & Becke, 1993). This is done to obtain the molecular descriptors such as partition coefficient, polar surface area, hydrogen bond donor, hydrogen bond acceptor and other quantum chemical properties of the compounds were calculated. All the 3D models were then saved as pdb file for further docking process. Other descriptors such as chemical hardness HOMO, LUMO, band gap, e.t.c were also calculated.

Molecular docking. In order to determine the binding affinity, inhibitory constant and to view the interaction that occurs between the protein receptor and the ligands, docking method is required. Bioinformatics tools were used and the protein receptor responsible for the yellow fever virus (1yks) was obtained from protein data bank (PDB) database. Protein data bank is the worldwide archive of most biological macromolecule. All the macromolecules in this database were determined using X-ray crystallography and NMR

method. The quality of the receptor used was evaluated using Ramachandran plot analysis through PROCHECK. The receptor was cleaned and free from water molecules, ligands, and other attachments that may hinder the docking process using Edu pymol version 1.7.4.4 and Discovery studio 4.1 visualizer which was also used to view and analyzed the docking result. The ligands were treated with Autodock tools version 1.5.6 and was also used to add hydrogen to the prepared protein receptor and then saved as pdbqt file format for the docking analysis. The same software was also used to determine the binding site of the receptor. Autoduck vina (Trott and Olson, 2010) with no graphical user interface was used for the docking process and the inhibitory constant k_i was then calculated from the obtained binding energy in kcal/mol.

$$k_i = e^{-\Delta G/RT} \quad (1)$$

Result and Discussion

Table 1 shows the molecular properties of the eight compounds built and optimized using Spartan 14 software. These properties are responsible for the quantitative structure-activity relationships (QSAR) and quantitative structure-property relationships (QSPR) analysis/modeling (Amalia and Lucia, 2018) and these properties accounted for the drug ability and cytotoxicity of any pharmaceutical drugs. The properties include Highest occupied molecular orbital (HOMO), Lowest unoccupied molecular orbital (LUMO), hydrogen bond donor (HBA), Hydrogen bond acceptor (HBD), partition coefficient (Log P), Area, volume, Polar surface area. These properties for the eight compounds are in agreement with the Lipinski rule of five (Cheng, et. al., 2007). That is, for a compound to be used as a drug candidate, the total number of nitrogen and oxygen atom count in the compound must not exceed 10, nitrogen-hydrogen and oxygen-hydrogen bonds must not exceed 5, molecular weight must be less than 500g/mol and partition coefficient (Log P) value must be less than 5. From the result presented in the table ligand 1a, 1b, 1c, 1d, 2a, 2b, 2c, 2d have molecular weight (amu) and log P of 439.91 and 2.32, 423.45 and 1.92, 474.35 and 2.88, 4.74.35 and 2.88, 445.91 and 3.20, 429.46 and 2.80, 480.35 and 3.07, 480.35 and 3.07 respectively with total number of oxygen and nitrogen count of 6 and 7. Also all nitrogen or oxygen to hydrogen bonds in the whole compounds are one. We can then say that the eight compounds pass Lipinski rule, hence they are good drug candidate. LUMO, HOMO and Energy gap were used to evaluate the reactivity and kinetic stability of two different species (reactants) and according to (Semire, et. al., 2012) and (Lofty, 2015) new molecular orbitals are formed when two orbitals of different reactant overlap each other, HOMO and LUMO energy is to allow a particular molecule to release and accept electrons easily most especially when the energy from HOMO and LUMO are high and low respectively. We could also observe from the result that all the compounds possess higher HOMO and lower LUMO energy value. Energy gap is obtained from HOMO and LUMO, this explains the kinetic stability of a protein–ligand complex.

Table 1. Cytotoxicity Parameters of the Eight Ligands

Molecular Properties	1a	1b	1c	1d	2a	2b	2c	2d
Molecular Weight (amu)	439.91	423.45	474.35	474.35	445.91	429.46	480.35	480.35
Polar Surface Area (PSA)	54.69	54.71	55.12	55.15	62.41	62.46	62.83	62.97
Hydrogen Bond Donor (HBD)	1	1	1	1	1	1	1	1
Hydrogen Bond Acceptor (HBA)	6	6	6	6	7	7	7	7
Log P	2.32	1.92	2.88	2.88	3.20	2.80	3.07	3.07

HOMO (eV)	-5.13	-5.11	-5.11	-5.10	-5.77	-5.75	-5.75	-5.73
LUMO (eV)	-2.05	-2.03	-2.04	-2.02	-1.55	-1.45	-1.55	-1.52
Energy gap (eV)	3.08	3.08	3.07	3.08	4.22	4.30	4.20	4.21

Low energy gap indicate the formation of protein-ligand complex of high stability and reactivity (Lofty, 2015). Therefore, the eight ligands 1a, 1b, 1c, 1d, 2a, 2b, 2c, 2d have energy gap (eV) of 3.08, 3.08, 3.07, 3.08, 4.22, 4.30, 4.20 and 4.21 respectively. Hence, complex formed from ligand 1a, 1b, 1c and 1d will be of high stability as compared to 2a, 2b, 2c and 2d because of their low energy gap. Polar surface area (PSA) of a ligands must be less than 140Å and below 60Å for a ligand to have high penetrating capacity into the cell membrane (Adejoro, et. al., 2016) the order of their penetrating power follows 2d > 2c > 2b > 2a > 1b > 1a > 1d > 1c. Compounds 1a – 1d will have a very good penetrating power as compared to 2a – 2d because of it PSA value less than 60Å.

Within the context of density functional theory (DFT), other chemical properties/descriptors such as chemical hardness (η), chemical potential and chemical softness (μ) are used in describing the thermodynamic process of a chemical reactivity, according to the partial differential equation (PDE) shown in equation 2:

$$\mu = \frac{1}{2}\left[\frac{\partial E}{\partial N}\right]_{v[r]} \quad (2)$$

Where E is the total energy of a system and N as the number of electrons at a constant external potential V(r). The equation above shows the first order partial derivatives of the variables stated above and this defines the chemical potential (μ). Also the second order partial derivatives of the same variables when external potentials remains constant gave the chemical hardness of a system according to the following equation (Lofty, 2015):

$$\eta = \frac{1}{2}\left[\frac{\partial^2 E}{\partial N^2}\right]_{v[r]} \quad (3)$$

Using finite difference method (FDM), chemical hardness and potential can be calculated as follows:

$$\eta = {}^{1}/_{2}\,[E_{HOMO} + E_{LUMO}] \quad (4)$$

$$\mu = {}^{1}/_{2}\,[E_{HOMO} - E_{LUMO}] \quad (5)$$

The level at which reactivity occurs can be quantify using chemical softness (S), it is the inverse of chemical hardness i.e,

$$S = \frac{1}{2\eta} \quad (6)$$

Nucleophilicity of a particular ligand according parr et al 1989 tells us the quantitative classification of the global nucleophile nature of a ligand. He further explain and proposed nucleophilicity index as an energy lowering measure as a result of electron flow between the donor and acceptor. Equation for nucleophilicity is represented below:

$$w = \frac{\mu^2}{2\eta} \quad (7)$$

Nucleophilicity (w) index explains the stability in energy when extra electron from the environment is added to the system (Lofty, 2015). All this descriptors as shown in Table 2 were obtained from Highest occupied molecular orbital (HOMO) and Lowest unoccupied molecular orbital (LUMO). From the result as presented in Table 2, we could observed that the chemical potentials of all the ligands are negative indicating that all the ligands are stable, therefore, they cannot undergo any decomposition.

Table 2. Chemical Hardness and softness, Ionization potential, Electronegativity and Nucleophilicity of the Ligands

Ligand Code	Chemical Hardness	Chemical Softness	Ionization potential	Electronegativity (μ)	Nucleophilicity (w)

	(η)	(S)			
1a	3.59	0.278	5.13	-1.54	0.330
1b	3.57	0.280	5.11	-1.54	0.332
1c	3.56	0.280	5.11	-1.54	0.333
1d	3.56	0.280	5.10	-1.54	0.333
2a	3.66	0.273	5.77	-2.11	0.608
2b	3.60	0.277	5.75	-2.15	0.642
2c	3.65	0.273	5.75	-2.10	0.604
2d	3.63	0.275	5.73	-2.11	0.613

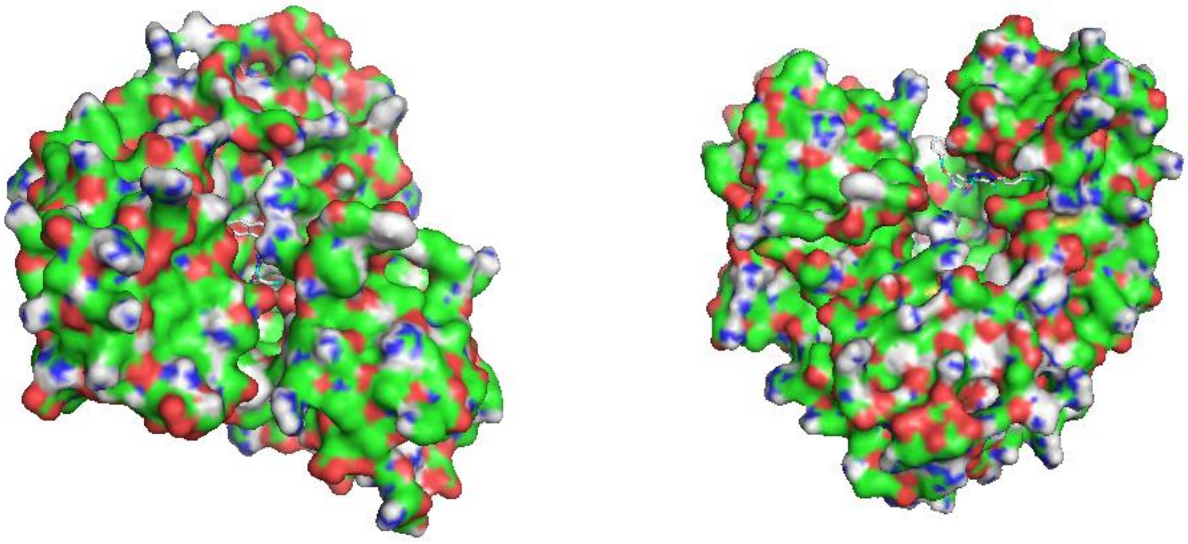
Since the calculated quantum chemical descriptors of the eight ligands presented in Table 2 are similar, we could also infer from the result that all the eight ligand will have similar stability and thermodynamic properties towards the protein receptors.

Docking Score Result

Table 3 shows the docking and scoring result of the eight ligands against yellow fever virus. During the docking, nine different conformations through monte carlo search process were obtained for each ligand with the receptor, the best and utmost binding conformation is the most negative value which in turn gave higher inhibition constant (k_i) which invariably shows that such a ligand have high tendency to inhibit a particular protein receptor responsible for certain diseases (Abel, et. al., 2019). All the ligands are good inhibitors with the receptor responsible for yellow fever virus (1yks) as they all shows very low affinity and higher inhibition constant (k_i) with exceptional inhibition value from ligand 1b and 2a. Hence, the two ligands have the greatest ability to inhibit the receptor (1yks). The result from the table also indicate amino acids residue at the biding site that actually contribute to the interaction of the ligands with the receptor. Figure 3 shows the surface representation and binding pocket of the ligands 1b and 2a respectively and the extent at which the two ligands bind to the receptor effectively, while from Figure 4, amino acids residue that involved in the interaction at the binding site were shown with hydrogen bond and hydrophobic interaction of the two ligands respectively. Figure 5 shows the Ramachandran plot of the protein receptor used in the study and from the plot we could observe that the protein receptor used is of a good quality.

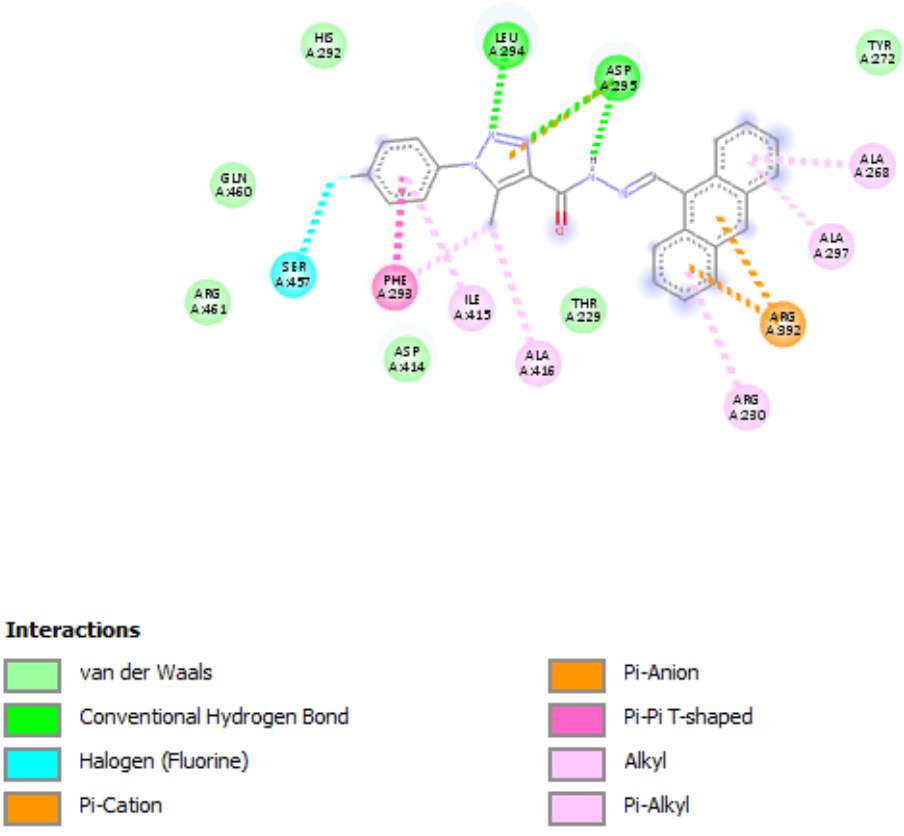
Table 3. Docking score result and Interaction between the Ligands and the Receptor (1yks)

	Affinity Kcal/mol	Inhibition constant (k_i)μM	Hydrogen Bond Interaction at the Binding Site	Distance
1a	-9.1	4.7×10^6	(i)ARG-604, LIG:H	(i) 2.69
1b	-9.7	1.3×10^7	(i)LEU-294, LIG:H (ii)ASP-295,LIG:H	(i) 2.03 (ii) 2.80
1c	-8.3	1.2×10^6	(i)SER-607, LIG: O	(i) 2.21
1d	-9.1	4.7×10^6	-	-
2a	-9.6	1.1×10^7	(i)ARG-604, LIG:H	(i) 2.65
2b	-9.0	4.0×10^6	-	-
2c	-9.2	5.5×10^6	(i)TYR-413, LIG:H	(i) 2.28
2d	-9.3	6.7×10^6	(i)LEU-294, LIG:H (ii) ASP-295, LIG:H	(i)1.96 (ii) 2.65

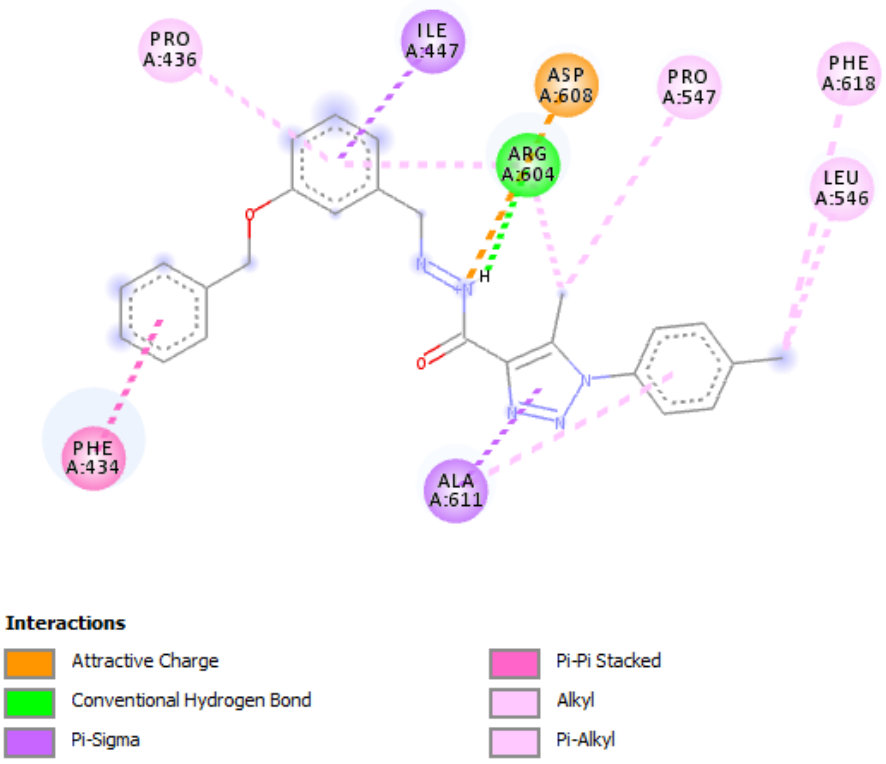


1b 2a

Figure 3. Surface Representation of Ligand 1b and 2a to the binding site of the Receptor



1a



1b

Figure 4. 2D Representation of the Ligand 1b and 2a binding to the amino residue at the binding site of the Receptor

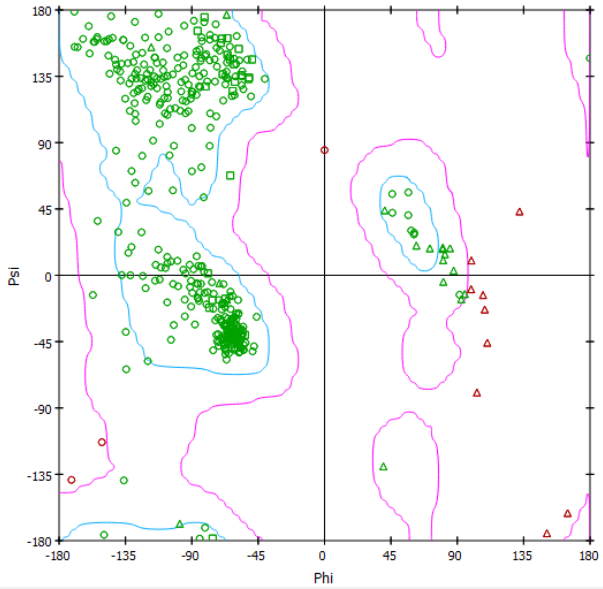


Figure 5. Ramachandran plot for Yellow fever virus (1yks)

Conclusion

The computational studies of 1,2,3- triazols derivatives reveals a reliable results showing that the eight compounds are promising chemical agent for combatting yellow fever. Hydrogen bonds contribute significantly to the receptor – ligand interactions and from the study, all the compounds shows a considerable amount of hydrogen bonding with the

receptor with a very high binding affinity and inhibition constants from ligand 1b and 2a. Therefore, the two ligands will outperform others when it comes to binding to the receptor responsible for yellow fever.

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