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Original Article

Theoretical Evaluation of the Potency of some Tetracycline Molecules as Anti-Brucella Agents: DFT and Molecular Docking Approaches

Dayo Felix LATONA[1]* and Oyeronke Damilola EESUOLA[2]

[1,2]*Department of Pure & Applied Chemistry, Osun State University Osogbo, Nigeria.*

**Corresponding Author: E-mail:* dayo.latona@uniosun.edu.ng

Phone No: +2348138780318

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ABSTRACT

Brucellosis is caused by an intracellar pathogens known as Brucella. It is a zoonotic disease that causes renal and cardiac failures in human beings and tetracycline is one of the prominent antibiotics employed as anti-brucella agent. In this research, molecular docking of some tetracycline molecules against Brucellosis protease was reported. In order to analyse the reactivities of the tetracycline molecules in vacuum and solvent phases, DFT reactivity descriptors of five Tetracycline molecules as anti-brucellosis at the B3LYP/6–311++G(d,p) level of theory was investigated. The inhibition based on the binding affinity values showed that inhibition was in the order: Anhydrotetracycline >Metatetracycline > Oxytetracycline > Tetracycline > Chlorotetracycline. Therefore, among the five tetracycline molecules studied, Anhydrotetrcycline is the most effective antibiotics for combating Brucellosis.

1. Introduction

Brucellosis is a disease caused by bacterial infection from animals to humans. It spreads by consuming raw or unpasteurized dairy. The symptom is fever and it is the main cause of osteoarthritis , renal and cardiac failures[1]. The six recognised Brucella species that are pathogenic to humans are Brucella Melitensis, B. abortus, B. suis and B. canis [2,3]. Human vaccines for brucellosis are still not licensed as a result animal vaccines are still being used for humans. However, identification and characterization of a suitable T cell epitope for combating Brucella SPP has been reported[4]. It is worthy of note that Brucellosis has been considered by the World Health Organization(WHO) to be one of the seven neglected zoonoses[5]. Brucellosis are facultative intracellular pathogens which are found predominantly in several organs like lungs, liver, bone marrow, synovium and spleen[6]. Total eradication of brucellosis will remain elusive as long as the natural reservoir (cattle, sheep, goat, humans) of brucella spp remains unprotected. It is worrisome that not a single attempt of clinical trial for Brucellosis have been reported to date [7]. However, antibiotics like tetracycline, trimethoprim-sulphamethoxazole, aminoglycosides, rifampicin, quinolones and chloramphenicol have been used for the treatment of Brucellosis in humans[8]. The present computation approach helps to ascertain the most effective antibiotic among tetracycline molecules for the treatment of human brucellosis strains.

2. Materials and Methods

2.1. Material

Quantum Chemical Method

The equilibrium geometries for the Tetracycline derivatives considered in this research were optimized at Density Functional Theory (DFT) with the standard 6-31G (d, p) basis set. The DFT method used consists of the three-parameter density functional, that includes Becke's gradient exchange correction and the Lee, Yang, Parr correlation functional (i.e. B3LYP)[9]. The sufficiency of polarized split-valence 6-31G (d,p) basis sets has been proved for calculation of the excited properties of ligands[10]. The optimized tetracycline structures were found to be suitable for docking with the Brucellosis

* *Corresponding author.* Tel.: +2348138780318
E-mail address: dayo.latona@uniosun.edu.ng
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protease. Consequently, the molecular parameters obtained are the LUMO, the HOMO, dipole moment and global molecular descriptors such as chemical hardness, softness and chemical potential.. All quantum chemical calculations were performed using Spartan '14 by wave function Inc.

The brucellosis receptor (PDB: 5u0c) was downloaded from protein data bank and cleansed. Discovery studio was used to clean the protein by removing water molecules and cofactors from it. The ligands and the receptor were converted to pdbqt format using auto dock tool 1.5.6.17. The grid box centre was (X = -22.233, Y = 26.468, Z = 72.634) and box size (X = 56, Y = 46, Z = 40). The spacing used was 1.00Å and docking was carried out using AutoDock Vina.

3. Results and Discussion

3.1. Molecular Descriptors

In this study, calculated molecular descriptors such as solvation energy, weight, hydrophobicity (Log P), volume (V), Area, polar surface area (PSA), ovality, dipole moment (DM), HOMO, and LUMO energies were obtained for the five tetracycline molecules (Tetracycline(T1), Oxytetracycline(T2), Metacycline(T3), Cholorotetracycline(T4) and Anhydrotetracycline(T5). The calculated HOMO for T1,T2,T3,T4 and T5 are -5.49 eV , -6.05 eV , -5.29 eV , -5.50eV and -5.44eV respectively. While the LUMO for T1, T2, T3, T4 and T5 are -2.04eV , -2.04eV , -2.05eV , -2.16eV and -2.05eV respectively. The realistic qualitative facts about the excitation properties of molecules are shown in the HOMO and LUMO descriptors [11]. Therefore, the calculated electronic descriptors band gaps which are essentially the left over ranges of energy not covered by any band as a result of the finite widths of the energy bands[12] was 3.45 eV, 4.01eV, 3.24 eV, 3.34 eV and 3.39 eV for T1, T2, T3, T4 and T5 respectively. The band gap is in the order; T2 < T1 < T5 < T4 < T3. The lower the band gap, the easier the excitation and the better the ability of a molecule to donate an electron (s) to the surrounding. Moreover, the log P values gives information on the tendency of a compound to dissolve in lipophilic (non-aqueous) solutions. However, for the compounds to permeate through the various biological membranes log P must not be more than 5. While lipophilicity gives clue to the distribution of a compound between non-aqueous and aqueous phase and therefore reveals the biological activity of ligands[13]. Furthermore, log P is an estimate of the lipophilicity of a compound[14]. Componds with high log P value greater than 5 may not have good oral absorption.[15]. The calculated log P are 3.65, 4.06 , 3.96 , 3.79, T4, and 3.14 for T1, T2, T3, T4 and T5 respectively. Suggesting that all the tetracycline compounds are effective in terms of lipophilicity. Ovality being the degree of deviation from perfect circularity of the cross section of the core or cladding of fiber[16] are 1.53, 1.52, 1.52, 1.54, and 1.52 for T1, T2, T3, T4 and T5 respectively. Furthermore, the dipole moment which is the product of the magnitude of the charge and the distance of separation between the charges[17] were calculated to be 11.1 debye, 13.13 debye , 9.72 debye , 9.93 debye and 10.24 debye for T5 for T1, T2, T3, T4 and T5 respectively. Since the nature of non-bonded interactions such as dipole – dipole interaction are relevant in ligand – receptor interactions; this has been accounted to contribute about 3 to 5 kJ/mol [18] to the ligand – receptor energy of interactions. However, large value of dipole moment has been attributed to the anomalous property of individual molecule [19]. Therefore compounds T1-T5 are desirable in term dipole moment values owing to their moderate values.

3.2. Docking and Scoring

The ligand - protein (receptor) intermolecular interactions are also investigated [20]. The docking simulation of each tetracycline compound (ligand) produced nine conformations and the best conformation was assumed to be the one with the least binding affinity in each docking. The binding affinities of interaction are shown in Table 1. Androtetracycline (T5) being the ligand with the least binding affinity is the most preferred tetracycline molecule studied for curing brucellosis as it is the best inhibitor ligand. The binding modes of the tetracycline compounds in the active sites of the enzyme shows that T1 has hydrogen bonding interaction with ARG A: 126 and unfavourable donor-donor interaction with THR A: 174 and a weak van der waal interaction with GLYA:124. T2 shows a pi- Anion interaction with GLU A: 82, three hydrogen bonding interaction with GLU A:96, GLY A:84, TUR A:94 and unfavourable donor-donor interaction with ALA A:87. T3 also showed three hydrogen bonding interactions with GLU A:82 , GLY A:122 and ALA A:87 and unfavourable donor-donor interation with GLY A:86 and piAlkyl interaction with TYR A:94 and ALA A:87. T4 shows two hydrogen bonding interaction with GLU A: 82, GLY A:122 and a pi-pi stacked with TYR A:94, TRP A:195 and an unfavourable donor-donor bonding with THR A:194. While T5 showed five hydrogen bonding interaction with TYR A:78, SER A:49, ARG A:52, THR A:101, TYR A:41 and a pi-Alkyl bonding and one van der waal interaction.

Table1: Docking scores of tetracycline molecules.

Ligand	Binding Affinity(kcal/mol)
T1	-7.80
T2	-8.20
T3	-8.60
T4	-7.60
T5	-9.10

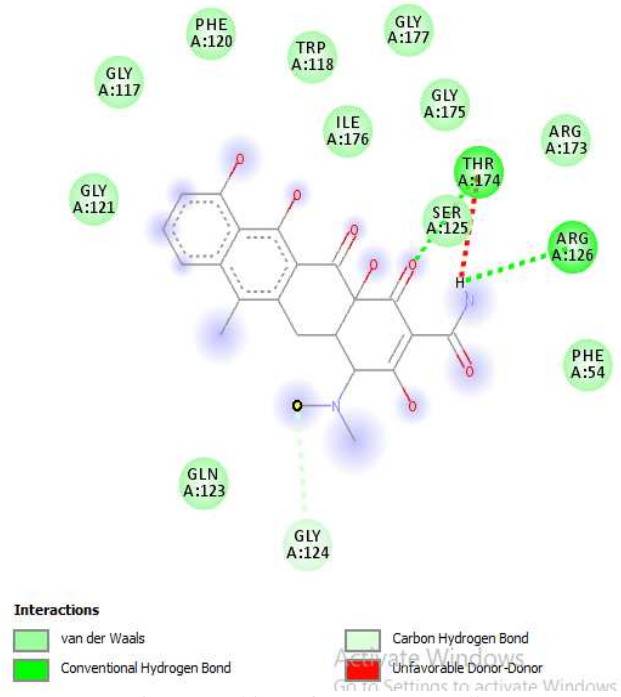

Fig 1. Docking of T1 (Tetracycline)

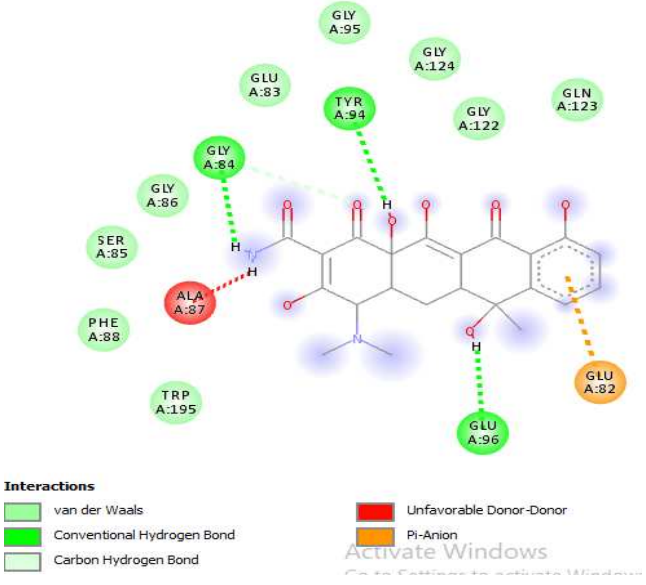

Fig 2. Docking of T2 (Oxytetracycline)

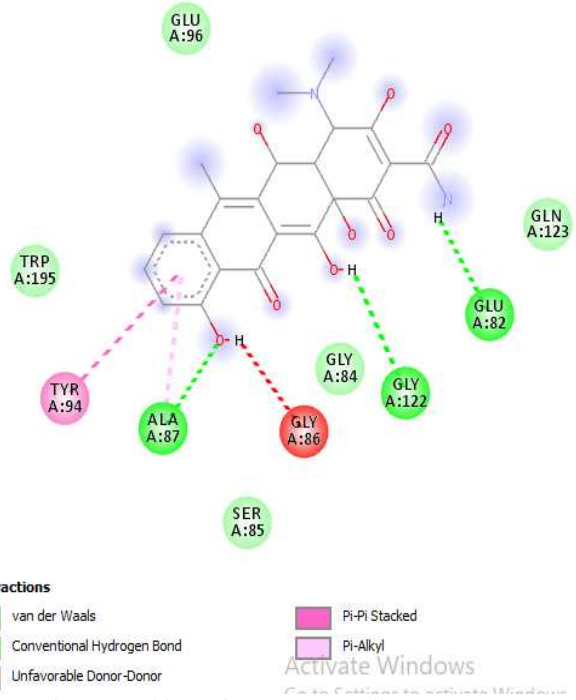

Fig 3. Docking of T3 (Metacycline)

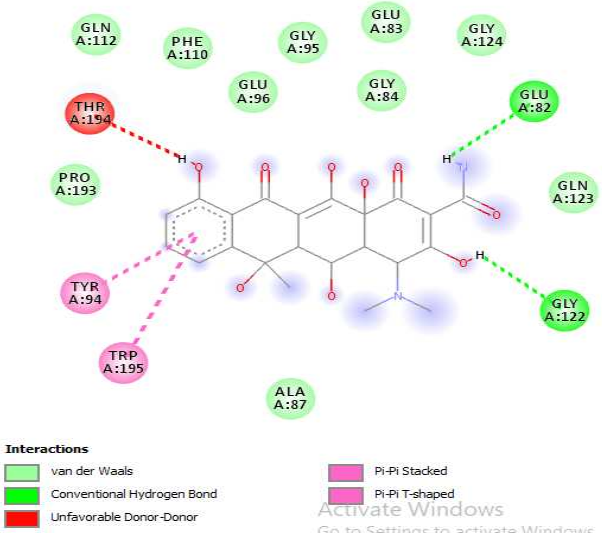

Fig 4. Docking of T4 (Cholotetracycline)

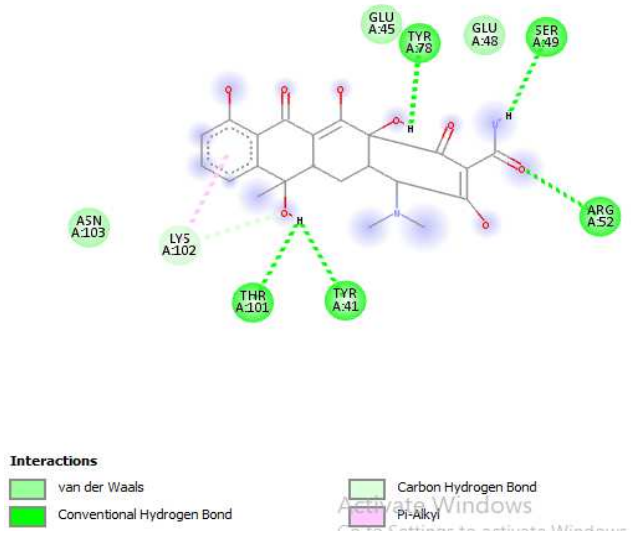

Fig 5. Docking of T5 (Anhydrotetracycline)

Tetracyclines remain to be important agents for the treatment of varieties of Antibacterial causing diseases. Anhydrotetracycline has been reported to be the first Tetracycline destructase inhibitor among the tetracycline molecules[21], It has been reported to be a viable tetracycline destructase that sets the stage for developing tetracyclines. Anhydrotetracycline exhibit bactericidal activity by targeting cytoplasmic membrane and has been found to be effective at lower concentrations than either tetracycline or doxycycline and has been shown to exhibit most potent binding with the repressor, 35-fold better than other tetracyclines[22].

4. Conclusion

Higher negative binding energy implies better stability of the complex. The negative values of binding energies observed in this research suggests that the ligands bound spontaneously with the receptor without consuming energy. Therefore, among the five tetracycline antibiotics investigated, However, contrary to the statement that Anhydrotetracycline is not a good antibiotic. This study has shown that Androtetracycline is the best inhibitor for combating brucella spp.

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Conflict of Interest

The authors declares no conflict of interest regarding this paper.

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