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Computational Studies on Syphilis protease inhibitors

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ABSTRACT: Syphilis is caused by a bacterium pathogen called Treponema Pollidum. It is the major cause of deaths among pregnant mothers in the third world nations and the incidence of congenital syphilis cannot be over-emphasized. However, antibiotics like Tetracycline have been reported to show tremendous antibacterial activity. Therefore, the anti-syphilis activity of some tetracycline molecules were investigated by molecular docking studies. The protein responsible for the bacterial disease was retrieved from protein data bank and docked against tetracycline compounds. Herein, we calculated several DFT reactivity descriptors for the five Tetracycline molecules at the B3LYP/6–311++G(d,p) level of theory in order to analyze its reactivity in vacuum and solvent phases. Theoretical B3LYP/6-31G (d , p) density functional theory has been employed to examine the electronic properties of donor-bridge-acceptor molecular system. Oxytetracycline, metacycline and chlorotetracycline showed high inhibition to the receptor with binding affinity of -9.6 kcal/mol. While tetracycline and anhydrotetracycline showed low inhibition with binding affinity of -7.6 kcal/mol.

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Keywords: Syphilis, Treponema Pallidum, congenital syphilis, antibiotics, inhibition, molecular docking.

Syphilis is caused by bacterium known as Treponema Pallidum and is transmitted either sexually or transmitted most especially from mother to child. The incidence of the disease has increased significantly over the last 10 years among homosexuals (Nyatsanzan and Tipple, 2016). It has tremendous effect on humans and the major cause of complicated pregnancy, still birth, intrauterine growth restriction and perinatal deaths (Genc and Ladger, 2000). Scientific reports revealed that it is the reason for 5% loss of pregnancies in Ethiopia (Schulz et al., 1990) and 24% of all still births in Zambia (Schulz et al., 1987). World Health Organization (WHO) estimates that each year maternal syphilis is responsible for 460,000 abortions and still births, 270,000 cases of congenital syphilis and premature babies (Finelli et al., 1998). Syphilis is more prevalent than HIV as reports showed that 115,045 persons were diagnosed with syphilis while 38,739 were infected with HIV in 2018. However, persons living with syphilis are susceptible to HIV infections (Pathela, 2005). The symptoms includes skin rash, pseudoparalysis, respiratory distress, bleeding and fever with the appearance of sore known as chancre on or around the external genitals or mouth (Davanzo et al., 1992). Antibiotics have proven to be effective in its care for syphilis. Single dose of benzathine penicillin prevents syphilis in asymptomatic patients (Radeliff et al., 1997) and the combination of benzathine penicillin and procaine have been used to treat asymptomatic congenital syphilis (Paryani et al., 1994). Moreover, doxycycline has been recommended as an alternative treatment of syphilis (Stamm, 2010). In fact doxycycline has been found to be effective regimen for the treatment of syphilis in Taiwan (Almeide et al., 2014). However, the continued occurrence of congenital syphilis has been reported to be indictment of the inadequate antenatal care services (Soloojee et al., 2004). Since antibiotics like penicillin and doxycycline have been found very potent in combating the bacterium, Treponema Pallidum, this research hopes to discover the best tetracycline antibiotic drug for curing syphilis by molecular docking approach.

MATERIALS AND METHODS

A personal laptop computer with the following specifications; 250 gigabyte hard drive, 8 gigabyte ram, 7th generation with intel core i5 processor was employed for the computational calculations. The selected compounds were optimized using Spartan, 14

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v 1.1.4 and the descriptors that described the antisyphilis protease activities were obtained. The optimized tetracycline compounds were docked into the active pocket of the main protease (PDB code: 6w637 using AutoDock 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 was set to be 1.00Å. The binding affinities and the molecular interaction for each complex were observed.

RESULTS AND DISCUSSION

Molecular Descriptors: Herein the 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 molecules of tetracycline molecules represented as Tetracycline (T1), Oxytetracycline(T2), Metacycline(T3), Chlorotetracycline(T4) and Anhydrotetracycline(T5) are shown in Table 1. The HOMO and the LUMO are vital descriptors that gives the excitation properties of molecules. The calculated HOMO are -5.49 eV for T1, -6.05 eV for T2, -5.29 eV for T3, -5.50eV for T4 and -5.44eV for T5 and the LUMO values are -2.04eV for T1, -2.04eV for T2, -2.05eV for T3, -2.16eV for T4 and -2.05eV for T5. Therefore, the difference in LUMO and HOMO which is the energy band gap are 3.45eV, 4.01eV, 3.24eV, 3.34Ev and 3.39eV for T1 to T2 respectively (Table 1). The band gap followed 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. Band gap plays a formidable role in protein – ligand interaction. Moreover, the calculated log P tells about the compound's ability to dissolve into lipophilic (non-aqueous) solutions. It is needed for the compounds to permeate through the various biological membranes. Lipophilicity unfolds the biological activity of ligands (Khaled et al., 2011). However, problems are likely to be encountered in oral absorption with compounds having log P >5 (Meanwell, 2011). The log P values obtained for the tetracycline compounds are 3.65, 4.06, 3.96, 3.79, and 3.14 for T1, T2, T3, T4 and T5 respectively. Therefore, all the tetracycline compounds are effective in term of lipophilicity. The calculated values for ovality which is the degree of deviation from perfect circularity of the cross section of the core or cladding of fiber (Leach, 2001) are 1.53, 1.52, 1.52, 1.54, and 1.52 for T1, T2, T3, T4 and T5 respectively. Also, the dipole moment which is the product of the magnitude of the charge and the distance of separation between the charges were obtained to be 11.1 debye , 13.13 debye , 9.72 debye , 9.93 debye and 10.24 debye for T1, T2, T3, T4 and T5 tetracycline compouds. Large value of dipole moment has been attributed to the anomalous property of individual molecule (Debenedetti, 2003). The moderate values of dipole moments for all the tetracycline made the values desirable.

Table 1: The calculated molecular descriptors from the compounds T1-T5 for anti-syphilis

M	HOMO (eV)	LUMO (eV)	Band gap	Log p	Dipole moment (Debye)	PSA	MW (amu)	HBD	HBA	Area (A^2)	Volume (A^3)	Ovality
T1	-5.49	-2.04	3.45	-3.65	11.40	145.62	444.44	6	10	407.11	407.03	1.53
T2	-6.05	-2.04	4.01	-4.60	13.13	157.50	460.44	7	11	411.03	413.23	1.53
T3	-5.29	-2.05	3.24	-3.96	9.72	139.63	442.42	6	10	401.12	402.99	1.52
T4	-5.50	-2.16	3.34	-3.79	9.93	144.02	478.89	6	10	419.30	420.60	1.54
T5	-5.44	-2.05	3.39	-3.14	10.24	127.52	426.43	5	9	395.18	394.97	1.52

**BG- Band gap, DM- Dipole moment, PSA- Polar surface area, MW- Molecular weight, HBD-Hydrogen bond donor, HBA- Hydrogen bond acceptor, A- Area, V- Volume.*

Docking and Scoring: The ligand - protein (receptor) intermolecular interactions was investigated. The docking simulation of each compound (ligand) produced nine conformations and the best conformation is assumed to be the conformation with highest free energy of binding (i.e. more negative value) for each docking. The free energies of interactions also known as binding energies for compounds T1-T5 are shown in Table 2. The binding affinity values are -6.70 kcal/mol, -6.90 kcal/mol, -6.90 kcal/mol, -6.90 kcal/mol, and -6.70 kcal/mol, -6.20 kcal/mol for T1, T2, T3, T4 and T5 respectively. The interaction between the ligand and the receptor are shown in figures 1-4. Interaction between tetracycline ligand and the protein receptor showed eight hydrogen bonds with four amino-acid residues involving VAL A:164, ILE A:140, ASP A:162 ALA A: 164 and two pi-sigma bonds with VAL A:141. Docking interaction with oxytetracycline showed five hydrogen bonds with ALA A:138, VAL A:164 and PHE A:142 and two unfavourable acceptor-acceptor bonds with ASP A:162 and a pi-sigma bond with VAL A:164 and two pi-Alkyl bonds with VAL A:164 and PRO A:165.

Furthermore, interaction between methycycline and the receptor showed eight hydrogen bonds with VAL A:164, PHE A:142, ILE A:140, ASP A:162 and ALA A:138 , one unfavourable donor-donor bond with PHE A:142 and an alkyl bond with VAL A:141.

Table 2: Docking scores of conformations of the studied tetracycline molecules.

Tetracycline Molecule	Binding Affinity(kcal/mol)
Tetracycline(T1)	-6.7
Oxytetracycline (T2)	-6.9
Metacycline (T3)	-6.9
Chlorotetraracycline(T4)	-6.9
Anhydrotetracycline (T5)	-6.7

Binding Interaction between Ligands and the receptor

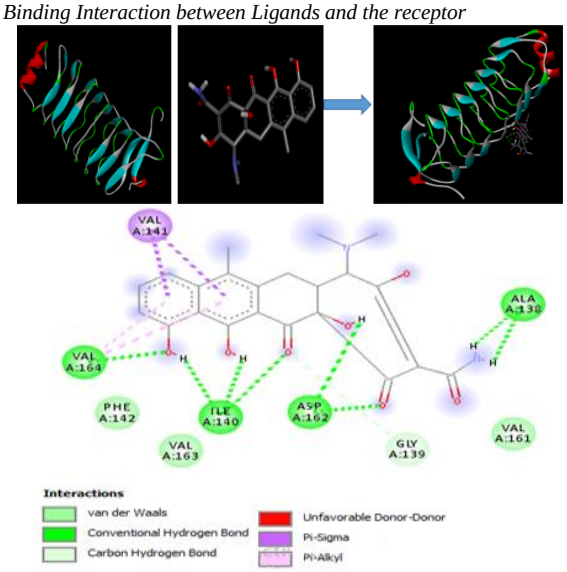


Fig 1: Molecular docking of tetracycline (T1)

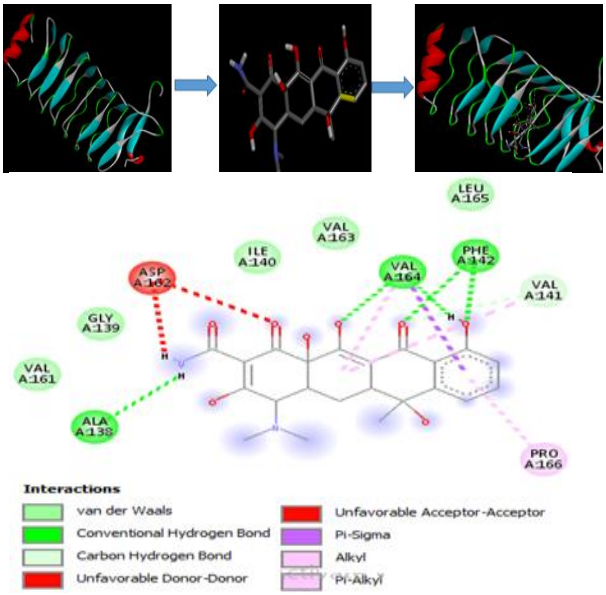
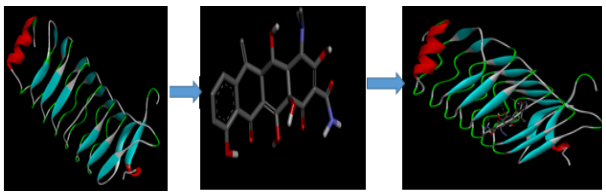


Fig 2: Molecular docking of Oxytetracycline (T2)



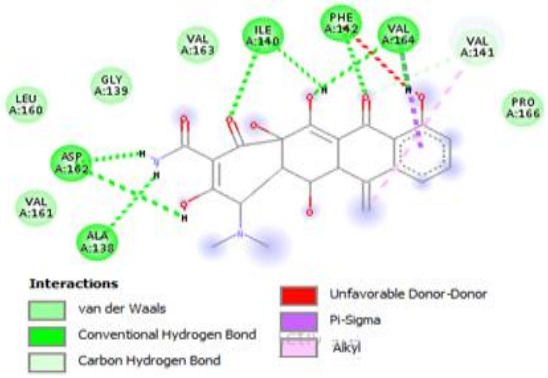


Fig 3: Molecular docking of Metacycline (T3)

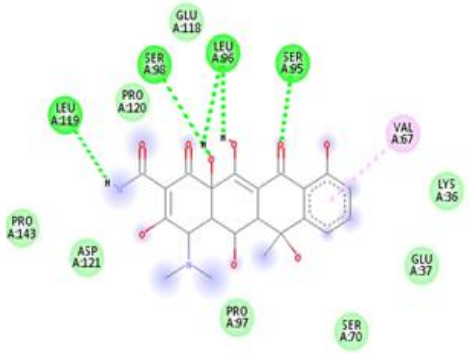
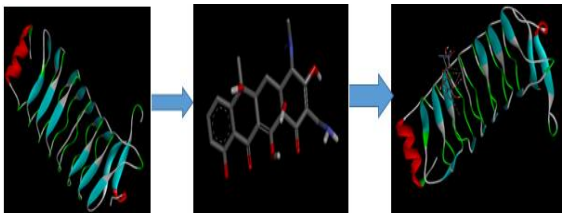


Fig 4: Molecular docking of Chlorotetracycline (T4)



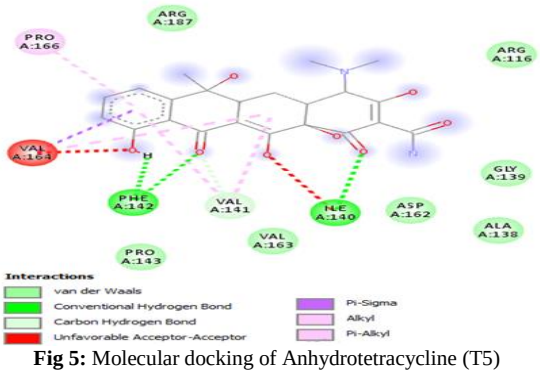


Fig 5: Molecular docking of Anhydrotetracycline (T5)

Chlorotetracycline interacted with the receptor via five hydrogen bonds with LEU A:119, SER A:90, LEU A:96 and SER A:95 and pi-alkyl interaction with VAL A:57. Moreover, anhydrotetracycline interacted with the amino-acid residue via three hydrogen bonds with PHE A:142 and ILE A:140, two unfavourable acceptor-acceptor bonds with VAL A:164 and ILE A:140 , three pi-alkyl bonds with PRO A:166, VAL A:141 and one pi-sigma bond with PRO A:166.

Conclusion: Syphilis is a disease that is prominently found in Africa. Hence, its total eradication cannot be over-emphasized. Antibiotics have been reported to be very potent as curatives. Herein, inhibition of the protein receptor by the ligands followed this order: oxytetracycline/metacycline/ chloroteracycline > tetracycline/anhydrotetracycline. Therefore, oxytetracycline, metacycline and chlorocycline exhibited high potency for combating syphilis than tetracycline and anhydrotetracycline.

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