Research Article
Volume 13:2,2020
DOI: 10.37421/jcsb.2020.13.307

Journal of Computer Science & Systems Biology

ISSN: 0974-7230+non

Open Access

In silico Molecular Studies of Selected Compounds as Novel Inhibitors for Phosphodiesterase-5 (PDE5) in the Management of Erectile Dysfunction

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Abstract

Erectile dysfunction is one of the major problems among men in today's world, and is characterized by trouble getting or keeping steady erection during sexual intercourse. Many drugs such as Viagra (a phosphodiesterase-5 inhibitor (PDE5)) are readily available in the market, but they are usually accompanied with numerous side effects such as headache, dizziness and vision problem. More so these drugs only offer short term remedy. Hence the need of finding a new remedy to arrest theseissues. In this study we utilized Schrodinger suite as the computational tool to screen about 2,000 compounds using PDE5 as target protein. Out of the 2,000 compounds screened, 6 leads compounds were found to be more potent compared toviagra based on binding affinity, with compound 6 and compound 4 exhibiting highest inhibitory attributes attaining docking score of -14.819 kcal/mol and -13.965 kcal/mol respectively. The hit molecules were further screened for ADME profiles. The outcome of this study revealed that several of the lead compounds are worth considering for further analysis.

Keywords: Docking studies • Viagra • Phosphodiesterase-5 (PDE5) • Erectile dysfunction • Binding affinity

Introduction

Erectile dysfunction is a type of sexual dysfunction attributed to incompetency to maintain a steady state of penis erection during sexual activity. It's estimated that erectile dysfunction affect about 10 millions in the United State of America, and approximately 150 million of the world population of men, making it possibly one of the most chronic health problem faced by men at the age of 40 and above [1,2]. Physical causes such as cardiovascular disease, diabetes mellitus and drug side effects can be identified in 80% of cases associated with erectile dysfunction [3]. Development of erection is a broad processing involving hormones, brain, blood vessels, muscle; and a problem with any of these can results to impotency, making it a difficult health challenge to mankind. Oxidative stress, excessive smoking and chronic alcoholism can worsen the erection of the penis [4]. It has also been suggested that erectile dysfunction may be an indicator of other diseases such as diabetes, hypertension, or atherosclerosis [5].

Phospodiesterase-5 is a cGMP-specific enzymes found in various tissues and mostly in the corpus cavernosum and the retina. It is a family of cyclic nucleotide PDEs that catalyzes cAMP and cGMP hydrolysis. L-arginine-nitric oxide guanylyl cyclase-cyclic guanosine monophosphate (cGMP) pathway act as smooth muscle relaxation, leading to penis erection. The endothelial cells secrete nitric oxide in the penis, where cGMP is produced. With this, relaxation of arterial muscle constitutes erection [6]. The key second messenger in the mediation of erection of the penis is cGMP, which is the primary substrate of PDE5.This implies that in men with erectile dysfunction,up regulation of cGMP in corpus cavernosum leads to erectile dysfunction and by downregulating cGMP-specific PDE5 gives an insight on improving erectile function with minimal side effect. In this case phosphodiesterase-5 is universally utilized as a therapeutic target in the management of erectile dysfunction.

Several inhibitors of phosphodiesterase-5 such as slidenafil (viagra) and tadalafil are orthodoxly accepted as standard medications for the treatment of erectile dysfunction [7]. These drugs function by blocking phosphodiesterase-5 from degradingits substrate, cyclic GMP in the smooth muscle cell, thereby dilating the corpora cavernosa of the penis [8]. In spite of their efficacy, side effect through post marketing monitoring include myocardial infarctions, low blood pressure, prolonged erections and hearing loss. Studies carried out in 2002 showed that Viagra and Cialis have the potential of increasing neurogenesis after stroke [9]. Another downside of these drugs is, it's short lived; and addiction remains one of the major problems among patients.

This study focused on the use of molecular docking to predict alternative compounds with druglike properties as inhibitors of the phosphodiesterase-5. Molecular docking is an interesting multidisciplinary field that provides understanding of drugbiomolecular interactions for rational drug design and discovery. It is a technique utilized to attain ligand-receptor complex with an optimized conformation and with the intention of possessing less binding free energy [10].

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Rec date: *20 January 2020;* ***Acc date:*** *13 March 2020;* ***Pub date:*** *20 March 2020*

Research Methodology

The computational tools used in present study are embedded in Schrodinger suites software(version 2018-4)on window operating system (Windows 10).

Ligand preparation

A library containing about 2,000 compounds with small molecular weights were used for this *insilico* studies. The preparation of the ligands was carried out using ligprep panel on Maestro 11.5 with an OPLS3 force field at pH 7.0 +/- 2.0 [11]. Desalt and generate tautomers options were selected and the stereoisomer computation was left to generate at most 32 per ligand. The output format was left as maestro.

Protein preparation

The protein, phosphodiesterase-5 with PDB ID: 1UDT was retrieved from RCSB directory (http://www.rcsb.org/pdb) and uploaded on the workspace of maestro 11.8. The downloaded protein was prepared via protein preparation wizard of Schrodinger suite. In preprocessing of the protein, bond orders was assigned, waters were deleted from 5.0 Å from het groups, het states was set at pH 7.0 +/- 2.0 [12]. Hydrogen bond was added, ions were removed. In the refine tab, H-bond network was optimized using PROPKA; water molecules with less than 3 H-bonds to non waters were removed [13]. The retrained minimization was carried out using OPLS3 force field with RMSD at 0.30 Å.

Receptor grid generation

The receptor grid file was generated using receptor grid generation panel, which represent the active sites of the receptor for glide ligand docking jobs. The ligand-binding site was defined by picking the co-crystallized ligand (viagra) of the protein structure on the workspace. The van der Waals radii of the receptor atoms with partial atomic charge was set scaling factor of 1.0 and partial cutoff of 0.25 to soften the potential for nonpolar parts of the receptor.

Molecular XP docking

The prepared library was docked into the active site of the protein (1UDT) using extra precision with the ligand sampling set generated as non refined. Prior to the docking of prepared compounds with PDE5, the co-crystallized ligand (viagra) is docked into the active site of the protein to predict the binding affinity and molecular interaction.

ADME predictions

The Absorption, Distribution, Metabolism, Excretion (ADME) and molecular properties of the lead compounds were predicted using Qikprop [14].

Validation of molecular docking results

The procedure for docking in this study was validated blasting the fasta sequence of PDE5database server of the CHEMBL. From the search result, bioactivities of compounds from the dataset with IC50 value of 671 and inhibition 962 of were downloaded. The file was edited using Microsoft excel to delete entries without pChEMBL Value. The saved file afterwards was uploaded on data warrior to convert the file format to sdf (2D structure). The compounds were prepared and docked with the same protein target used in this study. XP docking score of selected compounds were plot against pChEMBL Value to obtain r^2spearman correlation.

Results

Docking analysis

In the present study about 2,000 compounds were screened, and compounds with high docking score were picked. About six compounds have shown better binding affinity with PDES5 than Viagra. Compound 6 and compound 4 having the best Docking score. Docking scores of all the leads compounds and Viagra were listed in Table 1. Compound 6 and compound 4 has docking scores of -14.819 kcal/mol and -13.965 kcal/mol respectively. Among the leads compounds, compound 5 showed the least binding affinity with a docking score of -11.819 kcal/mol. In contrast the standard drug showed a docking score of -11.596 kcal/mol.

Table 1. Docking results with physico-chemical properties.

S.No	Entry name	IUPAC	Lipinski #violation	Docking Score	H-bond Acceptor	H-bond Donor	Molecular Weight	Rotatable Bonds
1	Compound 1	5-Hydroxy-6-methoxy-3-(4-methoxyphenyl)-4-oxo-4H-chromen-7-yl β-D-glucopyranoside	1	12.611	11	5	476.43	6
2	Compound 2	5-Hydroxy-6-methoxy-4-oxo-3-(2,4,5-trimethoxyphenyl)-4H-chromen-7-yl β-D-glucopyranoside	2	12.115	13	5	536.48	8

3	Compound 3	1,3,8,9-Tetrahydroxy-2-(3-hydroxy-3-methylbutyl)-4,7-bis(3-methyl-2-buten-1-yl)-11H-[1]benzofuro[2,3-b]chromen-11-one	1	-11.212	8	3	522.59	7
4	Compound 4	3-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-6-(2-hydroxy-3-methyl-3-buten-1-yl)-8-(3-methyl-2-buten-1-yl)-4H-chromen-4-one	0	-13.965	7	5	438.47	6
5	Compound 5	3-Methoxy-4-oxo-2-phenyl-4H-furo[2,3-h]chromen-6-yl β -D-threo-hexopyranoside	0	-11.89	10	4	470.43	5
6	Compound 6	(2S)-2-(2,4-Dihydroxyphenyl)-5,7-dihydroxy-8-(5-hydroxy-2-isopropenyl-5-methylhexyl)-2,3-dihydro-4H-chromen-4-one	0	-14.819	7	5	442.5	7
7	Compound 7	(2S)-2-(2,4-Dihydroxyphenyl)-5,7-dihydroxy-8-(5-hydroxy-2-isopropenyl-5-methylhexyl)-2,3-dihydro-4H-chromen-4-one	0	-12.068	7	2	466.52	5
8	Viagra	5-{2-Ethoxy-5-[(4-methyl-1-piperazinyl)sulfonyl]phenyl}-1-methyl-3-propyl-1,4-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one	0	-11.596	8	1	474.58	7

The hit molecules (Figure 1) were further accessed for interacting profiles with the protein target.

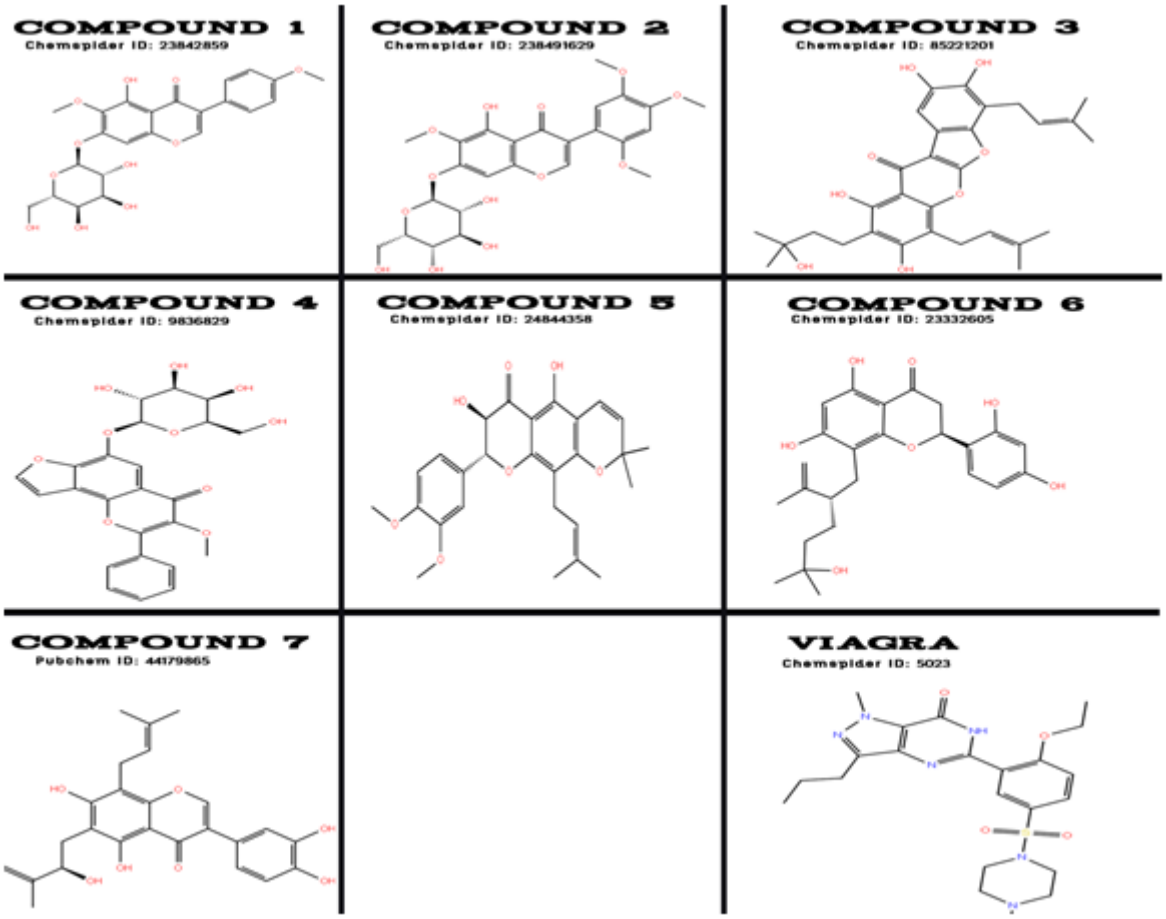

Figure 1. 2-D structure of hit compounds and standard drug.

Figures 2-9 showed the electrostatic potential at the surface of the active site of PDES-5 bound with lead compounds and standard drug (The green stick model).

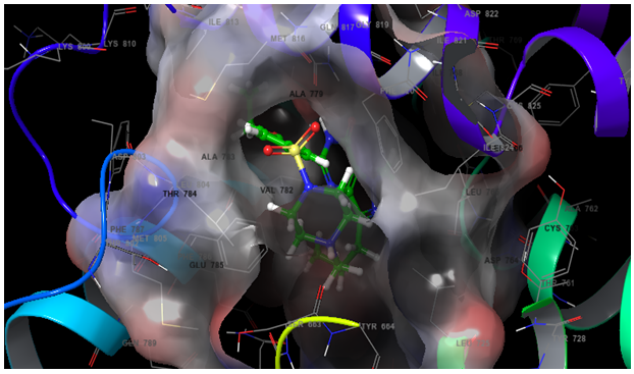

Figure 2. Electrostatic potential at the surface of the active site of PDES-5 bound with Viagra (the green stick model). The negative, positive and neutral charge of the binding site residues were denoted as red, blue and white color respectively.

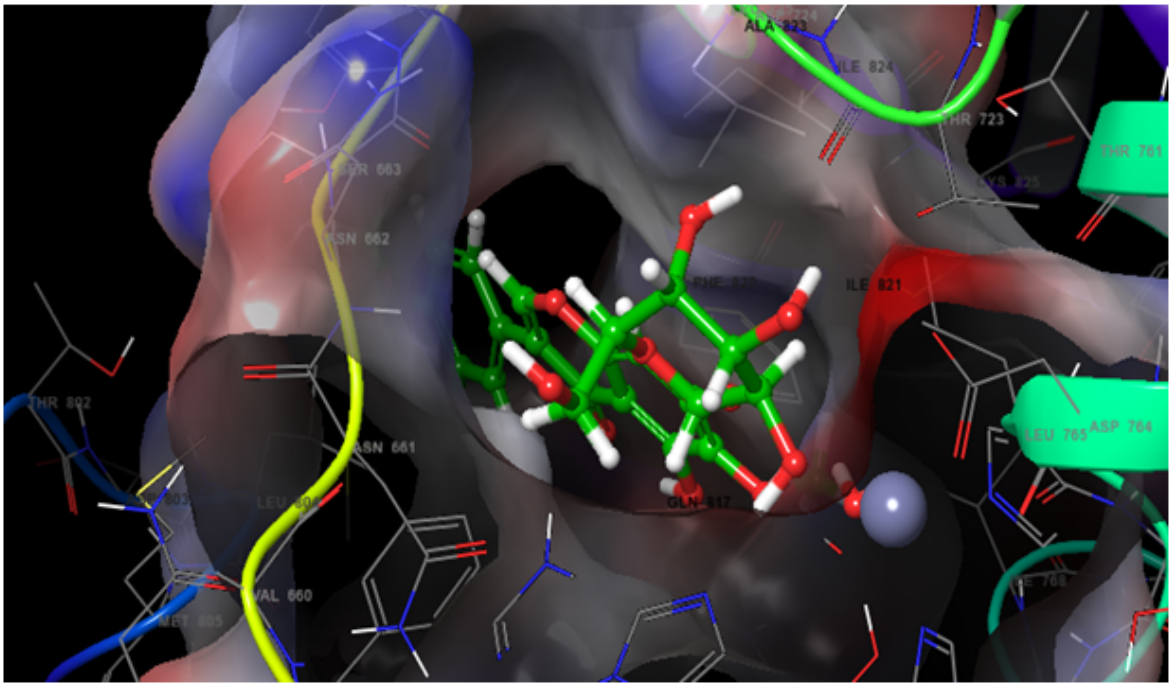

Figure 3. Electrostatic potential at the surface of the active site of PDES-5 bound with compound 1 (the green stick model). The negative, positive and neutral charge of the binding site residues were denoted as red, blue and white color respectively.

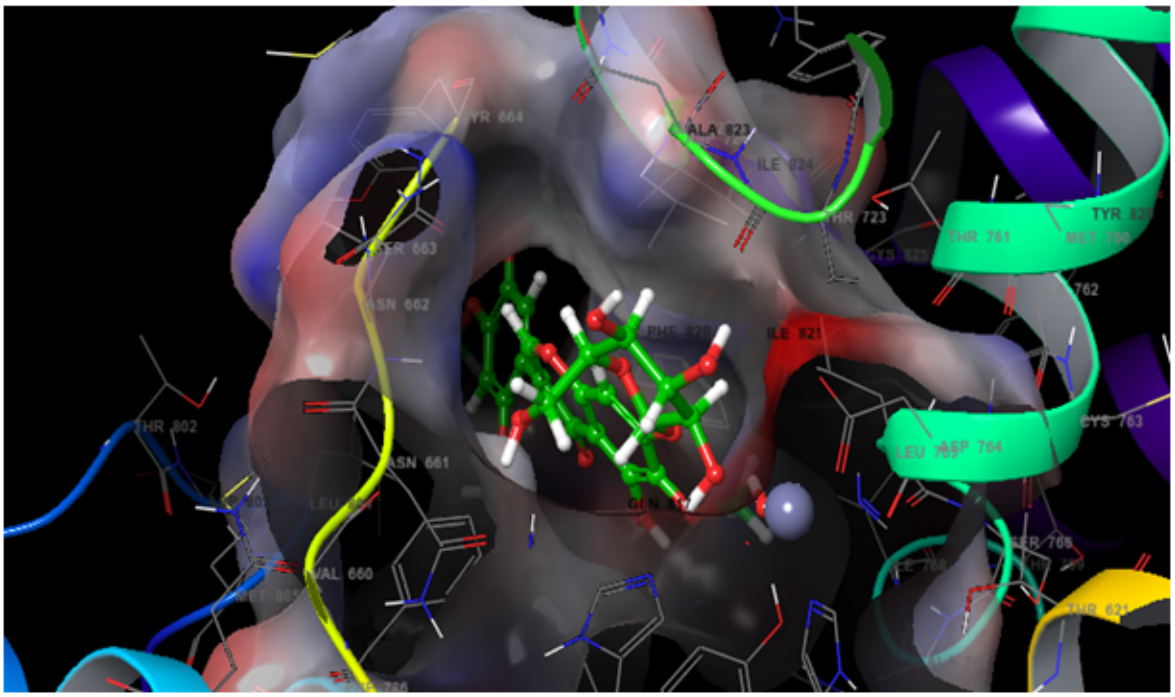

Figure 4. Electrostatic potential at the surface of the active site of PDES-5 bound with compound 2 (the green stick model). The negative, positive and neutral charge of the binding site residues were denoted as red, blue and white color respectively.

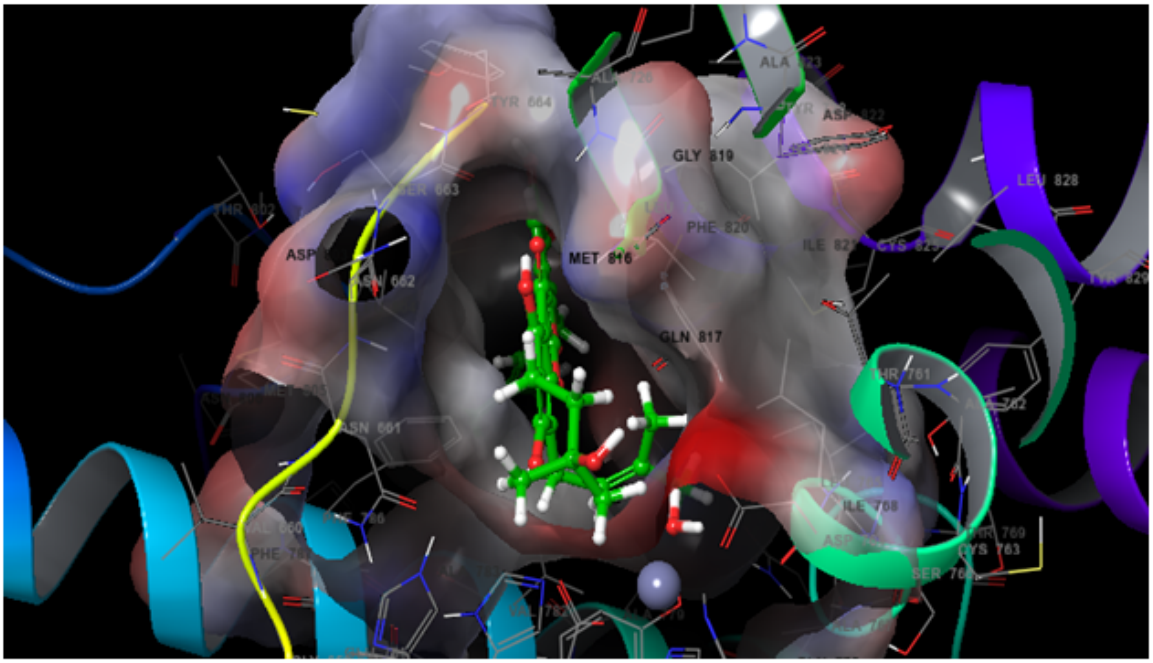

Figure 5. Electrostatic potential at the surface of the active site of PDES-5 bound with compound 3 (the green stick model). The negative, positive and neutral charge of the binding site residues were denoted as red, blue and white color respectively.

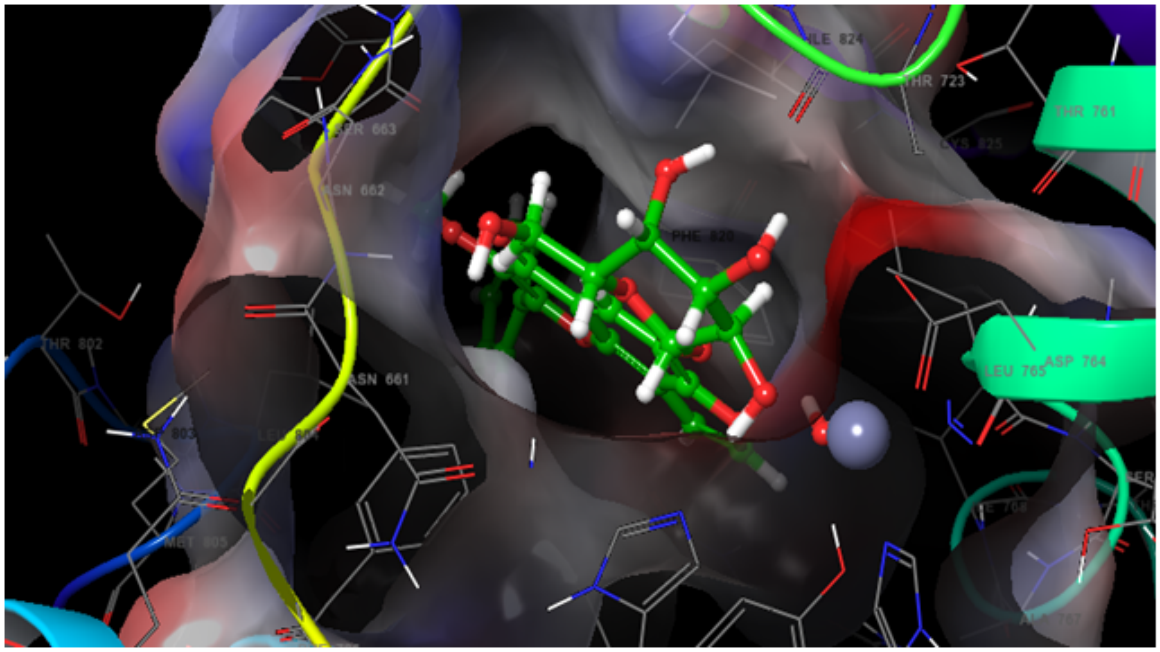

Figure 6. Electrostatic potential at the surface of the active site of PDES-5 bound with compound 4 (the green stick model). The negative, positive and neutral charge of the binding site residues were denoted as red, blue and white color respectively.

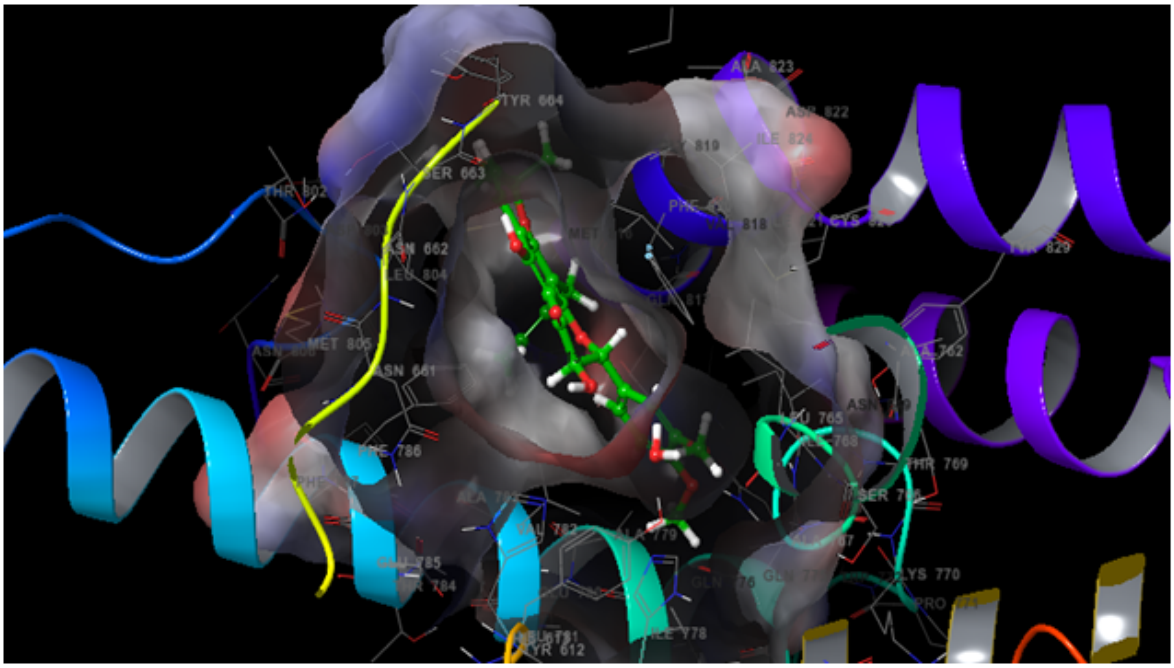

Figure 7. Electrostatic potential at the surface of the active site of PDES-5 bound with compound 5 (the green stick model). The negative, positive and neutral charge of the binding site residues were denoted as red, blue and white color respectively.

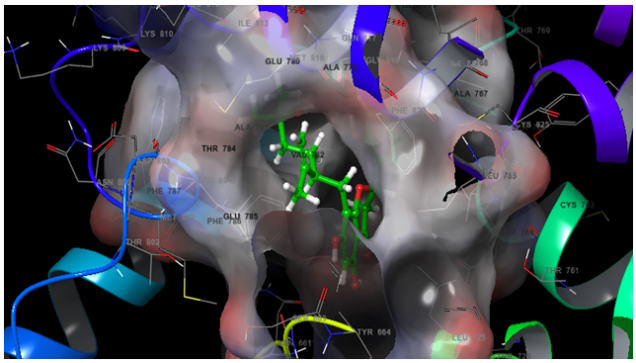

Figure 8. Electrostatic potential at the surface of the active site of PDES-5 bound with compound 6 (the green stick model). The negative, positive and neutral charge of the binding site residues were denoted as red, blue and white color respectively.

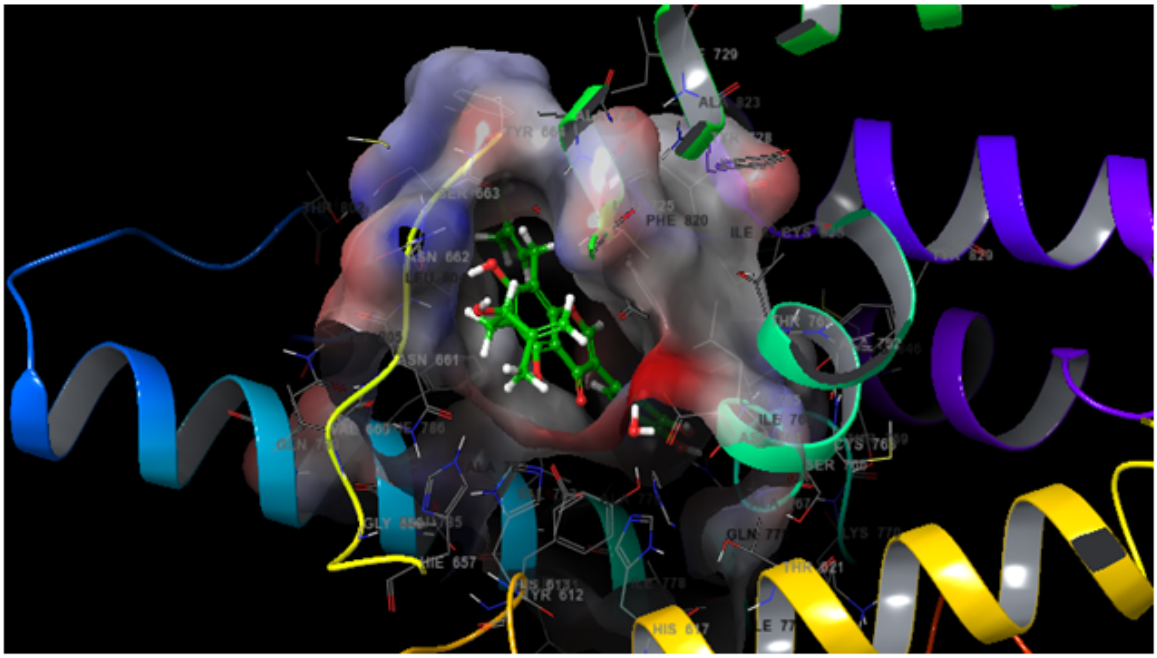

Figure 9. Electrostatic potential at the surface of the active site of PDES-5 bound with compound 7 (the green stick model). The negative, positive and neutral charge of the binding site residues were denoted as red, blue and white color respectively.

Figures 10-12 showed the 2D diagram of the hit compounds and viagra illustrating intermolecular interaction at the catalytic cavity of PSDE5.

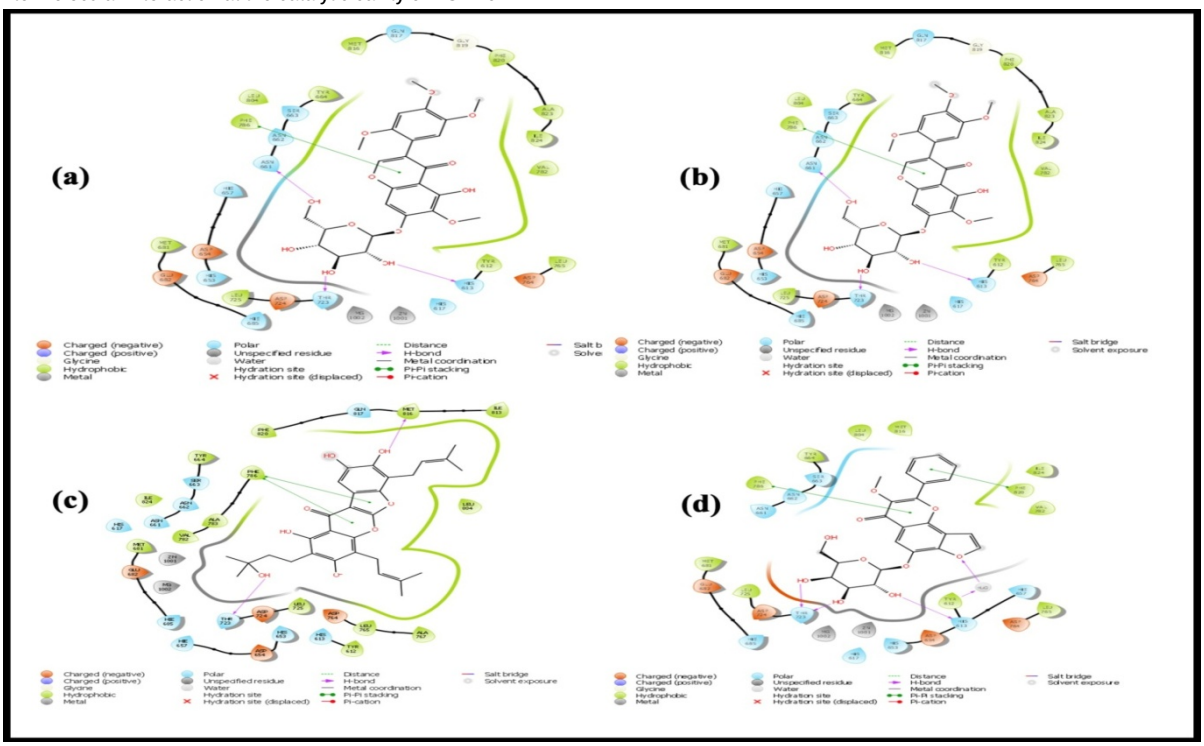

Figure 10. 2D diagram of (a) Compound 1 (b) Compound 2 (c) Compound 3 (d) Compound 4 illustrating intermolecular interaction at the catalytic site of phosphpdiesterase-5.

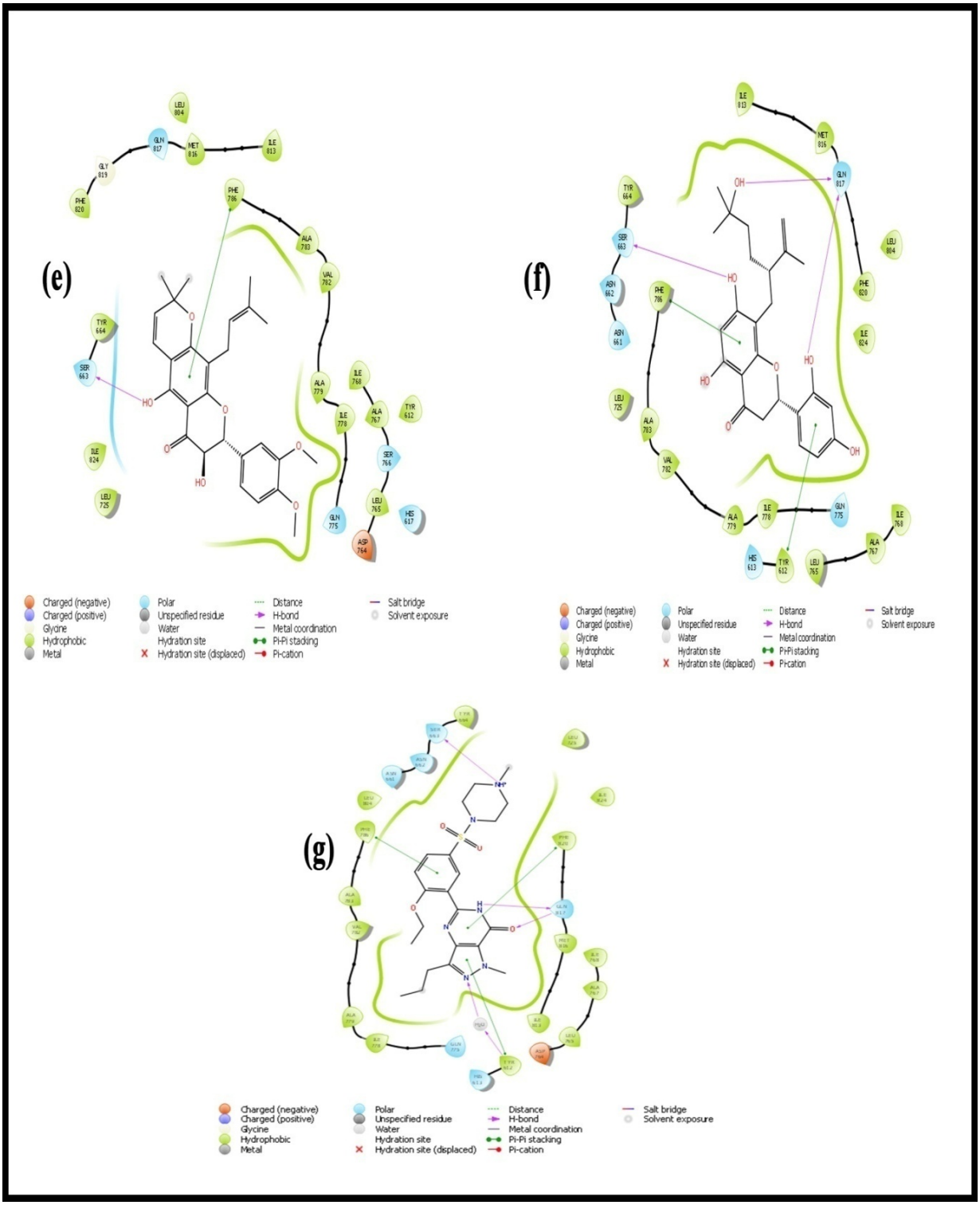

Figure 11. 2D diagram of (e) Compound 5(f) Compound 6 (g) viagra illustrating intermolecular interactions at the catalytic site of phosphpdiesterase-5.

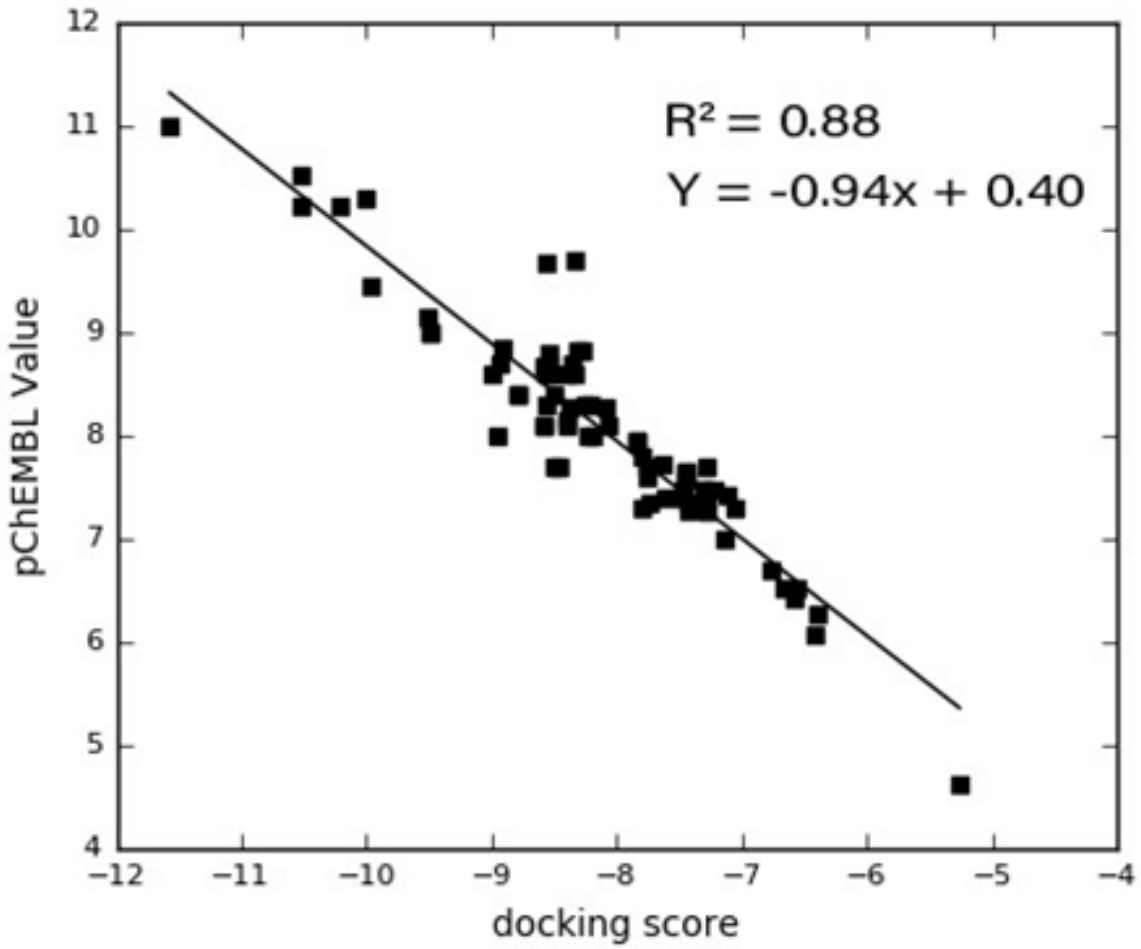

Figure 12. The correlation plot of experimentally determined pIC50 of posphodesterase-5 against their docking scores. The result of the plot showed correlation (r2) of 0.88 which signifies that docking experiment can reproduce the experimentally determined values of the inhibitors.

All of the ligands have shown common interactions with amino acid residues such as LEU765, PHE820, GLN817, MET816, TRY664, GLN775, HIS613, SER663, ASN662 and ASN661 at the binding pocket of PDES5.

ADME predictions

The analysis of the seven lead compounds using Lipinski rule of five is presented in Table2. All the compounds with the exception of compound 2 passed the rule of five.

Table 2. Pharmaco-kinetic properties of the hits compounds.

S.No	Entry Name	CYP1A2 Inhibitor	CYP2C19 Inhibitor	CYP2C9 Inhibitor	CYP2D6 Inhibitor	CYP3A4 Inhibitor	BBB Permeant
1	Compound 1	No	No	No	No	Yes	No
2	Compound 2	No	No	No	No	No	No
3	Compound 3	No	Yes	No	No	No	No
4	Compound 4	No	No	Yes	No	Yes	No
5	Compound 5	No	No	No	No	Yes	No
6	Compound 6	No	No	No	No	Yes	No
6	Compound 7	No	Yes	Yes	No	Yes	No
7	Viagra	No	No	Yes	No	Yes	No

Discussion

Docking studies were carried out to obtain accurate predictions of ligand conformation and orientation within a targeted binding site [15-17]. To identify the binding affinity of the compounds with the receptor, all the compounds were individually docked to the active site of phosphodiestrase-5 using glide docking algorithm. Glide docking uses hierarchical filters to find the best ligand binding locations in the defined receptor grid space [18,19]. The extra precision (XP) docking scores of the docked compounds were compared with the standard drug viagra. The hit molecules showed a docking score ranging from -11.89 kcal/mol to -14.819 kcal/mol. The three top docked compounds which are compound 6,4 and 1 have a docking score of -14.819 kcal/mol,-13.965 kcal/mol and 12.611 kcal/mol respectively. Rampogu et al.,reported that docking scores reflects the inhibitory activities of the ligand in protein-ligand complex. Therefore this result proves that the lead compounds may have relatively better inhibitory activities than viagra.The active site of PDE5 has been described as subdivided into 3 main region (M site, Q pocket and L region) based on its crystal structure in complex with slidenafil[20]. The 3 inhibitors already on the market, Viagra and co, occupy part of the active site, mainly around Q pocket and sometimes the M pockets and all the 3 interact with active site by interaction between the metal ions mediated through water, hydrogen bonding with the saddle of the Q pocked, and hydrophopic interaction with hydrophobic residues lining the cavity of the active site [21].

Several studies have shown that for inhibition to occur at the catalytic domain of PDE5, there must be hydrogen bond and hydrophobic interactions with Gln 817, a non-polar interaction formed by PHE820 and VAL782, and contacts with HIS613, LEU765 and PHE786 [1,2]. Interestingly, all the lead compounds formed a pi-pi stacking using its phenyl ring with PHE786. In addition Compound 4 and 7 also formed a π-π stacking with PHE820.Pi-pi interactions are a type of non-covalent interaction pivotal to biological events such as protein-ligand recognition by providing significant amount of binding enthalpy [22]. Consequently, Compound 1,2 and 4 formed an hydrogen interactions with HIS613, while Compound 6 formed hydrogen bond interaction with hydrophobic amino acid residue GLN817 using its hydroxyl group. The importance of hydrogen-bonds for its crucial role in evaluating the specificity of ligand binding has been reported by Wade and Goodford [23].

One of the most important components of drug discovery involves assessment of efficacy and toxicity of the new drug candidates. The initiation of ADME has greatly eliminate weak drug candidate in the early stage of drug development which further allow rsources to be focused on promising drug candidate [24]. A number of methods and tools exist to assess the physicochemical properties of a molecule that are able to affect the pharmacokinetic and pharmacodynamic properties [25]. We performed relevant physicochemical and pharmacokinetic properties of the lead compounds discovered in this study. The Lipinski rule of five (ROF) is one of the parameters needed before a compound is considered as drug candidate. According to Lipinski and his coworkers, a compound with drug-like attributes most not violoate more than one of the following rule:molecular weight <500Da, octanol-waterpartition coefficient <5, hydrogen bond donor ≤5, hydrogen bond acceptor ≤10 [26]. From our study, all the compounds except compound 2 obey the rule of five. Therefore these compounds can be considered as potential drug candidates.

Some other parameters such as human oral absorption, binding of the ligands to human serum albumin and blood brain barrier were also taken into consideration. All the lead compounds except compound 3 and 7 recorded a medium or high human oral absorption. Human serum albumin is the most abundant protein in the blood plasma and serves as a transport protein and considered to have low affinity and high capacity for binding [27].The lead compounds, however,fell within the normal ranges of their binding with human serum albumin which show their effectiveness in binding to target receptor.Taken together, this study provided insight on the tested compounds as inhibitor of PDES5.

Conclusion

In the present study, compound 4 seems to have better criteria than others as an inhibitor of posphodesterase-5; it has high human oral absorption, possesses excellent attributes as a potential drug candidate and showed a good docking score than the standard drug viagrain view of this. Further *in vitro* and *in vivo* biological investigations are needed to affirm its therapeutic effects in the management of erectile dysfunction.

Acknowledgement

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Author's Contributions

KikiowoBabatomiwa provided the study equipment and materials. Olusola Olalekan Elekofehinti and Toyin Mary Fadipe retrieved ligands and protein from their respective database. Opeyemilwaloye and Toyin Mary Fadipe wrote the manuscript with input from all authors. Olusola Olalekan Elekofehinti reviewed the article before submission.

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How to cite this article: Opeyemi Iwaloye, Elekofehinti Olusola Olalekan, Babatomiwa Kikiowo, and Fadipe Toyin Mary. "In silico Molecular Studies of Selected Compounds as Novel Inhibitors for Phosphodiesterase-5 (PDE5) in the Management of Erectile Dysfunction". J Comput Sci Syst Biol 13 (2020) doi: 10.37421/jcsb.2020.13.307