Docking and Virtual Screening Studies of Tetraketone Derivatives as Tyrosine Kinase (EGFR) Inhibitors: A Rational Approach to Anti-Fungi Drug Design

Article *in* Journal of Advanced Pharmaceutical Technology & Research · January 2017

CITATIONS
4

READS
110

4 authors, including:

Emmanuel Israel Edache
University of Maiduguri
29 PUBLICATIONS **49** CITATIONS
SEE PROFILE

Umar Sani
Newcastle University
3 PUBLICATIONS **6** CITATIONS
SEE PROFILE

Abatyough Terungwa Michael
Bingham University
6 PUBLICATIONS **15** CITATIONS
SEE PROFILE

J. Pharm. Med. Res. - Volume 3 Issue 1 (2017) 78–80

Share Your Innovations through JACS Directory

Journal of Pharmaceutical and Medicinal Research

Visit Journal at http://www.jacsdirectory.com/jpmr

ISSN: 2455-0280

Docking and Virtual Screening Studies of Tetraketone Derivatives as Tyrosine Kinase (EGFR) Inhibitors: A Rational Approach to Anti-Fungi Drug Design

S. Shafiu[1], E.I. Edache[2]*, U. Sani[3], M. Abatyough[4]

[1]*School of Applied Science, Nuhu Bamalli Polytechnic, Zaria, Nigeria.*
[2]*Department of Chemistry, Ahmadu Bello University, Zaria, Nigeria.*
[3]*College of Health Science and technology, TSAFE, Zamfara, Nigeria.*
[4]*Department of Chemistry, Bingham University, Abuja, Nigeria.*

ARTICLE DETAILS

Article history:
Received 25 May 2017
Accepted 12 June 2017
Available online 19 July 2017

Keywords:
Tyrosinase Enzyme
Tetraketone Compounds
Docking Simulation
Hyperpigmentation

ABSTRACT

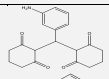
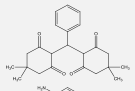
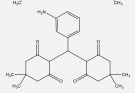
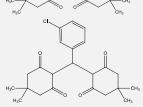
In this paper, an attempt was made to develop molecular docking studies on a series of tetraketone derivatives acting as protein tyrosine kinases (EGFR) inhibitors. Molecular docking analysis was carried out to better understand the interactions between EGFR target and inhibitors in this series. Hydrophobic and hydrogen bond interactions lead to identification of active binding sites of EGFR protein in the docked complex. The present study may lead to discovery of therapeutically potent agents against clinically very important dermatological disorders including hyperpigmentation as well as skin melanoma. Hence the model proposed in this work can be employed to design new derivatives of tetraketone with specific tyrosine kinase (EGFR) inhibitory activity.

1. Introduction

Molecular modeling and computational tools have become a close matching part to experiment in the understanding of molecular aspects of genetic systems [1]. The computational methods like molecular docking and quantitative structure activity relationships (QSAR) are employed to discover the new hits for various therapeutic targets [2]. Recent report highlighted the interface between computational approaches and experiment as essential tools in the drug discovery technology [3]. By means of the prominent rising interest towards the design of ligand-enzyme inhibitors, in this present study is to elucidate the molecular docking study of tetraketone analogs as tyrosinase inhibitor using computational tools that can be applied to understand interactions between inhibitors and their target proteins.

Tyrosinase is a copper-containing oxidase, which has activity for both catechols and cresol. It is responsible for browning reactions. The enzyme is reported to have two binding sites for aromatic substrates and a different binding site for oxygen-copper. The copper is probably Cu(I), with inactivation involving oxidation to Cu(II) ion. It's also called monophenol mono oxygenase. It truly is a copper containing enzyme present in crops, animal tissues and fungi that catalyses the creation of melanin [4]. Tyrosinase catalyses both the hydroxylation of monophenols to diphenols and the oxidation of o-diphenols to o-quinones M. Quinones are very reactive compounds, which can polymerize spontaneously to make large molecular weight compounds like melanin. Additionally they react with amino acids and proteins which create brownish colour. Nevertheless, lately it really is discovered that changes in melanin synthesis consequences in several epidermis effects like hyperpigmentation, freckles, ephelide, melasma and lentigo [5]. Additionally, tyrosinase may entail in neuromelanin development in mind and lead to neurodegeneration linked with parkinson's illness [6]. In crops, it causes unwanted enzymatic browning including bruised cut fruits and vegetables that leads to considerable decline in dietary values [7]. As tyrosinase inhibitors have a growing value because of tremendous use prospects in current decades, the different tyrosinase inhibitors are expressed from organic sources and synthesized. Among which some are appropriate to pharmaceutical and aesthetic areas [8]. The flavonoids were presumed to function as the best inhibitors which revealed the IC50 and Ki worth lower than 1 μM against *Agaricus bisporus* (mushroom) tyrosinase [9]. The development of tyrosine kinase inhibitors has therefore become an active area of research in pharmaceutical science. One could not, however, confirm that the compounds synthesized would always possess good inhibitory activity to Tyrosine kinase, while experimental assessments of inhibitory activity of these compounds are time-consuming and expensive. Consequently, it is of interest to develop a prediction method for biological activities before the synthesis. These analogs revealed especial inhibitory to tyrosinase. In present study tetraketone compounds (Table 1) were synthesized [10] by varying different carbonyl groups and their bioassay was carried against tyrosinase. The research aids in detecting and filtering successful compounds as tyrosinase inhibitors, which provide possible stuff on foods techniques, cosmetic livelihood and disciplines to hinder enzymatic browning. With the above facts and in continuation of our research for newer anti-fungi agent, we reported molecular docking studies on a series of tyrosinase inhibitors to provide further insight into the key structural features required to design potential drug candidates of this class.

Table 1 Compounds of tetraketone and their molecular structures

Comp.	Structure	IC_{50} (μM)	Docking Score
ID11		2.09	-7.0
ID15		2.61	-7.5
ID25		2.06	-6.7
ID27		3.19	-7.6

Docking studies, as the structures of more potential drug target are elucidated the opportunity for computers to perform initial binding studies is increasing. By computationally docking a ligand to a protein, one

*Corresponding Author
Email Address: edacheson2004@gmail.com (E.I. Edache)

Cite this Article as: S. Shafiu, E.I. Edache, U. Sani, M. Abatyough, Docking and virtual screening studies of tetraketone derivatives as tyrosine kinase (EGFR) inhibitors: a rational approach to anti-fungi drug design, J. Pharm. Med. Res. 3(1) (2017) 78–80.

limits concerns about assay complication such as compound solubility and the needs to maintain extensive physical compound libraries. The objective of computational docking is to determine how molecules of known structure will interact. The molecule may bind to receptor and modify their function [11].The docking studies was performed between receptor (EGFR, PDB code: 4R3P) and ligands by using PyRx-Python prescription (version 0.8) [12]. 4R3P (Fig. 1), retrieved from RCSB and prepared by Discovery Studio visualizer version 16.1.01 [13].

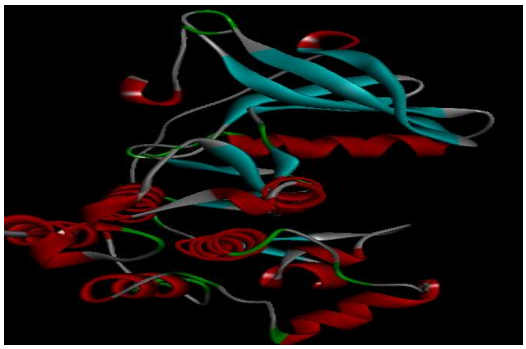


Fig. 1 Structure of 4R3P

2. Experimental Methods

3D structure of the emzyme tyrosinase with PDB code: 4R3P by Park et al., [14] and tetraketones by Khan et al., were taken from literature [10]. The protein structure was obtained from the data base online Protein Data Bank [15]. Two and three dimensional structure of tetraketones drawn using program package ChemDraw Ultra v12.0.2, 2010 [16].

2.1 Preparation of Protein Structure

The 3D co-ordinates of the crystal structure of EGFR (PDB ID: 4R3P) was downloaded from the Protein Data Bank [15]. EGFR (chains A) were selected for the docking simulations. Before docking all water molecules are removed from protein file 4R3P. After removing the water molecules H-atom were added to protein for correct ionization and tautomeric states of amino acid residues such as GLU, MET, ASP, THR, LEU, and GLY.

2.2 Preparation of Ligand Structures

The ligands used for docking study were selected from the literature [10]. The bioactive compounds that are mainly present in the plants were considered for the study. The ligand structures were generated using the tool ChemDraw ultra v12.0.2 [16]. Three-dimensional optimizations of the ligand structures were done and saved as 'PDF file'. Geometry optimizations of the ligands were performed using the semi-empirical (PM6) calculation method using Spartan '14 software [17]. The compounds included in the study are 2,2'-((3-aminophenyl)methylene)bis(cyclohexane-1,3-dione, 2,2'-(phenylmethylene)bis(5,5-dimethylcyclohexane-1,3-dione, 2,2'-((3-aminophenyl)methylene)bis(5,5-dimethylcyclohexane-1,3-dione and 2,2'-((3-aminophenyl)methylene)bis(5,5-dimethylcyclohexane-1,3-dione. The bioactive compounds considered for the study are listed in Table 1.

2.3 Protein-Ligand Interaction using PyRx (Autodock vina)

The docking studies were conceded by PyRx (*Autodock vina*) tools [12] version v0.8 programs. The searching grid extended above the preferred target proteins; polar hydrogen was added to the ligand moieties. Kollman charges were assigned and atomic solvation parameters were added. Polar hydrogen charges of the Gasteiger-type were assigned and the non-polar hydrogen was merged with the carbons and the internal degrees of freedom and torsions were set. Tetraketone compounds were docked to target protein complex (4R3P) with the molecule considered as a rigid body and the ligand being flexible. The search was extended over the whole receptor protein used as blind docking. Affinity maps for all the atom types present, as well as an electrostatic map, were computed with a grid spacing of 0.375 Å. The search was carried out with the Lamarckian Genetic Algorithm; populations of 150 individuals with a mutation rate of 0.02 were evolved for 9 generations. Evaluation of the results was done by sorting the different complexes with respect to the predicted binding energy. A cluster analysis based on root mean square deviation values, with reference to the starting geometry, was subsequently performed and the lowest energy conformation of the more populated cluster was considered as the most trustable solution.

3. Results and Discussion

In this present study, to understand the formation of hydrogen bond interactions between the tetraketone compounds and active sites of crystal structure of EGFR (PDB code: 4R3P) was used to explore their binding mode and docking study was performed by using PyRx (*Autodock vina*) [12]. Four (4) naturally occurring tetraketone compounds was retrieved from literature [10]. The 3D structure and energy minimization was done by Spartan '14 software [17]. All these chemical compounds and molecular properties were calculated by using Starpan '14 and were presented in Table 1. To date, several crystal structure of EGFR in complex with different inhibitors have been reported in the literature, quinazoline derivatives [18], are used as an inhibitors for tyrosine kinase (EGFR). In the present study we have used X-ray crystallography structure of tyrosinase (PDB code: 4R3P) (Fig. 1) in ternary complex against tetraketone compounds are used for the docking study.

3.1 Binding Site of the Protein

The detection of ligand-binding sites is often the starting point for protein function identification and drug discovery [19]. In our study, PyRx (*autodock vina*) predicted active site of the receptor EGFR (4R3P) with a higher average precision. The active site of EGFR (4R3P) comprises of amino acid residues such as GLU762, MET766, ASP855, THR854, THR790, LYS745, ALA743, LEU844, LEU792, MET793, GLY796, VAL726, GLY719 and LEU718. As most of the amino acid residues in the active site are hydrophobic so they are the main contributors to the receptor and ligand-binding interaction (Table 1).

3.2 Interaction between Tetraketone Compounds and 4R3P

The goal of ligand-protein docking is to predict the predominant binding model(s) of a ligand with a protein of known three dimensional structures [20]. To study the binding mode of tetraketone compounds in the binding site of crystal structure of EGFR (4R3P), docking simulations were performed by means of PyRx (autodock vina) program and docking scores were calculated from the docked conformations of the crystal structure of EGFR (4R3P)-inhibitor complexes. Four tetraketone compounds such as 2,2'-((3-aminophenyl)methylene)bis(cyclohexane-1,3-dione, 2,2'-(phenylmethylene)bis(5,5-dimethylcyclohexane-1,3-dione, 2,2'-((3-aminophenyl)methylene)bis(5,5-dimethylcyclohexane-1,3-dione and 2,2'-((3-aminophenyl)methylene)bis(5,5-dimethylcyclohexane-1,3-dione were docked into the active site of crystal structure of EGFR (4R3P) by using the same protocol. Docking studies yield crucial information concerning the orientation of the inhibitors in the binding pocket of the target protein. Several potential inhibitors have been identified through the docking simulation [21]. The majority of the ligand had a greater binding affinity with the target receptor crystal structure of EGFR (4R3P) has shown in Fig. 1. Inhibition was measured by the binding energy of chemical compounds possess (kcal/mol). It was depicted that aligned binding conformations of the tetraketone compounds in the binding pocket of the crystal structure of EGFR (4R3P), were derived from the docking simulations (PyRx software). The four tetraketone compounds such as 2,2'-((3-aminophenyl)methylene)bis(cyclohexane-1,3-dione, 2,2'-(phenylmethylene)bis(5,5-dimethylcyclohexane-1,3-dione, 2,2'-((3-aminophenyl)methylene)bis(5,5-dimethylcyclohexane-1,3-dione and 2,2'-((3-aminophenyl)methylene)bis(5,5-dimethylcyclohexane-1,3-dione were bind into the EGFR active sites. From the results it has been clearly observed 2,2'-((3-aminophenyl)methylene)bis(5,5-dimethylcyclohexane-1,3-dione (ID25) formed one hydrogen bond interaction with EGFR. The corresponding docking energy value of ID25 (-6.7 kcal/mol) with one H-bonding was shown in Fig. 4. The hydrogen bond was formed between GLU906 by a distance of 3.20 Å. The docking energy of ID11 (-7.0 Kcal/mol) was shown in Fig. 2, ID15 (-7.5 Kcal/mol) interaction with EGFR was presented in Fig. 3 and the ID27 (-7.6 Kcal/mol) binding with EGFR was shown in Fig. 5. The molecular docking studies of tetraketone compounds into EGFR binding site revealed very clear preference for the binding pocket. Residues GLU762, MET766, ASP855, THR854, THR790, LYS745, ALA743, LEU844, LEU792, MET793, GLY796, VAL726, GLY719 and LEU718 are important for the catalytic mechanism of EGFR. Any ligand which can bind to GLU762, MET766, THR854, THR790, LYS745, ALA743, GLY796, VAL726, GLY719 and/or LEU718 and prevent the substrate from binding to the active site can behave as an inhibitor of tyrosinase. These two key residues are positioned at the end of active site cleft. Usually binding of the substrate to EGFR occurs through a well-formed hydrophobic channel. So blocking the hydrophobic channel is an effective way to inhibit EGFR [19] have reported that active site residues of ASP and combination of ASP with GLY forms the calcium-binding loop, which is responsible of coordinating the Ca^{2+} required during catalysis [22].

Cite this Article as: S. Shafiu, E.I. Edache, U. Sani, M. Abatyough, Docking and virtual screening studies of tetraketone derivatives as tyrosine kinase (EGFR) inhibitors: a rational approach to anti-fungi drug design, J. Pharm. Med. Res. 3(1) (2017) 78–80.

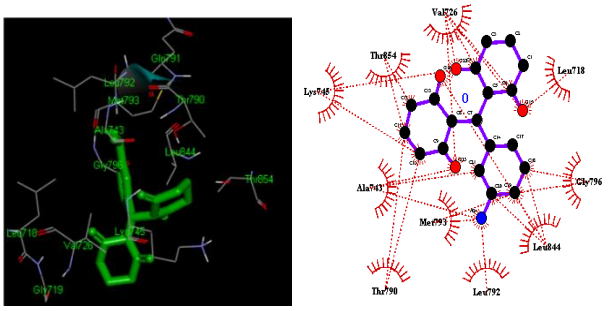


Fig. 2 Overlay of docked potent 2,2'-((3-aminophenyl)methylene)bis(cyclohexane-1,3-dione compound (ID11) at the active site of 4R3P produced using the PyRx, Discovery Studio and LigPlot+ program

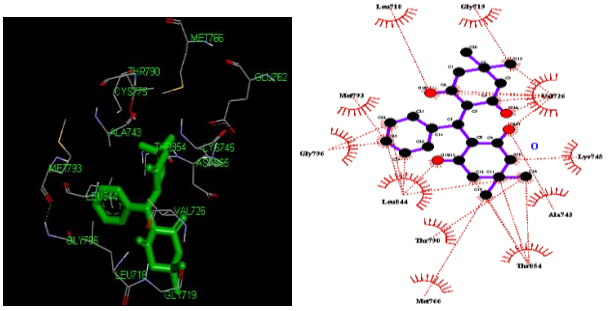


Fig. 3 Overlay of docked potent 2,2'-(phenylmethylene)bis(5,5-dimethylcyclohexane-1,3-dione compound (ID15) at the active site of 4R3P produced using the PyRx, Discovery Studio and LigPlot+ program

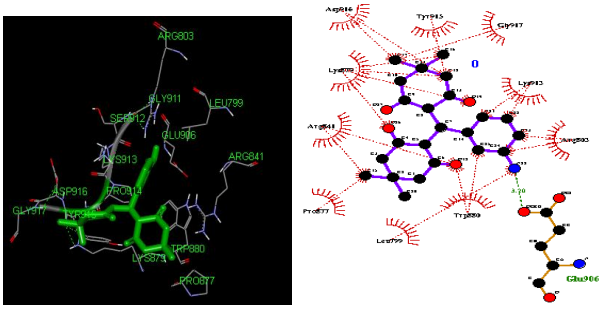


Fig. 4 Overlay of docked least potent 2,2'-((3-aminophenyl)methylene)bis(5,5-dimethylcyclohexane-1,3-dione compound (ID25) at the active site of 4R3P produced using the PyRx, Discovery Studio and LigPlot+ program

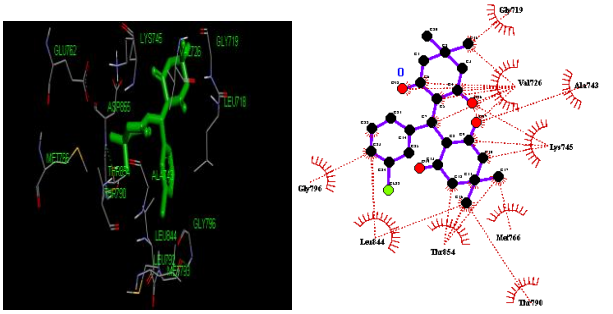


Fig. 5 Overlay of docked highest 2,2'-((3-aminophenyl)methylene)bis(5,5-dimethylcyclohexane-1,3-dione compound (ID27) at the active site of 4R3P produced using the PyRx, Discovery Studio and LigPlot+ program

4. Conclusion

Analysis of ligand-binding interaction with EGFR (PDB code: 4R3P) receptor can be useful for new preventive and therapeutic drug against tyrosinase. The results obtained from this study would be useful in understanding the inhibitory mode of tetraketone compounds as well as in rapidly and accurately predicting the activities of natural inhibitors on the basis of docking scores. These models also provide some beneficial clues in structural modification of designing natural inhibitors for the treatment of tyrosinase against EGFR (PDB code: 4R3P). The plant derived tetraketone compound such as 2,2'-((3-aminophenyl)methylene)bis(5,5-dimethylcyclohexane-1,3-dione forms one hydrogen bond interactions with EGFR (PDB code: 4R3P) and can be developed as an effective anti-fungi drug in near future.

References

[1] D.W. Smith, J. Rubenson, D. Lloyd, M. Zheng, J. Fernandez, et al, A conceptual framework for computational models of Achilles tendon homeostasis, Wiley Interdiscip. Rev. Syst. Biol. Med. 5 (2013) 523-538.

[2] H.M. Kumalo, S. Bhakat, M.E.S. Soliman, Theory and applications of covalent docking in drug discovery: merits and pitfalls, Molecules 20 (2015) 1984-2000.

[3] B. Honarparvar, T. Govender, G.E.M. Maguire, M.E.S. Soliman, H.G. Kruger, Integrated approach to structure-based enzymatic drug design: molecular modeling, spectroscopy and experimental bioactivity, Chem. Rev. 114 (2014) 493-537.

[4] M. Murakami, Y. Nakatani, G. Atsumi, G. Inoue, K.I. Kudo, Regulatory functions of phospholipase A2, Crit. Rev. Immunol. 17(3-4) (1997) 17225-17283.

[5] I. Kudo, M. Murakami, Phospholipase A2 enzymes, prostaglandins other lipid, Mediat. 68 (2002) 3-58.

[6] E. Boilard, Y. Lai, K. Larabee, B. Balestrieri, F. Ghomashchi, et al, A novel anti-inflammatory role for secretory phospholipase A2 in immune complex-mediated arthritis, EMBO Mol. Med. 2 (2010) 172-187.

[7] B.L. Nanda, A. Nataraju, R. Rajesh, K.S Rangappa, M.A. Shekar, et al, PLA2 mediated arachidonate free radicals: PLA2 inhibition and neutralization of free radicals by anti-oxidants--a new role as anti-inflammatory molecule, Curr. Top. Med. Chem. 7 (2007) 765-777.

[8] J.D. Clark, L.L. Lin, R.W. Kriz, C.S. Ramesha, L.A. Sultzman, et al, A novel arachidonic acid-selective cytosolic PLA2 contains a Ca^{2+}-dependent translocation domain with homology to PKC and GAP, Cell. 65 (1991) 1043-1051.

[9] N.G. Bazan, V. Colangelo, W.J. Lukiw, Prostaglandins and other lipid mediators in alzheimer's disease, prostaglandins other lipid, Mediat. 68 (2002) 197-210.

[10] K.M. Khan, G. M. Maharvi, M.T.H. Khan, A.J. Shaikh, S. Parveen, et al, Tetrakones: a new class of tyrosinase inhibitors, Bioorg. Med. Chem. 14 (2006) 344-351.

[11] R.B. Sharma, D. Chetia, Docking studies on quinine based antimalarial drugs for plasmepsin-II using bioinformatics tools, J. Pharm. Pharm. Sci. 5(3) (2013) 681-85.

[12] http://pyrx.sourceforge.net/downloads (Accessed on: 15/09/2016)

[13] http://www.accelyrs.com (Accessed on: 15/09/2016)

[14] E. Park, N. Kim, Z. Yi, A. Cho, K. Kim, Crystal structures of EGFR in complex with Mig6, Nat. Struct. Mol. Biol. 22 (2015) 703-711.

[15] http://www.rcsb.org/pdb/home (Accessed on: 17/09/2016)

[16] www.cambridgesoft.com (Accessed on: 16/09/2016)

[17] www.wavefun.com (Accessed on: 15/09/2016)

[18] N.N. Malleshappa, M.P.A. Harun, Comparative QSAR analysis and molecular docking studies of quinazoline derivatives as tyrosine kinase (EGFR) inhibitors: A rational approach to anticancer drug design, J. Saudi Chem. Soc. 17 (2013) 361-379.

[19] V. Srivastava, S.P. Gupta, M.I. Siddiqi, B.N. Mishra, Molecular docking studies on quinazoline antifolate derivatives as human thymidylate synthase inhibitors, Bioinfo. 4(8) (2010) 4357-365.

[20] R.R. Mittal, R.A. McKinnon, M.J. Sorich, Comparison data sets for benchmarking QSAR methodologies in lead optimization, J. Chem. Inf. Model. 49 (2009) 1810-1820.

[21] T. Sindhu, S. Rajamanikandan, D. Durgapriya, J.R. Anitha, S. Akila, et al, Molecular docking and QSAR studies on plant derived bioactive compounds as potent inhibitors of DEK on coprotein, Asian J. Pharm. Clin. Res. 4 (2011) 67-71.

[22] J.A. Pereanez, V. Nunez, A.C. Patino, M. Londono, J.C. Quintana, Inhibitory effects of plant phenolic compounds on enzymatic and cytotoxic activities induced by a snake venom phospholipase A2, Vitae 18 (2011) 295-304.

Cite this Article as: S. Shafiu, E.I. Edache, U. Sani, M. Abatyough, Docking and virtual screening studies of tetraketone derivatives as tyrosine kinase (EGFR) inhibitors: a rational approach to anti-fungi drug design, J. Pharm. Med. Res. 3(1) (2017) 78–80.