INTERNATIONAL JOURNAL OF CURRENT RESEARCH IN CHEMISTRY AND PHARMACEUTICAL SCIENCES
(p-ISSN: 2348-5213: e-ISSN: 2348-5221)
www.ijcrcps.com
DOI: 10.22192/ijcrcps Coden: IJCROO(USA) Volume 5, Issue 1 - 2018

Research Article

DOI: http://dx.doi.org/10.22192/ijcrcps.2018.05.01.005

Molecular Docking Studies of 1, 2, 4-Triazole Derivatives as Potential Anticancer Agents

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Abstract

In the current study, more than twenty of 1,2,4-triazole derivatives were designed based on topically aromatase inhibitor (letrozole and anastrozole) and tubulin polymerization inhibitors. Molecular docking studies carried out using Auto Dock 4.2 software to determine the best pose of ligands on these targets (aromatase and tubulin) and their potential mechanism. The results showed that binding energy values ranged from -9.04 to -9.96 and -6.23 to -7.54 Kcal/mol for aromatase and tubulin, respectively. Compound **1** had the best energy of docking on both targets. However, docking results showed that these compounds had more affinity to bond with Aromatase enzyme.

Keywords: Triazole, Aromatase inhibitor, Tubulin, Auto Dock

Introduction

Cancer, is a different group of diseases define by the proliferation and develop of abnormal cells(1-3). This disease, after cardiovascular problems, is more mortal disease in the world, thus, the development of novel and effective anticancer agents is main goals in the medicinal chemistry(4).

One of heterocyclic ring that had received much attention in medicinal chemistry is 1,2,4-triazole ring. Literature survey reveals that 1,2,4-triazole derivatives are known to possess many biological activities such as anti-microbial(5),analgesic(6), anti-convulsant(7), anti-inflammatory (8) and anticancer(9, 10) activities. There are many 1,2,4-triazolederivatives that applied in medicine, for example: anastrozole, letrozole, vorozole (breast cancer, aromatase inhibitors), fluconazole, itraconazole, terconazole (antifungal agents, 14-α-demethylase inhibitors).

To the best of our knowledge, many works have been reported to the synthesis of 1,2,4-triazole derivatives that inhibit tubulin polymerization. For example, a series of compounds that bearing the 1,2,4-triazole ring were synthesized by Zhang Q et al which Several of the these derivatives exhibited potent tubulin polymerization inhibitory activity as well as cytotoxicity against give cancer cell lines(11). Furthermore, novel 1,2,4-triazole compounds were synthesized by X. Ouyang et aland were shown to inhibit tubulin polymerization along with cell cycle arrest in A431 cancer cell line with IC_{50} values less than 10 nM. Binding experiments indicated that these compounds compete with colchicine for its binding site on tubulin(12).

Based on above mentioned and our previous studies on 1,2,4-triazole compounds(13) , we designed many 1,2,4-triazole derivatives and investigate their activity as aromatase or tubulin polymerization inhibitors using in autodock 4.2 software.

Materials and Methods

Data set

As depicted on fig. 1, more than twenty of 1,2,4-triazole compounds were designed based on letrozole, anestrazole and structure of above mentioned studies (11-13).

Preparation of Ligands

In this stage, the 3dimention structures of all designed 1,2,4-triazole compounds were generated by ChemBioDraw Ultra 14.0 and then converted to 3D mol_2 using OpenBabel 2.3.2. for minimization of energy of the structures molecular mechanic (MM+) and semiemperical (AM1) methods were applied by means of an in house TCL script using Hyperchem8(14, 15).

Preparation of Enzyme and protein

The pdb file for the crystal structure of human aromatase complex with androstenedione (3EQM) and tubulin protein (4YJ2) were retrieved from protein data bank (http://www.rcsb.org/pdb/home/home.do). All water molecules and co-crystal ligandwere removed. missinghydrogens were added and after calculating the Kollman united atom charges, non-polar hydrogens were merged into their corresponding carbons using AutoDock Tools. for this purpose, an in house application (MODELFACE) was applied(16).

Subsequently, the enzyme and protein were converted to PDBQT using MGLTOOLS 1.5.6.

Docking procedure

The docking procedure was carried out using AutoDock 4.2 and for automatic running of in parallel mode and using all system resources, an in house batch script (DOCKFACE) was used (14, 17). The batch script was applied to accelerate the virtual ligand screening stepwise. The procedures include ligands enzyme and protein preparation, grid maps generation, dpf files preparation and performing docking runs. Genetic algorithm (GA) method was used to conducting the molecular docking procedure to find the best pose of each ligand in the active site of the target enzyme and protein. Hundred independent GA runs were considered for each ligand under study. For Lamarckian GA; 27000 maximum generations; 2500000 maximum numbers of energy evaluations, a gene mutation rate of 0.02; and a crossover rate of 0.8 was applied. The grid maps of the protein were calculated using AutoGrid (part of the AutoDock package). The grid size and grid center of aromatase and tubulin in x, y, and z directions were summarized in Table 1.

Table 1.Parameters of grid box

Parameter Name	Aromatase	Tubulin
PDB ID	3EQM	4YJ2
No. of points in x	60	40
No. of points in y	74	40
No. of points in z	120	40
Grid spacing	0.375	0.375
Box X center	15.81	0.264
Box Y center	21.31	43.515
Box Z center	9.88	17.738

AutoDock Tools was used to produce both grid and docking parameter files (gpf and dpf). Finally, RMS tolerance of 2 Å was applied to analysis of Cluster of the docking results. Rigid protein-flexible ligand docking protocol were applied and all visualization of protein ligand interactions were performed using VMD software (Fig.1 and 2).

Docking validation

For docking validation, 18 active ligands and 63 inactive decoys were retrieved from ChEMBL database as SMILES format. The primary 3D generation of the structures was generated as mol_2 format by running of Open Babel 2.3.2 (18). The docking of these compounds was obtained based on the applied docking procedure for our designated ligands. the area under the curve (AUC) forreceiver operating characteristic (ROC) plot were calculated for active ligands and decoys using our application(19).

Results and Discussion

In the current study, more than twenty of 1,2,4-triazole compounds were docked on the active site of aromatase and binding site of colchicine and the results were summarized on the Table 2.

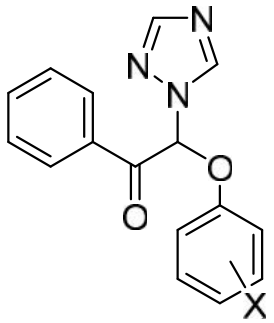

Table 2.Docking binding energy (Kcal/mol) of aromatase and tubulin

		Docking binding energy (Kcal/mol)	
Ligand/Receptor	**X**	**3EQM**	**4YJ2**
1	4-Cl	-9.96	-7.54
2	4-Br	-9.04	-6.31
3	2-OCH_3	-9.67	-7.17
4	4-NO_2	-9.86	-6.23
5	2-CH_3	-9.75	-7.40
6	4-CF_3	-9.82	-7.18
7	2-NH_2	-9.12	-7.22

As depicted on Table 2, the energy of compounds docked was ranged from -9.04 to -9.96 and -6.23 to -7.54 Kcal/mol for aromatase and tubulin, respectively. The energy of compounds docked on aromatase more than the energy of compounds docked on binding site of colchicine. These results indicated that these compounds had more affinity to bind on active site of aromatase. Interestingly, compound**1** provided the best energy of docking for both targets. These energy values were-9.96 and -7.54 Kcal/mol for aromatase and tubulin, respectively.

Docked poses of compound**1** were visualized to found the most important residue at the active site of both targets. As it was shown in the Fig 1, Fe of Heme of active site of aromatase coordinated with N4 of triazole ring and Arg115 interact with phenyl by pi-Arencation interaction.

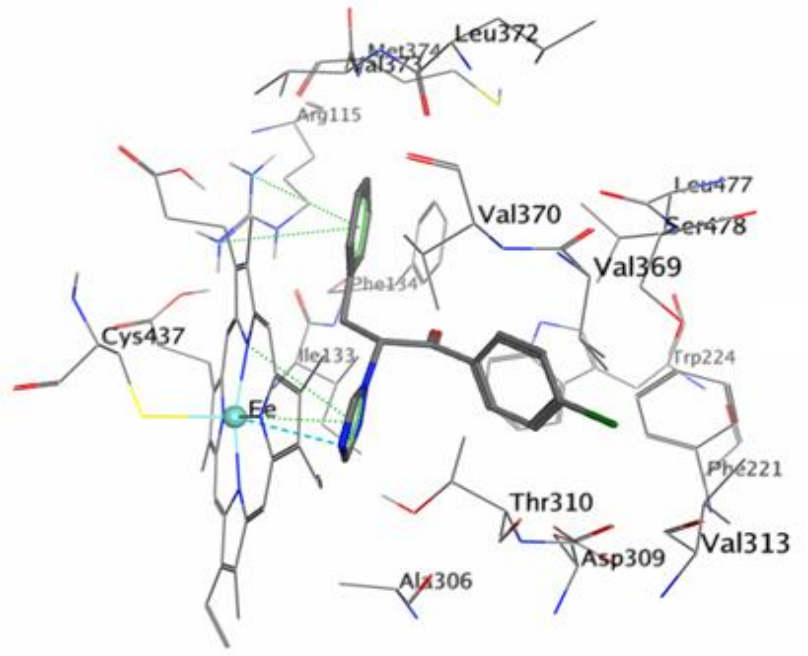

Fig. 1. Interactions of compound **1** with the residues in the active site of aromatase (3EQM).

Forthermore, the complex compound **1** with tubulin showed that Gly A146 is involve in hydrogen bond interaction with N4 of triazole ring. N2 of triazole ring intract with AlaA12 by hydrogen binding interaction. Lys B254 and Gly A143 make π-Aren cation interaction with phenyl and triazole ring, respectivly (Fig 2).

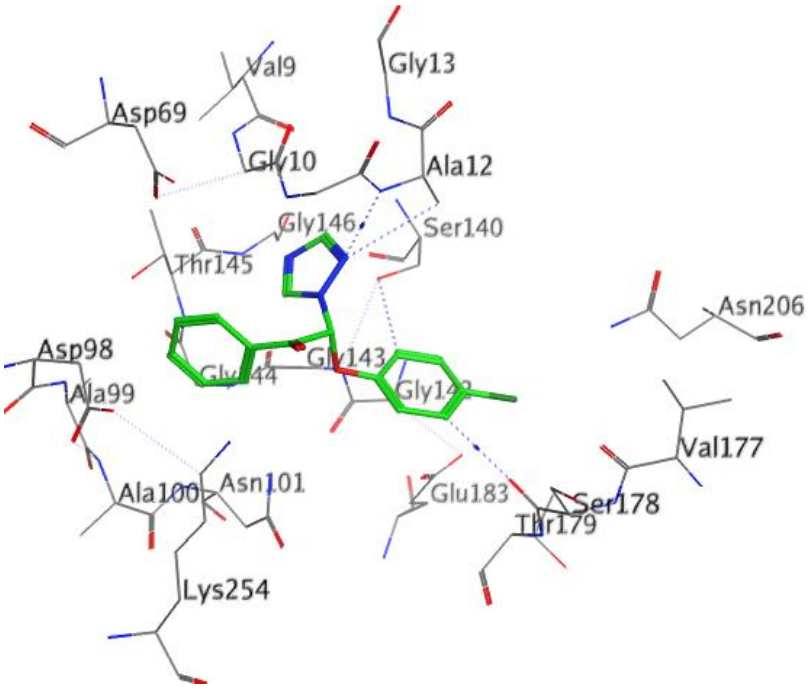

Fig.2. Interactions of compound **1** with the residues in the binding site of Tubulin (4YJ2).

Validation of docking protocol was investigated using ROC curve. As indicated in Fig 3. The ROC curve showed that the AUC is more than 0.8 and this protocol is valid.

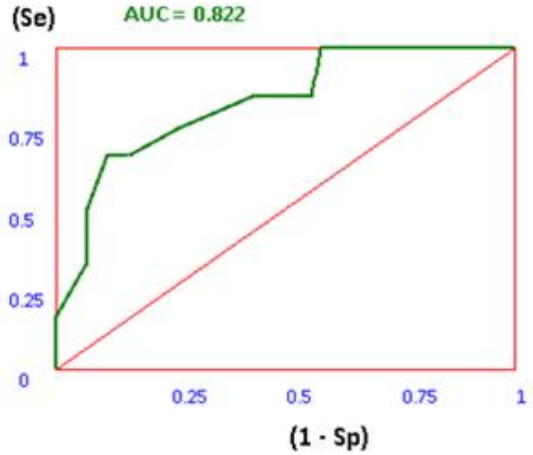

Fig **3**. ROC diagram for aromatase

Conclusion

1,2,4-triazoles derivatives are a promesing class of anticancer agents with outstanding cytotoxic activities. Inhibition of the aromatase and polimerization of tubulin are among the most accepted mechanism of action of triazole anticancer agents. To obtain the detailed molecular binding modes and binding sites for 1,2,4-triazoles derivatives, more than twenty of 1,2,4-triazole compounds were designed and their mechnism as aromatase or tubulin polimerization inhibitor investigated. The results of docking indicated that the designed compounds had potential to inhibit aromatase more than tubulin polimerization due to the binding energy for Aromatase was higher than tubulin binding energy. Furthermore, between these seven compounds, compound **1** with2-chloro subestitution, had the best binding energy for these two targets. However, it ishoped that these results will encourage further investigations of these substituted 1,2,4-triazoles aspotential anti-cancer agents.

Acknowledgments

The authors would like to thank research deputy Ahvaz Jundishapur University of medical sciences who support this work. Collaboration of medicinal chemistry, faculty of pharmacy, Ahvaz Jundishapur University of Medical Sciences, in providing the required facilities for this work is greatly acknowledged.

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DOI: 10.22192/ijcrcps.2018.05.01.005

How to cite this article:
Ayyub Mojaddami, Azar Mostoufi, Sahar Imani. (2018). Molecular Docking Studies of 1, 2, 4-Triazole Derivatives as Potential Anticancer Agents. Int. J. Curr. Res. Chem. Pharm. Sci. 5(1): 22-27.
DOI: http://dx.doi.org/10.22192/ijcrcps.2018.05.01.005