

## **Docking studies of Triazole derivatives as Aromatase Inhibitors targeted as Breast Malignancy Cells (MCF-7)**

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### **Abstract**

Triazoles and their derivatives are of complete magnitude in healing chemistry and are broadly old in evil patients for prophylaxis and medicine of sparkle threatening all-encompassing growth disease. Breast melanoma is a short of disease in which cells in breast handkerchief transformation and divide uncontrolled, typically in a lumps (or) mass. It is the nearly everyone customary menace and for the most part spend time at produce of malignant cells fall amid women worldwide. The anti-proliferative pastime of the compounds under cram was evaluated in vitro by MTT assay take a stab at against breast malignant cells. The compounds were characterized by analyzing their IR, Mass, 1H and 13C NMR shadowy facts and basic analysis. In vitro anticancer doings of the compounds was veteran by the nationwide growth institute. Docking studies was performed as an experimental to analysis the mechanisms and fastening modes of these compounds towards the aim DNA. Molecular docking studies were accepted out via Autodock 4.2 software. The consequences of molecular docking revise were second-hand to outshine cut back on the action and prediction of the necessary modes of these compounds.

**Key words:** Breast malignancy, Triazoles, Docking studies, MTT assay, Target DNA.

## I. INTRODUCTION

Triazole and its derivatives give an open span of applications in analytical, industrial, and remedial chemistry. It is besides accepted as pyrroldiazole and is a five membered heterocyclic compounds containing three nitrogen and carbon atoms. In attendance are two forms of triazole and has one pyrrole like nitrogen and two of pyridine like nitrogen. 1,2,4-triazole is (wonder nucleus) which possess almost every one of biological behaviour types. 1,2,4-triazole has careworn remarkable concentration to remedial chemists from two decades proper to its large actions variety, through toxicity and right pharmacokinetics and pharmacodynamics, medicinal chemistry and agrochemistry<sup>[1,2,3,4]</sup>. Journalism size up reveals that 1,2,4-triazole derivatives exhibit massive range of biological behaviour besides with antibacterial, antifungal, antitumor, anti-inflammatory, anti-tubercular, anti-depressant, anti-microbial, anti-parkinsonism, anti-diabetic activities<sup>[5,6,7]</sup>. There are lot of 1,2,4-derivatives that is being used in practice of medicine. For example fluconazole, itraconazole is an old antifungal drug and on the other hand, vorozole, letrozole and anastrozole are old non-steroidal drugs for the cure of for the most part cancer. In this kind of growth, breast malignancy is the second important reason of pest downfall amid women worldwide. It is the generally usually blight and the as a rule go to regularly foundation of bane loss amongst women worldwide. Of after everything else the mainly triumphant treatments rendered are the usage of aromatase inhibitors (AIs). Breast disease is a complex, diverse disease classified into hormone-receptor-positive, person epidermal intensification reason receptor-2 overexpressing (HER2+) and triple-negative breast scourge (TNBC) based on histological features. Endocrine therapy, the stronghold of dealing for hormone-responsive breast plague involves exhaust of selective estrogen receptor modulators (SERMs), selective estrogen receptor downregulators (SERDs) and aromatase inhibitors (AIs). Agents that aim at estrogen receptors(ER) and HER2 such as tamoxifen obtain been on the whole extensively second-hand therapeutics for breast cancer<sup>[8,9,10]</sup>. About 80% of breast cancers rely on the goods of hormone estrogen to grow. It happens more often than not appropriate to environmental and genetic factors such as diet, exercise, cigarette smoking, alcohol consumption, early menarche, late menopause. Distinct types of behaviour for breast malignant cells includes surgery, lookout lymph node biopsy, radiation therapy between these hormone therapy is the chief cure acts by suppressing the assembly of estrogen in the body. Aromatase enzyme the stage precise crucial responsibilities in the oestrogen up breast cancers and consequently establish itself as a capable drug candidate. The nearly all critical gesture transduction pathways are the EGFR, HER2, intracellular kinases cascades, copy gene complicated in booth proliferation, and protein that legalize the small room cycle. Oestrogen receptor helpful breast melanoma is defiant to tamoxifen and oestrogen receptor clear-cut signaling was unsaid to incorporate a chief function in this. Moreover the above-mentioned pointer pathways may hold crosstalk with estrogen needy DNA dictation. The drugs knotty in treating the estrogen certain breast cancers play-act each by interfering with oestrogen creation or by action. However, aromatase inhibitors play in merely on the oestrogen fashioned by breast malignancy cells. As apiece clinical inquiry the change of the third-generation aromatase inhibitors viz. Letrozole, Anastrozole and Exemestane as formerly stroke drugs for estrogen needy breast growth management is a considerable achievement. The inescapability of

prolonged application of these key outline drugs to care for breast cancer, develops separate resistance mechanisms in the scourge cells <sup>[11,12,13]</sup>. Further, triazole and thiazole derivatives were experienced for the anticancer motion against person (MCF-7) Breast malignant cells evaluated by in vitro assess via MTT assay. The focal focus of this article reveals the studies of docking having the compounds with antitumor activity. The newly synthesized compounds were preferred by the countrywide sarcoma institute (NCL) for in vitro group specialty screening. Anticancer assays were initially evaluated at one dose of the important anticancer take a shot at towards approximately 60section outline (con10)<sup>-5</sup>). Molecular docking is one of the nearly all often old methods in composition based drug design, scheduled to its faculty to predict the binding-conformation of trivial molecule ligands to the fitting intention necessary. In this article, demonstrate the triazole and triazole derivatives and their applications as challenging breast disease agents in the medicine industry <sup>[12,13]</sup>. The ADMET properties of drugs in concern with its pharmacological properties are typically viewed as a capacity of drug development. The paramount ligands after docking examination were subjected to predict <sup>[14]</sup>.

## II. AROMATASE INHIBITORS

### 2.1. Aromatase in Breast Cancer:

Aromatase inhibitors (AI's) as of use candidates tolerated been old in the action of hormone-dependent breast cancer. About 80% of breast cancers, just the once established, rely on equipment of the hormone estrogen to grow. Therefore, they are recognized as hormone-sensitive or estrogen-receptor-positive (ER+) cancers. Indeed, by strap to their receptors in the tumor, estrogens initiate signals that affect proliferation of immature cells in the neoplastic handkerchief. Thus, the core strategies to pleasure this sympathetic of scourge are hormone therapy by suppressing the fabrication of estrogen in the body. Aromatase, of the essence covering edge protein of the endoplasmic reticulum is a significant enzyme in the biosynthesis of estrogens. It catalyzes the keep up tread of estrogen biosynthesis from androgens. AIs measure through two evident mechanisms to inhibit the action of aromatase and so condense estrogen construction and are agreed to do by breast cancer <sup>[15,16,17]</sup>.

Type I inhibitors such as a tamestane, exemestane and formestane are analogues of AI that compel competitively but forever to the substrate-binding position of aromatase causing eternal inactivation of the enzyme. Although, AIs are now familiar and booming in the care of postmenopausal ER+  $\omega$  Breast cancer, manipulative novel drugs is significant and essential for selected reasons such as avoiding the jeopardy of visible arising resistances towards accessible drugs, plummeting toxicity, and undesirable margin property allied with prolonged use.

Cytochrome P450, otherwise famous as aromatase (CYP19), is an enzyme located in the endoplasmic reticulum. It comprises a polypeptide bind of 503 amino-acid residues and a prosthetic heme faction at its functional site. An androgenic-specific crevice consisting of hydrophobic and polar residues is situated inside the captivity of the aromatase fastening site. Such fissure is detailed for androsterone dine stitching the catalyze androgen to estrogen by means of a three-step process. All stairs requires one mole of O<sub>2</sub>, one mole of NADPH and NADPH cytochrome reductase. This outcome converts androstenedione, testosterone and 16  $\alpha$  - hydroxytestosterone to estrone, 17  $\beta$  -estradiol and 17  $\beta$  ,16  $\alpha$  -esterol, correspondingly to obstruct estrogen production, it is required to inhibit the enzyme through the work of aromatase

inhibitors(AIs).AIs are simply operational for post-menopausal women since they get something done not deter estrogen invention in the ovaries but accomplish no more than on the estrogen invention in the ovaries fashioned by breast malignancy cells. Therefore, AIs supply as front-line therapy for estrogen-dependent breast cancer <sup>[17,18]</sup>. Aromatase inhibitors that engaged in been old clinically container be categorized as first, second and third generations based on their evolution time or steroidal or nonsteroidal aromatase inhibitors (NSAIs) based on their structural similarity with steroids. Aminoglutethimide is the prototype non-steroidal inhibitor of aromatase. Evils with the plane sound effects and selectivity of aminoglutethimide led to the education of the second-generation of non steroidal aromatase inhibitors (fadrozole effect imidazole structure). However, this compound stagnant has particular nonselective inhibitory pastime with slow consideration for to progesterone, corticosterone and aldosterone biosynthesis. Competitive nonsteroidal inhibitors canister and be constructed with a triazole ring which is institute in the third origination of aromatase inhibitors. A good number of the non steroidal aromatase inhibitors of restorative substance operate covalently to dilemma to the substrate-binding position of aromatase by coordinating the heme. Heterocyclic nitrogen atom of triazole and triazole derivatives show business an essential position by coordinating with the heme iron of the aromatase enzyme. Nearly studied gain publicized that triazole derivatives be inflicted with hopeful aromatase inhibitors. Recent clinical studies exhibit given away those aromatase inhibitors remarkably the third-generation is additional of use than fulvestrant and tamoxifen for the reason that of their let fall segment special effects and top clinical efficacy <sup>[13,14,17]</sup>.

## 2.2. Method of action of AIs in Breast Cancer:

Aromatase inhibitors exert its action by inhibiting the action of the enzyme aromatase, which converts androgen into estrogens by a means called aromatisation. As breast handkerchief is stimulated by estrogens, decreasing their making is a feature of suppressing reappearance of the breast cancer handkerchief and the method of action of tamoxifen is complex. Clearly, its principle apparatus of action is mediated by its fastening to the estrogen receptor and the blocking of the proliferative measures oestrogen on mammary epithelium <sup>[13,15]</sup>.

## III. EQUIPMENTS AND METHODS

### 3.1. Data set:

More than twenty of 1,2,4-triazole compounds were deliberately based on letrozole, anastrozole and in addition based on the formation of docking studies.

### 3.2. Preparation of the ligands:

For the ligand preparation, the 3D structures of every one future triazole compounds were generated by marvin sketch and converted to 3D mol2 by means of OpenBabel 2.3.2. For Energy minimization of the structures was operated by resource of an in organization TCL lettering via Hyperchem8 with MM+ and AM1 methods. For these calculation, the polak-Ribiere conjugate pitch algorithm was employed with the RMS grade place to 0.0001 Kcal/(A.MOL) <sup>[14,15]</sup>.

### 3.3. Drug rendering property:

Drug-likeness convection guidelines explain an integrated equilibrium between molecular properties and structural skin that evaluate whether a compound is like to before now free drugs.

According to Lipinski's dictate of five, the fastening free energy morals of individuals' structures with apposite drug reproduction properties were calculated by means of docking studies. All the optimized structures were subjected to a gaping sparingly virtual selection toolbox (DruliTo). Consequently, according to prediction of ADME properties, it container be not compulsory that the lively compounds may experience a sound pharmacokinetic profile <sup>[18,19]</sup>.

### 3.4. Preparation of protein and enzyme structure:

The 3D gem construction of individual placental aromatase complexing with androstenedione (3EQM.pdb, solution 2.9A and R-value 0.244) was retrieved protein information edge (<http://www.rcsb.org/pdb/home/home.do>). Completely fill up molecules and co crystal ligands were removed, mislaid hydrogens were new and after formative the kollman united atom charges, non-polar hydrogens were merged into their corresponding carbons by means of AutoDock Tools and the enzymes were converted to PDBQT via MGLTOOLS 1.5.6 <sup>[18,19]</sup>.

### 3.5. Docking studies:

Molecular docking studies are second-hand to clarify the interaction of two molecules and to obtain the unsurpassed orientation of ligands which would produce an involved with general least amount energy. The insignificant molecule, identified as ligand, generally fits of laughter contained by the protein's fissure which is predicted by the search algorithm. These protein cavities are converted into operating after they get nearer in call with any exterior compounds and are as a result called as functioning sites and also so docking the stage and virtual responsibility in rational drug design. Certain in biological and pharmaceutical impact of molecular docking, large labors cover been directed toward civilizing the methods second-hand to predict docking. In plain words, Docking is a fashion which predicts the favorite orientation of one molecule to a second at what time touch to both others to grow a sure complex. The docking was completed by means of AutoDock software. Afterwards the pre-ligands were validated by means of AutoDock description 4.2 which is extra sufficient. The planned compounds were docked inside the semiprecious stone construction of targets and were experienced for the band energies and hydrogen bonding interactions with working sites. Docking studies make available the in order to realize out the crucial residues at the operating place of the target. Position or grading of the compounds is based largely on the band modes with anticyclone cover energies and enhance integer of hydrogen bonds. Output of every one of compounds was publicized in energy provision in Kcal/mol <sup>[18,19,20]</sup>.

### 3.6. Docking procedure:

Docking calculations were performed with AutoDock vina4.2 and for inevitable management of in analogy kind and via the Lamarckian Genetic Algorithm system resources an in back-to-back batch lettering (DOCKFACE) was used. The batch screenplay was planned to facilitate transmission stepwise. The procedures enter ligands and receptor preparation, grid maps generation, dpf annals preparation and performing docking runs. The molecular docking was conducted with a genetic algorithm (GA) means to retrieve the paramount pose of all ligand in the in action position of enzyme and protein. The grid maps of the protein were calculated by Auto grid (part of the Auto Dock package).The dimension of the grid was set to take account of not lone the dynamic situate but additionally sizeable portions of the surrounding surface. A grid package magnitude of 65x65x65Å in x, y and z information was built on the pinpoint of mound

of the co-crystal ligand in the active-site of aromatase points with a grid spacing of 0.375 Å was generated via AutoGrid. The grid was created at x, y and z coordinates of 83.35,49.60,50.60 which was reported as the edging situate residues <sup>[15,17,19]</sup>.

### 3.7. Docking validation:

For docking validation, 10 operating ligands and 70 immobile decoys were retrieved from ChEMBL list as SMILES plan. Iterative runs of OpenBabel 2.3.2 through a shell script provided the chief 3D invention of the structures as mol2 format. The docking of these compounds was obtained based on the functional docking route for our designated ligands. The two metrics of virtual showing as well as the spot under the curve (AUC) for receiver in service characteristics (ROC) plot and the maximum. The cost of the enrichment factor (EFmax) was calculated for involved ligands <sup>[19,20]</sup>.

### 3.8. ADME prediction:

The crucial pharmacokinetic properties such as Absorption, Distribution, Metabolism, Excretion (gastro intestinal absorption, head permeability) and the toxicity of the compounds be capable of be predicted by the ADMET-SAR (<http://www.admetexp.org>) database. In the ADMET-SAR, mesh based query tool is incorporating a molecular build-in edge enabling the file to be queried by SMILES and structural similarity search. It provides the newest and on the whole wide-ranging manually curated figures for diverse chemical coupled with notorious ADMET profiles (ADMETSAR@LMMD) <sup>[14]</sup>.

## IV. RESULTS AND DISCUSSION

In the modern study, other than twenty of 1,2,4-triazole compounds were docked on the effective place of aromatase and band location of colchicine and the domino effect was summarized. Parent name of the structure is 1,2,4-triphenyl-3-(1H-1,2,4-triazol-1-yl) butane-1-one has been docked based upon the above parent structure, ligands has been changed and many other compounds are designed. Compound 1 to 5 was designed by ligand 1(x-CO,r-F,r'-NO<sub>2</sub>),ligand 2 (x-CH<sub>2</sub>,r-Cl,r' - H), Ligand 3(x-CO,r-Cl, r' - H), Ligand 4(x-CO,r-Cl,r' -F)and ligand 5 (x-CO,r-cl,r' - cl) respectively, ready to dock <sup>[20]</sup>.

### 4.1. Antitumor activity:

In vitro anticancer actions of the synthesized compounds were evaluated against the human being cancer ranks MCF-7(human being adenocarcinoma) via MTT assay.The attempt was associated with the discount of tetrazolium salted by mitochondrial dehydrogenase of viable cells to style a down formazan result dissolved inDMSO and slow at 570 nm.All the veteran compounds prove remarkable cytotoxic leisure interest with IC<sub>50</sub>(50% Inhibition of tumor sect growth) morals ranging from 3.02 to 15.37 µM and docetaxel and tamoxifen were old as sure control, respectively <sup>[20]</sup>.

### 4.2. Docking results:

Analysis of the docking consequences was performed by means of AutoDock tools. Such tools

be capable of assist explicate which manner of interaction (e.g., hydrogen-bond,  $\pi$  -  $\pi$  interaction and cation-  $\pi$  interaction) contributed to ligand binding. The generally promising ligand strip posses as discovered by clustering histograms next to with their corresponding stitching energy were obtained from AutoDock Tools. Docked conformers of AI drugs were approved out by superimposing in cooperation structures followed by calculating their rifle suggest squared deviation (RMSD) in common to tell apart any conformational exchange that may show space upon protein binding. The RMSD of the superimposed structures were calculated. Additionally, the molecular properties of the optimized ligand structures were obtained from quantum element calculations via Gaussian 09 W at the B3LYP/6-31G(d) level. The intended compounds were docked inside the gemstone configuration of targets and were experienced for the compulsory energies and hydrogen bonding interactions with committed sites. Docking studies present the in order to come across out the crucial residues at the functional position of the target. Grading of the compounds is based for the most part on the cover modes with in height stitching energies and enhancing integer hydrogen bonds. As depicted on schedule 1, the energy of compounds docked ranged from -8.34 to -9.96 kcal/mol for aromatase. The energy of the compounds docked on aromatase new than the energy of the compounds docked on requisite sites of colchicine. These consequences indicated that these compounds had additional resemblance to compel on the effective position of aromatase. Interestingly, ligand 1-(4-chlorophenyl)-3,4-diphenyl-2-(1H-1,2,4-triazol-1-yl) butane-1,4-dione provided the top energy of docking for in cooperation targets. These energy morals were -9.93 kcal/mol for aromatase. The triazole of ligand 4sharp to edge and in aromatase full of the life location and in time to Fe pf shortens through its N4 atom. In addition, two - cation interactions were too observed, one interaction between triazole and porphyrin of lengthen group and the other was 4-chloro phenyl moiety of this ligand with Arg115 residue. It was experimental that this ligand in use the hydrophobic pouch with the residue Leu477, Trp224, Leu372, Ala306, Ile133, Val373 and Val370. Docked poses of ligand 4 were visualized to stumble on the nearly all key remains at the full of life position of mutually targets <sup>[20,21,22]</sup>.

### 4.3. Docking validation:

**ROC CURVE:** Validating of the docking protocol was investigated by the ROC curve. The ROC curve showed that the AUC is extra than 0.828 and this protocol is valid. The appliance of comparative in commission characteristic (ROC) in computational healing chemistry as a handy metric tool to evaluate the authenticity of docking protocols was primarily reported by Triballeau et al. Nowadays, it is generally used as a validating procedure. ROC cherish is the AUC for the plot of the sincere clear price (sensitivity) against the deceiving (clear-cut regard FPR or 1-specificity) at a variety of threshold settings. The ROC curve is as consequence the sensitivity as a party of 1-specificity. The AUC for ROC is calculated by trapezoidal integration reasoning as implemented in our in-house application. The extra AUC for ROC regard instrument that the docking protocol is new proficient to discriminate between functioning ligands and decoys <sup>[15,16]</sup>.

**EF-MAX:** It is an extra routine old to evaluate the value and excellence of docking protocol. EF (max) in likeness to ROC curves, it very much depends on the set of numeral of actives. As an occurrence of outcome, the EFmax of 4.75 showed that our functional docking sort out was validated. Its calculations were based on the Li et al. work .It measures that primitive fortification preserve be certainly obtained if the amount of involved ligands is greater than ever in a dataset <sup>[15,21,22]</sup>.

## V. CONCLUSION

In this article, conclude that triazole and its derivatives cover has been generally considered and out of the ordinary biologically behaviour receive has been reported for these compounds. The correlation between aromatase enzyme and anticancer activity has befallen the crucial theory of our research. Here, we deliberate roughly novel drugs based on anastrozole and letrozole frequently established as triazole compounds. The structures of newly synthesized compounds were characterized by IR, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR and magnitude shadowy breakdown and as well as were screened for in vitro anticancer action against breast growth group defense and capable fallout were obtained. Based on the program results, it was experimental that the compounds (lig4) are proved to be a large amount persuasive to anticancer interest against breast sarcoma booth track (MCF-7). The anticancer movement showed shows potential results. Additionally, molecular docking studies were agreed out to predict the probable molecular aim at for the synthesized molecules and the principles ever involve that these molecules are promising drug candidates. About 80% of breast cancers rely on food of hormone estrogen to grow of dead the nearly everyone victorious treatments rendered are manipulate of aromatase inhibitors (AIs). Aromatase enzyme the stage enormously crucial character in the oestrogen activist breast cancers and that's why establishes itself as a capable drug candidate. There are of use candidates old in medication of hormone needy breast cancer. Aromatase inhibitors are the course group of drugs which blocks the enzyme aromatase, the enzyme that converts androgens into estrogen. The interaction of aromatase with its inhibitors which were elucidated by docking studies indicated that the cover energies of the ligands are an occupation of the space between nitrogens of triazole of Fe inside. Lig4 showed that it has an extraordinary possibility to inhibit aromatase enzymes of docking required energy (-9.93kcal/mol). Here, we put forward that triazole and triazole derivatives compounds have a good binding source of drug design studies for this target and the results were shown. The understanding acquired from this research has key applications for the education of new and extra selective AIs agents.

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