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Theoretical Drug Design, Molecular Docking and ADME Study of New 1,3,4-Oxadiazole Derivatives: Promising Anticancer Agents Against Both Breast and Lung Cancers

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Abstract

Molecular docking simulation of seven (7) compounds of 2,5-Disubstituted-1,3,4-Oxadiazole was carried out so as to evaluate their theoretical binding affinities, targeting breast and lung cancers. The chemical structure of the molecules was accurately drawn using ChemDraw Professional 16.0 software. The designed compounds were checked for their selectivity towards ER and EGFR by using GOLD suite software. All the theoretically designed compounds exhibited excellent binding energies with the receptor active pocket and had promising activity with these proteins. Compound Y1 and Y2 shown the highest PLP Fitness values, with breast cancer protein ER, their values were (98.17, 98.15) respectively, and with lung cancer protein EGFR, their values were (98.88, 99.59) respectively. In-silico ADME and drug-likeness studies were performed by using the Swiss ADME server. The results showed that most of the compounds expected to be passively and highly absorbed from the GIT. Besides, all of the synthesized compounds satisfied the Rule of five (RO5).

Keywords: Oxadiazole, Anticancer, Docking Study, ADME Evaluation.

1. Introduction

Cancer is a group of various diseases resulted from the uncontrolled division of cells. They differ in the rate of cell growth, invasion of surrounding tissue and spreading to other parts of the body. It is a serious health problem, affecting many lives in developing as well as undeveloped countries, killing annually about 7 million people around the world [1]. Breast cancer is the second most common invasive cancer in women after skin cancer [2]. It affects 14 percent, i.e. 1 out of 7 women worldwide and it is strongly related to age with only five percent of all breast cancer incidents occurring in women under 40 years old [3]. Lung cancer is the leading cause of cancer-related mortality around the globe, resulted in approximately 25 percent of all cancer deaths [4]. The main risk factors associated with the initiation of lung cancer are smoking, exposure to asbestos, and inhalation of gaseous mutagens [5]. The collective effects arising from resistance and genotoxicity of the existing anticancer agents are the major challenges of modern medicinal chemistry, leading to increase the search for novel small molecule chemotherapeutic drugs, which are safe and efficient in order to prevent or even cure cancer [6]. The concept of computational chemistry such as computer-aided drug design (CADD) might save the time of discovering new molecules which also reduces the cost of synthesis [6].

In view of the constantly increasing incidence of various types of cancer, research on the anti-cancer properties of 1,3,4-oxadiazole derivatives seems to be of a particular interest. They have demonstrated so far their anticancer activities through anti-proliferative effects, including their action as Epidermal Growth Factor Receptor (EGFR) Inhibitors [14], Vascular Endothelial Growth Factor Receptor (VEGFR) Inhibitors [15], Endothelin Receptor (ET) Antagonists[16], Focal-adhesion kinase (FAK) inhibitors [17], Histone Deacetylase Inhibitors[18], Methionine aminopeptidase (MetAP) inhibitors[19], NF-κB (nuclear factor κB) inhibitors[20], Poly(ADP-ribose) Polymerase Inhibitors[21], Telomerase Inhibitors[22], Thymidine phosphorylase (TP) inhibitors[23]and Thymidylate synthase (TS) inhibitors[24].

The molecular docking studies are valuable tools for the development of new compounds with the prediction of their affinity, interaction with receptors, and the most significant biological activity. GOLD is

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a "genetic algorithm for docking flexible ligands into protein binding sites" it is part of CCDC GOLD suite (v.5.8.0), and has the advantage to predict the pose and gives perfect outcomes for virtual screening [25]. In-silico physicochemical properties of a molecule such as saturation, lipophilicity, polarity, size, solubility, and flexibility give vital information on whether the molecule can serve as a drug at an early stage of development [26]. SwissADME is a web tool that gives free access to a pool of rapid yet robust predictive models for physicochemical properties, pharmacokinetics, drug-likeness and medicinal chemistry friendliness, among which in-house proficient methods such as the BOILED Egg, iLOGP and Bioavailability Radar [28].

The aim of this study was to perform virtual screening of seven (7) new 2,5-Disubstituted-1,3,4-Oxadiazole derivatives through molecular docking strategy with ER protein and EGFR protein as the receptors, and identify a possible lead molecule to design new hypothetical molecules with improved binding affinities, and better molecular residual interactions with the receptors for both breast and lung cancers. Furthermore, in-silico Absorption, distribution, metabolism, and excretion (ADME) and druglikeness properties of the molecules were also evaluated.

2. Methodology

2.1. Chemical synthesis

The hypothesized synthesis pathway for compounds Y1-Y7, is derived from 5-styryl-1,3,4-oxadiazole-2-thiol, as the following scheme :

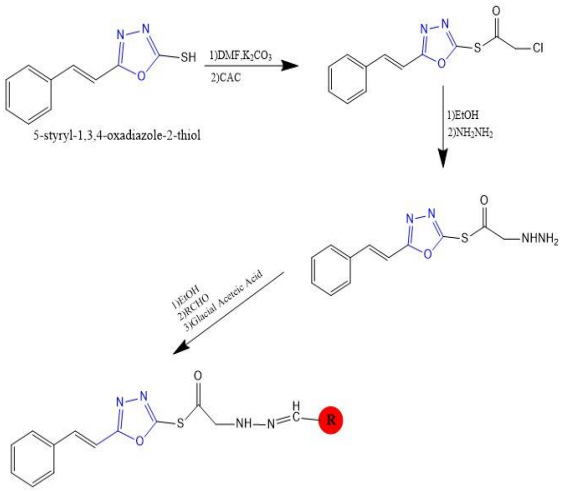


Fig.1. Hypothesized synthetic pathway of compounds (Y1-Y7).

DMF (N,N-Dimethyl formamide); K2CO3 (Potassium carbonate); CAC (Chloroacetyl chloride); EtOH (Ethanol); NH2NH2 (Hydrazine Hydrate); RCHO (different aldehydes).

2.2. Computer System and Software

Computer system (Dell), with the following specification properties; CPU Dual@ 0.30 GHz, Intel ® Core i3-6100U, 12 Gigabyte RAM was used throughout the present study. The software download and installed include fully licensed CCDC GOLD suite V. 2020.3.0 and Chemdraw Professional software V.16.0. Swiss ADME online software.

2.3. Drug Likeness Profile

Pharmacokinetic or ADME studies and other physicochemical properties of our designed compounds were determined by using the SwissADME online server www.swissadme.ch The chemical structure of newly designed compounds was drawn by using chemAxon's Marvin JS then converted into SMILE name. BOILLED Egg was used to determine the lipophilicity and polarity of small molecules [28].

2.4. Ligand/Receptor preparation and Molecular docking protocol

First, The chemical structure of the molecules was accurately drawn with using ChemDraw professional (v.16.0) Software, then energy minimization for our compounds was done by using Chem3D (v.16.0) and by applying the MM2 force field.

Second, the receptors loaded into the Hermes module of GOLD from the protein data bank PDB website: https://www.rcsb.org/, which are the crystal structures of Human Estrogen Receptor (ER) Protein (PDB code:1ERR) complexes with Tamoxifen and Epidermal Growth Factor Receptor (EGFR) protein (PDB code:4HJO) complexes with Erlotinib.

Before performing the docking process, the receptors were prepared by adding polar hydrogen atoms to get precise ionization and tautomeric positions of amino acid residues, then removing the crystallographic water molecules not involved in the active site, and finally the extraction of the original ligands from the receptors active sites was done. The newly designed ligands were docked by using the 3D structure of the prepared active targets 1ERR and 4HJO.

Setup of the receptors for the docking process was done by using Hermes visualizer software in the CCDC GOLD suite. The determination of the active sites is according to the original ligands interaction sites. The protein binding sites with all the protein residues characterize within the (10 A°) of the standard ligands for the docking process.

All the parameters used during the docking procedure were chosen as default settings. The number of generated positions was set as (10), while the top-ranked solution was kept as default, also the early termination choice was turned off. Furthermore,

Chemscore kinase was used as a configuration template. While the piecewise linear potential (ChemPLP) was utilized as a scoring function. Finally, the results were saved as mol.2 files. That provides information about the best binding manner, the free energy of binding, and docked poses. These results were studied precisely to define the best binding and interaction of our designed ligand with amino acid residues of the ER and EGFR receptors.

3. Results And Discussion

3.1. Chemical Synthesis

The target compounds to be designed (Compound Y1-Y7) are derivatives of 2,5-Disubstituted-1,3,4-Oxadiazole, the hypothesized synthetic pathway might be used can be as mentioned in Figure(1), using 5-styryl-1,3,4-oxadiazole-2-thiol, as the starting compound, since it's been used in literature with proven anticancer activity both in vivo and in vitro[22].

3.2. Molecular Docking and Virtual Screening

Molecular docking is a simulation technique that explores ligand's best binding pose with the active site of a target [14]. This technique involves the selection of 3D- coordinate space of the binding site in the target and calculating the binding affinity of the resultant orientation of the molecule within the binding site which forms the complex [14].

GOLD docking studies resulted in the prediction of binding energies and selectivity of the designed compounds to proteins (EGFR) and (ER) through studying the molecular contact among the active binding sites of the proteins and the designed compounds.

The inhibitory activities of designed compounds were rated depending on the value of PLP fitness. GOLD software also gave the distance of hydrogen bonding between the designed ligands and a specific protein as well as all bonds length were $\leq 10 A^{o}$.

Table (1) shows The PLP fitness of the docked compounds and Tamoxifen on ER protein. Docking results showed that Compounds [Y1 and Y2] have the highest PLP fitness value (98.17, 98.15) respectively. While all other compounds [Y3-Y7] exhibited less binding energies than the reference ligand Tamoxifen, which gave PLP fitness value (91.5).

Tamoxifen formed H-bond through its N1 atom with ASP351 amino acid (A.A) residue, and short contact binding through its aromatic rings system with A.A residues THR 347, TRP 383, MET 388, LEU 391, ARG 394, PHE 404, LEU 428, and LEU 525 of the receptor protein, as shown in Figure (2).

Compound [Y1] formed 2 H-bonds with THR347 through it Oxygen atom of both, the 1,3,4-oxadiazole ring and -C=O of the side chain. Furthermore, its hydrogen binding with A.A residues ARG394, GLU353, LEU387 happened with the para N,N-Bis(2-hydroxyethyl)amino substitution of the aromatic ring (-R), which also involved within short contact interaction , as shown in figures (3 and 4).

Figures (5 and 6) shows that compound [Y2] formed two hydrogen bonds, through it's –OH group of the naphthalene moiety, with HIS524 residue of the protein.

Table (2) reveals the PLP fitness of the docked compounds and Erlotinib on EGFR protein. Docking results are indicating that all the designed compounds present better binding energies with the receptor active pocket and expected promising activity with EGFR protein since it binds to the amino acids (AAs) residue of the active site through H-bonds along with hydrophobic interaction and other short contacts.

Compounds [Y1, Y2 and Y7] with EGFR protein showed the highest PLP fitness values (98.88, 99.59 and 94.48) respectively. Only compound [Y4] exhibited less binding energy than the reference ligand Erlotinib that gave PLP fitness value (86.06) and its N-1 atom formed H-bond with MTE769, (O-CH3) group with LYS704 and N-3 atom formed H-bond through H2O Bridge with THR766 and THR830 along with hydrophobic interactions as depicted in Figures (7 and 8).

As illustrated in figures (9 and 10) compound [Y1] formed 2 H-bond via Oxygen atom of the 1,3,4-Oxadizole ring with THR830, 1 H-bond via C=O of the side chain with LYS721, and other 2 hydrogen bonding with LYS692 and THR766, along with other short contacts that reinforce the binding and gave PLP value (98.88).

The best pose of compound [Y2] that gave PLP fitness value (99.59) formed one H-bond through –OH group of naphthalene system with the MET769, and 2 H-bonds with THR766 & THR830 via -N & -O atoms of 1,3,4-oxadiazole ring, along with short contact as shown in Figures (11 and 12). On the other hand, the PLP value for compound [Y7] was (94.48) and gave H-bonds with LYS 721, THR 830, MET 769 AAs as shown in figure (13).

3.3. In-silico ADME/Pharmacokinetic Predictions

It was established that the antagonistic response of inhibitors with an enzyme or a protein receptor cannot promise the suitability of an inhibitor as a potential drug [15]. Therefore, ADME (absorption, distribution, metabolism, and excretion) including drug-likeness analysis are important in the drug discovery which helps to make a rational decision on whether inhibitors can be administered to a biological system or not [10, 15]. In addition, inhibitors with poor ADME properties and high toxicity effects on the biological systems are often the major cause of most failed medicines in the clinical phase of experiments. Rule of

five (Ro5) or Lipinski's rule of five (5) by Christopher A. Lipinski in 1997 is a thumb-rule for evaluating drug-likeness and to decide if an inhibitor with a certain biological and pharmacological properties would be an orally active drug in the human body [10]. The rule states that a molecule or an inhibitor can be orally absorbed/active if two (2) or more of these thresholds; molecular weight (Mw) of molecule < 500, octanol/water partition coefficient (iLOGP) ≤ 5, number of hydrogen bond acceptors (nHBA) ≤ 10, number of hydrogen bond donors (nHBD) ≤ 5, and topological polar surface area (TPSA) < 40 Å2) are not violated. SwissADME server was used for in-silico prediction of the physicochemical and ADME properties of designed compounds. It is a supportive and free method to detect the ADME properties before the synthesis and biological testing. In addition to exclude ligands inadequate with an unacceptable pharmacokinetic profile [28].

From the output of some ADME and drug-likeness properties shown in Table 3.

These parameters including the topological polar surface area (TPSA), were used to describe the ability of drugs to permeate cells, compounds with TPSA<140Å2 which mean high permeability and bioavailability [28]. The results showed that compounds [Y2,Y4,Y5 and Y6] have TPSA <140Å2 range from (105.68-125.91). However, The results showed that all synthesized compounds have zero violations and so satisfied the RO5. All of the designed compounds have bioavailability of 0.55, except compound [Y6] which has a value of bioavailability score 0.1, as shown in Table (3).

Table 1 The Binding Energies for New 1,3,5-Oxadiazole Derivatives and reference ligand Tamoxifen Docked With 1ERR

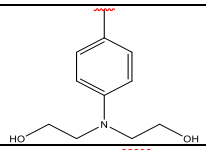
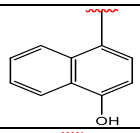
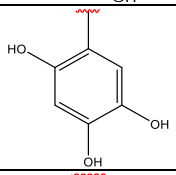
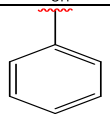
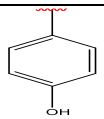
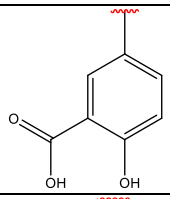
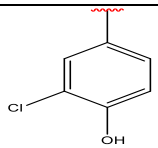
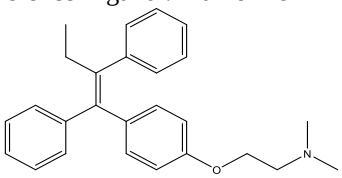
Compound	R	ER binding energy (PLP fitness)	Amino acid included in H-bonding	Amino acid included in short contacts
Y1		**98.17**	THR347, ARG394, GLU353, LEU387	MET 528, THR 347, PHE 404, ARG 394, GLU 353
Y2		**98.15**	HIS 24	LEU 354, LEU 536, ILE 424, MET 421, HIS 524
Y3		**87.47**	LEU 387, GLU 353	LEU 536, GLU 353, THR 374, MET 343, LEU 387, ARG 394
Y4		**87.33**	-	LEU 354, THR 347, ILE 424, PHE 404
Y5		**82.44**	THR347, GLU 353, ARG 394, LEU 387	THR 347, GLU 353, ARG 394, LEU 387, LEU 391
Y6		**81.83**	TYR526, THR347	THR 347, GLU 353, ARG 394, LEU 387, PHE 404
Y7		**80.78**	HIS 24	LEU 346, LEU 354, LEU 536, ILE 424, HIS 524
Reference Ligand : Tamoxifen 		**91.5**	ASP351	THR 347, TRP 383, MET 388, LEU 391, ARG 394, PHE 404, LEU 428, LEU 525

Table 2 The Binding Energies for New 1,3,5-Oxadiazole Derivatives and reference ligand Erlotinib docked with 4HJO

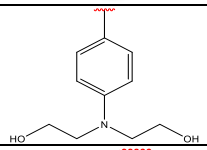
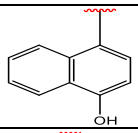
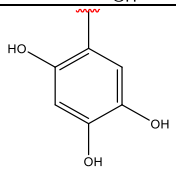
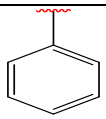
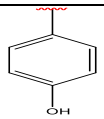
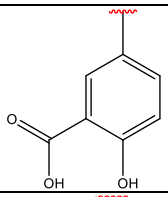
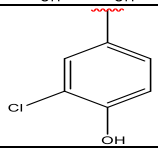
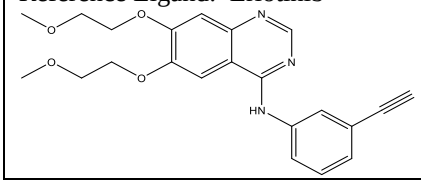
Compound	R	ER binding energy (PLPfitness)	Amino acid included in H-bonding	Amino acid included in short contacts
Y1		**98.88**	LYS 721, THR 766 THR 830, LYS 692	LYS 692, LEU 694, LYS 721, MET 742
Y2		**99.59**	THR830, THR766 MET 769	MET 742, ASP 831, THR 830, VAL 702, MET 769, THR 766
Y3		**88.29**	MET 769	MET 769, MET 742, LYS 710, THR 830
Y4		**82.92**	THR839, THR766, LYS 721	THR 839, THR 766, MET 742, VAL 702, LYS 721
Y5		**87.59**	MET769, THR766, THR830, LYS721	MET 769, LEYS 721, ASP 831, THR 766, THR 830, MET 742
Y6		**88.55**	LYS721, MET769, THR830, THR766	MET 742, ASP 831, THR 830 , LYS 721, THR 766, MET 769
Y7		**94.48**	LYS721, THR830, MET769	MET 742, MET 769, LYS 721, THR 830
Reference Ligand: Erlotinib 		**86.06**	MET 769,LYS704, THR766, THR830	ALA 719, CYS 773, LEU 834, LEU 694, GLY 695

Table 3 ADME and druglikeness parameters of compounds Y1-Y7

C	MW(g/ mol)	nHBD	nHBA	MR	TPSA(Å)	GI	BBB	BS	nLV
Y1	467.54	3	7	128.32	149.38	Low	No	0.55	0
Y2	430.48	2	6	121.71	125.91	Low	No	0.55	0
Y3	412.42	4	8	108.25	166.37	Low	No	0.55	0
Y4	364.42	1	5	102.18	105.68	High	No	0.55	0
Y5	380.42	2	6	104.20	125.91	High	No	0.55	0
Y6	424.43	3	8	111.16	163.21	Low	No	0.11	0
Y7	414.86	**2**	6	109.21	125.91	High	No	0.55	0

MW molecular weight, nHBD number of hydrogen bond donor, nHBA number of hydrogen bond acceptor, MR molar reactivity, TPSA topological polar surface area, GI gastrointestinal absorption, *BBB* blood–brain barrier permeation , *BS* Bioavailability Score, *nLV* number of Lipinski violation.

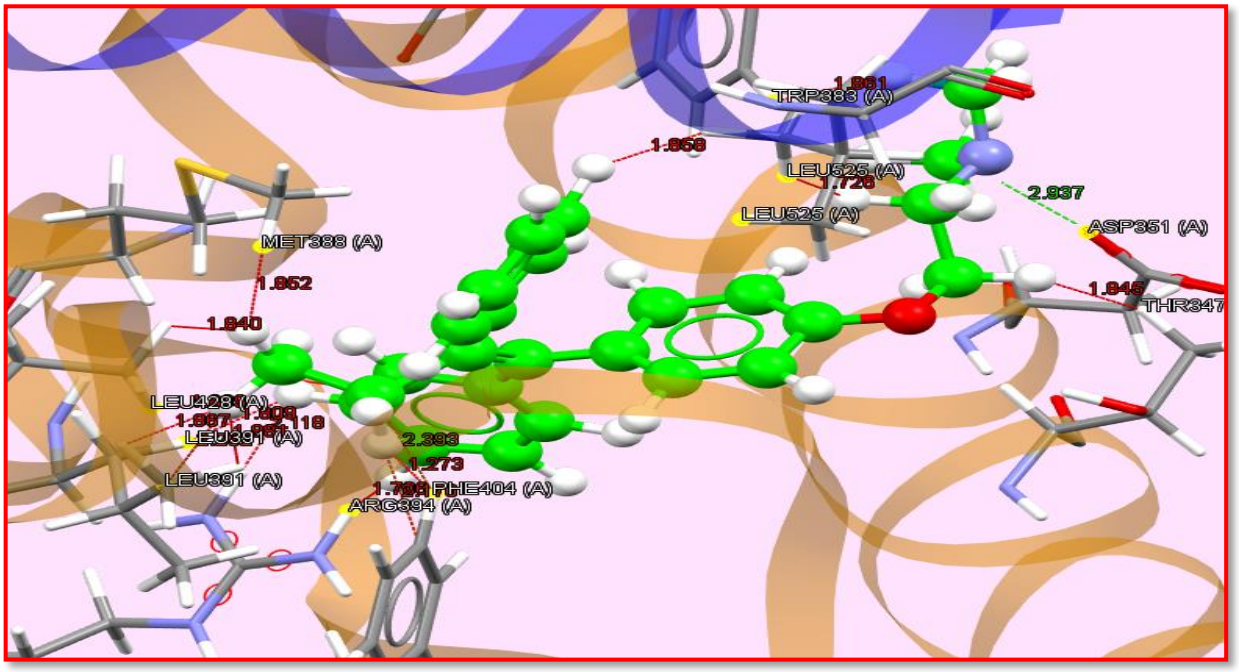


Fig.2. H-bond and short contact interaction profile for the reference ligand Tamoxifen binding with ER receptor (PDB code: 1ERR). The interaction between Tomxifen and amino acid residues by H-bond [ASP 351] represented in green while for short contact in red. [Tamoxifen ball and stick style, while amino acids in capped sticks].

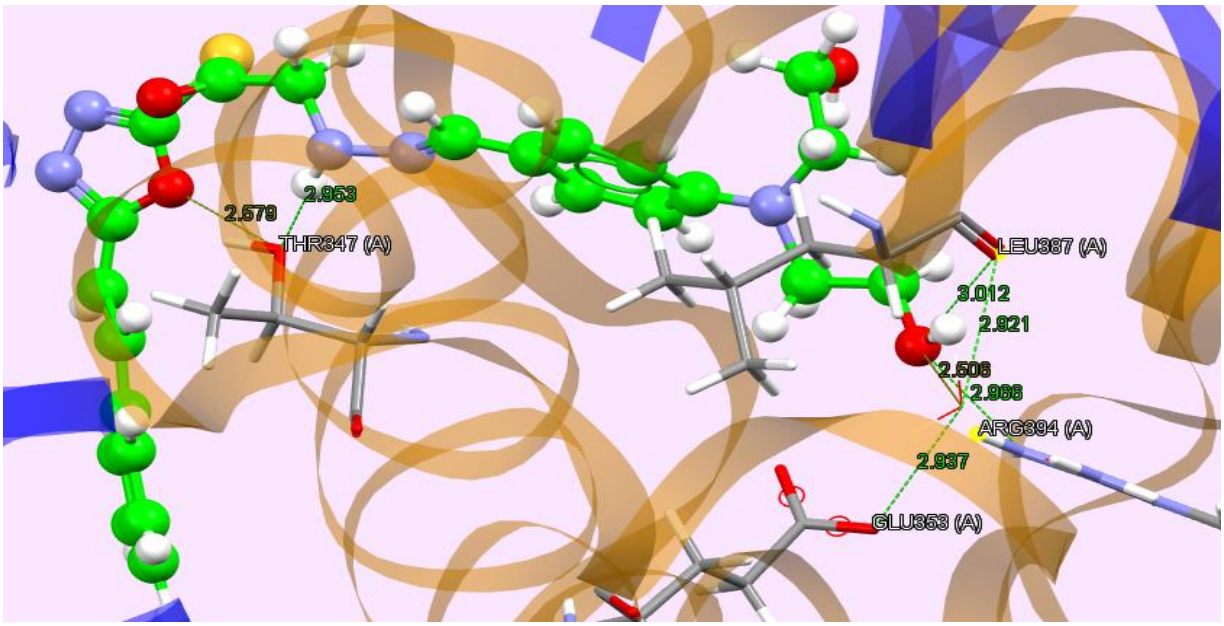


Fig.3. Compound Y1 binding with ER receptor (PDB code: 1ERR) interaction profile: H-bond interaction represented in green with amino acids residues [THR 347, ARG 394, GLU 353, LEU 387] [Compound Y1 ball and stick style, while amino acids in capped sticks]

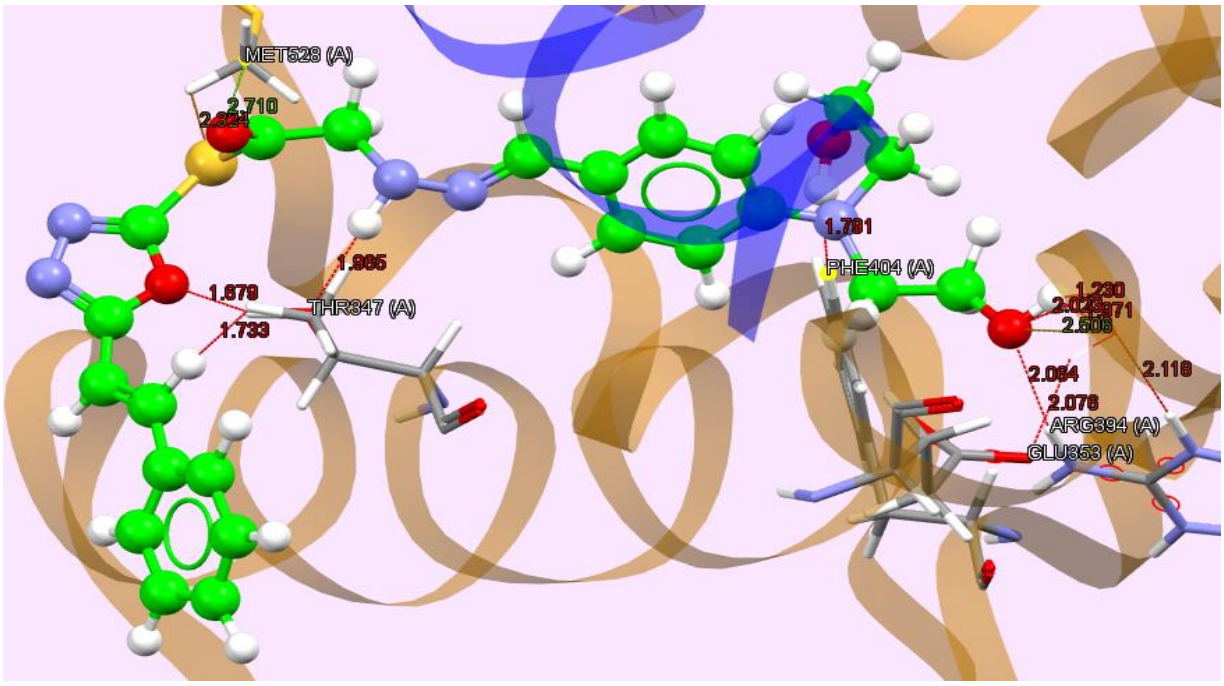


Fig.4. Compound Y1 binding with ER receptor (PDB code: 1ERR) interaction profile: Short contact interaction represented in red with amino acids residues [MET 528, THR 347, PHE 404, ARG 394, GLU 353]. [Compound Y1 ball and stick style, while amino acids in capped sticks]

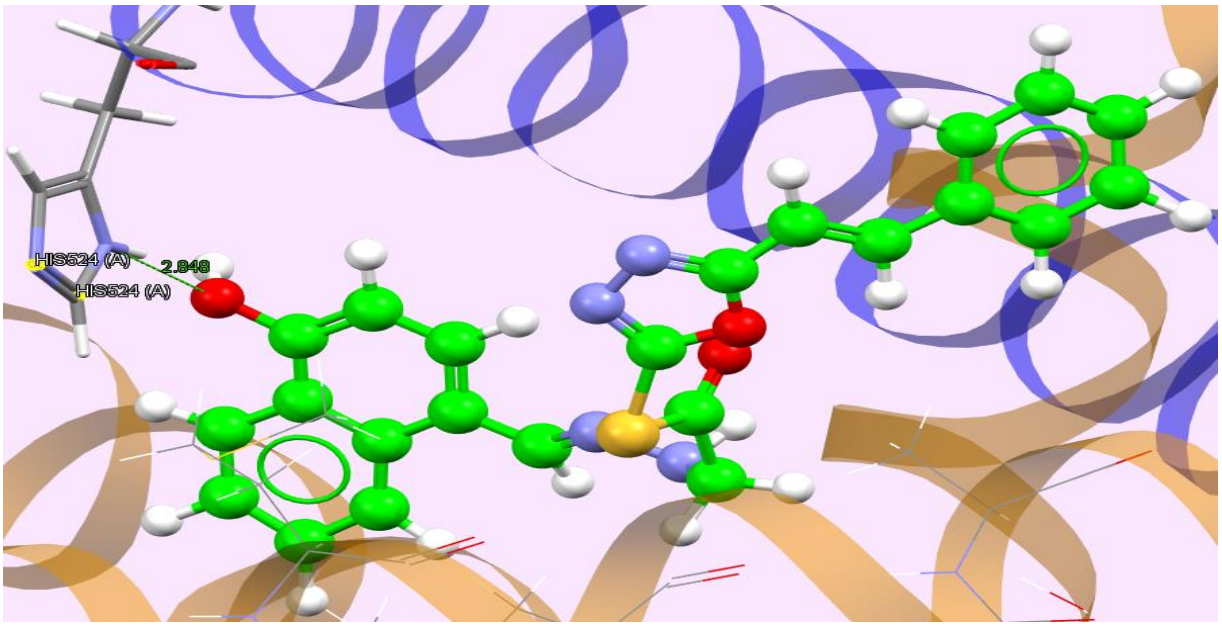


Fig.5. Compound Y2 binding with ER receptor (PDB code: 1ERR) interaction profile: H-bond interaction represented in green with amino acid residue [HIS 524] [Compound Y2 ball and stick style, while amino acids in capped sticks]

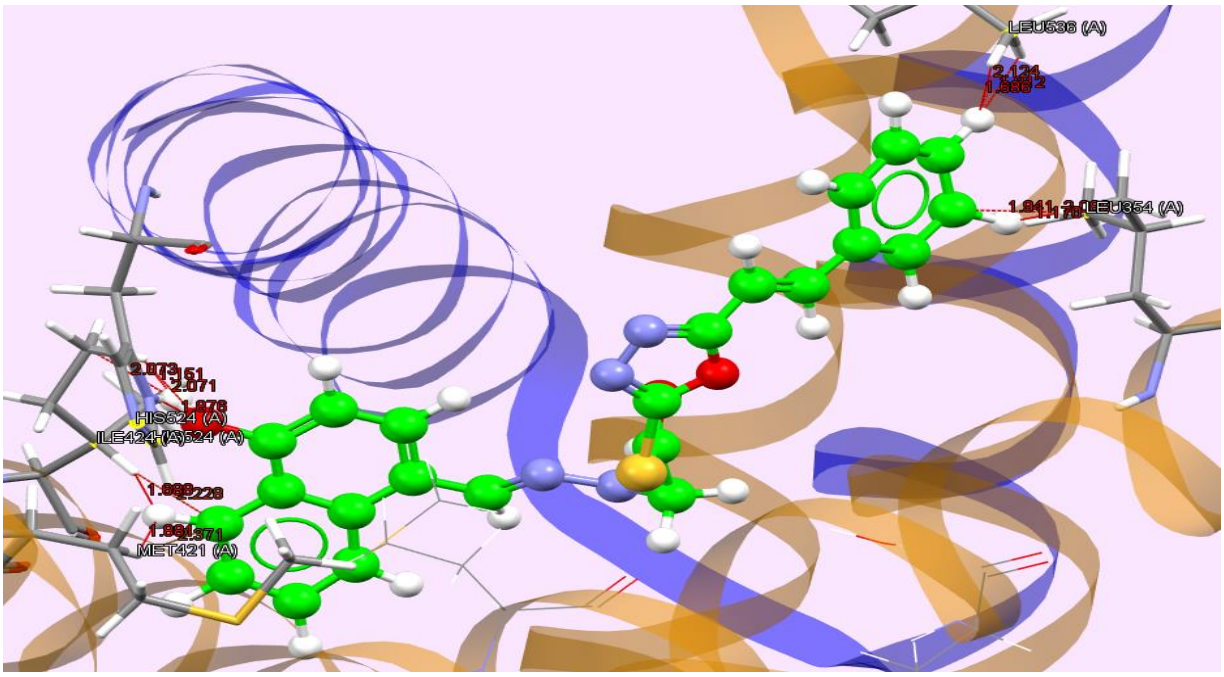


Fig.6. Compound Y2 binding with ER receptor (PDB code: 1ERR) interaction profile: Short contact interaction represented in red with amino acids residues [LEU 354, LEU 536, ILE 424, MET 421, HIS 524]. [Compound Y2 ball and stick style, while amino acids in capped sticks]

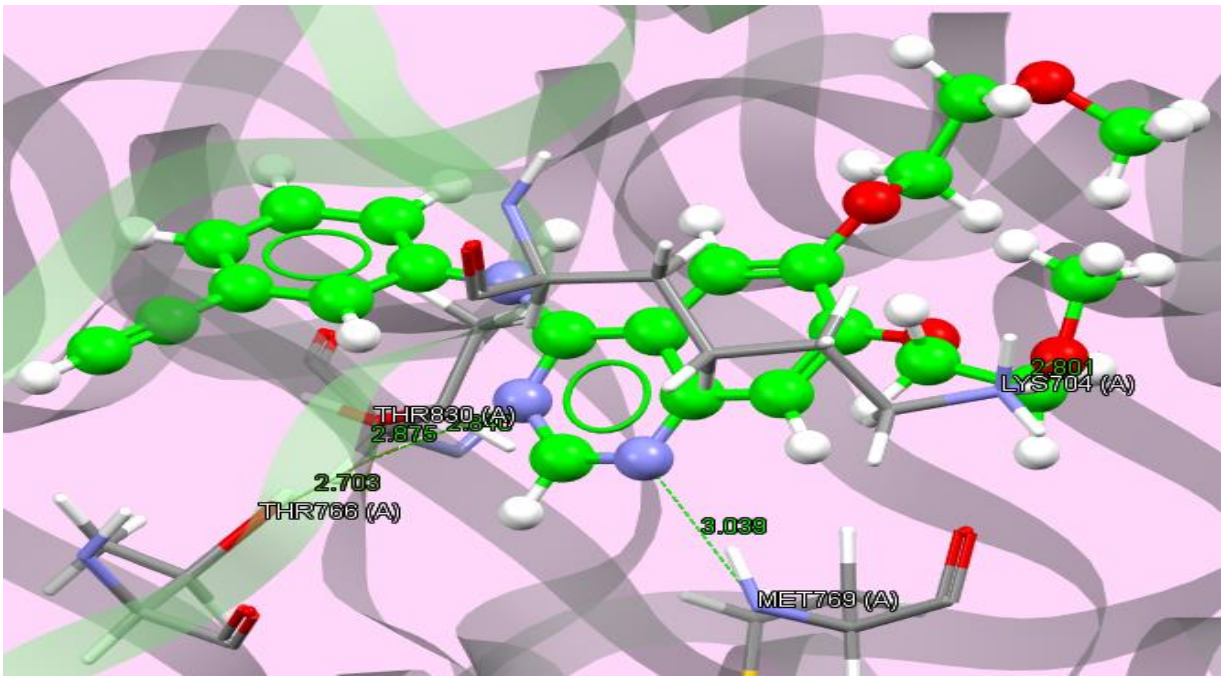


Fig.7. Interaction profile of the reference ligand Erlotinib with EGFR receptor (PDB code: 4HJO): H-bond interaction represented in green with amino acids residues [MET 769,LYS704, THR 766, THR 830] [Erlotinib ball and stick style, while amino acids in capped sticks]

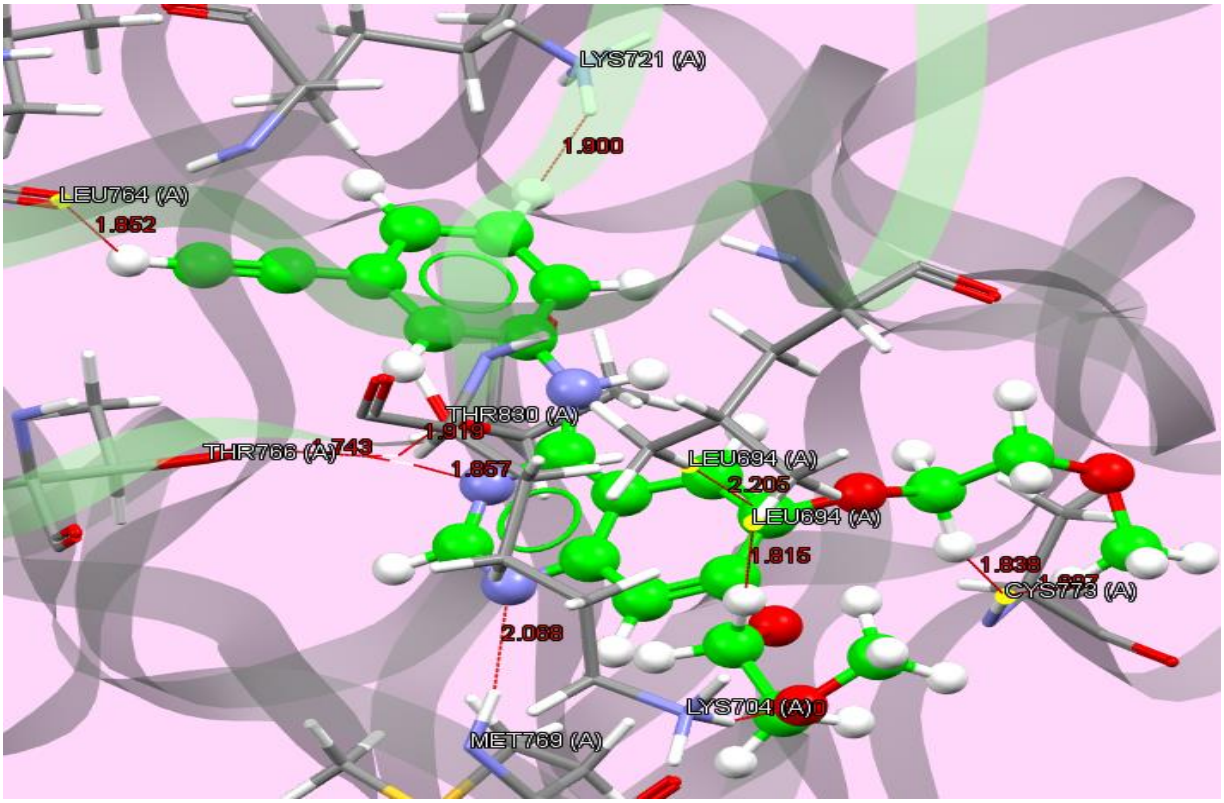


Fig.8. Interaction profile of the reference ligand Erlotinib with EGFR receptor (PDB code: 4HJO): Short contact interaction represented in red with amino acids residues [ALA 719, CYS 773, LEU 834, LEU 694, GLY 695]. [Erlotinib ball and stick style, while amino acids in capped sticks]

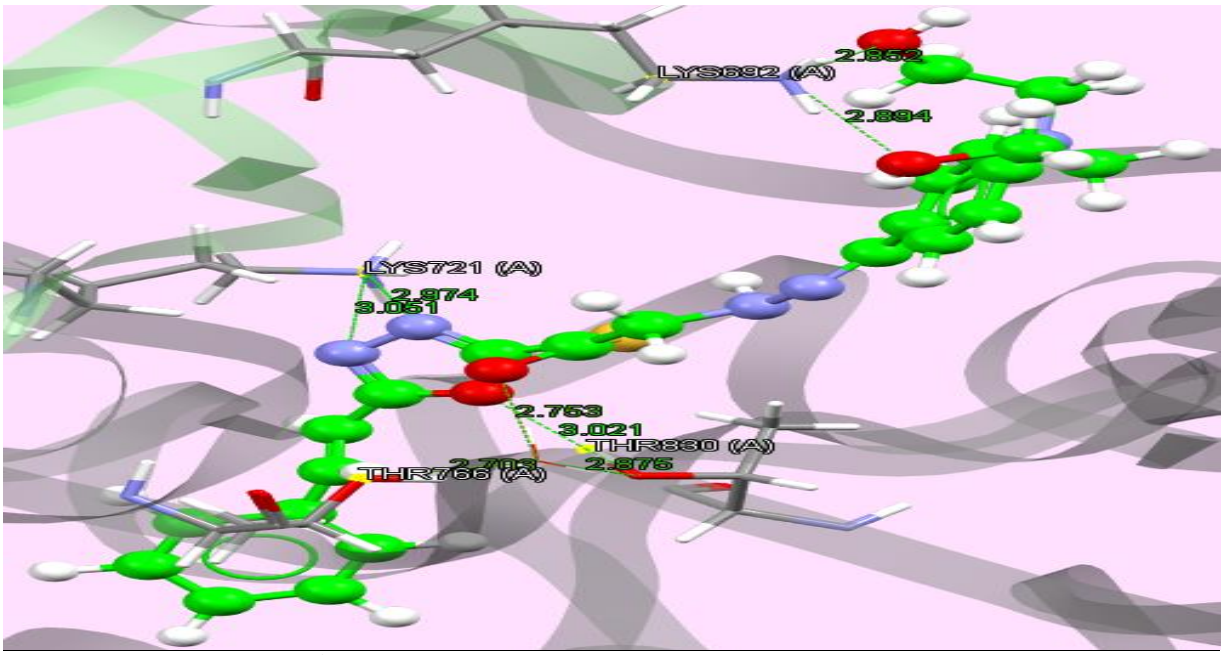


Fig.9. Compound Y1 Interaction profile with EGFR receptor (PDB code: 4HJO): H-bond interaction represented in green with amino acids residues [LYS 721, THR 766, THR 830, LYS 692] [Compound Y1 ball and stick style, while amino acids in capped sticks]

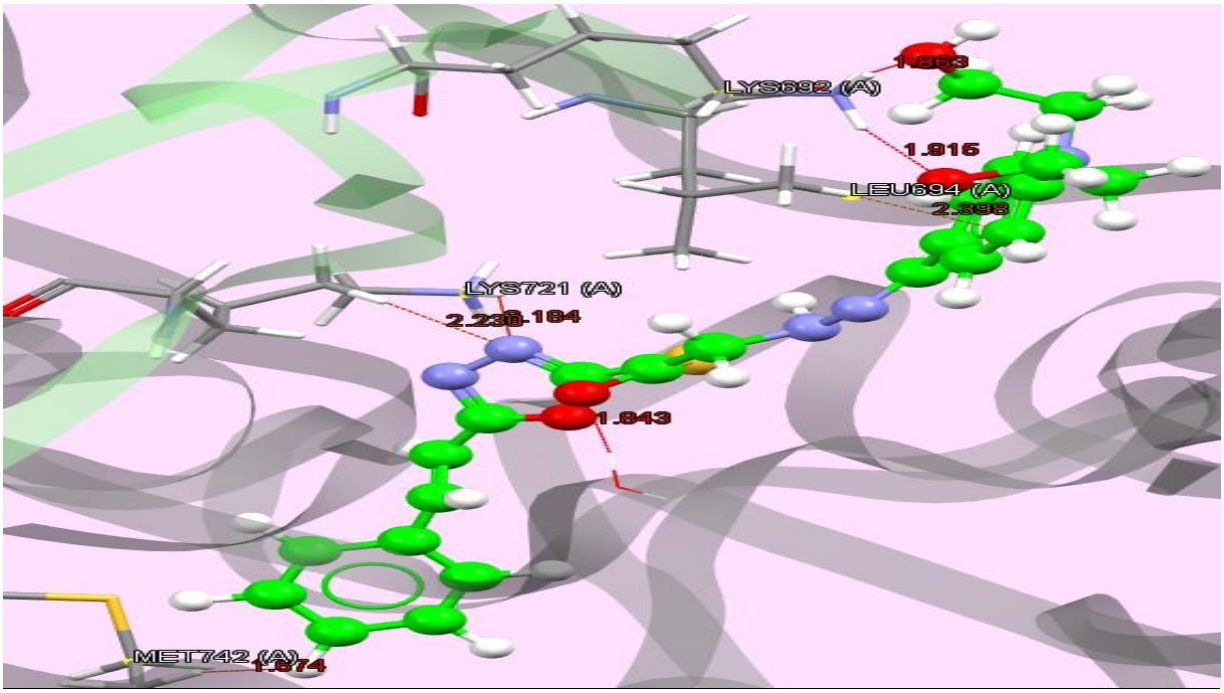


Fig.10. Compound Y1 Interaction profile with EGFR receptor (PDB code: 4HJO): Short contact interaction represented in red with amino acids residues [LYS 692, LEU 694, LYS 721, MET 742]. [Compound Y1 ball and stick style, while amino acids in capped sticks].

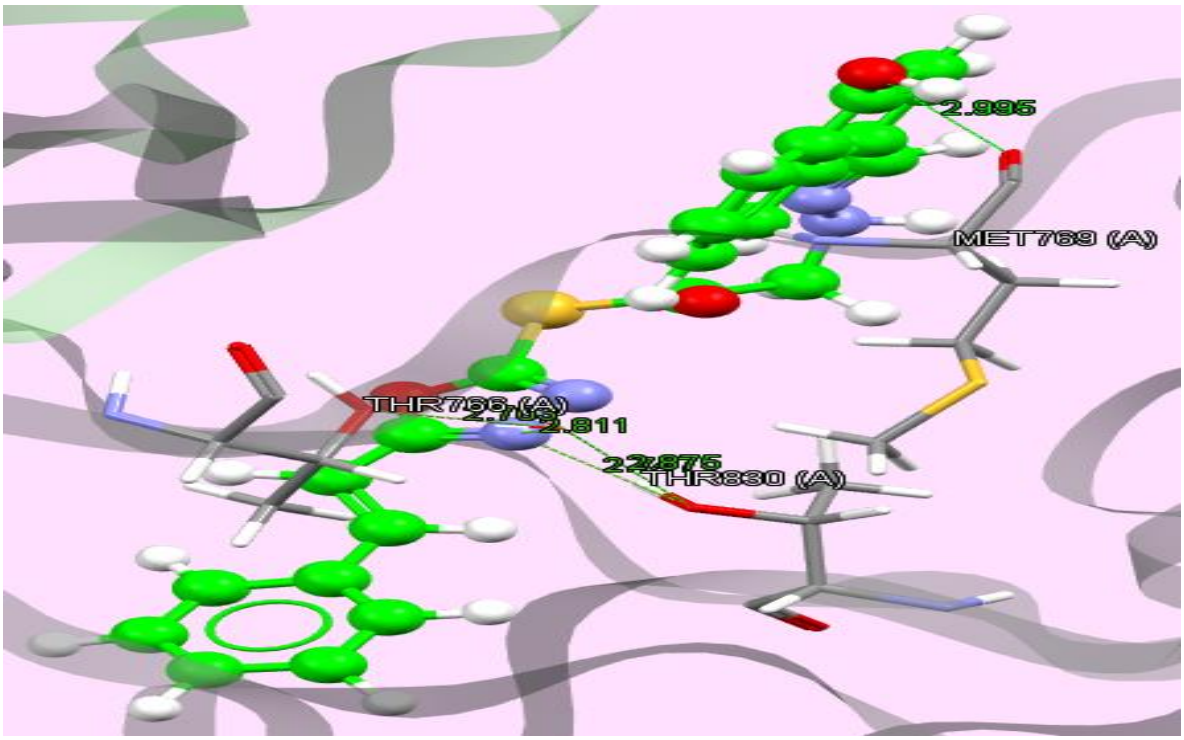


Fig.11. Compound Y2 Interaction profile with EGFR receptor (PDB code: 4HJO): H-bond interaction represented in green with amino acids residues [THR 830, THR 766, MET 769]. [Compound Y2 ball and stick style, while amino acids in capped sticks]

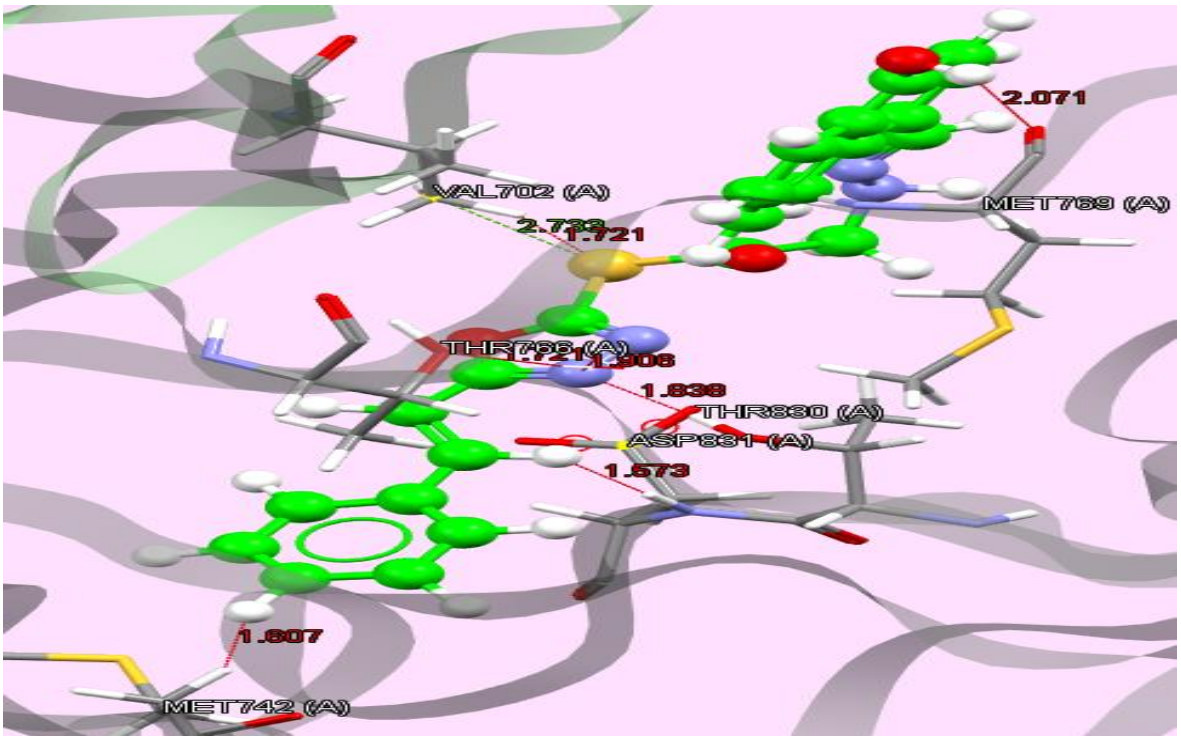


Fig.12. Compound Y2 Interaction profile with EGFR receptor (PDB code: 4HJO): Short contact interaction represented in red with amino acids residues [MET 742, ASP 831, THR 830, VAL 702, MET 769, THR 766]. [Compound Y2 ball and stick style, while amino acids in capped sticks]

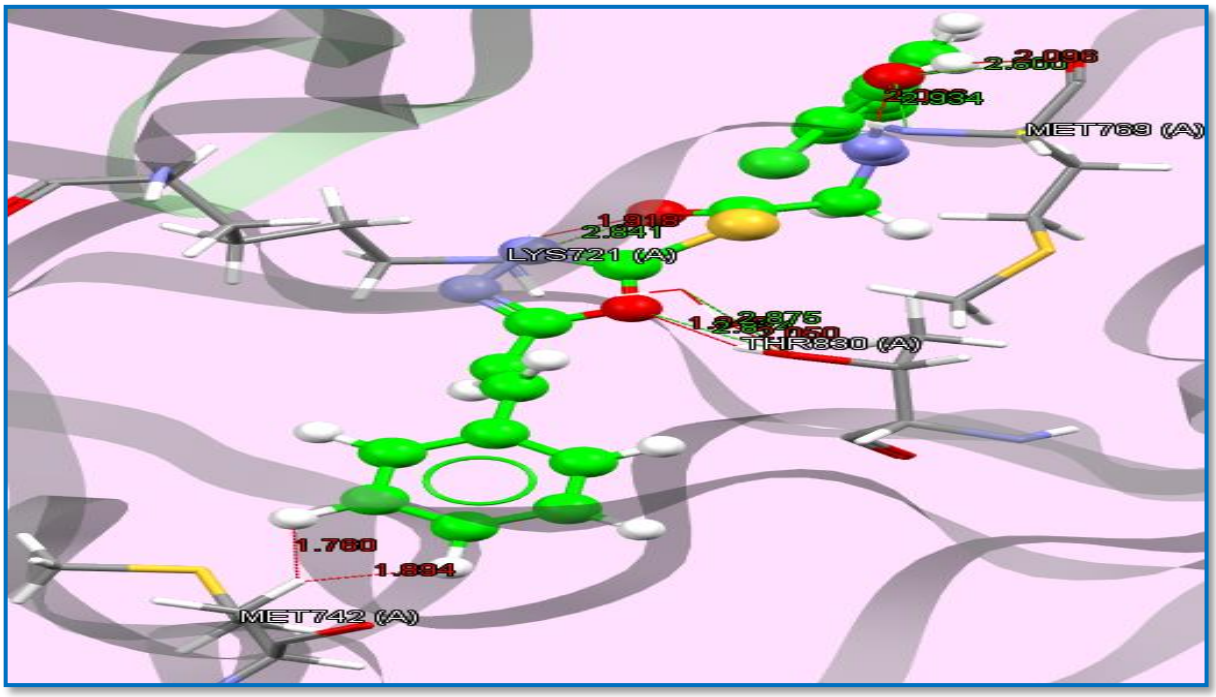


Fig.13. Compound Y7 Interaction profile with EGFR receptor (PDB code: 4HJO); H-bond interaction represented in green with amino acids residues [LYS 721, THR 830, MET 769] & Short contact interaction represented in red with amino acids residues [MET 742, MET 769, LYS 721, THR 830]. [Compound Y7 ball and stick style, while amino acids in capped sticks].

4. Conclusions

The present study designed new 1,3,4-Oxadiazole derivatives and evaluated them by using in-silico techniques. The GOLD docking results validated the potent anticancer activities against breast cancer and lung cancer, with majority of the identified compounds are showing good binding affinity with target proteins relative to the reference drugs (Tamoxifen and Erlotinib), with strongest anticancer compounds being [Y1 and Y2]. Furthermore, the SwissADME of all compounds were studied; and all of them satisfied RO5. These compounds can now be synthesized, analyzed chemically and evaluated individually for biological activity for anticancer actions, with the determination of their mechanism of action, and optimization in further studies.

Conflicts of interest

The authors declared no conflict of interest.

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