Pyridine Based Chalcone Derivatives as Inhibitor Against Breast Cancer: A Computational Approach.

Imran Musah Olalekan

Department of Science Laboratory Technology, The Oke-Ogun Polytechnic, Saki

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ABSTRACT

To evaluate the potency of two pyridine chalcone derivatives, CHA and CHB, against breast cancer, their inhibitory activities were assessed on four different cancer cell lines (6CZ2, 6CZ3, 6CZ4, and 5TWU) using the docking and scoring method. The binding energies of CHA on the four receptors were found to be -8.0, -8.5, -8.6, and -8.3 kcal/mol, respectively, and for the CHB ligand, they were -7.9, -8.3, -8.0, and 8.1 kcal/mol. A standard breast cancer drug, exemestane, was also docked with these cancer cell lines, yielding binding energies of -8.1, -8.9, 8.9, and -8.4 kcal/mol, respectively. Both ligands demonstrated good conformity with the standard drug, with CHA exhibiting higher binding energy than CHB. Additionally, both compounds adhere strictly to the Rule of Five (Lipinski's rule), suggesting that these drug-like compounds may be suitable for oral administration.

Keyords: Protein receptors, Pyridine chalcone, Docking, Scoring

INTRODUCTION

Abnormal cell proliferation in humans can result from a variety of factors, ranging from family history and lifestyle to environmental influences. Breast cancer, which is the most deadly and common form of cancer in women, can originate in different parts of the breast. It may be detected with medical instruments or felt as a lump. Most breast cancers begin in the milk ducts, a type referred to as ductal carcinoma, while others start in the milk-producing glands, known as lobular carcinoma. There are also sarcomas and lymphomas that develop in the other tissues of the breast; however, these are not typically classified as breast cancers[1]. Recent studies show that breast cancer in women can also be linked to artificial alterations in the size, shape, and contour of the breast due to implants. Additionally, breast cancer can metastasize by spreading to other parts of the body through blood and lymph vessels. Its symptoms include the formation of a new lump in the breast or armpit, swelling of part of the breast, skin irritation, nipple retraction or pain, discharge from the nipple that is not breast milk, and pain in any area of the breast[2].Significant efforts have been made by cancer researchers to design new anticancer agents that reduce side effects, thereby improving the odds of diminishing the risk of cancer globally. Many natural substances, such as chalcones, terpenoids, flavones, and flavonoids, have demonstrated anticancer, antibacterial, antifungal, and antimicrobial properties with minimal side effects. Numerous synthetic compounds modeled after natural product scaffolds have been developed from natural materials. Their effects on various diseases have been extensively studied by researchers, with chalcones being a notable lead structure[3-6]. Chalcones, aromatic ketone compounds present in certain plants, have a long-standing use in traditional medicine and have been proven to constitute the central core of a plethora of significant biological compounds. As one of the quintessential classes of flavonoids, chalcones are integral to the design of new pharmacological agents aimed at treating a diverse array of diseases. Furthermore, derivatives of pyridine chalcone have been demonstrated to possess a spectrum of biological activities. This study is focused on investigating the inhibitory activities of two such

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pyridine-chalcone derivatives against breast cancer receptors, employing a computational method [7-11].

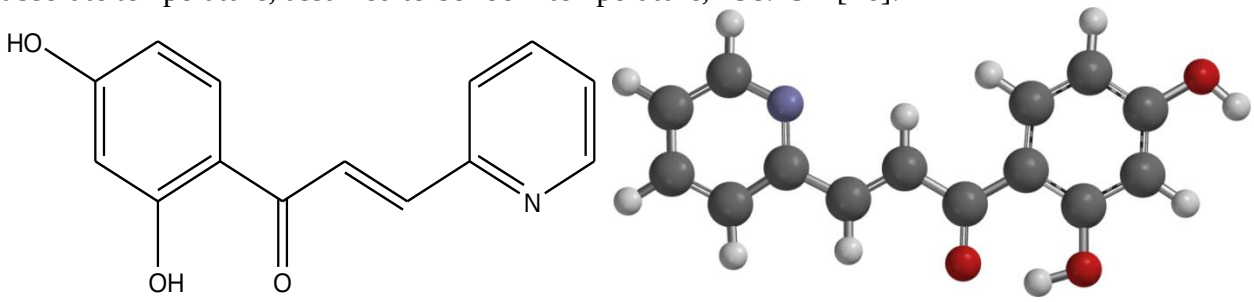
COMPUTATIONAL METHODS

Two derivatives of pyridine chalcone were constructed using Spartan 14 version 1.18 by Wavefunction Inc [12]. Geometry optimization and calculation of the two compounds were performed using density functional theory (DFT) with the 6-31G* basis set to obtain the molecular parameters responsible for the cytotoxicity of the compounds under investigation. The results were then saved as PDB files for docking studies[13]. The protein receptors responsible for breast cancer were obtained from the Protein Data Bank (PDB) [14] with no missing residues. A single strand was obtained by deleting multiple ligands, non-protein, and other protein parts from the PDB files. Autodock Tools version 1.5.6 was used to locate the binding site and to add hydrogen to the prepared protein receptor, which was then converted to PDBQT format for the docking process. Autodock Vina [15] was used for the docking process, and post-docking analysis was done using EduPyMOL version 1.7.4.4 and Discovery Studio 4.1 Visualizer. The inhibition constant was calculated using the following mathematical expression:

$$\Delta G = 2.303 * R * T \, logK_i$$

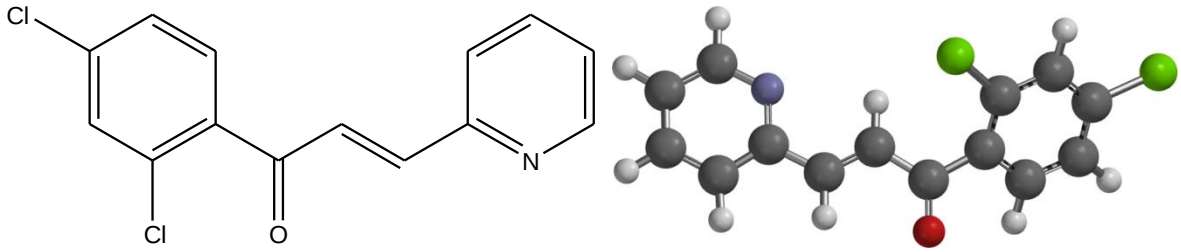
$K_i = e^{-\Delta G/RT}$[16]

Where ΔG is the binding affinity in kcal/mol, R is gas constant, 0.00199 kcal/mol/K and T is absolute temperature, assumed to be room temperature, 298.15K [16].



CHA = 3-(2, 4-dihydroxyphenyl)-1-(pyridin-2-yl) prop-2-ene-1-one

Figure1: 2D and Optimized 3D (Ball and Spoke) Structure of the CHA ligand



CHB = 3-(2, 4-dichlorophenyl)-1-(pyridin-2-yl) prop-2-ene-1-one

Figure 2: 2D and Optimized 3D (Ball and Spoke) Structure of the CHA ligand

RESULT AND DISCUSSION

Molecular Properties

The analysis of Density Functional Theory (DFT) was performed on two pyridine-chalcone derivatives and

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the breast cancer drug exemestane. The Quantitative Structure-Activity Relationship (QSAR) properties, including the Highest Occupied Molecular Orbital (HOMO), Lowest Occupied Molecular Orbital (LUMO), Band Gap (BG), Dipole Moment, Chemical Hardness (CH), Solvation Energy (SE), Molecular Weight (MW), Log P, Area, Volume, Ovality, Polar Surface Area (PSA), Polarizability, Hydrogen Bond Donor (HBD), and Hydrogen Bond Acceptor (HBA), were calculated. These properties contribute to the compounds' potency.

Both compounds adhere strictly to the Lipinski rule of five, which assesses drug-likeness based on criteria: Log P < 5, Molecular Weight < 500, HBD < 5, and HBA < 10. The HOMO and LUMO values for the ligands CH-A and CH-B are 4.98eV, -2.28eV with a 2.70eV band gap, and -4.65eV, -2.42eV with a 2.23eV band gap, respectively. These values indicate the ligands' complex stability and high reactivity with receptors. Ligands with higher HOMO values can donate electrons, and those with lower LUMO values can accept electrons from receptors. Lower band gaps correspond to higher complex stability [16,18].

The ligands also have low PSA values, less than 60Å², with 33.891Å² for CH-A and 20.766Å² for CH-B, suggesting good cell membrane penetration ability. Molecules with PSA values greater than 140Å² typically have poor penetrating power. Other parameters, such as dipole moment, solvation energy, ovality, and polarizability, were calculated and indicate the ligands' potency against breast cancer receptors. Therefore, the compounds are potentially suitable for oral administration.

Table 1: Molecular descriptors/parameters of the ligands

Molecular Parameters	CH-A	CH-B
Molecular formular	$C_{14}H_{11}NO_3$	$C_{14}H_9Cl_2NO$
Molecular weight (amu)	241.246	278.138
Dipole moment (debye)	2.79	3.01
Area (**Å^2**)	260.89	278.25
Volume (**Å^3**)	242.85	257.66
Ovality	1.39	1.42
Polar Surface Area (PSA)	33.891	20.766
Hydrogen Bond Donor (HBD)	2	0
Hydrogen Bond Acceptor (HBA)	4	2
Polarizability	60.20	61.27
Salvation Energy (kj/mol)	-74.51	-22.41
Log P	2.67	2.57
HOMO (eV)	-4.98	-4.65
LUMO (eV)	-2.28	-2.42
Band Gap	2.70	2.23
Chemical Hardness (eV)	3.63	3.54

Docking and Scoring Result

The table below presents the docking and scoring results. During the process, four different protein receptors associated with breast cancer were docked with two ligands (CHA and CHB) as well as with exemestane, a breast cancer drug. AutoDock Vina generated nine different binding modes, and the best binding mode is determined by the highest negative value. Therefore, the binding mode with the most negative value is considered to have the strongest inhibitory effect on the protein receptor[12]. CHA gave binding energy -5.0kcal/mol for 6CZ2, -8.5Kcal/mol for 6CZ3, -8.6kcal/mol for 6CZ4 and -8.3Kcal/mol for 5TWU. Also, CHB binds with -7.9Kcal/mol for 6CZ2, -8.3Kcal/mol for 6CZ3, -8.0Kcal/mol for 6CZ4 and -8.1Kcal/mol for 5TWU binding energy. The binding energy of the two ligands withthe receptors agree with the standard

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drug used during the work.In addition the binding energy of CHA are higher as compared to the binding energy of CHB against the four cancer receptors, hence, CHA will be more potent on breast cancer than CHA ligands. As a result of the two ligands conforming well with the standard drug, therefore the two compounds will be very suitable for the treatment of breast cancer.Further study using probability modeling [19-22] to understand the properties and binding interactions could be considered for this study to gain a better understanding of the interactions with breast cancer receptors and other protein receptors.

Table 2: Docking score results for Breast cancer receptors.

Receptors	CH- A		CH- B		Drug	
	ΔG(Kcal/mol)	K_i (μM)	ΔG(Kcal/mol)	K_i (μM)	ΔG(Kcal/mol)	K_i (μM)
6CZ2	-8.0	1.0136	-7.9	0.9868	-8.1	1.0138
6CZ3	-8.5	1.0144	-8.3	1.0141	-8.9	1.0151
6CZ4	-8.6	1.0146	-8.0	1.0136	-8.9	1.0151
5TWU	-8.3	1.0141	-8.1	1.0138	-8.4	1.0142

ΔG =Binding energy Ki =Inhibition constant

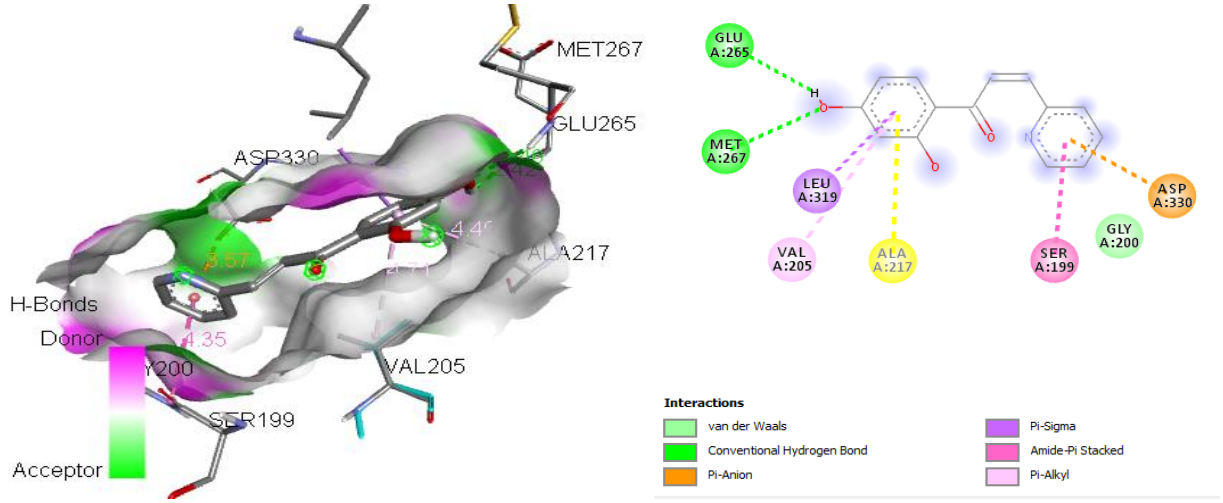

Figure 3: Hydrogen bond interaction and 2D analysis of CHA with 62Z3 proteinrecpetors.

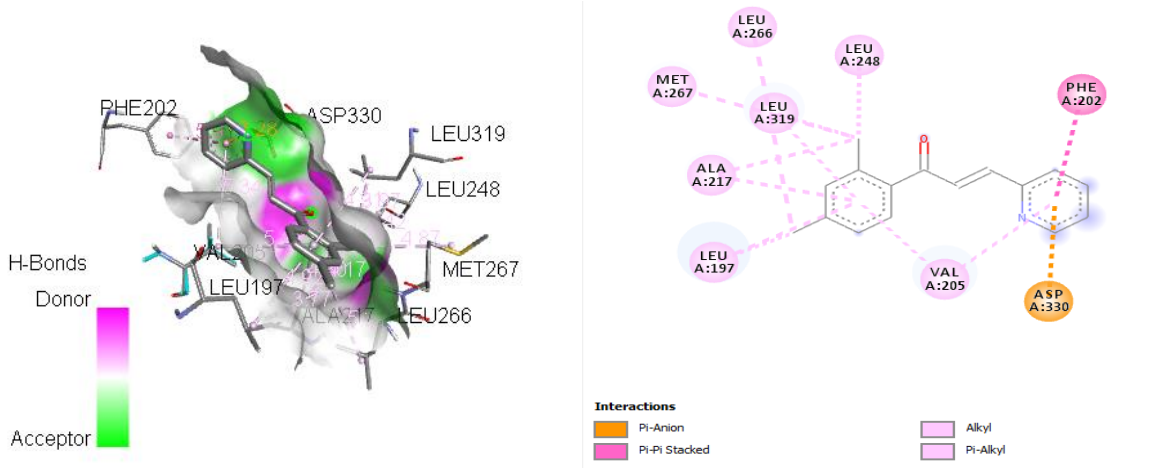

Figure 4: Hydrogen bond interaction and 2D analysis of CHB with 62Z3 proteinrecpetors.

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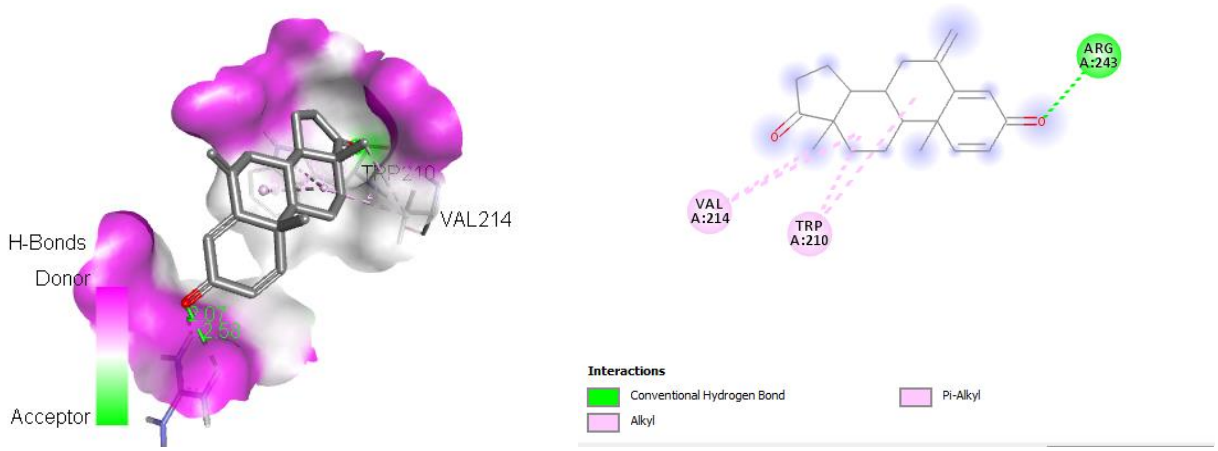

Figure 5: Hydrogen bond interaction and 2D analysis of the Drug with 62Z3 proteinrecpetors.

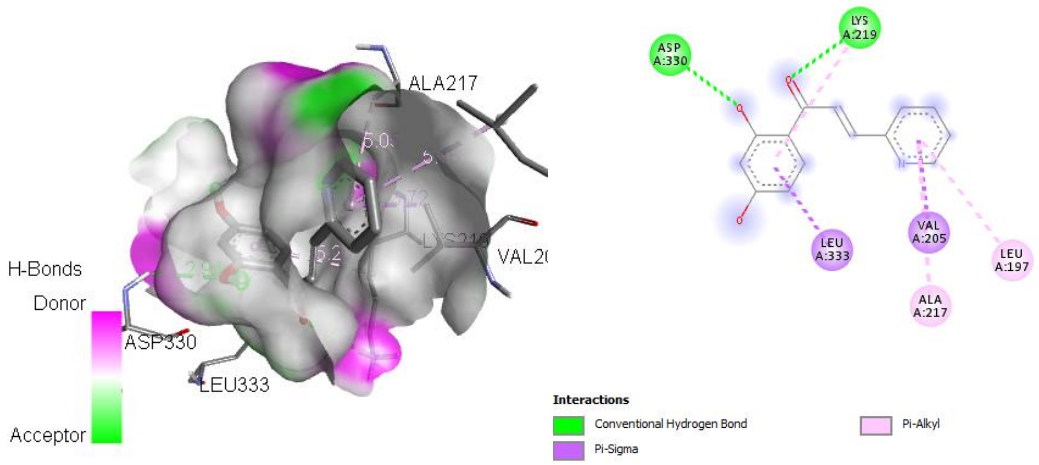

Figure 6: Hydrogen bond interaction and 2D analysis of CHA with 62Z4 proteinrecpetors.

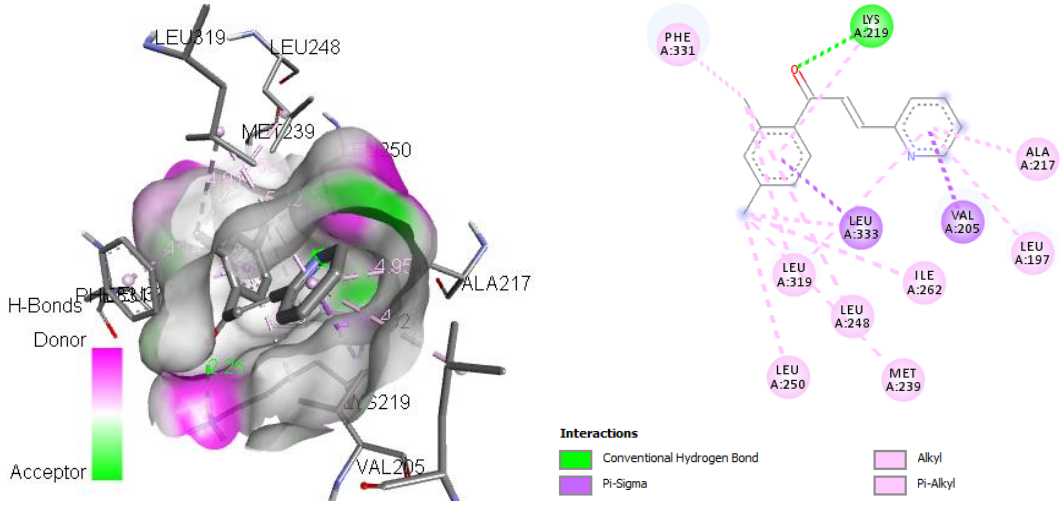

Figure 7: Hydrogen bond interaction and 2D analysis of CHB with 62Z4 proteinrecpetors.

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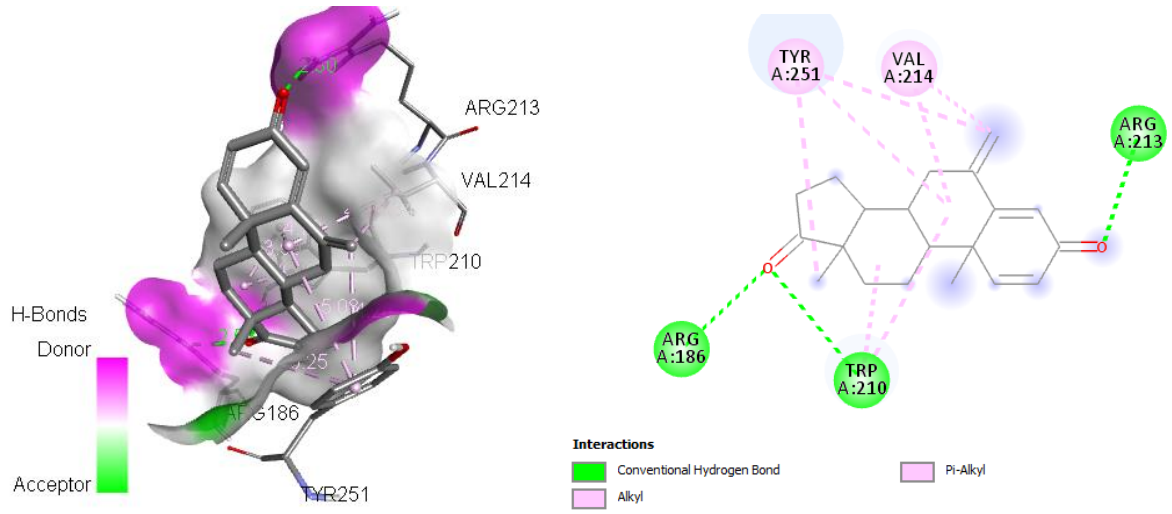

Figure 8: Hydrogen bond interaction and 2D analysis ofthe Drug with 62Z4 proteinrecpetors.

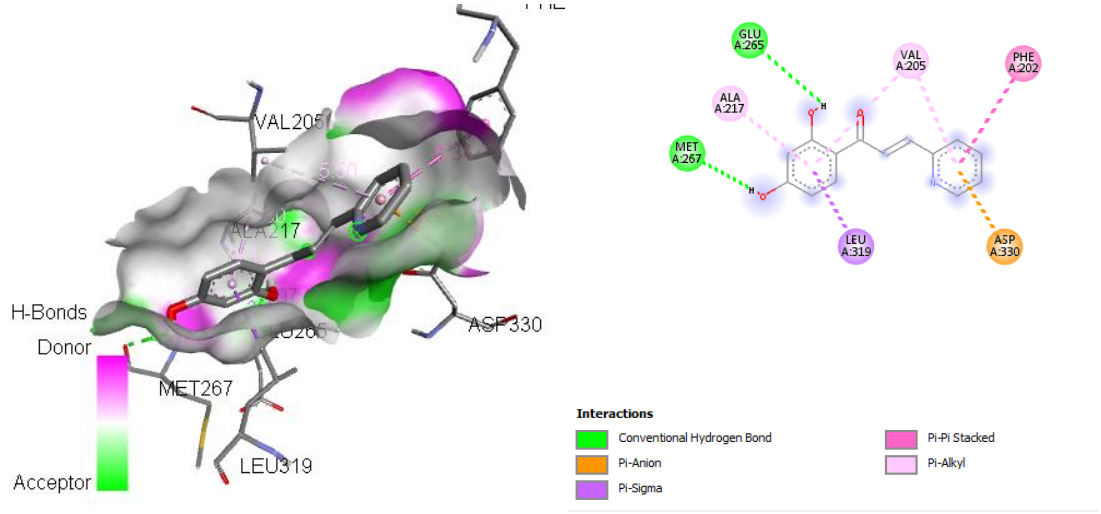

Figure 9: Hydrogen bond interaction and 2D analysis of CHA with 62Z2 proteinrecpetors.

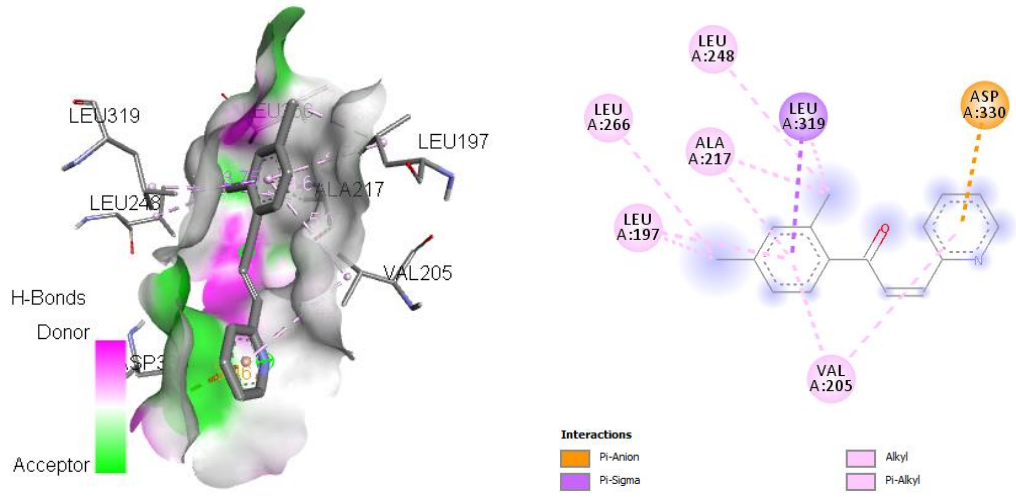

Figure 10: Hydrogen bond interaction and 2D analysis of CHB with 62Z2 proteinrecpetors.

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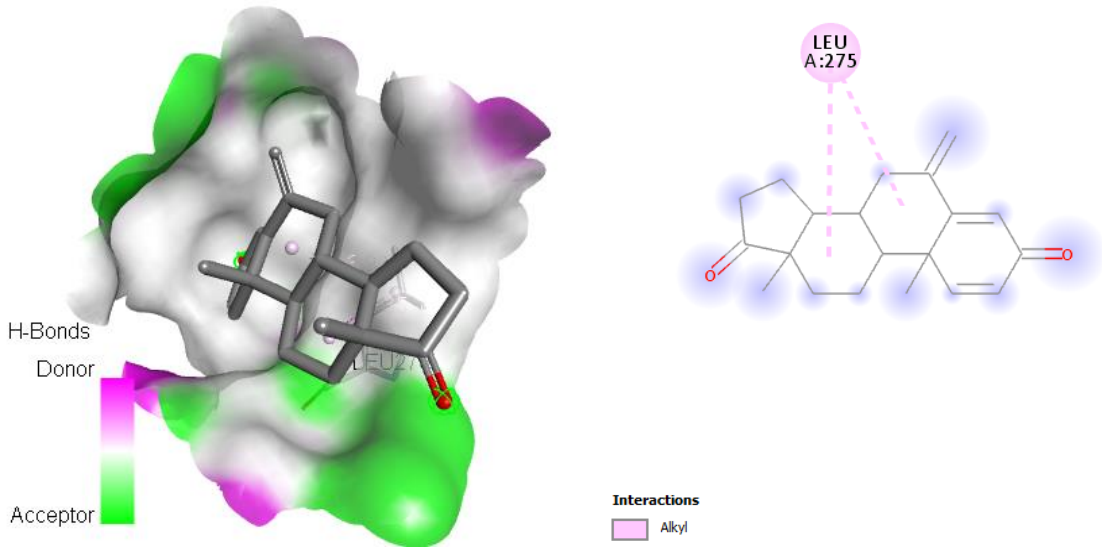

Figure 11: Hydrogen bond interaction and 2D analysis of the Drug with 62Z2 proteinrecpetors.

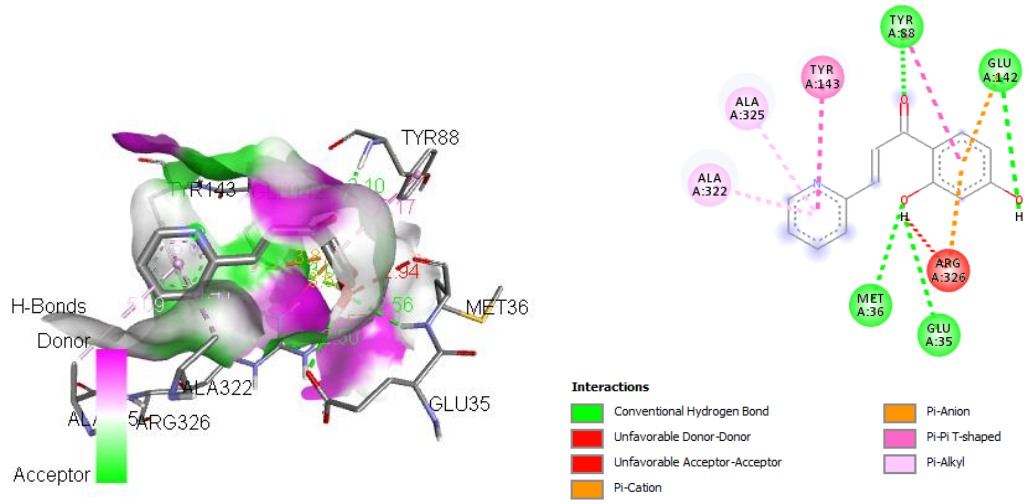

Figure 12: Hydrogen bond interaction and 2D analysis of CHA with 5TWU proteinrecpetors.

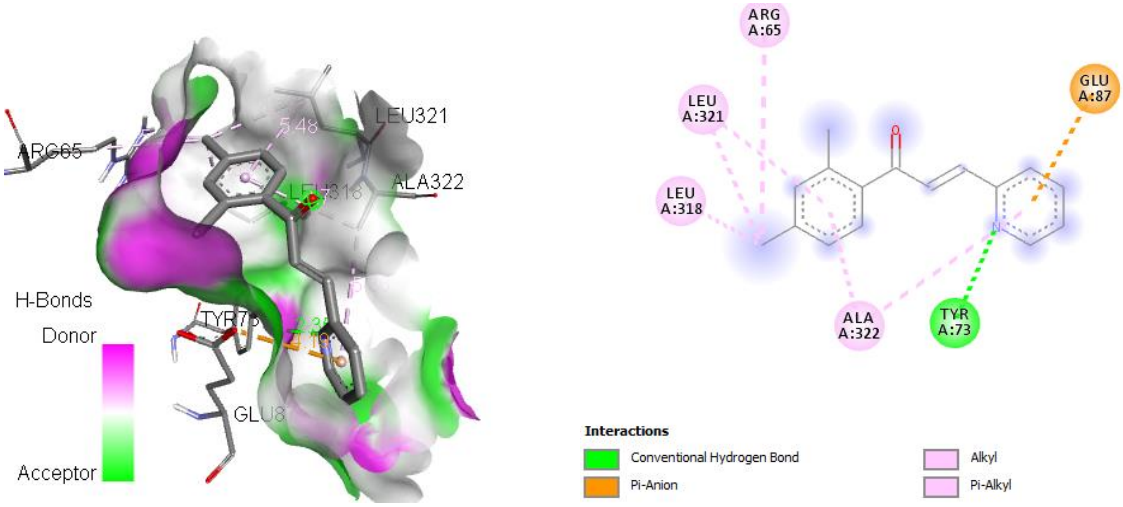

Figure 13: Hydrogen bond interaction and 2D analysis of CHB with 5TWU proteinrecpetors.

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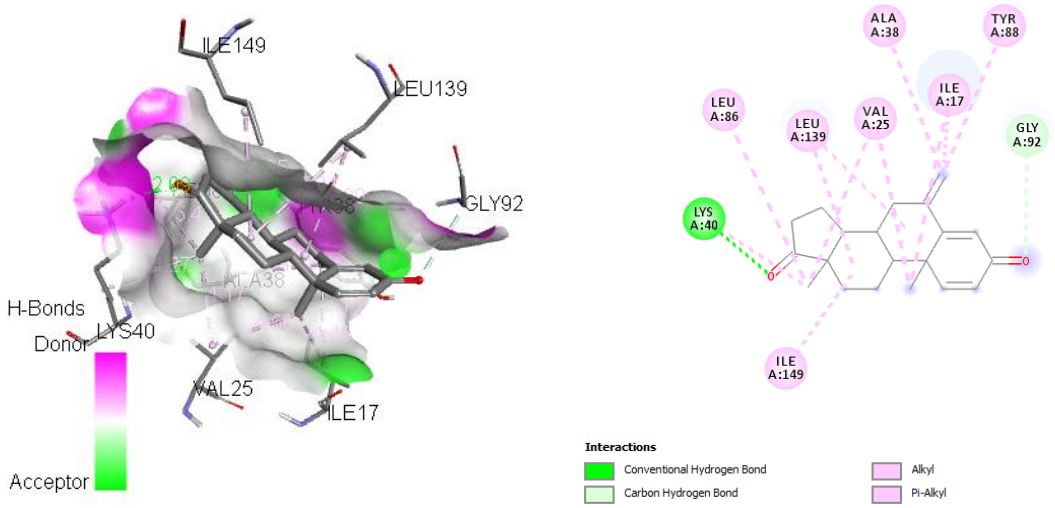

Figure 14: Hydrogen bond interaction and 2D analysis of the Drug with 5TWU proteinrecpetors.

SCORING RESULT

Receptors	CHA (Distance)	CHB (Distance)	Drug(Distance)
6CZ3	GLY200 (3.52) ASP300 (4.35) VAL205 (4.71) ALA217 (4.49) ASP330 (3.55)	PHE202 (5.91) ASP330 (3.28) LEU248 (4.42) ALA217 (4.18) MET267 (4.87)	VAL214 (5.18) TRP210 (4.77) ARG243 (2.07)
6CZ4	LEU197 (5.16) VAL205 (3.72) ALA217 (5.05) LYS219 (5.26)	LEU197 (4.96) VAL205 (4.14) ALA217 (4.95) MET239 (5.16) LEU250 (4.49) PHE331 (4.14) ILE362 (4.81)	ARG213 (2.30) VAL214 (4.34) TYR251 (4.20) TRP410 (4.22)
6CZ2	MET267 (2.43) LEU319 (3.45) ASP330 (3.40) ALA217 (4.12)	LEU197 (3.88) ASP330 (4.25) ALA217 (3.79) LEU319 (3.88) VAL205 (5.07)	LEU275 (3.93)
5KWU	ALA322 (4.41) ALA325 (5.09) GLU(142) (3.87) TYR143 (5.02)	LEU321 (5.48) ALA322 (5.36) ARG65 (5.22) LEU318 (4.52) GLU87 (4.19)	ILE149 (4.85) LEU139 (4.90) TYR88 (4.56) VAL25 (4.06) GLY92 (3.57) ALA38 (4.48) LYS40 (4.27)

Table 3: pocket information for active sites of Breast cancer receptors with the position of the amino acids residue and the distance in Armstrong (Å).

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CONCLUSION

The results of the computational docking study have demonstrated that the two newly synthesized compounds exhibit potent inhibition across all four targeted receptors, a finding underscored by binding energy values that align closely with those of the established pharmaceutical agent traditionally prescribed for breast cancer therapy. This promising correlation suggests that the molecular efficacy of these compounds could translate into a viable therapeutic strategy, potentially positioning them as innovative inhibitors with the capability to impede the proliferation of breast tumor cells. The compounds' mechanism of action, mirroring that of the standard drug, offers a new avenue for clinical exploration in the search for more effective breast cancer treatments.

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