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A Mechanistic Approach to enhance the efficiency of endoxifen by conjugating with anticancer tripeptides: In-Silico and molecular dynamics studies.

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ABSTRACT

Background: Globally, women are concerned about their health due to breast cancer. Researchers are focusing on enhancing the quality of life for breast cancer patients, as of right now, there isn't a single treatment that can be used to cure breast cancer permanently.

Aims: This research aims to enhance the effectiveness of tamoxifen derivative through conjugation with anticancer tripeptides, as ascertained through molecular docking studies.

Methods: We conducted an in-silico study with NGR and RGD tripeptides conjugated with tamoxifen derivatives using the AutoDock tool.

Results: The following significant binding energy interaction was observed with protein 3ERT like Endoxifen -7.2 kcal/mol; Tamoxifen-7.8 kcal/mol; 4-Hydroxy tamoxifen -7.9 kcal/mol; N- desmethyl tamoxifen -7.9 kcal/mol; NGR tripeptide -6.8 kcal/mol; RGD tripeptide -5.4 kcal/mol; P1-9.8 kcal/mol; P2-10.0 kcal/mol; P3 -11.0 kcal/mol; P4 -10.9 kcal/mol; P5 -8.5 kcal/mol. Furthermore, the interaction and stability behavior of the RGD tripeptide conjugated with endoxifen and NGR tripeptide complexes were analyzed for a 100-nanosecond (ns) time. Calculated RMSD values observed using molecular dynamics simulation (MDS) were found to be -0.3 nm respectively. RMSF calculation per residues showed a value near 0.2nm to -0.4nm and -0.2nm to -0.3nm respectively. Rg values remained between -1.9 nm to -1.95 nm. SASA analysis reveal the solvent behaviour of the complexes. The total number of hydrogen bonds was monitored during the simulation time and the results showed that around two hydrogen bonds were established with the active site for the RGD tripeptides conjugated with endoxifen. The hydrogen bonds were observed with LEU 536 and VAL534 residues and for NGR tripeptide conjugated with n-des methyl tamoxifen hydrogen bond observed with LEU 536 residues in the molecular docking.

Conclusion: Thus, significant docking interaction and stable dynamicity of endoxifen conjugated with tripeptides had the best docking and dynamic results. The next phase involves synthesizing these tripeptides and conjugating them with endoxifen for in-vitro cell line investigations.

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INTRODUCTION

Breast cancer, a disease that has plagued humanity for centuries, has been the subject of extensive research and analysis in recent years. This disease has had a staggering global burden, with incidence and mortality rates rising alarmingly in various regions of the world. According to recent data, around 1.1 million cases were recorded in 2004, and the number of patients is anticipated to rise to 4.07 million by 2040, with 1.4 million deaths (Baghdadi et al., 2022). This alarming trend is further corroborated by studies from Arab countries, India, Latin America, and Europe, which have all reported an alarmingly rising burden with associated incidence and mortality (Li et al., 2019). Tamoxifen (TAM) is the commonly approved adjuvant anti-estrogen treatment for women analyzed with estrogen receptor (ER)-positive breast cancer. Tamoxifen is a prodrug and is identified to have a weak affinity for the ER (Wakeling and Slater 1980). Its clinical efficacy is due to the metabolism by hepatic cytochrome P450 (CYP) enzymes to form the active metabolites 4-hydroxy-tamoxifen (4-OH-tamoxifen) and endoxifen (Desta et al., 2004; Goetz et al., 2005).

Catalyzed by the CYP2D6 enzyme, endoxifen is mainly produced by converting the tamoxifen metabolite N-desmethyl-tamoxifen (Mürdter et al., 2011; Desta et al., 2004; Klein et al., 2013). Since CYP2D6 is a very polymorphic gene with over 100 variant alleles,

the prevalence of which varies greatly throughout civilizations, causing inconsistencies in circulating endoxifen concentrations (Goetz et al., 2008; Borges et al., 2006). According to (Goetz et al., 2008; Borges et al., 2006; Schroth et al., 2009; and Dezentjé et al., 2015), lower tamoxifen response is linked to CYP2D6 changes that results in absent or reduced enzyme activity. Still, elevated serum levels of endoxifen are surprisingly related to improved outcomes.

Endoxifen (END), a secondary metabolite resulting from CYP2D6-dependent biotransformation of the primary tamoxifen metabolite, N-desmethyl tamoxifen (NDT), is a more potent antiestrogen than either NDT or the parent drug, tamoxifen. However, END's antitumor effects may be related to additional molecular mechanisms of action, apart from its impact on ER. In phase 1/2 clinical studies, the efficacy of Z-END, the active isomer of endoxifen, was evaluated in patients with endocrine-refractory metastatic breast cancer patients with gynecologic, desmoid, and hormone-receptor positive solid tumors, and demonstrated substantial oral bioavailability and promising antitumor activity (Jayaraman, S, et al., 2021) can cause significant side effects, including blood clots, endometrial cancer, and poor selectivity. Clinical studies have demonstrated that tamoxifen might be less effective in women with low CYP2D6 enzyme activity due to reduced endoxifen production (Goetz, 2018).

Anticancer peptides (ACPs), as small peptides containing amino acid sequences, are selective and toxic to cancer cells (Tyagi et al., 2015; Rai et al., 2025). ACPs are a superior choice of therapeutics compared with antibodies and small molecules due to their high selectivity, high penetration and easy modifications (Thundimadathil, 2012; Vlieghe et al., 2010; Otvos, 2008). (Peyressatre et al., 2015; Raucher and Ryu, 2015). NGR (Asparagine-Glycine-Arginine) and RGD (Arginine-Glycine-Aspartic acid) peptides serve as effective targeting agents for tumor therapies. NGR focuses on the vasculature of tumors, while RGD primarily targets tumor cells through integrin pathways (Thundimadathil, J. 2012). Studies indicate that RGD-modified systems improve chemotherapy drug efficacy and reduce side effects (Danhier, F et al., 2012). Thus, RGD and NGR peptides are considered to be potential vehicles for the delivery of chemotherapeutic drugs, cytotoxic peptides, and nanoparticles, (Laakkonen and Vuorinen, 2010; K. Chen and X. Chen, 2011). NGR peptides are found naturally in various human cell types (endothelial cells, epithelial cells, fibroblasts, and leukocytes. NGR peptide serves as a cell adhesion motif that selectively targets tumor blood vessels and other angiogenic vessels.

Protein-ligand docking is essential for identifying optimal binding interactions between compounds and target proteins. This approach predicts ideal combinations based on the structure of the target protein and potential molecules, focusing on three-dimensional characteristics. Docking assists in selecting compounds with favorable structural, and electronic properties. Molecular biology and drug development have benefited greatly from the application of molecular dynamics (MD) simulations in recent years. The behavior of proteins and other biomolecules is captured in these simulations at extremely fine temporal resolution and in complete atomic detail (Hollingsworth et al., 2018; Verma et al., 2017). These advantages have made computational methods crucial in drug discovery for exploring lead compounds (Diniz EMLP et al., 2017; Verma P et al., 2018).

In this study, we developed a series of conjugated NGR and RGD peptide derivatives using NDT and END, as these compounds hold hydrogen moieties that help amide bond formation with the carboxyl groups of NGR and RGD peptides. In dissimilarity, TAM and 4-OH-TAM lack of hydrogen moieties, making them inappropriate for such bonding. The structures of all synthesized compounds are presented in Figure 3. The binding affinity of TAM, its metabolites, tripeptides (NGR & RGD) and designed conjugated tripeptide derivatives (P1-P5) was predicted towards estrogen receptor (PDB ID: 3ERT) using molecular docking studies. Further, molecular dynamic simulations studied the energetically favourable protein-ligand complex in detail. The findings aim to contribute valuable insights for developing innovative drugs that enhance efficacy and provide improved treatments for breast cancer.

Methods

Molecular docking

Molecular docking is a technique that has been investigated for recognizing potent compounds without putting excessive exertion and investment into research (Chaurasiya S et al., 2016; Kaur P and Khatik GL, 2016). We use Autodock Tools-1.5.6 to investigate the activity in terms of binding affinity (Kcal/mol), and thereafter the outcomes are compared in binding affinity score for best-docked conformation. The structures of various ACPSs and derivatives of TAM were drawn with the help of Chem Biodraw (Fig. 1, 2, and 3) ultra and further converted to the 3D structure using ChemBiodraw 3D. All the designed structures were optimized by energy minimization using the MM2 method and converted to readable format at the ADT interface. The protein 3ERT was selected that was downloaded from the protein data bank. The outcomes of the results were analyzed by the Discovery Studio visualization tool that reveals close contact, hydrogen bonds, and hydrophilic, and hydrophobic interactions.

Molecular dynamic simulation study of compound P3

The MD simulation was carried out using Gromacs-2018.1 packages with amber99sbILDN force field. The structures were solvated in the triclinic box using the TIP3P water model. Four sodium ions were added to neutralize the structures. The topology of ligands was generated using an antechamber in AmberTools19. The energy minimization of both systems was performed using the steepest descent minimization of 5,000 steps (maximum number of minimization steps to perform)

to remove the weak Van der Waals contacts. Before the simulation run, each system was equilibrated for NVT (constant number of atoms, volume, and temperature) using a V-rescale thermostat for 100 ps at 300 K temperature and NPT (constant number of atoms, pressure and temperature) was performed at 1.0 bar by Parrinello Rahman barostat for 1000 ps. The molecular dynamic simulations ran for 100 ns, 3ERT with P3 compound where the coordinates were saved for the entire simulation period. MD simulations for protein or P3 compound were performed. The data presented is the average of the MD simulations. The calculation of electrostatic interactions was treated by the Particle-Mesh Ewald (PME) method. Van der Waals interactions were set at 1.2 nm. The Linear Constraint Solver (LINCS) algorithm was applied to constrain the covalent bonds, including heavy atom-H bonds during the molecular dynamics (MD) simulations. The gmx rms, rmsf, gyrate, gmx hbond, gmx sasa were used to calculate RMSD, RMSF, Rg, Hydrogen bonds and SASA respectively. MM-PBSA calculation was done to estimate the binding energy of ligands with protein (Kumari et al., 2014; Baker et al., 2001).

Results and discussion

Molecular docking

In this research, molecular docking studies were carried out for the newly designed drug-conjugated peptides (P1-P5) with the ATP binding site of the 3ERT receptor to get better insight into the binding modes, binding free energies, and amino acid interactions. The results were compared with molecular docking of parent molecules: tamoxifen and its metabolites (END, 4-OH-TAM, NDT) and parent peptides (NGR and RGD). Auto Dock 4.0 software was used to perform the molecular docking.

Tables 2 and 3 show that the TAM formed one hydrogen bond with 3ERT residue MET:522 with -7.8 kcal/mol of binding free energy while END formed a hydrogen bond with ASP:351 with an affinity energy of -7.2 kcal/mol. 4-OH-TAM and NDT formed a hydrogen bond with MET:522, similar to that of TAM with an affinity energy of -7.9 kcal/mol. The results indicated that TAM, 4-OH TAM and NDT showed similar binding affinity towards the estrogen receptor which might be due to their close structural similarity. However, the binding pose of END was different from the other molecules.

NGR peptide showed 5 H-bonds with 3ERT residue LEU: 345 through the oxygen atom, and GLY521, HIST 524, LEU387, GLU353, LEU345 through nitrogen atom of NGR peptide with affinity energy of -6.8kcal/mol. RGD peptide showed the two-hydrogen bonds with VAL; 534 through the nitrogen atom group of RGD and two-hydrogen bond with LYS:529, CYS:530 amino acid with affinity energy of -5.4 kcal/mol. NGR peptide showed a high affinity compared to the RGD peptide.

Numerous docking studies of peptide-drug conjugates have been published in the literature. For example, JF Liang and VC Yang (2005) reported that the doxorubicin structure was modified to

include the cell-penetrating peptide TAT. The intracellular distribution patterns and cell-killing activities of the synthesized doxorubicin–TAT combination differed from those of free doxorubicin. The doxorubicin–TAT combination was more effective at killing drug-resistant tumor cells and was far more permeable to drug-resistant cells than free doxorubicin.

According to a (2019) study by Shokri et al., the NGR conjugate versions of naproxen and ibuprofen had superior action against the SKOV-3 tumor cell line. Docking studies demonstrated that these conjugates bind to their receptors more effectively. For greater activity, choosing the ideal chemical bond and conjugation position was crucial. Contrary to original expectations, the peptide's carboxylic acid moiety is conjugated with the endoxifen's N-des methyl moiety using chemically stable linkages. The conjugation of tamoxifen and its metabolites with specific peptides resulted in novel compounds (P1-P5). Among the five drug-conjugates, RGD conjugate of endoxifen P3 formed **energetically** favourable and stable binding with the 3ERT binding site by establishing three hydrogen bonds with crucial amino acid residues **with affinity energy -11.0** kcal/mol. P3 **interacted with VAL:534 through nitrogen atom, LEU:536 through oxygen atom of RGD peptide moiety and LEU:525 through methyl group of endoxifen moiety**. Compound RGD conjugate of NDT **forms four hydrogen bonds VAL:534, VAL: 533 through the same nitrogen atom of RGD peptide, LEU:536 through the oxygen atom of RGD peptide moiety and LEU:525 through methyl group of N-des-methyl tamoxifen with affinity energy -10.9** kcal/mol. RGD conjugate of endoxifen (single drug**) forms two hydrogen atoms, LEU:536 and TYR:526 through the oxygen atom of RGD peptide moiety with affinity energy** -10.0 kcal/mol.

NGR conjugate of endoxifen **P1** formed **two H-bonds with one is CYS:530 through oxygen atom and the second is MET:528 through nitrogen atom of NGR peptide moiety with affinity energy -9.8** kcal/mol. NGR conjugate with N-des-methyl tamoxifen **P5 forms two H-bond with the same amino acid VAL:534 through nitrogen atom with affinity energy -8.5** kcal/mol. 2D binding mode of all novel compounds (P1-P5) inside 3ERT binding site is show in Fig 4-8.

It indicated that P3 (RGD conjugated with endoxifen) is a good compound for improving the efficacy of endoxifen, which is attributed to its effective interaction with the active site of 3ERT.

Molecular dynamic simulation study of compound P3

The RMSD of 3ERT was stable during the simulation time up to 100 ns with small fluctuations at 50 ns. The complex showed a steady RMSD of -0.3nm (Fig.9). RMSF indicates amino acid fluctuations in the protein active site. Usually, large fluctuations imply great flexibility in the complex. In the RMSF analysis of 3ERT with compound P3, amino acid residues between 300-350 and 450-550 regions had higher RMSF than the other residues. The RMSF values of the peptide drug conjugate (P3) ranged between -0.2nm and -0.4nm (Fig. 9). The radius of gyration (Rg) indicates the compactness of the protein-ligand complexes. The Rg values of the complexes remained stable in between -1.9 nm to -1.95 nm. The compactness suggested that the peptide drug conjugate (P3) stayed strongly bound to the active pocket of the estrogen receptor (Fig.9). SASA analysis reveals the solvent behavior of the complexes. The docked complex had an average value of 14-16 $nm^{2.}$ The compound formed stable hydrophobic interactions with the target site.

The total number of hydrogen bonds was monitored during the simulation time and the results showed that two hydrogen bonds were established with the active site. The hydrogen bonds were observed with LEU 536 and VAL534 residues in the molecular docking study.

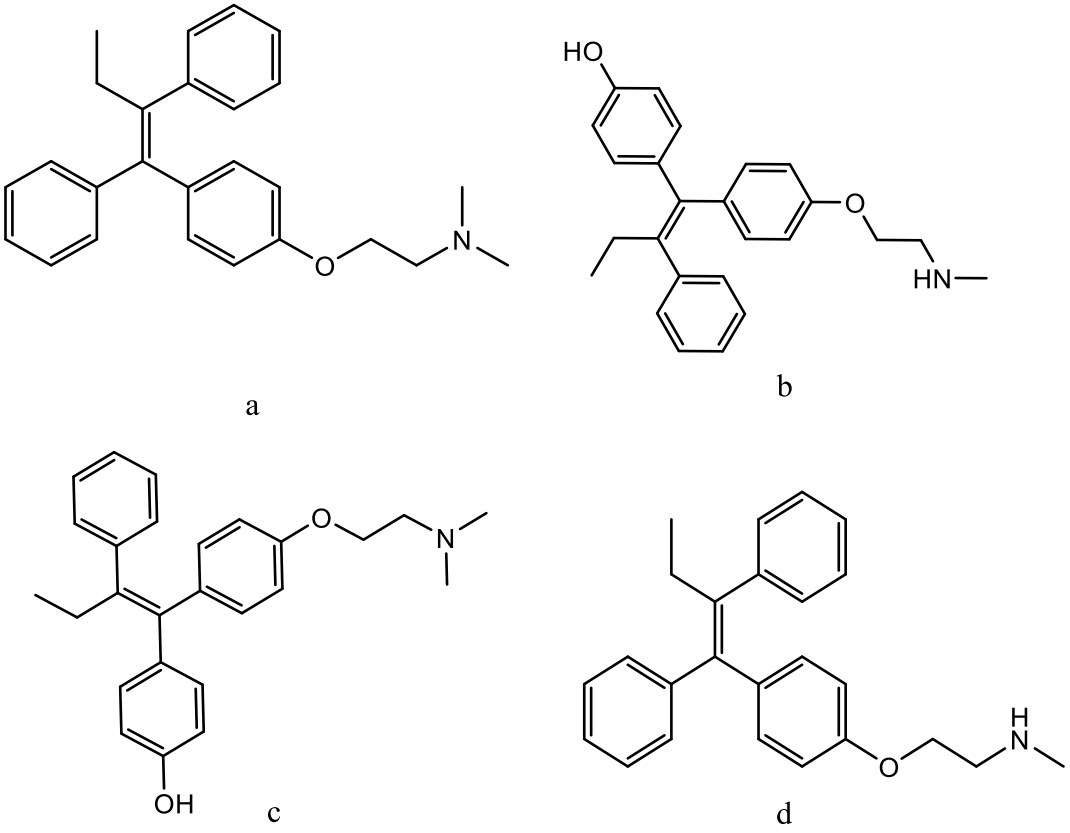


Fig. 1 Structures of tamoxifen and its metabolites a. TAM, b. END, c. 4-OH-TAM, d. NDT

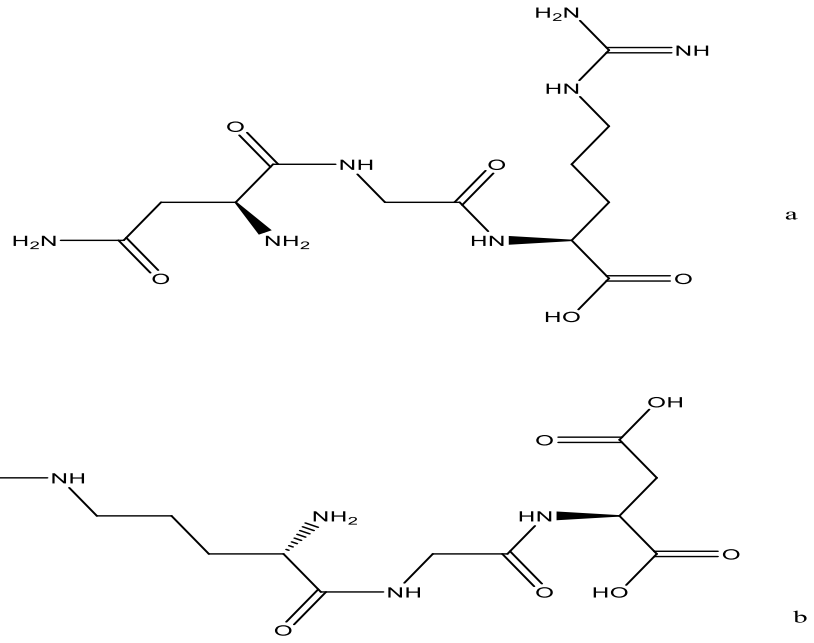
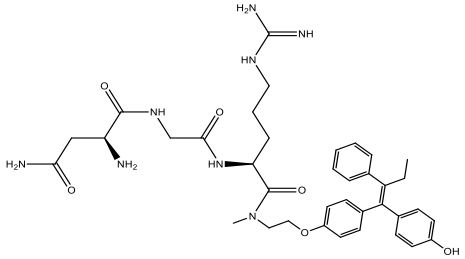
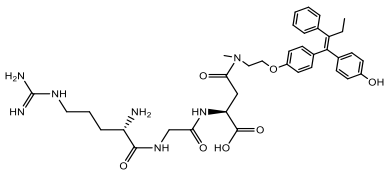


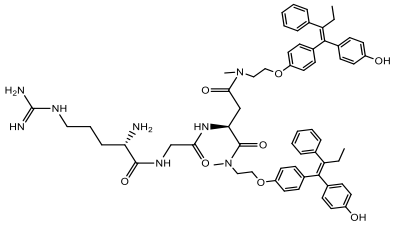
Fig. 2 Structures of tripeptides a. NGR and b. RGD



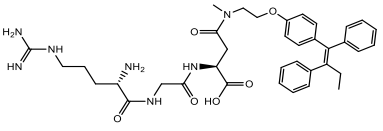
P1



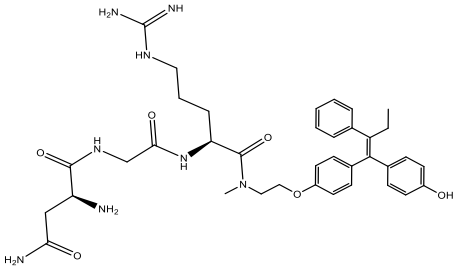
P2



P3



P4



P5

Fig. 3 Structures of conjugated compounds

Table 1: Compounds are classified into three groups

Drugs	Peptides	Designed Peptide-drug conjugates
Tamoxifen		
4-Hydroxy tamoxifen		
Endoxifen	NGR tripeptide RGD tripeptide	NGR tripeptide- Endoxifen (P1) RGD tripeptides-Endoxifen (P2) Endoxifen -RGD tripeptide- Endoxifen (P3)
N- desmethyl tamoxifen		N-des-methyl tamoxifen-RGD-N-desmethyl tamoxifen (P4)
		NGR tripeptides-N-desmethyl tamoxifen (P5)

Table 2: Molecular docking score

S.NO	Compound name	Binding energy
1.	TAM	-7.8
2.	END	-7.2
3.	4-OH-TAM	-7.9
4.	NDT	-7.9
5.	NGR	-6.8
6.	RGD	-5.4
7	P1	-9.8
8	P2	-10.0
9	P3	-11.0
10	P4	-10.9
11	P5	-8.5

Table 3: The best-designed ligands interact via hydrogen bonds and hydrophobic interactions.

S.no.	Compounds	Amino acids involved in interactions
1	TAM	H bond: MET:522 Pi-Pi: TRP-383 Alky, Pi-Alkyl: VAL-533, LEU-525, ALA-350, LEU-354, LEU-536.
2	END	H bond: ASP-351, Alkyl, Pi-alkyl: LEU: 525, LYS: 529
3	4-OH-TAM	H bond: MET:522 Pi-Pi stacked: TRP:383 Alky, Pi-Alkyl: VAL-533, LEU-525, ALA-350, LEU-354, LEU-536
4	NDT	H bond: MET:522 Pi-Pi stacked: TRP:383 Alky, Pi-Alkyl: VAL-533, LEU-525, ALA-350, LEU-354, LEU-536.
5	NGR	Conventional H bond: GLU: 353, LEU:387, LEU:346, HIS: 524, GLY:521 Carbon H bond: MET:388 Unfavorable donor-donor: ARG:394
6	RGD	Carbon H bond: LYS: 529 Conventional H bond: Val: 534, CYS: 530
7	P1	Conventional H bond: MET:528, CYS: 530 Alkyl, Pi-alkyl: MET: 421, LEU:525, ALA:350, LEU:346, LEU:387, TRP:383 Vander Waals: THR:347 Unfavorable acceptor-acceptor: GLU: 353
8	P2	Conventional H bond: LEU:536 Carbon H bond: TYR: 526 Alkyl, Pi-alkyl: MET: 421, MET:388, LEU: 524, LEU: 346, LEU: 387, ALA: 350 Self-bridge: ASP:351 Unfavorable acceptor-acceptor: 353
9	P3	Conventional H bond: VAL:534, LEU:536 Carbon H bond: LEU:525

		Pi-Pi Stacked: TYR: 526 Alkyl, Pi-alky: MET: 388, MET: 421, LEU: 387, LEU: 346, ALA:350 Pi-Sulfur: MET:522, MET: 343 Self-bridge: ASP:351 Unfavorable acceptor-acceptor: GLU: 353
10	P4	Conventional H bond: VAL: 534, VAL: 533, LEU:536 Carbon H bond: LEU:525 Pi-Pi Stacked: TYR: 526 Alkyl, Pi-alky: MET: 388, MET: 421, LEU: 387, LEU: 346, ALA:350 Pi-Sulfur: MET:522, MET: 343 Attractive charge: GLU:380 Unfavorable acceptor-acceptor: LYS: 529
11	P5	Conventional H bond: VAL: 534 Alkyl, Pi-alkyl: MET: 421, ALA: 350, LEU:545, LEU:387, LEU:346, MET:528

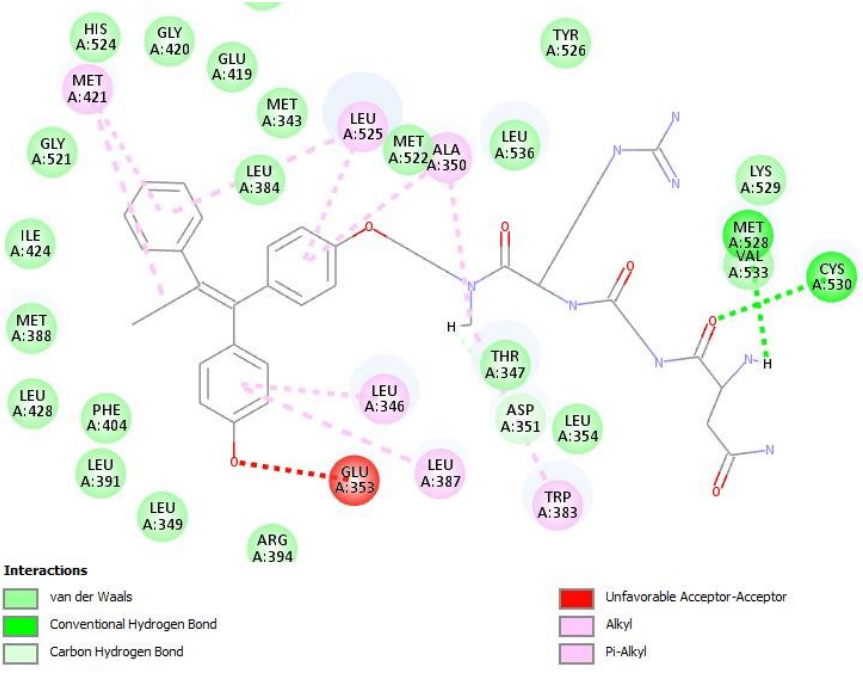


Fig.4. 2D binding mode of compound P1 inside 3ERT binding site

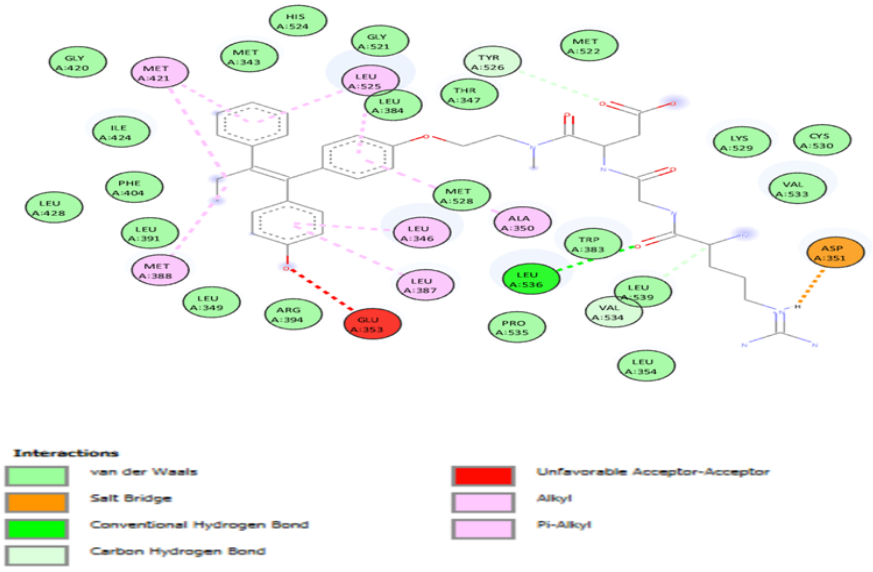


Fig.5. 2D binding mode of compound P2 inside 3ERT binding site

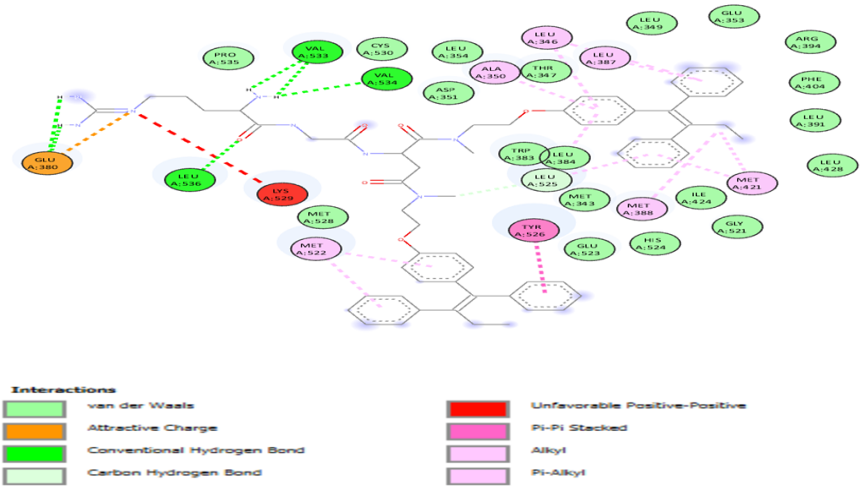


Fig.6. 2D binding mode of compound P3 inside 3ERT binding site

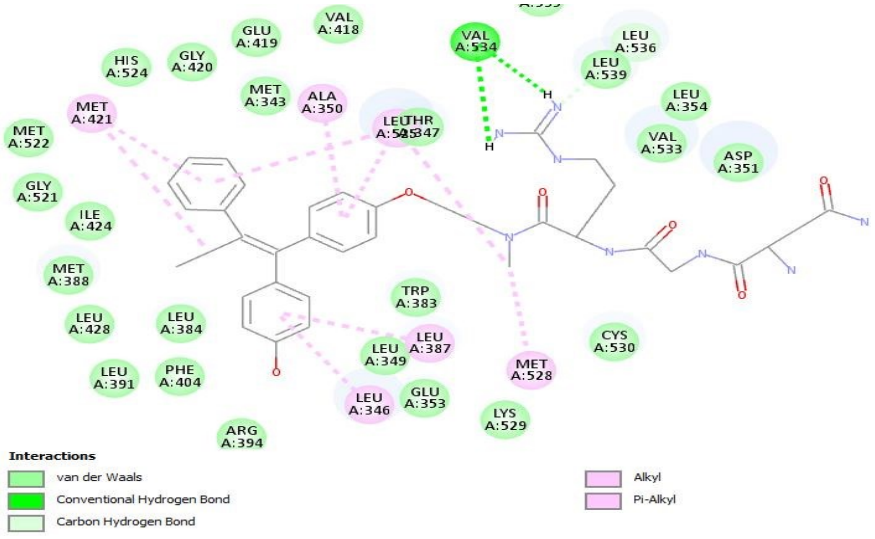


Fig.7. 2D binding mode of compound P4 inside 3ERT binding site

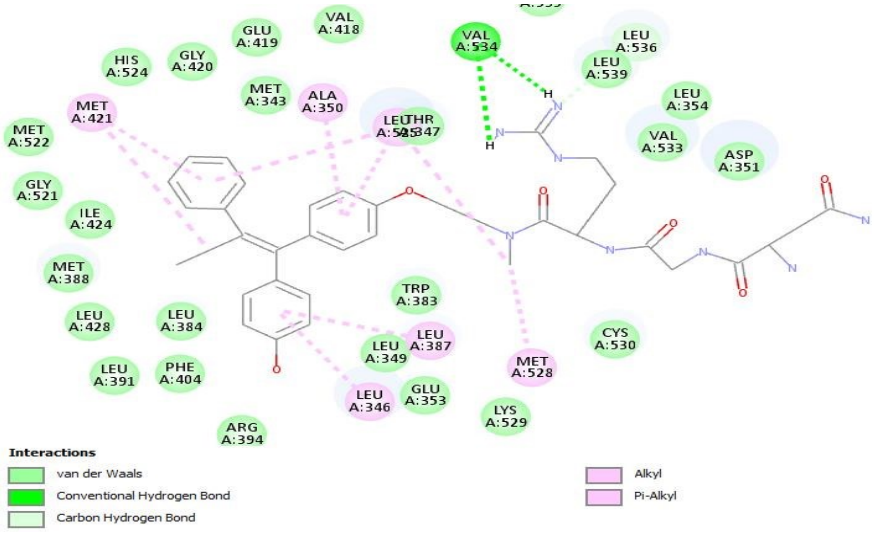
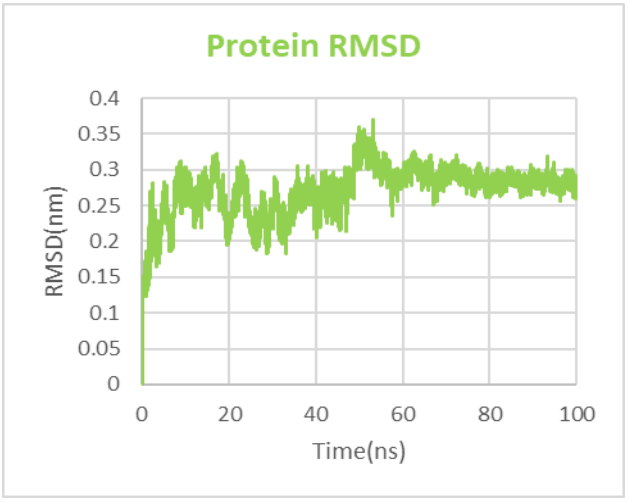
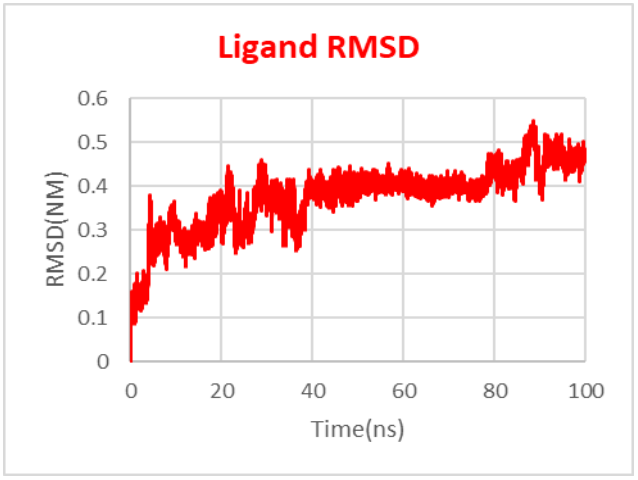


Fig.8. 2D binding mode of compound P5 inside 3ERT binding site

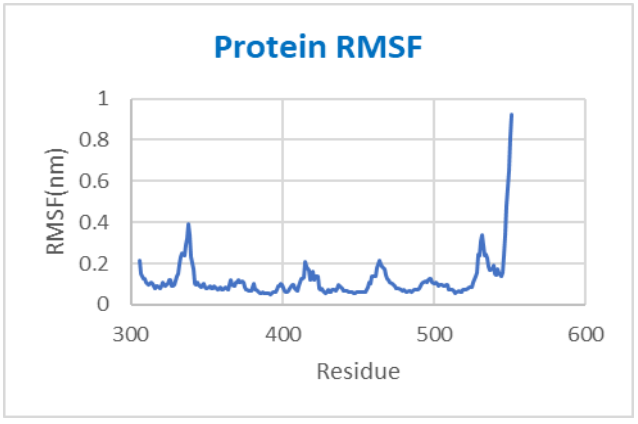
a


Protein RMSD
RMSD(nm)
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
0
20
40
60
80
100
Time(ns)

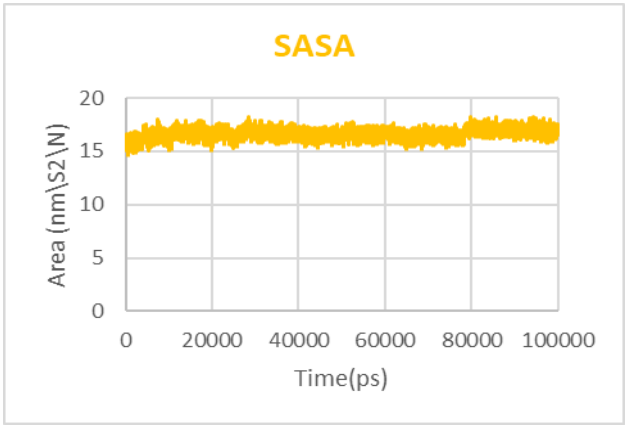
b


Ligand RMSD
RMSD(NM)
0.6
0.5
0.4
0.3
0.2
0.1
0
0
20
40
60
80
100
Time(ns)

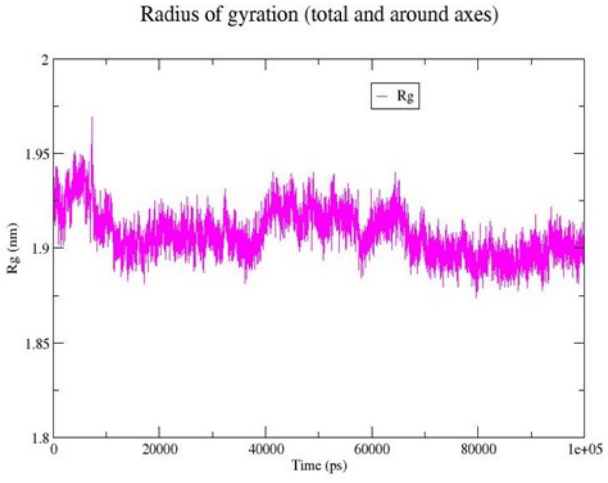
c


Protein RMSF
RMSF(nm)
1
0.8
0.6
0.4
0.2
0
300
400
500
600
Residue

d


SASA
Area (nm\S2\N)
20
15
10
5
0
0
20000
40000
60000
80000
100000
Time(ps)

e


Radius of gyration (total and around axes)
Rg
Rg (nm)
2
1.95
1.9
1.85
1.8
0
20000
40000
60000
80000
1e+05
Time (ps)

f

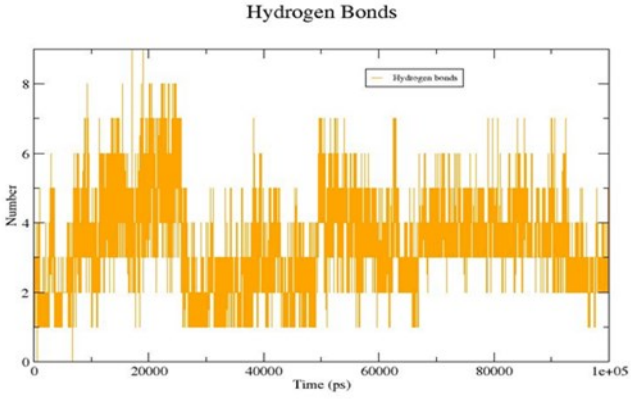

Hydrogen Bonds
Hydrogen bonds
Number
8
6
4
2
0
0
20000
40000
60000
80000
1e+05
Time (ps)

Figure 9: a) Plot of protein backbone RMSD over the 100 ns. b) steady RMSD of compound -0.3nm. c) RMSF of protein d) Solvent accessible surface area (SASA) of compound (P3) average value of 14-16 nm^2. e) Radius gyrate of the backbone over the -1.9 nm to -1.95 nm of the compound. f) Average number of hydrogen bonds between protein and ligand.

CONCLUSION

Breast cancer is still a major problem because of treatment resistance and the need for more potent drugs, even with the abundance of anticancer drugs available. The current effort aimed to create a new, stronger drug by utilizing AutoDock Vina software to analyze molecular docking and tripeptide conjugation with tamoxifen derivatives. Docking compounds with the 3ERT protein revealed strong binding affinities, including newly synthesized chemicals, compounds from a given dataset, and RGD-endoxifen. The docking score of -11.0kcal/mol was the highest for compound RGD-endoxifen.

The 3ERT complex's molecular dynamics simulations revealed a steady radius of gyration values, slight variations at 50 ns, and RMSD values up to 100 ns, all suggesting a tight binding of the RGD tripeptide conjugated with endoxifen. Constant hydrogen bonds substantiated strong binding stability with LEU 536 and VAL 534 residues, as well as stable solvent interactions indicated by SASA values. High elasticity was noted in two residue areas (between 300 and 350 and between 450 and 550). According to the study's findings, endoxifen conjugated with RGD tripeptide produced the best dynamic and docking outcomes. The next step is to synthesize these tripeptides and conjugate them with endoxifen to be used for in vitro cell line research.

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CONFLICT OF INTEREST

The authors affirm that there is no conflict of interest to disclose.

ABBREVIATIONS

WHO: World Health Organization, ER: estrogen receptor, CYP2D6: cytochrome P450 family 2 subfamily D member 6, ACPs: Anticancer peptides, RGD: Arginine-Glycine-Aspartic acid NGR: Asparagine-Glycine-Arginine, PDB: protein data bank, Rg: radius of gyration, MD: molecular dynamics, SASA: Solvent-accessible surface area, RMSD: Root mean square deviation, TAM: Tamoxifen, END: Endoxifen, 4-OH-TAM: 4-Hydroxy tamoxifen, NDT: N- desmethyl tamoxifen.

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