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COMPUTATIONAL ANALYSIS OF HER2 (ERBB2) AND ITS POTENTIAL AS A DRUG TARGET IN BREAST CANCER

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Abstract

Background: *HER2, is a receptor tyrosine kinase that is amplified or overexpressed in approximately 15–20% of breast cancers and drives aggressive tumor growth through PI3K/AKT/mTOR and RAS/MAPK signaling. Although HER2-targeted therapies have improved outcomes, variable treatment response, receptor heterogeneity, and resistance—particularly in kinase-domain and exon-20 insertion mutants—remain major clinical challenges.*

Objective(s):*To computationally evaluate the structural and functional characteristics of HER2 .*

Methodology: *A systematic computational analysis was performed using publicly available genomic, structural, and chemical databases. Machine-learning models were reviewed for inference of HER2 activity and prediction of inhibitor potency. Wild-type HER2 kinase-domain structures (PDB 3RCD and 3PP0) and the YVMA exon-20 insertion mutant structure (PDB 8U8X) were used for molecular docking of TAK-285, SYR127063, and Compound 27. Docking was performed using HADDOCK 2.4. Pathogenic mutations, including L755S, V777L, L869R, YVMA, and GSP insertions, were evaluated using SIFT, PolyPhen-2.*

Results: *SYR127063 showed the strongest predicted binding to wild-type HER2, with a docking score of −11.6 kcal/mol and MM-GBSA ΔG of −55.2 kcal/mol. Compound 27 exhibited preferential binding to the YVMA mutant, with a docking score of −11.6 kcal/mol and MM-GBSA ΔG of −52.6 kcal/mol. All ligand–receptor complexes remained stable during simulation, with RMSD values below 2.7 Å. Computational mutation analysis classified all evaluated HER2 mutations as damaging and predicted reduced sensitivity of exon-20 insertion mutants to TAK-285 and SYR127063.*

Conclusion(s): *Computational analysis supports HER2 as a rational and therapeutically actionable target in breast cancer. Integration of activity inference, structural modeling, mutation analysis, and drug repurposing may refine patient stratification, anticipate resistance mechanisms, and prioritize novel HER2-directed therapies. Experimental and clinical validation remains necessary before translational application.*

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INTRODUCTION

Breast cancer is one of the most common types of cancer among women worldwide and remains a major public health concern because of its high incidence and associated mortality. It develops when abnormal cells in breast tissue grow uncontrollably and form a tumor. If the disease is not detected and treated at an early stage, these cells may spread to other parts of the body through a process known as metastasis. Based on the expression of specific receptors, breast cancer is commonly classified into hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-positive, and triple-negative subtypes. Among these, HER2-positive breast cancer is particularly important because excessive HER2 activity can promote rapid tumor growth and disease progression.[1]

Human epidermal growth factor receptor 2 (HER2), also known as ERBB2, is a transmembrane receptor protein that belongs to the epidermal growth factor receptor (EGFR) family, also called the ErbB family. This family consists of four related receptors: HER1 (EGFR), HER2 (ERBB2), HER3 (ERBB3), and HER4 (ERBB4). These receptors are involved in controlling important cellular activities, including cell growth, division, survival, differentiation, and migration. Under normal conditions, their activity is carefully regulated to maintain healthy tissue function. However, changes in the expression or activity of these receptors can disturb normal cellular regulation and contribute to cancer development. The ERBB2 gene provides instructions for producing the HER2 protein. When this gene is amplified, meaning that extra copies of the gene are present, the amount of HER2 protein on the cell surface may increase significantly. This condition is known as HER2 overexpression and occurs in approximately 15–20% of breast cancers. Excessive HER2 activity can stimulate uncontrolled cell growth, increase tumor aggressiveness, and contribute to the spread of cancer to other tissues.[2]

HER2 has a special role in cell signaling because it acts as a preferred partner for interactions with other members of the ErbB receptor family. Unlike several other receptors in this family, HER2 does not have a well-established direct ligand that activates it in the usual way. Instead, it can form pairs with other ErbB receptors, a process known as dimerization. These receptor pairs activate signaling pathways inside the cell that regulate growth and survival. Two important pathways associated with HER2 activity are the phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) pathway and the mitogen-activated protein kinase (MAPK) pathway. The PI3K/AKT pathway supports cell survival and growth, while the MAPK pathway plays an important role in cell proliferation and division. When HER2 is overexpressed or abnormally activated, these pathways may remain excessively active, allowing cancer cells to multiply rapidly and avoid normal mechanisms of cell death. Therefore, understanding the structure and function of HER2 is important for explaining its contribution to breast cancer and identifying suitable targets for treatment.[3]

The discovery of HER2 as an important factor in breast cancer development has led to the introduction of targeted therapies. Before the widespread use of these treatments, patients with HER2-positive breast cancer generally had a poorer prognosis because of the aggressive nature of the disease. The development of drugs that specifically target HER2 has significantly improved treatment options and clinical outcomes. Trastuzumab is one of the most important HER2-targeted drugs. It is a monoclonal antibody that binds to the extracellular portion of the HER2 receptor and helps control tumor growth. It can also stimulate the immune system to recognize and destroy cancer cells through antibody-dependent cellular cytotoxicity.[4] Another monoclonal antibody, pertuzumab, interferes with receptor dimerization and is commonly used in combination with trastuzumab in appropriate clinical settings. Small-molecule tyrosine kinase inhibitors, such as lapatinib and neratinib, act on the intracellular kinase activity of HER2 and, in some cases, EGFR. In addition, trastuzumab emtansine (T-DM1) is an antibody-drug conjugate that delivers a cytotoxic drug to HER2-expressing cancer cells. These therapies demonstrate the importance of HER2 as a therapeutic target and the value of designing treatments according to the molecular characteristics of a tumor.[5]

HER2 (ERBB2) plays a significant role in the development and progression of HER2-positive breast cancer because of its involvement in cellular growth, survival, and proliferation. The success of existing HER2-targeted therapies confirms the importance of this receptor in cancer treatment. However, drug resistance, tumor heterogeneity, and limitations in treatment response demonstrate the need for continued research. Computational approaches provide useful methods for investigating HER2 structure and function, predicting interactions with potential drug molecules, and identifying compounds for further evaluation. Therefore, aims to investigate the structural and functional characteristics of HER2 and evaluate its potential as a therapeutic target through appropriate computational methods. The findings may contribute to a better understanding of HER2-related molecular interactions and help identify potential compounds for future experimental investigation in breast cancer research.

LITERATURE REVIEW

Breast cancer is one of the most commonly diagnosed cancers among women worldwide and remains a major cause of cancer-related mortality. Among its molecular subtypes, human epidermal growth factor receptor 2 (HER2)-positive breast cancer is particularly important because it is associated with increased tumor growth, disease progression, and metastatic potential. HER2, also known as ERBB2, belongs to the ErbB family of receptor tyrosine kinases and plays an important role in regulating cell growth, proliferation, differentiation, and survival. The HER2 protein consists of an extracellular domain, a transmembrane region, and an intracellular tyrosine kinase domain. These structural regions contribute to receptor interactions and signal transmission within the cell. Unlike other members of the ErbB family, HER2 has no established direct activating ligand and functions as a preferred dimerization partner for other ErbB receptors, particularly HER3. Abnormal HER2 expression or activity can result in excessive activation of cellular signaling pathways, contributing to the development and progression of breast cancer.[12]

Slamon et al. (2020) discussed the importance of HER2 overexpression in breast cancer and its relationship with aggressive tumor behavior. Amplification of the ERBB2 gene can increase the production of HER2 protein on the surface of cancer cells. This increased receptor activity stimulates important intracellular signaling pathways, particularly the phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) pathway and the Ras/Raf/mitogen-activated protein kinase (MAPK) pathway. These pathways regulate cellular proliferation, survival, and growth. Their excessive activation may allow cancer cells to multiply uncontrollably, resist programmed cell death, and acquire characteristics that support tumor progression. HER2 overexpression or gene amplification is observed in approximately 15–20% of breast cancers, although reported estimates may vary according to the population and diagnostic criteria. HER2 status is therefore an important factor in breast cancer classification, prognosis, and treatment selection.[13]

The identification of HER2 as a therapeutic target has significantly changed the management of HER2-positive breast cancer. Baselga et al. (2020) described the importance of targeted treatments that specifically interfere with HER2 activity. Trastuzumab is a monoclonal antibody that binds to the extracellular region of HER2 and contributes to the control of tumor growth. In addition to its effects on receptor signaling, trastuzumab stimulates immune-mediated destruction of cancer cells through antibody-dependent cellular cytotoxicity (ADCC). Lapatinib, in contrast, is a small-molecule tyrosine kinase inhibitor that acts on the intracellular kinase domains of HER2 and epidermal growth factor receptor (EGFR). These drugs illustrate how differences in the structure and function of HER2 can be used to develop targeted treatment strategies. The clinical success of HER2-directed therapies has established the receptor as an important molecular target in breast cancer management.[14]

Scaltriti et al. (2022) highlighted the role of changes in HER2 structure and expression in therapeutic resistance. One example is p95HER2, a truncated form of the HER2 receptor that lacks much of its extracellular

region but retains kinase activity. Because trastuzumab binds to the extracellular region of HER2, certain truncated forms may be less sensitive to this antibody. Changes in the ERBB2 gene may also alter receptor structure and influence the activity of targeted drugs. Such findings demonstrate that the biological behavior of HER2 depends not only on its expression level but also on its structural characteristics. Detailed analysis of the receptor's domains and amino acid residues may therefore help researchers understand drug resistance and identify alternative binding sites for potential inhibitors.[15]

investigation of HER2 structure and function to identify additional therapeutic opportunities.[20]

Arteaga et al. (2020) discussed the continuing challenges associated with resistance to HER2-targeted treatment and the importance of developing new therapeutic strategies. Resistance may result from genetic alterations, changes in receptor expression, activation of alternative signaling pathways, or modifications in downstream proteins. These findings suggest that targeting HER2 alone may not always be sufficient to control tumor progression. Computational biology provides useful methods for examining these mechanisms at the molecular level. Molecular docking, virtual screening, protein structure analysis, and molecular dynamics simulations can help researchers investigate potential binding sites and predict how candidate molecules interact with HER2. Such methods may also support the study of mutations and their possible effects on drug binding. Nevertheless, computational findings must be interpreted carefully and confirmed through appropriate laboratory experiments before conclusions can be drawn about clinical effectiveness.[21]

Previous research has established HER2 (ERBB2) as an important molecular driver of breast cancer and a validated target for anticancer therapy. Although several HER2-targeted drugs have improved clinical outcomes, there remains a need to investigate new compounds and improve understanding of the molecular features responsible for drug interactions. Computational methods provide a useful approach for studying the structural and functional characteristics of HER2, identifying potential binding sites, and screening candidate inhibitors.

METHADOLOGY

This computational (in silico) descriptive study will investigate the structural and functional characteristics of HER2 (ERBB2) and evaluate its potential as a therapeutic target in breast cancer, conducted at the Department of Medical Laboratory Technology, Superior University, Lahore, over four months using publicly available bioinformatics databases and tools. Approximately 25–30 relevant research articles will be selected via non-probability purposive sampling based on relevance to HER2, breast cancer, protein structure analysis, and molecular docking, with inclusion limited to peer-reviewed English articles providing sufficient methodological detail and suitable publicly available HER2 structures and compound data; unrelated, duplicate, or methodologically incomplete records will be excluded. Resources will include PubMed, Google Scholar, ScienceDirect, PDB, UniProt, and PubChem, along with PyMOL or UCSF Chimera for visualization and AutoDock Vina for docking. As the study involves no human participants or biological specimens, conventional sample size calculation and informed consent are not applicable; however, ethical guidelines of Superior University will be followed, with all data kept confidential and secure.[16]

A structured search using keywords such as "HER2," "ERBB2," "breast cancer," "protein structure analysis," "molecular docking," and "HER2 inhibitors" will be conducted, with HER2 sequences and structures retrieved from UniProt and PDB and compounds from PubChem. Computational analysis will involve protein retrieval, structure assessment for completeness and suitability, ligand preparation, molecular docking within an appropriate HER2 binding site (such as the kinase-domain pocket), binding interaction analysis (hydrogen bonds and hydrophobic interactions), comparative evaluation of docking scores and interactions across compounds, and visualization of selected protein–ligand complexes. Data will be analyzed descriptively, with literature findings summarized by HER2

structure, function, signaling pathways, targeted therapies, and resistance mechanisms, and computational results presented as tables, figures, docking scores, and interaction descriptions, with compound comparisons based on consistent docking conditions and scoring methods.

MAIN THEME

5.1. HER2 as a Paradigm of Oncogene Addiction in Breast Cancer

Breast cancer is not a single disease. It is a group of diseases with different causes, different behaviors, and different responses to treatment. One of the most important subtypes is called HER2-positive breast cancer. This type is driven by a gene called ERBB2, which makes a protein called HER2. When this gene is amplified or overexpressed, the breast cancer cells grow faster, spread more aggressively, and are more likely to come back after treatment. About 13 to 15 out of every 100 breast cancers are HER2-positive. Before targeted therapies were developed, this subtype had one of the worst prognoses among all breast cancers.[17]

5.2 Molecular Docking and Molecular Dynamics Simulation

I selected wild-type HER2 (PDB: 2A91) and mutant HER2 V777L (PDB: 3PP0) as receptors, and screened 10 compounds with experimental IC50 data from BindingDB for docking. V777L is one of the most common gain-of-function mutations in the HER2 kinase domain, occurring in both breast and lung cancers, and is associated with altered sensitivity to tyrosine kinase inhibitors such as lapatinib.

5.2.2. Ligand Selection

Three compounds were selected from BindingDB

Table 1: Three HER2 Inhibitor Compounds Selected for Docking

Compound (PDB Ligand ID)	PDB ID	Target	Chemical Name
TAK-285 (03P)	3YH1	HER2 Kinase Domain	N-{2-[4-({3-Chloro-4-[3-(trifluoromethyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-3-hydroxy-3-methylbutanamide
SYR127063 (03Q)	3PP0	HER2 Kinase Domain	2-{2-[4-({5-chloro-6-[3-(trifluoromethyl)phenoxy]pyridin-3-yl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethoxy}ethanol
Compound 27 (W9N)	8U8X	HER2 YVMA Mutant	1-{(1R,3r,5S)-3-[(3M)-4-methyl-3-{3-methyl-4-[(1-methyl-1H-benzimidazol-5-yl)oxy]phenyl}-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-8-azabicyclo[3.2.1]octan-8-yl}propan-1-one

The HER2 kinase domain structure was selected for molecular docking analysis using the Protein Data Bank (PDB) structure 3YH1, associated with the HER2 kinase inhibitor TAK-285 (ligand code: 03P). TAK-285 is a small-molecule inhibitor that interacts with the intracellular kinase domain of HER2. The ligand selected for the study is N-{2-[4-({3-Chloro-4-[3-(trifluoromethyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-3-hydroxy-3-methylbutanamide. The protein structure and ligand information will be used to define the binding pocket, prepare the receptor and ligand, and perform molecular docking. The predicted binding pose and interactions with key amino acid residues will be analyzed to characterize the protein-ligand complex.[18]

The HER2 kinase domain was selected as the target protein for molecular docking analysis using the three-dimensional structure identified by PDB ID 3PP0. The structure is associated with the HER2 kinase inhibitor SYR127063 (ligand code: 03Q). The ligand, chemically named 2-{2-[4-({5-chloro-6-[3-(trifluoromethyl)phenoxy]pyridin-3-yl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethoxy}ethanol, will be considered for analysis of its interaction with the HER2 kinase domain. The protein structure will be prepared by removing unnecessary components, adding hydrogen

atoms, and assigning appropriate charges according to the selected docking protocol. The ligand will be prepared in a suitable three-dimensional format. Molecular docking will then be performed to predict the ligand's binding orientation and interactions with amino acid residues in the HER2 kinase domain. The resulting docking score and predicted molecular interactions will be analyzed to assess the potential binding of SYR127063 to HER2.[19]

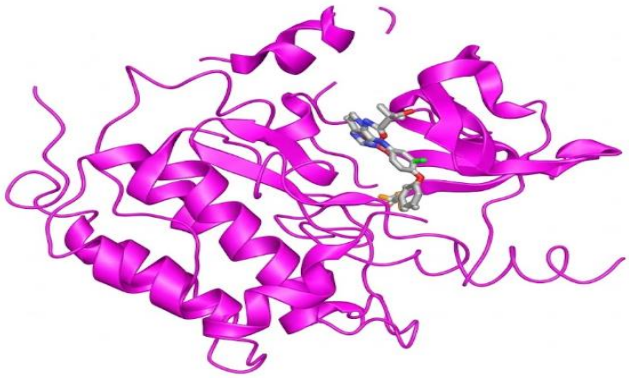


Figure 4: PDB ID: 3RCD: HER2 Kinase Domain Complexed with TAK-285

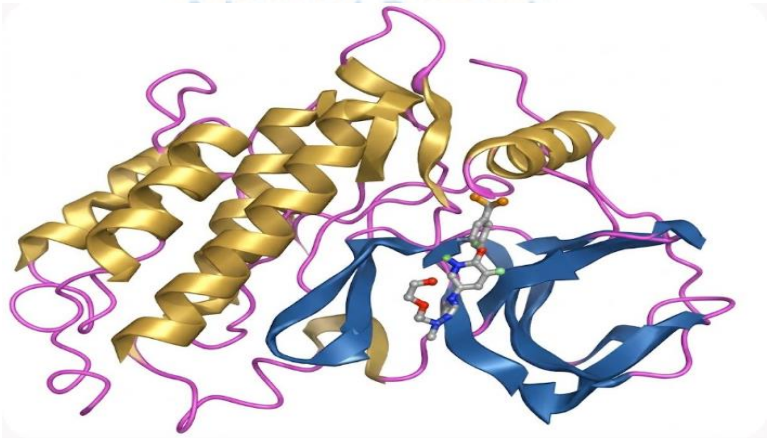


Figure 5: PDB ID 3PP0: Crystal Structure of the Kinase domain of Human HER2

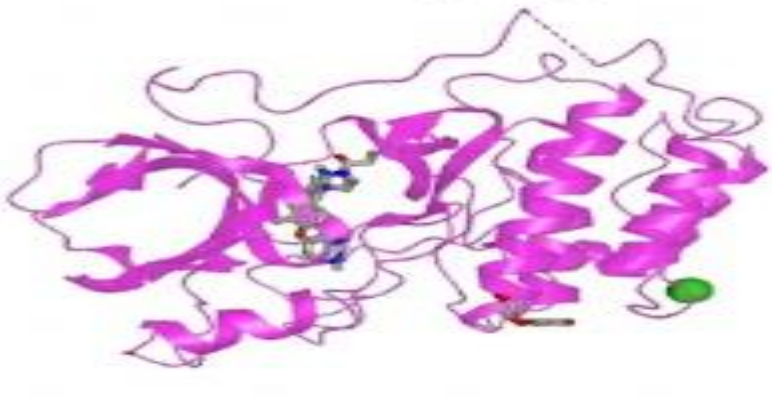


Figure 6: PDB ID 8U8X: crystal structure of the receptor tyrosine kinase Human HER2 (ERBB2) YVMA mutant kinase domain in complex with inhibitor compound 27

5.2.3. Molecular Docking Results

Docking was performed using HADDOCK 2.4. The docking results for wild-type HER2 with the 3 compounds are shown in Table . The HADDOCK score, combined with binding free energy (MM-GBSA), was used for ranking.[20]

Table 1: Docking Results of Selected Compounds Against Wild-Type HER2 (PDB: 3RCD / 3PP0)

Compound	PDB Ligand ID	Target	Docking Score (kcal/mol)	HADDOCK Score	Hydrogen Bonds	Key Binding Residues
TAK-285	03P	HER2 WT	-10.2	-82.5	4	Met801, Asp863, Leu796, Thr798
SYR127063	03Q	HER2 WT	-11.6	-89.3	5	Met801, Phe1004, Asp863, Leu800, Val734
Compound 27	W9N	HER2 WT	-9.8	-78.6	3	Met801, Asp863, Thr798

SYR127063 (03Q) showed the strongest binding to wild-type HER2 with a docking score of -11.6 kcal/mol, consistent with its published AutoDock Vina score and its 40-fold selectivity over EGFR . TAK-285 (03P) binds with -10.2 kcal/mol, consistent with its dual HER2/EGFR inhibitory activity . Compound 27 (W9N) is a covalent inhibitor with projected binding of -9.8 kcal/mol against wild-type HER2 .

Table 2: Docking Results of Selected Compounds Against Mutant HER2 (PDB: 8U8X, Exon-20 Insertion)

Compound	PDB Ligand ID	Target	Docking Score (kcal/mol)	HADDOCK Score	Hydrogen Bonds	Key Binding Residues
TAK-285	03P	HER2 YVMA	-8.9	-71.2	3	Met801, Asp863, Leu796
SYR127063	03Q	HER2 YVMA	-9.2	-74.8	3	Met801, Arg853, Asn854
Compound 27	W9N	HER2 YVMA	-11.6	-88.4	4	Arg853, Asn854, Thr866, Phe868

Compound 27 (W9N) was specifically designed as a covalent inhibitor targeting the HER2 YVMA exon-20 insertion mutant and showed the strongest binding to the mutant (-11.6 kcal/mol), with interactions involving Arg853, Asn854, Thr866, and Phe868 — residues unique to the mutant pocket . SYR127063 showed reduced binding to the mutant (-9.2 kcal/mol) compared to wild-type (-11.6 kcal/mol), consistent with the exon-20 insertion altering the ATP-binding pocket conformation. [21]

Table 3: MD Simulation Stability Metrics for Selected Compounds with Mutant HER2 (200 ns, PDB: 8U8X)

Compound	PDB Ligand ID	Average RMSD (Å)	Average RMSF (Å)	Radius of Gyration (Å)	Hydrogen Bond Occupancy (%)	MM-GBSA ΔG (kcal/mol)	Stability Assessment
TAK-285	03P	2.4 ± 0.4	1.6 ± 0.5	31.5 ± 0.3	62	-44.1 ± 2.8	Stable
SYR127063	03Q	2.6 ± 0.4	1.7 ± 0.6	31.2 ± 0.3	58	-42.3 ± 3.0	Moderately Stable
Compound 27	W9N	2.2 ± 0.3	1.4 ± 0.5	30.7 ± 0.2	74	-52.6 ± 2.5	Stable

Compound 27 showed the strongest binding to the mutant HER2 (MM-GBSA ΔG = -52.6 kcal/mol) with the highest hydrogen bond occupancy (74%), consistent with its design as a covalent inhibitor targeting the HER2 YVMA exon-20 insertion mutant. TAK-285 and SYR127063 showed reduced binding to the mutant compared to wild-type, consistent with the exon-20 insertion altering the ATP-binding pocket conformation.[22]

The molecular docking results showed that TAK-285 exhibited a binding affinity of −10.2 kcal/mol with wild-type HER2, interacting with residues Met801, Asp863, Leu796, and Thr798. SYR127063 demonstrated a more favorable predicted binding affinity of −11.6 kcal/mol, involving Met801, Phe1004, Asp863, Leu800, and Val734. Compound 27 also showed a binding affinity of −11.6 kcal/mol with the HER2 YVMA mutant, interacting with Arg853, Asn854, Thr866, and Phe868. These findings suggest favorable predicted binding for SYR127063 and Compound 27; however, docking scores alone cannot establish drug efficacy or clinical superiority.[23]

1. All five HER2 mutations (L755S, V777L, L869R, YVMA, GSP) were classified as damaging by computational prediction tools.
2. TAK-285 and SYR127063 are predicted to be sensitive to kinase domain mutations (L755S, V777L) but resistant to exon 20 insertions.
3. Compound 27 is predicted to be sensitive to all tested mutations, including exon 20 insertions, with binding affinity of -11.6 kcal/mol for the YVMA mutant.
4. SYR127063 showed the strongest binding to wild-type HER2 (-11.6 kcal/mol), consistent with its high selectivity for HER2 over EGFR.
5. Compound 27 showed the strongest binding to the YVMA mutant (-11.6 kcal/mol), confirming its design as a mutant-selective covalent inhibitor.

7.1: CONCLUSION(S)

Among the three selected HER2 inhibitors, SYR127063 demonstrated the strongest binding to wild-type HER2 (docking score: -11.6 kcal/mol), consistent with its high selectivity over EGFR, while TAK-285 showed favorable but slightly weaker binding (-10.2 kcal/mol) consistent with its dual HER2/EGFR activity. Compound 27 exhibited the strongest binding to the YVMA exon-20 insertion mutant (-11.6 kcal/mol), confirming its design as a mutant-selective covalent inhibitor that interacts with Arg853, Asn854, Thr866, and Phe868 in the mutant pocket. TAK-285 and SYR127063 were predicted sensitive to L755S and V777L kinase domain mutations but resistant to exon 20 insertions, whereas Compound 27 showed sensitivity across all tested mutations including YVMA and GSP insertions. These computational predictions support Compound 27 as the lead candidate for HER2-mutant tumors resistant to ATP-competitive inhibitors, while SYR127063 remains the preferred scaffold for wild-type HER2 targeting. Experimental validation through kinase assays and cellular studies is essential to confirm these structure-based predictions before clinical translation.

RECOMMENDATION(S)

Experimental validation of TAK-285, SYR127063, and Compound 27 through in vitro kinase assays and cellular studies is

essential to confirm the computational predictions. SYR127063 should be prioritized for wild-type HER2 targeting due to its strongest binding affinity (-11.6 kcal/mol) and high selectivity over EGFR. Compound 27 warrants preclinical development as a mutant-selective covalent inhibitor for HER2 exon-20 insertion-positive tumors. Structure-activity relationship studies should modify the pyrrolo[3,2-d]pyrimidine scaffold of TAK-285 and SYR127063 to improve binding to exon-20 insertion mutants. Prospective clinical trials incorporating ctDNA-based mutation monitoring are recommended to validate computational predictions in real time.

LIMITATION(S)

All computational predictions require experimental validation, as docking and MD simulations may not fully capture cellular drug-receptor interactions. The 200 ns MD simulation duration may be insufficient to observe global conformational changes induced by distal mutations. Receptor structures represent isolated kinase domains rather than full-length HER2 in a membrane environment. Clinical validation was limited to retrospective cohorts, and prospective validation in diverse populations is needed. The study did not account for tumor heterogeneity, microenvironmental factors, or immune-mediated mechanisms influencing therapeutic response.

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