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Molecular Docking and Molecular Dynamics Approaches to Evaluate the Specificity of the AS1411-Lapatinib Aptamer Complex in HER2-Positive Breast Cancer

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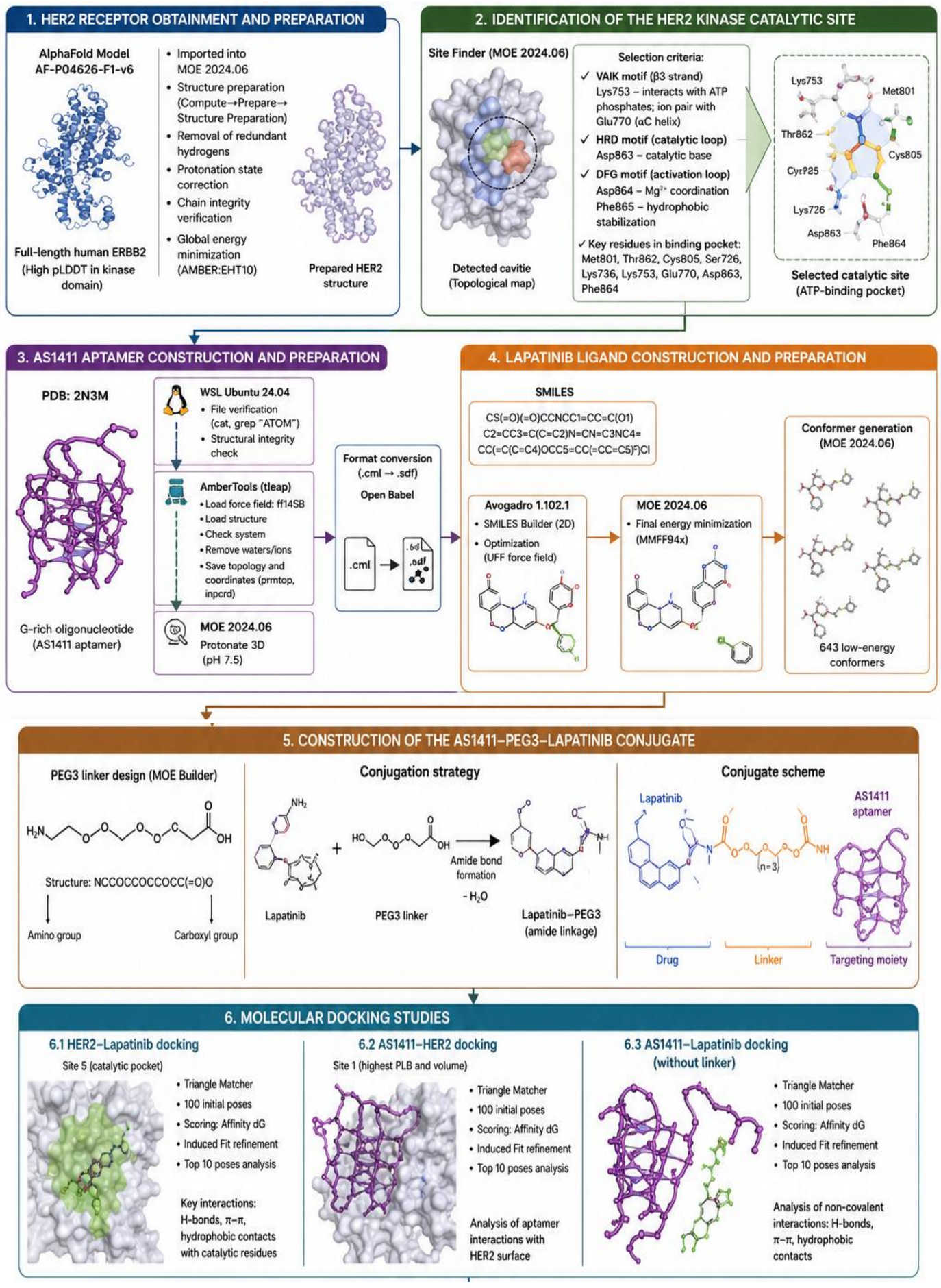
INTRODUCTION & AIM

HER2-positive breast cancer accounts for approximately 15–20% of breast cancer cases and is characterized by ERBB2 gene amplification and overexpression of the HER2 tyrosine kinase receptor. At the molecular level, this alteration promotes the constitutive activation of signaling pathways such as PI3K/AKT/mTOR and MAPK/ERK, which are associated with increased cell proliferation, tumor progression, metastasis, and therapeutic resistance. Although anti-HER2 targeted therapies have significantly improved patient survival, intratumoral heterogeneity and acquired resistance mechanisms continue to limit their clinical efficacy.

Lapatinib, a reversible dual inhibitor of HER2 and EGFR, acts on the intracellular tyrosine kinase domain through ATP-competitive inhibition and has demonstrated efficacy in tumors resistant to conventional therapies. However, its low bioavailability and systemic toxicity remain important therapeutic limitations. In this context, aptamers have emerged as promising biomolecules for selective drug targeting due to their high molecular affinity, structural stability, and ease of chemical modification.

AS1411, a guanine-rich aptamer with a stable G-quadruplex conformation, selectively recognizes nucleolin overexpressed in tumor cells, promoting cellular internalization and intracellular accumulation. Therefore, the present study aimed to evaluate, through in silico tools, the interaction between AS1411 and Lapatinib, as well as its potential targeting toward HER2-overexpressing cells. Molecular docking and molecular dynamics simulations were employed to analyze binding affinity, conformational stability, and energetic behavior of the proposed complex.

METHOD



RESULTS & DISCUSSION

Molecular docking analyses support the feasibility of the AS1411–Lapatinib system as a targeted strategy against HER2-positive breast cancer. The HER2–Lapatinib complex exhibited binding affinities ranging from −9.12 to −12.51 kcal/mol, involving key catalytic residues such as Lys753, Glu770, Met801, Cys805, Thr862, and Asp863, which are known to participate in ATP-pocket recognition and HER2 inhibition (Aertgeerts et al., 2011). The AS1411–HER2 complex displayed highly favorable interaction energies (−62.70 to −47.34 kcal/mol) and low refinement RMSD values (0.30–3.37 Å), indicating stable binding and structural compatibility. Interactions with Glu876, Tyr877, Arg896, Arg897, and Arg898 suggest potential modulation of kinase regulatory regions. Furthermore, AS1411–Lapatinib showed comparable binding energies (up to −12.51 kcal/mol) and an average RMSD of 2.51 Å, supporting the stability of the aptamer–drug complex. These findings are consistent with previous studies highlighting the structural stability and targeting potential of AS1411 G-quadruplex aptamers in cancer therapy (Bates et al., 2009; Kejnovská et al., 2023).

Molecular docking analysis of the HER2–Lapatinib, AS1411–HER2, AS1411–Lapatinib, and AS1411–PEG3–Lapatinib systems.

Complex	Site	PLB	Hyd	Side	Residues
HER2–Lapatinib	5	198	35	70	LEU726, GLY727, VAL734, ALA751, ILE752, LYS753, GLU770, MET774, SER783, LEU796, THR798, GLN799, LEU800, MET801, TYR803, GLY804, CYS805, ASP808, HIS809, GLU812, ASN813, ARG849, ASN850, LEU852, THR862, ASP863, PHE864, SER1002, THR1003, PHE1004, ASP1019, GLU1021, PRO749, LYS860, GLY804
AS1411–HER2	5	198	35	70	ARG898, GLU876, PHE1185, TYR877, ARG896, ARG897, ALA879, ASP880.
AS1411–Lapatinib	1	154	10	62	DG9, DT10, DT11, DG12, DT13, DG15, DT16, DG17, DG18, DG26, DG27, DT328 DG1, DG2, DG6, DG8, DT14
AS1411–PEG3–Lapatinib	5	198	35	70	ALA751, ASP1019, GLU1021, PRO749, ALA751, LYS860, GLY804

Site: predicted binding site; PLB: protein–ligand backbone interactions; Hyd: number of hydrogen bonds;
Side: number of side-chain interactions; **Residues**: interacting amino acids (in blue boxes: key residues involved in binding).

CONCLUSIONS

The docking results support the feasibility of the AS1411–PEG3–Lapatinib conjugate as a targeted therapeutic system against HER2-positive breast cancer. Lapatinib maintained favorable interactions within the HER2 catalytic region, while AS1411 displayed stable binding to the receptor, suggesting its suitability as a targeting element. Moreover, the stable association observed between AS1411 and Lapatinib indicates that aptamer functionalization is unlikely to impair the drug's binding capabilities. The identification of key interacting residues and favorable docking parameters across all evaluated complexes provides structural evidence supporting the rational design of the proposed conjugate. Overall, the computational findings suggest that the integration of AS1411, PEG3, and Lapatinib may enhance molecular targeting while preserving therapeutic functionality, warranting further validation through molecular dynamics simulations and experimental studies.

FUTURE WORK/ REFERENCES/ACKNOWLEDGMENT

FUTURE PERSPECTIVES
- Molecular dynamics simulations of the HER2–Lapatinib and AS1411–PEG3–Lapatinib complexes.
- Binding free energy calculations (MM/PBSA and MM/GBSA) to further characterize molecular interactions.
- In vitro validation in HER2-positive breast cancer cell lines.
- Evaluation of the targeting efficiency and therapeutic potential of the proposed conjugate.

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