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ORIGINAL

Computational identification of era antagonists derived from natural products for breast cancer treatment

Identificación computacional de antagonistas de erα derivados de productos naturales para el tratamiento del cáncer de mama

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ABSTRACT

Estrogen receptor alpha-positive (ERα+) breast cancer remains the most prevalent hormone-driven malignancy in women. While current endocrine therapies target ERα, emerging drug resistance underscores the need for novel antagonists. This study computationally evaluates natural compounds from the ZINC database as potential ERα antagonists using multi-stage in silico approaches. Molecular docking (HTVS, SP, XP) identified two compounds, ZINC000085627072 and ZINC000085592636, with superior binding affinities (XP scores: -14,811 and -14,366 kcal/mol) compared to the reference antagonist H3B-9224 (-13,620 kcal/mol). MM-GBSA binding free energy calculations further corroborated their stability, yielding energies of -61,51 , -88,77, and -85,38 kcal/mol for ZINC000085627072, ZINC000085592636, and H3B-9224, respectively. Pharmacokinetic profiling via ADME analysis revealed acceptable properties for both natural compounds. Molecular dynamics (MD) simulations over 100 ns demonstrated stable binding: ZINC000085592636 and H3B-9224 exhibited comparable RMSD trajectories (~3 Å), while ZINC000085627072 showed moderate fluctuations (~4 Å). Protein-ligand flexibility analysis (RMSF) revealed average ligand-RMSF values of 1,4 ±1,14 Å (ZINC000085627072), 1,2 ±0,4 Å (ZINC000085592636), and 1,4 ±1,1 Å (H3B-9224), with protein-RMSF consistently at ~3 Å, indicating minimal structural fluctuations. These results suggest ZINC000085627072 and ZINC000085592636 as promising ERα antagonists with superior predicted affinity to H3B-9224, warranting further experimental validation. This integrated computational framework highlights the potential of natural product-derived scaffolds in addressing ERα+ breast cancer drug resistance.

Keywords: Breast Cancer; Estrogen Receptor A; Natural Compounds; Molecular Docking; ADMET; MD.

RESUMEN

El cáncer de mama con receptores de estrógeno alfa positivos (ERα+) sigue siendo el tumor maligno de origen hormonal más frecuente en las mujeres. Aunque las terapias endocrinas actuales se dirigen al ERα, la resistencia emergente a los fármacos subraya la necesidad de nuevos antagonistas. Este estudio evalúa computacionalmente compuestos naturales de la base de datos ZINC como posibles antagonistas del ERα utilizando enfoques in silico de múltiples etapas. El acoplamiento molecular (HTVS, SP, XP) identificó dos compuestos, ZINC000085627072 y ZINC000085592636, con afinidades de unión superiores (puntuaciones XP: -14,811 y -14,366 kcal/mol) en comparación con el antagonista de referencia H3B-9224 (-13,620 kcal/mol). Los cálculos de energía libre de unión MM-GBSA corroboraron aún más su estabilidad, arrojando energías de -61,51, -88,77 y -85,38 kcal/mol para ZINC000085627072, ZINC000085592636 y H3B-9224, respectivamente.

El perfil farmacocinético mediante análisis ADME reveló propiedades aceptables para ambos compuestos naturales. Las simulaciones de dinámica molecular (MD) durante 100 ns demostraron una unión estable: ZINC000085592636 y H3B-9224 mostraron trayectorias RMSD comparables (~3 Å), mientras que ZINC000085627072 mostró fluctuaciones moderadas (~4 Å). El análisis de flexibilidad de la proteína-ligando (RMSF) reveló valores medios de RMSF del ligando de 1,4 ±1,14 Å (ZINC000085627072), 1,2 ±0,4 Å (ZINC000085592636) y 1,4 ±1,1 Å (H3B-9224), con un RMSF de proteína constante en ~3 Å, lo que indica fluctuaciones estructurales mínimas. Estos resultados sugieren que ZINC000085627072 y ZINC000085592636 son antagonistas prometedores del ERα con una afinidad prevista superior a la de H3B-9224, lo que justifica una mayor validación experimental. Este marco computacional integrado destaca el potencial de los andamios derivados de productos naturales para abordar la resistencia a los fármacos contra el cáncer de mama ERα+.

Palabras clave: Cáncer de Mama; Receptor de Estrógeno A; Compuestos Naturales; Acoplamiento Molecular; ADMET; MD.

INTRODUCTION

Breast cancer (BC) is a result of overexpression of genes that lead to uncontrolled cellular growth, and, in 2020 it accounted for 2,3 million cases and 685000 deaths.[1,2,3] Furthermore, BC is considered the second leading of death among postmenopausal women after ovarian cancer where it is associated with 15 % of cancer related death in women while 70 % of women with breast cancer have identified estrogen receptor alpha (ERα) expression while breast cancer itself.[4,5,6,7]

Estrogen and progesterone are steroidal hormones produced by the ovaries of premenopausal women while in the postmenopausal women aromatase enzyme plays a predominant role in production of estrogen by its activity on androgens.[8] With regard to the immunohistochemical expression of prognostic markers; BC is divided to estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) and the proliferation marker Ki67.[8,9] Estrogen receptors have two subtypes; ERα and ERβ, where dysregulation of ERα (G-protein coupled receptor) signaling and activation by estradiol is associated with the oncogeneses and prognosis of BC through G protein-induced signal transduction mechanisms while ERβ role is much more complex and hypothesized that, the single nucleotide polymorphism (SNP), ERß TXIB variants have a significant role in BC development.[1,4,8,10,11]

The treatment lines for BC are chemotherapy, hormonal therapy, surgery and radiation, although the heterogenous nature of BC biology and development of molecular resistance to chemotherapy will reduce the drug efficacy in addition to cytotoxicity.[12,13] Food and drug administration (FDA) has approved hormone therapy for treatment of ERα+BC like tamoxifen in 1977, letrozole approved in 2002 and fulvestrant.[6,8,14,15] Tamoxifen is an estrogen receptor modulator (SERM) that can enhance survival rates of patients with BC, reduces the recurrence rate and prevents BC development in premenopausal women with high risk.[5,8] However, long-term use of tamoxifen; the unanticipated estrogenic action of tamoxifen will increase the likelihood for endometrial cancer as well as intrinsic and extrinsic resistance.[8,16,47,18] Although, aromatase inhibitors (AIs) are used as standard in treatment of postmenopausal women with hormone positive breast cancer, the emerged resistance has reduced their efficacy. AIs are either steroidal type, like exemestane, that bind the enzyme irreversibly through hydrogen bond or non-covalent reversible binding in the non-steroidal type like letrozole and anastrozole.[19] Another treatment option is fluvestrant which is a selective estrogen receptor degrader (SERD), it has poor pharmacokinetics that led to development of second generation SERDs and some of the developed molecules are in clinical trials phase II/III (Elacestrant, RG6171, SAR439839, and AZD9833).[6]

ERα comprises 6 binding domains, of them is the ligand binding domain (LBD), domain E, which composed of C-terminal helix called H12 that controls the receptor's antagonist state, hence upon ligand binding (e.g. tamoxifen) to LBD, H12 agonistic state will be suppressed where H12 is unable to cap ligand binding domain hence the stable antagonist conformation can result.[11,20,21,22] Additionally, ERα activation by 17ß-estradiol will result in oncogenesis where downstream signaling activates adenosine monophosphate (cAMP), PI3K/AKT, and endothelial nitric oxide synthase, in turn will increase cAMP and hence Ca+2 mobilization and activation of ER+ C-terminal.[11,14,22,23]

More specifically, ERα is received considerable interest as an active target in development of anticancer drugs targeting estrogen receptors.[24] ERα+ antagonists compete with endogenous estrogen to bind to estrogen receptor, hence mutation of LBD leads to resistance to these antagonist.[25,26] Resistance to endocrine therapy is the main challenge in treatment of ERα+BC where the cell signaling adapt many escaping pathways and in turns cell cycles adapt alternative cell proliferation of tumors.[7,27]

The traditional methods of drug discovery and development involve synthesis/extraction of active molecules, understanding the biological pathways of different drug targets proposed to be innovates in cancer therapy,

further in vitro and in vivo testing to assess the efficacy, selectivity and specificity.[28,29] Furthermore, assessment of safety toxicity profile in different populations is performed through several steps of clinical trials which need high budgets, long times (10-15 years) and above all there is of failure at some stages.[30,31,32]

Nevertheless, the application of computational aided drug design (CADD) methods is increasingly used and applied in drug discovery and development because it enables, through different methods and models, the investigation of activity and interaction of several molecules against biological targets in many diseases including cancer.[33,34,35] Additionally, the toxicity profile, drug likeness and stability of the tested molecules with target protein/receptor could be predicted.[31] Crizotinib, Axitinib, Gefitinib, Erlotinib, Lapatinib, Abiraterone and Imatinib are anticancer drugs discovered by CADD and approved by FDA.[36,37] CADD methods accelerate and facilitate drugs discovery and development due to the reduced costs, facilities and the short time needed to have a clear prediction of several properties of the investigated hits/molecules.[25,31,38]

METHOD

In silico methods followed in this research have been carried out using Maestro v12.8 from Schrödinger except for molecular dynamics simulation which have been performed using Academic Desmond v6.5 by D.E. Shaw Research.

Protein and ligand preparation

The crystal structure of the protein was retrieved from the Protein Data Bank with PDB ID 6CHZ (www.rcsb.org/structure/6chz) and resolution 1,68 Å. The 3D structure of the protein was prepared for docking using Protein Preparation Wizard of Maestro v13.5 of Schrödinger which mandate the preparation to be in three consecutive steps.[39] In the beginning, pre-preprocessing was applied in which all of the missing hydrogen atoms, missing bonds, zero-order bonds to metals and disulfide bonds, incomplete side chains and loops and the water molecules beyond 5 Å were removed, then the het states were generated at 7 ± 2 pH by Epik tool. Thereafter; PROPKA tool at a pH of 7.0 was used to determine the protonation state of 6CHZ following to optimization and determination of hydrogen bonds orientations to the crystalized water molecules. In the last step; the restrained minimization process under the OPLS4 force field was applied to the refined protein.

A natural library of compounds (270,540) was downloaded from the Zinc database (https://zinc.docking.org/). These compounds were subjected to energy minimization under OPLS4 force field using the MacroModel tool of Maestro. This step was crucial to ensure that all ligands in the library were adequately prepared for subsequent computational processes.[40]

Grid generation of protein receptor

The protein's binding cavity was determined in the place where the ligand (H3B-9224) bound to the protein 6CHZ using the Receptor Grid Generation tool of Maestro. This tool utilizes the coordinates of a ligand with the protein to create a 3D grid with precise dimensions, representing the receptor's active area.[41]

Molecular docking

Molecular docking enable identification of the interactions between the protein and the ligand as well as the best conformations and orientations by using several docking algorithms.[28] The ligands (270,540 structures) were filtered based on their binding strength to the receptor in an efficient manner. This involved a three-stage evaluation process: high-throughput virtual screening (HTVS) for quick and random initial screening, followed by standard precision (SP) and finally, extra precision (XP).[42]

MM-GBSA calculation

The free binding energy of the top hits complexed with 6CHZ was further analysed using Molecular Mechanics-Generalized Born and Surface Area (MM-GBSA) with the Prime tool of Maestro, which accounted for the influence of the solvent in the binding energy calculation. The energy calculations of the minimized structures were performed using the VSGB solvation model and OPLS3e force field. binding free energy calculations would give an accurate prediction of affinity of ligands toward the protein.[43]

ADME prediction

ADME analysis will assess the pharmacokinetics of the molecules and drug-likeness properties putting into consideration violation from Lipinski's rule of Five.[25] The top compounds, based on the docking scores obtained from XP docking, were subjected to ADME analysis to predict their pharmacokinetic properties using the QikProp tool from Schrödinger. This initial assessment played a crucial role in mitigating the risk of failure in subsequent stages of drug development.

Molecular Dynamics (MD) simulations

MD simulations use model of interatomic interaction to predict the dynamics of protein's atoms that in

complex with a ligand over a period of time, hence aiding in the assessment of complex stability and the identification of non-binding interactions with the target.[2] The chosen molecules from XP docking underwent MD simulations using the academic Desmond v6.5 by D.E. Shaw Research. To commence the simulation process, the biological system was configured using the System Builder panel, involving placing the protein-ligand complexes in TIP3P solvent molecules within an orthorhombic box (10 × 10 × 10 Å), adding Na+ and Cl− ions to neutralize charges and achieve physiological salt concentration, and minimizing the system's energy using the OPL3Se force field. The simulation proceeded at a temperature of 300 K and a pressure of 1 bar, ensuring equilibrium with the NPT ensemble class for 100ns where 1000 frames for each system were obtained during the simulations.[44]

RESULTS

Molecular docking and MM-GBSA binding free energy study

Molecular docking predicts the structural features of ligand that enhances its binding to the protein binding cavity and its mode of binding. In this term, a library of 270,540 natural compounds have been docked on ERα (PDB ID: 6CHZ) using glide XP-mode of Schrödinger suite. The two top compounds (ZINC000085627072, ZINC000085592636) with the highest docking scores have been compared to the co-crystalline ligand H3B-9224 of ERα (The chemical structures have been presented in figure 1). The docking scores of the two top compounds were -14,811 , -14,366 Kcal/ mol for ZINC000085627072 and ZINC000085592636, respectively, which are higher than that obtained for the reference H3B-9224 which has docking score -13,620 Kcal/ mol (table 1).

Table 1. XP-docking scores and MM-GBSA value of the top natural compounds and the reference docking scores

Molecule	XP-G Score (Kcal/mol)	MM-GBSA dG Bind (Kcal/mol)
ZINC000085627072	-14,811	-61,51
ZINC000085592636	-14,366	-88,77
Reference B3H-9224	-13,620	-85,38

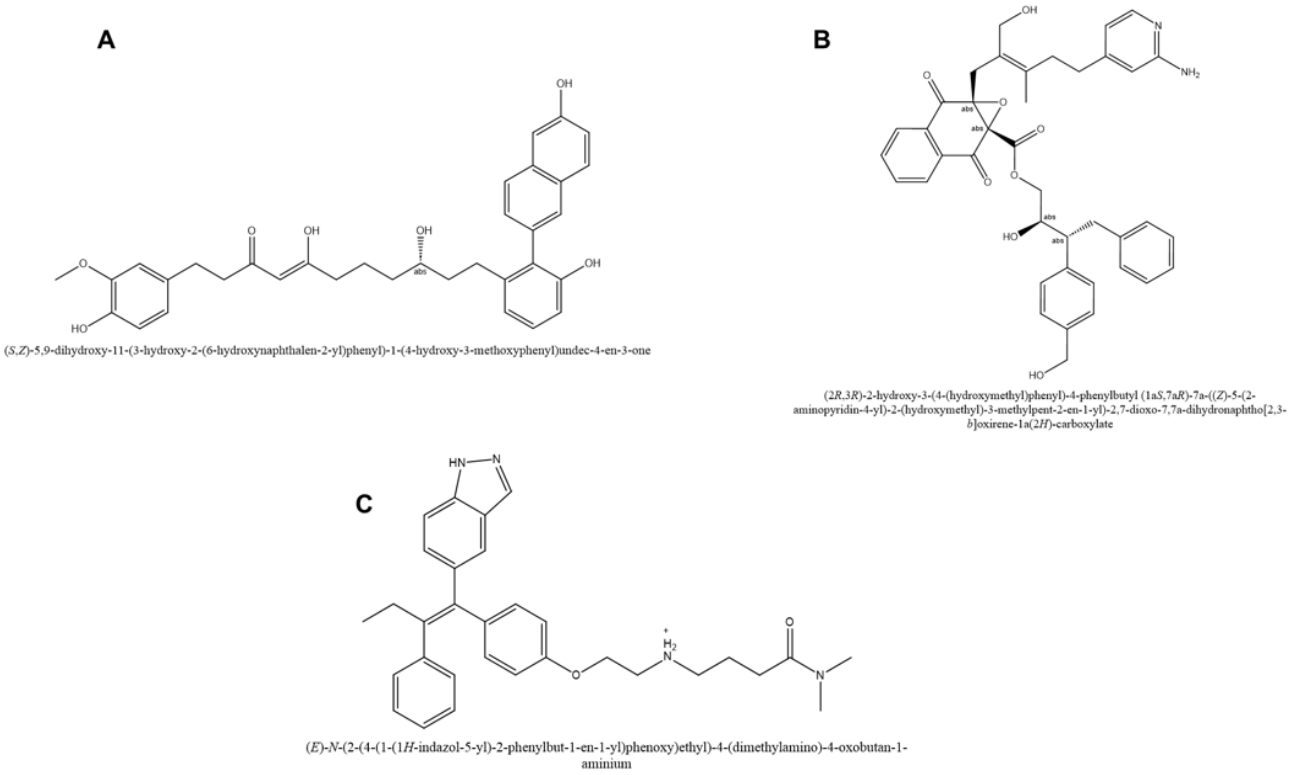

Figure 1. Chemical structures of: A) ZINC000085627072, B) ZINC000085592636, C) the reference B3H-9224

Furthermore, for the seek of convenience, looking deeply on the pattern of interactions of the obtained compounds with the target proteins 6CHZ; π-π stacking, polar interactions, hydrogen bond, hydrophobic interactions are the predominant interactions observed for all compounds (table 2 and figure 2A-C).

Table 2. Intermolecular interactions of the top natural compounds and the reference docking scores with binding sites of ERα (PDB ID: 6CHZ)

Compound	π-π interaction	Polar interaction	H-bond interaction	Hydrophobic interaction
ZINC000085627072	PHE404	THR347, HID524	THR347, ASP351, GLU353, ARG394	MET343, LEU346, LEU349, ALA350, LEU354, TRP383, LEU384, LEU387, MET388, LEU391, PHE404, MET421, ILE424, LEU428, MET522, MET528, LEU525, CYS530, LEU536, PHE404
ZINC000085592636	TYR526	THR347, HID524, ASN532	GLU353, CYS530, ARG353	MET343, LEU346, LEU349, ALA350, LEU354, TRP383, LEU384, LEU387, MET388, LEU391, LEU394, LEU397, PHE404, MET421, ILE424, MET522, LEU525, TYR526, MET528, VAL533, LEU536, CYS530, LEU539
Reference H3B-9224	PHE404	THR347, HID524	ASP351, GLU353, ARG394	MET343, LEU346, LEU349, ALA350, LEU354, TRP383, LEU384, LEU387, MET388, LEU391, PHE404, MET421, ILE424, LEU428, MET522, LEU525, TYR526, LEU536

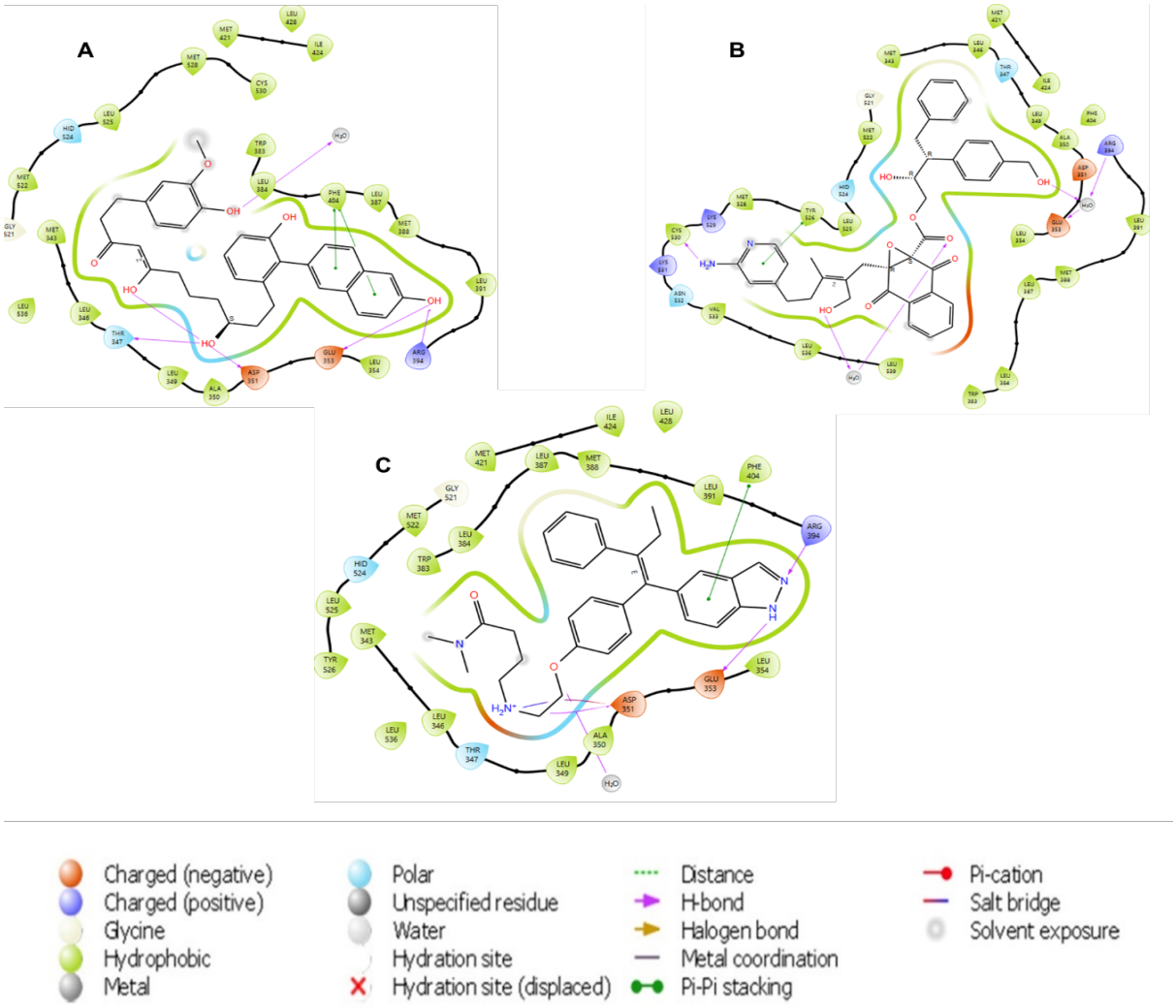

Figure 2. Two-dimensional (2D) interactions of the top-ranked ligands A) ZINC000085627072, B) ZINC000085592636, C) the reference B3H-9224 with the binding pocket residues of ERα (PDB ID: 6CHZ) protein after glide XP-docking

A very closed investigation; we can observe that ZINC000085627072 showed π-π stacking *via* PHE404 in the manner as observed for the reference H3B-9224 whereas ZINC000085592636 showed π-π stacking *via* TYR596 (figure 2A-C).

Polar interactions have been observed through binding to residues THR347 and HID524 residues for ZINC000085627072 and the reference while ZINC000085592636 showed additional polar interaction through binding to ASN532 residue. Furthermore, the hydrogen bonds have been formed *via* THR347, ASP351, GLU353, ARG394 residues for ZINC000085627072, while ZINC000085592636 formed H-bonds *via* GLU353, CYS530 and ARG394 residues in the same way observed for the reference H3B-9224 (table 2 and figure 2A-C).

All the three compounds have shown hydrophobic interactions *via* MET343, LEU346, LEU349, ALA350, LEU354, TRP383, LEU384, LEU387, MET388, LEU391, PHE404, MET421, ILE424, LEU428, MET522, LEU525, CYS530, LEU536, but further another hydrophobic interaction of ZINC000085592636 have been through TYR526, LEU539, TYR526, VAL533, LEU394, LEU397 whereas the reference H3B-9224 showed additional hydrophobic interaction *via* TYR526. ZINC000085627072 and ZINC000085592636 exerted unique hydrophobic interaction through MET428 (table 2 and figure 2A-C).

The magnitude of strength of the binding affinity has been evaluated by calculating the binding free energy using Molecular Mechanics energies combined with Generalized Born and Surface Area (MM-GBSA) by the prime Module of Schrödinger. Only ZINC000085592636 has displayed MM-GBSA of -88,77 Kcal/mol that is higher than that of the reference H3B-9224 (-85,38 Kcal/mol) whereas ZINC000085627072 has MM-GBSA value of -61,51 Kcal/mol as seen in table 2.

ADME Prediction

Prediction of ADME properties provide the greatest advantages in the process of drug discovery and development. ADME prediction provides insight of physicochemical and pharmacokinetics and properties of molecules and the eligibility of druggability, such as oral bioavailability, absorption, distribution, metabolism, and excretion. Lipinski's rule of five is an indicator for the drug-likeness of the investigated compounds, further this rule mandate no more than four violations out of five are acceptable.[2] Combined parameters with molecular flexibility are critical features for oral bioavailability.[45] In this study; ADME and drug likeness have been evaluated using Schr**o**dinger's QikProp tool. ADME results were evaluated according permeability across MDCK cells (QPPMDCK), and binding affinity to serum albumin (QPlogKhsa). According to Lipinski's rule of five in this study the three compounds manifested one violation from the rule of five hence revealing drug-like property (table 3).

Table 3. Predicted ADME properties of the top natural compounds and the reference

Compound	QPlogS[a]	QPlogHERG[b]	QPPCaco[c]	QPlogBB[d]	QPPMDCK[e]	QPlogKhsa[f]	Rule Of Five
ZINC000085627072	-6,945	-7,781	44,839	-3,553	17,256	0,636	1
ZINC000085592636	-3,64	-5,987	28,688	-3,078	10,649	-0,116	1
Reference H3B-9224	-1,965	-8,228	12,411	-0,854	5,829	0,789	1

a. Predicted aqueous solubility (acceptable range -6,5 to 0,5).

b. Predicted cardiac toxicity (<-5).

c. Predicted caco cell permeability in nm/s (accepted range: < 25 is poor and >500 is great) caco-2 cells are good model for the gut-blood barrier.

d. Predicted blood brain barrier permeability (acceptable range -3-1,2).

e. Predicted apparent MDCK cell permeability in nm/s (acceptable range: 25 is poor and >500 is great).

f. Predicted human serum albumin binding (acceptable range (-1,5–1,5).

Further analysis of pharmacokinetics properties predicted from ADME analysis of the tested compounds have elicited that ZINC000085627072, ZINC000085592636 and the reference H3B-9224 are within the acceptable range for some properties. Additionally, ZINC000085627072, ZINC000085592636 have shown BBB permeability (QPlogBBB < -3). Further, ZINC000085627072 showed poor solubility (QPlog = -6,945). ADME analysis revealed some concerns about BBB permeability and cardiotoxicity (QPlogHERG > -5) have been observed.

Molecular dynamics simulations (MD)

Molecular dynamics simulations give more realistic estimation of molecule's mechanics depending on Newton's equation of motion, this equation predicts the atomic movement within protein and ligand environment within a specified time frame using physical-dependent intermolecular interactions.[24,46] In that term, MD can assess the functional and structural stability of proteins and protein−ligand complexes.[1] Therefore, in this study MD simulations have been carried out throughout 100 ns for the top two natural compounds (ZINC000085627072, ZINC000085592636) with the highest docking scores and the reference molecule B3H-9224 using the Academic Desmond software to have a clear insight of the stability of ligand-protein complex. The MD simulations results

are; root mean square error of deviation (RMSD), root mean square error of fluctuation (RMSF) and protein ligands contact histogram (figures (3-6)).

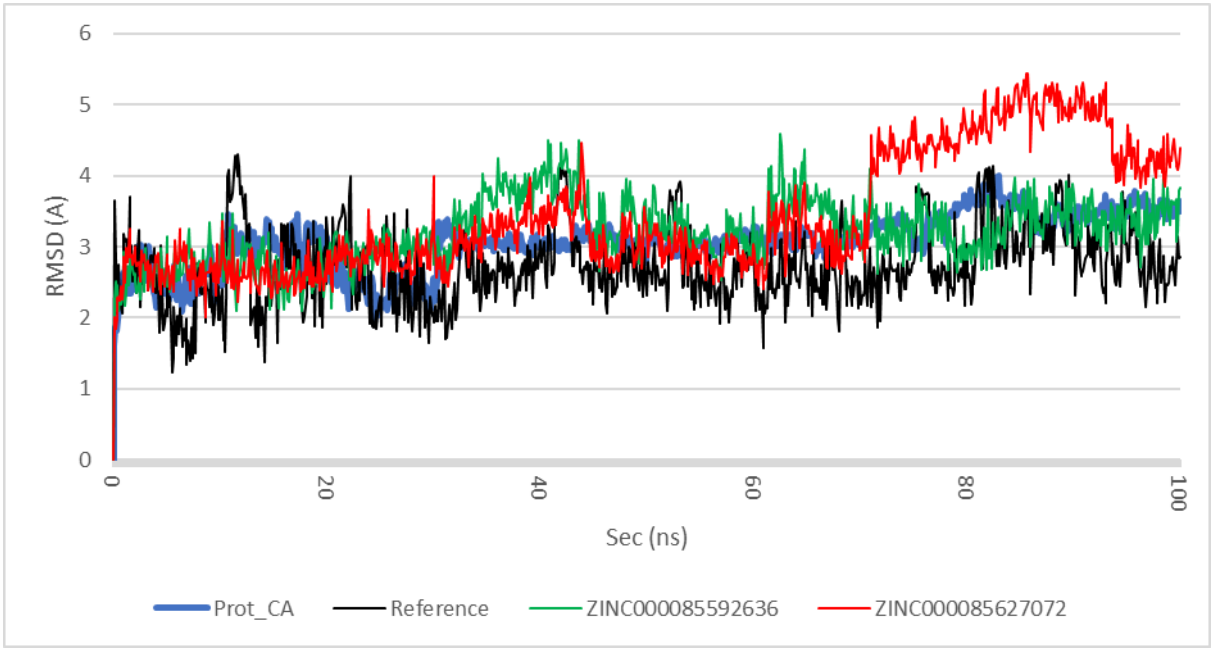

Figure 3. Root Mean Square Deviation (RMSD) plot of the protein backbone and ligands atomic position throughout 100 ns molecular simulation of the three investigated systems using Desmond: the top-ranked ligands ZINC000085627072, ZINC000085592636, the reference B3H-9224 with the binding pocket residues of ERα (PDB ID: 6CHZ) protein

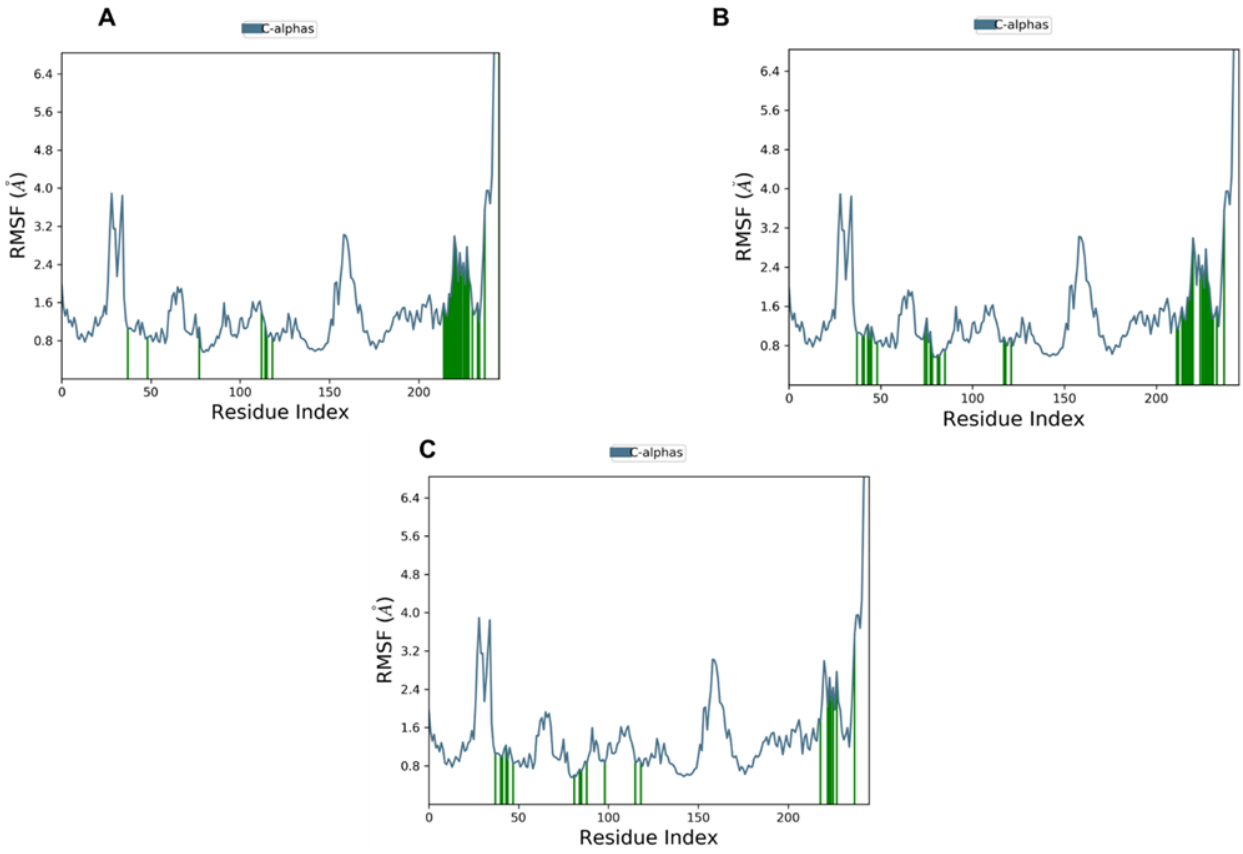

Figure 4. Root mean square fluctuation (RMSF) plot of the Cα atoms of the binding pocket of ERα (PDB ID: 6CHZ) protein: A) ZINC000085627072, B) ZINC000085592636, and the reference H3B-9224

To have a comprehensive conceptualization and understanding the stability of binding proximity in ligand-protein complex, we get further for analysing the root mean square error of deviation (RMSD). RMSD is used to measure the scaly distance from the protein and ligand throughout the trajectory where fluctuation in the range

of 1-3 Å are acceptable for the small globular proteins, otherwise it means the protein undergo conformational changes. In this work, The RMSD of 6CHZ Cα, ZINC000085627072, ZINC00008559263 and the reference H3B-9224 were stabilized within the first 20 ns with an average RMSD of 3 Å. However, ZINC000085627072 showed a fluctuation around 5 Å between 70-90 ns after which it was maintained around 4 Å to the end of the simulation as shown in figure 3A-C.

In order to evaluate the remaining variance throughout MD simulation we get further to analyze root mean square error of fluctuation (RMSF) which provides an estimation of the stability of the amino acid residues along the protein-ligand complex. In figure (4A-C), peaks indicate areas of the protein that fluctuate the most during the simulation. Moreover, it is observed that the tails (N- and C-terminals) fluctuated more than any other part of the protein while α-helices and β-strands (secondary structures) shown to be more rigid than the unstructured part of the protein, thereby fluctuate less than the loop regions. ZINC000085627072 (figure 4A) RMSF is in the range 0,87-2,99 Å except for MET543 residue which fluctuates at 3,56 Å whereas ZINC000085592636 (figure 4B) exerted RMSF in the range 0,58-2,99 Å except MET543 residue that fluctuated at 3,56 Å. Compared to RMSF of the reference, one can observed fluctuations with Cα residues are in the range 0,61 – 1,77 Å except for the MET543 residue at 3,65 Å (figure 4C).

The average ligand RMSF (figure 5A-C) has been found to be 0,91± 0,62 **Å**, 0,57± 0,4 **Å,** 0,96± 0,64 **Å**, respectively, for ZINC000085627072, ZINC000085592636 and the reference B3H-9224. While the average RMSF fluctuations of the protein with these compounds is in the range 1,2 – 1,4 Å.

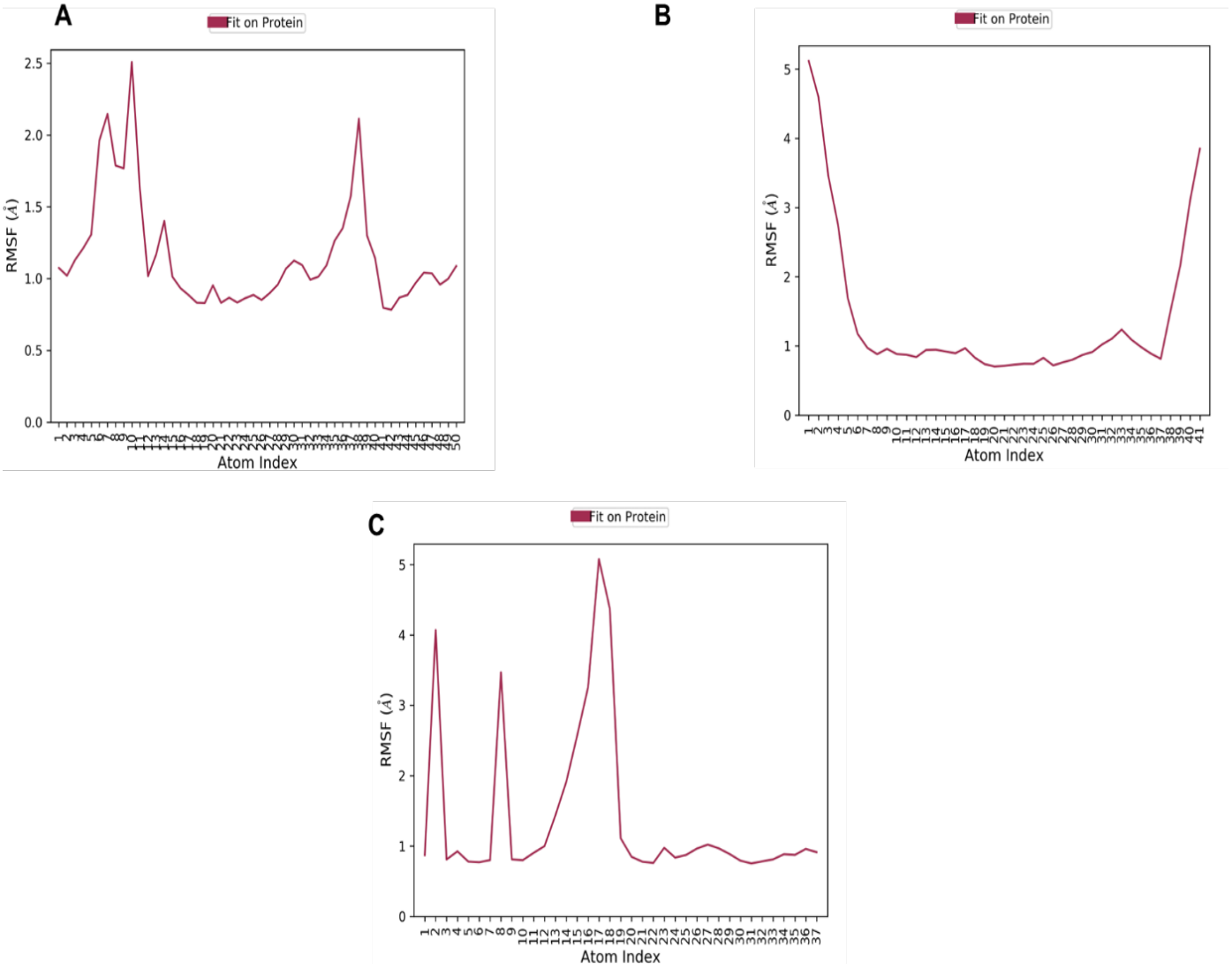

Figure 5. Root mean square fluctuation (RMSF) plot of the ligands atomic position throughout 100 ns molecular simulation of the investigated systems using Desmond: the top-ranked ligands A) ZINC000085627072, B) ZINC000085592636, and the reference H3B-9224 with the binding pocket residues of ERα (PDB ID: 6CHZ) protein

A detailed investigations of protein-ligan histograms (figure 6A-C) has precluded that, during the simulation.

In one hand, ZINC000085627072 (figure 6A) has been stabilised by hydrogen bonds *via* LYS520 (4,7 %), HIS524 (2,8 %), LEU525 (3,3 %), SER527 (24,3 %), MET528 (24,3 %), CYS530 (17,8 %), LYS531 (9 %), ASN532 (33,7 %). Additionally, hydrophobic stabilization has been through MET343 (5,6 %), LEU354 (46,8 %), TRP383 (64,3 %), MET521 (11,9 %), VAL418 (9,3 %), ILE424 (3,9 %), HIS524 (17 %), LES525 (20,8 %), TYR526 (1,8 %), MET528 (26 %), CYS530 (4,3 %), LEU536 (31,9 %), LEU539 (9,5 %), MET543 (6,9 %). Furthermore, water bridge with LYS520 (4,7 %), GLY521 (22,7 %), GLU523 (4,3 %), HIS524 (18,7 %), LEU525 (15,3 %), SER527 (20,8 %), MET528 (6,7 %), CYS530 (11,1 %), LYS531 (34,3 %), ASN532 (11,7 %), VAL533 (35,6 %), VAL534 (31,9 %) has been observed.

On the other hand, ZINC000085592636 (figure 6B) has been stabilized with 6CHZ binding pocket by hydrogen bonds *via* THR347 (2,9 %), LEU384 (6,7 %), MET517 (3,9 %), GLY521 (24,1 %), ASN532 (22,7 %), VAL534 (62,1 %), LEU536 (3,1 %). Hydrophobic stabilization has been exerted through: ALA530 (21 %), TRP383 (52,7 %), LEU384 (52,7 %), LEU387 (19,8 %), MET388 (32 %), ILE424 (7,6 %), LEU525 (8,5 %), LEU536 (19,8 %), LEU539 (16,8 %). Water bridge stabilization has been seen *via* THR347 (21,3 %), ALA530 (93,3 %), MET517 (15,2 %), LYS520 (24,1 %), GLU523 (8,8 %), HIS524 (8,4 %), ASN532 (5,6 %), VAL533 (21,3 %), VAL534 (23,6 %), LEU536 (9,2 %). While, the reference H3B-9224 (figure 6C) has been stabilized by hydrogen bonding with GLU353 (1,4 %) and ARG394 (9 %), also hydrophobic stabilization has been through MET343 (6,5 %), LEU346 (4 %), ALA350 (55,5 %), LEU387 (4,7 %), LEU391 (21,6 %), PHE404 (33,8 %), MET421 (2 %), ILE424 (36,6 %), MET528 (2,2 %). Further, water bridge hydrogen bonding has been observed with LEU349 (13,7 %), GLU353 (52,3 %), LEU387 (55,5 %), ARG394 (5,2 %), PHE404 (21,6 %), HIS524 (3,3 %).

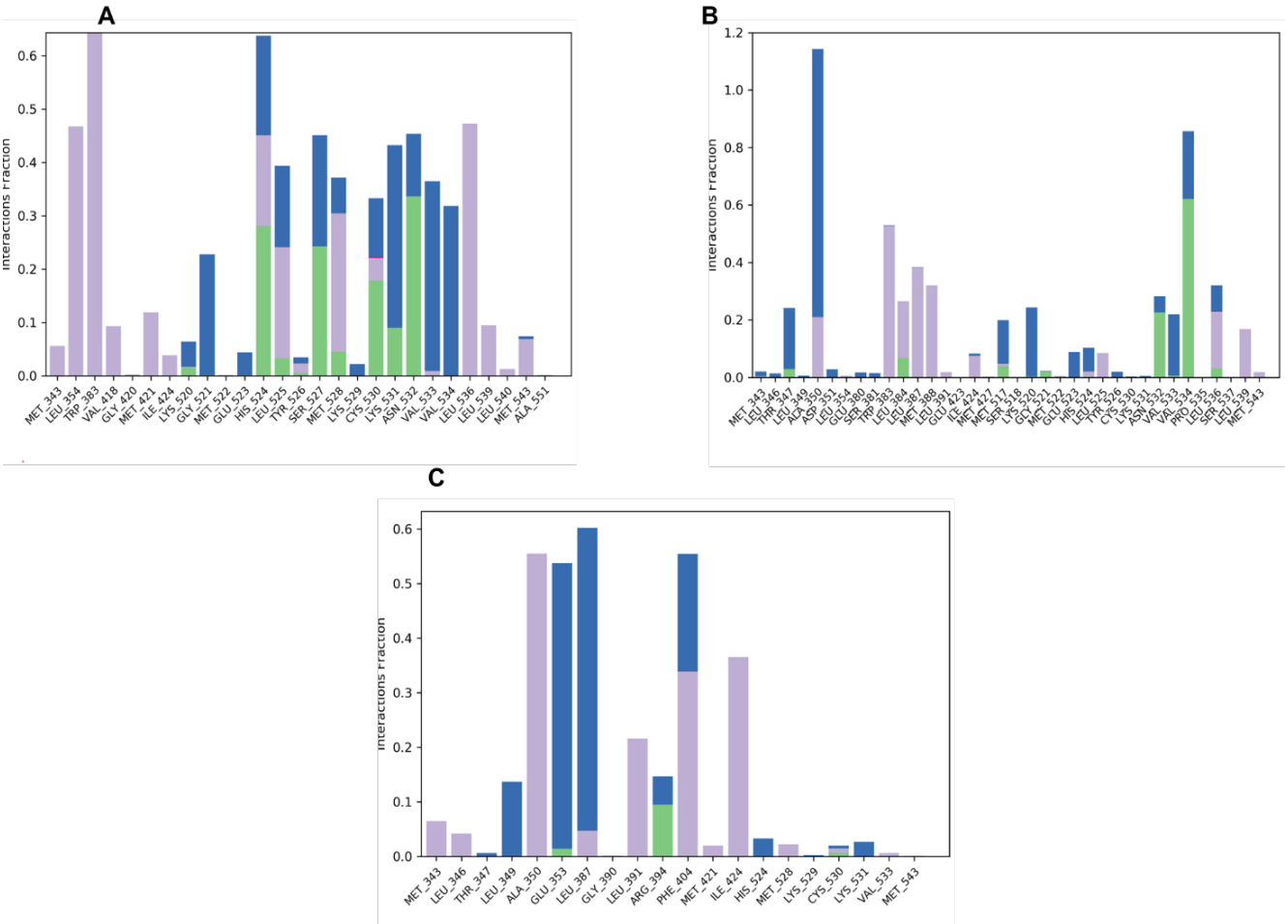

Figure 6. Protein-ligands contacts histogram showing important interacting residues of the binding pocket of ERα protein (PDB ID: 6CHZ) with the top ranked ligands throughout 100 ns MD simulation using Desmond software: A) ZINC000085627072, B) ZINC000085592636, and the reference H3B-9224

DISCUSSION

ERα+BC type is the most prevalent in women worldwide where estrogen is overexpressed, hence leads to cell proliferation, survival and metastasis.[6,45] Many hormonal drugs have been developed to target the mutagenic pathway in ERα+ BC and have been approved by FDA like SERMS, SERDS, AIs.[47] Although, the so-called resistance (innate or extrinsic) has reduced the efficacy, hence cure of ERα+ BC needs further understanding of biological pathway of this type and developing other effective molecules.[48] Additionally, one third of resistance to endocrine therapy is due the gain of function resistance (GOF) in which the mutation occurs in amino acids

Y537 and D538, that results in constitutive activation of ER. Consequently this leads to limit the therapeutic response to tamoxifen and fulvestrant.[6,18]

Estrogen has a crucial role in promoting cancer cell growth and differentiation and been considered a hot target, in this regard, many small molecules are under phase I clinical trial targeting several pathways of estrogen like SERMs: Bazedoxifene, Lasofoxifene, Acolbifene, SERDs: AZD9496 E, Elacestrant, LSZ102, GDC-0927.[8]

In the quest for a new class of drugs with improved potency and ability to overcome development of resistance a study discovered H3B-5942 which is an oral selective ER covalent antagonist (SERCAs) targeting the wild and mutant ERα via covalent binding to CYS530 that proved better activity than tamoxifen and fulvestrant toward MCF7 cell line. It is also suggested that the Micheal acceptor part of H3B-5942 structure has been exposed to CYS530 residue by an assistant of hydrogen bonds formed with the linker side chain. H3B-5942 has proved safety and tolerability in Phase I clinical trials and passed to Phase II trials.[49] Although, it has been reported that CYS530 mutations could lead to the decreased efficacy of H3B-5942.[8]

CADD is being revolutionized in drug discovery and development and proven to be effective way in sake for potential anticancer drugs.[31,32,50] This study aimed to identify alternative small compounds from a natural origin to treat ERα+BC using in silico methods. The docking results obtained within ERα ((PDB ID: 6CHZ) binding cavity has shown that two natural compounds (ZINC000085627072, ZINC000085592636) from ZINC natural library have higher docking scores (-14,811, -14,366 Kcal/mol, respectively) than the co-crystalized ligand H3B-9224 (-13,620 Kcal/mol) which have suggested better binding affinity than the reference. Furthermore, these compounds have been subjected to MM-GBSA calculations to explore the energy of binding to 6CHZ and ZINC000085592636 showed higher value (-88,77 Kcal/mol) than the reference HEB-9224 (-85,38 Kcal/mol) which proved the higher binding to 6CHZ.

To understand the binding modes of these compounds we went further to investigate 2D-interactions with 6CHZ as seen in figure 2A-C. ERα is a nuclear receptor and its LBD is the site for binding of endogenous hormones where the C-terminal helix (H12) of LBD-E will cap ER binding site in the agonistic state and when an external compounds bind to ERα in LBD this H12 cannot cap this site and antagonism state is conserved.[51] Consistent with earlier study, it has been proven that the binding residues are crucial for the activity toward 6CHZ have elicited by ZINC000085627072, ZINC000085592636 in approximately similiar modes as obbserved for the reference H3B-9224.[49] A noteworthy observation is that H3B-9224 (the co-crystalizes ligand with 6CHZ) ,which is a saturated synthetic analogue of H3B-5942, has exhibited the same helix12 conformation in LBD and binding mode of the pharmacophore but weaker antiproliferative activity due to absence of Michael acceptor that disrupt the covalent antagonism than H3B-5942.[49] H3B-9224 interacted via its secondary amino group with ASP351 which has been stated important for its activity which is the binding observed in SERMs.[49] Although, ZINC000085627072 formed hydrogen bond with ASP351 through its hydroxyl group whereas ZINC000085592636 bound to CYS350 via its secondary amino group by hydrogen bond interaction.

Alghamdi et al., studied the activity of constituents of Lycium shawii Roem. Extract against 6CHZ which has precluded that the top scored ligands have bound to 6CHZ by GLU423, ILU424, MET421, HIS524, LEU384, LEU387, LEU525, LEU346, ALA350, further the investigated ligands have shown lower docking scores than our findings.[52] In contrast, ZINC000085627072, ZINC000085592636, H3B-9224 have shown some of the binding residues observed in this study.

Another study by Sehrawat et al., has explored the activity of chlorogenic acids and their derivatives against several targets in breast cancer of them is 6CHZ. The study has revealed that the higher docking score was -9,35 Kcal/mol with MM-GBSA -53,89 Kcal/mol which again preclude lower binding affinity than the current findings. Additionally, 2D interactions with 6CHZ has been exploited by π-π stacking via PHE404, hydrophobic interactions via PHE404, LEU391, ILE424, LEU428, MET388, MET421, LEU387, MET522, LEU384, LEU525, TRP383, MET343, LEU346, LEU349, LEU539, LEU428, ILE424, MET343, LEU391, LEU354, CYS530 and ALA350 and hydrogen bonds through GLU353, ARG394, and ASP351 which are consistent with binding modes observed by the top two natural compounds and H3B-9224.[53] The stabilization of binding through residues observed in the reference H3B-9224 and findings in literature has validate the activity investigated natural compounds as depicted in table 2 and figure 3A-C. Additional study conducted by Mass et al., has also revealed some of the binding residues of some synthesized molecules toward 6CHZ via LEU346, THR347, ASP351, ASN532, GLU353.[54]

Prediction of physicochemical and pharmacokinetic properties will have extra value in the process of drug discovery and development.[55,56] The pharmacokinetics study encountered prediction of ADME properties of these three molecules which have shown one violation from Lipinski's rule of five, approximately acceptable solubility, cell permeability, good binding affinity of albumin and thereby suggest the druggability. Although, we moved further to study the stability of binding with 6CHZ through MD simulations; in this regard the RMSD and RMSF of the three compounds (ZINC000085627072, ZINC000085592636, H3B-9224) have shown approximately the moderately stable fluctuations within the protein binding cavity that been through several residual interactions. Ligand binding to 6CHZ could have an impact in some conformation changes of the protein that will affect binding site and hence might later affect the biological activity.

CONCLUSIONS

The rapid and complex evolvement of ERα+BC is challenging and mandate discovery and development of active leads. Hence, natural compounds were subjected to computational studies, including molecular docking, MM-GBSA, ADME, MD simulations to preclude effective molecules against ERα+BC. Two natural compounds have shown higher docking scores than the co-crystalized ligand and hence were subjected for further ADME and MD simulations. ADME studies shown one violation from Lipinski's rule of five for the two natural compounds and the reference. Further analysis of RMSD and RMSF from MD simulation precluded favorable and convergent fluctuations. This study suggests the two natural compounds might be considered promising leads for further *in vitro* studies.

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BIBLIOGRAPHIC REFERENCES

1. Masand VH, Al-Hussain SA, Alzahrani AY, Al-Mutairi AA, Hussien RA, Samad A, Zaki MEA. Estrogen Receptor Alpha Binders for Hormone-Dependent Forms of Breast Cancer: e-QSAR and Molecular Docking Supported by X-ray Resolved Structures. ACS Omega. 2024;9:16759-74. https://doi.org/10.1021/acsomega.4c00906.

2. Warude BJ, Wagh SN, Chatpalliwar VA, Yildirim M, Celik I, Rudrapal M, Khan J, Chinnam S, Garud AA, Neharkar VS. Design, docking, MD simulation and in-silco ADMET prediction studies of novel indolebased benzamides targeting estrogen receptor alfa positive for effective breast cancer therapy. Pharmacia. 2023;70:307–16. https://doi.org/10.3897/pharmacia.70.e100356.

3. Morelos-Garnica LA, Guzmán-Velázquez S, Padilla-Martínez II, García-Sánchez JR, Bello M, Bakalara N, Méndez-Luna D, Correa-Basurto J. In silico design and cell-based evaluation of two dual anti breast cancer compounds targeting Bcl-2 and GPER. Sci Rep. 2023;13:1–14. https://doi.org/10.1038/s41598-023-43860-x.

4. Cao H, Sun Y, Wang L, Pan Y, Li Z, Liang Y. In silico identification of novel inhibitors targeting the DNA-binding domain of the human estrogen receptor alpha. J Steroid Biochem Mol Biol. 2021;213:1–9. https://doi.org/10.1016/j.jsbmb.2021.105966.

5. Alamri A, Rauf A, Khalil AA, Alghamdi A, Alafnan A, Alshammari A, Alshammari F, Malik JA, Anwar S. In Silico Screening of Marine Compounds as an Emerging and Promising Approach against Estrogen Receptor Alpha-Positive Breast Cancer. Biomed Res Int. 2021:1–7. https://doi.org/10.1155/2021/9734279.

6. Disch JS, Duffy JM, Lee ECY, Gikunju D, Chan B, Levin B, Monteiro MI, Talcott SA, Lau AC, Zhou F, Kozhushnyan A, Westlund NE, Mullins PB, Yu Y, Von Rechenberg M, Zhang J, Arnautova YA, Liu Y, Zhang Y, McRiner AJ, Keefe AD, Kohlmann A, Clark MA, Cuozzo JW, Huguet C, Arora S. Bispecific Estrogen Receptor α Degraders Incorporating Novel Binders Identified Using DNA-Encoded Chemical Library Screening. J Med Chem. 2021;64:5049–66. https://doi.org/10.1021/acs.jmedchem.1c00127.

7. Lumachi F, Brunello A, Maruzzo M, Basso U, Basso S. Treatment of Estrogen Receptor-Positive Breast Cancer. Curr Med Chem. 2013;20:596–604. https://doi.org/10.2174/092986713804999303.

8. Bafna D, Ban F, Rennie PS, Singh K, Cherkasov A. Computer-aided ligand discovery for estrogen receptor alpha. Int J Mol Sci. 2020;21:1–49. https://doi.org/10.3390/ijms21124193.

9. Panis C, Pizzatti L, Herrera AC, Corrêa S, Binato R, Abdelhay E. Label-free proteomic analysis of breast cancer molecular subtypes. J Proteome Res. 2014;13:4752–72. https://doi.org/10.1021/pr500676x.

10. Bilal FS, Tanvir F, Ahmad S, Mustafa R, Fatima G. In-silico drug discovery from phytoactive compounds against estrogen receptor beta (ERß) inducing human mammary carcinoma. Sci Partn J. 2024:1–17.

11. Liu Y, Ma H, Yao J. ERα, a key target for cancer therapy: A review. Onco Targets Ther. 2020;13:2183–91. https://doi.org/10.2147/OTT.S236532.

12. Bansode P, Anantacharya R, Dhanavade M, Kamble S, Barale S, Sonawane K, Satyanarayan ND, Rashinkar G. Evaluation of drug candidature: In silico ADMET, binding interactions with CDK7 and normal cell line studies of potentially anti-breast cancer enamidines. Comput Biol Chem. 2019;83:107124. https://doi.org/10.1016/j.compbiolchem.2019.107124.

13. Widiyana AP, Widiandani T, Siswodihardjo S. 5-O-Acetylpinostrobin derivatives inhibit estrogen alpha and progesterone receptors through a molecular docking approach. Pharm Educ. 2024;24:244–50. https://doi.org/10.46542/pe.2024.243.244250.

14. Sahayarayan JJ, Rajan KS, Vidhyavathi R, Nachiappan M, Prabhu D, Alfarraj S, Arokiyaraj S, Daniel AN. In-silico protein-ligand docking studies against the estrogen protein of breast cancer using pharmacophore based virtual screening approaches. Saudi J Biol Sci. 2021;28:400–7. https://doi.org/10.1016/j.sjbs.2020.10.023.

15. O'Boyle NM, Barrett I, Greene LM, Carr M, Fayne D, Twamley B, Knox AJS, Keely NO, Zisterer DM, Meegan MJ. Lead Optimization of Benzoxepin-Type Selective Estrogen Receptor (ER) Modulators and Downregulators with Subtype-Specific ERα and ERß Activity. J Med Chem. 2018;61:514–34. https://doi.org/10.1021/acs.jmedchem.6b01917.

16. Thongon N, Boonmuen N, Suksen K, Wichit P, Chairoungdua A, Tuchinda P, Suksamrarn A, Winuthayanon W, Piyachaturawat P. Selective Estrogen Receptor Modulator (SERM)-like Activities of Diarylheptanoid, a Phytoestrogen from Curcuma comosa, in Breast Cancer Cells, Pre-osteoblast Cells, and Rat Uterine Tissues. J Agric Food Chem. 2017;65:3490–6. https://doi.org/10.1021/acs.jafc.7b00769.

17. De Marchi T, Kuhn E, Dekker LJ, Stingl C, Braakman RBH, Opdam M, Linn SC, Sweep FCGJ, Span PN, Luider TM, Foekens JA, Martens JWM, Carr SA, Umar A. Targeted MS Assay Predicting Tamoxifen Resistance in Estrogen-Receptor-Positive Breast Cancer Tissues and Sera. J Proteome Res. 2016;15:1230–42. https://doi.org/10.1021/acs.jproteome.5b01119.

18. Lu AS, Rouhimoghadam M, Arnatt CK, Filardo EJ, Salem AK. Proteolytic Targeting Chimeras with Specificity for Plasma Membrane and Intracellular Estrogen Receptors. Mol Pharm. 2021;18:1455–69. https://doi.org/10.1021/acs.molpharmaceut.1c00018.

19. Nosseir O, Syam Y, Hashim A, El-Haggar R, Anwar M, Zaghary W. In Silico ADME Prediction and Molecular Docking of 1,2,3-Triazole-based Compounds Against Human Aromatase Cytochrome P450. J Adv Pharm Res. 2023;7:232–42. https://doi.org/10.21608/aprh.2023.225722.1231.

20. Alamri AM, Alkhilaiwi FA, Khan NU, Mashat RM, Tasleem M. Exploring pathogenic SNPs and estrogen receptor alpha interactions in breast cancer: An in silico approach. Heliyon. 2024;10:e37297. https://doi.org/10.1016/j.heliyon.2024.e37297.

21. Chakraborty S, Cole S, Rader N, King C, Rajnarayanan R, Biswas PK. In silico design of peptidic inhibitors targeting estrogen receptor alpha dimer interface. Mol Divers. 2012;16:441–51. https://doi.org/10.1007/s11030-012-9378-x.

22. Pavlin M, Spinello A, Pennati M, Zaffaroni N, Gobbi S, Bisi A, Colombo G, Magistrato A. A Computational Assay of Estrogen Receptor α Antagonists Reveals the Key Common Structural Traits of Drugs Effectively Fighting Refractory Breast Cancers. Sci Rep. 2018;8:1–11. https://doi.org/10.1038/s41598-017-17364-4.

23. Ashtekar SS, Bhatia NM, Bhatia MS. Development of leads targeting ER-α in breast cancer: An in silico exploration from natural domain. Steroids. 2018;131:14–22. https://doi.org/10.1016/j.steroids.2017.12.016.

24. Rajagopal K, Kalusalingam A, Bharathidasan AR, Sivaprakash A, Shanmugam K, Sundaramoorthy M, Byran G. In Silico Drug Design of Anti-Breast Cancer Agents. Molecules. 2023;28:1–27. https://doi.org/10.3390/molecules28104175.

25. Abdullahi SH, Uzairu A, Shallangwa GA, Uba S, Umar AB. Computational modeling, ligand-based drug design, drug-likeness and ADMET properties studies of series of chromen-2-ones analogues as anti-cancer agents. Bull Natl Res Cent. 2022;46:1–25. https://doi.org/10.1186/s42269-022-00869-y.

26. Flach KD, Zwart W. The first decade of estrogen receptor cistromics in breast cancer. J Endocrinol. 2016;229:R43–R56. https://doi.org/10.1530/JOE-16-0003 .

27. Ervina M, Pratama M, Poerwono H, Ekowati J, Widyowati R, Matsunami K, Sukardiman. In silico estrogen receptor alpha antagonist studies and toxicity prediction of Melia azedarach leaves bioactive ethyl acetate fraction. J Adv Pharm Technol Res. 2021;12:236–41. https://doi.org/10.4103/japtr.JAPTR_198_21.

28. Iwaloye O, Ottu PO, Olawale F, Babalola OO, Elekofehinti OO, Kikiowo B, Adegboyega AE, Ogbonna HN, Adeboboye CF, Folorunso IM, Fakayode AE, Akinjiyan MO, Onikanni SA, Shityakov S. Computer-aided drug design in anti-cancer drug discovery: What have we learnt and what is the way forward? Inform Med Unlocked. 2023;41:1–20. https://doi.org/10.1016/j.imu.2023.101332.

29. Leelananda SP, Lindert S. Computational methods in drug discovery. Beilstein J Org Chem. 2016;12:2694–718. https://doi.org/10.3762/bjoc.12.267.

30. Prada-Gracia D, Huerta-Yépez S, Moreno-Vargas LM. Application of computational methods for anticancer drug discovery, design, and optimization. Bol Med Hosp Infant Mex (English Ed. 2016;73:411–23. https://doi.org/10.1016/j.bmhime.2017.11.040.

31. Sadybekov AV, Katritch V. Computational approaches streamlining drug discovery. Nature. 2023;616:673–85. https://doi.org/10.1038/s41586-023-05905-z.

32. Romano JD, Tatonetti NP. Informatics and computational methods in natural product drug discovery: A review and perspectives. Front Genet. 2019;10:1–16. https://doi.org/10.3389/fgene.2019.00368.

33. Sliwoski G, Kothiwale S, Meiler J, Lowe EW. Computational methods in drug discovery. Pharmacol Rev. 2014;66:334–95. https://doi.org/10.1124/pr.112.007336.

34. Cerchia C, Basurto JC, Lupo A, Lavecchia A. Applications of Generative AI. Front Drug Discov. 2024:1–2. https://doi.org/10.1007/978-3-031-46238-2.

35. Koborova ON, Filimonov DA, Zakharov AV, Lagunin AA, Ivanov SM, Kel A, Poroikov VV. In silico method for identification of promising anticancer drug targets. SAR QSAR Environ Res. 2009;20:755–66. https://doi.org/10.1080/10629360903438628.

36. Prada-gracia D, Huerta-yépez S, Moreno-vargas LM. Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID- 19 . The COVID-19 resource centre is hosted on Elsevier Connect , the company ' s public news and information. Bol Med Hosp Infant Mex. 2020;73:411–23.

37. Cui W, Aouidate A, Wang S, Yu Q, Li Y, Yuan S. Discovering Anti-Cancer Drugs via Computational Methods. Front Pharmacol. 2020;11:1–14. https://doi.org/10.3389/fphar.2020.00733.

38. Brogi S, Ramalho TC, Kuca K, Medina-Franco JL, Valko M. Editorial: In silico Methods for Drug Design and Discovery. Front Chem. 2020;8:1–5. https://doi.org/10.3389/fchem.2020.00612.

39. Alzain AA, Elbadwi FA, Shoaib TH, Sherif AE, Osman W, Ashour A, Mohamed GA, Ibrahim SRM, Roh EJ, Hassan AHE. Integrating computational methods guided the discovery of phytochemicals as potential Pin1 inhibitors for cancer: pharmacophore modeling, molecular docking, MM-GBSA calculations and molecular dynamics studies. Front Chem. 2024;12:1–14. https://doi.org/10.3389/fchem.2024.1339891.

40. Edris A, Ibraheem W, Makki AA, Elshamly EM, Elhag R, Osman W. Dynamics Studies, Molecules. 2023;28:1–19.

41. Ibraheem W, Makki AA, Alzain AA. Phthalide derivatives as dihydrofolate reductase inhibitors for malaria: molecular docking and molecular dynamics studies. J Biomol Struct Dyn. 2023;41:5127–37. https://doi.org/10.1080/07391102.2022.2080114.

42. Mukhtar RM, Abdelmoniem N, Elrufaie HA, Edris A, Ghaboosh H, Mahgoub MA, Garelnabi EAE, Osman W, Sherif AE, Ashour A, Ghazawi KF, Samman WA, Alhaddad AA, Bafail R, Ibrahim SRM, Mohamed GA, Alzain AA. Unlocking the potential of approved drugs for the allosteric inhibition of tropomyosin-receptor kinase A using molecular docking and molecular dynamics studies. Front Chem. 2023;11:1–12. https://doi.org/10.3389/fchem.2023.1205724.

43. Alzain AA, Elbadwi FA. De Novo Design of Cathepsin B1 Inhibitors as Potential Anti-Schistosomal Agents Using Computational Studies. Adv Appl Bioinforma Chem. 2022;15:29–41. https://doi.org/10.2147/AABC.S361626.

44. Ali AM, Makki AA, Ibraheem W, Abdelrahman M, Osman W, Sherif AE, Ashour A, Ibrahim SRM, Ghazawi KF, Samman WA, Alzain AA. Design of Novel Phosphatidylinositol 3-Kinase Inhibitors for Non-Hodgkin's Lymphoma: Molecular Docking, Molecular Dynamics, and Density Functional Theory Studies on Gold Nanoparticles. Molecules. 2023;28:1–19. https://doi.org/10.3390/molecules28052289.

45. Yadav DK, Kumar S, Saloni, Singh H, Kim MH, Sharma P, Misra S, Khan F. Molecular docking, QSAR and ADMET studies of withanolide analogs against breast cancer. Drug Des Devel Ther. 2017;11:1859–70. https://doi.org/10.2147/DDDT.S130601.

46. Adelusi TI, Oyedele AQK, Boyenle ID, Ogunlana AT, Adeyemi RO, Ukachi CD, Idris MO, Olaoba OT, Adedotun IO, Kolawole OE, Xiaoxing Y, Abdul-Hammed M. Molecular modeling in drug discovery. Inform Med Unlocked. 2022;29:100880. https://doi.org/10.1016/j.imu.2022.100880.

47. Alamri A, Rauf A, Khalil AA, Alghamdi A, Alafnan A, Alshammari A, Alshammari F, Malik JA, Anwar S. In Silico Screening of Marine Compounds as an Emerging and Promising Approach against Estrogen Receptor Alpha-Positive Breast Cancer. Biomed Res Int. 2021;2021:1–7. https://doi.org/10.1155/2021/9734279.

48. Allred DC, Brown P, Medina D. The origins of estrogen receptor alpha-positive and estrogen receptor alpha-negative human breast cancer. Breast Cancer Res. 2004;6:240–5. https://doi.org/10.1186/bcr938.

49. Puyang X, Furman C, Zheng GZ, Wu ZJ, Banka D, Aithal K, et al. Discovery of selective estrogen receptor covalent antagonists for the treatment of ERαWT and ERαMUT breast cancer. Cancer Discov. 2018;8:1176–93. https://doi.org/10.1158/2159-8290.CD-17-1229.

50. Fantacuzzi M, Agamennone M. Computational Methods in the Design of Anticancer Drugs. Pharmaceuticals. 2024;17:1–4. https://doi.org/10.3390/ph17040404.

51. Pokhrel R, Tang T, Holub JM. Monitoring ligand-mediated helix 12 transitions within the human estrogen receptor α using bipartite tetracysteine display. Org Biomol Chem. 2020;18:6063–71. https://doi.org/10.1039/d0ob01234c.

52. Alghamdi R, Abutaha N, Almekhlafi FA, Wadaan MA. Investigation of Lycium shawii Roem . Extract. 2021;I:1–9. https://doi.org/10.18805/IJAR.BF-1751.Submitted.

53. Sehrawat R, Rathee P, Rathee P, Khatkar S, Akkol EK, Khatkar A, Sobarzo-Sánchez E. In silico design of novel bioactive molecules to treat breast cancer with chlorogenic acid derivatives: a computational and SAR approach. Front Pharmacol. 2023;14:1–24. https://doi.org/10.3389/fphar.2023.1266833.

54. Mass EB, de Lima CA, D'Oca MGM, Sciani JM, Longato GB, Russowsky D. Synthesis, Selective Cytotoxic Activity against Human Breast Cancer MCF7 Cell Line and Molecular Docking of Some Chalcone-Dihydropyrimidone Hybrids. Drugs Drug Candidates. 2022;1:3–21. https://doi.org/10.3390/ddc1010002.

55. Alzain AA, Ismail A, Fadlelmola M, Mohamed MA, Mahjoub M, Makki AA, Elsaman T. De novo design of novel spike glycoprotein inhibitors using e-pharmacophore modeling, molecular hybridization, ADMET, quantum mechanics and molecular dynamics studies for COVID-19. Pak J Pharm Sci. 2022;35:313–21. https://doi.org/10.36721/PJPS.2022.35.1.SUP.313-321.1.

56. Opo FADM, Rahman MM, Ahammad F, Ahmed I, Bhuiyan MA, Asiri AM. Structure based pharmacophore modeling, virtual screening, molecular docking and ADMET approaches for identification of natural anti-cancer agents targeting XIAP protein. Sci Rep. 2021;11:1–18. https://doi.org/10.1038/s41598-021-83626-x.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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