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Research Article

Design, docking, MD simulation and *in-silco* ADMET prediction studies of novel indole-based benzamides targeting estrogen receptor alfa positive for effective breast cancer therapy

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Abstract

Breast cancer is one of the most common malignancies in women, afflicting millions of lives each year. Our current study suggests that the development of the most promising 7-substituted -1-(4-(piperidine-1-yl methoxy)benzyl)-1H-indole-3-carboxamide derivatives results in potent anticancer agents through *in-silico* investigations. The molecular docking was performed against estrogen receptor alpha (ER-α) positive (PDB ID: 3UUD) of breast cancer cells to anticipate the binding modes of the designed compounds and the likely mode of action. The interactions between the ligands and amino acid residues were thoroughly elucidated. The stability of the docked protein-ligand complexes was further confirmed by 100 ns molecular simulations methods. From *in-silico* studies, indole-based benzamides exhibited satisfactory physicochemical, drug-likeness and toxicity properties. To conclude, the most promising substituted benzamide analogs on the indole ring could serve as a possible modulator against ER-α positive breast cancer.

Keywords

breast cancer, estrogen receptor alpha, indole scaffold, benzamide, bazedoxifene, docking, molecular dynamics, swiss admet

Introduction

Breast cancer (BC) affects women globally at any age after puberty with increasing incidence in the future. Human breast cancer is the second largest cause of death in women. In 2020, there was 2.3 million women diagnosed with BC, with 685 000 deaths worldwide. As of the end of 2020, there were 7.8 million active instances of BC in women over the previous five years. Around 50% of BC develops in women due to BC risk factors other than gender, such as being female or being over the age of 40. Obesity, radiation exposure, excessive alcohol and tobacco consumption, reproductive disorders, and a family history of BC are all risk factors for BC (Ginsburg et al. 2020; Stoltenberg et al. 2020). Estrogen and the estrogen receptor (ER) are known to be prominent drivers of breast carcinogenesis and progression. In the case of estrogen-sensitive BC, the first-line treatment was hormonal therapy (Ariazi et al. 2006; Stein et al. 2006; Yager and Davidson 2006; Stingl 2011; Yue et al. 2013; Shoda et al. 2015; Ouellet et al. 2016). ER is in charge of managing the record of atomic DNA, which is thought to be a big part of breast malignant growth signal generation and provides a book biomarker of BC (Sotiriou et al. 2013). Selective estrogen receptor modulators (SERMs) that act on the ER, have been used in the clinical treatment of BC. SERMs are designed to compete with endogenous estrogens in order to regulate the activation of eestrogen receptors (Huang et al. 2010). Ligand demonstrates an ER-mediated mechanism of action regulated by two distinct activation functions (AFs), AF-1 at the N terminus and AF-2 in the ligand-based domain (LBD). Growth factors regulate AF-1 activity via the MAP kinase pathway, whereas AF-2 activity is regulated by ligand binding to ER. According to recent structural studies, ligands modulate AF-2 activity by directly changing the structure of the LBD. A conformational change involving the translocation of helix-12, which is located on the C-terminus of the LBD, is requisite for AF-2 action (Shiau et al. 1998). SERMs bind to the ER and can function as receptor agonists or antagonists by altering receptor conformation and modifying co-activators (Jordan 2007; Swaby 2007; Pinkerton and Thomas 2014). Tamoxifen and raloxifen are two examples of SERMs that have been used in first and second line clinical treatment for ER resistant BC (Egea et al. 2000; Miller et al. 2001; Lindsay et al. 2009; Singla et al. 2018; Hendy et al. 2019; Tsuji et al. 2022).

The work presented here is based on the structure-based drug design (Srinivasan et al. 2017; Pang et al. 2018) which has focused on the computational investigation of indole-based benzamides targeting the AF-2 domain of ER (Brzozowski et al. 1997; Lavecchia and Di Giovanni 2013; Xiong et al. 2017). The entire ER protein consists of five different domains. Stimulation function 1 (AF-1) is found in domain A/B (N-terminal), and it participates in ER transcriptional activity by changing conformation in response to oestrogen activation (Lionta et al. 2014; Alsayari et al. 2017). The crystal structure (PDB ID: 3UUD) of the homo dimer estrogen receptor alpha (ER-α) represents a human estrogen receptor-ligand-binding domain in complex with estrogen. It provides a suitable guiding template for studying the binding interactions of designed ligands within the AF-2 cavity where interactions can be viewed up to the proximity of 0.02 Å (Martinkovich et al. 2014).

Bazedoxifene (BSD, 1H-indo-5-ol, 1-[[4-[2(hexahydro-1H-azepin-1-yl)ethoxy]methyl] acetic acid, 2-(-4-hydroxyphenlyl)-3-methyl) is an indole derivative and third-generation SERM, which acts as an estrogen receptor antagonist in breast cancer (Huang et al. 2010; Sotiriou et al. 2013). This novel indole derivative functioned as a first-hand scaffold to work on and prepare congeners that would have similar binding properties in AF2 domain and modulate the transcriptional effects of ER-α. The chemical structure of the bazedoxifene is given in Fig. 1 (Riggs and Hartmann 2003).

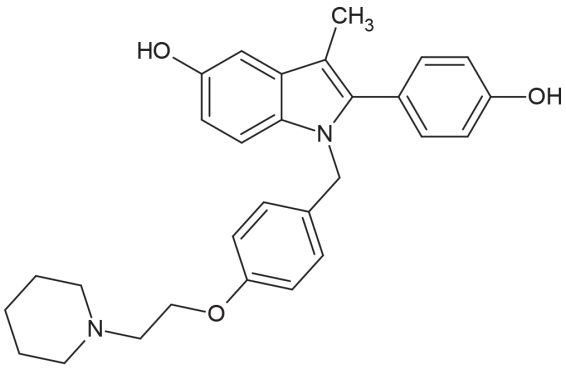


Figure 1. Chemical structure of bazedoxifene.

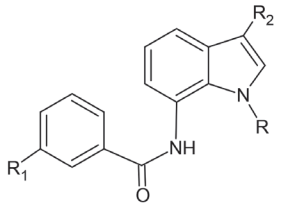
In designing, the scaffold of indole-based analogues involves substitution at the 7th position with benzamide, 3rd position with amide group and 3□ position with different alkyl group with ester and alkyl halide functional group and 1st position substituted with 1-((4ethylphenoxy)methyl)piperidine and 1-((4ethylphenoxy)ethyl)piperidine is mentioned in Table 1. The important amino acid residues (3UUD) that have been comprehensively studied and reported to constitute partly the AF-2 domain of ER-α, are His 524, Arg 394, Leu 428 (conventional hydrogen interactions), Met 343, Met 421, Thr 347, Leu 349, Glu 353, Gly 521 (van der Waals force of attractions), and Phe 404 (Pi –Pi stack interactions) have been reported between estrogen hormone and ER-α in 3UUD (Makar et al. 2020).

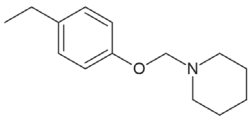
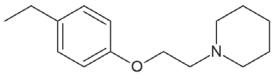
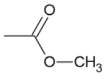
Materials and methods

Molecular docking

The molecular docking software, AutoDock Vina (Virtual screening tool) was employed for the docking study, and the Biovia Discovery Studio visualizer was used to study the 2D and 3D interactions of the ligand-receptor complex after docking. Molecular docking analyses were performed via the CB-Dock server (http://clab.labshare.cn/cb-dock/php/) (Liu et al. 2020). CB-Dock automatically

Table 1. Chemical structure of designed indole-based benzamides.



Comp.	R	R_1	R_2
B73aIII			
B73aV			

identifies binding sites, calculates center and size, customizes docking box size based on query ligands, and then performs protein-ligand docking with AutoDock Vina 1.1.2 version (Cao and Li 2014). For estrogen receptors (PDB ID: 3UUD) containing hERa-LBD (Y537S) served as co-crystal structure was obtained from the Protein Databank (https://www.rcsb.org/structure/3UUD) (Delfosse et al. 2012). The missing atoms and residuals in the estrogen receptor were modeled via AlphaFold Protein Structure Database on UCSF ChimeraX v1.5. Active site coordinates were determined as x:22, y:4, z:5, and 27*27*27 $Å^3$ by CD-Dock curvature-based cavity detection approach (CurPocket) (Varadi et al. 2022). For molecular docking validation, the RMSD value between cocrystal ligand (EST) and docked estrogen was determined. The 3D and 2D visualizations were performed with PyMOL v2.4 and BIOVIA Discovery Studio Visualizer v21.

Molecular dynamics simulation

The molecular dynamics (MD) simulation study was performed with Gromacs v2021.2 (Abraham et al. 2015). MD input files were created via the CHARMM-GUI server solution builder (https://charmm-gui.org/) (Jo et al. 2008). Topology files of protein-ligand complexes were created with CHARMM36m force fields (Huang et al. 2017). Protein-ligand complexes were solvated with the TIP3 water model and neutralized by adding 0.15 M KCl. It was neutralized in 5000 steps and equilibrated at 1 atm pressure and 300 K with 0.3 ns duration NVT/NPT ensemble. The 150 ns MD simulation was performed, and 1500 frames were recorded. The root mean square deviation (RMSD), the root mean square fluctuation (RMSF) and radius of gyration (Rg), and solvent accessible surface area (SASA) analyzes were performed with gmx rms, gmx rmsf, gmx hbond and gmx sasa scripts. For RMSD, RMSF, H bond, and SASA trajectory analyses, graphics were made with QtGrace v0.2.6 tools, and MD animation videos were made with UCSF Chimera v1.15.

ADMET

The ADMET data of ligands were evaluated on pkCSM (http://biosig.unimelb.edu.au/pkcsm/prediction/) and SwissADME (http://www.swissadme.ch/index.php/) software (Pires et al. 2015; Daina et al. 2017).

Results and discussion

Molecular docking

Molecular docking is a computational tool used to monitor the formation of a stable protein-ligand complex between the active site of the protein and ligand molecule (Celik and Tallei 2022). The docking process was done in AutoDock Vina software (Trott and Olson 2010). The results of docking between the ER (PDB ID: 3UUD) and B73aIII, B73aV, and cocrystal ligand, estradiol (EST); vina score, cavity volume ($Å^3$), center, docking size, H bond, and hydrophobic bond forming amino acids and bond distances are shown in Table 2. It was observed that between B73aIII and ER, H bonds with Trp393 amino acid at a distance of 2.87 Å and Arg394 amino acid at a distance of 3.09 Å exist. The same amino acids make H-bond between the ER and the B73aV ligand. However, it was observed that their distance was different. It is seen that Trp398 forms a bond at a distance of 2.97 Å and Arg394 at a distance of 3.36 Å.

Fig. 2 presents the redocking poses of the cocrystal ligand EST, while the orange-colored ligand shows the EST's natural pose, the magenta colored-ligand shows a self-docking pose.

Amino acids located in the active site of the ER interact with the ligand in different types of bonds. It has been shown that an amino acid can form different bonds with different

Table 2. AutoDock Vina molecular docking interaction energies, parameters, and contact residues of the compounds B73aIII, B73aV, and cocrystal ligand estradiol (EST) with ER (PDB ID: 3UUD).

Compounds	Vina score	Cavity volume (Å³)	Center (x, y, z)	Docking size (x, y, z)	Contact residues	
					H Bonds	Hydrophobic
B73aIII	-8.7	1383	16, 5, 7	27, 27, 27	Trp393 (2.87 Å), Arg394 (3.09 Å)	Glu323, Pro324, Pro325, Ile326, Glu353, His356, Met357, Ile386, Leu387, Gly390, Leu391, Glu397, His398, Leu403, Phe445, Lys449
B73aV	-8.0	322	-3, 14, -5	29, 29, 29	Trp393 (2.97 Å), Arg394 (3.36 Å)	Leu320, Glu323, Pro324, Pro325, Ile326, Glu353, His356, Met357, Trp360, Ile386, Leu387, Gly390, Leu391, Trp393, Arg394, Gly442, Glu443, Phe445, Lys449
EST	-10.9	1383	16, 5, 7	27, 20, 20	Arg394 (3.19 Å), His524 (2.95Å)	Met343, Leu346, Thr347, Leu349, Ala350, Glu353, Leu384, Leu387, Met388, Gly390, Leu391, Phe404, Met421, Ile424, Leu428, Gly521, Leu525

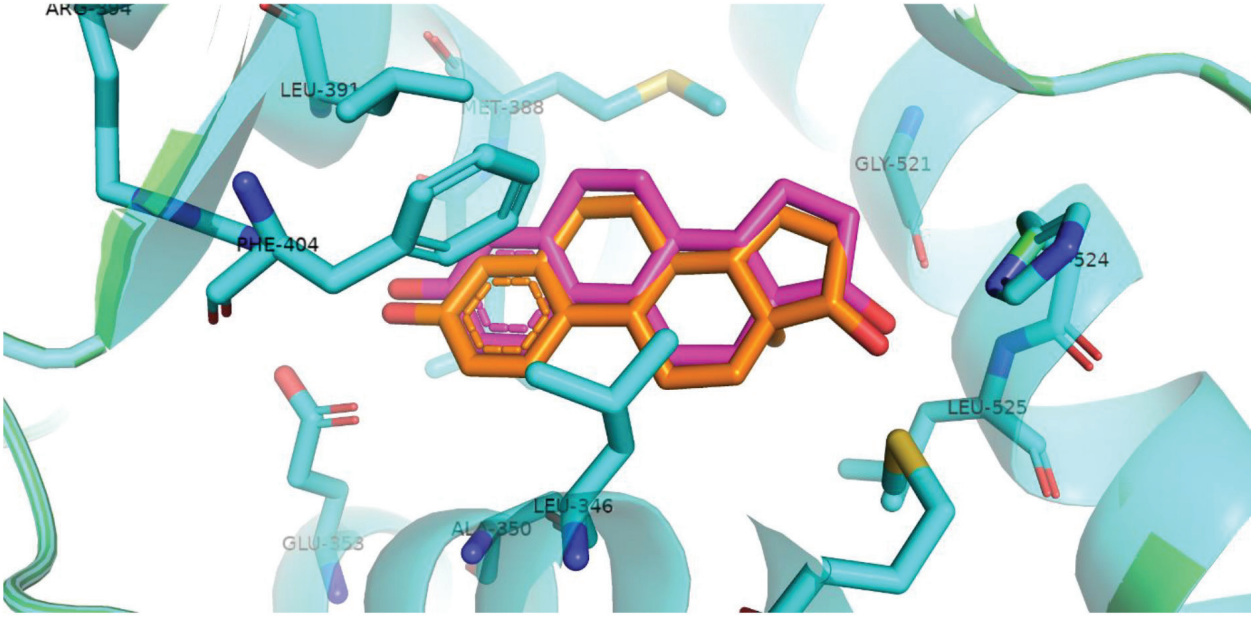


Figure 2. Redocking poses of the cocrystal ligand EST (PDB ID: 3UUD). Natural pose (orange) and self-docking pose (magenta) of EST (RMSD: 0.078).

parts of the ligand. Conventional hydrogen bond, van der Waals, carbon-hydrogen bond, π-anion, π-donor hydrogen bond, π-sigma, alkyl, π-alkyl bonds were observed. On the contrary, it was observed that an unfavorable hydrophobic bond was formed between the Ile356 amino acid of receptor molecule and the ligand B73aIII. In Fig. 3A, B, the binding poses and interaction diagrams between compound B73aI-II and ER are given. This figure shows the bond types and related amino acids. Likewise in Fig. 3C, D, binding poses and interaction diagrams between the compound B73aV and the estrogen receptor, in which the types of bonds and related amino acids appeared, are given.

Molecular dynamics simulation

EST, B73aIII, and B73aV molecules were performed in MD simulations for examination of protein-ligand complex stability (Celik et al. 2022). In MD simulations, the interaction energy and movements of the ligand-receptor complex have been studied (Yildirim and Celik 2022). The values of the RMSD, RMSF, Rg, and SASA are shown in graphic form in Fig. 4. RMSD and RMSF values are considered to review the stability of the complex during the simulation (Sohrab and Kamal 2022; Eşilçayır 2022). When examining the Rg value for the stability of the complex, the SASA value was examined for the estimation of the conformation changes of the protein. From the analysis of RMSD and RMSF trajectories, the formation of stable protein-ligand complexes was observed for both the compounds (B73aIII/EST and B73aV/EST) throughout the duration of 150 ns. Analyses of Rg and SASA trajectories also support the stability between the ligands (B73aIII and B73aV) and protein molecules, EST.

ADMET predictions

In ADMET studies, the molecular weights of ligands, LogP values, the characteristics of drug-likeness, the bioavailability scores, absorption, distribution, metabolism, excretion, and toxicity properties were evaluated (Rudra-

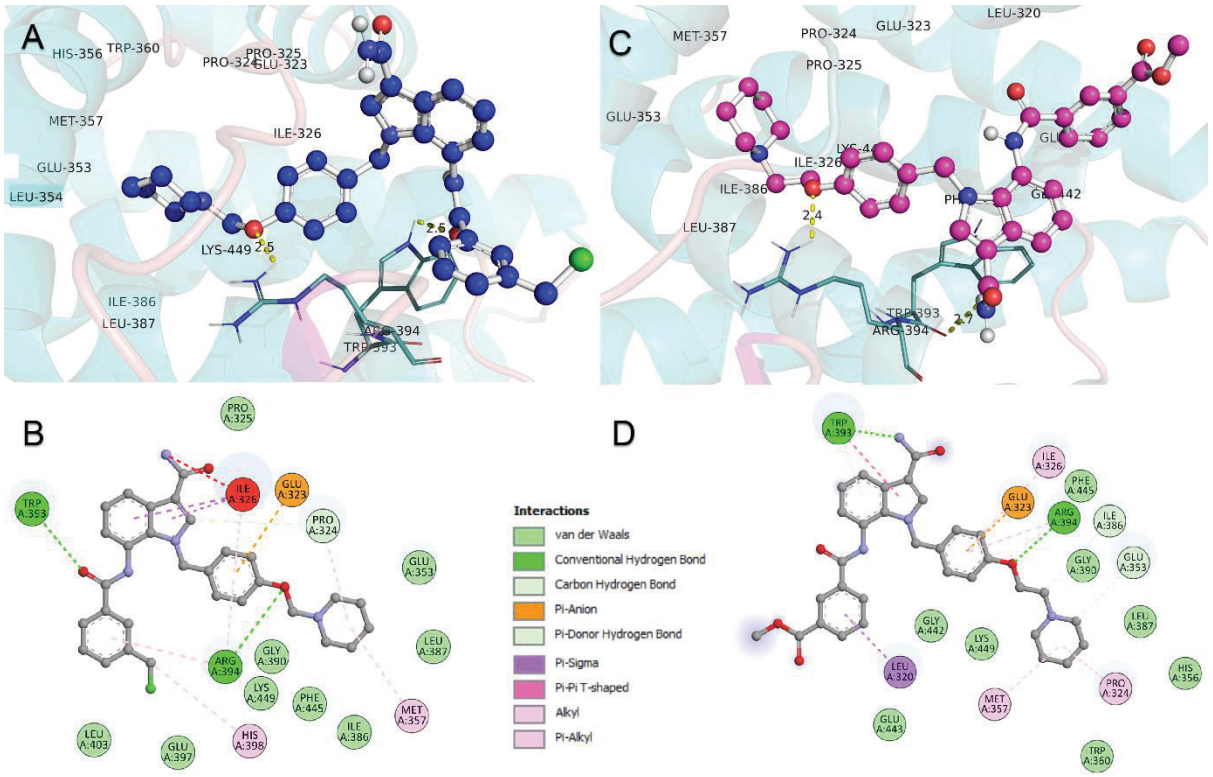


Figure 3. (**A**, **B**) Binding poses and interaction diagrams compound B73aIII and ER, (**C**, **D**) B73aV and ER complex.

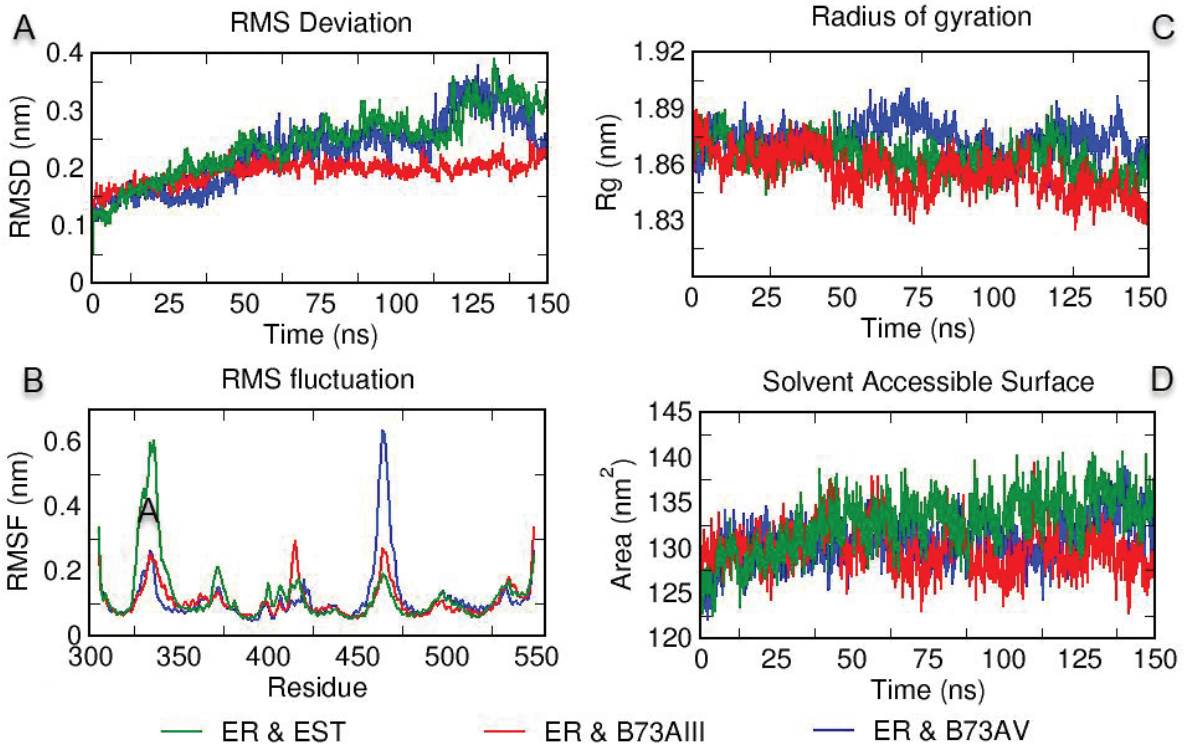


Figure 4. Molecular dynamic simulation results of receptor-ligand complexes monitored for 150 ns **(A)** RMSD value, **(B)** RMSF fluctuation, **(C)** Radius of gyration (Rg), **(D)** Solvent accessible surface area (SASA).

pal et al. 2022a; Rashid et al. 2022; Celik et al. 2022; Umar et al. 2022; Pasala et al. 2022a). The descriptive properties of B73aIII, B73aV, and EST ligands and the estimated values of drug-likeness are shown in Table 3. Drug-likeness is known as the 5 rules of Lipinski, and drug candidate ligands are required to follow these rules or the number of violations must be less than 4. The ligands exhibited satistafctory drug-likeness properties in terms of Lipinski's rule of 5 and other rules (Ghose, Veber, Egan, and Muegge rules) related to physicochemical/ pharmacokinetic

parameters. Only one violation was observed as per Lipinski's rule of 5. The bioavailability score was also found to be satisfactory.

Table 4 shows the results obtained from the pkCSM software. Absorption properties such as solubility in water, the permeability of CaCO-2, distribution characteristics such as VDss value in man, BBB permeability, CNS permeability, which metabolic pathway they are metabolized with (CYP2D6 inhibitiory activity), excretion, and various toxicity characteristics are available from this table. All the pharmacokinetic and toxicity parameters were found to be within the accaeotbale limit for B73aIII and B73aV.

In Fig. 5, the chemical structures, bioavailability radars, and boiled-egg images of the examined ligands are given. In bioavailability radars, the ligand is expected to be in the pink area. The boiled egg image shows us BBB permeability, HIA and PGP+, and PGP- properties. The molecule is defined as PGP^+ or PGP^- depending on whether it is cleared

Table 3. Descriptive properties of ligands examined in pkCSM and SwissADME software and estimated values of drug-likeness.

Descriptor	Value		
	B73aIII	**B73aV**	**EST**
Molecular weight	531.056	554.647	272.388
LogP	5.6018	4.6921	3.2651
Rotatable bonds	9	10	0
Acceptors	5	7	2
Donors	2	2	1
Surface area	226.679	238.381	120.496
Drug-likeness	**B73aIII**	**B73aV**	**EST**
Lipinski	Yes; 1 violation: MW>500	Yes; 1 violation: MW>500	Yes; 0 violation
Ghose	No; 2 violations: MW>480, MR>130	No; 3 violations: MW>480, MR>130, #atoms>70	Yes
Veber	Yes	No; 1 violation: Rotors>10	Yes
Egan	Yes	Yes	Yes
Muegge	Yes	Yes	Yes
Bioavailability score	0.55	0.55	0.55

Table 4. ADMET data of ligands examined in pkCSM software.

Property	Model name	Predicted Value			Unit
		B73aIII	**B73aV**	**EST**	
Absorption	Water solubility	-5.332	-5.065	-4.356	Numeric (log mol/L)
Absorption	Caco-2 permeability	0.987	0.71	1.513	Numeric (log Papp in 10^{-6} cm/s)
Absorption	Intestinal absorption (human)	89.409	87.114	97.263	Numeric (% Absorbed)
Absorption	Skin permeability	-2.785	-2.864	-3	Numeric (log Kp)
Absorption	P-glycoprotein substrate	Yes	Yes	No	Categorical (Yes/No)
Absorption	P-glycoprotein I inhibitor	Yes	Yes	Yes	Categorical (Yes/No)
Absorption	P-glycoprotein II inhibitor	Yes	Yes	No	Categorical (Yes/No)
Distribution	VDss (human)	0.108	-0.17	0.403	Numeric (log L/kg)
Distribution	Fraction unbound (human)	0.01	0.059	0.185	Numeric (Fu)
Distribution	BBB permeability	-0.826	-1.024	0.128	Numeric (log BB)
Distribution	CNS permeability	-1.993	-2.413	-2.232	Numeric (log PS)
Metabolism	CYP2D6 substrate	No	No	No	Categorical (Yes/No)
Metabolism	CYP3A4 substrate	Yes	Yes	Yes	Categorical (Yes/No)
Metabolism	CYP1A2 inhibitor	No	No	No	Categorical (Yes/No)
Metabolism	CYP2C19 inhibitor	No	No	Yes	Categorical (Yes/No)
Metabolism	CYP2C9 inhibitor	Yes	No	No	Categorical (Yes/No)
Metabolism	CYP2D6 inhibitor	No	No	No	Categorical (Yes/No)
Metabolism	CYP3A4 inhibitor	Yes	Yes	No	Categorical (Yes/No)
Excretion	Total Clearance	1.172	0.991	1.025	Numeric (log ml/min/kg)
Excretion	Renal OCT2 substrate	No	No	Yes	Categorical (Yes/No)
Toxicity	AMES Toxicity	No	No	No	Categorical (Yes/No)
Toxicity	Max. Tolerable dose (human)	0.467	0.313	-0.723	Numeric (log mg/kg/day)
Toxicity	hERG I inhibitor	No	No	No	Categorical (Yes/No)
Toxicity	hERG II inhibitor	Yes	Yes	Yes	Categorical (Yes/No)
Toxicity	Oral Rat Acute Toxicity (LD50)	2.466	2.542	1.779	Numeric (mol/kg)
Toxicity	Oral Rat Chronic Toxicity (LOAEL)	2.214	2.323	1.893	Numeric (log mg/kg_bw/day)
Toxicity	Hepatotoxicity	Yes	Yes	No	Categorical (Yes/No)
Toxicity	Skin sensitivity	No	No	No	Categorical (Yes/No)
Toxicity	*T. Pyriformis* Toxicity	0.31	0.316	1.154	Numeric (log ug/L)
Toxicity	Minnow toxicity	-0.697	-0.165	0.583	Numeric (log mM)

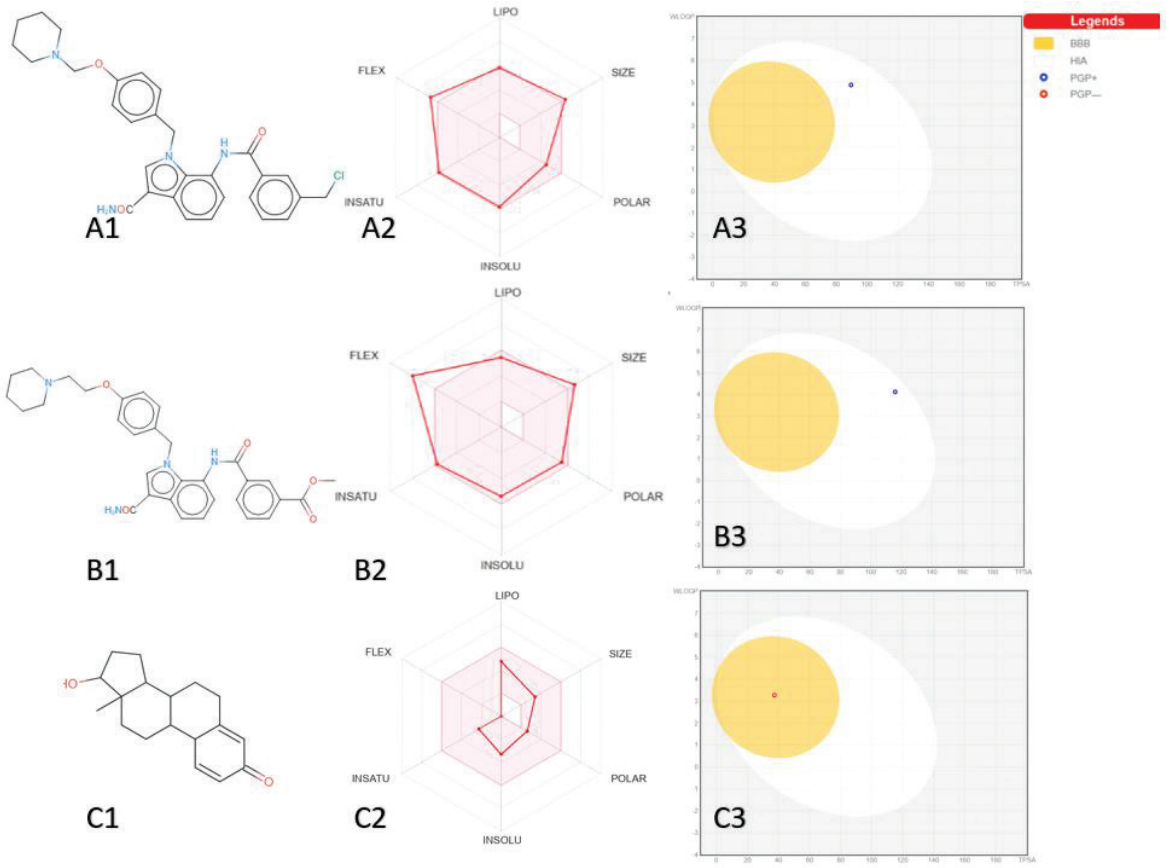


Figure 5. **(A1)** Chemical structure of the B73aIII **(A2)** Bioavailability radar diagram of the B73aIII, **(A3)** 'BOILED-Egg' images of the B73aIII in SwissADME software, **(B1)**Chemical structure of the ligand B73aV, **(B2)** Bioavailability radar diagram of the B73aV, **(B3)** 'BOILED-Egg' images of the B73aV in SwissADME software, **(C1)** Chemical structure of the cocrystal ligand EST, **(C2)** Bioavailability radar diagram of the EST, **(C3)** 'BOILED-Egg' images of the EST in SwissADME software. (Boiled-egg images indicate BBB (Blood-Brain barrier) permeability, HIA (gastrointestinal absorption), PGP^+ and PGP^- (P glycoprotein)).

from the central nervous system by P-glycoprotein (Ghosh et al. 2021; Junejo et al. 2021; Othman et al. 2021; Annavarapu et al. 2022; Zothantluanga et al. 2022; Rudrapal et al. 2022b; Devasia et al. 2022; James et al. 2022; Pasala et al. 2022b; Rudrapal et al. 2022c; Rudrapal et al. 2022d; Kumar et al. 2022; Rudrapal et al. 2022e; Archana et al. 2022).

Conclusion

In this study, novel estrogen receptor (ER) inhibitors based upon the indole-based benzamide scaffold were designed and developed by molecular modeling methods. The 7-substituted-1-(4-(piperidin-1-ylmethoxy)benzyl)-1H-indole-3-carboxamide derivatives would have the potential to modulate ER-α in breast cancer. Molecular docking, molecular dynamics and ADMET studies revealed the binding modes, protein-ligand stability and *in-silico* pharmacokinetic/toxicities of indole-based benzamide derivatives. Finally, it is concluded that the newly designed indole-based benzamides can be used as selective estrogen receptor modulators (SERMs) against ER-α positive breast cancer.

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