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Small Molecules Inhibit Extranuclear Signaling by Estrogen: A Promising Strategy to Halt Breast Cancer Progression and Metastasis

Imaobong Etti, Chukwuemeka Nwafor and Grace Essien

Abstract

The sex hormone estrogen plays critical roles in reproductive and sexual development. It regulates the expression and activity of key signaling molecules critical in various cellular signaling pathways. These signals are mediated by its binding to estrogen receptors alpha ($ER\alpha$) and beta ($ER\beta$). $ER\alpha$ has been shown to greatly participate in extranuclear signaling, inducing tumorigenesis and breast cancer metastasis. Small molecules from plants are reported with better selectivity toward tumorigenic cells with negligible toxicity when compared to their synthetic counterpart. The molecules used in this study were first probed for their drug-likeness and their pharmacokinetic profile was elucidated before docking them to the ligand binding domain of the human $ER\alpha$ followed by a post docking prime analysis. All tested molecules had good drug-like and pharmacokinetic properties when compared to about 95% of orally available drugs as predicted by qikprop. The docking results revealed a strong binding interaction with $ER\alpha$, influenced mostly by the vicinal diol groups of the studied molecules. These resulted in a conformational change, inducing receptor dimerization and altering the interactions of the sex hormone with other proteins. The studied ligands are promising in strongly inhibiting the binding of estrogen to $ER\alpha$, thus limiting its extranuclear signaling.

Keywords: sex hormones, human estrogen receptor alpha ($hER\alpha$), molecular docking, pharmacokinetics, extracellular signaling, breast cancer

1. Introduction

Estrogen plays an important role in mammary gland development and has been implicated in the initiation and progression of breast cancer [1]. There are two major receptors with which this sex hormone binds to mediate its biological activities. These receptors are estrogen receptors, alpha and beta ($ER\alpha$ and $ER\beta$). $ER\alpha$ is present mainly in mammary gland, uterus, ovary (thecal cells), bone, male reproductive organs (testes and epididymis), prostate (stroma), liver, and adipose tissue. By contrast, $ER\beta$ is found mainly in the prostate (epithelium), bladder, ovary (granulosa cells), colon, adipose tissue, and immune system. Both subtypes are

markedly expressed in the cardiovascular and central nervous systems. The alpha subtype has a more prominent role on the mammary gland and uterus, as well as on the preservation of skeletal homeostasis and the regulation of metabolism. The beta subtype seems to have a more profound effect on the central nervous and immune systems [2]. In terms of sequence homology, the ER β shows a high homology to ER α in the DBD (more than 95% amino acid identity) and in the LBD (~55% amino acid identity) [3, 4]. However, the NTD of ER β is shorter than that of ER α with a very poor sequence homology of only ~15% compared to that of ER α (**Figure 1A and B**).

The major ER subtype is the ER α which has been reported in about 70% of breast cancer cases [7]. In addition to the well-studied nuclear functions of ER α , it also participates in extranuclear signaling which involve growth factor signaling components, adaptor molecules and the stimulation of cytosolic kinases [8]. ER α extranuclear pathways have the potential to activate gene transcription, modulate cytoskeleton, and promote tumor cell proliferation, survival, and metastasis. Inhibition of ER α extranuclear actions is, thus, a promising strategy to curb breast tumor progression and may be useful in preventing ER α positive metastasis.

Commonly used endocrine therapies include: selective estrogen receptor modulators (such as tamoxifen, raloxifene, toremifene), aromatase inhibitors (such as anastrozole, letrozole and exemstane) and selective estrogen receptor downregulators (such as fulvestrant). Unfortunately, tumor cells readily develop resistance to these therapies in a progressive manner, a major obstacle limiting the success of breast cancer treatment. Resistance may be de novo or acquired and has been shown to be influenced by complicated crosstalks. These resistance to available therapies combined with their undue toxicities provoke the search into small molecules from plant, deemed

Figure 1. Sequence organization of estrogen receptors, ER α and ER β (A and B) and the 3D structures of studied ligands (C). (A) Shows different domains highlighted in different colors: NTD = amino terminal domain (in red); DBD = DNA binding domain (in green); hinge region in blue; LBD = ligand-binding domain (in yellow); F region located towards the C-terminal end (in gray). Amino acid sequence position is given for each domain. (B) Shows 3-dimensional structures of ER α (left) and ER β (right) bound to estradiol (PDB structures 1A52 [5] and 3OLS [6]). (C) Shows 3D structures of all studied ligands.

to be less toxic [9] which can destabilize and/or downregulate the commonly implicated estrogen receptor ($\text{hER}\alpha$) in a bid to intercept the complicated crosstalks [10].

There are critical steps in the development of effective pharmacotherapy, with many phases and stages within each of them. The first step which is discovery and development involve target discovery and validation, lead refinement as well as preclinical development. This is often followed by preclinical research, which tests the new drug on non-human subjects for efficacy, toxicity, and pharmacokinetic (PK) information with unrestricted dosages. Preclinical research involves *in vivo*, *in vitro*, *ex vivo* and *in silico* assays. The next step is the clinical development and involves clinical trials and volunteer studies to fine-tune the drug for human use before submitting for a holistic FDA review. The final critical step is the FDA post-market safety monitoring. It cost so much before a suitable drug candidate finally gets to the market and failure which frequently taunts the process can better be imagined than experienced.

Several promising drug candidates have failed to reach the market due to their poor pharmacokinetic properties. Many compounds with promising pre-clinical medicinal properties may not even stand a chance of being tried because of their non-drug-likeness except after rigorous improvement which may end up increasing toxicity. Today, with the advancement in medical and pharmaceutical sciences, computational techniques has proven useful for early prediction of the absorption, distribution, metabolism, excretion and toxicity (ADMET) profile of potential drug molecules before subjecting them to rigorous pre-clinical and clinical testings [11]. *In silico* approaches like molecular docking has been successfully applied in the screening and selection of potent drugs in the treatment of diseases [12]. These techniques are now extensively employed by pharmaceutical companies for screening for lead compounds to facilitate entrance of potential drug molecules with good drug-like-properties into the market while eliminating molecules with poor profile [13]. The purpose of this study was to investigate the pharmacokinetic properties and drug-likeness of the selected small molecules and investigate its inhibitory potential to the $\text{ER}\alpha$, with the view of mitigating this sex hormone's receptor extranuclear signaling.

2. Materials and methods

2.1 Computer hardware and software

The molecular docking simulation was performed on the Lenovo Precision workstation 6.1.7600 running Intel® Core™ i5 Duo Processor, 4.0GB RAM, 436 GB hard disk and AMD Radeon graphics card (Lenovo PC HK Limited, China). The 3D structures of the small molecules were obtained from the National Centre for Biotechnology Information, Pubchem database www.ncbi.nlm.nih.gov/pccompound) in SDF format and prepared with Maestro, using ligprep version 3.6 (LigPrep 2015). The solution x-ray crystal structure of the human $\text{ER}\alpha$ (3UUD, 1.60 Å resolution) was retrieved from the protein databank (www.rcsb.org) using Discovery Studio visualizer 4.5 (Accelrys, USA). Protein-ligand docking simulation was performed using the Schrodinger molecular docking suite version 2018-4.

2.2 Preparation of ligands and protein

The ligands were prepared using LigPrep, a utility of Schrodinger software suit that combines tools for generating 3D structures from 1D (Smiles) and 2D (SDF) representation. Molecular mechanics force fields, optimized potentials for liquid simulations-2005 (OPLS_2005) with default settings were employed for the ligand minimization and the ligands were thereafter filtered for computational studies.

The crystal structure of hER α (3UUD) was prepared using Schrodinger protein preparation wizard tool (Glide), which performed the following steps: assigning of bond orders, addition of hydrogens, optimization of hydrogen bonds by flipping amino side chains, correction of charges and minimization of the protein complex. All the bound water molecules, ligands and cofactors were removed (preprocess) from the protein and the output file was saved in maestro format. The idle side chains were neutralized before restrained minimization of co-crystallized complex, which reoriented side chain hydroxyl groups and alleviated potential steric clashes. The complex obtained was minimized using OPLS_2005 force field with Polack-Ribiere Conjugate Gradient (PRCG) algorithm. The minimization was terminated when the energy gradient converged below 0.05 kcal/mol [14].

2.3 Prediction of pharmacokinetic properties and drug-likeness

The molecular weight, number of hydrogen bond donor, number of hydrogen bond acceptor and octanol–water partition coefficients were used to verify the compounds adherence to Lipinski's rule of five which qualifies their drug-likeness. To nominate drug candidates, certain pharmacokinetics descriptors that portray their drug-likeness [15] were investigated using the QikProp module of the Schrodinger Suite, a program designed by Professor William L. Jorgensen [16]. In addition to predicting physically significant and pharmaceutically relevant molecular descriptors, QikProp also provides ranges for comparing predicted descriptors of each compound with those of 95% of drugs known for oral use. The pharmacokinetic descriptors evaluated were: molecular weight (Mwt), total solvent accessible surface area (SASA), Donor hydrogen bond (DonorHB), number of acceptable hydrogen bond (Accept HB), predicted octanol/water partition coefficient (QPlogPo/w), predicted aqueous solubility (QPlogS), predicted apparent Caco-2 cell permeability (QPPCaco), predicted brain/blood partition coefficient (QPlogBB), number of likely metabolic reactions (#metab), human oral absorption, van der Waals surface area of polar nitrogen and oxygen atoms (PSA) and prediction of plasma protein binding (Khsa). Cytochrome P450 inhibitory promiscuity and inhibition of the human ether-a-go-go-related gene was also accessed via admerSAR web server. The analysis in the present study was run on QikProp at the normal processing mode with default settings (QikProp 2018). The prepared ligands were used as input structures and their pharmacokinetics profiles with respect to properties shared by 95% of drugs known for oral use were evaluated. Compliance or deviant of the tested potential drug candidates to the Lipinski's rule of five was also examined before they were considered drug-like [17].

2.4 Docking studies

Docking studies were carried out using Glide XP of the Schrodinger Suite (Maestro Version 11.8 and Glide version 8.0, 2018-4) docking program following the reported standard procedures [18]. Each ligand was individually docked onto the LBD of the hER α using Glide extra precision (XP) mode. In the course of the docking, several binding poses were generated for each ligand and the best binding pose was selected at the end of the docking process.

2.5 Calculation of ligand free energy of binding with the hER α using the MM-GBSA approach prime energy analysis

The Prime MM-GBSA or 'molecular mechanics energies combined with the generalized Born and surface area continuum solvation' approach was used in the

post-assessment of free energy of binding of ligands-hER α complex [19]. This approach uses the OPLS_2005 all-atom force field for protein residues, ligands and cofactors [20, 21]. The input structures for these calculations were taken from a pose viewer file Glide output after the docking study.

The following descriptors were generated by the prime MM-GBSA approach:

1. MM-GBSA_ ΔG_{bind} (ligand binding energy (ΔG_{bind}))
2. MM-GBSA_E_complex (energy of the complex ($G_{complex}$))
3. MM-GBSA_E_protein (energy of the receptor without the ligand ($G_{protein}$)) and
4. MM-GBSA_E_ligand (energy of the unbound ligand (G_{ligand})).

The total free energy (ΔG_{bind}) of binding is expressed as:

$$\Delta G_{bind} = G_{complex} - (G_{protein} + G_{ligand}) \quad (1)$$

The other parameters for the complex were:

1. Prime Coulomb energy (ΔG_{bind} coulomb)
2. Prime Van der Waals energy (ΔG_{bind} vdW)
3. Prime Hydrogen Bond (ΔG_{bind} H-bond)

The MM-GBSA scoring and experimental binding affinity data of the binding site for the molecules on hER α were recorded.

3. Results

3.1 The structures of the protein and studied ligands

The 3D structures of the studied ligands are as shown in **Figure 1c**. Complete X-ray structure of of the hER α (**Figure 2A**) and its binding amino acids depicted with green sticks are as shown in **Figure 2B** above.

Figure 2.
(A) Complete X-ray structure of hER α shown as ribbon (B) active amino acids shown in green sticks at the catalytic site of hER α .

Compounds	MW ^A	SASA ^B	Donor HB ^C	AcceptHb ^D	QPlogPo/w ^E	QPlogS ^F	QPPCaco ^G	QPlog BB ^H	#metab ^I	Human Oral Absorption (%) ^J	PSA ^K	KHSA ^L	Rule of Five ^M
Myricetin	318.239	522.36	5	6	−0.279	−2.557	7.666	−2.817	6	28.186	161.312	−0.493	1
Estradiol	272.386	510.237	2	2.45	4.00	−4.672	1221.948	−0.366	4	100	43.693	0.438	0
Catechin	290.272	513.734	5	5.45	0.466	−2.648	53.247	−1.904	7	60.572	115.499	−0.42	0
Pinobanksin	272.257	492.522	2	4.95	1.472	−3.088	211.884	−1.171	5	77.194	97.055	−1.68	0
Pinocembrin	256.257	486.989	1	3.25	2.383	−3.684	431.998	−0.83	5	88.067	77.67	0.136	0
Gelangin	270.241	488.021	2	3.75	1.791	−3.296	193.621	−1.221	3	78.363	95.964	−0.041	0
Pinostrobin	270.284	509.441	0	3.25	3.084	−3.844	1427.908	−0.351	5	100	63.409	0.181	0
Tamoxifen	371.521	725.086	0	2.75	6.525	−5.833	2203.131	0.366	3	100	11.493	−7.4	1

Range for 95% known drugs: A (Molecular weight = 130.0–725.0); B (Total solvent accessible surface area = 300.0–1000.0); C (Donor HB = 0.0–6.0); D (Accept HB = 2.0–20.0); E (Predicted octanol/water partition coefficient = −2.0–6.5); F (Predicted aqueous solubility = −6.5–0.5); G (Predicted apparent Caco-2 cell permeability = < 25 poor, >500 great); H (Predicted brain/blood partition coefficient = −3.0–1.2); I (Number of likely metabolic reactions = 1–8); J (% Human oral absorption = > 80% → High, < 25% → Poor); K (van der Waals surface area of polar nitrogen and oxygen atoms = 7.0–200.0); L (Human serum albumin = −1.5–1.5); M (Number of violations of Lipinski's Rule of Five; mol MW < 500, QPlogPo/w < 5, donor HB ≤ 5, accept HB ≤ 10. Compounds that satisfy these rules are considered drug-like).

Table 1.
Pharmacokinetic properties of studied ligands.

3.2 Pharmacokinetic profile of tested ligands

All the tested compounds obeyed the Lipinski's rule of five (see **Table 1**). From the result of cell permeability using the caco-2 model, estradiol, pinostrobin and tamoxifen showed a great permeability prediction while moderate permeation was observed with catechin, pinobanksin, pinocembrin and gelagin (**Table 1**). Myrecetin, on the other hand showed very poor predicted cell permeability. All studied ligands had good predicted aqueous solubility (log S), and their blood brain barrier prediction, surface area of solvent absorption, predicted number of possible metabolic transformations, as well as polar surface area was within the range set for orally available drugs (see **Table 1**). For the prediction of plasma protein binding, tamoxifen had a score of -7.4 , which was not within the stipulated range of -1.5 - 1.5 , howbeit, other ligands had a good plasma protein prediction. Pinostrobin, tamoxifen, estradiol and pinocembrin had high predicted oral bioavailabilities

Figure 3.
3D and 2D molecular interaction of gelagin (a, a1), myrecetin (b, b1) and pinobanksin (c, c1) with crucial amino acids at the ligand binding domain of hERα.

while moderate oral bioavailabilities were observed with Gelatin, pinobanksin, and catechin. Myricetin had the least predicted human oral availability.

3.3 Protein-ligand interactions

Structurally, each of the studied ligand contained the basic flavone skeleton linked by a three-carbon chain forming a closed pyran ring. Considering hydrogen bond interactions of the studied molecules with active amino acids of the estrogen receptor, from the results, the 7-OH of gelatin (**Figure 3 (a & a1)**) formed one hydrogen bond with Glycin 521 at a distance of 1.89 Å and a π -cation interactions with phenylalnine 404 and histidine 524. The 3¹- OH and 4¹- OH groups of myricetin each established 1H bond with glutamic acid 353 residue at distances of 1.59 Å and 1.74 Å respectively. A firm interaction was also observed with Arginine 394 by the 4¹- OH of myricetin at distances of 1.97 Å and 2.26 Å. The 8- OH of myricetin also established 1H bond with histidine 524 and glycin 521 at 1.90 Å. There was also a π -interaction of this ligand with phenylalanine 404 and histidine 524 (**Figure 3 (b & b1)**). In **Figure 3 (c & c1)** 1H bond each was established between the 8- OH of

Figure 4. 3D and 2D molecular interaction of pinostrobin (d, d1), pinocembrin (e, e1) and with crucial amino acids at the ligand binding domain of hER α .

pinobankskin and Glycine 521 and Methionine 388 at distances of 1.78 Å and 1.89 Å respectively. A pi-pi interaction was also observed between the ligand and phenylalanine 404 as well as histidine 524. A pi-pi interaction was formed between pinostrobin and phenylalanine 404 of the hER α while its 8- OH group formed one hydrogen bond with glycine 521 at 1.78Å (**Figure 4 (d & d1)**). Pinocembrin (**Figure 4 (e & e1)**) established a pi-cation interaction with phenylalanine 404 and histidine 524 while its 5-OH group formed 1H bond with leucine 387 at 1.89 Å. A strong interaction was observed between its 8- OH group and glutamate 353 at 1.57 Å. Tamoxifen, on the other hand, established 1H bond with Arginine 394 at 2.34 Å and a pi-cation interaction with phenylalanine 404 and histidine while estradiol, the native ligand had 1H bond each with glutamate 353 and histidine 524 at distances of 1.80Å and 2.04Å respectively (**Figure 5 (f and g)**). A pi-pi interaction was also observed with histidine 524 and phenylalanine 404.

3.4 Post docking prime analysis of studied ligands

From the prime energy calculations, the quantity of free energy of binding, ΔG_{bind} calculated from Eq. (1) was in the following order: estradiol>myricetin>catechin>gelagin>pinobankskin>pinocembrin>pinostrobin (**Figure 6**). Other components which contributed to the electrostatic interaction like the quantity of prime coulomb energy of the complex (ΔG_{bind} coulomb), prime van der Waals energy of the complex interaction (ΔG_{bind} vdW), the quantity of prime hydrogen bonding interaction are as presented in **Table 2**.

Figure 5.
Molecular interaction of tamoxifen (f) and estradiol (g) with crucial amino acids at the ligand binding domain of hER α .

Figure 6.
The free energy of binding ΔG_{bind} (kcal/Mol) for the studied ligands with the hER α binding site.

Molecules	ΔG_{bind} Coloumb	ΔG_{bind} Hbond	ΔG_{bind} lipophilic	ΔG_{bind} vdW
Myricetin	-34.6588	-2.2352	-34.5106	-33.2389
Estradiol	-20.0967	-2.04811	-66.6318	-47.0585
Catechin	-28.643	-2.94963	-39.0821	-23.3243
Pinobanksin	-13.6085	-0.092	-36.3471	-35.5581
Pinocembrin	-14.97	-0.99013	-36.5651	-26.7548
Gelangin	-9.44593	-0.16506	-34.4349	-37.5343
Pinostrobin	-5.32169	-0.2392	-41.3577	-25.8845

Table 2.
Output properties from a prime MM-GBSA calculation for the studied ligands.

4. Discussion

Estrogen, a major sex hormone plays an important role in mammary gland development and in the initiation and progression of breast cancer. The activities of estrogen are being mediated via its unique receptors, ER α and ER β . The former (ER α), is the major ER subtype in the mammary epithelium. Upon activation of the hER α following its occupation, the receptor translocates to the nucleus, where it interacts with the target gene promoters of estrogen response element to mediate nuclear as well as extranuclear signaling [8, 22]. This results in the regulation of numerous critical cellular processes and is implicated in the dilemma of breast cancer. Research reveals that ER α extranuclear pathways, which are incited by undue activation of hER α have the potential to activate gene transcription, modulate cytoskeleton, and promote tumor cell proliferation, survival, as well as metastasis. The expression of extranuclear components ER α is deregulated in tumors, thus, serving as an important target for tumorigenic and metastatic control. Resistance to available endocrine therapies provokes metastasis and frustrates the management of this disease, thus, reducing the survival rate of patients bearing such tumors [23, 24]. This study evaluated the inhibitory potential of the reported small molecules from nature against hER α in a bid to suppress its downstream signaling.

The high attrition rate of new chemical entities has been attributed majorly to poor pharmacokinetic profile [25]. The reported ligands have been shown to be drug-like, having satisfied the Lipinski’s rule of five [17] and also possess pharmaceutically relevant properties when compared to 95% of orally available drugs [16]. Hence, these compounds are fit in their current state to be developed into drugs without any modification/optimization except myricetin. Myricetin showed poor human absorption when examining its caco-2 permeability and human oral bioavailability. This observed poor absorption of myricetin will retard how quickly and how much of it will reach its intended target (site) of action. Hence, this phytoconstituent will require optimization to prevent its failure in the market [26].

Aqueous solubilities and human oral absorption are critical for oral dosage formulation and their *in silico* prediction had been reported to correlate well with *in vivo* bioavailabilities [27]. According to Bergström 2005 [28], aqueous solubility and intestinal permeability are the two rate-limiting barriers for oral drug absorption while the therapeutic potential of a drug is dependent on its bioavailability [29]. All the tested compounds showed positive human intestinal absorption.

Following absorption, the drug or intended drug molecule will circulate through the body, permeating different tissues at varying speed, depending on its ability to cross membranes. Some drugs migrate very slowly from the bloodstream because

they get tightly bound to proteins circulating in the blood. Others quickly leave the bloodstream and enter other tissues because they are less tightly bound to blood proteins. There are also possibilities for virtually all molecules of a drug to bind tightly to blood proteins. It is worthy of note that irrespective of how promising a drug molecule is, its efficacy will be lost if its maximum concentration gets bound to plasma proteins. This will eventually result in the decrease of effective concentration at the site of action in the tissues, as only unbound drugs can be available for pharmacological activity [14]. To predict the distribution of the studied ligands, their plasma protein binding and blood brain barrier penetration was investigated. Unlike all compounds which showed good distribution, tamoxifen, however, did not comply within the range, indicating its high potential binding to albumin. This observation was in line with previous report on the high binding affinity of tamoxifen to serum albumin [30, 31]. Considering blood brain barrier permeation, studied compounds showed no tendency of crossing it. This can be explained by the lipophobicity of the studied ligands. It therefore means that they will not provoke any significant central effect that will result in subsequent toxicity.

Another key parameter is metabolism, which is responsible for the elimination of drugs from the body. Through metabolism, drug molecules can also be converted into pharmacologically more active substrates. In this study, the molecules were investigated to predict their possible number of biotransformation which could point to potential toxicities [32, 33]. From the results, all the compounds complied with the range of metabolic reactions displayed by 95% of orally available drugs. Some of the phytoligands were predicted to possess cytochrome P450 (CYP 450) inhibitory promiscuity, revealing their capacity to bind to and decrease or diminish the activity of multiple different CYP 450 isoform enzymes [34]. It should be noted that all the molecular descriptors predicted by qikprop are exclusively for drugs intended for oral delivery. This route of drug administration is still the most preferred route for new chemical entities (NCEs) in spite of advances in drug delivery methods. Oral mode of drug delivery is convenient, cheap and has high patient compliance. Using the *in silico* prediction of pharmacokinetics-related profile of intended drug molecules helps to reduce the rate of attrition of new chemical entities in clinical trial and reduces the cost of bringing a candidate drug to the market.

In modern drug discovery, molecular docking has been gainfully employed in the screening and selection of potent inhibitors [35] especially when the anticancer target has been identified. In this study, structurally similar phytochemicals from plant origin were used to probe for binding interaction with the human estrogen receptor α . As a prerequisite, the molecular docking protocol was validated. From the results, the redocked binding pose of the native ligand was correctly reproduced within the root mean square tolerance of 2 Å. This distance is an indication of an appropriate reproducibility for a docking experiment [36, 37]. This reproducibility of the redocked native ligand was similar to the poses of the docking control reported by Hocker *et al.* (2013) [38].

Inhibiting hER α is a valid approach in ameliorating the progression of breast cancer. This study revealed strong binding affinities of the investigated compounds to the hER α . This interaction which was depicted in their free energy of binding was greatly influenced by the vicinal diol groups. The residues of estrogen receptor which partook in this binding interaction was earlier reported to play critical roles in the inhibition of the ligand binding domain of the hER α [39, 40]. The interaction of these compounds with the binding domain of hER α , created a conformational change in the receptor, inducing its dimerization, thus, interrupting its downstream signaling as well as crosstalks [41]. The conformational change observed in the estrogen receptor upon interaction with the studied ligands will also impair phosphorylation on hER α specific residues, impairing ligand-independent estrogen

receptor activation. It is promising that these interactions with the sex hormone's receptor, hER α with provoke breast cancer cell death, thus halting its progression to immortality [42].

5. Conclusion

The potential of the studied drug-like small molecules to inhibit estrogenic signaling is a vital approach that should be exploited in the management of metastatic breast cancers.

Conflict of interest

The authors declare no conflict of interest.

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