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In-silico ADME, TOXICITY PREDICTION, MOLECULAR DOCKING STUDIES OF CHALCONE-MORPHOLINO THIAZOLE DERIVATIVES AS POTENTIAL ESTROGEN RECEPTOR: A ANTAGONISTS FOR BREAST CANCER THERAPY

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ABSTRACT

Breast cancer remains a major global health challenge, particularly hormone-dependent subtypes driven by estrogen receptor alpha (ERα) signalling. Although endocrine therapies have improved clinical outcomes, resistance and adverse effects necessitate the development of alternative molecular scaffolds. In this study, a series of chalcone–morpholino thiazole derivatives (1a–1j) were evaluated using structure-based molecular docking against ERα (PDB ID: 3ERT). Docking validation was performed using 4-hydroxytamoxifen as a reference. Compounds 1e, 1a, and 1f exhibited the most favourable binding energies (−10.09 to −10.05 kcal/mol), approaching the reference ligand (−11.57 kcal/mol). Interaction analysis revealed stable hydrophobic accommodation with supportive π-interactions and hydrogen bonding. ADMET prediction indicated good gastrointestinal absorption and acceptable drug-likeness for most derivatives, although aqueous solubility may require optimisation. Frontier molecular orbital analysis demonstrated suitable electronic characteristics supporting receptor interaction. These findings identify selected derivatives as promising ERα-targeted candidates, warranting further biological validation, contributing to Sustainable Development Goal 3 (Good Health and Well-Being).

Keywords: Estrogen Receptor Alpha (Erα), 4-Hydroxytamoxifen, Breast Cancer, Chalcone Derivatives. Structure-Based Molecular Docking Simulations

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INTRODUCTION

Breast malignancy continues to impose a substantial global health burden, particularly in women, and its incidence is steadily increasing.[1] A large proportion of diagnosed cases are hormone-responsive and depend on estrogen receptor alpha (ERα)[2] signalling for cellular proliferation and survival. Activation of ERα by endogenous estrogens triggers transcriptional pathways that support tumour growth and metastatic progression.[3] Although endocrine therapies such as Tamoxifen and Fulvestrant[4] have significantly improved clinical outcomes in ERα-positive breast cancer, the emergence of therapeutic resistance and associated limitations necessitates the development of new molecular scaffolds with improved anticancer activity.[5] Heterocyclic chalcone frameworks have attracted considerable interest in medicinal chemistry due to their structural adaptability and wide-ranging pharmacological properties, including anticancer[6], anti-inflammatory[7], and antimicrobial[8] properties. Their α,β-unsaturated carbonyl system allows functional diversification and incorporation of additional pharmacophores to enhance biological performance. Hybridization strategies combining chalcone moieties with thiazole and morpholine fragments may offer improved receptor affinity and pharmacokinetic balance. In our earlier synthetic and biological investigation, compounds 1a–1j demonstrated measurable cytotoxic activity across multiple cancer cell lines.[9] However, the precise molecular target underlying their activity was not established. The present study aims to elucidate whether these derivatives interact with ERα at the molecular level using computational docking, pharmacokinetic prediction, and electronic structure analysis.[10,11] By integrating binding evaluation with ADMET and frontier orbital descriptors, we seek to identify the most promising candidates for further therapeutic development aligned with Sustainable Development Goal-3 (Good Health and Well-Being).

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EXPERIMENTAL

Molecular Docking Protocol

Docking studies were performed using AutoDock 4.2 with the crystal structure of human ERα (PDB ID: 3ERT). The protein structure was retrieved from the Protein Data Bank and prepared by removing water molecules and adding polar hydrogens using MGL Tools 1.5.6. Grid parameters were set with 0.375 Å spacing, centred at x = 29.719, y = −1.91, z = 23.804, with dimensions of 50 × 56 × 52 points to encompass the ligand-binding domain. The Lamarckian Genetic Algorithm was employed, generating 10 conformations per ligand. Docking protocol validation was performed by re-docking 4-hydroxytamoxifen into the active site, yielding a binding energy of −11.57 kcal/mol.

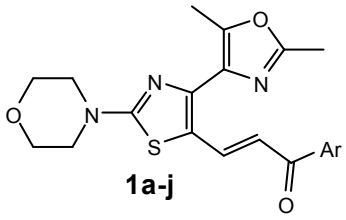
ADMET Prediction

Pharmacokinetic parameters including molecular weight (MW), AlogP, hydrogen bond donors (HBD), hydrogen bond acceptors (HBA), topological polar surface area (TPSA), rotatable bonds (RB), gastrointestinal absorption (GI), blood–brain barrier permeability (BBB), CYP2D6 inhibition, hepatotoxicity, and plasma protein binding (PPB) were predicted using established in silico ADMET prediction tools.

Frontier Molecular Orbital (FMO) Analysis

Frontier molecular orbital energies (HOMO and LUMO) were calculated to evaluate electronic properties. Derived descriptors, including ionisation potential (I), electron affinity (A), electronegativity (χ), and chemical hardness (η) were computed using standard equations.

RESULTS AND DISCUSSION



1a-j

1a; Ar = 3,4,5-trimethoxyphenyl
1b; Ar = 3,5-dimethoxyphenyl
1c; Ar = 4-methoxyphenyl
1d; Ar = 4-pyridyl
1e; Ar = 4-methylphenyl
1f; Ar = 4-(dimethylamino)pheny
1g; Ar = 4-nitrophenyl
1h; Ar = 3,5-dinitrophenyl
1i; Ar = 4-chlorophenyl
1j; Ar = 4-bromophenyl

Fig.-1: Chemical Structures of Synthesized Chalcone–Morpholino Thiazole Derivatives (1a–1j)

Molecular Docking Analysis and Binding Interactions

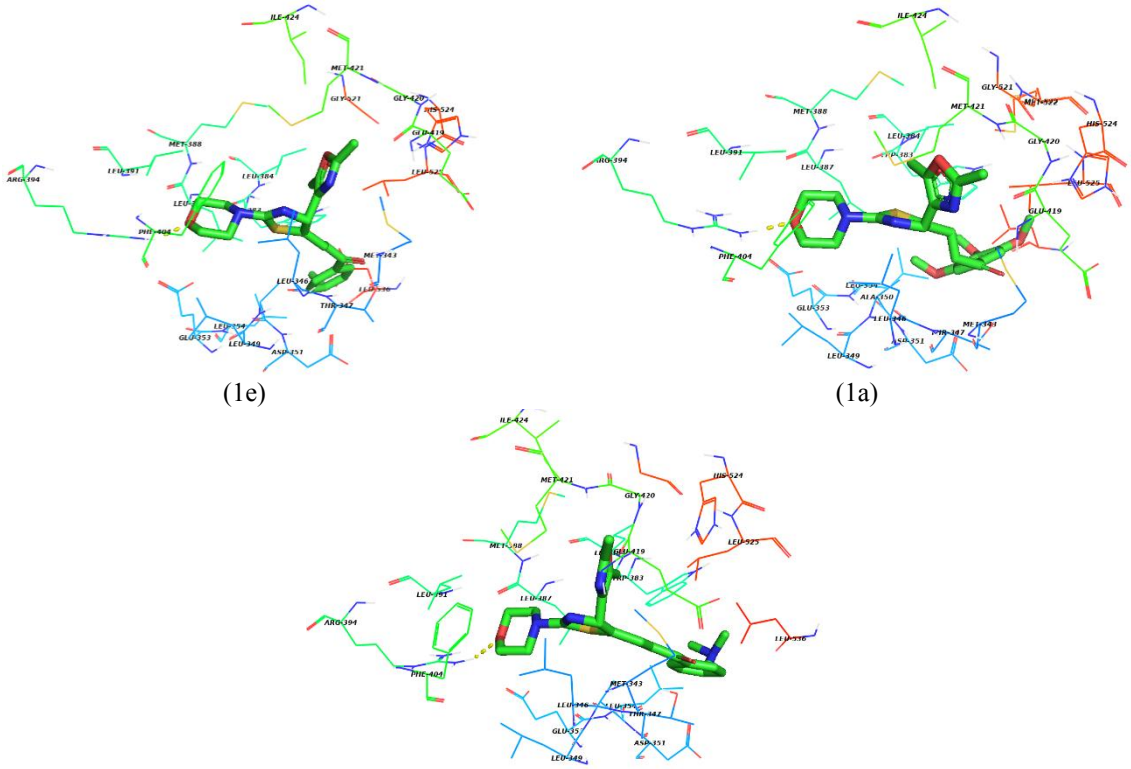
To assess the potential binding affinity and mode of interaction of ligands with the Human Estrogen Receptor α (hERα, PDB ID: 3ERT), molecular docking studies were executed. The validation of docking protocol was first established by re-docking the co-crystallised antagonist, 4-Hydroxytamoxifen (4-OHT), which yielded a high docking score of -11.57 kcal/mol, consistent with its known potent affinity for ERα. The results revealed a spectrum of binding affinities across the designed series, with three compounds, 1e, 1a, and 1f, demonstrating exceptionally strong binding, as evidenced by their high negative docking scores (Table-1). The full ranking of all ten ligands provides crucial insights into the structure-activity relationship within this chemotype.

Table-1: Docking Scores of all Synthesised Ligands against hERα (PDB ID: 3ERT)

S. No.	Ligand	Docking Score (kcal/mol)
1	1e	-10.09
2	1a	-10.06
3	1f	-10.05
4	1b	-9.88
5	1i	-9.78
6	1j	-9.78
7	1c	-9.49
8	1g	-9.24
9	1d	-9.20
10	1h	-8.57
	4-OHT (Reference)	-11.57

Analysis of High-Affinity Binders (1e, 1a, 1f)

The top three ligands (1e, 1a, 1f) all achieved docking scores nearing -10.1 kcal/mol, indicating very strong predicted binding affinity. A detailed analysis of their interactions reveals a consistent binding mode characterised by an extensive network of hydrophobic interactions within the receptor's core. All three compounds engage critically with key residues Leu387, Leu391, Met421, and Trp383. Ligand 1e distinguishes itself with the most complex interaction profile, forming additional π-based interactions (π-sigma, π-alkyl) with His524 and Phe404, and a strategic hydrogen bond with Arg394, which likely contributes to its top ranking. The ability of these ligands to recapitulate key interactions observed with 4-OHT provides a strong structural rationale for their high predicted activity.



(1e) (1a)

(1f)

Fig.-2: Binding Interactions of High-Affinity Ligands (1e, 1a, and 1f) within the Ligand-Binding Domain of Human Estrogen Receptor Alpha (PDB ID: 3ERT). Amino Acid Residues within 5 Å are shown in Line Representation, and Ligands are Displayed in Ball Model Format

Analysis of Mid-Affinity Binders (1b, 1i, 1j, 1c)

Ligands in this group (-9.78 to -9.49 kcal/mol) maintain strong binding but lack the breadth of interactions seen in the top tier. 1b and 1i show a strong reliance on hydrophobic contacts with core residues (e.g., Leu346, Met343, Met421). 1i also shows potential for specific interactions, including a Pi-Sulfur interaction with Met388, which may contribute to its stability. 1c's interaction profile is notable for its very high number of leucine residues, suggesting strong van der Waals packing but potentially less optimal polar or π-interactions, explaining its slightly lower score. 1j's data appears to be an outlier with an impossibly long list of leucines, suggesting a possible error in the generation of the 2D diagram; its score suggests it is a valid mid-affinity binder, but its specific interactions cannot be reliably determined from the provided data.

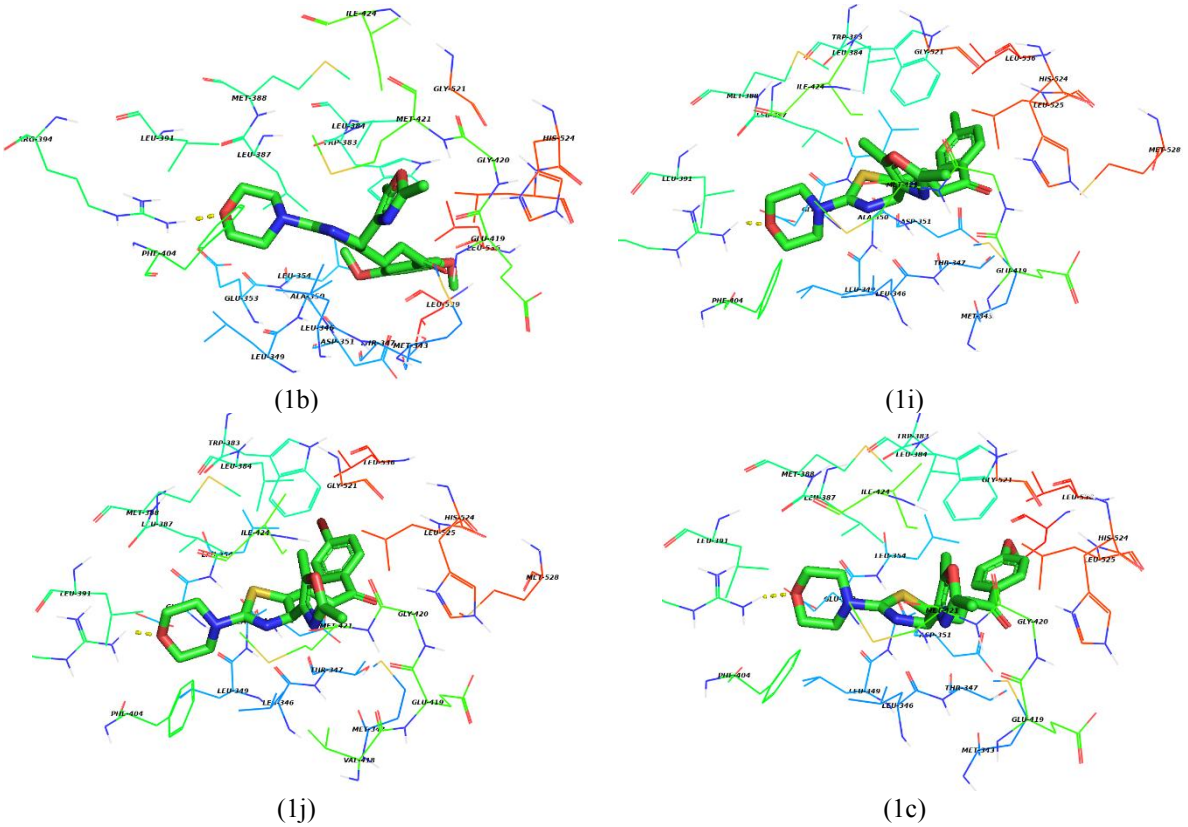


Fig.-3: Binding-Site Interaction Profiles of Mid-Affinity Ligands (1b, 1i, 1j, and 1c) Docked into the Erα Binding Pocket. Residues within 5 Å Are Represented in Line Format

Analysis of Lower-Affinity Binders (1g, 1d, 1h)

The lower scores of this group (-9.24 to -8.57 kcal/mol) correlate with simpler interaction profiles. 1g and 1d engage with a smaller subset of the key hydrophobic residues (e.g., Leu349, Leu391, Ala350). 1d does form a hydrogen bond with Asp351, a key residue for antagonism, but this alone is insufficient for high affinity without robust hydrophobic stabilisation. Ligand 1h has the lowest score (-8.57 kcal/mol); its provided interaction list is nonsensical and truncated, indicating a potential failed docking pose or a fundamental issue with the ligand's fit within the binding pocket, consistent with its poor predicted affinity.

Comparative Analysis with 4-Hydroxytamoxifen and SAR Conclusions

The docking score of the reference drug 4-OHT (-11.57 kcal/mol) serves as a benchmark for high-affinity binding. The scores of our top ligands are notably high and approach the affinity of 4-OHT. A crucial observation is the significant overlap in key interacting residues between our top ligands and 4-OHT. All high-affinity compounds, like 4-OHT, engage critically with the fundamental hydrophobic niche formed

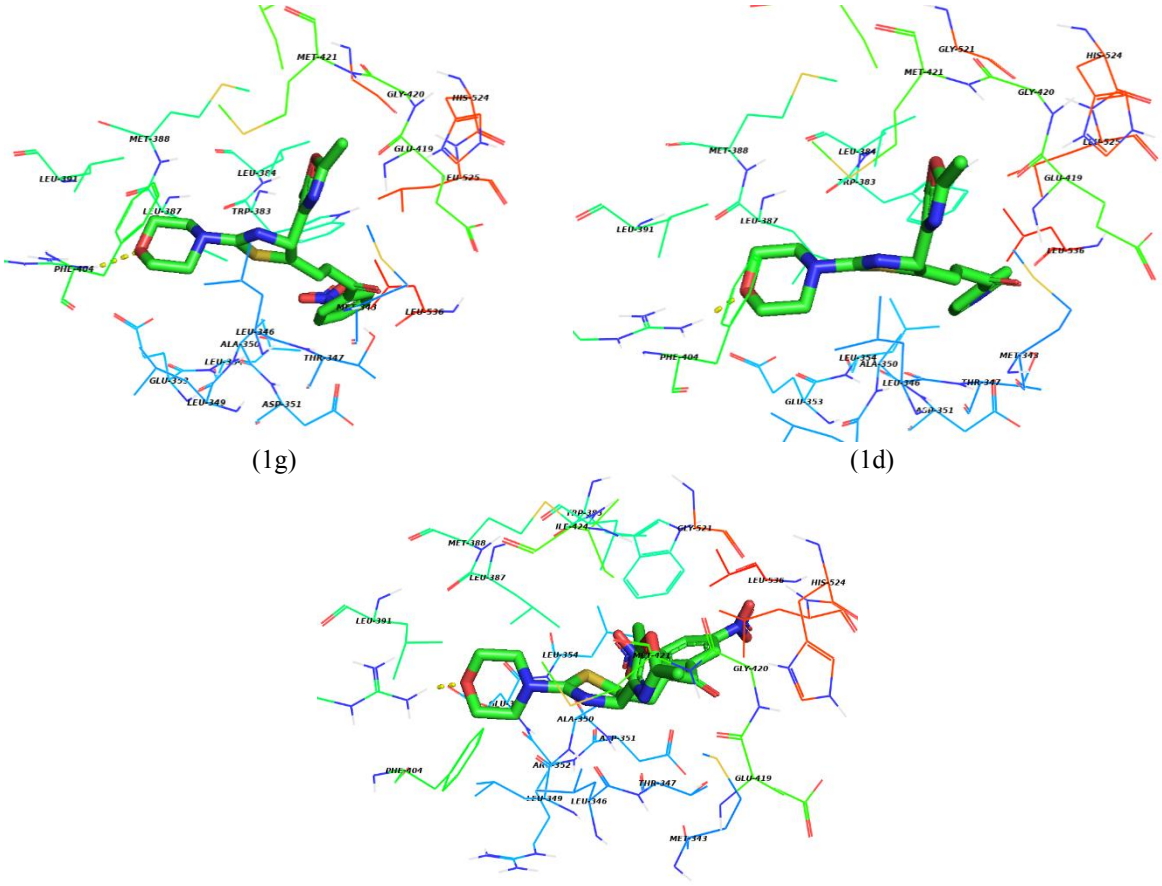
by Leu346, Met421, Leu387, and Leu391. The structure-activity relationship (SAR) that emerges from this data highlights several key determinants for high affinity.

Hydrophobic Core Engagement

The number and strength of interactions with the leucine-rich hydrophobic core (e.g., Leu387, Leu391, Leu346) are the primary drivers of binding affinity.

Role of Methionine 421

Consistent interaction with Met421 is a hallmark of all mid-to-high affinity binders, mirroring its importance in 4-OHT binding.



(1g) (1d)

(1h)

Fig.-4: Docking Interaction Analysis of Lower-Affinity Ligands (1g, 1d, and 1h) in the ERα Active Site, Highlighting Key Residue Contacts

Impact of Polar and π-Interactions

The superior performance of 1e suggests that adding specific polar (H-bond with Arg394) and π-interactions (with His524/Phe404) to the robust hydrophobic foundation can enhance affinity towards the level of 4-OHT. Chemical Group Substitution: The variance in scores between ligands with the same scaffold (e.g., 1e vs. 1d) is directly attributable to the chemical nature of their substituents, which modulates their ability to form these critical van der Waals and polar contacts. The in-silico docking analysis has successfully identified 1e, 1a, and 1f as promising high-affinity binders to hERα, with predicted binding energies that are highly competitive with the established drug 4-OHT. The consensus in binding mode with 4-OHT and the emerging SAR are particularly encouraging. These computational findings provide a strong rational basis for prioritising these compounds for further in vitro and in vivo biological evaluation as potential breast cancer therapeutics. The synthesised series offers a valuable platform for further medicinal chemistry optimisation.

Comprehensive ADMET Properties of Ligands 1a-1j

Computational pharmacokinetic screening revealed that most derivatives comply with Lipinski's criteria, suggesting acceptable oral drug-likeness. Predicted gastrointestinal absorption exceeded 90% for the majority of compounds, supporting favourable permeability characteristics. None of the molecules was predicted to inhibit CYP2D6, indicating a reduced probability of metabolic drug–drug interactions. A recurring limitation within the series is the prediction of limited aqueous solubility, likely attributable to the aromatic and hydrophobic nature of the scaffold. Additionally, elevated plasma protein binding values were observed for several derivatives, which may influence the unbound pharmacologically active fraction. Notably, the 3,5-dinitro derivative (1h) displayed deviations, including a higher hydrogen bond acceptor count and predicted hepatotoxicity, making it less suitable for progression. In contrast, the pyridyl analogue 1d showed comparatively balanced properties, including moderate solubility and lower plasma protein binding.

Property	1a	1b	1c	1d	1e	1f	1g	1h	1i	1j	Ideal Range
MW(Da)	485.56	455.53	425.50	393.49	409.54	438.58	454.50	499.50	429.95	474.40	≤ 500
AlogP	3.38	3.26	2.98	1.92	3.52	3.11	2.90	2.73	3.52	3.67	≤ 5
HBD	0	0	0	0	0	0	0	0	0	0	0
HBA	9	8	7	7	6	7	10	13	6	6	≤ 10
TPSA(Å²)	106.41	96.56	86.71	95.22	76.86	86.08	126.56	176.85	76.86	76.86	
RB	8	7	6	5	6	8	7	7	6	6	≤ 10
Lipinski Violations	1 (MW> 500)	0	0	0	0	0	1 (MW> 500)	2 (MW> 500, HBA> 10)	0	0	≤ 1
Solubility (Class)	Poor	Poor	Poor	Moder ate	Poor	Poor	Poor	Poor	Poor	Poor	Solubl e
GI Absorption	High	High	High	High	High	High	High	Low	High	High	High
BBB Permeant	No	No	No	No	No	No	No	No	No	No	No (for this target)
CYP2D6 Inhibitor	No	No	No	No	No	No	No	No	No	No	No
HIA(% Absorbed)	93.7%	93.70 %	93.7%	94.49 %	93.70 %	93.70 %	85.94 %	73.10%	93.70%	93.70 %	>80%
PPB (% Bound)	95.21 %	94.42 %	93.59%	87.71 %	95.37 %	93.59 %	92.45 %	91.24%	95.47%	95.60 %	<90%
Hepatotoxic	No	No	No	No	No	No	No	Yes	No	No	No

MW: Molecular Weight; AlogP: Octanol/water partition coefficient; HBD/HBA: Hydrogen Bond Donors and Acceptors, both archetypical descriptors; TPSA: Topological Polar Surface Area, a noteworthy polarity indicator; RB: Rotatable Bonds, reflecting amenable flexibility; HIA: Human Intestinal Absorption, an imperative pharmacokinetic parameter; PPB: Plasma Protein Binding, a promulgated measure of distribution.

Frontier Molecular Orbital Analysis

Compounds 1a, 1e, and 1f exhibit properties more aligned with electron donation. Their HOMO energy levels are higher, with compound 1f (−5.28 eV) standing out as the strongest electron donor. These molecules also show lower hardness values (1.64–1.67 eV), indicating that they are softer, more chemically reactive, and better suited for charge transfer. Their lower electrophilicity indices, particularly for 1f (3.91 eV), support a donor-dominant role in receptor–ligand interactions. Among them, 1f emerges as the most reactive donor candidate due to its highest HOMO level and soft nature, suggesting that it can establish strong orbital overlap with receptor residues. Therefore, while compounds 1f and 1i contribute through strong electron-accepting interactions, compounds 1a, 1e, and 1f contribute through donor-driven mechanisms, highlighting two complementary modes of binding to ERα.

Table-2: Frontier Molecular Orbital Energies and Derived Electronic Descriptors of Selected High-Affinity Compounds

System	HOMO EV	LUMO EV	I (eV)	A (eV)	χ (eV)	η (eV)
1a	-5.418	-2.148	5.418	2.148	3.783	1.635
1e	-5.486	-2.174	5.486	2.174	3.830	1.656
1f	-5.286	-1.942	5.286	1.942	3.614	1.672

Note: Energies are given in eV. I = -E_HOMO, A = -E_LUMO, χ = -1/2(E_HOMO + E_LUMO), η = -1/2(E_HOMO - E_LUMO), $\delta = 1/\eta$, $\omega = \chi^2/2\eta$.

CONCLUSION

The present in silico investigation identified chalcone–morpholino thiazole derivatives 1e, 1a, and 1f as promising estrogen receptor alpha antagonists based on strong docking scores, favourable binding interactions, and acceptable pharmacokinetic predictions. These compounds demonstrated binding affinities approaching that of 4-hydroxytamoxifen and reproduced key hydrophobic and polar interactions within the ERα ligand-binding domain. ADMET profiling indicated high oral absorption and low drug–drug interaction risk, although solubility optimisation may be required. Frontier orbital analysis further supported their electronic suitability for receptor binding. Collectively, these findings provide a rational computational foundation for prioritising these derivatives for experimental validation and contribute toward Sustainable Development Goal-3 (Good Health and Well-Being) by supporting the discovery of novel therapeutic candidates for breast cancer management.

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CONFLICT OF INTERESTS

The author declares no conflict of interest.

AUTHOR CONTRIBUTIONS

The present work is related to *SDG-3: Good Health and Well-Being*. All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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REFERENCES

1. H. Sung, J. Ferlay, R.L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal and F. Bray. *CA: A Cancer Journal for Clinicians*, **71**, 209(2021), https://doi.org/10.3322/caac.21660
2. S. J. Nass, and H. L. Moses. *"Committee on developing biomarker-based tools for cancer screening, diagnosis, and treatment." Cancer Biomarkers: The Promises and Challenges of Improving Detection and Treatment. Washington (DC): Institute of Medicine* (2007).
3. B. Huang, M. Warner, and J.-Å. Gustafsson, *Molecular and Cellular Endocrinology*, **418**, 240(2015), https://doi.org/10.1016/j.mce.2014.11.015
4. Early Breast Cancer Trialists' Collaborative Group, *The Lancet*, **365**, 1687(2005).
5. R. Jeselsohn, G. Buchwalter, C. De Angelis, M. Brown and R. Schiff, *Nature Reviews Clinical Oncology* **12**, 573(2015), https://doi.org/10.1038/nrclinonc.2015.117

6. M. P. Neves, S. Cravo, R. T. Lima, M. H. Vasconcelos, M. S. J. Nascimento, A. M. S. Silva, M.Pinto, H. Cidade and A. G. Corrêa, *Bioorganic & Medicinal Chemistry*, **20**, 25(2012), https://doi.org/10.1016/j.bmc.2011.11.042
7. J. Rojas, M. Payá, J. N. Domínguez and M. L. Ferrándiz, *European Journal of Pharmacology*, **465**, 183(2003), https://doi.org/10.1016/S0014-2999(03)01457-2
8. K. Liaras, A. Geronikaki, J. Glamočlija, A. Ćirić and M. Soković, *Bioorganic & Medicinal Chemistry*, **19**, 3135(2011), https://doi.org/10.1016/j.bmc.2011.04.007
9. M.R. Rachala, T.C. Maringanti, and L. Eppakayala, *Results in Chemistry*, **5**, 100977(2023), https://doi.org/10.1016/j.rechem.2023.100977
10. G.M. Morris, M. Lim-Wilby, 2008, Molecular Docking. In: Kukol, A. (eds) Molecular Modeling of Proteins. Methods Molecular Biology™, Vol 443. Humana Press, pp. 365-382, https://doi.org/10.1007/978-1-59745-177-2_19
11. L. G. Ferreira, R. N. Dos Santos, G. Oliva and A. D. Andricopulo, *Molecules*, **20**, 13384(2015), https://doi.org/10.3390/molecules200713384

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