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Molecular Docking and ADMET Evaluation of Fluoro-Hydroxyxanthone Derivatives as Potential Estrogen Receptor Alpha Inhibitors

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ABSTRACT: Fluoro-hydroxyxanthone derivatives (X1–X10) were investigated as potential inhibitors of estrogen receptor alpha (ER-α) through molecular docking and in silico ADMET profiling. The docking protocol was validated through a redocking procedure, yielding a Root Mean Square Deviation (RMSD) of 0.81 Å, which confirmed the method's reliability. Compounds X6–X10 demonstrated favorable binding affinities ranging from −7.32 to −7.46 kcal/mol, although these values remained lower than those of the native ligand, estradiol (−10.69 kcal/mol), and tamoxifen (−9.21 kcal/mol). These compounds formed key hydrogen bond interactions with Glu353 and Arg394, similar to estradiol, suggesting a correct binding orientation within the receptor's ligand-binding domain. Structural modifications, particularly the introduction of hydroxyl and fluoro substituents, contributed to the enhanced binding energies observed in these top-performing compounds. ADMET analysis further indicated that compounds X6–X10 complied with Lipinski's Rule of Five, had acceptable oral bioavailability, metabolic stability, and the ability to cross the blood–brain barrier. However, all derivatives were predicted to exhibit mutagenic potential and hepatotoxicity, which may limit their safety profiles. In conclusion, fluoro-hydroxyxanthone derivatives, especially X6–X10, represent promising molecular scaffolds for further optimization and development as potential anti-breast cancer agents targeting ER-α.

Keywords: Fluoro-hydroxyxanthone, Cancer, ER-α, Molecular Docking, ADMET

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INTRODUCTIONS

Globally, cancer continues to be a significant cause of mortality, responsible for approximately one in six fatalities. Data from GLOBOCAN (2022) indicate an estimated 20 million active cancer cases and 9.7 million annual cancer-related deaths, reflecting an increase from 2018, when 18.1 million active cases and 9.5 million deaths were reported. Projections suggest a further rise, with an anticipated 22 million cases and 18.2 million deaths by 2050 (Bray et al., 2024). Breast cancer currently represents the most prevalent malignancy worldwide, comprising 12.5% of all newly diagnosed cancer cases each year (Dolatkhah et al., 2020). Notably, approximately 85% of patients with breast cancer report no family history of the disease (Siegel et al., 2024). These epidemiological trends highlight the critical need for enhanced research efforts, early detection strategies, and therapeutic advancements aimed at mitigating the global burden of breast cancer and improving patient survival in the coming decades.

One of the principal factors contributing to the development of breast cancer is the overproduction of estrogen. The estrogen receptor (ER), a nuclear receptor, is predominantly activated upon binding to its natural ligand, 17β-estradiol, commonly referred to as estrogen (Miziak et al., 2023). Estrogen receptor alpha (ER-α) is well established as a key player in immune surveillance, resistance to apoptosis, metastasis, and cell proliferation. The overactivity of estrogen may lead to an increase in ER-α expression, which can contribute to the progression and sustenance of various breast cancer types (Liu et al., 2020). Consequently, the ER-α protein represents a compelling molecular target for the development of novel anticancer therapeutics.

In silico methodologies, particularly molecular docking simulations, offer a highly effective means of predicting the inhibitory potential of designed compounds against specific target protein receptors, thereby circumventing the substantial time and resource demands associated with compound isolation and chemical synthesis (Brogi et al., 2020). Among the advanced anticancer compounds, xanthone has garnered significant interest due to its distinctive and uncomplicated structure, which exhibits a broad spectrum of activity against various cancer cell lines. This efficacy is contingent upon the specific chemical structures involved (Kurniawan et al., 2021). Hydroxyxanthone derivatives exhibit significant cytotoxic activity against WiDr, MCF7, and HeLa cancer cell lines, emphasizing the critical role of hydroxyl substituents in enhancing anticancer efficacy (Fatmasari et al., 2022). Similarly, the anticancer potential of halogenated xanthone derivatives has been extensively reported. Notably, the introduction of a chloro substituent at the para-position of 3-hydroxyxanthone resulted in a 1.85-fold increase in anticancer activity, as evidenced by a reduction in the IC_{50} value from 100 μM to 54 μM (Kurniawan et al., 2021).

Furthermore, the incorporation of a chloro substituent into hydroxyxanthone derivatives enhanced their anticancer activity against T47D and HeLa cell lines, and a bromo substituent was found to improve cytotoxic efficacy against P388 cancer cells (Yuanita et al., 2019, 2021). A quantitative structure–activity relationship (QSAR) analysis of hydroxyxanthone derivatives, identifying several novel fluoro-substituted compounds with predicted IC_{50} values ranging from 0.0005 to 1.59 μg/mL (Sugara et al., 2021). However, these derivatives have not yet been evaluated through molecular docking studies further to elucidate their potential interactions with target protein receptors.

In light of the preceding findings, hydroxyxanthone derivatives bearing fluoro substituents will be systematically evaluated for their binding affinity and interaction stability with the estrogen receptor alpha (ER-α) through molecular docking simulations. In addition, comprehensive absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiling will be conducted to assess their physicochemical properties and pharmacokinetic suitability, thereby informing their potential as viable anticancer drug candidates.

MATERIALS AND METHODS

Materials

The molecular docking study of fluoro-hydroxyxanthone derivatives was performed using a computer equipped with an Intel i5-13400 processor, a GTX 1650 graphics card, and 32 GB of RAM. As illustrated in Figure 1, the fluoro-hydroxyxanthone derivatives were derived from a QSAR analysis conducted by a previous study (Sugara et al., 2021).

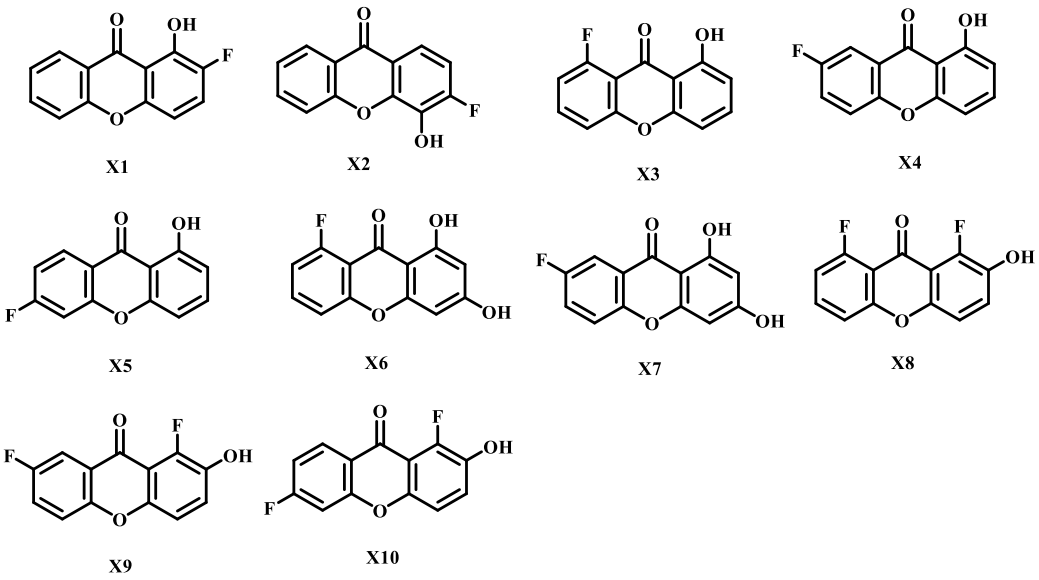

Figure 1. The structure of Fluoro-hydroxyxanthone derivatives

METHODS

Molecular docking study

The Estrogen Receptor Alpha protein (PDB ID: 6CBZ) was retrieved from the Protein Data Bank (https://www.rcsb.org/), and its preparation, including the isolation of the native ligand and removal of water molecules and other residues, was conducted using Chimera (Pettersen et al., 2004). The fluoro-hydroxyxanthone derivatives were constructed as three-dimensional structures using Avogadro and further optimized with the DFT 6-21G method via Orca. Molecular docking and redocking were performed using AutoDock4 (Morris et al., 2009) with a grid box size of 40 × 40 × 40 $Å^3$, centered at coordinates 14.97, 0.588, and 5.61 for the x, y, and z axes, respectively, employing 50 runs of the Lamarckian Genetic Algorithm. The docking results were visualized using Discovery Studio Visualizer (Fuhrmann et al., 2010).

ADMET Prediction

The PDB structures of fluoro-hydroxyxanthone derivatives were converted to SMILES format using Discovery Studio Visualizer, then individually submitted to the pkCSM web server (Pires et al., 2015) for analysis. Physicochemical and ADMET properties were selected through the ADMET menu, and the server generated comprehensive data for each compound, including Lipinski's Rule of Five and various parameters related to absorption, distribution, metabolism, excretion, and toxicity.

RESULTS AND DISCUSSION

To evaluate the binding affinity of ten fluoro-hydroxyxanthone derivatives, molecular docking was carried out using Estrogen Receptor Alpha (ER-α) as the target protein, for which estradiol serves as the co-crystallized ligand. Before docking, the reliability of the docking protocol was established through a redocking procedure, where the native ligand was re-docked into the binding site. A Root Mean Square Deviation (RMSD) value of less than 2 Å was obtained, confirming the validity of the docking methodology according to standard benchmarks (Huey et al., 2007). These results confirm the robustness of the docking parameters applied in this study. The redocking of the native ligand, estradiol, to the ER-α protein yielded a binding energy of –10.69 kcal.mol^{-1} and an RMSD value of 0.81 Å, indicating high accuracy. As depicted in Figure 2, the superimposition of the ligand structures before and after docking revealed negligible deviation. The attainment of RMSD values below 2 Å reflects the methodological reliability and suitability of the applied docking settings for evaluating the binding interactions of fluoro-hydroxyxanthone derivatives.

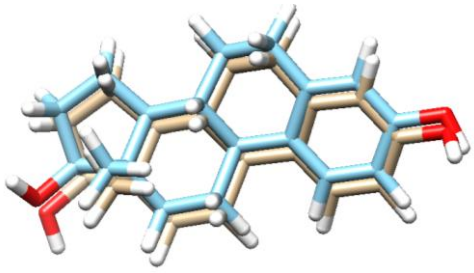

Figure 2. The superimposed structures of estradiol before docking (white) and after docking (blue)

The fluoro-hydroxyxanthone derivatives (**X1**–**X10**) were docked into the same binding site as estradiol, the endogenous ligand of the estrogen receptor alpha (ER-α). As presented in Table 1, their predicted binding energies ranged from –6.38 to –7.46 kcal·mol^{-1}, which are less harmful than those of estradiol (–10.69 kcal·mol^{-1}) and tamoxifen (–9.21 kcal·mol^{-1}), indicating comparatively lower binding affinity than the reference ligands. The data suggest that hydroxyl substitution at the C-3 position of the xanthone scaffold strengthens the ligand–receptor interactions, as reflected by the decrease in binding energies from –6.41 kcal·mol^{-1} (**X3**) and –6.31 kcal·mol^{-1} (**X4**) to –7.44 kcal·mol^{-1} (**X6**) and –7.46 kcal·mol^{-1} (**X7**). Furthermore, fluorine substitution was found to enhance the binding affinity, as observed for **X3** (–6.41 kcal·mol^{-1}) relative to its

fluorinated analogues **X8** (–7.42 kcal·mol^{-1}), **X9** (–7.32 kcal·mol^{-1}), and **X10** (–7.43 kcal·mol^{-1}).

Table 1. Docking result of flouro-hydroxyxanthone derivatives

Compound	Binding Energy (kcal/mol)	Inhibition constant (Ki) (μM)	Hydrogen bond interactions
X1	-6.57	15.36	Ala350, Glu353, Arg394
X2	-6.52	16.76	Leu346, Arg394
X3	-6.41	20.18	Leu346
X4	-6.38	21.01	Ala350, Glu353
X5	-6.61	14.17	Ala350, Glu353
X6	-7.44	3.53	Leu346, Glu353
X7	-7.46	3.43	Leu346
X8	-7.42	3.66	Glu353, Arg394
X9	-7.32	4.31	Glu353, Arg394
X10	-7.43	3.57	Glu353, Arg394
Estradiol	-10.69	0.02	Glu353, Arg394, His524, His521
Tamoxifen	-9.21	0.18	-

Based on the binding energy data, the superior performance of **X6**–**X10** compared with **X1**–**X5** can be rationalized by the combined electronic, steric, and hydrogen-bonding effects of the hydroxyl and fluorine substituents. The hydroxyl moiety serves as a potent hydrogen-bond donor and acceptor, enabling directional interactions with key polar residues such as Glu353, Arg394, and Leu346, as indicated in Table 1. These specific interactions stabilize the ligand within the receptor cavity and compensate for desolvation penalties, resulting in a net gain in binding free energy. The incorporation of fluorine further modulates the physicochemical properties of the xanthone core. Owing to its high electronegativity and small van der Waals radius, fluorine exerts a strong electron-withdrawing effect, which decreases the π-electron density of the aromatic system and alters its frontier orbital distribution. This electronic perturbation enhances π–π stacking and dipole–dipole interactions with aromatic and polar residues within the binding pocket. In addition, the compact steric profile of fluorine facilitates tighter hydrophobic packing and increased dispersion interactions within the nonpolar subpockets of ER-α. The synergy between the hydrogen-bonding potential of hydroxyl groups and the electronic and steric tuning conferred by fluorine provides a coherent explanation for the more favorable docking scores of **X6**–**X10**.

The inhibition constant (Ki), which represents the dissociation constant of the enzyme–inhibitor complex formed during docking, serves as an indicator of binding affinity. A lower Ki value corresponds to reduced complex dissociation and, consequently, more substantial inhibitory potential. The Ki is calculated using the equation $Ki = \exp(\Delta G / (R \cdot T))$, where ΔG denotes the binding free energy, R is the universal gas constant (1.987 cal·K^{-1}·mol^{-1}), and T is the temperature (298.15 K) (Morris et al., 1998). Compounds **X6**–**X10** exhibited lower Ki values (3.42–4.31 μM) than **X1**–**X5** (14.17–21.01 μM), consistent with their superior docking scores and highlighting their potential as promising ER-α modulators for breast cancer therapy.

Comparative interaction analysis with estradiol (Figure 3) provides deeper insight into the structural basis of ligand recognition and receptor modulation within the ER-α

binding domain. Estradiol, as the native ligand (ΔG = −10.69 kcal·mol^{-1}), forms an extensive hydrogen-bonding network with Glu353, Arg394, His524, and Thr34.

In contrast, tamoxifen (ΔG = −9.21 kcal/mol) lacks hydrogen bonding interactions and primarily engages Leu346, Leu387, Phe404, and Met421 through hydrophobic and π-alkyl interactions. The fluoro-hydroxyxanthone derivatives **X6**–**X10** (ΔG = −7.46 to −7.32 kcal·mol^{-1}) exhibit an intermediate binding mode, preserving the critical Glu353–Arg394 hydrogen-bond interactions characteristic of estradiol, while engaging in π–π stacking interactions with Phe404 and Leu387. Additional halogen (F) and hydrophobic contacts with Met421 and Leu346 further stabilize the ligand–receptor complex. Although their binding affinities are weaker, these compounds maintain crucial receptor interactions, suggesting a selective modulator profile with potential partial agonist characteristics rather than complete antagonism.

Physicochemical and ADMET properties

Within the framework of rational drug design, a comprehensive evaluation of physicochemical and ADMET (absorption, distribution, metabolism, excretion, and toxicity) parameters is a fundamental step in determining the pharmacokinetic feasibility and safety profile of candidate molecules. Among the established guidelines for assessing oral bioavailability, Lipinski's Rule of Five remains the most widely recognized benchmark, stipulating that compounds with molecular weights below 500 Da, log P values under 5, no more than 10 hydrogen bond acceptors, five hydrogen bond donors, fewer than 10 rotatable bonds, and a topological polar surface area below 140 Å^2 are generally more likely to exhibit favorable pharmacokinetic properties (Lipinski, 2004). As summarized in Table 2, all fluoro-hydroxyxanthone derivatives (X6–X10) conform to these criteria, demonstrating molecular compactness and balanced polarity consistent with drug-like characteristics. Their calculated log P values (2.49–2.93) reflect moderate lipophilicity, an optimal physicochemical attribute that facilitates efficient membrane permeation while maintaining sufficient aqueous solubility, a critical equilibrium often associated with enhanced oral absorption and bioavailability.

The Caco-2 cell permeability assay serves as a well-established in vitro surrogate model for the human intestinal epithelial barrier. It is extensively employed to predict the absorption potential of orally administered drug candidates (Panse & Gerk, 2022). In general, compounds exhibiting Caco-2 permeability values greater than 0.90 are considered to possess high permeability and efficient passive transcellular diffusion across the intestinal mucosa. The predicted Caco-2 permeability values for the fluoro-hydroxyxanthone derivatives (−4.97 to −4.80) fall substantially below this threshold, suggesting limited passive diffusion through the epithelial membrane. Nonetheless, all compounds demonstrated favorable intestinal absorption predictions, implying that alternative uptake mechanisms, such as facilitated transport or paracellular diffusion, may compensate for their restricted passive permeability. This observation is consistent with their moderate lipophilicity and relatively compact molecular framework, which collectively support the feasibility of transport-mediated intestinal uptake despite suboptimal passive permeability indices.

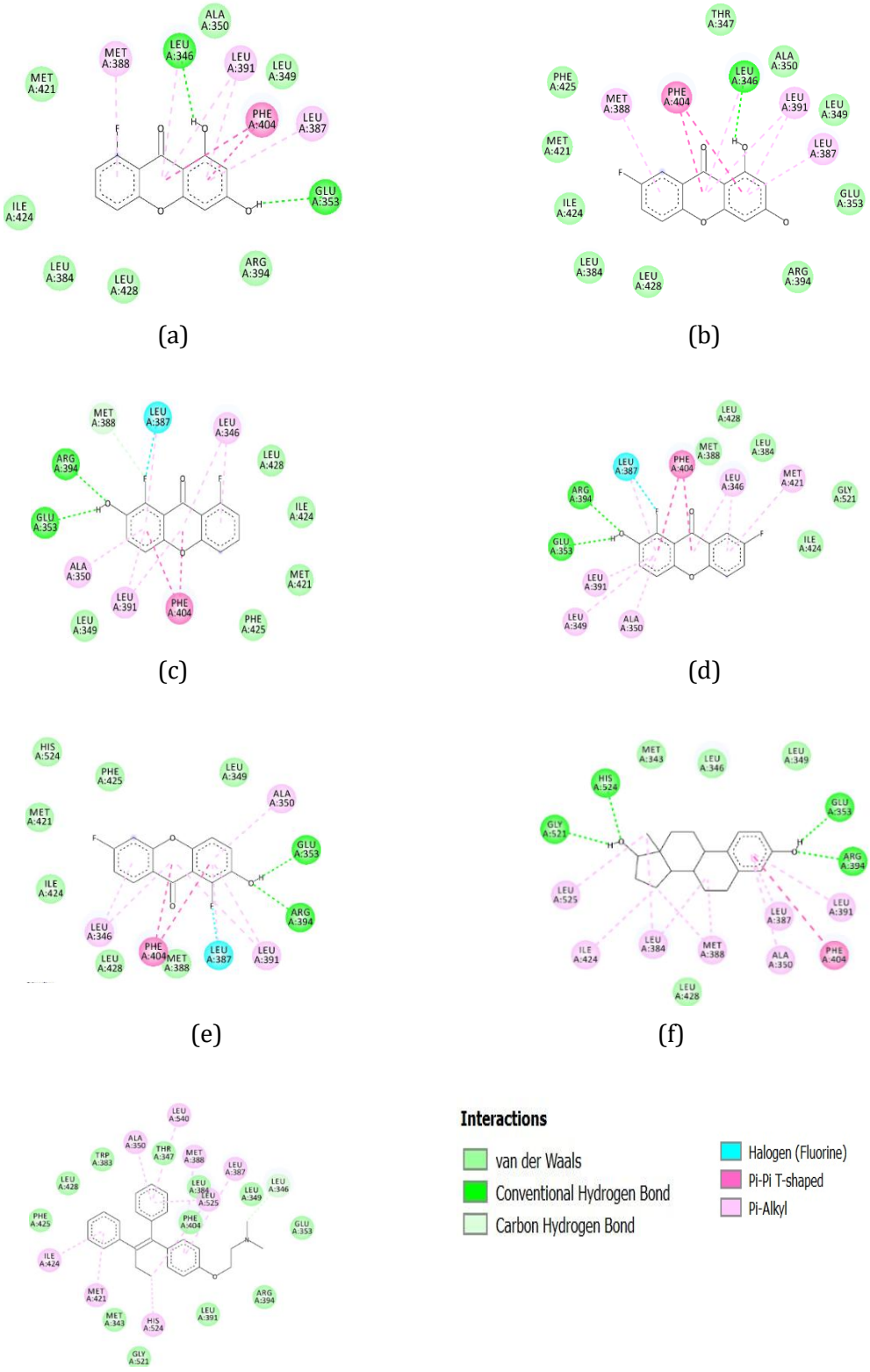

Figure 3. The 2D-interactions of ligands: (a) **X6**, (b) **X7**, (c) **X8**, (d) **X9**, (e) **X10**, (f) estradiol, and (g) tamoxifen

Table 2. Physicochemical and ADMET properties of Fluoro-hydroxyxanthones

	Properties	Compound				
		X6	X7	X8	X9	X10
Physicochemical	Molecular weight	246.193	246.193	248.184	248.184	248.184
	log P	2.497	2.497	2.930	2.93	2.93
	Rotatable bond	0	0	0	0	0
	H-bond acceptor	4	4	3	3	3
	H-bond donor	2	2	1	1	1
	Surface area	70.67	70.67	50.44	50.44	50.44
Absorptio	$CaCO_2$ permeability	-4.97	-4.84	-4.80	-4.82	-4.82
	Intestinal absorption	Absorbed	Absorbed	Absorbed	Absorbed	Absorbed
	Skin permeability	-1.66	-1.42	-2.51	-2.51	-2.60
Distribution	VDss	1.15	1.14	1.27	1.24	1.25
	BBB permeability	Penetrable	Penetrable	Penetrable	Penetrable	Penetrable
	CNS permeability	-1.81	-1.77	-1.61	-1.56	-1.59
Metabolism	CYP2D6 substrate	No	No	No	No	No
	CYP3A4 substrate	No	No	No	No	No
	CYP2D6 inhibitor	No	No	No	No	No
	CYP3A4 inhibitor	Yes	Yes	Yes	Yes	Yes
Excretio	Total clearance	3.73	3.86	4.7	5.15	5.29
	Renal OCT2 substrate	No	No	No	No	No
	AMES Toxicity	Yes	Yes	Yes	Yes	Yes
Toxicity	Max. Tolerated dose	0.81	1.13	1.03	1.04	1.04
	hERG inhibitor	No	No	No	No	No
	Hepatoxicity	Yes	Yes	Yes	Yes	Yes
	Skin sensitization	Yes	Yes	Yes	Yes	Yes

The distribution characteristics of the fluoro-hydroxyxanthone derivatives further highlight their favorable pharmacokinetic potential. The predicted log VDss (volume of distribution at steady state) values (1.14–1.27), exceeding the established threshold of 0.45, indicate extensive tissue distribution and a strong propensity for extravascular partitioning. Additionally, all compounds were predicted to traverse the blood–brain barrier (BBB), with central nervous system (CNS) permeability values (–1.81 to –1.56) falling within the range indicative of moderate CNS access. This property may confer therapeutic relevance for hormone-dependent malignancies with a propensity for brain metastasis, although it simultaneously necessitates careful safety assessment concerning potential central neurotoxic effects.

The predicted metabolic profiles revealed that all fluoro-hydroxyxanthone derivatives are not substrates of the principal cytochrome P450 isoenzymes, namely CYP2D6 and CYP3A4. This observation implies a reduced likelihood of extensive hepatic biotransformation, thereby suggesting enhanced metabolic stability, a potentially prolonged elimination half-life, and improved systemic bioavailability. The excretion data further demonstrated that the total clearance values for these derivatives ranged from 3.73 to 5.29 $mL/min^{-}/kg^{-}$, indicative of a moderate elimination rate compatible with sustained plasma exposure. Moreover, none of the compounds were predicted to act as substrates of the renal Organic Cation Transporter 2 (OCT2), suggesting that their excretion is primarily mediated through passive renal filtration or hepatic metabolism rather than active renal secretion. This characteristic minimizes the risk of transporter-mediated nephrotoxicity and supports a favourable excretion profile consistent with drug-like pharmacokinetic behaviour.

The toxicity profiling indicated that none of the fluoro-hydroxyxanthone derivatives were predicted to inhibit the hERG potassium channel, thereby suggesting a low propensity for cardiotoxic effects. Conversely, all compounds tested positive in the AMES mutagenicity assay and exhibited hepatotoxic potential, implying possible genotoxic and hepatic safety concerns. These adverse predictions may be attributed to the presence of the conjugated aromatic xanthone core and the electron-withdrawing fluorine substituent, which together may promote the formation of reactive intermediates that can induce cellular damage. Furthermore, all derivatives were predicted to exhibit skin sensitization properties, underscoring the need for cautious evaluation of potential dermal exposure risks.

Overall, the fluoro-hydroxyxanthone derivatives display an advantageous balance between physicochemical and pharmacokinetic characteristics, complying with Lipinski's criteria and exhibiting satisfactory distribution and metabolic stability. Nevertheless, the consistent mutagenic and hepatotoxic predictions underscore the need for structural optimization. Strategic molecular modifications, such as repositioning the hydroxyl group or bioisosteric substitution of fluorine with less electron-withdrawing or sterically benign moieties, could mitigate these toxic liabilities while maintaining receptor-binding affinity. Consequently, these compounds should be viewed as initial scaffolds, backed by encouraging computational data, which necessitate further modification and in vitro confirmation before being considered as potential therapeutic options.

CONCLUSION

The molecular docking analysis of fluoro-hydroxyxanthone derivatives (X1–X10) against the ER-α protein demonstrated that compounds X6–X10 exhibited more moderate binding affinities (−7.44 to −7.32 kcal/mol) and lower inhibition constants (3.43 to 4.31 μM) compared to other analogs. These derivatives formed key hydrogen bond interactions with residues Glu353, Arg394, and Leu346, which are critical binding sites also involved in estradiol interaction, suggesting proper ligand orientation and potential biological relevance. Compounds X6–X10 showed strong ER-α binding and fulfilled key drug-likeness criteria. ADMET profiles suggest good absorption, distribution, and metabolic stability. However, predicted mutagenicity and hepatotoxicity require further investigation.

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AUTHOR CONTRIBUTION

FH: Conceptualization, Supervision, Investigation, Writing – review & editing, Validation, ADP: Writing – review & editing, Funding acquisition, RLW: Methodology, Visualization, NNSNMK: Methodology, Investigation, Formal analysis, EY: Methodology, Investigation

CONFLICT OF INTEREST

"None"

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