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MOLECULAR DOCKING STUDIES AND *IN-SILICO* ADME EVALUATION OF SOME HYBRID 2-QUINOLINONE DERIVATIVES CONTAINING CINNAMIC ACID AS ANTI-BREAST CANCER DRUGS

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ABSTRACT

Cancer has been classified as the second leading cause of death worldwide after cardiac arrest, and this has resulted in a series of studies by various scholars, both in experimental and theoretical science. While those in experimental science focus on synthesis and evaluation, the theoretical or computational scientist screens the synthesised and even unreported compounds against the targeted receptor. ***This study aimed at investigating the potential and mechanism of interaction, drug-likeness, and pharmacokinetics of five 2-quinolinone derivatives containing cinnamic acid as anti-breast cancer drugs through molecular docking and in-silico pharmacokinetic prediction. Molecular docking was carried out between the experimentally validated five 2-quinolinone derivatives (3-(7-hydroxy-4-methyl-2-oxo-2H-quinolin-1-ylamino)-3-phenyl acrylic acid (1), 3-(7-hydroxy-4-methyl-3,6,8-tribromo-2-oxo-2H-quinolin-1-ylamino)-3-phenyl acrylic acid (2), 3-(7-Acetoxy-4-methyl-3,6,8-tribromo-2-oxo-1H-quinolin-1-ylamino)-3-phenyl acrylic acid (3), 3-(7-(β-hydrazino, β-p-chlorophenyl-vinyloxy-4- methyl-2-oxo-1H-quinolin-1 -ylamino] -3-phenylacrylic acid hydrazide (4) and 2,2-(Diacetyl)-1-[β-(4-methyl-2-oxo-2H-quinolin-7-yloxy-β-(4-chlorophenyl)vinyl]-hydrazine (5)) against breast cancer cell line (MCF-7). The 2-quinolinone derivatives were optimised geometrically (DFT, B3LYP), after which they were***

docked with the targeted protease (protein data bank ID: 3ERT), and their pharmacokinetic properties were predicted as well. The co-crystallised ligand-protein of the protease was used as a standard to provide the basis for validation of the docking score, and for the interaction of amino acid residues involved in the interaction. The result of the molecular docking obtained using this method showed a docking score of (-24.9422, -28.713, -24.0162, -28.9148, and -29.3984 kcal/mol). The interactions with some significant amino acid residues demonstrated the success of the molecular docking interaction. Compounds 1 and 5 firmly adhere to all of Lipinski's rule's requirements, according to the pharmacokinetic predictions, and they also have outstanding GIA and bioavailability. Furthermore, 2-quinolinone derivative hybrids have the potential to be the lead compound for an efficacious ERα antagonist that might be used to treat breast cancer, in addition to providing insight into how the compound binds to the MCF-7 receptor.

Keywords: ADMET; Docking; 3ERT; 2-quinolinone; MCF-7

INTRODUCTION

Cancer is the rapid proliferation of abnormal cells that have the tendency to invade other body parts, resulting in high mortality rates [1, 2]. It has recently been reported that about 10 million people died from cancer worldwide in 2020 [3], with a projected increase of about 16.4 casualties by 2040 [4]. Breast cancer is among the most common cancers, accounting for about thirty to fifty percent of the incidence of cancer-related death, along with other cancers such as lung and colon cancers [5].

The available treatment options for cancer include surgery, chemotherapy, radiotherapy, and treatments involving the use of hormones. [5]. These treatment options still pose some threats, such as dose-related toxicity and selectivity, in their applications [5–6]. Hence, it is necessary to explore or develop effective treatment options to mitigate these challenges [6–7]. It has been reported that 70% of breast cancers express the estrogen receptor (ER) [8]. It is possible to target breast cancer that is estrogen receptor-positive by preventing the receptors from functioning, either by preventing the generation of estrogen with aromatase inhibitors or the process via which specialised modulators of oestrogen receptors bind to oestrogen [8]. Within the nuclear receptor family, there are two subtypes of oestrogen receptors: beta (ERβ) and alpha (ERα) (ERβ). The most significant predictors of the prognosis of breast cancer are ERα receptors, which are expressed in 75 percent of cases of these two subcategories [8].

Several authors have reported a significant number of quinolinone derivatives exhibiting potent antiproliferative activity and inducing apoptosis in most cancer cell lines [9–11]. Bakare [11] only reported the synthesis and evaluation of the compounds as potential anticancer agents against MCF-7 cell lines. There is no report in her paper on the possible mechanism of action of these compounds against the receptor.

To explore new bioactive molecules targeting breast cancer, this study involved molecular docking studies and *in silico* ADMET/pharmacokinetic evaluation of some quinolones. Since quinolinone derivatives have been used to treat many different forms of cancer, including breast cancer [9–11].

A recent area of study in cancer research is the development of anticancer medications using both natural and synthetic materials. Numerous methods are used to assess the medications' potential, including calculation, in *vivo,* and in vitro methods. Molecular docking has been extensively utilised in the prediction and development of cancer therapies [9–11].

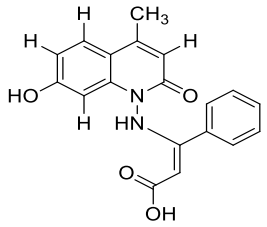
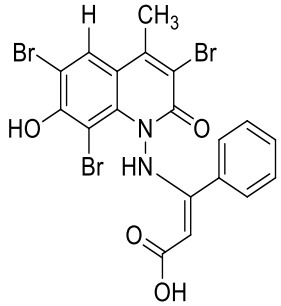
Recently developed computational approaches to drug discovery (such as molecular docking and QSAR) have the advantage of prompt identification of some promising anti-cancer therapies, which may open the door to the development of highly effective medications at affordable prices [12]. There have been reports of the use of such techniques producing favourable results in the development of MCF-7 inhibitors for breast cancer [13]. Furthermore, the utilisation of in silico techniques can serve as a useful supplement to current in vitro biological activity methodologies, hence expediting drug development and circumventing the time, expense, and inconvenience associated with animal testing [13].

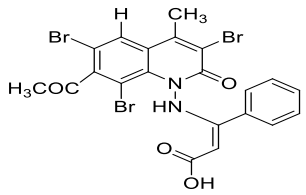
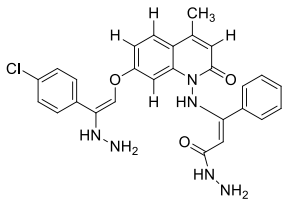
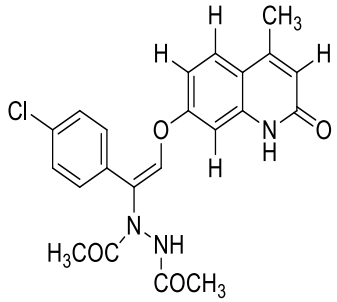
METHODS

Experimental data set

In this study, a set of five recently synthesised hybrid 2-quinolinone derivatives containing cinnamic acid [11] (3-(7-hydroxy-4-methyl-2-oxo-2H-quinolin-1-ylamino)-3-phenyl acrylic acid **(1),** 3-(7-hydroxy-4-methyl-3,6,8-tribromo-2-oxo-2H-quinolin-1-ylamino)-3-phenyl acrylic acid (**2**), 3-(7-Acetoxy-4-methyl-3,6,8-tribromo-2-oxo-1H-quinolin-1-ylamino)-3-phenyl acrylic acid **(3),** 3-(7-(β-hydrazino, β-p-chlorophenyl-vinyloxy-4-methyl-2-oxo-1H-quinolin-1-ylamino]-3-phenylacrylic acid hydrazide (4) and 2,2-(Diacetyl)-1-[β-(4-methyl-2-oxo-2H-quinolin-7-yloxy-β-(4-chlorophenyl)vinyl]-hydrazine (**5**)) [11] were used as anti-breast cancer drugs that targeted the MCF-7 human breast cancer cell line. Their chemical structures (2-dimensional structures) were sketched using the ChemDraw Ultra v.11.0 software [14]. Table 1 displays the sketched structures together with their IUPAC names and experimental biological anti-cancer activity (IC_{50} (M)/MCF-7) values [11].

Table 1: 2D drawn structures of compounds 1, 2, 3, 4, 5

ID	2D Structure	IUPAC Name	IC_{50} (μM)/MCF-7 [11]
1		(Z)-3-((7-hydroxy-4-methyl-2-oxoquinolin-1(2H)-yl)amino)-3-phenylacrylic acid	3.02±0.17
2		(Z)-3-phenyl-3-((3,6,8-tribromo-7-hydroxy-4-methyl-2-oxoquinolin-1(2H)-yl)amino)acrylic acid	3.83±0.21

3		(Z)-3-((7-acetyl-3,6,8-tribromo-4-methyl-2-oxoquinolin-1(2H)-yl)amino)-3-phenylacrylic acid	>100
4		(Z)-3-((7-(((E)-2-(4-chlorophenyl)-2-hydrazinylvinyl)oxy)-4-methyl-2-oxoquinolin-1(2H)-yl)amino)-3-phenylacrylohydrazide	36.32±0.31
5		(E)-N'-acetyl-N-(1-(4-chlorophenyl)-2-((4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)oxy)vinyl)acetohydrazide	63.39±0.28

Computational/ theoretical process

Structure geometry optimization of the compounds

In order to get the optimal conformation, energy minimization was applied to the compounds' derived 2-dementional structure [14]. The procedures and techniques used have been previously discussed [14].

Ligand/target pre-docking preparation

This study used the Molecular Docking Assay ER (protein data bank ID: 3ERT) to test compounds for efficacy against breast cancer cells. The PDB-formatted 3-dimensional structures were collected from the RSCB Protein Data Bank at https://www.rcsb.org/. Doxorubicin was compared to the selected compounds, which were employed as positive control ligands. Using the Biovia Discovery Studio programme, the compounds' 3D structures were modelled [14, 15].

Molecular Docking Simulations using ICM-Molsoft

In order to evaluate the binding mechanism and affinity between the ligand and receptor, we successfully finished the molecular docking calculation with the aid of ICM-Molsoft (http://www.molsoft.com/servers.html) [16]. The docking calculations were performed using Discovery Studio 2017 to visualise the binding interaction mode and to construct the protease [15]. The process of optimising and preparing proteases as well as the mechanism of compound-protease docking have both been described in the literature [17].

After the docking runs were successfully finished, the alternative conformations of the complexes and the associated docking scores (kcal/mol) were determined. As the optimal posture, it was determined to be the stable conformation with the maximum negative binding score [17]. It was possible to view how the ligand-protein complexes interacted using the Discovery Studio Visualizer programme [15].

ADME Evaluation

It is vital to evaluate the potential drug candidates' metabolism in order to avoid any potential hazards. In this, Lipinski's rule of five is used to define some parameters that regulate both the drug-likeness and pharmacokinetic investigations. The ADME and pharmacokinetics of the compounds were predicted with a free online tool called SwissADME. The method involved converting the optimised structure to sdf format and importing it into the interface, which was then converted to its respective SMILE and subsequently displayed the predicted property **[**18].

The study's findings are shown in Table 1, along with the binding energy (kcal/mol), number of flexible bonds (Nflx), hydrogen bond energy (Hbnd), and hydrophobic bond energy (Hphb). To assess each compound's potential as a breast cancer inhibitor, it was docked with the breast cancer protease crystal structure. The compounds were assigned scores based on the weighed factor of the ICM scoring function [17]. The smaller the ICM score value, the more likely it is that the compound is an inhibitor. Where Evw., Eel., Ehp., and Esf. are van der Waals, electrostatic, hydrogen bonding, and non-polar and polar atom solvation energy changes between complexed and uncomplexed states, respectively; Eint. is the compound internal strain [17].

RESULTS AND DISCUSSION

Docking Simulation

Figure 1 represents the 3D docking mode of the co-crystalized native ligand of the target protease (PDB entry: 3ERT). The results of the docking showing various interaction energy terms for compounds (1, 2, 3, 4, and 5) are presented in Table 2. The 2D interaction with the active site amino acid of the receptor is shown in Figures 2a–2f **(**compounds 1, 2, 3, 4, and 5, with the target protease (PDB entry: 3ERT)**.**

The docking results presented in Tables 2 and 3 as well as Figures 2 and 3 provide the docking score, nature of interactions with associated amino acid residues of the active site of the receptor, 2D interaction of the standard inhibitor, and the studied compounds, respectively. The study's findings are shown in Table 2, along with the binding energy (kcal/mol), number of flexible bonds (Nflx), hydrogen bond energy (Hbnd), and hydrophobic bond energy (Hphb). To assess each compound's potential as a breast cancer inhibitor, it was docked with the breast cancer protease crystal structure. The compounds were assigned scores based on the weighed factor of the ICM scoring function [17]. The smaller the ICM score value, the more likely it is that the compound is an inhibitor. Where Evw., Eel., Ehp., and Esf. are van der Waals, electrostatic, hydrogen bonding,

and non-polar and polar atom solvation energy changes between complexed and uncomplexed states, respectively; Eint. is the compound internal strain [17].
The obtained binding scores of compounds 1, 2, 3, 4, and 5 are shown to be -24.9422 kcal/mol, -28.713 kcal/mol, -24.0162 kcal/mol, -28.9148 kcal/mol, -29.3984 kcal/mol, and -25.8929 kcal/mol, respectively, with excellent hydrogen bond energies of -4.65021 kcal/mol, -4.32363 kcal/mol, -1.9697 kcal/mol, -5.19065 kcal/mol, -1.03562 kcal/mol, and -2.2 kcal/mol (Table 2).

It could be seen that the binding scores for compounds 1, 2, 3, 4, 5, and co-crystallized ligand are in the order of 5 (-29.3984 kcal/mol) > 4 (-28.9148 kcal/mol) > 2 (-28.713 kcal/mol) co-crystallized ligand (25 kcal/mol) > 1 (-24.9422 kcal/mol) > 3 (-24.0162 kcal/mol), which is the measure of the stability of their interaction with the receptor [17].

Compounds 1, 2, 3, 4, and 5 were all shown to form Conventional Hydrogen Bonds (C-H-Bos) with some important amino acid residues of the active site of the receptor (CYS530, THR347, ASP351), (CYS530, MET528, THR347), (CYS530, MET528, THR347, CYS530, MET528), (LEU536, CYS530, MET522), and (THR347). Other forms of interactions observed with the receptor include hydrophobic and electrostatic interactions, which account for the stability of the docked compounds with the receptor. There were also similar amino acid residues of these compounds with those of the co-crystal structure of the cancer receptor (PDB ID: 3ERT) active side (Figures 1and 2), which entails the good therapeutic potential of the studied compounds against breast cancer cells [8].

Table 2: Molecular docking score using **ICM-Molsoft** software package and associated energy terms of the interaction of compounds 1, 2, 3, 4, 5 and Doxorubicin

Comp ID	Score	Natom	Nflex	Hbond	Hphob	Vwlnt	Eintl	Dsolv	SolEl	mfScore
3	-24.9422	41	2	-4.65021	-6.08933	-20.8268	3.86182	11.324	3.08556	-56.2928
4	-28.713	41	2	-4.32363	-7.45396	-25.6258	10.0116	10.0878	6.18173	-101.622
7	-24.0162	45	2	-1.9697	-7.86092	-25.0138	9.77748	10.2457	3.58106	-83.1256
9	-28.9148	62	4	-5.19065	-8.27973	-35.419	5.41982	20.3872	11.3539	-78.4237
10	-29.3984	50	2	-1.03562	-8.83521	-37.6636	6.75285	11.5116	10.5625	-137.101
Co-crystal ligand	-25.19	58	5	-2.2	-10.03	-28.96	9.003	9.407	9.098	-11.98

Nflx =Number of flexible bonds, Hbnd =hydrogen bond energy, Hphb= hydrophobic bond energy, Evw= van der Waals, Eel= electrostatic, Ehb = hydrogen bonding, Esf= non-polar and polar atom solvation energy changes, Eint. = internal strain.

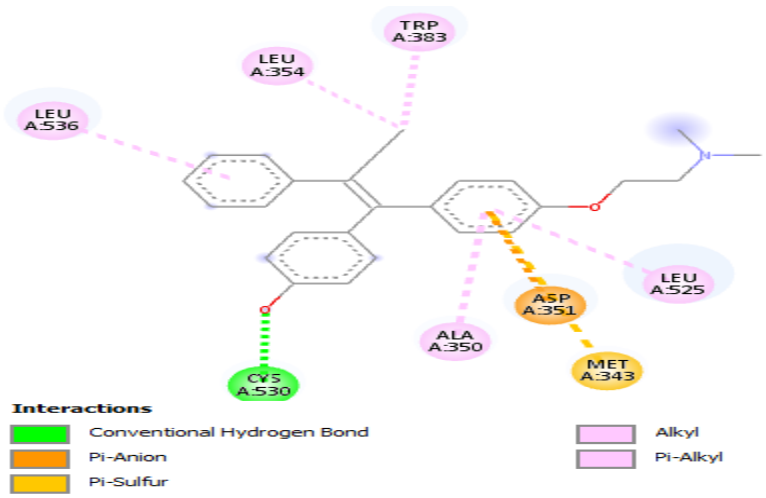


Figure 1: Co-crystal structure of the cancer receptor 4-hydroxytamoxifen (OHT) (PDB ID: 3ERT)

Table 3: The binding interactions of the anti-cancer drugs and standard anti-cancer inhibitor with the target (PDB code: 3ERT)

Compound ID	Amino acid Residue	Interaction Distance (Å)	Type	(ΔG) Binding energy (kcal/mol)
1	CYS530	1.75164	C-H-Bo	
	THR347	2.04909	C-H-Bo	
	RES1:H5 - RES1:O3	2.07233	C-H-Bo	
	ASP351	2.85633	C-H-Bo	
	LYS529	2.52321	Carbon Hydrogen Bond	
	: RES1 - :RES1	4.18801	Π-Π T-shaped	
	VAL533	4.12644	Alkyl	-24.9422
	VAL533	5.3384	Π-Alkyl	
	LEU536	5.00365	Π-Alkyl	
	CYS530	5.26884	Π-Alkyl	
	VAL533	4.31804	Π-Alkyl	
	LEU525	4.50501	Π-Alkyl	
	CYS530	2.20639	C-H-Bo	
2	MET528	2.74607	C-H-Bo	
	:RES1:H2 -RES1:O3	2.06414	C-H-Bo	
	THR347	2.31987	C-H-Bo	-28.713

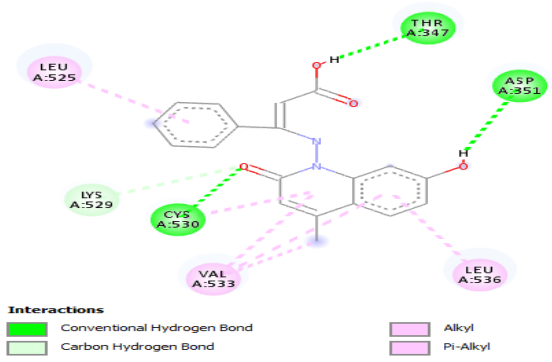
	LYS529	2.43688	Carbon Hydrogen Bond	
	RES1:O3 -RES1:BR3	3.32803	Halogen (Cl, Br, I)	
	ASP351	3.32204	Π-Anion	
	MET522	5.44838	Π-Sulfur	
	RES1 - RES1	4.26491	Π-Π T-shaped	
	ALA350	3.46143	Alkyl	
	ALA350	3.92421	Alkyl	
	LEU525	4.81146	Alkyl	
	MET528	5.34155	Alkyl	
	LEU354	4.49319	Alkyl	
	TRP383	4.07833	Π-Alkyl	
	ALA350	5.2591	Π-Alkyl	
	ALA350	4.15079	Π-Alkyl	
	LEU525	4.92307	Π-Alkyl	
	LEU525	5.42571	Π-Alkyl	
	LEU536	5.39245	Π-Alkyl	
	CYS530	2.20639	C-H-Bo	
3	MET528	2.74607	C-H-Bo	
	RES1:H2 - :RES1:O3	2.06414	C-H-Bo	
	THR347	2.31987	C-H-Bo	
	LYS529	2.43688	Carbon Hydrogen Bond	-24.0162
	CYS530	1.70308	C-H-Bo	
	MET528	2.21474	C-H-Bo	
	RES1:H2 - :RES1:O2	1.92456	C-H-Bo	
	RES1 - :RES1	4.3985	Π-Π Stacked	
	LEU354	4.97095	Alkyl	
	LEU536	4.59769	Alkyl	
	LEU525	3.99866	Alkyl	
	MET522	5.19232	Alkyl	
	LEU536	4.35494	Alkyl	
	TRP383	4.1157	Π-Alkyl	

	TRP383	5.19625	Π-Alkyl	
	ATRP383	3.1776	Π-Alkyl	
	LEU525	5.21793	Π-Alkyl	
	LEU525	5.10182	Π-Alkyl	
	LEU536	5.4489	Π-Alkyl	
	VAL533	4.2062	Π-Alkyl	
	LEU536	2.63989	C-H-Bo	
4	CYS530	2.34182	C-H-Bo	
	MET522	3.01483	C-H-Bo	-28.9148
	MET522	2.49181	C-H-Bo	
	RES1:H5 - :RES1:O2	1.91108	C-H-Bo	
	LEU536	3.19338	Π-Donor Hydrogen Bond	
	CYS530	5.69542	Π-Sulfur	
	TRP383	5.28117	Π-Π T-shaped	
	LEU354	5.00438	Alkyl	
	LEU539	5.17309	Alkyl	
	LEU536	4.19305	Π-Alkyl	
	LEU536	5.01204	Π-Alkyl	
	LEU525	5.31996	Π-Alkyl	
	MET528	5.4701	Π-Alkyl	
	PRO535	5.25386	Π-Alkyl	
	THR347	2.44492	C-H-Bo	
5	GLY420	2.9798	Halogen (Cl, Br, I)	
	ASP351	4.60733	Π-Anion	
	MET343	5.39057	Π-Sulfur	
	MET421	5.42894	Π-Sulfur	
	LEU346:C,O;THR347	4.85068	Amide-Π Stacked	
	ILE424	5.11445	Alkyl	
	TRP383	4.65041	Π-Alkyl	-29.3984
	HIE524	4.44567	Π-Alkyl	

	ALA350	4.01243	Π-Alkyl	
	LEU525	4.54745	Π-Alkyl	
	LEU525	4.94853	Π-Alkyl	
	LEU525	5.03431	Π-Alkyl	
Co-crystal ligand 4-hydroxytamoxifen (OHT)	CYS530	2.00332	C-H-Bo	
	ASP351	4.99885	Π-Anion	
	MET343	5.71934	Π-Sulfur	
	LEU354	4.54269	Alkyl	
	TRP383	4.69586	Π-Alkyl	-25.
	TRP383	3.73011	Π-Alkyl	
	ALA350	4.46214	Π-Alkyl	
	LEU525	4.41901	Π-Alkyl	
	LEU536	4.4912	Π-Alkyl	

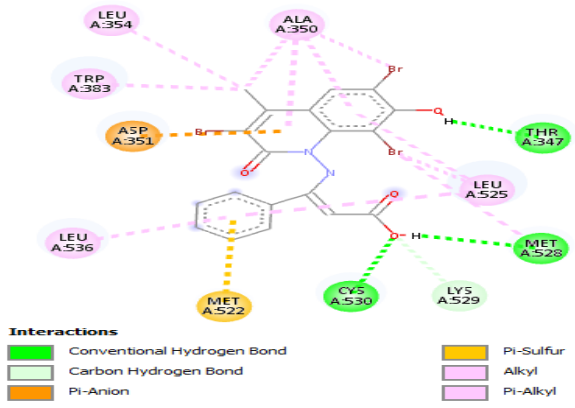
C-H-Bo

(a)



Compound 1

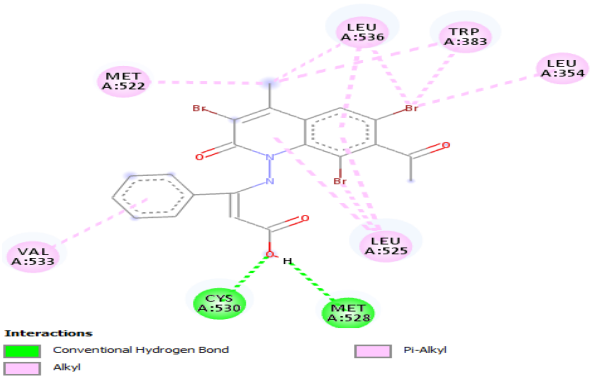
(b)



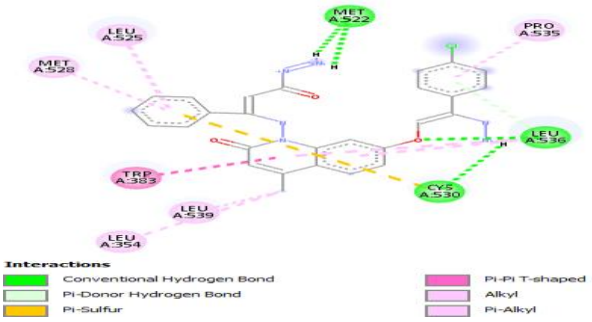
Compound 2

(d)

(c)



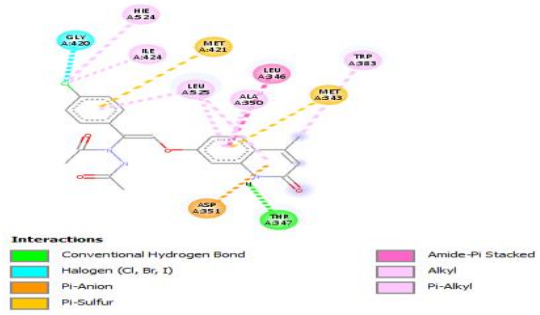
Compound 3



Compound 4

(e)

(f)



Compound 5

Figure 2: 2D binding interactions between the compounds 1, 2, 3, 4 and 5 with the target protease (PDB entry: 3ERT)

Drug-likeness/pharmacokinetics/ADME profile

The drug-likeness, pharmacokinetics, and ADME are presented in Table 4 and Figures 3 and 4, respectively. Table 4 displays the projected pharmacokinetic parameter outcome. Based on the compounds' lower molecular weight, consensus log of less than five, topological polar surface area of less than 140, and hydrogen-bond donors and acceptors of less than five and ten, respectively, Lipinski's factors for oral bioavailability were predicted to be met completely by compounds 1 and 5, while compound 4 violated only one, with compounds 2 and 3 violating two rules, which can still be considered as bioavailable [19]. According to Table 4 [20], these compounds' scores demonstrate that they all have good drug-likeness and an acceptable bioavailability score, indicating that they do not violate the Lipinski's completely. A radar of compounds' bioavailability is depicted in Figure 3. A primary scan of a compound's drug-likeness is provided by the bioavailability radar. The results displayed in Figures 3a-e indicate that every compound passed the drug-likeliness assessment.

The other ADME parameters presented in Table 4 include the blood-brain barrier (BBB) permeant, gastrointestinal absorption (GIA), the five cytochrome P450 enzymes (CYP1-A2, CYP2-C19, CYP2-C9, CYP2D6, and CYP3-A4), and P-glycoprotein (P-gp) substrates. The (BBB) permeant

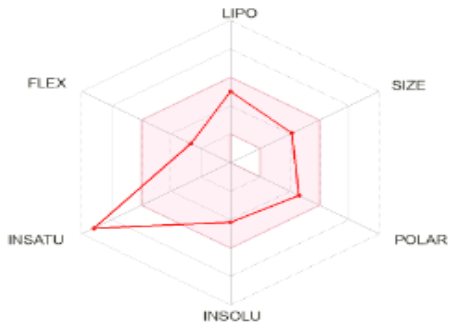
attribute was not found among the compounds and was shown to be a non-substrate of (P-gp) (Table 4 and Figure 4). The compounds all exhibited high GIA, with the exception of compound 4, which had a low GIA. The effect of the compounds on the important five cytochrome P450 enzymes (CYP1-A2, CYP2-C19, CYP2-C9, CYP2-D6, and CYP3-A4) presented in Table 4 also revealed compounds 1 and 4 as non-inhibitors of all five enzymes. Compound 2 is shown to inhibit two of the enzymes (CYP1A2 and CYP2C9), while compound 3 inhibits three (CYP1-A2, CYP2-C19, and CYP2-C9). More so, compound 5 is shown to be an inhibitor of CYP2-C19, CYP2-C9, and CYP3-A4 [21].

As presented in Table 4, there was no PAIN alert indication for the investigated compounds; such an outcome entails the true biological activity of a particular compound irrespective of the targeted protease, i.e., the absence of false biological activity [22][23].

Table 4: Pharmacokinetics/ADME predictions of the compounds (**1, 2, 3, 4 and 5)**

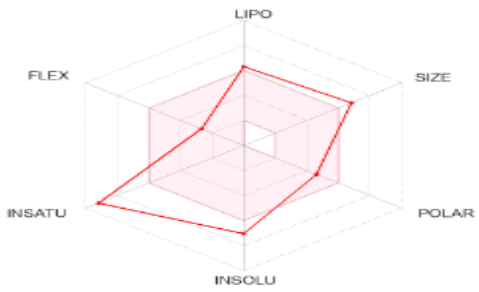
S/N	MW	#H-bond acceptors	#H-bond donors	TPSA	Consensus Log P	GI absorption	BBB permeant	Pgp substrate	CYP1-A2 inhibitor	CYP2-C19 inhibitor	CYP2-C9 inhibitor	CYP2-D6 inhibitor	CYP3-A4 inhibitor	Liπnski #violations	Bioavailability Score	PAINS #alerts	Synthetic Accessibility
1	336.34	4	3	91.56	2.51	High	No	No	No	No	No	No	No	0	0.56	0	2.92
2	573.03	4	3	91.56	4.32	High	No	No	Yes	No	Yes	No	No	2	0.56	0	3.09
3	599.07	4	2	88.4	4.64	High	No	No	Yes	Yes	Yes	No	No	2	0.56	0	3.25
4	516.98	5	5	136.43	3.09	Low	No	No	No	No	No	No	No	1	0.55	0	3.93
5	425.86	4	2	91.5	3.17	High	No	No	No	Yes	Yes	No	Yes	0	0.55	0	3.28

(a)



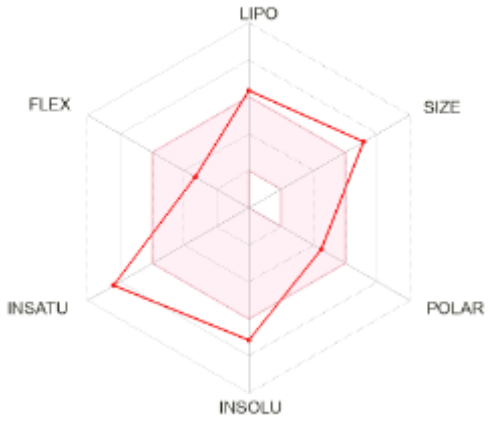
Compound 1

(b)



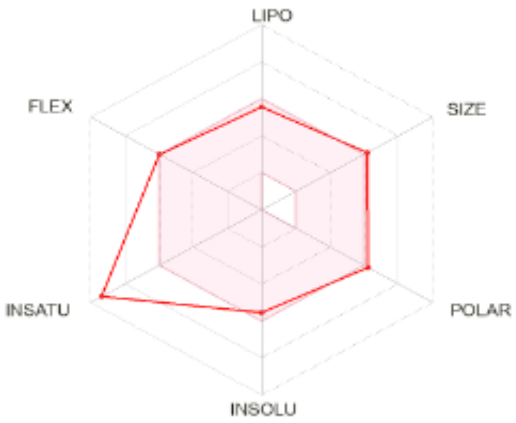
Compound 2

(c)



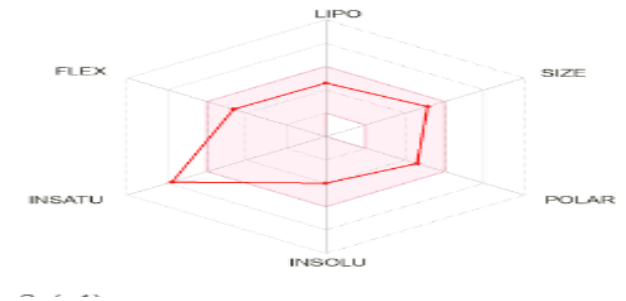
Compound 3

(d)



Compound 4

(e)



Compound 5

Figure 3: Bioavailability radar of compounds 1, 2, 3, 4 and 5

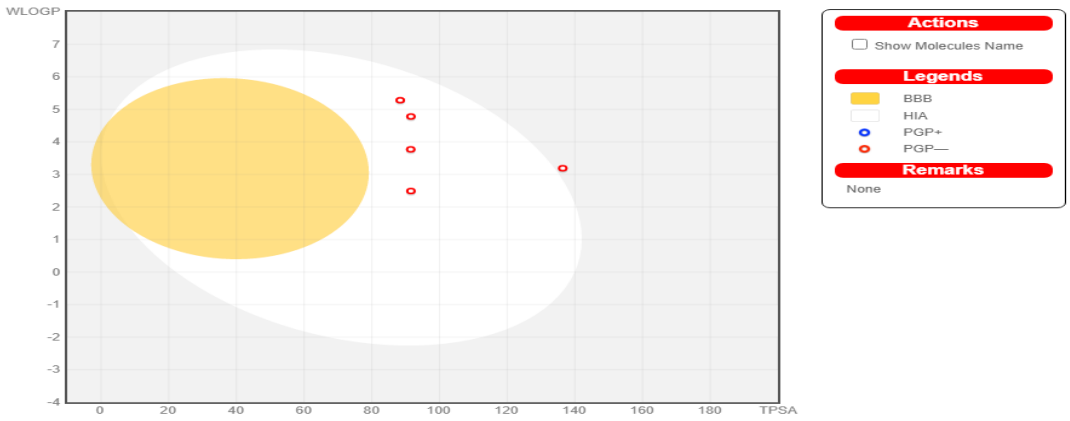


Figure 4: BOILED-Egg for compounds 1, 2, 3, 4, and 5

Conclusions

The pharmaceutical industry has developed a keen interest in the use of computational technologies for drug development because of their affordability and effectiveness. The studied five 2-quinolinone derivatives (1, 2, 3, 4 and 5) showed strong bond-free energy (-24.9422, -28.713, -24.0162, -28.9148 and -29.3984 kcal/mol), respectively to ERα, while had -25.19 kcal/mol. In addition, the docking analysis confirmed that both hybrid 2-quinolinone derivatives containing cinnamic acid have the potential to inhibit ERα (3ERT), respectively, through hydrophobic and hydrogen bond interactions. Overall, it can be concluded that the five 2-quinolinone derivatives have more potential to be better drug candidate for further preclinical studies *in-vivo* using animal models with good pharmacokinetics.

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