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MOLECULAR DOCKING VIRTUAL SCREENING, DRUG-LIKENESS AND PHARMACOKINETICS (ADMET) PROPERTIES PREDICTION OF SOME ENDOMETRIAL CANCER AGENTS

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ABSTRACT
Endometrial or uterine cancer is a malignancy arising from the endometrium of the uterus. Women have a 1 in 40 life-time risk of being diagnosed with endometrial cancer, the fourth most common malig¬nancy among women. Endometrial cancer is the most common gynecological malignancy in the developed world. The binding mode of some endometrial cancer agents in the active site of human estrogen receptor (PDB1*1P) (receptor) was studied via molecular docking. Molecule 6 was identified to have the highest binding energy of -10.1 kcal/mol among other selected compounds which might be as a result of hydrogen bond interactions formed with ASP480 amino acid residues and hydrophobic/other interactions formed with LEU508, LEU479 and ILE451 amino acid residues in the active site of the receptor. The drug-likeness properties of these selected endometrial cancer agents were predicted following the Lipinski's rule of five and were found to be orally active and bioavailable as they obeyed the used filtering criterion. Based on the pharmacokinetic properties predicted, they were seen to have good ADMET properties. This research proposed a way for designing potent endometrial cancer agents against their target enzyme (human estrogen receptor).

Keywords: Endometrial cancer, estrogen receptor, Lipinski's rule, malignancy

INTRODUCTION

Cancer is a chronic abnormal cell disorder or a lethal disease demonstrates by immortality and unrestricted cell division. Cancer cells may be invasive, aggressive and metastatic and generally spread into various organs in the body (Jemal et al., 2011).

Endometrial or uterine cancer is a malignancy arising from the endometrium of the uterus. Women have 1 in 40 lifetime risk of being diagnosed with endometrial cancer, the fourth most common malig¬nancy among women (Barr et al., 2016). Uterine cancer is the most common gynecologic malignancy in the United State. Stage I malignancies comprises the majority of endometrial cancers. Postmenopausal bleeding is the most common presentation (Boggess et al., 2008).

Endometrial cancer is the most common gynecological malignancy in the developed world. The majority of cases can be divided into two broad categories based on clinic-pathological and molecular characteristics; Type I oestrogen-dependent with endometrioid morphology and Type II non-estrogen-dependent with serous papillary or clear cell morphology (Llauradó et al., 2012).

The concept of computational chemistry like computer-aided drug design (CADD) might save the time of discovering or designing new compounds with better potency, and also reduce the cost of synthesis. Molecular docking virtual simulation is very important when carrying out a structure-based drug design (SBDD) which predicts the binding affinities an orientation when two molecules bind with each other to form a stable complex (Ibrahim et al., 2021).

Molecular docking is one of the most frequently used methods in structure-based drug design, due to its ability to predict the binding conformation of the small molecules to the appropriate target binding site (Ferreira et al., 2015). Characterization of the binding behavior plays an important role in the rational design of drugs as well as elucidating the fundamental biochemical processes. Molecular docking in the pharmaceutical industry is powerful in silico approach for discovering of novel therapies for unmet medical needs predicting drug-target interactions, it provides binding affinity between drugs and target at the atomic level and elucidates the fundamental pharmacological properties of a specific drug (Shadrack et al., 2018).

Drug-likeness properties give the conditions or criteria for a drug potency of a particular chemical compound. include the use of Lipinski's rule of five to predict the drug-likeness of the selected drugs, which states that if any chemical violates more than two of these criteria (Molecular weight $\leq$ 500g/mol, Number of hydrogen bond donor $\leq$ 5, Number of hydrogen bond acceptors $\leq$ 10, calculated Log P $\leq$ 5 and the molecule are said to be impermeable or badly absorbed (Li et al., 2019; Lipinski, 2004).

The ADMET properties also known as pharmacokinetics properties describe the fate of a small molecule (drug/ligand) in the body of a living organism. The acronym stands for absorption, distribution, metabolism excretion and toxicity (ADMET) (Olasupo et al., 2020).

The aim of this study is to virtually screen and predict the pharmacokinetics properties of some endometrial cancer inhibitors.

MATERIAL AND METHODS

Software and computational environment

A HP655-PC computer system with the following specification: AMD E1- 1200 APU with Radeon at 1.40GHz, 4GB of RAM was utilized to explore the nature of interactions between the active site of estrogen and the compounds under investigation (ligands) with the help of Pyrex virtual screening software, Chimera and Discovery studio.

Data collection

Twenty-two (22) sets of endometrial cancer agents were gotten from the literature and used in this work.

Structure generation, stable geometry calculations and ligand preparation

In this work, the 2D structures of the dataset were drawn using Chemdraw 12.0 software. After generation of the 2D structure of the studied molecules, the 2D structures were automatically converted to 3D by the Spartan 14 software before energy minimization. Energy minimization was carried out to reduce constraints in the structures before finding the most stable geometry of the studied molecules. The most stable geometry of the studied molecules was ascertained using density functional theory (DFT) at B3LYP/6-311G* level of theory. Ligands were prepared before the docking analysis from the optimized structure of the drugs and saved in pdb file format using Spartan 14 (Ibrahim et al., 2020a).

Protein retrieval and preparation

The 3D structure of the receptor was retrieved from the RCSB pdb database. The enzyme was prepared with the help of a discovery studio visualizer for the docking analysis. In the course of its preparation, polar hydrogen was added. Water molecule and co-ligands were eliminated from the crystals structure and saved in pdb file format (Abdullahi et al., 2020).

Docking based virtual screening analysis

The docking of the ligands to the binding pose of the enzyme was achieved with the help of Autodock vina of Pyrex virtual screening software. After a successful docking procedure, since Pyrex was used there is a need to re-couple the docked ligand and the receptor for further investigation (Ibrahim et al., 2020b). UCSF Chimera software was used for the re-coupling of the docked ligand and the receptor. Discovery studio was used to achieve the visualization of recoupled complexes in order to view the nature of the interaction between the ligand and the receptor (Ibrahim et al., 2019).

ADMET and drug-likeness properties prediction

The pharmacokinetics (ADMET) properties and the drug-likeness of the studied compounds were predicted using pkCSM (http://structure.bioc.cam.ac.uk/pkCSM) and SwissADME (http://www.swissadme.ch/index.php) a free web tool used in evaluating ADMET properties and drug-likeness of small molecules (Daina et al., 2017; Ibrahim et al., 2020c).

RESULTS AND DISCUSSION

Molecular docking

The nature of the interactions between some endometrial cancer agents and the active site of human estrogen receptor alpha (PDB ID 1*1P) was studied using molecular docking. Table 1 shows the binding affinities and mode of interaction of the studied molecules. The binding affinities of the studied molecules range from -3.3 Kcal/mol to -10.1 Kcal/mol, respectively. From the result of the docking virtual screening (Table 1), molecule 6 was identified to have the highest binding affinity of -10.1 Kcal/mol among the other selected compounds followed by molecule 19 with the binding affinity of -9.0 Kcal/mol, molecule 17 with a binding affinity of -8.8 Kcal/mol, molecule 2 with a binding affinity of -8.1 Kcal/mol and molecule 4 having the lowest binding affinity of -3.3 Kcal/mol among the studied molecules.

Table 1: Binding affinities and nature of the interaction of the studied molecules and estrogen receptor.

S/N	Binding Energy	Conventional Hydrogen Bond	Carbon Hydrogen Bond	Hydrophobic and other interactions
1	-7.6	ASP351	LEU384, LEU346, TRP383 LEU349, THR 347, GLU 353, HIS 524, LYS 531, LEU 428, MET 343, MET421	LEU 387, LEU 391, MET 388, LEU 525, ALA 350,
2	-8.1	LEU409 and GLN414	LEU 408, LEU 410, TYR 331, ASN 407, PRO 333, LYS 408	PHE 337, PHE 425, CYS 530, ILE 424, PHE 404
3	-7.7	MET343, ASP 351	LEU 428, LEU 536, LEU 346, LEU 354, ILE 424, ARG 394, LYS 531, THR 347, GLU 353	LEU 525, LEU 391, MET 388, LEU 387, LEU 384, ALA 350, CYS 530
4	-3.3	CYS381	LEU 525, ARG 515, GLU 380, GLU 523, ASN 519, TYR 526, TRP 383, ASN 532, LYS 531, LEU 536	MET 522
5	-7.5	LEU387 & LEU346	LEU 384, LEU 391, LEU 349, LEU 525, PHE 404, THR347, ALA 350, MET 388	GLU 353
6	-10.1	ASP480	ASN 455, HIS 476, THR 483, LEU 504, LEU 509	LEU 508, LEU 479, ILE 451
7	-7.1	LYS 531 and CYS 530	LEU 387, LEU 354, LEU 384, LEU 428, MET 388, MET 421, MET 343, PHE 404, PHE 425, ILE 424, HIS 524, TRP 383, LEU 539, THR 347	ALA 350, LEU 346, LEU 536 & ASP 536
8	-7.0	ASN 407	LEU 408, LEU 409, LEU 410, PRO 336, ARG 335, PRO 333, THR 334, TYR 331, GLN 414	PHE 337
9	-7.4	LEU:387 and GLU:353	PHE 404, PHE 425, LEU 525, LEU 346, LEU 384, THR 347, LEU 428, MET 388, MET 343, TRP 383,	ALA 350, LEU 391 CYS 530
10	-7.9	ARG 394	PHE 404, PHE 425, LEU 525, LEU 346, LEU 384, THR 347, LEU 428, MET 388, MET 343, TRP 383, CYS 530	TRP 383, LEU 354, LEU 536

11	-7.3	LEU 320, VAL 446, GLY 442, LYS 449	LEU 384, LEU 349, PHE 425, MET 421, MET 343, MET 388, TRP 383, THR 347, ILE 424, HIS 524, GLU 353, ARG 394, CYS 530	LEU 391, ALA 350, LEU 525, LEU 346, LEU 349, LEU 387
12	-7.9	PRO 324, PRO 325, GLY 390, PHE 445,	LEU 525, LEU 346, LEU 384,LEU 349, ASP 351, MET 388, ME T 343, THR 347, LYS 531, TRP 383 ASN 455, ILE 451,	ILE 326 & GLU 323
13	-3.4	LEU 387, ARG 394, GLU 353	ILE 452, ILE 514, SER 512, GLU 385ILE 452, SER 456, ASN 455, THR 483, GLU 385, HIS 516, LEU 509, HIS 476, TYR 459	LEU 391, ALA 350, CYS 530
14	-7.9	LEU 511, ARG 515, SER 456	ARG 515, THR 483, ASP 480, HIS 476, LEU 509, SER 512 LEU 428, LEU 346, LEU 387, LEU 391,	PHE 404, MET 388, ME T 343, ALA 350, PHE 425, MET 421
15	-7.1	SER 512, ARG 515	LEU 428, LEU 384, LEU 387, PHE 425, MET 388, GLY 521, THR 347, CYS 530	LEU 479, LEU 508, ILE 451
16	-3.9	ASN 455	TYR 526, ASN 532, ILE 424	ILE 451, LEU 508, LEU 479, LEU 511 & MET 522
17	-8.8	GLU 353, ARG 394	HIS 398, SER 395, MET 396, PRO 325, PRO 406, ARG 394	LEU 384, LEU 525, ILE 424 THR 347,
18	-7.6	PRO 324, GLU 397, TRP 393, GLU 323	LEU 539, LEU 346, LEU 354, LEU 428, LEU 384,	PHE 404, LEU 525, ALA 350, LEU 346, LEU 536
19	-9.0	LEU 346	ARG 548, ASP 545, ARG 363	ILE 326, LEU 403, LYS 531, ASN532, ASP351, PRO535, VAL533,
20	-7.2	GLN 375, LYS 362	MET:522, LEU 536, LYS 531, GLU 523, SER 518, ASN 519, GLU 380, CYS 381	LEU391, LEU525, LEU387, MET388, ALA 350, MET421, ILE424, PHE425 LEU544 CYS530
21	-7.7	ASN 532	TYR526 LEU525, THR347, LEU525, LEU354,	VAL368, ALA546, LEU 372, LEU372, LEU345
22	-6.5	ASN 532	MET522, LYS531, CYS530, ASP531	LEU354, LEU536, CYS381, ,LEU536

From Table 1, molecule 6 the most potent identified mol among other selected compounds with a binging affinity -10.1 Kcal/mol formed a conventional hydrogen bond with ASP480 and carbon-hydrogen bond with the following amino acid residues ASN455, HIS476, THR483, LEU504 and LEU509, respectively which might be primarily responsible for its high binding affinity. Not only the mentioned ones but also hydrophobic and other interactions with LEU508, LEU479 and ILE451 amino acid residues were observed. The 2D structure of molecule 6 in complex with the human estrogen receptor alpha is shown in Figure 1.

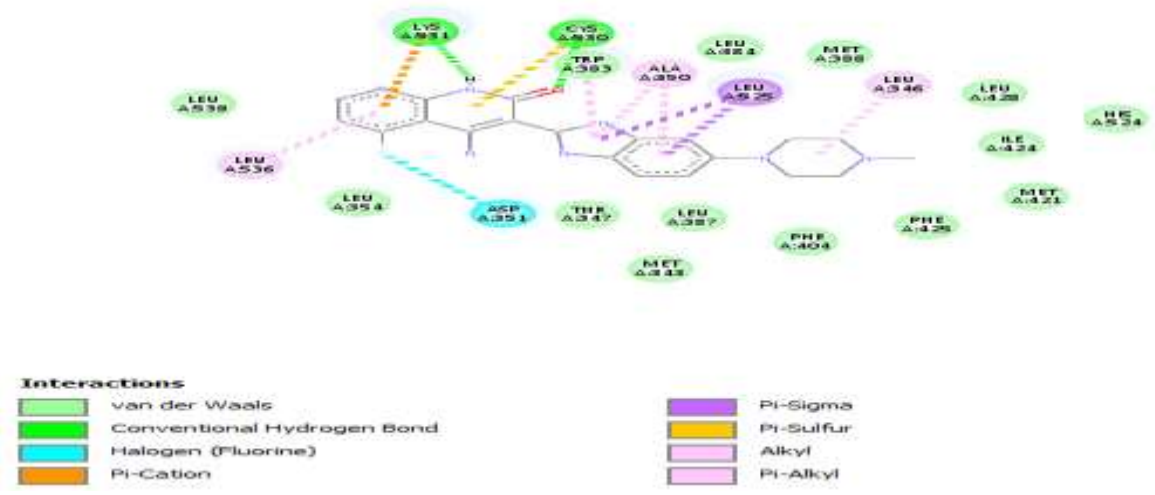

Figure 1: 2D structure of molecule 6 in complex with the human estrogen receptor alpha

Next among the molecules identified with higher binding affinities was molecule 19 (-9.0 kcal/mol) where it interacted with the active site of the human estrogen receptor alpha through a conventional hydrogen bond with LEU346 amino acid residue. Besides this, it also interacted with the active site of the human estrogen receptor alpha through carbon-hydrogen bonds with ARG548, ASP545 and ARG363 amino acid residues, respectively. Not only had that, but it also formed hydrophobic and other interactions with ILE326, LEU403, LYS531, ASN532, ASP351, PRO535 and VAL533 amino acid residues, respectively. The 2D structure of molecule 19 in complex with the human estrogen receptor alpha is shown in Figure 2.

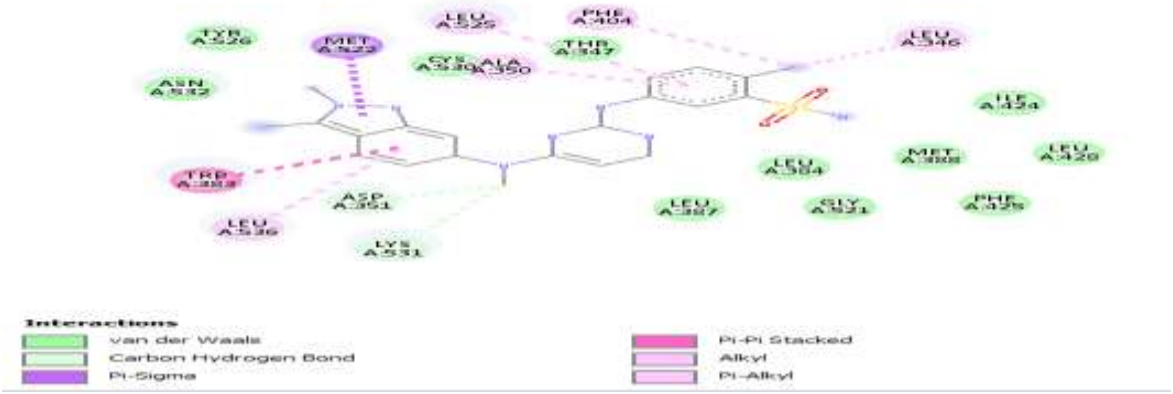

Figure 2: 2D structure of molecule 19 in complex with the human estrogen receptor alpha

The third molecule identified with higher binding affinity was molecule 17 (-8.8 Kcal/mol). The conventional hydrogen bond between the molecule and active site of the human estrogen receptor alpha with GLU353 and ARG394 amino acid residues were observed. HIS398, SER395, MET396, PRO325, PRO406 and ARG394 amino acid residues in the active site of the human estrogen receptor-alpha were seen to have formed a carbon-hydrogen bond with molecule 17, respectively. Hydrophobic and other interactions between the molecule and LEU384, LEU525, ILE424 and THR347 amino acid residues were also observed. The 2D structure of molecule 17 in complex with the human estrogen receptor alpha is shown in Figure 3.

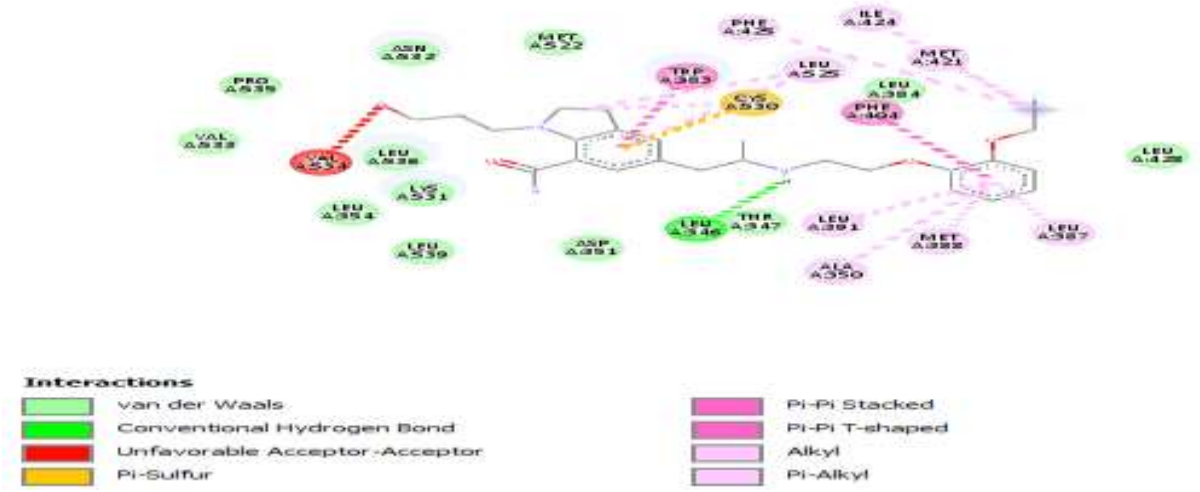

Figure 3: 2D structure of molecule 17 in complex with the human estrogen receptor alpha

The one that comes after molecule 17 among the identified ones with higher binding affinities was molecule 2 (-8.1 Kcal/mol). It was seen to form a conventional hydrogen bond with LEU409 and GLN414 amino acid residues and a carbon-hydrogen bond with LEU408, LEU410, TYR331, ASN407, PRO333 and LYS408 amino acid residues, respectively. Apart from the conventional and carbon-hydrogen bonds, it formed hydrophobic and other interactions in the active site of the human estrogen receptor alpha with PHE337, PHE425, CYS530, ILE424 and PHE404 amino acid residues, respectively. The 2D structure of molecule 2 in complex with the human estrogen receptor alpha is shown in Figure 4.

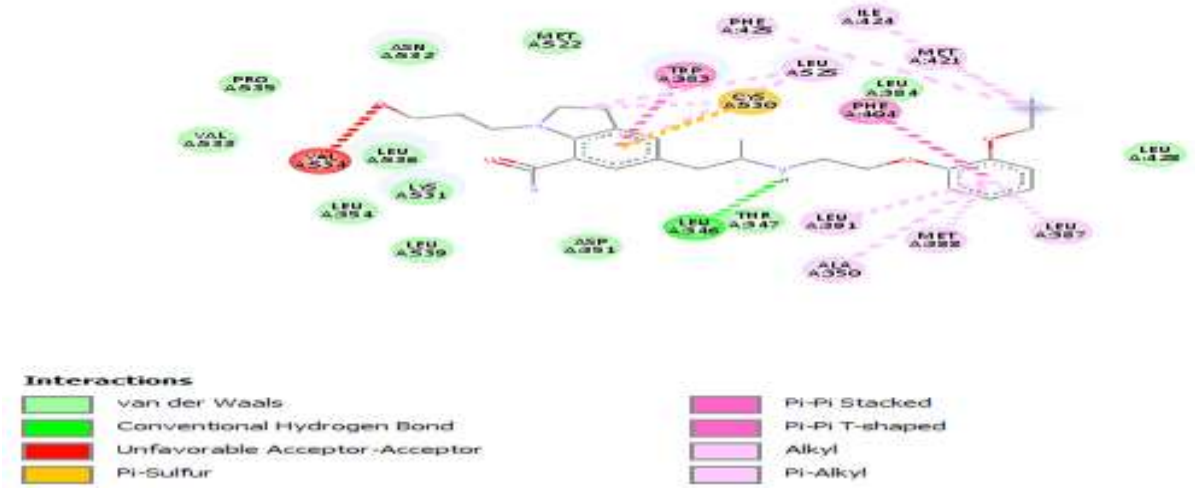

Figure 4: 2D structure of molecule 2 in complex with the human estrogen receptor alpha

Drug-likeness properties

The drug-likeness properties of all the endometrial cancer agents were predicted to confirm the viability of the drugs employing SWISSADME online web tools. The drug-likeness properties of the reported compounds are presented in Table 2. From the Table, none among the identified compounds with higher binding affinities was found to violate any of the condition/ criteria (Molecular weight ≤ 500, Number of hydrogen bond donors ≤ 5, Number of hydrogen bond acceptors ≤ 10, and Calculated Log p ≤ 5) set by the Lipinski's rule of five. This confirms that the identified compounds are orally active and bioavailable.

Table 2: The drug likeness of studied molecules

S/N	MW	HB Donor	HB acceptor	WLOGP	Lipinski Violations	Synthetic accessibility
1	293.37	0	4	2.93	0	2.21
2	386.47	2	3	4.42	0	3.11
3	441.46	2	8	3.84	0	4.52
4	501.51	2	7	5.52	1	3.09
5	369.23	2	6	1.01	0	3.32
6	182.18	2	4	0.07	0	2.65
7	426.55	1	3	3.58	0	3.95
8	392.43	3	4	2.21	0	3.2
9	418.4	7	9	2.05	1	5.06
10	254.28	3	5	1.18	0	4.65
11	446.9	1	7	4.32	0	3.26
12	319.4	1	2	3.05	0	2.85
13	385.48	0	4	3.48	0	4.42
14	328.41	4	4	1.81	0	3
15	430.53	0	6	4.29	0	6.39
16	443.49	2	6	4.36	0	2.87
17	384.51	0	4	4.58	0	5.21
18	273.35	1	2	2.55	0	3.1
19	425.51	2	6	3.11	0	3.85
20	382.58	0	0	7.53	0	3.37
21	482.82	3	8	6.88	0	3.04
22	495.53	3	8	3.95	0	3.87

The plot of WLOGP against TPSA (Boiled-egg plot) to predict gastrointestinal absorption and brain penetration of the selected molecules was shown in Figure 5. It can be seen from the plot that only a few of the molecules possess the BBB permeability properties. Almost all of the studied compounds are within the GI absorption region except three (3) compounds.

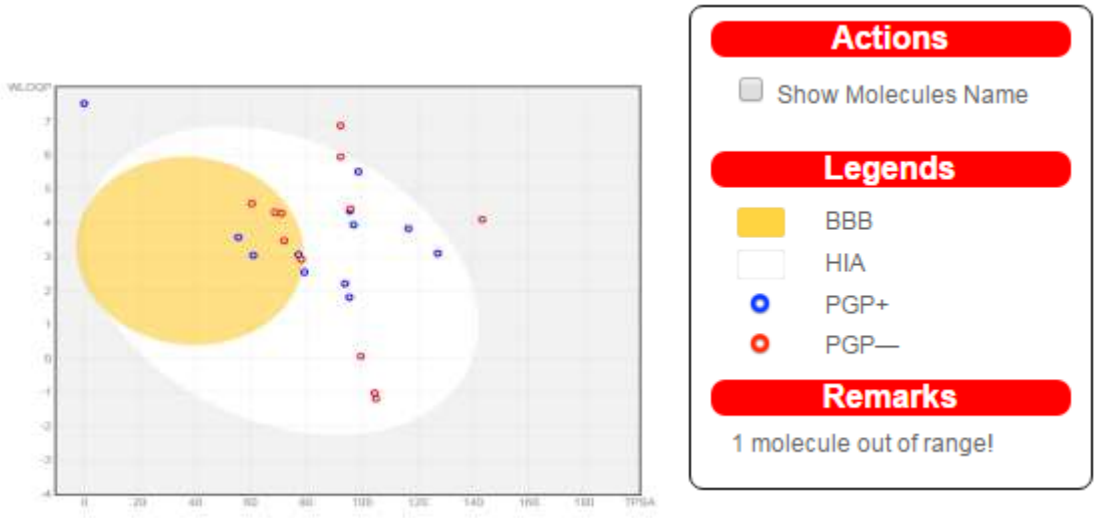

Figure 5: The boiled egg plot of the reported compounds

ADMET properties

The pharmacokinetic (ADMET) properties of all the endometrial cancer agents were predicted employing pkCSM online web tools. The ADMET properties of the reported compounds are shown in Table 3. All the reported compounds have absorbance values between 36.5 to 100% as the values passed the minimum recommended values of 30% which indicates good human intestinal absorption. The minimum recommended values for the blood-brain barrier (BBB) and central nervous system permeability is > 0.3 to < -1 Log BB and > -2 to < -3 Log PS respectively. As for these compounds, Log BB is between -0.122 to 1.038 for all which implies that the compounds are better distributed to the brain except for those that are not within the accepted values. Log PS for all is between -0.696 to -3.895 which are considered to penetrate the central nervous system except for those that are not within the accepted values. The enzymatic metabolism of drugs shows the biotransformation of a drug in the body. The most important among the CYP families is 3A4 which is the reported compounds were found to be substrate and inhibitors of it including the identified potent compounds. The reported compounds showed a high value of total clearance but within the accepted limit of a drug molecule in the body. Furthermore, all the reported compounds were found to be non-toxic except a few. The overall ADMET properties of these compounds most especially the identified compounds indicate their good pharmacokinetic profiles (Table 3).

Table 3: The ADMET properties of the studied molecules

	Absorption	Distribution		Metabolism CYP Substrate		CYP Inhibitors					Excretion	Toxicity
S/N	Intestinal absorption	BBB perm. (Log BB)	CNS perm. (Log PS)	2D6	3A4	1A2	2C19	2C9	2D6	3A4	Total Clearance	AMES
1	91.668	-1.117	-2.097	Yes	Yes	Yes	Yes	Yes	No	Yes	0.115	Yes
2	97.527	-1.44	-3,257	No	Yes	No	No	Yes	No	Yes	0.538	No
3	100	-0.678	-3.043	No	Yes	No	Yes	Yes	No	Yes	0.156	No
4	68.723	-0.619	-3.457	No	No	No	No	No	No	No	1.072	No
5	69.074	-1.074	-3.541	No	No	No	No	No	No	No	0.169	No
6	100	-0.678	-2.043	No	Yes	No	Yes	Yes	No	Yes	0.156	No
7	36.5	-1.135	-3.895	No	No	No	No	No	No	No	0.414	No
8	97.527	-1.44	-3.257	No	No	No	No	Yes	No	Yes	0.538	Yes
9	85.732	-1.235	-2.322	No	Yes	No	Yes	Yes	No	Yes	0.36	No
10	93.469	-0.417	-2.815	No	Yes	No	Yes	Yes	No	Yes	0.429	No
11	91.668	-1.117	-2.097	Yes	Yes	Yes	Yes	Yes	No	Yes	0.115	Yes
12	87.598	-1.162	-2.097	No	Yes	No	Yes	Yes	No	Yes	0.044	No
13	100	-0.525	-2.402	No	Yes	Yes	Yes	Yes	No	Yes	1.094	No
14	74.729	-1.032	-3.202	Yes	No	Yes	No	Yes	Yes	No	0.956	No
15	76.671	-1.063	-2.306	No	Yes	Yes	Yes	Yes	No	Yes	0.864	Yes
16	97.735	-0.496	-2.849	No	Yes	No	Yes	No	No	No	0.501	No
17	96.342	-0.485	-2.416	No	Yes	No	Yes	No	No	Yes	0.707	No
18	95.413	1.038	-0.696	No	Yes	Yes	No	No	No	No	0.652	No
19	90.141	-0.9	-2.549	No	Yes	No	No	No	No	Yes	0.967	No
20	93.178	-0.122	-2.163	No	Yes	No	No	No	Yes	Yes	0.914	Yes
21	97.899	0.452	-1.757	No	Yes	No	No	No	No	No	0.547	No
22	92.84	-1.337	-3.409	No	Yes	No	No	No	No	Yes	0.778	No

CONCLUSION

Molecular docking, drug-likeness and pharmacokinetic studies were carried out on twenty-two set of endometrial cancer agents. This study confirmed the endometrial cancer agent's inhibitory activities, their safety through their pharmacokinetic profiles and could be used as potential drugs for the treatment of endometrial or uterine cancer.

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