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 lifetime risk of being diagnosed with endometrial cancer, the fourth most common malignancy 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 uncontrolled 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 malignancy among women (Barr et al., 2016). Uterine cancer is the most common gynecological 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-oestrogen-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 ≤ 500g/mol, Number of hydrogen bond donor ≤ 5, Number of hydrogen bond acceptors ≤ 10, calculated Log P ≤ 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.

| S/N | Binding Energy | Conventional Hydrogen Bond | Carbon Hydrogen Bond | Hydrophobic and other interactions |
|-----|----------------|---------------------------|---------------------|----------------------------------|
| 1   | -7.6           | ASP351                    | LEU384, LEU346, TRP383, LEU349, | LEU 387, LEU 391, MET 388, |
|     |                |                           | THR 347, GLU 353, HIS 524, LYS 531, | LEU 525, ALA 350, |
|     |                |                           | LEU 428, MET 343, MET 421           |                                  |
| 2   | -8.1           | LEU409 and GLN414         | LEU 408, LEU 410, TYR 331, ASN 407, | PHE 337, PHE 425, CYS 530, ILE 424, PHE 404 |
|     |                |                           | PRO 333, LYS 408                     |                                  |
| 3   | -7.7           | MET343, ASP 351           | LEU 428, LEU 536, LEU 346, LEU 354, | LEU 525, LEU 391, MET 388, |
|     |                |                           | ILE 424, ARG 394, LYS 531, THR 347, | LEU 387, LEU 384, ALA 350, |
|     |                |                           | GLU 353                             | CYS 530                          |
| 4   | -3.3           | CYS381                    | LEU 525, ARG 515, GLU 380, GLU 523, | MET 522                           |
|     |                |                           | ASN 519, TYR 526, TRP 383, ASN 532, |                                  |
|     |                |                           | LYS 531, LEU 536                     |                                  |
| 5   | -7.5           | LEU387 & LEU346           | LEU 384, LEU 391, LEU 349, LEU 525, | GLU 353                           |
|     |                |                           | PHE 404, THR347, ALA 350, MET 388   |                                  |
| 6   | -10.1          | ASP480                    | ASN 455, HIS 476, THR 483, LEU 504, | LEU 508, LEU 479, ILE 451          |
|     |                |                           | LEU 509                             |                                  |
| 7   | -7.1           | LYS 531 and CYS 530       | LEU 387, LEU 354, LEU 384, LEU 428, | ALA 350, LEU 346, LYS 536 & MET 536 |
|     |                |                           | MET 388, MET 421, MET 343, PHE 404, |                                  |
|     |                |                           | PHE 425, ILE 424, HIS 524, TRP 383, |                                  |
|     |                |                           | LEU 539, THR 347                     |                                  |
| 8   | -7.0           | ASN 407                   | LEU 408, LEU 409, PRO 336, ARG 335, | PHE 337                           |
|     |                |                           | PRO 333, THR 343, TYR 331, GLN 414  |                                  |
| 9   | -7.4           | LEU:387 and GLU:353       | PHE 404, PHE 425, LEU 525, LEU 346, | ALA 350, LEU 391, |
|     |                |                           | LEU 384, THR 347, LEU 348, MET 388, | CYS 530                           |
|     |                |                           | MET 343, TRP 383                     |                                  |
| 10  | -7.9           | ARG 394                   | PHE 404, PHE 425, LEU 525, LEU 346, | TRP 383, LEU 354, LEU 536          |
|     |                |                           | LEU 384, THR 347, LEU 348, MET 388, |                                  |
|     |                |                           | MET 343, TRP 383                     |                                  |
From Table 1, molecule 6 the most potent identified mol among other selected compounds with a binding 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.
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, PRO353 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](image)

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](image)

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, CY530, 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.
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

| S/N | Intestinal absorption | BBB perm. (Log BB) | CNS perm. (Log PS) | Metabolism | CYP Substrate | CYP Inhibitors | Excretion | Toxicity | AMES |
|-----|----------------------|--------------------|--------------------|------------|---------------|---------------|-----------|----------|------|
| 1   | 91.668               | -1.117             | -2.097             | Yes        | Yes           | Yes           | Yes       | Yes      | Yes  |
| 2   | 97.527               | -1.44              | -3.257             | No         | Yes           | No            | Yes       | No       | Yes  |
| 3   | 100                  | -0.678             | -3.043             | No         | Yes           | Yes           | Yes       | Yes      | Yes  |
| 4   | 68.723               | -0.619             | -3.457             | No         | No            | No            | No        | No       | No   |
| 5   | 69.074               | -1.074             | -3.541             | No         | No            | No            | No        | No       | No   |
| 6   | 100                  | -0.678             | -2.043             | No         | Yes           | Yes           | Yes       | Yes      | Yes  |
| 7   | 36.5                 | -1.135             | -3.895             | No         | No            | No            | No        | Yes      | Yes  |
| 8   | 97.527               | -1.44              | -3.257             | No         | No            | Yes           | No        | Yes      | Yes  |
| 9   | 85.732               | -1.235             | -2.322             | No         | Yes           | Yes           | Yes       | Yes      | Yes  |
| 10  | 93.469               | -0.417             | -2.815             | No         | Yes           | Yes           | Yes       | Yes      | Yes  |
| 11  | 91.668               | -1.117             | -2.097             | Yes        | Yes           | Yes           | Yes       | No       | Yes  |
| 12  | 87.598               | -1.162             | -2.097             | No         | Yes           | Yes           | Yes       | Yes      | Yes  |
| 13  | 100                  | -0.525             | -2.402             | No         | Yes           | Yes           | Yes       | Yes      | Yes  |
| 14  | 74.729               | -1.032             | -3.202             | Yes        | No            | Yes           | Yes       | Yes      | Yes  |
| 15  | 76.671               | -1.063             | -2.306             | No         | Yes           | Yes           | Yes       | Yes      | Yes  |
| 16  | 97.735               | -0.496             | -2.849             | No         | Yes           | Yes           | Yes       | Yes      | Yes  |
| 17  | 96.342               | -0.485             | -2.416             | No         | Yes           | Yes           | Yes       | Yes      | Yes  |
| 18  | 95.413               | 1.038              | -0.696             | No         | Yes           | Yes           | Yes       | No       | Yes  |
| 19  | 90.141               | -0.9               | -2.549             | No         | Yes           | Yes           | Yes       | No       | Yes  |
| 20  | 93.178               | -0.122             | -2.163             | No         | Yes           | Yes           | Yes       | No       | Yes  |
| 21  | 97.899               | 0.452              | -1.757             | No         | Yes           | Yes           | Yes       | No       | Yes  |
| 22  | 92.84                | -1.337             | -3.409             | No         | Yes           | Yes           | Yes       | No       | Yes  |
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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