Influence Of Benzophenone And Pyrazine On Janus Kinase-Signal Transducer In Ovarian Cancer: In Silico Analysis

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Abstract
The sixth most common cancer in women worldwide is ovarian cancer. Ovarian cancer claims the lives of more women each year than any other condition affecting the female reproductive system. It is the most deadly cancer of the female reproductive system and the fifth greatest cause of cancer-related fatalities. It also has the highest mortality rate among gynaecologic cancers. The current study assists in determining the impact of benzophenone and pyrazine derivatives on ovarian cancer *Insilico* on Janus kinase-signal transducer. The binding modes of two molecules are predicted via computational docking. The protein human JAK STAT's 3D structure was obtained from the protein data bank . Binding affinity characteristics were identified in Auto Dock and were compared to the standard Paclitaxcel. The benzophenones molecule showed the highest binding affinity with JAK STAT (-7.6). The paclitaxcel molecule showed the binding affinity with JAK STAT (-7.7). Chloropyrazine showed the binding affinity with JAK STAT (-3.7). Marvin sketching by PyRx 0.9 was used for the molecular docking investigations. Based on the results benzophenone have strong binding affinities that are comparable to those of regular paclitaxcel. The molecules of the ligands have shown energy minimization of -7.6 to -3.7 kcal, which may be used to enhance, predict, and validate *in vitro* and *in vivo* studies.

Keywords: Ovarian cancer, Benzophenone, Pyrazine, PyRx 0.9, Janus kinase, Auto Dock

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1. INTRODUCTION
Cancer is a condition in which some cells in the body develop uncontrolled andspread to other regions of the body [1]. Cancer may develop practically any place in thehuman body, which contains billions of cells. Human cells normally develop and proliferate (a process known as cell division) to generate new cells when the body requires them. Cells die as they get old or injured, and new cells replace them. Cancer is the world's second greatest cause of mortality, accounting for an estimated 9.6 milliondeaths. Women are more likely to develop breast, colon cancers, lung, cervical, and thyroid cancers [2].

Ovarian Cancer:
A total of 230,000 females are diagnosed worldwide, with 150,000 dying as a result of the condition [4]. The primary reasons for ovarian cancer therapy failure include late presentation, high recurrence, and medication resistance [5]. Primary cytoreductive surgery followed by chemotherapy is the usual treatment for advanced ovarian cancer [6].

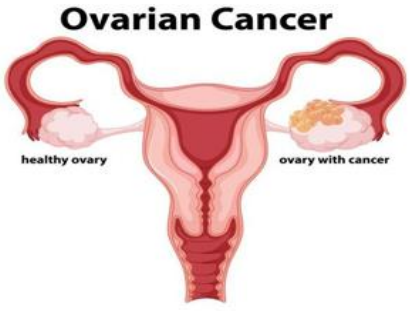

Fig 1 – Ovarian Cancer

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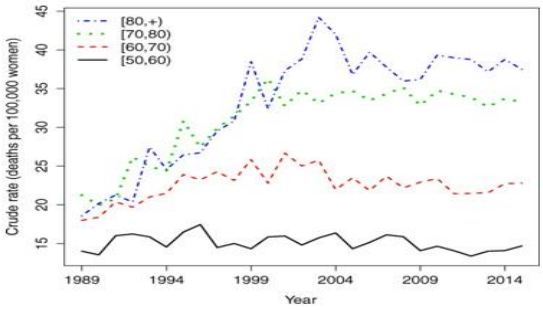


Fig 2 – Mortality rate of Mortality rate of ovarian cancer

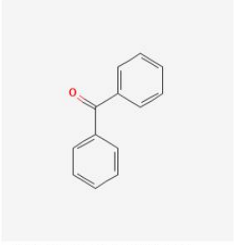
Table 1 – Types and Grades of Ovarian cancer

TYPES OF OVARIAN CANCER	GRADES OF OVARIAN CANCER
SEROUS	Grade 1 (Low Grade serous ovarian cancer)
MUCINOUS	Grade 2 (High Grade serous ovarian cancer)
ENDOMETRIOID	Grade 3 (High Grade serous ovarian cancer)

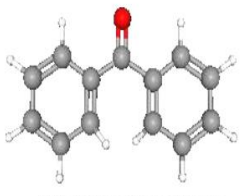
Around 70–80% of ovarian cancer fatalities are caused by High-Grade Serous Ovarian Cancer , and the 5-year survival rate has not significantly risen over the past few decades [7]. Risk factors for OC include being overweight, smoking, having an earlier or later menstrual cycle, and having a family history of OC [9]. More than 70% of OC cases are discovered at an advanced stage due to the confusing symptoms [10]. The 5-year survival rate of OC is often less than 40% . The poor prognosis and high mortality are mostly caused by the lack of early and effective detection techniques [12].The key to developping more effective diagnostic and therapeutic approaches is regarded to be the identification and understanding of novel biomarkers and specific targets of OC. The survival of ovarian cancer cells as tumor spheroids in peritoneal fluid is controlled by growth factors present in the peritoneal milieu and associated receptors on tumor cells [18–20].

2. MATERIALS AND METHODS

Benzophenone Molecular Weight: 182.22g/mol

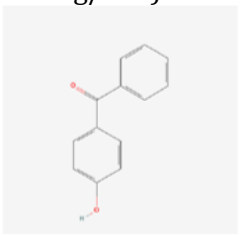


2D structure of benzophenone

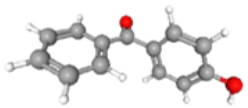


3D structure of benzophenone

4-Hydroxy benzophenone Molecular weight: 198.22g/mol)

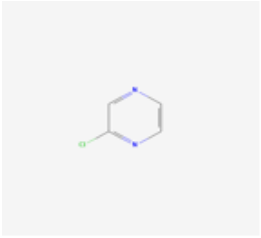


2D Structure

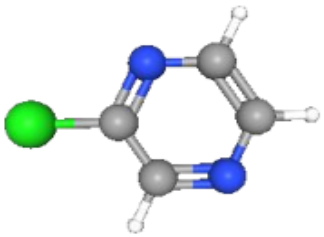


3D Structure

2-Chloropyrazine Molecular weight: 114.53g/mol



2D Structure



3D Structure

2.1 Identification of therapeutic targets

With a complete target pharmacophore database, online web servers were employed to assess the chemicals for prospective therapeutic targets (22). Following the study of the compounds, the Fit score, Normalized fit score, and Z^1score were calculated. Pharmacop-hore interaction features were assigned to the 25 drugs based on the protein–ligand combination. A higher score means the compound will have more activity against the macromolecules targeted, which is critical for achieving the best match with the ideal environment. (23). Following that, the compounds were analyzed using UniProt to establish their subcellular localization before being finalized based ontheir interaction with the protein.(24).A library was developed for the 25 molecules. The molecules were chosen for their diverse heterogeneous character and anti-cancer potential.

2.2 Pharmacophore mapping for identifying a therapeutic target

Pharmacophore mapping was conducted using pharma mapper, and three compounds (2-chloropyrrazine, 4-hydrooxybenzophenone, and benzophenone) were observed to interact with cancer-related proteins based on the fit score, normalized fit score, and z^1 score. The compounds' hydrophobic interaction and hydrogen acceptor characteristics were also

identified.

2.3 Digital screening and docking

2.3.1 Preparation of protein and identification of active site

The protein human JAK STAT's 3D structure was obtained from the protein databank. From the protein-ligand interaction profile (PLIP), the active site amino acid residues were determined.

2.3.2 Molecular docking

Binding affinity characteristics were identified in Auto Dock and were compared to the standard - Paclitaxcil, a well-known anticancer drug. The binding energy was found out through Auto Dock is the energy of the protein-ligand interaction. This value represents the degree to which proteins and ligands interact. The binding energy of the ligands was showing that the compounds were successfully bound to the JAK STAT active site. JAK STAT's bonds and Pi-Pi interactions with these substances were investigated.

3. RESULTS AND DISCUSSION

3.1 Identification of therapeutic targets

The molecules were developed into a library. The compounds were selected due to their wide range of heterogeneous characteristics and possible anti-cancer properties along with compounds showing reports of anticancer activity in reviews. The following molecules were added to the library. Calculations were made for the Fit score, Normalized Fit score, and Z^1score. Based on the protein-ligand combination, the 25 compounds were given pharmacophore interaction properties and their subcellular localization **(Table - 2)**

Table 2 – Library of Molecules and Target protein with Fit score Z^1 Score

S.No	Molecule	Target protein	Fit Score	Normalized FitScore	Z^1 Score	Subcellular localizationn
1.	Camptothecine sodium	Proto-oncogene serine/threonine - protein kinasePim-1	2.996	0.9986	0.253	Nucleus, Cytoplasm and Cytosol
2.	Sauchinone	Bone morphogenetic protein 2	3	1	1.112	Extracellular region, Plasma Membrane
3.	Benzophenone	Mitogen- activated protein kinase 8	2.927	0.9756	2.104	Cytoplasm and Cytosol
4.	Deoxygedunin	Steryl-sulfatase	3	1	1.043	Endoplasmic reticulum
5.	Gedunin	Bone morphogenetic protein 2	2.986	0.9952	1.004	Extracellular region, Plasma Membrane
6.	4- hydroxybenzo phenone	Progesterone receptor	2.994	0.7484	1.627	Cytoplasm and cytosol
7.	Methyl angolensate	Caspase-7	3	1	0.7821	Cytoplasm and Cytosol
8.	3-bromoquinoline	Apolipoprotein A-II	2.808	0.936	1.434	Extracellular region
9.	Abscisic acid	Aldo-keto reductase family 1 member C2	2.999	0.9996	0.9056	Cytoplasm and Cytosol
10.	Vanillin	cAMP-specific 3,5- cyclic phosphodiesterase4B	2.62	0.8734	0.4688	Cytoskeleton Cytosol, Nucleus, Plasma vesicle
11.	Ethyl vanillin	Phosphatidyl inositol-4, kinase catalytic subunit gamma isoform	2.916	0.972	1.3659	Cytoplasm and Cytosol, Plasma membrane
12.	Veratraldehyde	Glucosylceramidase	2.464	0.8214	-0.302	Lysosome
13.	Isovanillin	Glucosylceramidase	2.461	0.8202	-0.217	Lysosome
14.	5 Hydroxy auranetin	Oxysterols receptor LXR- beta	2.961	0.9869	1.1829	Nucleus
15.	6-Hydroxyluteolin	Prothrombin	2.994	0.9981	0.6641	Extracellular region
16.	2-chloropyrazine	Cell division protein kinase 2	2.919	0.7297	2.134	Cytoplasm
17.	Xanthomicrol	Oxysterols receptor LXR- beta	2.97	0.99	1.065	Nucleus
18.	Pedalitin	Prothrombin	2.993	0.9976	0.823	Extracellular region
19.	Nevadensin	Cholinesterase	2.978	0.9927	1.038	Extracellular region
20.	Baicalein	Tyrosine- protein kinase HCK	2.971	0.9904	1.0886	Lysosome, Cytoplasm
21.	Garcinone E	Amine oxidase	2.988	0.9959	0.6787	Mitochondrion
22.	Diosmetin	Carbonic anhydrase2	2.96	0.9867	1.0143	Plasma membrane, and Cytosol
23.	Mangiferin	Glucosylceramidase	2.938	0.9792	0.9161	Lysosome
24.	Uralenol	Complement factor B	2.99	0.9965	0.4169	Extracellular region
25.	Casticin	Cholinesterase	2.964	0.9881	1.1357	Extracellular region

3.2 Molecular docking

JAK- STAT and Benzophenone hydrogen bonds and Pi-Pi interactions were investigated. Benzophenone had the highest binding affinity with JAK (-7.6) of all the tested compounds, with zero conventional hydrogen bonding, five hydrophobic interactions (VAL 87, TYR 107, LEU 108, GLY 111, ASP 170), two pi-sigma reactions (LEU 31, VAL 39), three pi-alkyl interactions (ALA 56, ALA 159, ALA 169), and one pi-sulfur interaction (MET105)

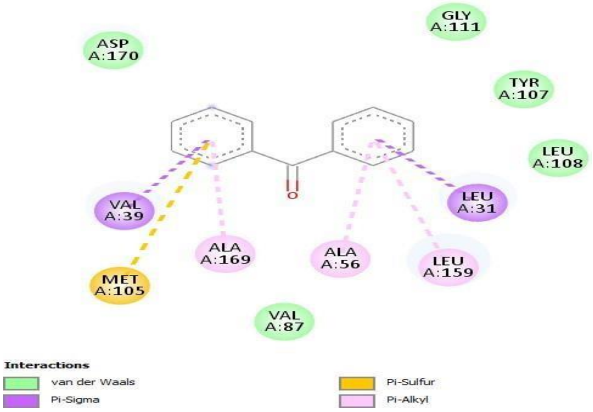


Fig 3 – 2D Interaction of Benzophenone & JAK STAT

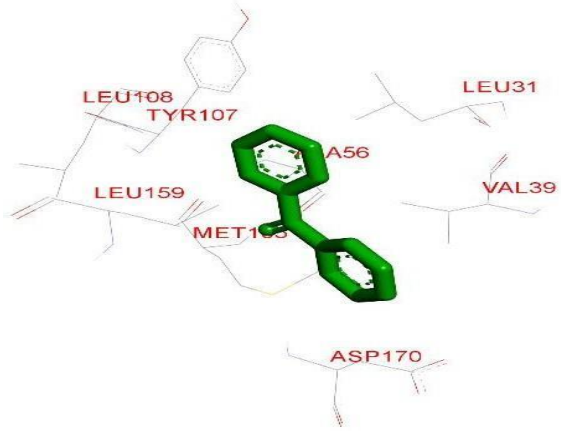


Fig 4 – 3D interaction of Benzophenone & JAK- STAT

JAK- STAT and 4 Hydroxy benzophenone hydrogen bonds and Pi-Pi interactions were investigated.4 Hydroxy benzophenone has binding affinity with JAK (-7.3) of all the tested compounds, with zero conventional hydrogen bonding, five hydrophobic interactions (VAL 87, TYR 107, LEU 108, GLY 111, ASP 170), two pi-sigma reactions (LEU 31, VAL 39),three pi-alkyl interactions (ALA 56, ALA 159, ALA 169), and one pi-sulfur interaction (MET105)

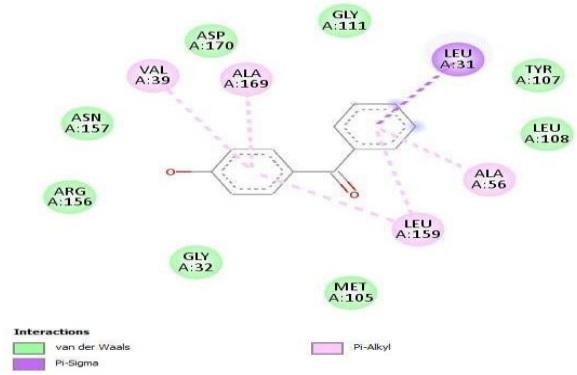


Fig 5 – 2D Interaction of 4 Hydroxy benzophenone & JAK STAT

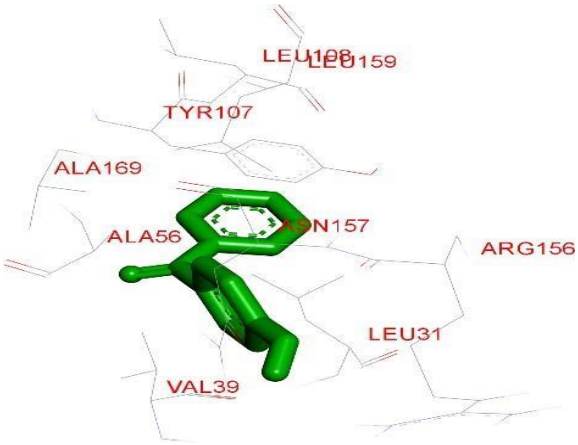


Fig 6 – 3D Interaction of 4 Hydroxy benzophenone & JAK-STAT

The paclitaxel molecule showed the binding affinity with JAK STAT (-7.5) and JAK STAT protein-paclitaxel complex made zero conventional-hydrogen bonding, six hydrophobic interactions (TRP125, VAL129, LEU132, GLY 133, GLY135, TYR143), one pi-sigma interactions (VAL128), three pi-pi stacked interactions (TYR108, PHE111, TYR136) and three pi-alkyl interactions (ALA107, LEU138, ALA139).

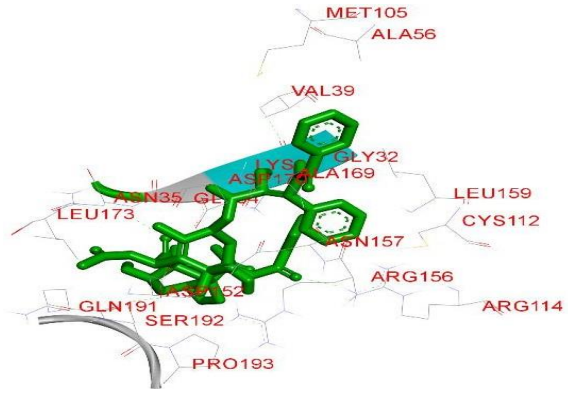


Table 3 – Binding Affinity of molecules

LIGAND	BINDING AFFINITY
BENZOPHENONE	-7.6
4-HYDROXYBENZOPHENONE	-7.3
2-CHLOROPYRAZINE	-3.7
PACLITAXEL(STD)	-7.7

4. CONCLUSION

The present work, the Janus kinase-signal transducer proteins binding energy and location were calculated along with the molecules. In the current study, Janus kinase-signal transducer protein was docked with the ligands Benzophenone and Pyrazine. The results of the current investigation showed that a good docking value, a suitable binding location, electrostatic, Vander Waals forces of attraction, Pi-Pi bonds, Pi-Sigma bonds, and energies necessary for binding. These *in silico* studies showed a respectable binding energy value, with JAK STAT values between -7.3 Kcal and -3.7 Kcal, which is acceptable and similar with that of the common paclitaxel. 2-chloropyrazine showed a lower binding affinity. The protein human JAK STAT's 3D structure was obtained from the protein data bank. From the protein-ligand interaction profile (PLIP), the active site amino acid residues were determined Along with docking scores, significant interactions five hydrophobic interactions, hydrogen bonds and Pi-Pi interactions between residues and the binding site were observed. Ovarian cancer drugs can be developed using *in silico* research, and their processes can be investigated using *in vitro* and in vivo experiments.

5. Acknowledgments

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6. Conflicts of Interest:

The authors declare no conflict of interest.

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