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MOLECULAR DOCKING AND ANALYSIS OF LAWSONE DERIVATIVES AS POTENT INHIBITORS IN MUTANT BRCA 1 PROTEIN IN BREAST CANCER

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ABSTRACT

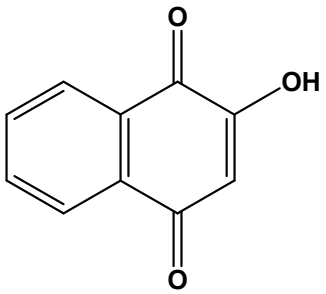
Breast cancer is one of the dangerous types of cancer that affect women. BRCA1 and BRCA2 genes are responsible for the tumor progression in breast cancer patients. In the current work, we are focusing on *in silico* molecular docking analysis of hydroxynaphthoquinone (Lawsone) derivatives. The docking results were compared with the standard drug, Olaparib which is currently used in BRCA1 mutated breast cancers. From the docking studies, using Discovery studio 2018 software, it was found that the derivatives had good binding affinity with the target protein. Various interactions were observed in all the, ligands namely DPDHN (1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)amino) naphthalene-1,4-dione, PAN, TAN [2-(thiolanilino) - 1, 4- naphthoquinone], HAN 2-[(O-hydroxyphenyl)amino]-1,4-naphthaquinone) except BP (5H-Benzo[a]phenoxazin-5-one) and the parent compound Lawsone. According to the docking scores and various types of interactions, we suggest that the derivatives, HAN and TAN pose to be potent lead molecules against BRCA1 mutant breast cancer.

Keywords: Hydroxynaphthoquinones, Lawsone, BRCA1, Docking, Discovery studio

1. INTRODUCTION

Cancer is a genetic disease which can result from both internal factors such as hormones, inherited mutations, and immune conditions or from external factors

such as diet, tobacco, radiation, chemical exposure or infectious organisms etc. Breast cancer is a dangerous type of cancer commonly seen in woman. Breast cancer is one of the malignant tumor which starts in the cells of breast. In 2019, approximately 268, 600 new cases of malignant breast cancer were diagnosed in woman and 2670 was diagnosed in men **[1]**. There are many inherited mutations in breast cancer. BRCA 1 and BRCA 2 are the two mutated genes responsible for the inherited breast cancer. If we possess the inherited copy of BRCA gene from our parents then we have high risk of getting inherited breast cancer in our life time. The function of BRCA 1 is repairing the DNA and it is a tumor suppressor gene. BRCA1 and BRCA2 [**2]** genes are generally expressed in breast tissues. If the DNA repair is not being properly done then it may lead to breast cancer. BRCA1 and BRCA2 genes are described as breast cancer susceptibility genes and breast cancer susceptibility proteins **[3]**. Hydroxynaphthoquinones are one of the largest and diverse groups of plant secondary metabolites found in nature which are involved in various redox reactions that are taking place in plants. Lawsone (2-hydroxy-1,4-naphthoquinone) is a red orange dye found in the leaves of henna plant *(Lawsonia inermis)* **[4]**. From the literature, it has been found that, different derivatives of Lawsone were synthesized and various in vitro and in vivo biological studies were carried out and it has been concluded that structural modifications of lawsone led to the improvement of biological activity **[5]**. In this current work, we have selected some imino derivatives of Lawsone as ligands, for docking studies, using commercial software, Discovery studio 2018. The ligands which were subjected to computational screening are ((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)amino) naphthalene-1,4-dione (DPDHN), 2-[(Para – methyl) anilino]-1, 4-naphthoquinone (PAN), 2-(Thiol anilino) -1, 4- naphthoquinone(TAN), 2-[(O-hydroxyphenyl)amino]-1,4-naphthaquinone (HAN) and 5H-Benzo[a]phenoxazin-5-one (BP). The synthesis of these ligands were reported by Kavitha Rani P.R *et al* **[6-8]**. The structure of the ligands are given in the **Figure 1**.



Lawsone (Parent Compound)

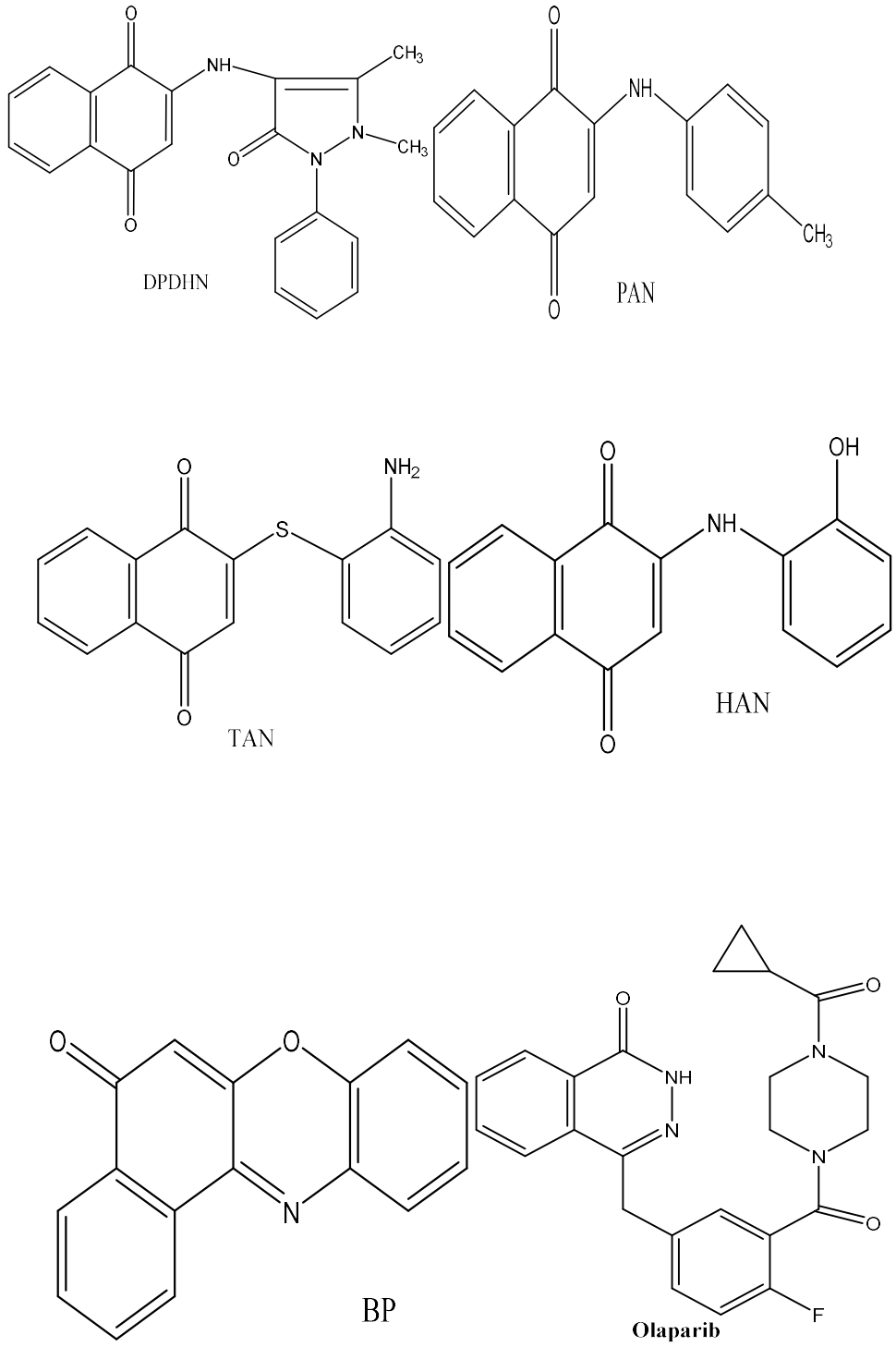


Figure 1: Structure of ligands

2. MATERIALS AND METHODS

2.1. Protein data bank

The crystal structure of MDC1 BRCT T2067D in complex with a minimal recognition tetrapeptide with an amidated C-terminus with PDB ID: 3K05 were retrieved from PDB (Protein Data Bank) with a resolution of 1.33A°. The amino acid residues that interact with the compounds in the binding pocket of BRCA1 are mainly Thr1898, Gly1899, Val1901, Arg1932, Arg1933, and Lys1936.

2.2. Marvinsketch v 5.3.0

The derivatives of lawsone which were previously synthesized were used in the docking analysis. The ligands were sketched using Marvinsketch5.3 and the geometry cleaned and saved as .sdf format.

2.3. Molecular docking studies

Docking Analysis of the target with the synthetic ligands was analyzed using the docking software, Discovery studio 2018. Before docking, the targets and ligands were preprocessed for optimizing and minimizing the structure and generating its conformers respectively **[9]**. Library docking was performed for identifying the binding affinity with the targets using Charmm as forcefield. Library docking (Libdock) consists of three steps, protein preparation, ligand preparation and molecular docking. The protein 3K05 was preprocessed by removing the bounded ligands and ions and the structure converted into the energy minimized structure. The ligands were prepared and its conformers generated. The preliminary docking analysis were conducted by selecting Thr1898, Gly1899, Val1901, Arg1932, Arg1933, and Lys1936 as binding site residues of the protein with the ligands, BP, DPDHN, HAN, PAN and TAN. Olaparib was used as the standard drug.

3. RESULTS AND DISCUSSION

From the docking results (**Table 1 and Figure 1-5**), it was found that the standard drug, Olaparib had docking score of 97kcal/mol with four strong hydrogen bonding interactions with THR A: 1898, VAL A: 1935, LYS A: 1936 and GLY A: 1918. Other Interactions with THR A: 1934 was carbon hydrogen bond interactions, ALA A: 1920 amino acid with pi-alkyl interactions. Pi-anion interactions with aminoacid GLU A: 2016 and CYS A:1939. The ligands HAN and TAN gave docking scores of 66.97kcal/mol and 66.69kcal/mol respectively interacting with the amino acid residues, Thr1898 with a bond distance of 3.06A^0 and Lys1936A^0 with a bond distance of 2.14 A^0 respectively. In ligands HAN, the different amino acids, VAL A:1935 interacted through pi-sigma interactions, THR A: 1898 through hydrogen bonding interactions, Lys A: 1936, CYS A: 1939 and ALA A:1920 through pi-alkyl interactions, GLU A: 2016 through pi-anion interactions and THR A:1934 through carbon-hydrogen bond interactions. The ligand DPDHN gave a low docking score value of 38.18 kcal/mol and had interactions with LYS A:1936 through hydrogen bonding at a distance 2.70 A^0 . The other interactions of DPDHN were with ALA A:1920 and VAL A:1935 through pi-alkyl interactions, GLU A:2016 and CYS A: 1939 through pi-anion interactions and LYS A: 1936 through carbon-hydrogen bond interactions. The ligand PAN also had a low docking score

value of 39.78 kcal/mol exhibiting hydrogen bond interactions with GLY A: 1918, ALA A 1920 at a distance of 1.73 A^0 and 3.07 A^0 respectively. The amino acids CYS A: 1939 and VAL A: 1935 interacted through pi-alkyl interactions and GLU A: 2016 and LYS A: 1936 through pi-anion interactions. The amino acid, SER A: 1919 exhibited carbon - hydrogen bond intractions. The ligand, BP gave a good docking score of 53.54 kcal/mol but had no interactions with amino acids.

Table 1: Docking Score and Interactions of Lawsone derivatives

S. No.	Name of the ligand	Docking score	Interacting Residue	Distance (in A^0)
1	LAWSONE	44.42	Ser1919	1.81
2	BP	53.54	Nil	Nil
3	DPDHN	38.18	Lys1936	2.70
4	HAN	66.97	Thr1898	3.06
5	PAN	39.78	Ala1920, Gly1918	3.07 1.73
6	TAN	66.69	Lys1936	2.14
7	OLAPARIB	97.00	THR1898 VAL1935 LYS1936 GLY1918	2.75 2.33 2.26 2.52

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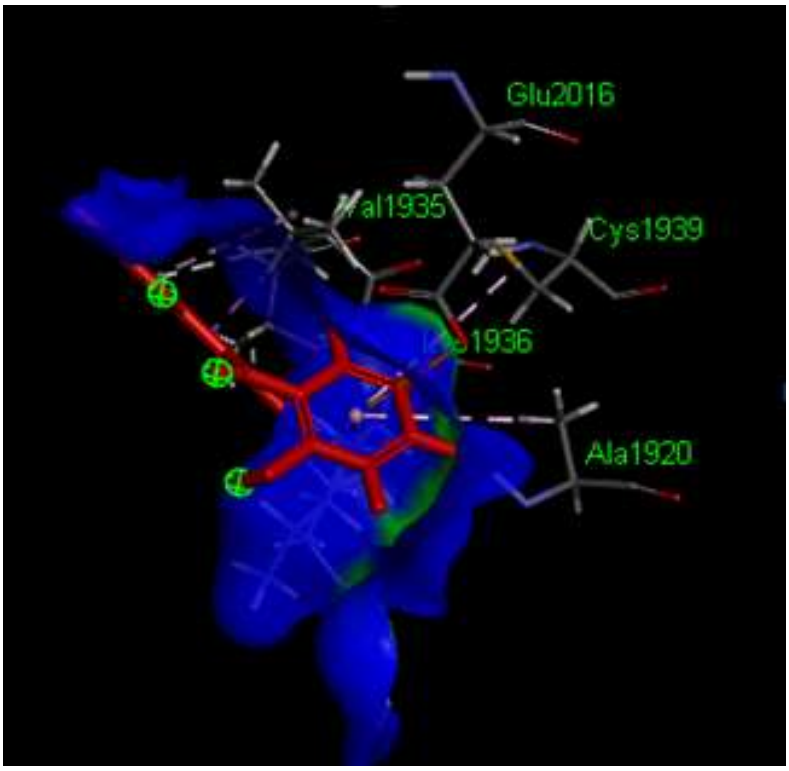

Figure 2: Docking image of LAWSONE

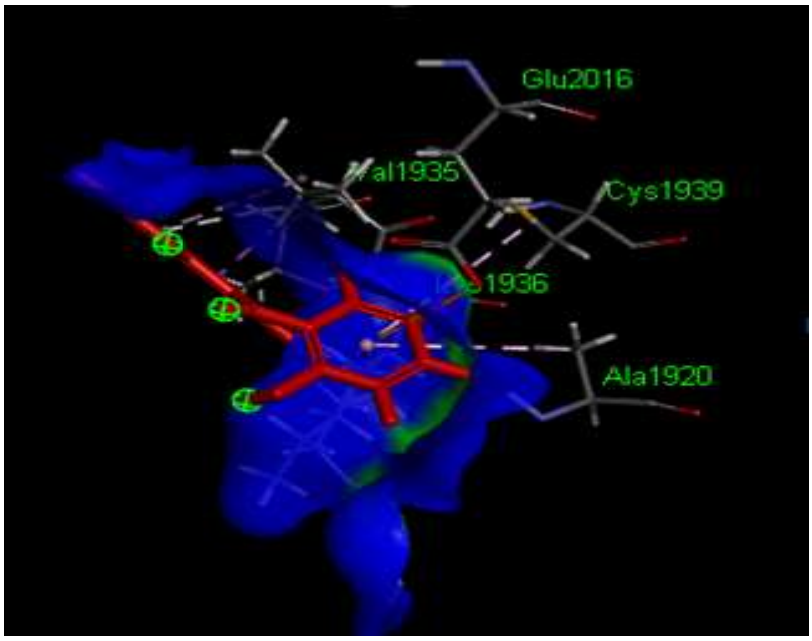

Figure 3: Docking image of HAN

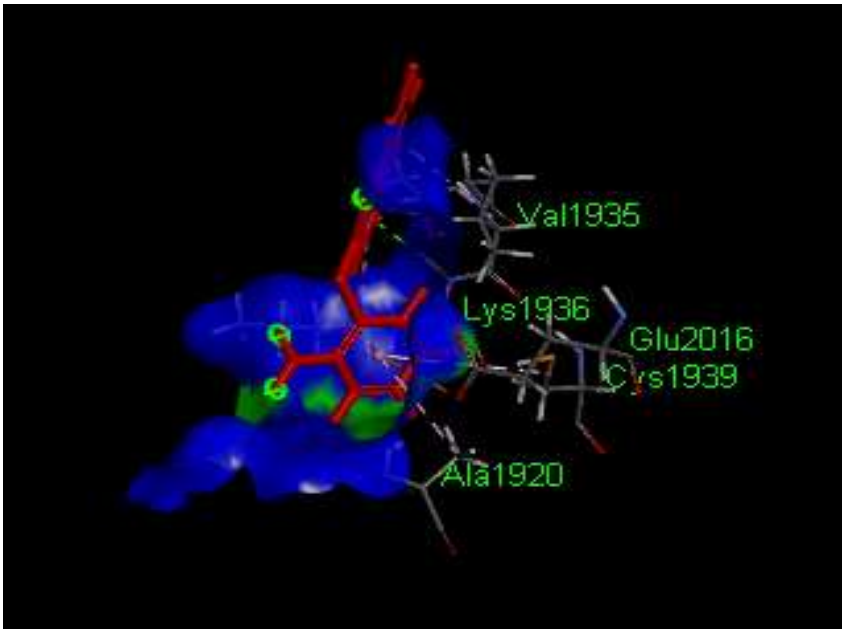

Figure 4: Docking image of TAN

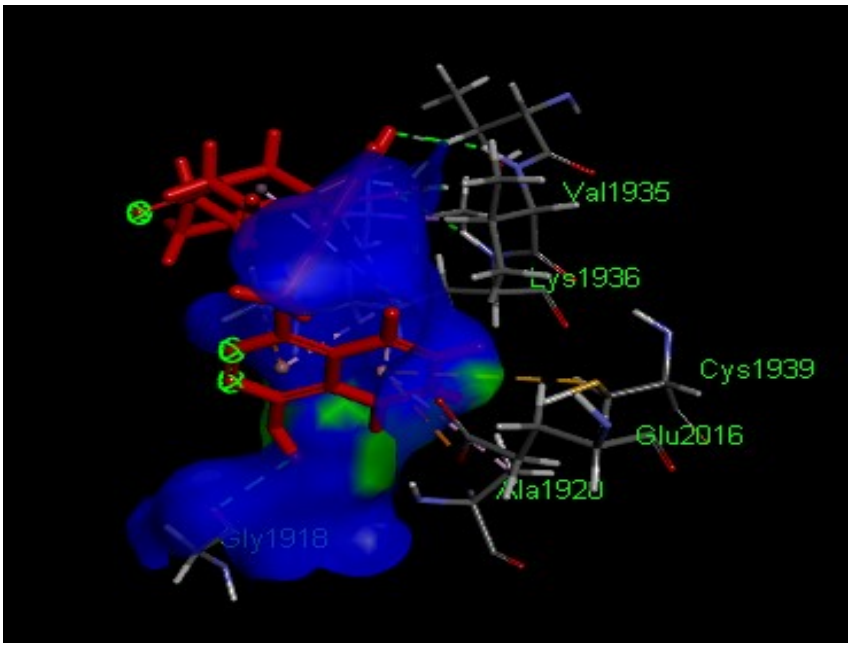

Figure 5: Docking image of Olaparib

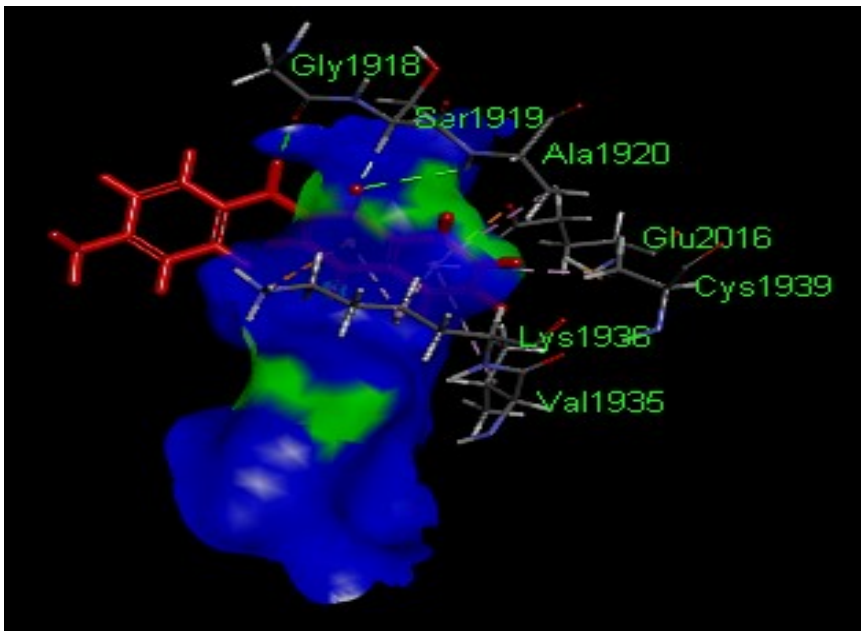

Figure 6: Docking image of PAN

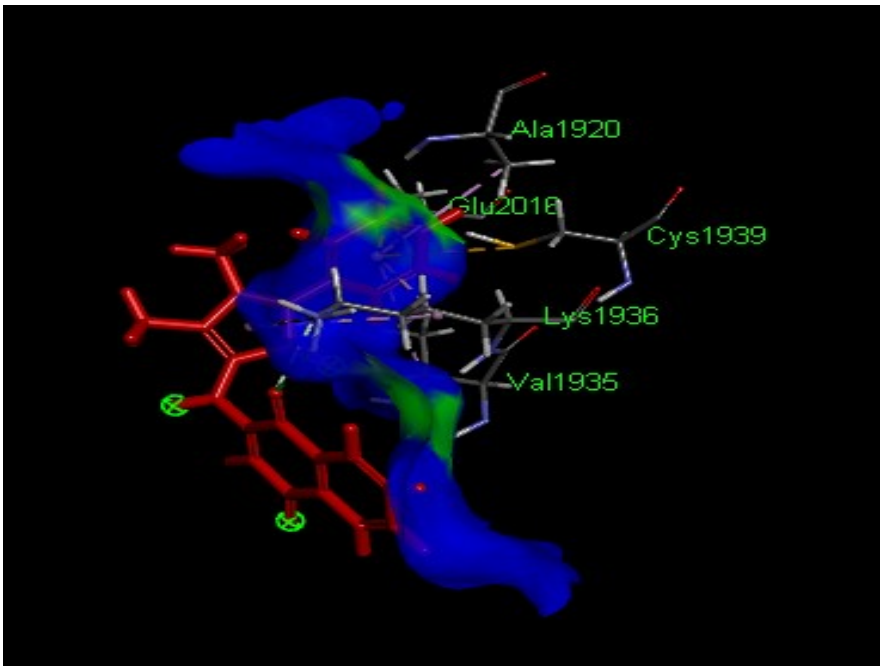

Figure 7: Docking image of DPDHN

CONCLUSION

In silico studies revealed that the lawsone derivatives had relatively lesser binding energy when compared with that of the standard drug, Olaparib. The derivatives HAN and TAN had better docking scores than the other derivatives as well as the parent compound, Lawsone. Hence from this study, we have found that the derivatisation of Lawsone has led to more potent molecules. Thus the ligands, HAN and TAN poses to be lead molecules as inhibitors against BRCA1 mutant breast cancer. Hence this study has widened the scope of developing Lawsone derivatives as promising anticancer agent against breast cancer.

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