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Potential of 4-Hydroxypropiophenone against Matrix Metalloproteinase 10: An *In-silico* docking study

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Abstract

Objective: The present study focused on molecular computational analysis to identify the potential compound, which can block the protein (Matrix metalloproteinase 10) responsible for lung cancer. Lung cancer is currently the second most common cancer in both men and women and is the top cause of all cancer. Matrix metalloproteinase 10 (PDB ID: 3V96) is a zinc-dependent proteolytic enzyme capable of breaking down basement membranes and most extracellular matrix (ECM) components. Matrix metalloproteinases have been implicated in lung tumor proliferation, invasion, and metastasis. Considering the side effects of the anticancer drugs, the present study was undertaken to substantiate the inhibitory potential of 4-hydroxypropiophenone (4-HPPP) against the receptor protein Matrix metalloproteinase 10. **Materials and Methods:** Structure of human Matrix metalloproteinase 10 was retrieved from the Protein Data Bank and the structures of 4-HPPP compounds have been collected from PubChem database. Molecular docking and drug likeness studies were performed for 4-HPPP to evaluate and analyze the anti-lung cancer activity. **Result**: Docking studies have been carried out in the active site of Matrix metalloproteinase 10 by using Discover Studio Version 4.5 (Biovia Dassault System, USA). The LibDock Score value was 62.8644KDa. **Conclusions:** The results of this study can be implemented in the drug designing pipeline.

Keywords: Lung cancer, Matrix metalloproteinase 10, 4-hydroxypropiophenone , extracellular matrix, *In silico* .

Introduction

Cancer may be defined as a progressive series of genetic events that occur in a single clone of cells because of alterations in a limited number of specific genes (Solomon *et al*, 1991). The human cancer has provided evidence that malignant progression is associated with genetic change. It has been suggested that some genetic alterations in tumors may be the result of direct or indirect processes related to environmental chemical exposure (McMahon, 1994).However, the drugs used for this therapy have a narrow therapeutic index, and often the responses produced are only just palliative as well as unpredictable. In contrast, targeted therapy that has been introduced in recent years is directed against cancer-specific molecules and signalling pathways and thus has more limited nonspecific toxicities (AmitArora and Eric Scholar, 2005). Lung cancer is one of the most common malignancies in the world and is the leading cause of cancer-related deaths in the United States (Landis *et al.*, 1998). Lung cancer occurs in multiple histologic types as classified by conventional light microscopy. The four major types include squamous cell carcinoma, adenocarcinoma, large cell carcinoma, and small cell undifferentiated carcinoma. Together, these four types of lung cancer account for > 90% of lung cancer cases in the United States (Churg, 1994). The most effective treatment for Non-small Cell Lung Cancer (NSCLC) is surgical

resection, but this modality is limited by the fact that 65% of patients have advanced disease at the time of diagnosis (Naruke *et al.*, 1988) . Matrix metalloproteinases (MMP) are zinc-dependent proteolytic enzymes capable of breaking down basement membranes and most extracellular matrix (ECM) components. Matrix metalloproteinases expression and activation are carefully regulated in physiological conditions in order to prevent uncontrolled destruction of body tissues but this regulation is modified or disrupted in pathological processes, including cancer (Davidson *et al.*, 2002). Matrix metalloproteinases have been implicated in lung tumor proliferation, invasion, and metastasis (Egeblad and Werb, 2002). The stromelysin subfamily [stromelysin 1 (Mmp3), 2 (Mmp10) and 3 (Mmp11)] is often overexpressed in NSCLC (Bodey B *et al.*, 2001). Interestingly, Mmp10 is highly expressed in NSCLC tumors but not tumor-associated stromal cells, whereas Mmp3 and Mmp11 are expressed predominantly in stroma (Gill JH *et al.*, 2004). Based on these observations, Matrix metalloproteinases 10 are currently studied for the development of cancer vaccines for NSCLC and other malignancies. 4-hydroxypropiophenone (4-HPPP), it is a phenolic compound derived from spices possess potent anticarcinogenic activities. It has been found a valuable drug for checking the growth of lung metastases secondary to certain malignant tumors such as chorionepitheliomas or nephrobiastomas. 4- HPPP is of greater therapeutic value and with even less estrogenic activity, several new fluorine containing aromatic hydroxy ketones were prepared for biological investigation (Buu-Hot NGPH *et al*., 1952). 4- HPPP also the anticalcium effect can participate, besides the beta-adrenolytic and the membranostabilizing effects, in the antidysrhythmic activity.

The target based drug discovery is having higher potential over other methods (Horn L *et al*., 2012). It is essential to find out the binding energy between the ligand and receptor. Our previous study already proved novel compound for skin cancer by computational approach (Hemalatha S *et al*., 2015). Molecular docking is an important tool in structural molecular biology and computer- assisted drug designing. Structure- Based Design (SBD) and the related Fragment- Based Design (FBD) are well established strategies in the rational development of small molecule drugs. Knowledge of how a small molecule binds into a protein affords considerable advantages, both in terms of prioritizing compounds for early stage screening, through to optimizing potency and selectivity discovery studio delivers a comprehensive scalable portfolio of scientific tools, tailored to support and assist SBD and FBD strategies from hit discovery through to late stage lead optimization. In the current study, molecular docking was carried out with 4-HPPP as the ligand molecule and the protein MMP10 (3V96) which is found abundantly in lung cancer, as the receptor molecule. The docking calculations were performed using DS v4.5.

Materials and Methods

Docking Analysis:

The computational technique strongly supports and helps to identify the novel and more potent inhibitors through the mechanism of drug-receptor interaction. PDB is a repository for the three-dimensional structure data of large biological molecules, such as protein and nucleic acids (Dykstra KD *et al*., 2007). The structure of Matrix metalloproteinase 10 was retrieved from PDB (3V96). After obtaining the final model, the possible binding sites of 3V96 were searched using Computed Atlas of Surface Topography of Proteins (CASTp) (Binkowski TA *et al*., 2003). Using ChemSketch the structure of the ligand molecule, in this case, 4-HPPP is generated using their SMILES notation obtained from PubChem and saved in .mol format for the docking calculation. The generated structure of 4-HPPP is shown in Figure 1. A flexible docking calculation was carried out using Discovery Studio v4.5 (Biovia Dassault System, USA).

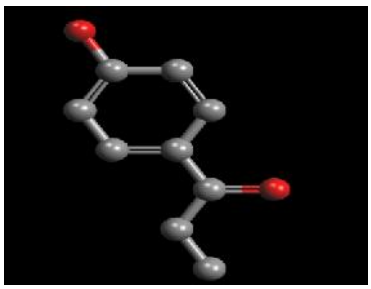

Figure.1 Shows the structure 4-hydroxypropiophenone

Results and Discussion

The target protein and inhibitors were geometrically optimized. Given the three-dimensional structure of a target receptor molecule usually a protein, chemical compounds having potential affinity towards it are designed rationally, with the aid of computational methods. Detailed bioinformatics analysis offers a convenient methodology for efficient *in silico* preliminary analysis of possible function of new drug. Figure 2 shows the structure Matrix metalloproteinase 10 which is used as the receptor molecule.

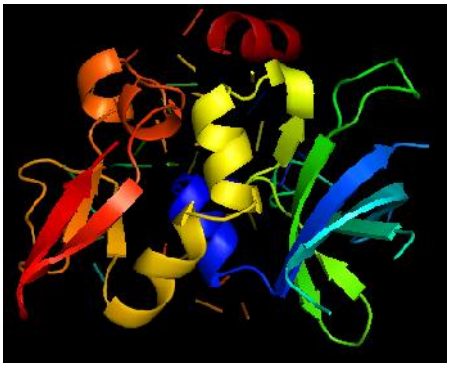

Figure.2 Structure of Matrix metalloproteinase 10 (PDB ID: 3V96)

Molecular docking study shows that the inhibitory pathway of the potential drug target against NSCLC using Bioinformatics tools (Warren G L *et al*., 2009). In the present investigation, the 4-HPPP was selected to identify its potential as a bioactive compound against NSCLC. Matrix metalloproteinase 10 receptor is considered to play an important role in the pathology of NSCLC activities and hence targeted mostly while administering the drug for NSCLC. 4-HPPP satisfied the Lipinski's properties. The selected ligand and Matrix metalloproteinase 10 receptor were subjected to docking studies using commercial tool Discover Studio Version 4.5 (Biovia Dassault System, USA). Ligand were docked with the target receptor. The energy value obtained as LibDock score was found to be 62.8644KDa with two hydrogen bonds at distance 3.00Å and 2.01Å and is illustrated in Figure 3.

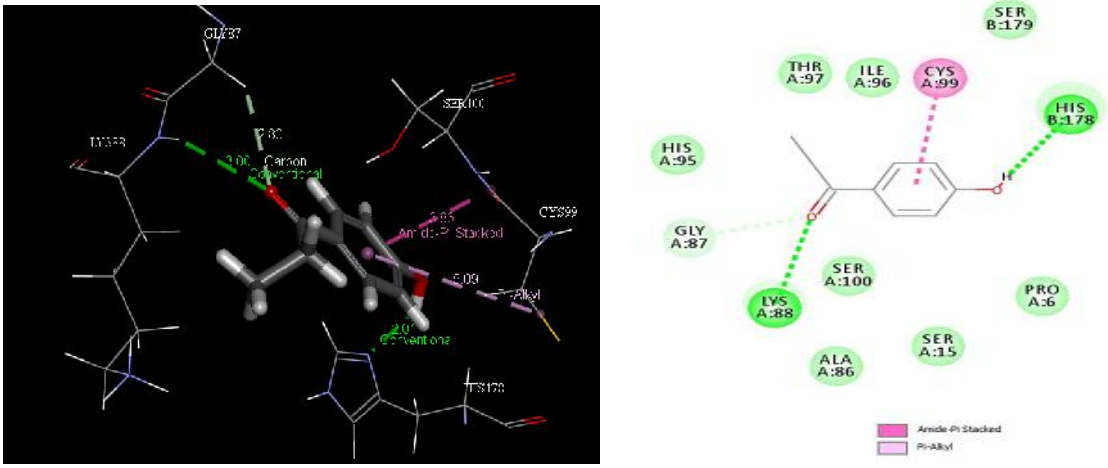

Figure. 3 3D and 2D Representation of the Docked Complex of 4-hydroxypropiophenone to that of the Target Matrix metalloproteinase 10 Protein.

After completing protein-ligand docking, the result was obtained in histogram format. It shows the overall interaction, hydrogen, hydrophobic interaction and favorable region. 2D interaction diagram shows the receptor, including amino acid residues, water and metal atoms in the active site where the ligand was bound. Interactions, such as hydrogen bond, charge-charge interaction and Pi interaction between the surrounding residues and the ligand occurred in four

favorable regions at GLY 87, LYS 88, CYS 99 and HIS178 and are illustrated in Figure 4 a 3D surface was created and colored based on hydrogen bond character, with receptor donors colored in green and receptor acceptors in cyan. The histogram shows that the ligand formed three hydrogen bonds with the residues GLY 87, LYS 88, and HIS178 are illustrated in Figure 5. Another 3D surface was created and colored by hydrophobic character based on Kyte – Doolittle scale, with receptor hydrophilic region colored in blue and receptor hydrophobic region in brown. The histogram for hydrophobicity shows that the ligand formed only one hydrophobic interaction with the residue CYS99 and is shown in Figure 6.

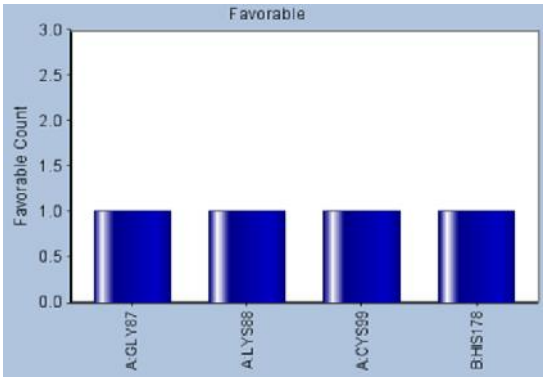

Figure.4 shows the histogram of the interaction and Favorable region

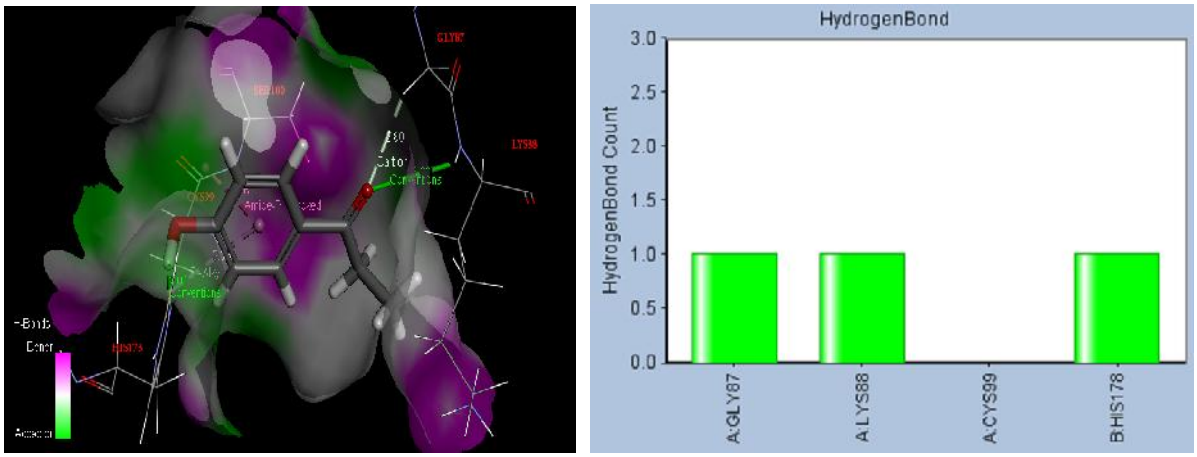

Figure.5 shows the 3D and histogram of Hydrogen Bond Interaction

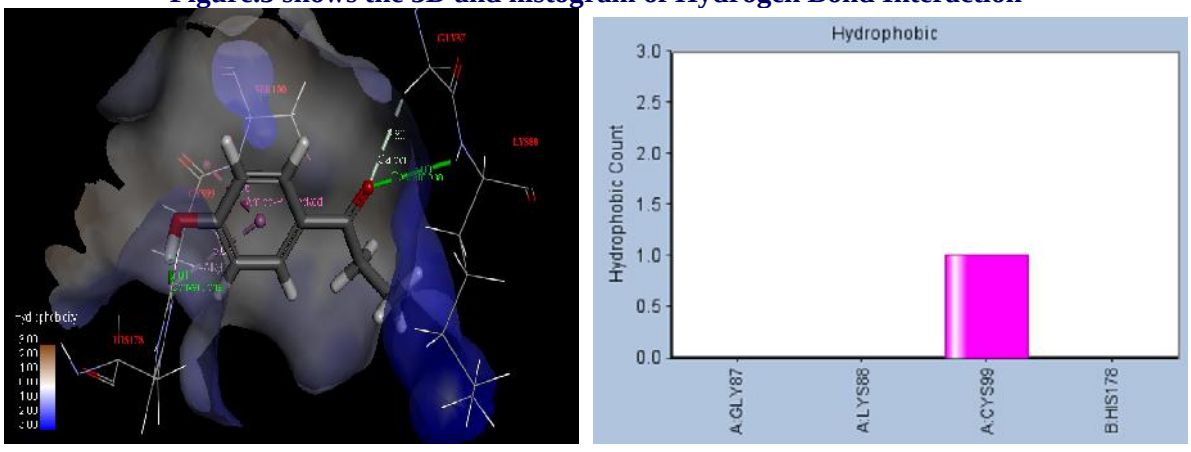

Figure.6 shows the 3D and histogram of Hydrophobic Bond Interaction

Conclusion

The current study was undertaken to substantiate that the compound 4-HPPP is capable of inhibiting the receptor Matrix metalloproteinase 10 which is targeted mostly for lung cancer. The results of the present study clearly show that 4-HPPP has a strong binding affinity towards the receptor protein MMP10 as evidenced by the LibDock score. Thus by targeting MMP10 with 4-HPPP, it can be a useful drug while treating the NSCLC.

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