Research Article

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INVESTIGATIONAL CANCER DRUG INHIBITS THE EXTRACELLULAR SIGNAL REGULATED PROTEIN KINASES (ERK1): AN *IN-SILICO* APPROACH

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ABSTRACT

The aim of this research was to study the investigational cancer drug used in inhibiting the skin cancer responsible protein by *In-silico* analysis. The computational technique strongly supports and helps to identify the novel and more potent inhibitors through the mechanism of drug-receptor interaction. The chemical compounds were selected from the drug bank as ligand molecule. The structures of the target protein (PDB ID: 3SA0), were obtained from the RCSB Protein Data Bank, http://www.rcsb.org/pdb. The protein ligand docking was performed in flexible docking. Discovery Studio is a well-known suite of software for molecular docking. It is developed and distributed by Accelrys. In the present investigation we performed an *In-silico* study. Ingenol Mebutate, Methyl lestosterone and Ponatinib from drug bank was used. Ligands were docked with the target receptor. The energy values were denotes in Lib Dock Score 71.6538 KDa, 29.4515 KDa, and 118.603 KDa.

Keywords: Skin cancer, ERK1, Transcriptional factors AP-1 and NF-κB**,** Ingenol Mebutate, Methyl lestosterone, Ponatinib

INTRODUCTION

Skin cancer is the uncontrolled growth of cancer cells in the skin. Left untreated, these cells can spread to other organs and tissues, such as lymph nodes and bone. Skin cancer is the most common cancer in the United States, affecting one in five Americans during their lifetimes, according to the skin cancer foundation[1]. Skin cancer, including melanoma and non-melanoma, represents a major public health problem as the incidence of skin cancer is equivalent to the incidence of cancers in all other organs combined[2,3]. p53 mutation is responsible for around half of human cancers, in p53 mutation 10-20 % human melanoma occurred[4]. Normal signs and symptoms of melanoma skin cancer are unusual sores, lumps, blemishes, markings, or changes in the way an area of the skin looks or feels may be a sign of melanoma or another type of skin cancer. Metastatic melanoma is a life-threatening disease[5]. Melanoma is a malignant tumor that arises from melanocytes, dendritic cells embryological derived from the neural crest. Melanocytes normally produce melanin, a pigment that defines the color of the skin and minimizes tissue damage from ultraviolet (UV) radiation[6]. It is the most aggressive form of skin cancer, and its incidence is increasing at a rate greater than any other form of cancer; further, it remains one of the most difficult cancers to treat[7]. Metastatic melanoma is characteristically accounts for 80 % of skin cancer deaths[8]. In the United States skin cancer accounts for over 40 % of all malignancies, and its incidence is increasing. Overall, melanoma is the eighth most common cancer diagnosed in the United States and although it accounts for only 4–5 % of all skin cancer diagnoses but it causes the majority of all skin cancer deaths[9]. Malignant melanoma is one of the most rapidly increasing cancers in the world with an increasing incidence rate in recent decades. An estimated 76, 250 new melanoma cases have been diagnosed in the United States in 2012 and 9180 are expected to die[10]. Melanoma has a high tendency to metastasize to brain tissue, the molecular alterations of early-stage melanoma progression to brain metastasis (MBM) is very limited. MBM-specific genomic and epigenomic alterations are a key initial step in understanding its aggressive nature and identifying specific novel druggable targets[11]. Non-melanoma skin cancer (NMSC) is the most common form of malignancy in humans and represents nearly 95 % of all cutaneous neoplasms[12]. Two most prevalent forms are basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Epidemiologic studies investigating the prevalence of NMSC in the general population indicate that the number of cases has increased rapidly over the last 2 decades. The incidence of NMSCs was estimated at 1.3 million cases for the year 2000 and is increasing. More than 1,000,000 new cases and 1000 deaths were reported in the United States in 2009. BCC is the most common skin cancer and composes 75 % of NMSC. SCC is the second most common skin cancer, accounting for 20 % of cases of NMSC[13]. Excessive exposure of the skin to solar ultraviolet (UV) radiation is one of the major factors for the development of skin cancers, including non-melanoma[14]. Actinic keratosisis another type of red, pink, or rough patch of skin. It is common skin lesions that appear after long-term exposure to ultraviolet radiation[15]. Ultraviolet (UV) irradiation is the leading factor in the development of skin cancer, prompting great interest in chemo preventive agents for this disease. Norathyriol is a metabolite of mangiferin found in mango, *Hypericum elegans* and *Tripterospermum lanceolatum* and is known to have anticancer activity. Mechanistic investigations

determined that norathyriol acted as an inhibitor of extracellular signal-regulated kinase (ERK) 1/2 activity to attenuate UVB-induced phosphorylation in mitogen-activated protein kinases signaling cascades. The xanthone moiety in norathyriol acted as an adenine mimetic to anchor the compound by hydrogen bonds to the hinge region of the protein ATP-binding site on ERK2. Norathyriol inhibited *in vitro* cell growth in mouse skin epidermal JB6 P^+ cells at the level of G (2)-M phase arrest. In mouse skin tumorigenesis assays, norathyriol significantly suppressed solar UV-induced skin carcinogenesis, indicated that norathyriol mediates its chemo preventive activity by inhibiting the ERK-dependent activity of transcriptional factors AP-1 and NF-κB during UV-induced skin carcinogenesis[16]. The target-based drug discovery is having higher potential over other methods[17], it is essential to find out the binding energy between the ligands and the receptors. Our previous study already proved novel compound for breast, liver cancer by computational approach[18,19]. 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 these study four ligand molecules from the drug bank using for various cancer treatment and skin cancer responsible protein 3AS0 as target was selected for molecular docking by Discover studio-Accelrys.

MATERIALS AND METHODS

The computational Technique strongly supports and helps to identify the novel and more potent inhibitors through the mechanism of drug-receptor interaction.

Preparation of ligand structures

The chemical compounds were selected from the drug bank. Chem Sketch (Chemically intelligent drawing interface freeware developed by Advance Chemistry Development, Inc., (http://www.acdlabs.com) was used to construct the structure of the ligands. The ligand molecules were generated and the three dimensional optimizations were done and then saved. MOL file (a file format for holding information about the atoms, bonds, connectivity and coordinates of a molecule); the properties of selected ligand molecules cited in Table 1.

Properties of Ligand Molecules

Table 1: Properties of selected ligand from drug bank

Properties	Ingenol Mebutate	Methyl lestosterone	Ponatinib
Molecular formula	$C_{25}H_{34}O_6$	$C_{20}H_{30}O_2$	$C_{29}H_{27}F_3N_6O$
Molecular Weight	430.53386 [g/mol]	302.451 [g/mol	532.55949 [g/mol]
H bond acceptors	6	2	8
H donors	3	1	1

Ligand

Ingenol mebutate was approved by the FDA in January 2012 and it is marketed under the name Picato®. Picato gel is indicated for the topical treatment of actinic keratosis. Before approval, Ingenol mebutate was called PEP005 as an investigational drug. PEP005 is a selective small molecule activator of protein kinase C (PKC) extracted from the plant *Euphorbia peplus*, whose sap has been used as a traditional medicine for the treatment of skin conditions including warts and cancer. PEP005 also has potent anti-leukemic effects, inducing apoptosis in myeloid leukemia cell lines and primary AML cells at nano molar concentrations. Ponatinib is a novel Bcr-Abl tyrosine kinase inhibitor that is especially effective against the T315I mutation for the treatment of chronic myeloid leukemia. FDA approved on December 14, 2012. The selected ligand 2D structure is shown in Figure 2.

Ligand Structure

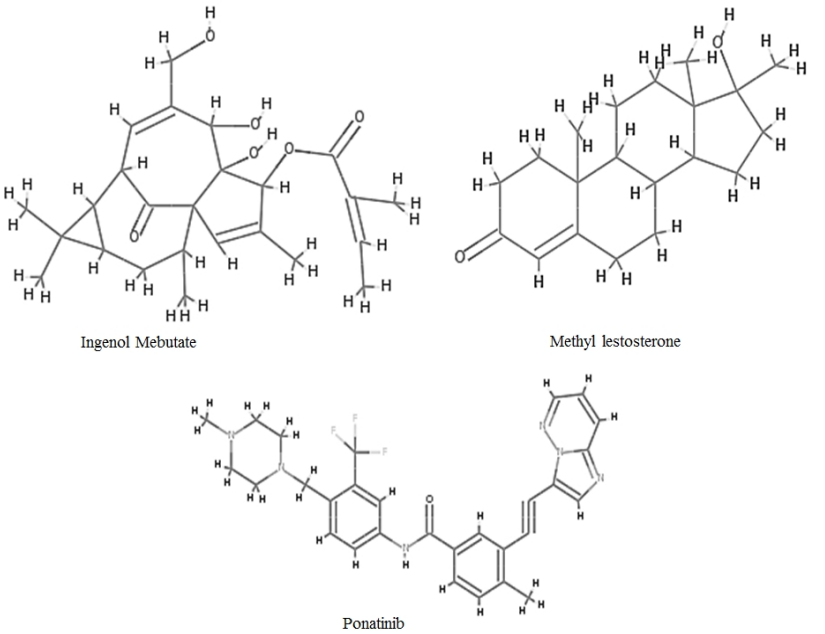

Figure 1: 2D Representation of Ligand Molecules

Prepare macromolecule structures

The structures of the target protein (PDB ID: 3SA0) (Figure 2), were obtained from the RCSB Protein Data Bank, http://www.rcsb.org/pdb. The macromolecule structure was opened in, PROTEIN PREPARATION wizard. It was enabled to identify potential problems. It automatically fixes and prepare protein structure. The missing loop was build, the side chains of missing residues are optimized, and then alternate conformations are managed.

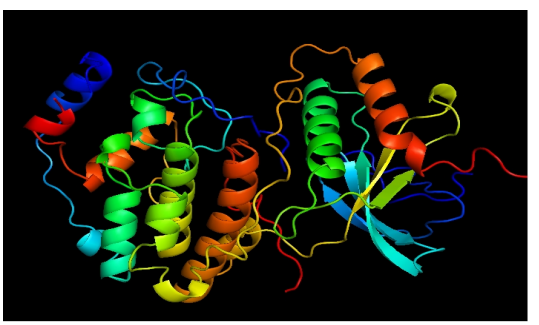

Figure 2: Structures 3SA0 protein

Protein-Ligand Docking

Discovery Studio is a well-known suite of software for molecular docking. It is developed and distributed by Accelrys. The protein ligand docking was performed in flexible docking.

RESULT AND DISCUSSION

Molecular docking is an important tool in structural molecular biology and computer-assisted drug designing. It finds the suitable inhibitors for receptor, binding energy between the ligands and receptors. The molecular docking predicts the binding ability of the ligand molecule with the receptor molecule. This computational technique strongly supports and helps to identify the novel and more potent inhibitors through the mechanism of drug-receptor interaction. Hence, in the present investigation we performed an *In-silico* study. Ingenol Mebutate, Methyl lestosterone, Ponatinib from drug bank was used. Ligands were docked with the target receptor. The energy values were denotes in Lib Dock Score 71.6538 KDa, 29.4515 KDa and 118.603 KDa. After complete protein ligand docking the result was obtained in histogram format it shows the overall interaction, hydrogen, hydrophobic interaction and favorable region Figure 3, 4 and 5.

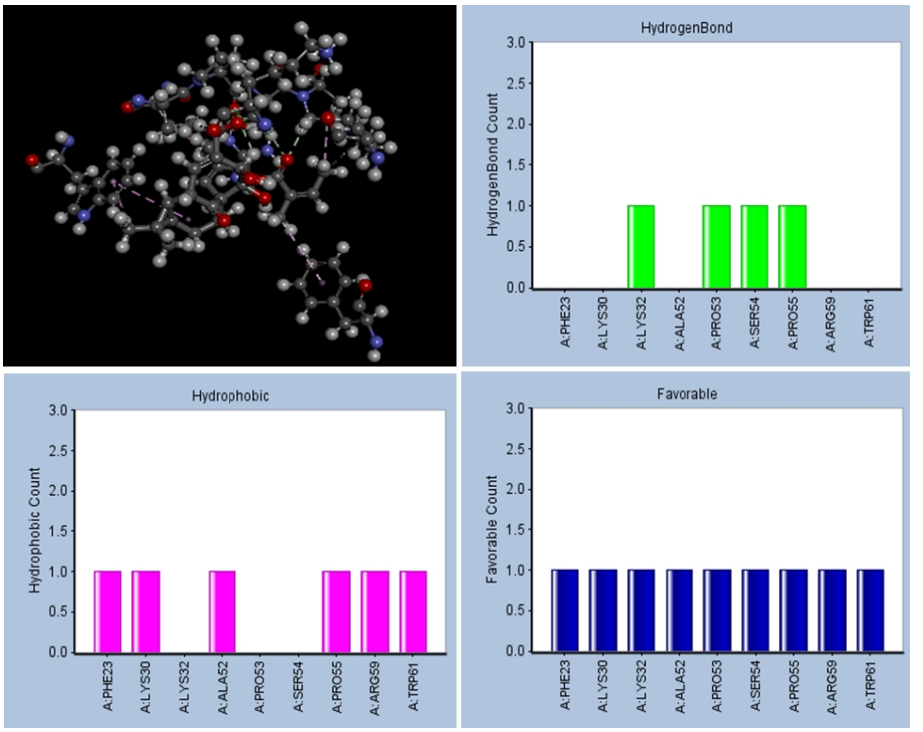

Figure 3: Protein interaction with Ingenol Mebutate

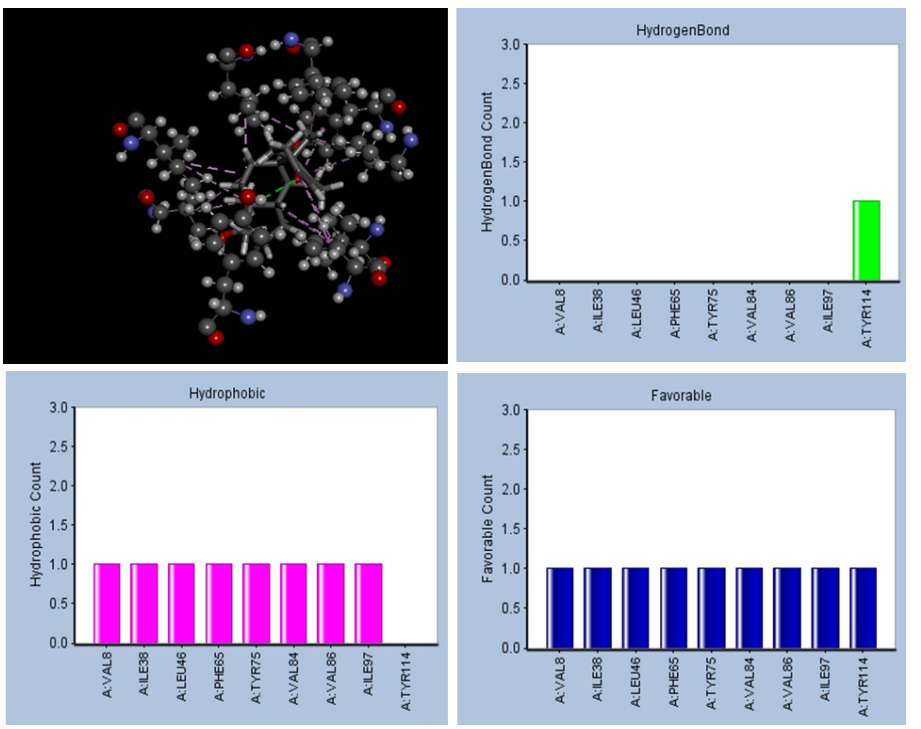

Figure 4: Protein interaction with Methyl lestosterone

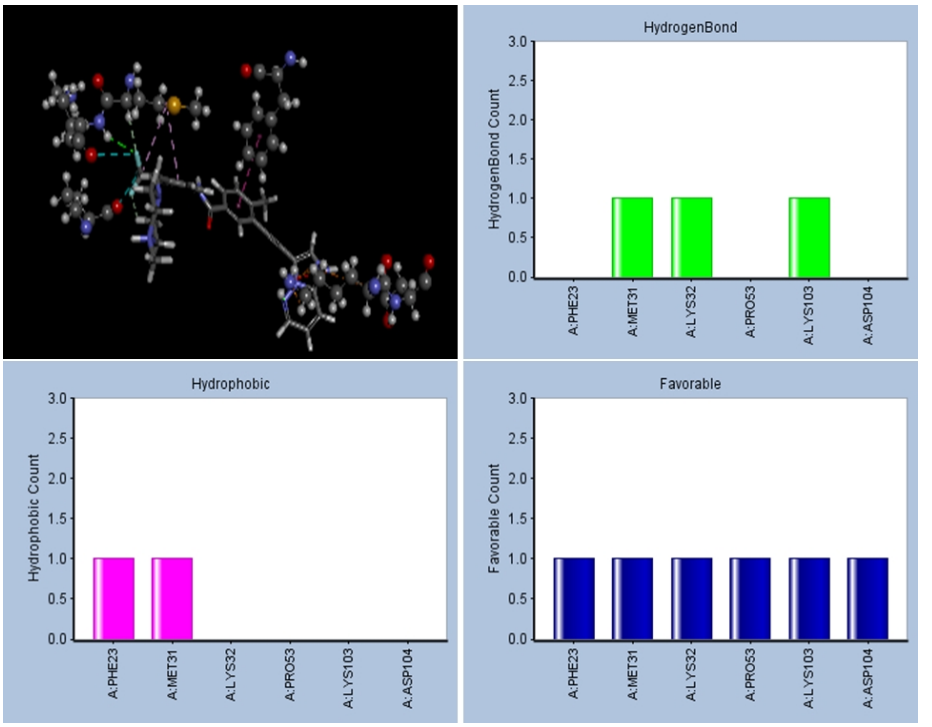

Figure 5: Protein interaction with Ponatinib

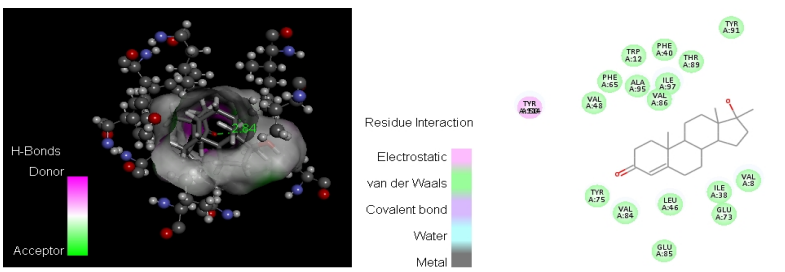

Figure 6: 3D and 2D interaction Ingenol Mebutate with 3AS0

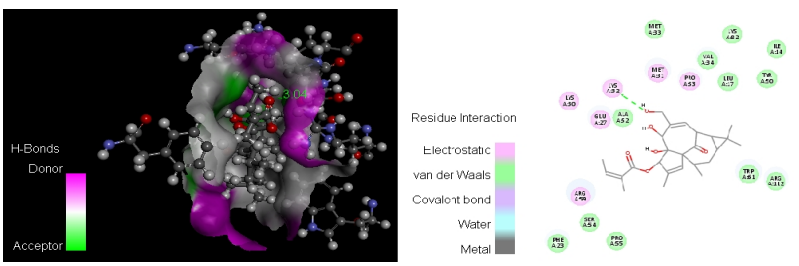

Figure 7: 3D and 2D interaction Methyl lestosterone with 3AS0

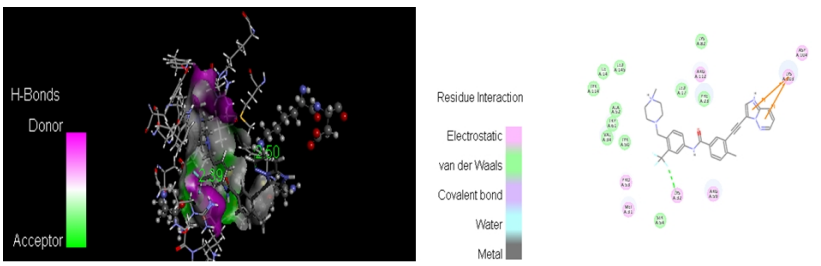

Figure 8: 3D and 2D interaction Ponatinib with 3AS0

The 3D surface was created and colored by hydrogen bond character, with receptor donors colored in green and receptor acceptors in cyan. 2D diagram defined receptor, including amino acid residues, water and metal atoms. Interactions, such as hydrogen bond, charge-charge interaction and Pi interactions between the surrounding residues and the ligand were displayed. Solvent accessibility of the ligand atom and the amino acid residues are shown in light blue shading surrounding the atom or residue. Heavier shading indicates more exposure to solvent (Figure 6, 7 and 8).

CONCLUSION

Thus, the present *In-silico* docking study also suggests that the compounds are capable of inhibition to skin cancer. The results of the present study clearly showed that Ponatinib has a strong interaction and binding with target protein (receptor molecules of cancer) as evidenced by its high binding energy Lib dock score.

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