1 INTRODUCTION

Cancer is a general term used to explain a group of complex diseases, about more than 100. It is characterized by multiplication; invasion and metastasis. There are different types of cancers based on their origin and organ where it infects. Cancer is caused by various abnormalities occurring in the affected cells. Tumorogenesis or carcinogenesis is complex multistep event that convert normal cell to a cancerous cell, involves the accumulation of mutations that deregulated the cell cycle (Gallie et al., 1999, Bergers and Benjamin, 2003). Cancer is considered primarily as a environmental disease, since 90 % of the cases are due to environmental issues and remaining 5% may be due to genetic and other factors (Anand et al., 2008).

The burden of cancer is high and increasing worldwide. One in eight deaths worldwide is due to cancer. Globally, cancer causes more deaths than AIDS, T.B and Malaria combined. Cancer is second leading cause of death in economically developed countries and third leading cause of death in developing countries (Jemal et al., 2008). Better prevention, early detection, and advances in treatment have helped some developed nations with lower incidence and mortality rates for certain cancers, but still in most parts of the world, cancer is a growing problem. It is estimated that cancer killed 7.6 million people around the world in 2007, and this figure is expected to rise to 17.5 million by 2050 simply due to the growth and aging of the population. Today, most cancers are linked to a few controllable factors – tobacco use, poor diet, lack of exercise, and infectious diseases. Tobacco use is the most preventable cause of death worldwide. If current trends in tobacco use continue, 650 million people alive today will eventually die of tobacco-related diseases, including cancers of the lung, esophagus, and bladder. In the developed world, poor diet, inadequate physical activity, and obesity are second only to tobacco as cause of cancer (Levitz et al., 2004).

Most of the chemicals can induce cancer by mutation and these agents are known as mutagens (Yashin et al., 2009). These mutations or epimutations can happen either in tumor suppressor genes or oncogenes. The point mutations like changes in DNA sequences (Weiher et al., 1983), or chromosomal aberrations (Bonassi et al., 2000) like translocation, deletion and
amplification are responsible for initiation of cancer. All mutagens are carcinogenic in nature but all carcinogens are not mutagenic in character (Yashin et al., 2009). Studies reveals use age of tobacco in any forms can induce many forms of cancer like cancer of larynx, oral cavity, lungs, pancreas etc (Kuper et al., 2002). Obesity and physical activity also matters for the death by cancer. It is noticed that excess body weight can also induce the cancer and leads to death (Anand et al., 2008). Diet with low fibers, vegetables, bran, whole grain, processed red meat. Contaminates like aflatoxin B\textsubscript{1} induce liver cancer and high salted food (Brenner et al., 2009) can induce colon cancer and gastric cancer (Rock et al., 2012).

Infectious diseases and viral infections can induce cancer and world’s 18% of the cancer death is due to infections (Anand et al., 2008). Different oncovirus are identified that can cause cancer like Human Papilloma Virus (HPV), Epstein- Barr virus, Hepatitis B virus. Bacterial infections also sometimes lead to cancer like infection of \textit{H. pylori} induced gastric carcinoma (Cunningham et al., 2010). Both ionizing and non ionizing radiations can induce cancer and is responsible for 10% of the death (Brenner et al., 2001). Less than 0.3% of the population is suffering from cancer due to heredity and it found that colorectal, breast and ovarian cancer is more common by heredity (Lynch and de la Chapelle, 2003, Prat et al., 2005, Russo et al., 2009).

Free radicals are the species carrying unpaired electrons and due to this unpaired electrons, they are found to have high reactivity. Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) were the hot discussion for last few years regarding their role in inflammation, ageing and cancer (Halliwell and Gutteridge, 1985). They are generated in biological system during irradiation with ionizing and non ionizing radiations, due to metal cheleated reactions, produced during inflammation, or produced as a bi product during mitochondria catalysed electron transport system (Cadenas, 1989). These radicals are known for their duel role in biological systems, since they can be beneficial or harmful to the system (Valko et al., 2004). In higher concentration these ROS are important mediators are in cell structure damage known as oxidative stress. This damages caused by the free radicals can develop cancer. Antioxidants are the one which protect the cell components from oxidation and prevent the cellular damage. Enough laboratory evidences from chemical, cell culture and
animal studies indicates that antioxidants delays or prevent the incidence of cancer (Kornhauser et al., 1995).

Apoptosis or programmed cell death, with characteristic morphology and highly regulated endogenous mechanism plays a key role in maintaining the normal homeostasis of the body. The homeostasis is a result of balance between tissue proliferation, differentiation and apoptosis (Maioral et al., 2013). But malignancies are characterized by excessive growth due to the failure of above mentioned mechanisms. These apoptotic mechanisms have an important role in the embryonic development, tissue modeling, immune regulation, and tumor regression. But the genetic change disrupts the apoptosis and result in tumorogenesis and drug resistance (Kaufmann and Earnshaw, 2000). Apoptosis can be induced by activating mitochondria (intrinsic pathway) or death receptors (extrinsic pathway) results in the activation of capsizes. The process of apoptosis is characterized by the changes in the cells like fragmentation of DNA, chromatin condensation, cell shrinkage and membrane blebbing. A recent report explains that, those drugs which compromise the structural and functional integrity of mitochondria can be an alternative against neoplasm. Death signal can be detected by the mitochondria, results in the collapse of mitochondrial potential are triggered and apoptotic factors as Cytochrome C are released to cytosol (Winter et al., 2010, Kuete and Sandjo, 2012). These factors activate caspases and culminating apoptosis. An imbalance in the oxidative metabolism can also result in cell death known oxidative stress. The main organelle involved in this process is mitochondria because it consumes cellular oxygen and responsible for the release of reactive oxygen species, (ROS). Under this condition normal cells will undergo an adaptation process with their antioxidant defense mechanism (Lou et al., 2010). On the other hand the tumor cells either will fail or possess limited adaptation mechanism to these changes. The antitumor agents can trigger the ROS production have potential therapeutic benefits if relate the increase of ROS to increase of cell death.

There are different strategies to treat cancer which includes radiation therapy, chemotherapy and surgical treatment. The selection of therapy depends on the stage and location of the tumor growth. In radiation therapy high energy radiations like X rays, gamma rays were used to irradiate the tumor to shrink and kill the cancerous cells. Radiation therapy produces the effects by damaging DNA directly or produces free radicals which in turn damage
DNA. Radiation therapy can kill other cells too. Chemotherapy is a term used to explain about the treatment of cancer with one or more cytotoxic anticancer drugs under a standardized regimen. Cancer chemotherapy is performing along with other treatment systems like radiation and surgical treatment. These chemotherapeutic agents can be employed based on the cancer and how advanced the conditions. Chemotherapy can be used to cure, control or erase the symptoms of cancer. Traditionally all chemotherapeutic agents kills the rapidly growing cancer cells, along with this it harms the growth of normal cells. These agents produce their anticancer effect either by interfering with their ability to grow or multiplication. These agents affect the growth of cells in bone marrow, hair follicles and GIT. This will leads to marked side effects like myelosuppression, alopecia and mucositis. Cancer surgery is to achieve different goals like prevention, diagnosis, staging and primary prevention debulking and relieve the symptoms. Surgical treatment is the one where complete removal of the tumor without affecting rest of the tissue.

There are different strategies in performing the chemotherapy for cancer by the present day drugs. It includes with an intension to cure or prolong the life of the patient. The present drugs employed in the cancer treatment can be categorized in to two classes,

I. Drugs which act directly on the cells, known as cytotoxic drugs
II. Drugs which alter the hormonal background

The various class of drugs employed in the treatment for cancer is given

1. Alkylating agents (Schabel Jr, 1976, Hickman, 1992, Pratt, 1994, Avendano and Menendez, 2008): these agents can alkylate the nucleophilic center in DNA, stops the division. The compounds alkylate the guanine residue of DNA on the nitrogen at the 7th position of the purine ring. These agents can damage the fast growing normal cells like bone marrow, GIT and hair follicles. These agents a reported to have carcinogenic potential also. Cyclophosphamide, Melphalan, Chlorambucil, Melphalan, are the commonly used alkylating agents.

2. Anti-Metabolites (Hickman, 1992, Pratt, 1994, Wallace and Fraser, 2003): These are the molecules possess a structural similarities with a metabolites, which compete, replace, or inhibit the metabolites and interfering the normal metabolic activities of the cell.
They have high structural similarity to that of metabolites and can be incorporated into DNA or RNA and prevent the function and multiplication. Different classes of anti-metabolites are available and they are purine antagonist, pyrimidine antagonist and folate antagonist.

3. Natural products (Clark, 1996, da Rocha et al., 2001, Newman et al., 2003, Jordan and Wilson, 2004): Ancient times itself natural products find attraction in medicine and large number of natural products gain a high momentum in the cancer chemotherapy and found to be highly effective. One of most successful natural products identified is vinca alkaloids obtained from *Catharanthus roseus* and found to effective against Hodgkin’s disease and some forms of Leukemia. Taxans, Paclitaxel, and docetaxel are found to be effective against certain cancers like ovarian, and breast. Etoposides are another class of compounds found to be highly effective against testicular cancer and small cell lung cancer, obtained from *Podophyllum peltatum*.

4. Antibiotics (Nicolaou and Dai, 1991, Avendano and Menendez, 2008): Large number of anticancer antibiotics were identified and employed extensively to compact the effect of cancer. They include anthracylines, actinomycin, bleomycin, and dactinomycin. They exhibit their anticancer activity either by intercalating DNA, attack cell membranes by lipid peroxidation or intercalate the grooves in DNA. These antibiotics are used for the treatment of carcinomas of breast, lungs, testicles, choriocarcinoma, Wilms tumor and many sarcomas. These anticancer antibiotics offer higher toxicity includes cardiac toxicity, toxic to oesteoclasts and decrease plasma calcium level.

5. Drugs altering the hormonal milieu (Avendano and Menendez, 2008): Hormones essentially steroidal hormones play a major role in the induction and growth of tumors. Introduction of an anti hormone that can block the effects of these hormones will be an effective anticancer agent. Thus compounds which can act on these receptors like estrogen and androgen receptors can employed for the treatment of breast and prostatic cancers.
Figure 1: Dynamic equilibrium between microtubules and tubulin dimers. (Jordan and Wilson, 2004)
1.1 MICROTUBULES AS THE TARGETS

Microtubules are filamentous structures as part of cytoskeleton responsible for the movement within the eukaryotic cell. They are long filamentous, tube shaped protein involved in the development and maintenance of cell. These microtubules have very prominent role in cell signaling, mitosis. Microtubules are composed of tubulin, which is made up of two globular protein subunits units, α and β tubulins in head to tail fashion (Teicher, 2008). There is a dynamic equilibrium is exists between free tubulin dimmers and microtubules (Fig.1) and is highly sensitive to external factors.

These microtubules are important in cell division helps the migration of daughter chromosomes in to either side of the cell before cell cleavage in to daughter cells. The significance of microtubules in cell division and mitosis makes it as an important target in cancer drug design and development. These microtubules and their dynamics can act as the targets for diverse class of compounds. These compounds elicit their action either by disrupting the equilibrium, by binding to the tubulin, inhibiting the polymerization, or inhibiting the depolimerization by stabilizing them. This way these compounds inhibit the formation of mitotic spindles and know as antimitotic agents.

This microtubule offers different binding sites for the drugs acting on them and smothers microtubule dynamics, and thereby blocking mitosis at the metaphase/anaphase transition and inducing cell death. The antitumor agents can be divided in to two based on their behavior and are

I. Microtubule destabilizing agents : Vinca alkaloids, Colchicine and Combretastains

II. Microtubule stabilizing agents: Paclitaxel, Polyisoprenyl benzophenones58,59

There are three main binding sites were identified in tubulins where drugs can bind and designated by the name of best finding ligands as Vinca, Colchicine and Taxol sites.

Vinca binding site: Alkaloids obtained from the leaves of Catharanthus roseus shows potent cytotoxic effects by destabilizing the microtubule assembly (fig 2).
Figure 2: Antimitotic drugs bind to microtubules at diverse sites. (McGrogan et al., 2008)
These compounds bind to the distinct region in beta subunit of tubulins and produce the cytotoxic effect is known as Vinca binding site. Other than these Vinca alkaloids other compounds like Dolastatins, Cryptophycin25 also bind with this same site and produce the cytotoxic effect. The remarkable side effect of these Vinca alkaloids is their neurotoxin potential and development of cross resistance.

Colchicine binding site: Colchicine, an alkaloid obtained from *Colchicum autumnale*, widely employed in the treatment of gout. Many drugs which can bind with this binding site are Colchicine (5), Combretastain (6), 2-methoxyestradiol (7), Podophyllotoxin (8) etc. Colchicine is known for the toxicity and other compounds are under clinical investigation for the efficacy.

Taxol binding site: The compounds binding to this site is known as microtubule stabilizing agents. Paclitaxel obtained from the bark of yew tree, *Taxus brevifolia*. The binding site of Taxol in tubulins is beta subunit and is the inside surface of the subunit. Taxol is one of most successful natural product widely employed for the treatment of breast, lung and ovarian cancer. Even though Taxol and its derivatives are found to be effective, they also not away from drawbacks like resistance, marked neurotoxicity, myelosuppression, and solubility problems with water. The fig. 2 explains the different class of antimitotic agents interacts with binding sites in microtubules.

Combretastain (CA4) simple molecule obtained from the bark of *Combretum caffrum*, possess a 1, 2-diarylethyle scaffold (Pettit *et al.*, 1982, Pettit *et al.*, 1986, Pettit *et al.*, 1989). The structures possess two simple aromatic rings linked by a double bond in cis configuration (Tron *et al.*, 2006). Despite the low molecular weight and simple structure CA 4 is found to be one of the most potent tubulin polymerization inhibitor. Studies showed CA 4 is a powerful inhibitor but has low water solubility.
To compensate the solubility issues a more water soluble prodrug CA-4P was developed and selected as a lead molecule for in vivo studies (Young and Chaplin, 2004, Thomson et al., 2006). Unlike other anticancer agents clinical trial data of CA-4P shows it doesn’t possess any toxicities like bone marrow toxicity or alopecia. Because of the simplicity in the structure and easy to synthesize CA-4 has great attraction of medicinal chemist. The molecule can be subdivided into three main elements, ring A, ring B and a double bond Fig 3. Various analogues of this compound can be prepared very easily and modifications on the three parts of the molecule. A series of compounds possess the same molecular framework, as that of CA-4, two aromatic rings linked by various moieties such as enones (chalcones) 10, alkenes (stilbene) 11, and ethers 12 are considered to be analogues of CA-4 (Ducki et al., 2004).

Among these, chalcones are found to be more interesting due to the simplicity in structure, easy to synthesize and obtain in high purity. Chalcones are 1,3-diphenyl 2-propene-1-one, possessing two aromatic rings connected by a three carbon $\alpha, \beta$ unsaturated carbonyl system (Ethiraj et al., 2013). The, $\alpha, \beta$ unsaturated carbonyl system of chalcones will react with thiol functionalities instead of amino or hydroxyl moieties. Thus interaction with nucleic acid may not happen and reduce the risk of mutation (Dimmock et al., 1999). This makes chalcones one of the safest scaffolds in medicinal chemistry. It is considered as the precursors of flavonoids and isoflavonoids. The Chalcones possessing structural similarity with Combretastatin are known to hold a wide range of biological activities such as antiangiogenic (Mojzis et al., 2008) cytotoxic,
antioxidant (Anto et al., 1995), antimalarial (Chen et al., 1997), antileishmanial (Nielsen et al., 1998), anti-inflammatory (Hsieh et al., 1998), anti-tumor and antibacterial properties (Kumar et al., 2003). Chalcones and its derivatives are found to inhibit various enzymes in the cellular system including xanthenes oxidase, aldose reductase, epoxide hydrolase, protein tyrosine Kinas, and quinone reductase (Nowakowska, 2007). Chalcones can provide large number of derivatives by incorporating various heterocyclic rings in to the enone system. A range of heterocycles like pyrazolines (Pinto et al., 1998, Rathish et al., 2009, Rahman and Siddiqui, 2010), isoxazole, thiazine and oxazine derivatives (Kalirajan et al., 2009)obtained from chalcones due to the presence of a bifunctional, -3 dinucleophile. Pyrazolines are important nitrogen containing heterocyclic compounds, and are reported to have anti-microbeal (Karthiskeyan et al., 2007, Hamada and Sharshira, 2010, 2011), anti-inflammatory (Reddy et al., 2008, Sivakumar et al., 2010b, Sondhi et al., 2012) anti-cancer (Abdalla et al., 2012, Jainey and Bhat, 2012, Patel et al., 2012, Marella et al., 2013b), anti-oxidant (Bandgar et al., 2012, Gawande et al., 2013), anti-viral (Joshi and Singhal, 2012, Tantawy et al., 2012), anti-depressant (Sui et al., 2012), anti-diabetic (Marella et al., 2013a), anti-mycobacterial (Shaaban et al., 2012, Baseer et al., 2013, Marella et al., 2013a), and anti-malarial property (Thakur et al., 2012). Pyrazolines found applications as dyestuff, analytical reagents, and in agro industry. Therefore, the pyrazoline moiety has a predominant role in medicinal chemistry since it is part of many scaffolds which showing impressive array of activity. More over pyrazolines play an important role in heterocyclic chemistry and used extensively as synthon in organic chemistry. Pyrazoline derivatives exhibit growth inhibitory properties on several cancer cell lines (Johnson et al., 2007b) and also act as effective inhibitors of heptosyltransferase (Burja et al., 2010). Some of the pyrazolines were effective in inhibiting the accumulation of prion protein (Kimata et al., 2007), abnormal protease resistant form. When pyrazolones were the part of a tricyclic system, it is expected to possess cytotoxicity nature by inhibiting tubulin polymerization (Kalirajan et al., 2009).

Xanthenes and its derivatives are found to be the parent compounds for many natural products and are used as versatile synthons due to their reactive inbuilt pyran ring (Shaterian et al., 2009). Synthesis of xanthenes and its derivatives attracted medicinal chemist for their wide spectrum of biological activities and therapeutic properties like
antibacterial, antifungal, antiviral (Jamison et al., 1990), anti-inflammatory, antioxidant and anticancer (Mulakayala et al., 2012). These compounds are also employed as antagonist for paralyzing the actions of Zoxazolamine and in photodynamic therapy. Naturally occurring xanthenes like Diversonol and BlennolideC exhibiting potent cytotoxic activity against various cell lines. Xanthenes are considered as a high priority structures in combinatorial drug discovery programme due to their diverse biological activity and therapeutic properties (Venu Madhav et al., 2009). They are widely used as dyes fluorescent materials for visualization of bio-molecules and laser technologies due to their spectroscopic properties.

The most common method for the synthesis of xanthenes derivatives involves the condensation of aryl aldehydes with 1,3-cyclohexanediones or 5,5-dimethyl-1,3-cyclohexanedione (Mulakayala et al., 2012). This reaction is performed in presence of various protonic acids or a range of Lewis acids like InCl₃.4H₂O (Fan et al., 2005a), FeCl₃.8H₂O (Fan et al., 2005b) or heterogeneous catalyst such as Dowex50W (Shakibaei et al., 2007), NaHSO₄.SiO₂ (Das et al., 2007), polyaniline p- toluene sulphonate (John et al., 2006), silica sulphuric acid (Seyyedhamzeh et al., 2008), PPA-SiO₂ (Kantevari et al., 2007), TiO₂/SO₄, Amberlyte, SbCl₃/SiO₂ and Fe²⁺- montmorillonite. Nanomaterials like TiO₂ under solvent free condition is also used for the condensation reactions (Zhang et al., 2013). Recently ionic liquids and ethylene glycol also can be used for this condensation reaction.

Some of these methodologies suffer from disadvantages, like low yields, long reaction time, harsh reaction conditions, and the requirement of excess catalysts/reagents or special apparatus, use of toxic organic solvents. To avoid these limitations, the discovery of a new and efficient catalyst with high catalytic activity, short reaction time, and simple reaction working-up for the preparation of xanthenes under neutral, mild and practical conditions is of prime interest.
1.2 MOLECULAR DOCKING

Molecular docking is a well reputable computational technique which predicts the preferred orientation of one molecule to another when they interact each other to form a stable complex (Lengauer and Rarey, 1996). Molecular docking can be different levels depends on the interacting specie, ligand-protein docking, protein–protein docking. The small molecule involved in docking is known as ligand the macro molecule may be a protein or a nucleic acid and is known as receptor. These ligands will interact with the cavities present in the macromolecule and will get activation when comes in contact with these ligands. Molecular docking will helps to understand the orientation of ligands thus predicts the affinity and activity. Hence docking plays a major role in rational drug design (Kitchen et al., 2004)

1.2.1 TYPES OF INTERACTIONS

Different types of interactions are possible between the macromolecule and ligands and stability of the complex is favored by the strength and type of interactions (Knegtel et al., 1997, Andrusier et al., 2007). The interactive forces are,

I. Electrostatic forces: There is an electrostatic force can experience between the interacting species if they possess charges on it. The possible interactions are charge – charge, charge – dipole and dipole- dipole between the interacting species.

II. Electrodynamic forces: Interactions like Van der Waal’s will experience between the ligand and receptor.

III. Steric forces: Atoms of different size approach each other and get interacted each other, these steric forces will experiences. This will result in chemical reactions and free energy of the system.

IV. Solvent related forces: These forces can experiences when the interaction of solvent with either protein or ligand. Hydrogen bond and hydrophobic interactions are considered as solvent mediated forces.

Molecular docking involves two sections
I. Search Algorithms: These search algorithms help to identify all possible conformations of a molecular complex in the given environment. It will recognize the position and orientation of interacting species (Ewing and Kuntz, 1997, Halperin et al., 2002). These search algorithms will calculate the energy of interactions between the interacting species. Different algorithms used to commonly in the docking tools are

i. Molecular dynamics
ii. Monte Carlo Algorithms
iii. Genetic algorithms
iv. Fragment-based methods
v. Point complementary methods
vi. Distance geometry methods
vii. Systematic searches

II. Scoring function (Jain, 2006): Scoring function is used to predict the strength of non-covalent interaction between the ligand and the macromolecules. It is expressed as mathematical equations considering all type of interactions involves in the complex formation.

1.2.2 TYPES OF DOCKING

Different type of molecular docking is there and they are,

I. Rigid Docking is the one where the geometry of both the receptor and ligand were kept rigid in nature.

II. Flexible docking otherwise known as induced fit docking; here the ligand is kept flexible. Here many conformations of the ligand will generate and calculate the binding energy of the best fit conformation with the active site.
1.2.3 STEPS INVOLVED IN MOLECULAR DOCKING

The various steps involved in molecular docking are

Step 1: Building the receptor- in this step the crystalline 3D structure of target protein or enzyme is downloaded from the Protein Data bank (PDB) and modified. This preparation involves removal of water molecules, generation of side chains, stabilizing the charges, filling the missing residues according the available parameters.

Step 2: Identification of active sites- Second step in the molecular docking is the identification of active sites within the receptor. One receptor may possess many actives sites and the interesting active sites may be selected for the interaction studies. The water molecules, endogenous ligands, heteroatoms and metal ions have to remove from the site before docking.

Step 3: Ligand preparation – The ligands for the docking can be obtained from various databases like PubChem, ZINC or can be sketched using drawing tools like Marvin sketch, Chemsketch or Chemdraw. The ligands employed for docking should pass the criteria for Lipinski rule of five. The rule is important for drug development where a pharmacologically active lead structure is optimized stepwise for increased activity and selectivity, as well as drug-like properties.

Step 4: Docking- Docking is the final step in the protocol where the ligands are allowed to interact with active sites of the receptor (Wu et al., 2003). The scoring function generates the score based on the interaction and will define the best ligand for the particular active site of the receptor (Shoichet et al., 2002).

1.3 QUANTITATIVE STRUCTURE ACTIVITY RELATIONSHIP

Quantitative Structure Activity Relationship Studies is an undeniable view in modern medicinal chemistry and biochemistry. The concept of QSAR is to transform the searches for the compounds with defined properties using knowledge in chemistry and experience in to a mathematically quantified form (Karelson et al., 1996). Once a better
correlation is defined between the molecular structure and biological response is defined any number of compounds including those not yet synthesized can screen with the aid of computer. This will helps to select the most promising compound to synthesize and test for the desired biological response in the laboratory. Thus QSAR helps in accelerating the drug development programme and conserves the resources (Hansch et al., 2002). Last few years have been apprehensive in QSAR predictability. Medicinal community doubted QSAR models to live up to expectations in predicting biological responses (Kalani et al., 2012). A close perusal of published work reveals that researchers have emphasized and discussed more of statistical part of QSAR models, while application domain remained unexplored. In general, a QSAR models is assessed on the basis of statistical parameters like $R^2$, $R^2_\lambda$, S.E., F-stat, $R^2_{CV}$ and many others to record overall structure-activity relationship in a given set of objects and estimation of their biological responses. Interpretation and conclusion of such QSAR models may be erroneous and illusive unless an individual substitution impact in objects could not be explained. Medicinal chemists want QSAR models to be concluded in terms of bio-chemical aspects rather than statistics and numerical presentations. To be simplified, a chemist wants to know the effect of substitution of an atom or group on its biological response.