Drug design

Design

A drug Is a substance that we used mostly In our dally lives. It Is a chemical substance with physiological effects when ingested or introduced into our bodies. The response produce can either be beneficial or harmful. Toxins and poisons can be classified as drugs. This report the term 'drug' Is for medicinal or pharmaceutical purposes. Drugs used to prevent or treat diseases. Drug design also known as rational drug design is the creative process of discovering or finding a new drug eased on the knowledge of a biological target.

Modern drug discovery involves the identification of screening hits, medicinal chemistry and optimization of those hits to Increase the affinity, selectivity (to reduce the potential of side effects efficacy/ potency, metabolic stability (to increase the half-life), and oral availability. Once a compound that fulfils all of these requirements has been identified, it will begin the process of drug development prior to clinical trials. One or more of these steps may, but not necessarily, Involve computer-aided drug design. Humanity has been has been consuming and experimenting with drug substance for centuries.

This dates back in the early days of human civilization when drugs were not only used for their therapeutic properties but they were also used in association with religion and spiritual healing. This all changed when chemistry reached a high level of maturity principles and methods started to be applied and drug researches were performed this then gave rise to drug discovery and design. In the sass drug design and discovery started following scientific techniques and round the 1810 essential foundations of chemical theory had been laid.

Drugs are mostly discovered by accident or by " luck". Drug discovery deals with the synthesis and design of the drug. It is not the drug itself that that gets discovered but the active ingredient of the lead component. Lead compound discovery is the starting point of drug discovery and design. It can be discovered from various sources either natural for example venom from animals or plant flora. The lead compound can consist of desirable characteristics and of undesirable characteristics such as crease in metabolism, toxicity, heart problems etc.

The lead compound can be modified to enhance their desired effects and to eliminate or reduce the undesirable effects. In this report will be discussing the drug design and discovery process In details and the analytical techniques used in small molecule drugs. Small molecule drugs 1 OFF 7000 Dalton to be exact. 6. ANALYTICAL TECHNIQUES USED IN ADD 6. 1 X-ray crystallography X-ray crystallography uses x-ray on crystals. X-rays are electromagnetic waves with a short wavelength of 0. 01-100 NM. This helps because the atomic structures have nod lengths of 0. -0. 2 NM, thus able to resolve atomic details. This method determines atomic and molecular structure of crystals. It is used in drug design and discovery as a standard technique for three dimensional structures. It is the only method that determines the absolute configuration of a molecule. The drug compound of protein molecules to be studied using an x-ray, must be in crystalline form. This allows the compound or the molecules are orderly arranged in building blocks containing a molecule protein. This then form imaginary cubes termed unit cell. Figure 6. . 1) Figure 6. 1. 1 : Crystalline molecules in AD (Unit cells) X-ray beams are the focused on different of these unit cells, a AD diffraction

pattern is created consisting of many diffraction spots. Each diffraction spot has an intensity which is the summation of constructive interference by the atoms in the molecule at a certain orientation, and the dimensions and pattern are due to the geometric positions of these atoms within the protein molecule. The phase angles of the diffraction beams are determined by complex mathematical functions. From Figure 6. 2 we can see that X-ray crystallography has three basic steps. The first step which is the most difficult is obtaining a crystalline structure of the molecule to be studied. The crystals should be large greater than 0. 1 mm in all dimensions. And it should be pre in composition and regular in structure. The second step is placing the crystal in an intense X-ray beam (monochromatic x-rays) this produces regular pattern reflections. With the gradual rotation of the crystal the previous reflections disappear and new ones appear; the intensity of every spot is corded at every orientation of the crystal.

Multiple data sets may have to be collected, with each set covering slightly more than half a full rotation of the crystal and typically containing tens of thousands of reflections. (http://en. Wisped. Org/ wick/X-ray_crystallography, 25-04-13). The third step compotes the combine data with complementary chemical information to produce and refine a model of the arrangement of atoms within the crystal. The disadvantage about this technique is that it requires protein crystals which are very difficult to obtain because the process itself is difficult.

Once the structure has been determined the next step is the designing of the potential drug molecules. Figure 6. 1. 2: Steps in X-ray structure determination Figure 6. 1. 3: NORM instrument NORM is another technique

for determining the AD structures on compounds. It is as powerful as X-ray crystallography the difference is that NORM requires that the compound be in solution, rather than in crystal form. This technique provides information about the number and types of atoms in a molecule and also about the electronic environment around the atoms.

The principle of NORM is that is uses difference radiation to excite atoms, usually 1 H (protons) and ICC-atoms, to switch their spins from aligning with the magnetic field to aligning against an applied magnetic field. The range of frequencies required for excitation and complex splitting are characteristics of the chemical structure of the molecule. Figure 6. 1. 4: Alignment with applied magnetic field Spins can be classified as +1/2 or -1/2. Atoms such as 1 H, ICC, NON, NON and 31 P have nuclei consisting of protons with unpaired spins. The spin of the nucleus can align in two energy states when an external magnetic field is applied.

Applied energy at the right frequency results in resonance and the spin flips from one energy state to another, as seen in figure above and according to the formula: where h, is Planks constant; y is magnetometer ratio of a particular nucleus and Boo is the applied magnetic field. The energy difference between the spins aligning with or against the magnetic field depends on the power of the magnetic field applied. The field difference is proportional to the energy difference. The NORM spectrum also provides information about the number of nuclei under each environment.

This information is given by the area under each resonant peak representing the relative number of nuclei of each type. 6. 2. 2 NORM Drug Discovery

NORM is also used to investigate the dynamic interactions of lagans-receptor binding. NORM has to important properties namely chemical shift and nuclear spin relaxation. When a protein receptor and lagans bind, they disturb the micro-chemical environment of the protein nuclei through bond formation, Hydrogen bonding or van deer Walls forces. The switching of the resonance frequency reflects the power of the interaction.

The nucleus flips to another spin state by absorbing the magnetic energy. After a limited time, the spin state reverts to the original state through an equilibrium process. Small molecules with fast rotational motions have slow relaxation rates. The interaction of a lagans binding to a target slows the rotational motions. The relaxation time therefore changes. This is noted over the nuclear overhauls effects (Noses), which are a measure of rotational motions of molecules. In small molecules a negative NONE is indicative of the binding of the protein target. - phenols benzene acid Nicotine acid sake of nicotine acid and 2-phenols benzene acid in the presence of a target enzyme. Adding of a target enzyme, in pop kinas, causes the binding of lagans and the enzyme to cause line broadening and attenuation of the resonance peaks (2nd peak spectrum). This affects the peaks of 2-phenols benzene acid (from 7. 2 pump to 6. 6 pump). 6. 3 Capillary Electrophoresis Capillary electrophoresis (CE) also known as capillary zone electrophoresis is a technique that separates the analyses within the capillary in to their different electrophoresis nobilities.

It is broadly used to its versatility and high separation rower in pharmaceutical analyses. CE wasn't recognized into the drug design and discovery scene and its use has been limited until recent years. The growing

instrumental improvement and demand for analytical information has lead to a continuously growing range of routine electrophoresis applications throughout pharmaceutical discovery and design. 6. 3. 1 Principle of CE It applies a high potential of (10-Kiev) to carry out separation to a narrow (25-75 pm) fused capillary filled with mobile phase. The mobile phase consists of aqueous components and contains electrolyte.

Analyses migrate from in the applied electric field on a rate dependent on their charge and ionic radius. Electro-osmotic flow causes neutral analyses to migrate through the column towards the cathode. 6. 3. 2 CE in drug discovery and design In the drug discovery process separation science has become increasingly important since various decisions at every step need to be considered. These decisions are made in the basis of the results by separation techniques. Capillary electrophoresis provides straight forward access to complementary information.