Chapter 5

In silico SCREENING OF ISOLATED COMPOUND

In this chapter, detailed druglikeness analysis of isolated compound using OSIRIS (Actelion) PROPERTY EXPLORER are described.

5.1 Drug Discovery:

Drug discovery and development is an intense, lengthy and an interdisciplinary endeavour. Drug discovery is mostly portrayed as a linear, consecutive process that starts with target and lead discovery, followed by lead optimization and pre-clinical in vitro and in vivo studies to determine if such compounds satisfy a number of pre-set criteria for initiating clinical development. For the pharmaceutical industry, the number of years to bring a drug from discovery to market is approximately 12-14 years and costing upto 1.2—1.4 billion dollars. Traditionally, drugs were discovered by synthesizing compounds in a time-consuming multi-step processes against a battery of in vivo biological screens and further investigating the promising candidates for their pharmacokinetic properties, metabolism and potential toxicity. Such a development process has resulted in high attrition rates with failures attributed to poor pharmacokinetics (39%), lack of efficacy (30%), animal toxicity (11%), adverse effects in humans (10%) and various commercial and miscellaneous factors. Today, the process of drug discovery has been
5.1: Drug Discovery:

revolutionized with the advent of genomics, proteomics, bioinformatics and efficient
technologies like, combinatorial chemistry, high throughput screening (HTS), virtual
screening, de novo design, in vitro, in silico ADMET screening and structure-based
drug. In silico methods can help in identifying drug targets via bioinformatics tools.

They can also be used to analyze the target structures for possible binding/active sites, generate candidate molecules, check for their drug likeness, dock these molecules with the target, rank them according to their binding affinities, further optimize the molecules to improve binding characteristics.

The use of computers and computational methods permeates all aspects of drug
discovery today and forms the core of structure-based drug design. High-performance
computing, data management software and internet are facilitating the access of huge
amount of data generated and transforming the massive complex biological data into
workable knowledge in modern day drug discovery process. The use of complementary
experimental and informatics techniques increases the chance of success in many stages
of the discovery process, from the identification of novel targets and elucidation of their
functions to the discovery and development of lead compounds with desired properties.
Computational tools offer the advantage of delivering new drug candidates more quickly
and at a lower cost. Major roles of computation in drug discovery are; (1) Virtual
screening & de novo design, (2) in silico ADME/T prediction and (3) Advanced
methods for determining protein-ligand binding.

As structures of more and more protein targets become available through crystallography, NMR and bioinformatics methods, there is an increasing demand for computational tools that can identify and analyze active sites and suggest potential drug molecules that can bind to these sites specifically. Also to combat life-threatening diseases such as AIDS, Tuberculosis, Malaria etc., a global push is essential. Millions for Viagra and pennies for the diseases of the poor is the current situation of investment in Pharma R & D. Time and cost required for designing a new drug are immense and at an unacceptable level. According to some estimates it costs about $880 million and 14 years of research to develop a new drug before it is introduced in the market Intervention of computers at some plausible steps is imperative to bring down the cost and time required in the drug discovery process (Bussiere, 2006).
Researchers have invented computational tools to decode and rapidly determine whether natural compounds collected in oceans and forests are new—or if these pharmaceutically promising compounds have already been described and are therefore not patentable. These progress will advance the speed of the process by which it is possible to discover and describe new and biologically active molecules from organisms such as marine cyanobacteria, also known as blue-green algae. This, in turn, will accelerate the timeline for bringing new experimental therapies into clinical application.

**5.2 *In silico* screening of Natural products:**

*In silico* screening is the use of computational chemistry techniques to analyze large chemical databases in order to identify possible new drug candidates. Virtual screening techniques range from simple ones, based on the presence or absence of specific substructures, or match in calculated molecular properties, up to sophisticated virtual docking methods aimed at fitting putative ligand molecules into the target receptor site.

Druglikeness may be defined as a complex balance of various molecular properties and structure features which determine whether particular molecule is similar to the known drugs. These properties, mainly hydrophobicity, electronic distribution, hydrogen bonding characteristics, molecule size and flexibility and presence of various pharmacophoric features influence the behavior of molecule in a living organism, including bioavailability, transport properties, affinity to proteins, reactivity, toxicity, metabolic stability and many others. The diversity of possible drug targets (of which each requires a different combination of matching molecular characteristics) is so enormous, that we do not believe that it is possible to find a common denominator for all of them and to express molecule drug-likeness by a single magic number. Simple count criteria (for example limits for molecular weight, logP, or number of hydrogen bond donors or acceptors) also have relatively limited applicability and are useful only to discard obvious non-drugs.
5.2.1 LogP (octanol/water partition coefficient):

LogP is calculated by the methodology developed by Molinspiration as a sum of fragment-based contributions and correction factors. Method is very robust and is able to process practically all organic and most organometallic molecules.

5.2.2 Molecular Polar Surface Area TPSA:

It is calculated based on the sum of fragment contributions. O- and N- centered polar fragments are considered. PSA has been shown to be a very good descriptor characterizing drug absorption, including intestinal absorption, bioavailability, Caco-2 permeability and blood-brain barrier penetration.

5.2.3 Molecular Volume:

Method for calculation of molecule volume developed at Molinspiration is based on group contributions. These have been obtained by fitting sum of fragment contributions to “real” 3D volume for a training set of about twelve thousand, mostly drug-like molecules. 3D molecular geometries for a training set were fully optimized by the semiempirical AM1 method.

5.2.4 “Rule of 5” Properties:

It is a set of simple molecular descriptors used by Lipinski in formulating his “Rule of 5” The rule states, that most “drug-like” molecules have log P < 5, molecular weight < 500, number of hydrogen bond acceptors < 10, and number of hydrogen bond donors < 5. Molecules violating more than one of these rules may have problems with bioavailability. The rule is called “Rule of 5”, because the border values are 5, 500, 2*5, and 5.

5.2.5 Number of Rotatable Bonds - nrotb:

This simple topological parameter is a measure of molecular flexibility. It has been shown to be a very good descriptor of oral bioavailability of drugs (Joe et, al.1997). Rotatable bond is defined as any single non-ring bond, bounded to nonterminal heavy
(i.e., non-hydrogen) atom. Amide C-N bonds are not considered because of their high rotational energy barrier.

5.3 Calculation of Druglikeness of Isolated compounds -1:

5.3.1 Glyceryl elaidate:

From the molecular properties and drug-likeliness of Compound 1 & 2, it is observed that all the parameters are in within the limit of a good drug candidate, except the LogP, which is a bit high (>5). Its drug likeliness score is also quite impressive (0.223) (Fig; 5.1)

5.3.2 Glyceryl oleate:

The in silico screening elaidate results same drug score with glyceryl elaidate. Both the isolated structures are found in cis and trans form, thus the drug score of the two compound are same (Fig; 5.2).
5.3.2: Glyceryl oleate:

The drug score value combines all other predictions into one grand total.

- Score from cLogP: 0.195 (cLogP = 6.477)
- Score from logS: 0.658 (logS = -4.343)
- Score from molweight: 0.849 (molweight = 356.0)
- Score from drug-likeness: 0.0 (drug-likeness = -29.253)
- No Risk of Mutagenicity, Score: 1.0
- No Risk of Tumorigenicity, Score: 1.0
- No Risk of Imprinting effects, Score: 1.0
- No Risk of Reproductive effects, Score: 1.0

The drug-score is 0.227

Figure 5.1: In silico screening of druglikeness of glyceryl elaidate using ACTELION (OSIRIS) PROPERTY EXPLORER.
Boiling Point: 926.38 [K]
Melting Point: 469.82 [K]
Critical Temp: 893.48 [K]
Critical Press: 11.22 [Bar]
Critical Vol: 1249.5 [cm³/mol]
Gibbs Energy: -380.29 [kJ/mol]
\( \log P \): 5.5
MR: 104.72 [cm³/mol]
Henry's Law: 5.86
Heat of Form: -986.57 [kJ/mol]
CLogP: 6.6822
CMR: 10.3868

Figure 5.2: In silico screening of druglikeness of glyceryl oleate using ACTELION (OSIRIS) PROPERTY EXPLORER.