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QSAR BY HANSCH ANALYSIS

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Introduction

The identification of a new drug molecule using the traditional medicinal chemistry approach requires a lot of synthesis, time and money. It was identified that out of billion molecules synthesized, around one or two molecules reach the clinical trials. This produces hurdle in the discovery new chemical entities (NCEs) for the treatment of various diseases by the traditional drug discovery process. The aforementioned facts necessitated the researchers to search for the alternate methods which determine the biological activity of the molecules without synthesizing them. Since the 1960s, enormous efforts have been made by various investigators to develop quantitative parameters to describe the biological activity. During this period, Hansch and co-workers made important breakthroughs for biological QSAR with electronicsa=, stereo, and hydrophobic parameters to be known as the Hansch Analysis.

Hansch *et al.* in 1960 identified the nonlinear (parabolic) dependence of biological activity with log P and gave the following equation.

$$Log(1/C) = a\ log\ P - b\ (log\ P^2) + c \quad ....(1)$$

Where, 1/C = Measure of biological activity; Log P = log of octanol-water partition coefficient; a,b,c = Regression coefficients

By taking the other types of molecular interactions into account Hansch and Fujita included descriptors for steric and electronic into equation 1, and gave the following model popularly known as Hansch model.

Log (1/C) = a (lipophilic descriptor) + b (Electronic descriptor) + c (Steric descriptor) + d (other descriptors) + e ….(2)

Representation of Hansch equation:

The typical Hansch equation can be represented as follows

$$Log\ \kappa = 6.577\ (\pm\ 0.993)\ AN + 0.094\ (\pm\ 0.019)\ log\ P - 2.542\ (\pm 1.237)\ NUFD + 1.081\ (\pm\ 0.346)$$

$n = 37 \quad r = 0.908 \quad r^2_{cv} = 0.689 \quad F = 51.55 \quad s = 0.129$ ….(3)

Where, n = number of compounds, r = correlation coefficient, r^2_{cv} = cross validated r^2 obtained by leave one out (LOO) method, F = Fischer's statistics and s = standard error.

Facts to be considered during the development of a Hansch model:

i. Rule of thumb

The 'Rule of Thumb' gives information about the number of parameters to be selected for regression analysis in QSAR based on the number of compounds. According to this rule for a QSAR model development one should select one parameter per five compound data set.

ii. Selection of training and test sets

This division must be performed such that points representing both training and test sets are distributed within the whole descriptor space occupied by the entire data set, and each point of the test set is close to at least one point of the training set.

iii. Cross validated r^2 (r^2_{cv} or q^2)

The q^2 is calculated by 'leave one out' method, where a model is built with N-1 compounds and the N^{th} compound is predicted. Each compound is left out of the model derivation and predicted in turn. The value of $q^2 > 0.5$ is the basic requirement for declaring a QSAR model to be a valid one.

iv. Multicolinearity (autocorrelation) observed between the parameters

The multicolinearity (autocorrelation) i.e. high interrelationship among the parameters should be noted from the correlation matrix constructed and the highly interrelated parameters should not be combined in regression analysis. The multicolinearity between the parameters is indicated by the any one of the following on addition of an additional parameter to the QSAR model viz. change in signs of the coefficients, change in the values of previous coefficient, change of significant variable into insignificant one or an increase in standard error of the estimate.

v. Outlier detection and its removal

An outlier in a QSAR model is a substance that is in some way different from the rest (majority of the substances used to estimate the QSAR model and for

which the model is not valid. If the numbers of outliers are less in number, then it can be removed from the QSAR model development by stating valid reason for their removal. If the numbers of outliers are more then they can be divided into two or three subsets and regression can be preformed separately for them to get better correlation.

vi. Detection of systemic errors

The systemic error in a QSAR model is determined by the plot of observed activity against the residual activity. The propagation of residuals on both the sides of zero indicates that there is no systemic error in development of QSAR model.

Steps involved in Hansch analysis:

The following steps are followed for developing a Hansch equation

1. Divide the molecules into training and test sets
2. Sketch and energy minimize the molecules under test
3. Calculate the molecular descriptors
4. Convert the biological units into logarithmic units
5. Derive QSAR equation using training set by linear or multiple linear regression (MLR)
6. Cross validate the QSAR model by
   i. Calculation of r^2_{cv} (q^2)
   ii. Ability of developed QSAR model to predict the biological activity of test set which is excluded from the model development.

Merits of Hansch analysis

1. Correlates activities with physicochemical parameters
2. "Outside" predictions are possible

Limitations of Hansch analysis

1. There must be parameter values available for the substituent's in the data set
2. A large number of compounds is required.
3. Depends on biological results (Chance of error)
4. Interrelationship of parameters
5. Groups should be selected in such a way that it should contain at least one representative from each cluster.
6. Lead optimization technique, not a lead discovery technique.
7. Risk of failure in "too far outside" predictions

PRINCIPLES OF DRUG DESIGN

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Drug design, sometimes referred to as rational drug design or simply rational design, is the inventive process of finding new medications based on the knowledge of a biological target. The drug is most commonly an organic small molecule that activates or inhibits the function of a biomolecule such as a protein, which in turn results in a therapeutic benefit to the patient. In the most basic sense, drug design involves the design of small molecules that are complementary in shape and charge to the biomolecular target with which they interact and therefore will bind to it. Drug design frequently, but not necessarily relies on computer modeling techniques. This type of modeling is often referred to as computer-aided drug design. Finally, drug design that relies on the knowledge of the three-dimensional structure of the biomolecular target is known as structure-based drug design.

Aims

The central aim of the course is to impart an understanding of what medicinal chemists consider when attempting to design new pharmaceuticals. The course will describe the principles involved in modern drug design and drug discovery, and especially with reference to compounds in current clinical usage. Topics to be covered will include:

- An introduction to the basis of drug development, molecular size, shape and charge in drug action, quantitative structure-activity relationships and drug design
- Antibacterial and antifungal chemotherapy
- Enzyme inhibitors as drugs
- Antiviral and anticancer chemotherapy

In addition, there will be a series of lectures given by speakers from the pharmaceutical industry. The material in these lectures will also be examinable; however, there

will not be a separate question on the exam paper specifically for these lectures.

Objectives

- To understand how to relate chemical structure to biological activity
- To understand how to conduct a structure-activity analysis
- To appreciate the various approaches to drug discovery and to be able to exemplify them

Challenges And Approaches In Overcoming Drug Resistance

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Drug resistance is a common concern for the development of novel antiviral, antimicrobial and anticancer therapies. To overcome this problem, several strategies have been developed, many of which involving the theme of this review, the use of structure-based drug design (SBDD) approaches. These include the successful design of new compounds that target resistant mutant proteins, as well as the development of drugs that target multiple proteins involved in specific biochemical pathways. Finally, drug resistance can also be considered in the early stages of drug discovery, through the use of strategies to delay the development of resistance. The purpose of this brief review is to underline the usefulness of SBDD approaches based on case studies, highlighting present challenges and opportunities in drug design.

A Parallel Progression Approach To Drug Design

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To be successful in drug design it is necessary that all facets of drug, namely pharmacokinetics, pharmacodynamic, metabolism and toxicity are tackled early in the drug development phase. The present work seeks to exploit the high potential of in silico pharmacokinetic (PK) and pharmacodynamic (PD) approaches to reduce the attrition rate of leads in the later and costlier stages of the discovery pipeline. We propose a methodology in which 'parallel' information can be generated in silico to simultaneously optimize the pharmacokinetics (PK) and pharmacodynamic (PD) of lead candidates. We demonstrate the approach for β-blockers, which have far from satisfactory pharmacokinetics. Using a variety of tools in molecular modelling, models have been developed for important PK parameters such as volume of distribution (log Vd) and clearance (log Cl) which together influence the half life of a drug and simultaneously for PD in terms of the inhibition constant (pKi). To the best of our knowledge, it is the first time that such an approach has been applied to concurrently analyze the PK-PD models and after iterative to and fro cycling through the developed models, modifications on the marketed β-blockers have been proposed with optimized PK and PD profiles. We present here some of the resultant re-engineered β-blockers with half-lives between 6-10 hours and pKi values greater than 8. The improved β-blockers have been further analyzed by docking and affinity studies. Finally, these molecules have been subjected to and passed through a round of metabolic and toxicological assessment. Thus, such a parallel progression approach which helps tune various facets of the drug simultaneously, would be an invaluable tool during the drug development process.

Drug Repositioning- The Beginning of a New Era of Drug Discovery

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Drug development is a costly and failure-prone process and, in recent years, the pharmaceutical industry has experienced a difficult period whereby productivity has not kept pace with increases in research and development costs. As a consequence, quite recently research efforts focused on a novel paradigm for drug development, named drug repurposing, to discover novel pharmacological applications of existing drugs. Computational approaches for drug repositioning focused mainly on small-scale applications, such as the analysis of specific classes of drugs or drugs for specific diseases. Large-scale applications, involving a relatively large number of drugs and diseases, count only a few examples. Despite the availability of many drug repositioning methods, they all suffer from a serious limitation: the inference task is performed in an inhomogeneous similarity space induced by the relationships existing between drugs and a second type of entity (e.g. disease, target, or ligand set), thus making difficult the integration of multiple sources of biomolecular and chemical data into a homogeneous pharmacological space.

Use of Docking in Designing Kinase Inhibitors- A case study

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We report the discovery of aurora kinase inhibitor using the fragment-based virtual screening by multi-docking strategy. Among a number of fragments collected from eMololecules, we found four fragment molecules showing potent activity (>50% at 100 µM) against aurora kinase. Based on the explored fragment scaffold, we selected two compounds in our synthesized library and validated the biological activity against Aurora kinase.

The aurora kinase, which belongs to the group of serine/threonine kinases, has been identified as a crucial regulator of the centrosome function in mitosis. In mammals, the aurora family consists of three kinase members, known as aurora-A, -B, and -C, respectively. All aurora kinases share nearly 70% sequence homology among family members . Despite these high similarities, aurora kinases are clearly distinguishable by means of subcellular localization, their expression patterns, and the timing of their activity. Aurora-A is localized to centrosomes during the early S phase and is essential for centrosome maturation and separation, bipolar spindle assembly, and mitotic entry and exit. Aurora-A is frequently overexpressed in many human tumors, including those of breast, ovarian, lung, and colorectal cancers . Aurora-A plays a critical role in the cell cycle and in carcinogenesis, and it has been studied as an anticancer therapeutic target by many researchers. Various aurora-A kinase inhibitors have been reported to have undergone Phase I/II clinical trials to target certain types of cancers. For instance, CYC116, a type of pyrimidine analogue, is an orally available aurora kinase inhibitor that is currently undergoing Phase I clinical trials. MLN8054, a type of benzopyrimidoazepine analogue, is a potent and selective aurora-A inhibitor with a half maximal inhibitory concentration of a substance (IC50) value of 4 nM: It is also under Phase I research for malignant tumors.

Our goal was to discover a potent fragment to serve as an aurora-A kinase inhibitor leading to the development of a preclinical drug. To find a hit compound, the typical high-throughput screening (HTS) method from the huge chemical library having full-size molecules, i.e., 400~500 Dalton of molecular weight, is carried out. However, this typical HTS method is too expensive in terms of time and energy efficiency. We ruminated on a low-cost and highly effective approach with high reliability criteria to overcome the disadvantages of the typical HTS method. According to the literature, a fragment has the low affinity for proteins, but typically a good ligand efficiency that represents high-quality interactions with its target protein. Since it is well known that fragment screening is efficient in the early stages of drug discovery, we applied

the fragment-based virtual high-throughput screening (vHTS) approach to achieve the aforementioned advantages and carried out a docking experiment with a fragment library into the active site of the aurora-A kinase via the X-ray crystallography method.

Molecular Modeling

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Molecular modeling techniques provide a powerful tool to study the properties of molecules and their interactions at the molecular level. The use of computational techniques to predict interaction patterns and molecular properties can inform the design of drug delivery systems and therapeutic agents. Dendrimers are hyperbranched macromolecular structures that comprise repetitive building blocks and have defined architecture and functionality. Their unique structural features can be exploited to design novel carriers for both therapeutic and diagnostic agents. Many studies have been performed to iteratively optimise the properties of dendrimers in solution as well as their interaction with drugs, nucleic acids, proteins and lipid membranes. Key features including dendrimer size and surface have been revealed that can be modified to increase their performance as drug carriers. Computational studies have supported experimental work by providing valuable insights about dendrimer structure and possible molecular interactions at the molecular level. The progress in computational simulation techniques and models provides a basis to improve our ability to better predict and understand the biological activities and interactions of dendrimers. This review will focus on the use of molecular modeling tools for the study and design of dendrimers, with particular emphasis on the efforts that have been made to improve the efficacy of this class of molecules in biomedical applications.