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Insilicopharmacology: An overview

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ABSTRACT

Drug discovery process is a critical issue in the pharmaceutical industry since it is a very cost-effective and time consuming process to produce new drug potentials and enlarge the scope of diseases incurred. Drug target identification, being the first phase in drug discovery is becoming an overly time consuming process. In many cases, it produces inefficient results due to failure of conventional approaches like *in vitro* and *in vivo* to investigate large scale data. Sophisticated *in silico* approaches has given a tremendous opportunity to pharmaceutical companies to identify new potential drug targets which in turn affect the success and time of performing clinical trials for discovering new drug targets. Insilico pharmacology includes databases, quantitative structure-activity relationships, similarity searching, pharmacophores, homology models and other molecular modeling, machine learning, data mining, network analysis tools and data analysis tools that use a computer.Computational (*in silico*) methods have been developed and widely applied to pharmacology hypothesis development and testing. Such methods have seen frequent use in the discovery and optimization of novel molecules with affinity to a target, the clarification of absorption, distribution, metabolism, excretion and toxicity properties as well as physicochemical characterization. The main goal of this work is to review *in silico* methods for drug discovery process with emphasis on identifying drug targets, where there are genes or proteins associated with specific diseases.

Key words:-target identification, in vitro& in vivo, data bases, pharmacophores, data mining, etc.

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INTRODUCTION

A drug is a substance used in the diagnosis, treatment, or prevention of a disease or as a component of a medication. The drug discovery process is aimed at discovering molecules that can be very rapidly developed into effective treatments to fulfill unmet medical needs for both endogenous diseases, that arise from in-born sequence errors in germ cells or spontaneous (or agerelated) mutations in somatic cells and exogenous diseases, that arise from an infectious vector. In most basic sense, drug design involves design of small molecules that are complementary in shape and charge to the bimolecular target to which they interact and therefore will bind to it. Drug discovery process(as depicted in figure 1) is a critical issue in the pharmaceutical industry since it is a very cost-effective and time consuming process to produce new drug potentials and enlarge the scope of diseases incurred.

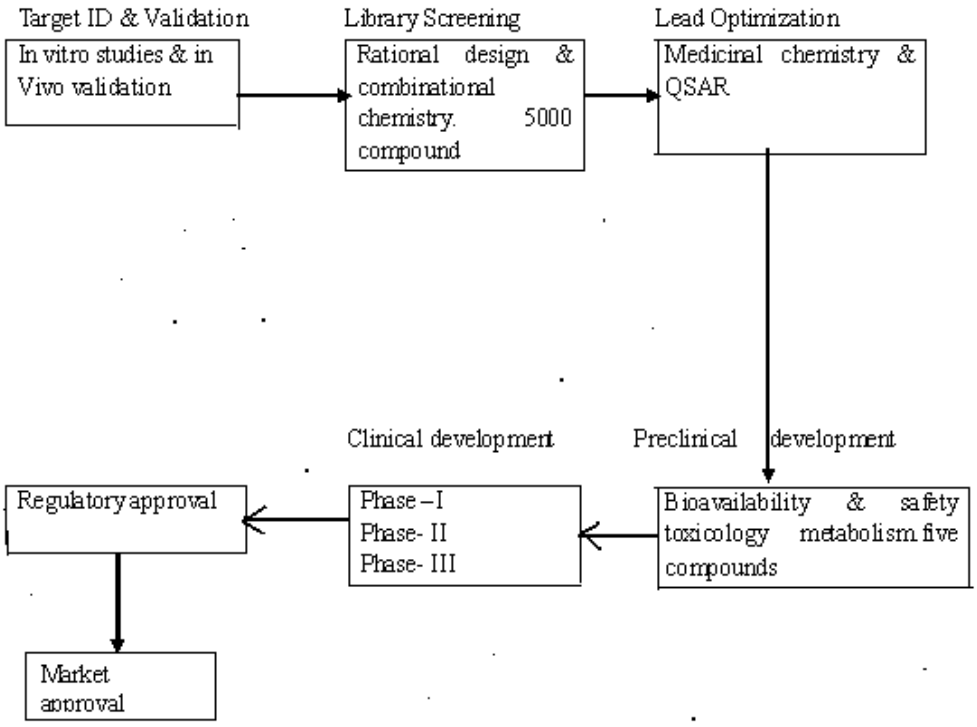

Figure 1 Drug Discovery process

Drug target identification, being the first phase in drug discovery is becoming an overly time consuming process. In many cases, such produces inefficient results due to failure of conventional approaches like *in vivo* and *in vitro* to investigate large scale data. Sophisticated *in silico* approaches has given a tremendous opportunity to pharmaceutical companies to identify new potential drug targets which in turn affect the success and time of performing clinical trials for discovering new drug targets..*In silico* is an expression used to mean "performed on computer or via computer simulation. *In silico* drug designing is a form of computer-based

modeling whose technologies are applied in drug discovery processes. Unlike the historical method of drug discovery, by trial and- error testing of chemical substances on animals, and matching the apparent effects to treatments, *in silico* drug design begins with a knowledge of specific chemical responses in the body or target organism and tailoring combinations of these to fit a treatment profile. The main goal of this work is to review *in silico* methods for drug discovery process with emphasis on identifying drug targets, where there are genes or proteins associated with specific diseases. This review provides a succinct overview of several recent approaches that employ bioinformatics for the systematic characterization of the targets of bioactive compounds.

History and Evolution of In Silico Approaches

Drug design and related disciplines in drug discovery did not wait for the advent of informatics to be born and to grow as sciences. The earliest intuitions and insights in structure–activity relations can be traced to the nineteenth century. A relation between activity and a physicochemical property was firmly established by Meyer (1899)[2] and Overton (1901)[3], who proposed a "Lipoid theory of cellular depression"such as the higher the partition coefficient between a lipid solvent and water, the greater the depressant action. Such papers paved the way for the recognition of lipophilicity and electronic properties as major determinants of pharmacodynamics and pharmacokinetics responses, as best illustrated by the epoch-making and still ongoing work of Corwin Hansch (Hansch and Fujita, 1964; Hansch, 1972)[4], a founding father of drug design.

Other pioneers saw that chemical structure [(that is, the nature and connectivity of atoms in a molecule, in fact the two-dimensional structure (2D) of compounds)] also played an essential role in pharmacological activity. The conceptual jump from 2D to three-dimensional (3D) structure owes much to the work of Cushny (1926)[5], whose book summarises a life dedicated to relations between enantiomerism and bioactivity. This vision was expanded in the mid-twentieth century by the discovery of conformational effects on bioactivity. In parallel with our growing understanding of the concept of molecular structure, a few visionary investigators in the late nineteenth and early twentieth centuries (for example, John Langley, Paul Ehrlich and Alfred Clark;) reviewed development of concept of receptors, namely the targets of drug action. The analogies between receptors and enzymes were outlined by Albert (1971)[6].

The converging lines of progress in chemistry and biology generated a flood of information and knowledge which went beyond the usual capacity of in cerebro data handling and was a driving force in the emergence and development of computer sciences. Hansch was among the very first

in the 1950s to use calculators and statistics to arrive at quantitative relations between structure (in fact, parameters and descriptors) and activity.

Types of Drug Design[7-9]:-

There are two types of drug design;(as depicted in figure no.2) one is "rational drug design" and the other is "structure based drug design".

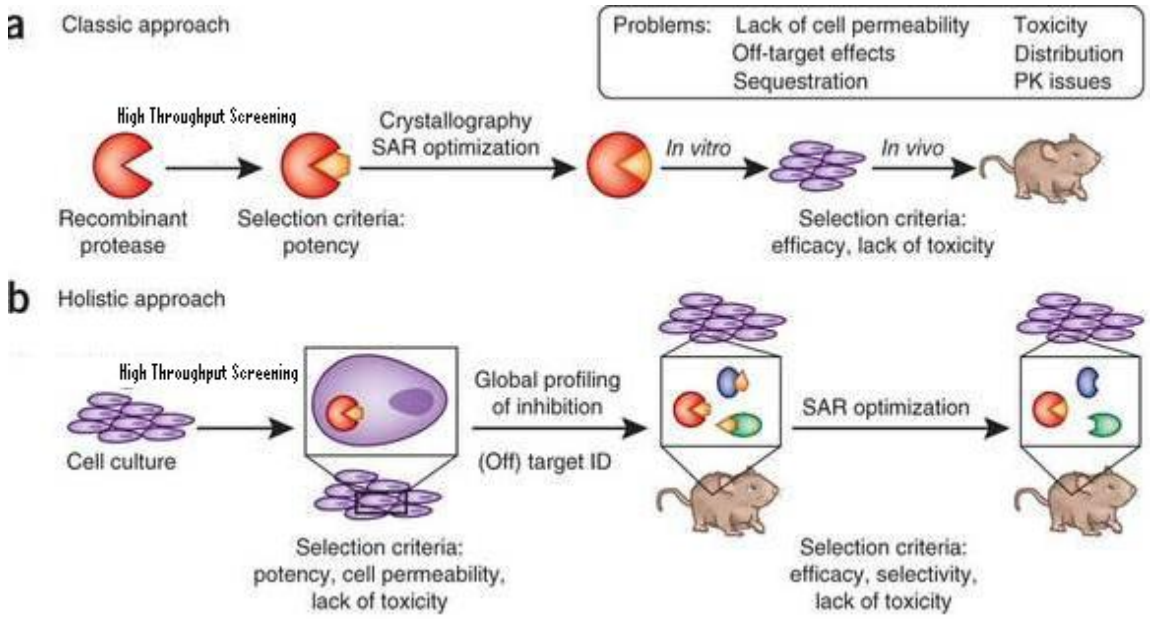

Figure 2:Holistic & Classsic Approch For Drug Design

Rational Drug Design (RDD):-

Rational drug design is a process used in the biopharmaceutical industry to discover and develop new drug compounds. RDD uses a variety of computational methods to identify novel compounds, design compounds for selectivity, efficacy and safety, and develop compounds into clinical trial candidates. These methods fall into several natural categories such as, structure based drug design, ligand-based drug design, de novo design and homology modeling, depending on how much information is available about drug targets and potential drug compounds.

Structure Based Drug Design (SBDD):-

Structure-based drug design is one of the first techniques to be used in drug design. Drug targets are typically key molecules involved in a specific metabolic or cell signaling pathway that is known, or believed, to be related to a particular disease state. Drug targets are most often proteins and enzymes in these pathways. Drug compounds are designed to inhibit, restore or otherwise modify the structure and behavior of disease related proteins and enzymes. SBDD uses the known 3D geometrical shape or structure of proteins to assist in the development of new drug

compounds. The 3D structure of protein targets is most often derived from x-ray crystallography or nuclear magnetic resonance (NMR) techniques. X-ray and NMR methods can resolve the structure of proteins to a resolution of a few angstroms (about 500,000 times smaller than the diameter of a human hair). At this level of resolution, researchers can precisely examine the interactions between atoms in protein targets and atoms in potential drug compounds that bind to the proteins. This ability to work at high resolution with both proteins and drug compounds makes SBDD one of the most powerful methods in drug design. Structure- based design refers specifically to finding and complementing the 3D structure of a target molecule such as a receptor protein. Chemists may be guided to subsets of compounds with desired features to complement 3-dimensional shape of the site. From the geometry and functionalfeatures of the binding site, complementary structures of a compound (ligand) are so designed as to have high binding affinity with the target molecule.

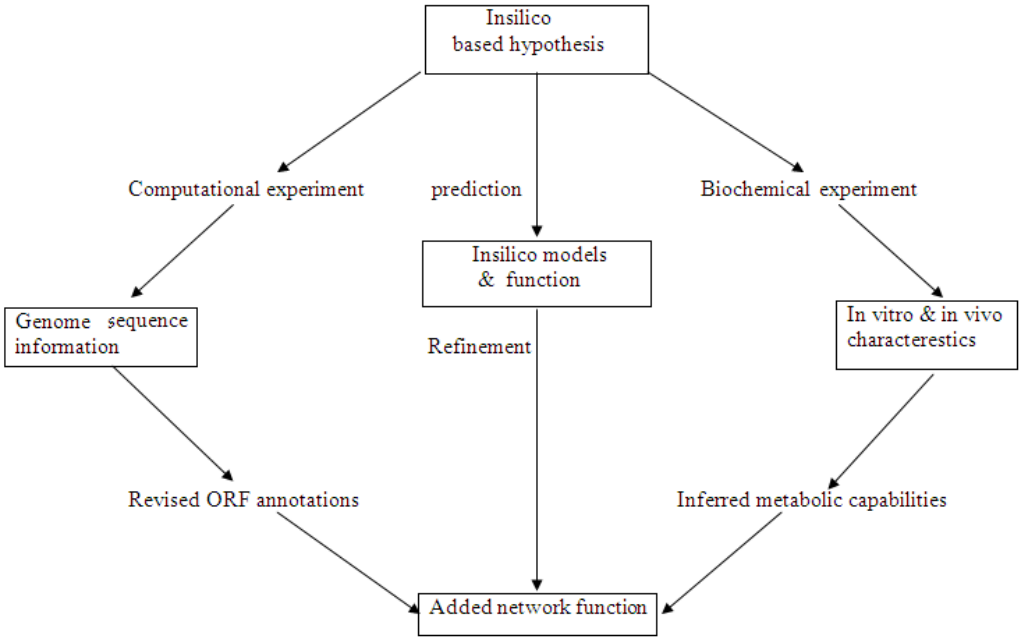

Figure 3:Collection Of Experimentel Data & Subsequent Refinement Of The Model Based On These Data

Modern Drug Discovery Pipeline[10]:

Drug discovery process operates on a target-based approach, in which the organism is seen as a series of genes and pathways and the goal is to develop drugs that affect only one gene or molecular mechanism in order to selectively treat the deficit causing the disease without producing side effects. Computers can be used to simulate a chemical compound and design chemical structures that might work against it. Enzymes attach to the correct site on a cell membrane, which causes the disease. A computer can show scientists what the receptor site

looks like and how one might tailor a compound to block an enzyme from attaching there small-molecule as shown in figure 3

IN SILICO BIOLOGY[11]:-

Many other fields of science and engineering have developed systems science and complicated mathematical simulations to a high level of sophistication. These capabilities influence our everyday life. The chemicals that we all use originate from refineries and other highly integrated chemical processes with complex control structures that rival those of living cells.Mathematical model building in biology is likely to differ, at least initially, from that practiced in the physicochemical sciences. In these fields, one starts with basic thermodynamic concepts such as chemical potential, fundamental rate equations such as the diffusion equation, and the basics of electrochemistry such as the Nernst equations. These equations are based on fundamental physical theories and concepts, and contain a large number of parameters, most of which can be individually measured.

The Challenges of In Silico Biology[12]

Moving from a reductionist paradigm to one that views cells as systems will necessitate changes in both the culture and the practice of research. The advent of high-throughput technologies, such as genomics and proteomics, is enabling biologists to study cells as systems. This is not only creating a whole new set of logistical problems, but also forcing a conceptual reevaluation of the concept of cells as a collection of individual cellular components. What do we do with this developing list of cellular components and their properties? As informative as they are, these lists basically give us the molecules that make up cells and their individual chemical properties. How do we now arrive at the biological properties that arise from these detailed lists of chemical components**.**

The Iterative Model-Building Process[13]:-

The process of building mathematical models of complex biological processes and their computer simulation will be an iterative one.Insilico organisms are computer representations of their in vivo counterparts. Initial versions will be synthesized using genomic, biochemical, and physiological data.

Table 1:physiochemical factors constraining metabolic function

Sr.no	Factor	Types of Constrains
1.	Capacity maximum fluxes	Nonadjustable association rates
2.	Connectivity systemic stoichiometry	Hard nonadjustable constraints
3.	Rates, mass action , enzyme kinetics & regulation	Highly adjustable by an evolutionary process
4.	Others osmotic pressure & electroneutrality	Hard nonadjustable constraints

Table 2: Methods for Drug Design

Sr. no.	Methods	Advantages	Disadvantages	Applications
1.	Descriptor based methods[15-18]	A fair reflection of the size, shape and liphophilicity of molecules.	Only consider the generic properties.	Applicable for the determination of moleculer weight, molar refractivity & partition coefficient.
2.	Rule based methods [19-21]	Study of biotransformation of ligands.	Only consider metabolic transformations.	Applicable for prediction of sites labile to drug metabolism.
3.	Knowledge based methods[22-24]	Converts interatomic distance contributions in ligand protein complexes into fair potential functions.	Only based on knowledge.	Estimation of free energy of molecules interactions when docking ligands into protein molecules.
4.	Virtual ligand screening [25-28]	Scoring & ranking of molecules based on affinity for a certain target.	It only considers scoring and ranking of molecules.	Scoring & ranking of molecules in large chemical libraries.
5.	Ligand based method [29-32]	Geometrical representations are applied.	Only consider structural representations.	Multiple conformations of bioactive ligand is well established.
6.	Target based methods[33-36]	It is based on docking and scoring study.	Based on structural information of target.	Method is useful for expected conformation & orientation of ligand into protein cavity.
7.	Virtual affinity profiling[37-42]	It extends QSAR along with chemical entities.	Potential side effects of compound due to off target affinity.	Estimation of pharmacological profile of molecule on multiple target.

Simplicity from Complexity[14]:-

It is clear that even though the molecular composition of living cells is complex (i.e. their genotype) the number of distinct behaviors (i.e. their phenotypes) that they display is much fewer. This important principle of simplicity from complexity is emerging from singular value decomposition of gene.

What is rate limiting[14]?

High-throughput experimeaintal technologies are generating biological data at unprecedented rates, and the pace will only accelerate. The bioinformatic infrastructure that tabulates, curates, and makes these data retrievable is developing. Many initial visualization tools and statistical analysis methods, such as clustering, are becoming available for data analysis.

Table 3:-List of Softwares

Sr.no	Name of softwares	Applications
1.	Gene predictors (chemgenome2.0)	Whole genome analysis.
2.	Bhageerath	Predict native like structure for small globular proteins.

3.	Sanjeevani	A complete drug design software.
4.	Binding affinity prediction of protein ligand server	Compute the binding free energy of protein complexes.
5.	Binding affinity prediction of protein ligand containing zinc	Compute the binding free energy of protein complexes.
6.	Drug DNA interaction energy	Calculate the drug DNA interaction energy.
7.	Paradock automated server for rigid docking	Predict binding site of the ligand in receptor target site.
8.	Active site prediction	-
9.	Lipnski filters	Cheks whether drug satisfy the five lipnski rule.
10	Gene evaluaors	Characterize a DNA sequence as a gene or non gene.
11.	Protein structure generation	Structure generation from a given dihedral.
12.	Persistent lenth	Filters the globule protein evaluation.
13.	Hydrophobicity	Filters the globule protein evaluation.
14.	Radius of gyration	Filters the globule protein evaluation.
15.	Packing fraction	Filters the globule protein evaluation.
16.	Protein structure optimizer	Energy minimizing protein.
17.	Progen -in	Protein regularity index.

EXAMPLES OF IN SILICO PHARMACOLOGY:-

Drug Target Examples:-

Enzymes[43]

The ubiquitin regulatory pathway, in which ubiquitin is conjugated and deconjugated with substrate proteins, represents a source of many potential targets for modulation of cancer and other diseases. The recent crystal structure of a mammalian de-ubiquitinating enzyme herpesvirus-associated ubiquitin specific protease(HAUSP), which specifically de-ubiquitinates the ubiquitinated p53 protein, may also assist in drug development despite the peptidic nature of its substrate.

Cathepsin D is an aspartic protease found mainly in lysosomes, which may have a role in β-amyloid precursor protein release and hence may well be a target for Alzheimer's disease. Cathepsin D may also be elevated in breast cancer and ovarian cancer hence a means to modulate this activity could be beneficial in these diseases Pharmacophore- and structure-based approaches have been used to optimize an acylurea hit for human glycogen phosphorylase.

kinases[44-47]**:**

The kinases represent an attractive family of over 500 targets for the pharmaceutical industry, with several drugs approved recently. Kinase space has been mapped using selectivity data for small molecules to create a chemogenomic dendrogram for 43 kinases that showed the highly homologous kinases to be inhibited similarly by small molecules. Virtual screening methods have been applied quite widely for kinases to date. The structure-based design method has

produced new potent inhibitors of cyclin dependent kinaseI starting from the highly similar apo cyclin dependent kinaseII and the positioning of olomoucine.

drug-metabolizing enzymes and transporters[48-49]:

The UDP-glucuronosyltransferases are a class of versatile enzymes involved in the elimination of drugs by catalysing the conjugation of glucuronic acid to substrates bearing a suitable functional group, so called phase II enzymes. There have been numerous QSAR and pharmacophore models that have been generated with relatively small data sets for rat and human enzymes. Human UGT1A1, UGT1A4 and UGT1A9 all have in common two hydrophobes and a glucuronidation feature, while UGT1A9 has an additional hydrogen bond acceptor feature. Sulfotransferases, a second class of conjugating enzymes, have been crystallized and a QSAR method has also been used to predict substrate affinity to SULT1A3. To the best of our knowledge, computational models for other isozymes have not been developed. In general, conjugating enzymes have generally been infrequently targeted for in silico models. Perhaps because of a paucity of in vitro data and limited diversity of molecules tested, they have been less widely applied in industry.

Receptors[50-51]:

The α-amino-3-hydroxy-5-methyl-4-isoxazole propionate receptor is central to many central nervous system (CNS) pathologies and ligands have been synthesized as anticonvulsants and neuroprotectants. There is currently no 3D structure information and therefore a four-point Catalyst HIPHOP pharmacophore was developed with 14 antagonists. This was then used to search the Maybridge database and select eight compounds for testing of which six of these were found to be active in vivo as anticovulsants.

Nuclear Receptors[52-53]:

Nuclear receptors constitute a family of ligand-activated transcription factors of paramount importance for the pharmaceutical industry since many of its members are often considered as double-edged swords. On the one hand, because of their important regulatory role in a variety of biological processes, mutations in nuclear receptors are associated with many common human diseases such as cancer, diabetes and osteoporosis.

Ion Channels[54]:-

Therapeutically important channels include voltage-gated ion channels for potassium, sodium and calcium that are present in the outer membrane of many different cells such as those responsible for the electrical excitability and signalling in nerve and muscle cells. These represent validated therapeutic targets for anaesthesia, CNS and cardiovascular diseases.

Transcription Factors[55]:-

A cyclic decapeptide with activity against the AP-1 transcription factor was used to derive a 3D pharmacophore to which low energy conformations of non-peptidic compounds were compared. New 1-thia-4-azaspiro[4,5]decane and benzophenone derivatives with activity in binding and cell-based assays were discovered as AP-1 inhibitors in a lead hopping approach.

Antibacterials[56]:-

Twenty deoxythymidine monophosphate analogues were used along with docking to generate a pharmacophore for Mycobacterium tuberculosis thymidine monophosphosphate kinase inhibitors with the Catalyst software.

Antivirals[57]:-

Neuroamidase is a major surface protein in influenza virus. A structure-based approach was used to generate Catalyst pharmacophores and these in turn were used for a database search and aided the discovery of known inhibitors. The hit lists were also very selective.

Other Therapeutic Targets[58]:-

The integrin VLA-4 (α4β1) is a target for autoimmune and inflammatory diseases such as asthma and rheumatoid arthritis. The search for antagonists has included using a Catalyst pharmacophore derived from the X-ray crystal structure of a peptidic inhibitor. This was used to search a virtual database of compounds that could be made with reagents from the available chemicals directory.

Limitations of Insilicopharmacology[59-60]:-

1. Models may be generated with a narrow homologous series of pharmacologically relevant molecules (local model) or a structurally diverse range of molecules (global model). These two approaches have their pros and cons, respectively.
2. The applicability domain of the local model may be much narrower than for the global model such that changing to a new chemical series will result in prediction failure.
3. Global models may also fail if the predicted molecule falls far enough away from representative molecules in the training set. These limitations are particularly specific to QSAR models.
4. The QSAR models are generally local in nature and this will limit lead hopping to new structural series, whereas global models may be more useful for this feature.

APPLICATIONS OF IN SILICO PHARMACOLOGY:-

1. Finding new antagonists or agonists for a target using an array of methods either in the absence or presence of a structure for the target.

2. Computational methods may also aid in understanding the underlying biology using network/pathways based on annotated data (signalling cascades).
3. Insilico pharmacology and in silico methods in general are the reduction in the number of molecules made and tested through database searching to find inhibitors or substrates, increasing speed of experiments through reliable prediction of most pharmaceutical properties from molecule structure.
4. Multiple optimization of numerous predicted properties, possibly either weighting in silico pharmacology models by importance (or confidence in the model and or data), as well as data set size and diversity.
5. With the recent availability of crystal structures for several mammalian drug-metabolizing enzymes, there is still considerable difficulty in reliable metabolism predictions.

CONCLUSIONS:-

High-throughput experimental technologies are not only forcing researchers to accommodate the systems point of view in cellular and molecular biology, but also enabling us to study cells as systems. It contain development of methods including databases, quantitative structure–activity relationships, similarity searching, pharmacophores, homology models and other molecular modelling, machine learning, data mining, network analysis tools and data analysis tools that use a computer. We have introduced how some of these methods can be used for virtual ligand screening and virtual affinity profiling. Although these methods are not proven yet to ‘discover drugs' alone, they represent progress by increasingly demonstrating their ability to deliver enrichment in identifying active molecules for the target of interest when compared with random selection or other traditional methods. Insilico drug discovery minimizes the time required for invention of new drug molecules.

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