"COMPUTER-AIDED DRUG DESIGN (CADD) & MOLECULAR MODELLING IMPORTANCE IN PHARMACEUTICAL SCIENCES."

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Abstract

Computer-aided drug design (CADD) depends on the extent of structure and other information available regarding the target (enzyme/receptor/protein) and the ligands. The theoretical basis of CADD involves molecular mechanics, quantum mechanics, molecular dynamics, structure-based drug design (SBDD), ligand-based drug design (LBDD), homology modeling, ligplot analysis, molecular docking, de novo drug design, pharmacophore modeling and mapping, virtual screening (VS), quantitative structure-activity relationships (QSARs), In silico ADMET (absorption, distribution, metabolism, excretion and toxicity) prediction etc. CADD centre was created to foster collaborative research between biologist, biophysicists, structural biologists and computational scientists. The major goal of the CADD centre is to initiate these collaborations leading to the establishment of research projects to discover novel chemical entities with the potential to be developed into novel therapeutic agents.

Keywords: Bioinformatics, Softwares, Homology modeling, Ligplot analysis, Molecular docking, De novo drug design, Pharmacophore modeling, Virtual screening (VS), Quantitative structure-activity relationships (QSARs), Lipinski's rule.

❖ INTRODUCTION

Advances in the field of biochemistry, molecular biology and mobile biology, facilitated by using traits in genomics and proteomics, are producing a massive wide variety of novel organic goals that may be exploited for therapeutic intervention. To facilitate the discovery of novel healing marketers, rational drug design methods in mixture with structural biology provide wonderful capability. The trendy technological advances are (QSAR/QSPR, shape-based totally layout and bioinformatics). Drug discovery and developing a brand new medicine is an extended, complicated, high-priced and exceptionally unstable procedure that has few friends in the commercial global. This is why laptop-aided drug design (CADD) tactics are being widely used inside the pharmaceutical industry to accelerate the method. The value benefit of using computational equipment within the lead optimization section of drug improvement is full-size. On an average, it takes 10-15 years and US $500-800 million to introduce a drug into the marketplace, with synthesis and trying out of lead analogues being a large contributor to that sum. Therefore, it's far beneficial to apply computational equipment in hit-to-lead optimization to cowl a wider chemical space at the same time as reducing the quantity of compounds that should be synthesized and examined in vitro.

Computational methods of drug design are based totally on a postulate that pharmacologically active compounds act via interaction with their macromolecular targets, especially proteins or nucleic acids. Major factors of such interactions are surfaces of molecules, electrostatic pressure, hydrophobic interplay and hydrogen bonds formation. These factors are mainly taken into consideration at some point of evaluation and prediction of interaction of molecules.

❖ HISTROY

- Early 19th century - extraction of compounds from plants (morphine, cocaine).
- Late 19th century - fewer natural products used, more synthetic substances. Dye and chemical companies start research labs and discover medical applications.
- 1905 - John Langley: "The concept of specific receptors"
- 1909 - First rational drug design.
- Goal: safer syphilis treatment than Atoxyl.
- Paul Erhlich and Sacachiro Hata.
- Synthetic: 600 compounds; evaluated ratio of minimum curative dose and maximum tolerated dose. They found Salvarsan (which was replaced by penicillin in the 1940's)
- 1960 - First successful attempt to relate chemical structure to biological action quantitatively.
- Mid to late 20th century - understand disease states, biological structures, processes, drug transport, distribution, metabolism. Medicinal chemists use this knowledge to modify chemical structure to influence a drug's activity, stability, etc.

COMPUTER-AIDED DRUG DESIGN (CADD):[2,3]

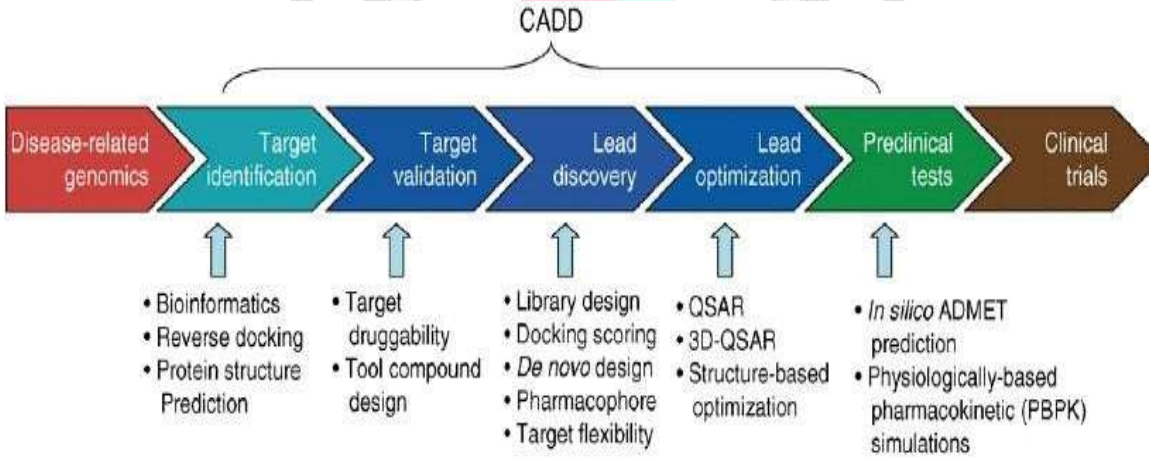

Figure 1: *In* Computer-aided drug design.

Computer-aided drug design is a pc era that designs a product and files the design's technique. CADD can also facilitate the manufacturing system through shifting unique diagrams of a products materials, methods, tolerances and dimensions with unique conventions for the product in query (2). It can be used to supply both two-dimensional or 3-dimensional diagrams, that can then when rotated to be considered from any attitude, even from the inside searching out. The channel of drug discovery from concept to marketplace includes seven fundamental steps: ailment choice, target selection, lead compound identification, lead optimization, pre-medical trial trying out, medical trial checking out and pharmacogenomic optimization. In practice, the closing five steps required to skip again and again. The compounds for trying out may be obtained from herbal supply (Plants, animals, microorganisms) and by using chemical synthesis. These compounds can be rejected as perspectives owing to absence or low hobby, life of toxicity or carcinogenicity, complexity of synthesis, inadequate performance etc. As a result simplest one of a hundred thousand investigated compounds may be delivered to the market and one average fee of improvement of latest drug rose as much as 800 million bucks. The discount of time-ingesting and value of the last ranges of drug trying out is not likely due to strict kingdom popular on their cognizance. Therefore essential efforts to increasing performance of development of medicine are directed to levels of discovery and optimization of ligands [3].

(a) STRUCTURE-BASED DRUG DESIGN (SBDD): Structure-based drug design is the technique to be used in drug design. Structure-based drug design helps in the discovery process of new drugs [5]

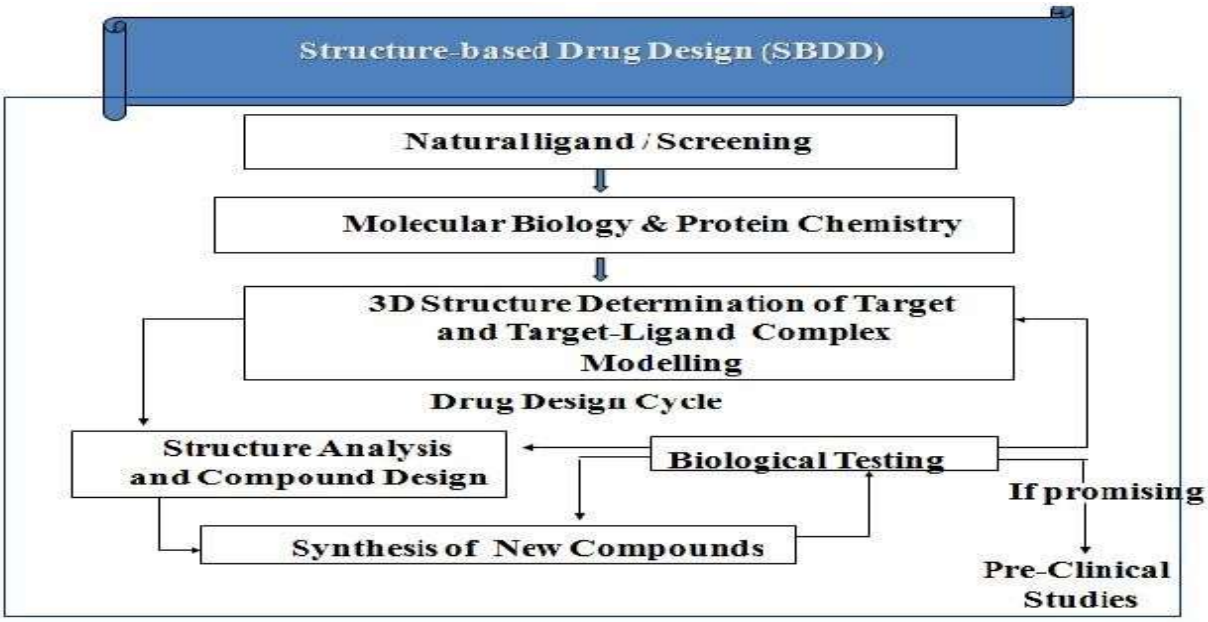

Figure 2: Structure-based drug design .

b) LIGAND- BASED DRUG DESIGN (LBDD):

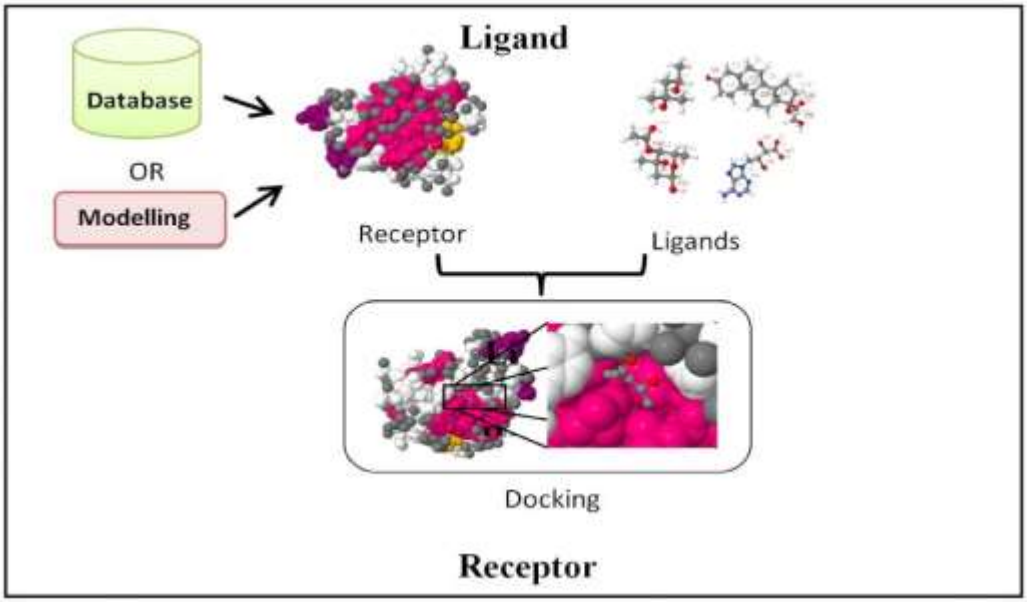

Figure 3: Ligand-based drug design .

The ligand-based drug design approach involves the analysis of ligands known to interact with a target. These methods use a set of reference structure collected from compounds known to interact with the target of interest and analysis their 2D or 3D structure

In some cases, usually in which data pertaining to the 3D structure of a target protein are not available, drug design can instead be based on process using the known ligands of a target protein as the starting point.

This approach is known as "ligand-based drug design"[6]

BIOINFORMATICS IN COMPUTER-AIDED DRUG DESIGN:

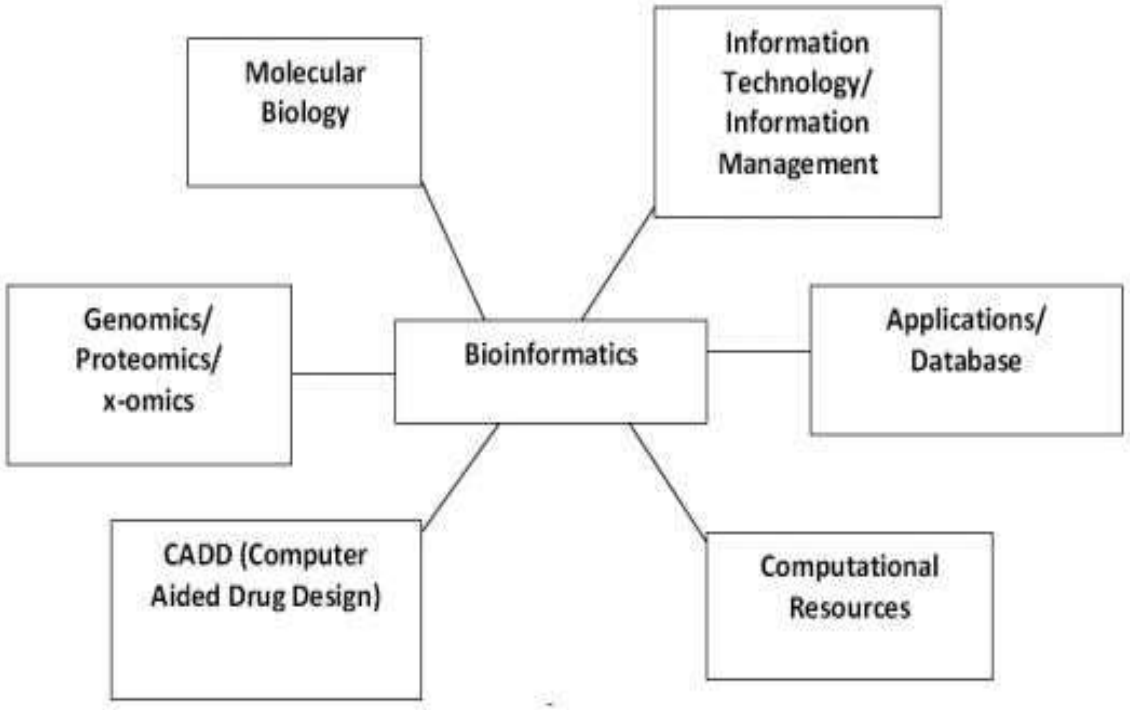

Figure 4: Bioinformatics in computer-aided drug design

A few years ago, National Institutes of Health (NIH) created Biomedical Information Sciences and Technology Initiative (BISTI) to examine the current state of bioinformatics in the United States. Computeraided drug design is a specialized discipline that uses computational methods to simulate drug-receptor interactions as there is considerable overlap in CADD research and bioinformatics [7].

VARIOUS TYPES OF SOFTWARES USED FOR COMPUTER-AIDED DRUG DESIGN

: Auto dock tools, UCSF chimera 1.10, Ligand scout 3.12, Rasmol, Chem draw utra 12, Chem sketch, Marvin sketch, Padel-descriptor, NCSS 10, Analyse-it.

PARAMETERS: Some important parameters of computer-aided drug design are described as below.

(a) HOMOLOGY MODELING[9]

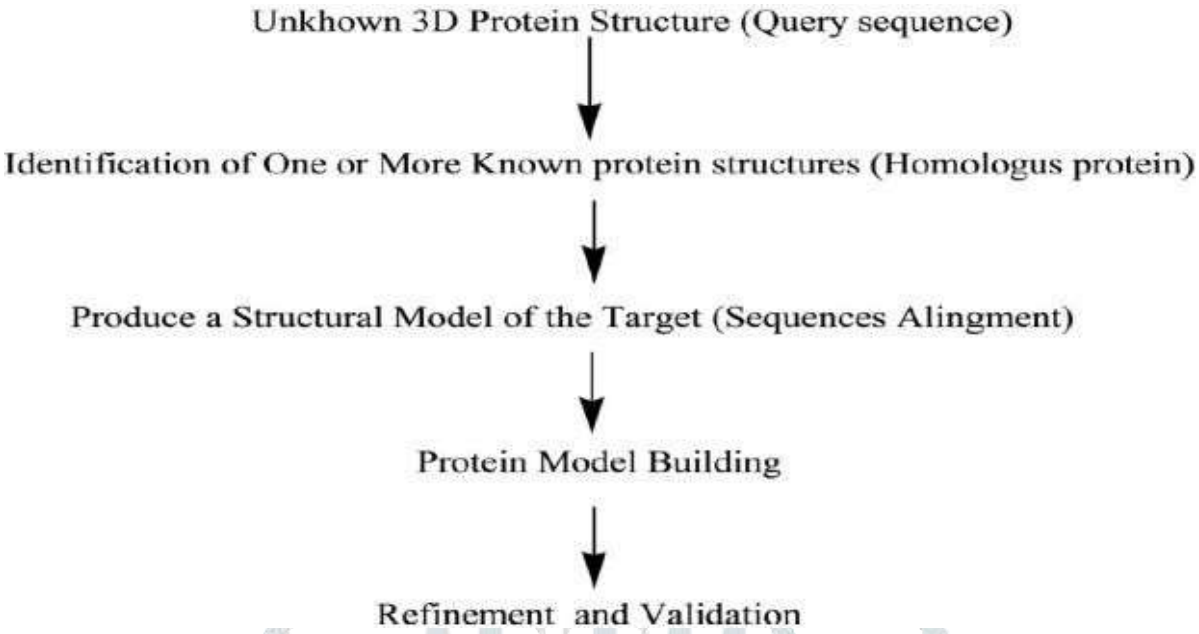

Figure 5: Structure prediction by homology modelling.

In the absence of experimental structures, computational methods are used to predict the 3D structure of target proteins. Comparative modeling is used to predict target structure-based on a template with a similar sequence, leveraging that protein structure is better conserved than sequence, i.e., proteins with similar sequences have similar structures. Homology modeling is a specific type of comparative modeling in which the template and target proteins share the same evolutionary origin. Comparative modeling involves the following steps:

(1) Identification of related proteins to serve astemplate structures,
(2) Sequence alignment of the target and templateproteins,
(3) Copying coordinates for confidently alignedregions,
(4) Constructing missing atom coordinates of targetstructure,
(5) Model refinement and evaluation.

Several computer programs and web servers exist that automate the homology modeling process e.g., PSIPRED and MODELLER**.** Major goal of structural biology involve formation of protein-ligand complexes; in which the protein molecules act energetically in the course of binding. Therefore, perceptive of protein-ligand interaction will be very important for structure-based drug design. Lack of knowledge of 3D structures has hindered efforts to understand the binding specificities of ligands with protein. With increasing in modeling software and the growing number of known protein structures, homology modeling is rapidly becoming the method of choice for obtaining 3D coordinates of proteins. Homology modeling is a representation of the similarity of environmental residues at topologically corresponding positions in the reference proteins. In the absence of experimental data, model building on the basis of a known 3D structure of a homologous protein is at present the only reliable method to obtain the structural information. The knowledge of the 3D structures of proteins provides invaluable insights into the molecular basis of their functions [9].

(b) LIGPLOT ANALYSIS: Ligplot analysis a computer program that generates schematic 3D representations of protein-ligand complexes from standard 'protein data bank (PDB)' file input[10].

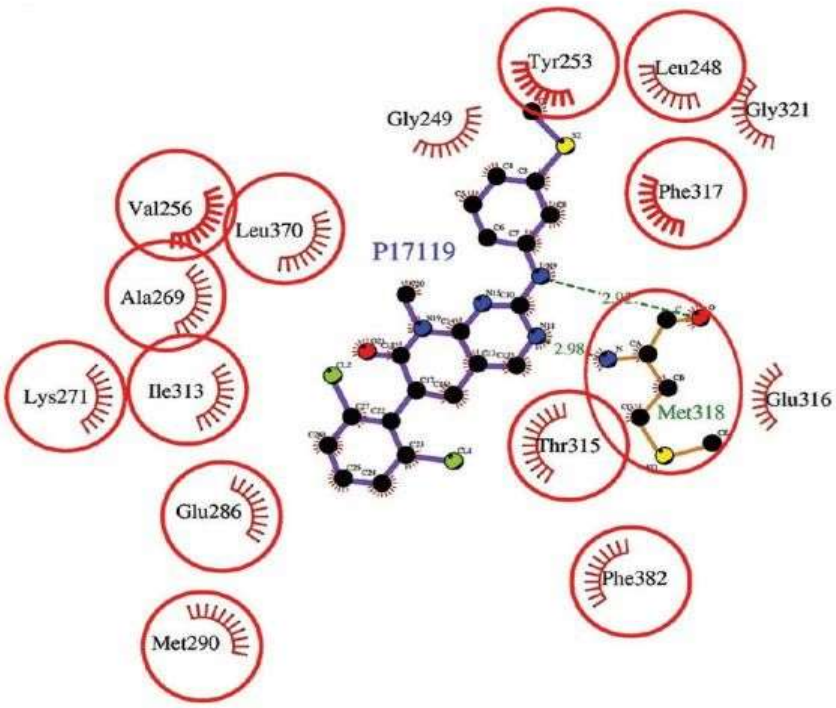

Figure 6: Ligplot analysis [The red circles and ellipses in each plot indicate protein residues that are in equivalent 3D positions to the residues in the first plot. Hydrogen bonds are shown as green dotted lines, while the arcs represent residues making non-bonded contacts with the ligand].

(c) MOLECULER DOCKING:

Figure 7: Molecular docking.

Molecular docking is the computational modeling of the structure of complexes formed by two or more interacting molecules. The goal of molecular docking is the prediction of the three dimensional structure. Docking plays an important role in the rational design of drugs. The aim of molecular docking is to achieve an optimized conformation for both the protein and ligand so and relative orientation between protein and ligand so that the free energy of the overall system is minimized. Molecular recognition plays a key role in promoting fundamental biomolecular events such as enzyme-substrate, drug-protein and drug-nucleic acid interaction [11].

❖ **Docking theory:** The following docking theory topics are available [11]:

1. CDOCKER: Uses a random preliminary ligand placement and full CHARMm forcefield-based docking.
2. LibDock: Fast docking-based on binding site features ('hotspots').
3. LigandFit: Docking-based on an initial shape match to the binding site.
4. MCSS: Uses CHARMm to dock fragments by using a unique computationally efficient Multiple Copy Simult neous Search algorithm.

Drug-receptor interactions occur on atomic scales. To form a deep understanding of how and why drug compounds bind to protein targets, we must consider the biochemical and biophysical properties of both the drug itself and its target at an atomic level. Swiss PDB (protein data bank) is an excellent tool for doing this. It can predict key physico-chemical properties, such as hydrophobicity and polarity that have a profound influence on how drugs bind to proteins [6].

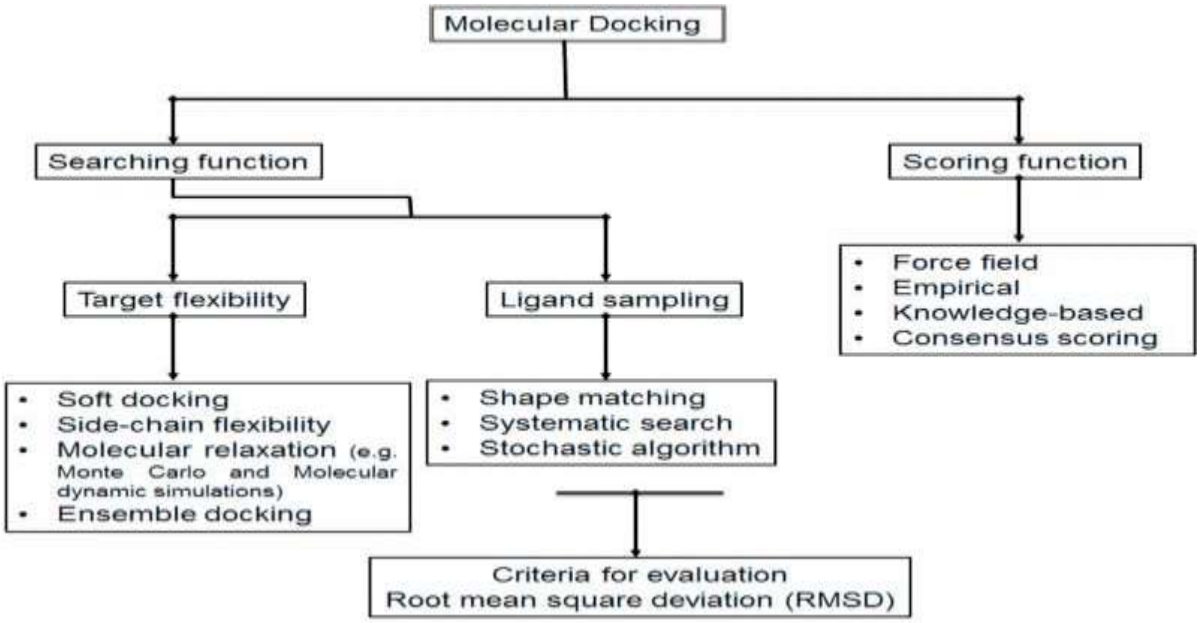

Figure 8: Methods used for protein-ligand docking.

Applications and importance of molecular docking: The uses of docking programmes to indicate the nature of the atoms and functional groups present in the 3D (three-dimensional) structures also enable to examine the binding of a drug to its target site [12].

(d) DE NOVO DRUG DESIGN: De novo design is the uses of docking programmes to design new lead structures that fit a particular target site.

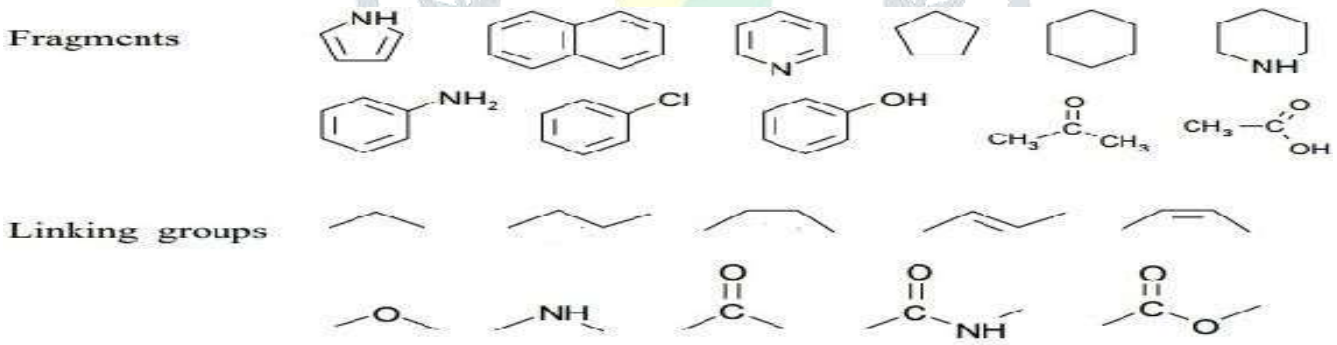

Figure 9: Different fragments and other linking groups used in de novo drug design methodology.

Step 1: Determination of binding pocket on target receptor

↓

Step 2: Prediction of interaction sites of target receptor through Ligplot

↓

Step 3: Placing the fragments or other linking groups with pharmacophore models at pre-defined interaction site to provide feasible interactions with the residues in the site of the target receptor

↓

Step 4: Structurally modification of the fragments to provide possible interactions with the residues in the site of the target receptor

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Step 5: Joining all fragments together to yield a complete single molecule

Figure 10: Steps of de novo drug design methodology.

(e) PHARMACOPHORE-BASED DRUG DESIGN:

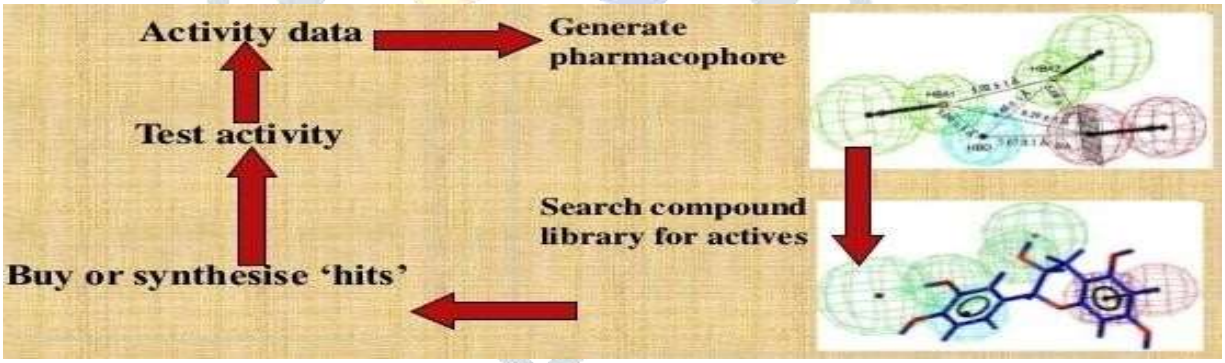


Figure 11: Pharmacophore-based drug design .

A pharmacophore is an abstract description of molecular capabilities which might be crucial for molecular identity and reputation of a ligand via a biological macromolecule. Typical pharmacophoric features consist of hydrophobic centroids, aromatic rings, hydrogen bond acceptors, hydrogen bond donors, high-quality fee and poor price. Pharmacophore tactics have end up one of the predominant tools in drug discovery after the beyond century's development. Various ligand-based totally and structurebased techniques were evolved for improved pharmacophore modeling. A pharmacophore model may be mounted both in a ligand-based totally way, by way of superposing a fixed of energetic molecules and extracting common chemical capabilities that are essential for his or her bioactivity, or in a structure-based way, with the aid of looking feasible interplay points between the macromolecular objectives and ligands. Pharmacophore methods were used drastically in virtual screening [(14)].

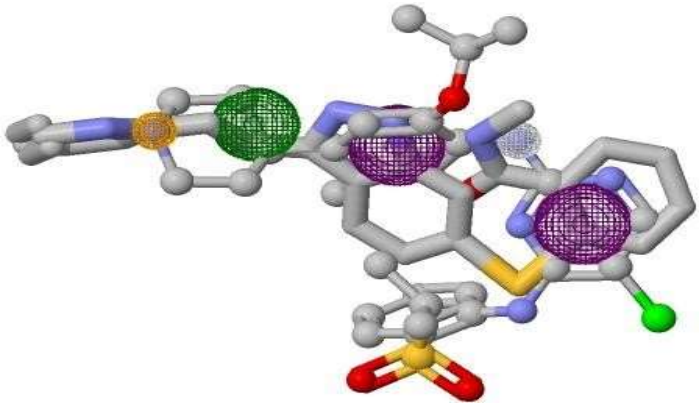


Figure 12: Pharmacophore .

- **Colours of Pharmacophoric Features** [16]**:**

1. Hydrogen bond acceptor: Orange,
2. Hydrogen bond donor: White, a tool for searching databases for compounds with
3. Aromatic ring: Magenta, similar pharmacophores
4.Hydrophobic centroid:

(f) VIRTUAL SCREENING (VS):

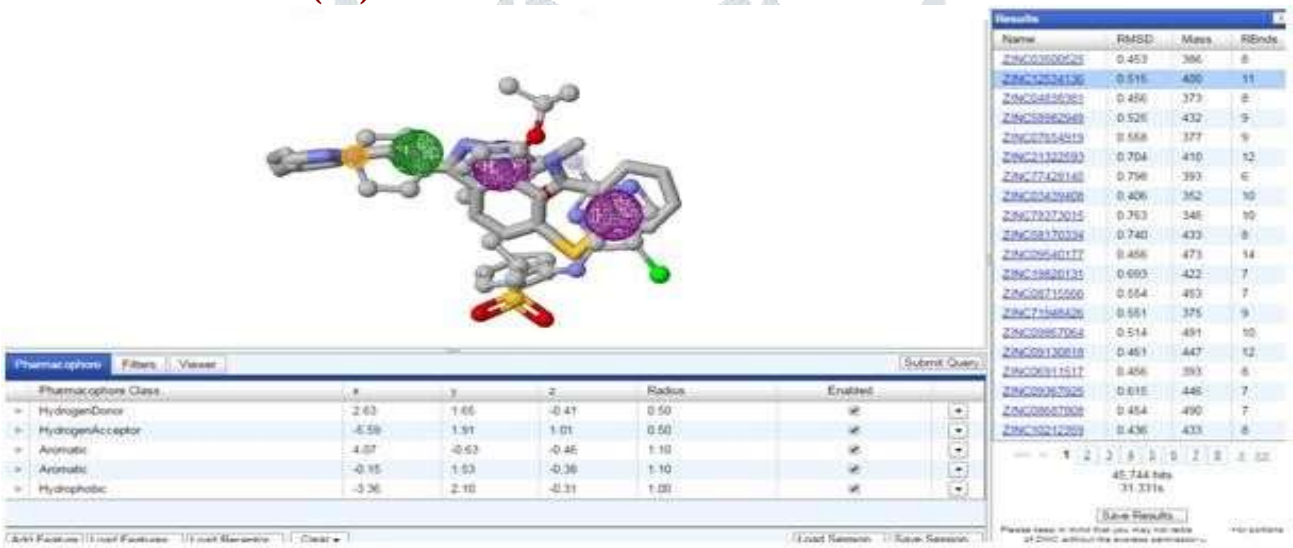


Figure 13: Virtual screening from the pharmacophoric model through Zinc pharmer web server .

Virtual screening is a computational approach where big libraries of compounds are assessed for his or her ability to bind specific web sites heading in the right direction molecules including proteins and nicely-compounds examined. Virtual screening is a computational approach used in drug discovery research. By the usage of computer systems, it deals with the short seek of huge libraries of chemical shape for you to identify those systems which might be maximum probably to bind to a drug goal, generally a protein receptor or enzyme. Virtual screening has turn out to be an crucial a part of the drug goal, usually a protein receptor or enzyme. Virtual screening has become an imperative part of the drug discovery process. Related to the more general and long pursued idea of database looking, the time period "virtual screening" is particularly new. Virtual screening has in large part been a numbers recreation that specialize in questions like how are we able to filter down the enormous chemical area of over 1060 conceivable compounds to a viable wide variety that can be synthesized, bought and examined. Although filtering the whole chemical universe might be a fascinating question, more realistic virtual screening eventualities cognizance on designing and optimizing focused combinatorial libraries and enriching libraries of to be had compounds from in-residence compound repositories or seller offerings. It is less highly-priced than excessive-throughput screening, quicker than traditional screening, scanning a massive variety of ability capsules like molecules in very less time [16][17]

(g) QUANTATIVE STRUCTURE-ACTIVITY RELATIONSHIPS (QSARs):

Quantitative structure-activity relationship (QSAR) modeling pertains to the construction of predictive models of biological activities as a function of structural and molecular information of a compound library. The concept of QSAR has typically been used for drug discovery and development and has gained wide applicability for correlating molecular information with not only biological activities but also with other physicochemical properties, which has therefore been termed quantitative structure-property relationship (QSPR) [(18)]. Typical molecular parameters that are used to account for electronic properties, hydrophobicity, steric effects, and topology can be determined empirically through experimentation or theoretically via computational chemistry [(19)]. A given set of data sets is then subjected to data pre-processing and data modeling through the uses of statistical or machine learning techniques. This review aims to cover the essential concepts and techniques that are relevant for performing QSAR/QSPR studies through the uses of selected examples from our previous work [(19)(20)(21)]

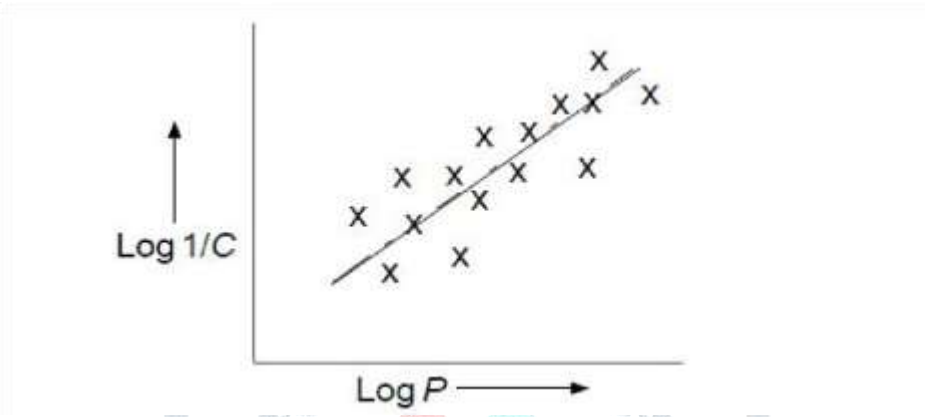


Figure 14: A hypothetical plot of the activity (Log1/C) of a series of compounds against the logarithm of their partition coefficients parameters (LogP) .

(h) *IN SILICO* ADMET (ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION, TOXICITY) AND DRUG SAFETY PREDICTION:

Lipinski's rule is related to ADMET (absorption, distribution, metabolism, excretion and toxicity which states that, in general, an orally active drug has no more than one violation of the following components . [22,23,24,25,26,27,28,29]:

1. Hydrogen bond donor (the total number of nitrogenhydrogen and oxygen-hydrogen bonds) in a molecule is not more than 5.
2. Hydrogen bond acceptor (all nitrogen or oxygen atoms) in a molecule is not more than 10.
3. Molecular weight (MW) of a molecule is less than 500 daltons or 800 gms.
4. Octanol-water partition coefficient (LogP) of a molecule is not greater than 5.
5. Polar surface area (PSA) of a molecule is notgreater than 190 $Å^2$.
6. The range of molar refractivity (MR) of a moleculeis in between 40 to 130.
7. The range of total number of atoms in a molecule isin between 20-70.
8. The range of total number of rotatable bonds in amolecule is not greater than 10.

• **Importance:** The rule is important to keep in mind during drug discovery when a pharmacologically active lead structure is optimized step-wise to increase the activity and selectivity of the compound as well as to ensure drug-like physicochemical properties are maintained.

There are various *in silico* tools to predict ADMET (absorption, distribution, metabolism, excretion and toxicity) like 1) ALOGPS, 2) E-dragon, 3) Padeldescriptors etc [(30)].

❖ PRINCIPLES GOVERNING CADD

- **Molecular Mechanics**
- **Quantum Mechanics**

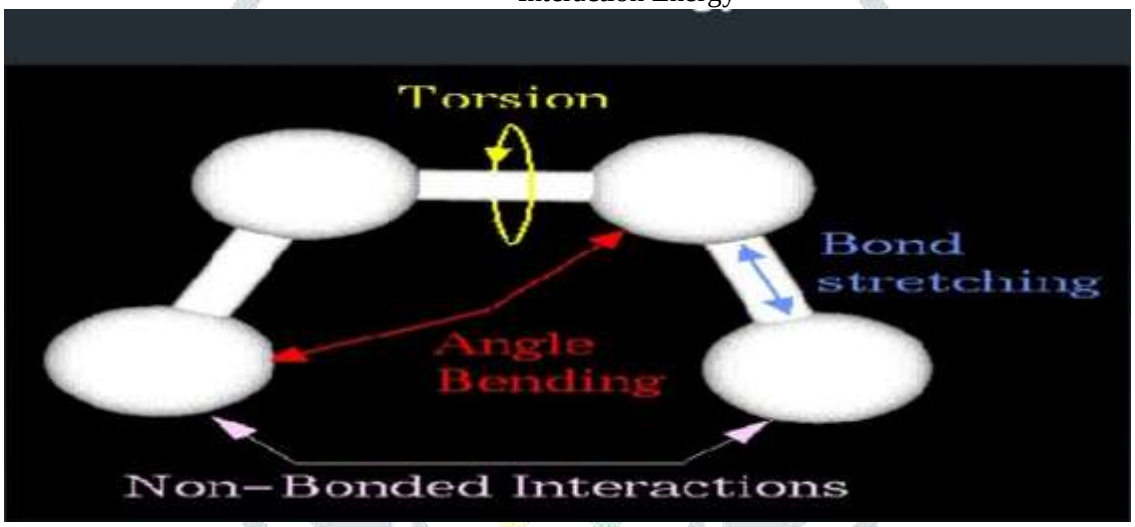
❖ Molecular Mechanics :-

- Molecular mechanics refers to the use of classical mechanics to model the geometry and motions of molecules.
- Molecular mechanics methods are based on the following principles:

l) Nuclei and electrons are lumped into atom-like particles
2) Atom-like particles are spherical and have a net charge.
3) Interactions are based on springs and classical potentials.
4) Interactions must be preassigned to specific sets of atoms.
5) Interactions determine the spatial distribution of atom-like particles and their energies.

- The objective: to predict the energy associated with a giv conformation of a molecule.
- A simple molecular mechanics energy equation is given by:

Energy = Stretching Energy + Bending Energy
+Torsion Energy + Non-Bonded
Interaction Energy



Stretching Energy :-

- The stretching energy equation is based on Hooke's law.
- This equation estimates the energy associated with vibration about the equilibrium bond length.

Bending Energy :-

- The bending energy equation is also based on Hooke's law.
- This equation estimates the energy associated with vibration about the equilibrium bond angle
- The larger the value , the m ore energy is required to
- deform an angle (or bond) from its equilibrium value

Torsion Energy :-

- The torsional energy represents the amount of energy that must be added to or subtracted from the Stretching Energy + Bending Energy + Non-Bonded Interaction Energy terms to make the total energy agree with experiment
- A-controls the amplitude of the curve, n-controls its periodicity, (∈- shifts the entire curve along the rotation angle axis (tau).

Non Bonded Energy :-

- The non-bonded energy represents the pair-wise sum of the energies of all possible interacting non-bonded atoms i and j:

- **Quantam Mechanics**
  - Quantum theory uses well known physical constants ,such as velocity of light, values for the masses & charges of nuclear particles to calcaulate molecular properties
  - The equation from which molecular properties can be derived from schrodinger equation

HV=EV

Quantum theory is based on Schrodinger's equation:

• E-energy of the system.

• H-is the Hamiltonian operator which includes both kinetic and potential energy

HV=EV

Full wave function Electron wave function

Quantum mechanics methods are based on the following principles:-

- Nuclei and electrons are distinguished from each other.
- Electron-electron and electron-nuclear interactions are explicit.
- Interactions are governed by nuclear and electron charges (i.e. potential energy) and electron motions.
- Interactions determine the spatial distribution of nuclei and electrons and their energies. [31].

❖ OBJECTIVES OF CADD

- To change from:
  - Random screening against disease assays
  - Natural products, synthetic chemicals

- To:
  - Rational drug design and testing
  - Speed-up screening process
  - Efficient screening (focused, target directed)
  - De novo design (target directed)
  - Integration of testing into design process
  - Fail drugs fast (remove hopeless ones as early as possible)

❖ ADVANTAGES OF CADD

1. Less Time require
2. Accuracy
3. information about the disease
4. Increase productivity & higher quality designs .
5. screening is reduced
6. Database screening & optimization
7. less manpower is required
8. CADD gives valuable information about target molecules,
9. The latest advancements like QSAR, combinatorial chemistry different databases & available new software tools provide a basis for designing of ligands & inhibitors that require specificity.

❖ APPLICATION OF CADD

- Determine the lowest free energy structures for the receptor-ligand complex Search database and rank hits for lead generation
- Calculate the differential binding of a ligand to two different macromolecular receptors

- Study the geometry of a particular complex Propose modification of a lead molecules to optimize potency or other properties de novo design for lead generation
- Library design
- Design Review and Evaluation. Review and Evaluation is checking whether the designed part has been designed properly. [32].

❖ BENEFITS OF CADD

CADD methods and bioinformatics tools offer significant benefits for drug discovery programs.

➢ Cost Savings :-

The Tufts Report suggests that the cost of drug discovery and development has reached $800 million for each drug successfully brought to market. Many biopharmaceutical companies now use computational methods and bioinformatics tools to reduce this cost burden. Virtual screening, lead optimization and predictions of bioavailability and bioactivity can help guide experimental research. Only the most promising experimental lines of inquiry can be followed and experimental dead-ends can be avoided early based on the results of CADD simulations.

➢ .Time-to-Market :-

The predictive power of CADD can help drug research programs choose only the most promising drug candidates. By focusing drug research on specific lead candidates and avoiding potential "deadend" compounds, biopharmaceutical companies can get drugs to market more quickly.

➢ Insight :-

One of the non-quantifiable benefits of CADD and the use of bioinformatics tools is the deep insight that Molecular models of drug compounds can reveal intricate, atomic scale binding properties that are difficult to envision in any other way.

When we show researchers new molecular models of their putative drug compounds ,their protein targets and how the two bind together, they often come up with new ideas on how to modify the drug compounds for improved fit. This is an intangible benefit that can help design research programs.

CADD and bioinformatics together are a powerful combination in drug research and development. An important challenge for us going forward is finding skilled ,experienced people to manage all the bioinformatics tools available to us, which will be a topic for a future.

➢ Speed up Drug Development :-

Researchers in Germany report an advance toward the much awaited era in which scientists will discover and design drugs for cancer, arthritis, AIDS and other diseases almost entirely on the computer, instead of relying on the trial-and-error methods of the past .In the report, Michael C. Hutter12 and colleagues note that computer-aided drug design already is an important research tool. The method involves using computers to analyze the chemical structures of potential drugs and pinpoint the most promising candidates. Existing computer programs check a wide range of chemical features to help distinguish between drug-like and nondrug materials. These programs usually cannot screen for all features at the same time, an approach that risks over looking promising drug-like substances .In the new study, researchers describe a more gradual and efficient system. Their new program uses an initial quick screen for drug-like features followed immediately by a second, more detailed screen to identify additional drug -like features. They applied this new classification scheme to a group of about 5,000 molecules that had previously been screened for drug-like activity. The new strategy was more efficient at identifying drug-like molecules "whereby up to 92 percent of the non drugs can be sorted out without losing considerably more drugs in the succeeding steps," the researchers say.[34] [35]

❖ SUCCESSFUL CADD APPROACHES TO THE TREATMENT OF NEURODEGENERATIVE DISORDERS

The success of CADD has resulted in its being recognized as an important technique in the research and pharmaceutical fields. There are many examples of the successful application of CADD, but here we describe its successes with respect to the design of drugs for the treatment of NDs. Amyloid-β is an important therapeutic target in Alzheimer's disease [65]. Chen et al. used an in silico approach to study a series of peptides against the fibrillar form of Aβ, and reported two highly active compounds [66]. These peptides were subsequently found to inhibit the neurotoxic effects of Aβ on neuroblastoma cells.

BACE-1 is an enzyme that has been reported to be essential for β-amyloid generation [67]. Research suggests inhibition of this enzyme stops the production of β-amyloid, and thus, prevents NDs like Alzheimer's disease [68]. This finding has made BACE-1 an important therapeutic target for NDs. During the last few years, several computational approaches have been used to study the structural behavior of BACE-1 and to design their inhibitors [69-71].

ROCK-I and NOX2 are among the most attractive potential therapeutic targets for several NDs [72-75]. Inhibition of these two enzymes constitutes treatment for neurological diseases like autism spectral disorder, Alzheimer, and fragile X syndrome. Alokam et al. reported the successful use of CADD to design dual inhibitors for these enzymes [76], by employing a combination of pharmacophores and using a molecular docking approach to identify chemical entities. In vitro validation of selected chemical entities demonstrated their inhibitory potentials against ROCK-I and NOX2. (36).

HDAC'6 is a member of the class IIb Histone deacetylases (HDACs) family and is usually found in cytosol in association with non-histone proteins [77, 78]. HDAC6 has been widely reported to be a crucial therapeutic drug target for several NDs [79-81]. The implementation of CADD has been reported to result in the design of a potential inhibitor of this enzyme. In one study conducted by Goracci et al., a virtual screening approach was used to identify potential inhibitors for HDAC6, and these were then subjected to in vitro testing. The results obtained showed inhibitors had low cytotoxicities, suggesting potential for drug development [82]. Several other reports have described the successful use of CADD in the NDs. (37) (38) (39) (40)

❖ . LIMITATIONS

- ✓ Despite a number of successful applications of CADD to modern drug design, it has its limitations. In particular, like any computer assisted hypothetical system results must be validated in actual systems, and many lead molecules identified using CADD have failed to exhibit desired activities in biological systems [83, 84].
- ✓ Several parameters must be met before potential compound to be approved as potent lead/drug, as it has to pass several pharmacological criteria. In fact, an average of only 40% of lead/drug candidates passes the different phases of clinical trials and obtains approval for clinical use. (41) (42)
- ✓ Any computational tool based on pre-defined algorithms and scripts has its limitations, and the computational tools/methods used in CADD, such as, molecular docking, virtual screening, QSAR, pharmacophore modeling, and molecular dynamics, have their own limitations (43)
- ✓ Furthermore, ADME and many toxicity prediction tools are not supported by solid experimental data, and many examples of the failure of these computational approaches can be found in the literature [89, 90]
- ✓ To overcome limitations and improve accuracy in terms of predicting potent leads, regular updates of tools and algorithms are needed. Database reliability and high quality validated experimental molecules is to be developed and updated because many pharmacophores do not pass biological activity process due to non-availability of good quality data sets.
- ✓ Databases should contain detail data on genomics and proteomics, high quality sequence information, physicochemical properties, and structures. (44)

❖ CONCLUSION

The drug discovery and improvement system is a long and high priced one. It starts from goal identity, after that, validates the goals and identifies the drug candidates before any newly determined drug is placed available on the market. It must go through excessive preclinical and exams and get the FDA approval. Computer-aided drug layout (CADD) is a natural out growth of theoretical chemistry, the traditional function of which entails the advent and dissemination of a penetrating conceptual infrastructure for the bioinformatics, chemical sciences, mainly at the atomic and molecular stages.

The main goal to decrease the level of producing value degree. In unique, the sturdy mathematical flavour of CADD hyperlinks among mathematical and the chemical sciences, and to the past, present and destiny roles of interdisciplinary studies at the interface among these subjects. The troubles constitute basis issues for the present examine. The developing range of chemical and organic databases; and explosions in currently to be had software program equipment are imparting a far stepped forward foundation for the design of ligands and inhibitor with preferred specificity. In the present era of drug discovery, the application of CADD counts up the most important accountability, and provides computational tools and algorithms that save time, costs, and reduce the risk of detecting non-viable developmental

leads. The discovery of a new lead/drug using recent CADD paradigms requires a systematic understanding of the molecular and pathological conditions induced by diseases. Early diagnosis of NDs remains a huge challenge for researchers and clinicians. However, CADD can assist researchers studying interactions between drugs and receptors. The pharmacoinformatic approach is being applied to modern drug discovery and is providing much basic knowledge regarding drug-receptor interactions. Novel technologies and computational algorithms are required to move the CADD approach forward, as new developments are likely to lead to tools for disease identification and the screening of potential lead compounds. The emerging field of neurological studies, which includes neuroproteomics and neurogenomics, may aid understanding of the neuronal alterations associated with NDs. Furthermore, the application of technologies associated with neuroproteomics, neurogenomics, and next generation sequencing, and genome wide association studies may result in the identification of novel therapeutic targets and ultimately improve our ability to treat NDs.

❖ REFERENCES

1. Veselovsk;AV, Ivanov AS 2003; Strategy of computeraided drug design; Russian academy of medical science; 3(1); 33-40.
2. Yun T, Weiliang Z, Kaixian C, Hualiang J 2006; New technologies in computer-aided drug design: Toward target identification and new chemical entity discovery; Drug discovery today: technologies; 2006; 3(3); 307-313.
3. Pranita PK, Madhavi MM, Rishikesh VA, Rajesh JO, Sandip SK 2012; Computer-aided drug design: an innovative tool for modeling; Journal of medicinal chemistry; 2012; 2; 139-148.
4. Pugazhendhi D, Umamaheswari TS 2013; In silico methods in drug discovery–a review; International journal of advanced research in computer science and software engineering;; 3(5); 680-683.
    a. http://www.slideshare.net/adammbbs/structurebased-drug-design-48389641/12; Structure-based drug design (Docking and de novo drug design); Authored by Adam Shahul Hameed; Anna University Chennai; Available online from 2015.
5. Silvana G 2013; Computer-based methods of inhibitor prediction; Intech open science and open minds; ; Chapter 3; 73-90. (http://cdn.intechopen.com/pdfs-wm/40599.pdf)
6. Satyajit D, Sovan S, Kapil S 2010; Computer-aided drug design - a new approach in drug design and discover;; 4(3); 146-151.
7. Choudhary L.K., Shukla A., Zade S., Charde R 2011; (C.A.D.D.)-a new modern software-based approach in drug design and discovery; International journal of pharmaceutical chemistry;; 1(1); 10-20.
8. Vyas VK, Ukawala RD, Ghate M, Chintha C 2012 ; Homology modeling a fast tool for drug discovery: current perspectives; Indian journal of pharmaceutical sciences;; 74(1); 1–17.
9. Roman AL, Mark BS 2011; LigPlot+: Multiple ligandprotein interaction diagrams for drug discovery; Journal of chemical information and modeling;; 51; 2778-2786.
10. Alejandra HS, Aldo YT, Victor A, Héctor VC, Claudia MB 2013;; Protein-protein and protein-ligand docking; Intech open science and open minds; Chapter 3; 64-81.(http://cdn.intechopen.com/pdfs-wm/44790.pdf)
11. Gaba M, Gaba P, Singh S, Gupta GD 2010; An overview on molecular docking; International Journal of Drug Development and Research;; 2(2); 219-231.
12. Gareth T, Medicinal chemistry an introduction; Computer-aided drug design (Chapter-4); John Wiley and Sons Ltd; 2007; 2nd edition; 128-130.
13. http://www.slideshare.net/8055679610/finalpresentation66; Pharmacophore Modeling in Drug Designing; Authored by Vinod Tonde; Rajmata jijau shikshan prasarak mandal's college ofpharmacy, Dudulgaon, Pune-412105; Available online from 2014.
14. Udugade BV, Gawade SP 2016; 3D QSAR and pharmacophore modeling on substituted cyanopyrrolidines as type ii anti-diabetic agents potential dipeptidyl peptidase-iv inhibitors; Pharmacophore (An international research journal);; 7(5); 342-348.
15. David RK, Carlos JC 2012; ZINC Pharmer: pharmacophore search of the ZINC database; Nucleic acids research;; 40; 409-414.
16. Reddy AS, Pati SP, Kumar PP, Pradeep HN, Sastry GN 2007; Virtual screening in drug discovery-A computational perspective; Current protein and peptide science;; 8; 329-351.
17. Chanin N, Chartchalerm INA, Thanakorn N, Virapong PA 2009; Practical overview of quantitative structure-activity relationship; EXCLI Journal;; 8; 74-88.
18. Anu G, Dr. Manish G, Dr. Komal S 2016; A Practical overview of quantitative structure-activity relationship;; 5(2); 427-437.

19. Denis F, Eugene M, Alexander T; 2010; Trust but verify: On the importance of chemical structure curation in cheminformatics and QSAR modeling research; Journal of Chemical Information and Modeling; 2010; 50(7); 1189–1204.
20. Gareth T, Medicinal chemistry an introduction; Structure–activity and quantitative structure relationships (Chapter-3); John Wiley and Sons Ltd; 2007; 2nd edition; 93.
21. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ; Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings; Advanced drug delivery reviews; 2001; 46(1-3); 3–26.
22. Lipinski CA 2004; Lead- and drug-like compounds: the rule-of-five revolution; Drug discovery today: Technologies;; 1(4); 337–341.
23. Leo A, Hansch C, Elkins D; Partition coefficients and their uses; Chemical reviews; 1971; 71(6); 525–616.
24. Ghose AK, Viswanadhan VN, Wendoloski JJ 1999; A knowledge-based approach in designing combinatorial or medicinal chemistry libraries for drug discovery. 1. A qualitative and quantitative characterization of known drug databases; Journal of combinatorial chemistry; 1999; 1(1); 55–68.
25. How to cite this article: Injamul Hoque, Arkendu Chatterjee, Somenath Bhattacharya, Raj Biswas.(2017). An Approach of Computer-Aided Drug Design (CADD) Tools for In Silico Pharmaceutical Drug Design and Development.Int. J. Adv. Res. Biol. Sci. 4(2): 60-71. DOI: http://dx.doi.org/10.22192/ijarbs.2017.04.02.009
26. Veber DF, Johnson SR, Cheng HY, Smith BR, Ward KW, Kopple KD; Molecular properties that influence the oral bioavailability of drug candidates; Journal of medicinal chemistry; 2002; 45(12); 2615–2623.
27. Access this Article in Online Website: www.ijarbs.com Subject: PharmaceuticalSciences Quick Response Code DOI:10.22192/ijarbs.2017.04.02.009
28. Congreve M, Carr R, Murray C, Jhoti H 2003; A 'rule of three' for fragment-based lead discovery?; Drug discovery today; 2003; 8(19); 876–877.
29. Oprea TI, Davis AM, Teague SJ, Leeson PD 2001; Is there a difference between leads and drugs? A historical perspective; Journal of chemical information and modeling; 2001; 41(5); 1308– 1315.
30. Leeson PD, Springthorpe B; The influence of drug-like concepts on decision-making in medicinal chemistry; Nature reviews drug discovery; 2007; 6(11); 881–890.
31. RamaKrishna K, Rao CVK, Rao RS; ChemoInformatics Part I: Molecular descriptors in omnimetrics research; Journal of applicable chemistry; 2015; 4(4); 1024-1144.
32. Ghose AK, Viswanadhan VN, Wendoloski JJ 1999; A knowledge-based approach in designing combinatorial or medicinal chemistry libraries for drug discovery. 1. A qualitative and quantitative characterization of known drug databases; Journal of combinatorial chemistry; 1999; 1(1); 55–68.
33. .eber DF, Johnson SR, Cheng HY, Smith BR, Ward KW, Kopple KD; Molecular properties that influence the oral bioavailability of drug candidates; Journal of medicinal chemistry; 2002; 45(12); 2615–2623.
34. .Congreve M, Carr R, Murray C, Jhoti H 2003;; A 'rule of three' for fragment-based lead discovery?; Drug discovery today; 8(19); 876–877.
35. Madonna R., Novo G., Balistreri C.R. . 2016; Cellular and molecular basis of the imbalance between vascular damage and repair in ageing and age-related diseases: As biomarkers and targets for new treatments. Mech. Ageing Dev. 2016;159:22–30. [http://dx.doi. org/10.1016/j.mad.2016.03.005]. [PMID: 26993150]. [PubMed] [Google Scholar]Anand R, Gill KD. 2014.
36. Silberberg D 2011;. The high impact of neurologic disorders in developing countries: the struggle for global recognition. Neurology. 2011;77(3):307–308. [http://dx.doi.org/10.1212/WNL.0b013e3182285da9]. [PMID: 21768602]. [PubMed] [Google Scholar]
37. . Ke Z., Zhang X., Cao Z., Ding Y., Li N., Cao L., Wang T., Zhang C., Ding G., Wang Z., Xu X., Xiao W. 2016; Drug discovery of neurodegenerative disease through network pharmacology approach in herbs. Biomed. Pharmacother. 2016;78:272–279. [http:// dx.doi.org/10.1016/j.biopha.2016.01.021]. [PMID: 26898452]. [PubMed] [Google Scholar]
38. Lausted C., Lee I., Zhou Y., Qin S., Sung J., Price N.D., Hood L., Wang K. 2014;. Systems approach to neurodegenerative disease biomarker discovery. Annu. Rev. Pharmacol. Toxicol. 2014;54:457–481. [http://dx.doi.org/10.1146/annurev-pharmtox-011613-135928]. [PMID: 24160693]. [PubMed] [Google Scholar]
39. Morris G.P., Clark I.A., Vissel B. 2014;2:135; Inconsistencies and controversies surrounding the amyloid hypothesis of Alzheimer's disease. Acta Neuropathol. Commun.. [PMID: 25231068]. [PMC free article] [PubMed] [Google Scholar]
40. Zeng H., Wu X. Alzheimer's disease drug development based on computer-aided drug design. Eur. J. Med. Chem. 2016;121:851–863. [http://dx.doi.org/10.1016/j.ejmech.2015.08.039]. [PMID: 26415837]. [PubMed] [Google Scholar]

41. 3,Baig M.H., Ahmad K., Roy S., Ashraf J.M., Adil M., Siddiqui M.H., Khan S., Kamal M.A., Provazník I., Choi I. 2016;Computer Aided Drug Design: Success and Limitations. Curr. Pharm. Des. 2016;22(5):572–581. [http://dx.doi.org/10.2174/1381612822666 151125000550]. [PMID: 26601966]. [PubMed] [Google Scholar]
42. Scotti L., Scotti M.T. Computer aided drug design studies in the discovery of secondary metabolites targeted against age-related neurodegenerative diseases. Curr. Top. Med. Chem. 2015;15(21):2239–2252. [http://dx.doi.org/10.2174/1568026615666150610143510]. [PMID: 26059353]. [PubMed] [Google Scholar]
43. Daina A, Blatter MC, Baillie Gerritsen V, Palagi PM, Marek D, Xenarios I, et al 2017; Drug Design Workshop: A Web-Based Educational Tool To Introduce Computer-Aided Drug Design to the General Public. Journal of Chemical Education.; 94(3):335-44.
44. Pan S.Y., Zhou S.F., Gao S.H., Yu Z.L., Zhang S.F., Tang M.K., Sun J.N., Ma D.L., Han Y.F., Fong W.F., Ko K.M 2013; New perspectives on how to discover drugs from herbal medicines: CAM's outstanding contribution to modern therapeutics. Evid. Based Complement. Alternat. Med. 2013;2013:627375. [http://dx. doi.org/10.1155/2013/627375]. [PMID: 23634172]. [PMC free article] [PubMed] [Google Scholar]