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Review on “Computer Aided Drug Design"

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ABSTRACT

Using mathematical equations, computer-aided drug design software predicts the structure and value of attributes of known, unknown, stable, and molecular species. Molecular modelling, Molecular mechanics, Molecular docking, Quantum mechanics, Hybrid QM/MM, and QSAR are some of the methods used in molecular docking investigations.A typical drug discovery cycle, from lead identification to clinical trials, is anticipated to take around a year. The addition of computer-aided drug design technologies to a company's R&D methodologies could result in a 50 percent cost reduction in medication design and development.

The fatal coronavirus disease 19 (COVID-19) pandemic that broke out recently is causing severe health worries around the world. The lack of licensed medications or vaccines remains a problem, necessitating the development of new medicinal compounds. By reducing costs and time, computer-aided drug design has helped to speed up the drug discovery and development process. We emphasize two significant areas of computer-aided drug design (CADD) in this review article: ligand-based and structured-based drug discovery. This review article explains the benefits and applications of computer-aided drug design in the design and discovery of medication molecules, as well as how it can aid in the management of terminal diseases.

Computational techniques are useful tools for interpreting and guiding trials in order to speed up the development of antibiotic drugs. The two most common forms of computer-aided drug design (CADD) methodologies are structure-based drug design (SBDD) and ligand-based drug design (LBDD). SBDD approaches examine 3-dimensional structural information from macromolecular targets, such as proteins or RNA, to discover critical locations and interactions that are important for their biological functions. This information can then be used to create antibiotic medications that compete with the target's vital interactions, interrupting the microorganism's biological pathways that are necessary for survival (s). LBDD approaches use known antibiotic ligands as a target to build a structure-activity relationship (SAR) between their physicochemical qualities and antibiotic activities, which can be used to improve existing medications or guide the development of novel compounds with improved activity. Standard CADD techniques for both SBDD and LBDD will be discussed in this chapter, with a particular emphasis on methodologies and targets frequently examined in our laboratory for antibiotic drug discovery.

Key words: Molecular modeling, Molecular mechanics, Molecular docking, Quantum mechanics, Hybrid, QM/MM, QSAR, Covid - 19,ligand bases

Introduction-

Since its inception in 1981, computer-aided drug design (CADD) has been credited with establishing modern trends in chemical characterisation in drug discovery. When compared to HTS, it is a step forward because it involves little chemical design or prior knowledge, but it can produce several hit compounds from which interesting candidates have been chosen.

CADD's typical role in drug discovery is to separate large compound libraries into smaller clusters of predicted active compounds, allowing lead compounds to be optimized by improving biological properties (such as affinity and ADMET) and building from a nucleating site by combining fragments with optimized function.Computational techniques are used in computer-aided drug design to find, create, and analyze medicines and other physiologically active compounds. The ligand-based computer-aided drug discovery (LB-CADD) method examines ligands that have been shown to interact with a target of interest. These approaches analyze the 2D or 3D structures of a set of reference structures gathered from chemicals known to interact with the target of interest. The main goal of these methods is to forecast the nature and strength of a molecule's binding to a target. Ab initio quantum chemistry methods, also known as density functional theory, are frequently used to provide optimized parameters for molecular mechanics calculations in order to predict the conformation of a small molecule and model conformational changes in the biological target that may occur when the small molecule binds to it. The results also give an estimate of the drug candidate's electrical characteristics (electrostatic potential, polarizability, and so on) that will affect binding affinity. CADD approaches can increase the chances of identifying compounds with desired properties, speed up hit-to-lead development, and increase the chances of a drug overcoming the various hurdles of preclinical testing

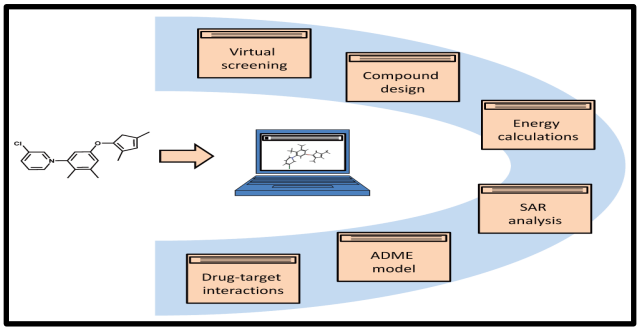

Fig - 1 computer aided drug design

Objective of CADD

To switch from
1) random screening against illness assays
2) targeted screening against disease assays
3) Synthetic chemicals vs. natural products
To
1) Rational medicine development and testing
2) Increase the speed of the screening process
3) Increase the efficiency of the screening
4) Design from scratch
5) Testing as part of the design process
6) Fail medications quickly.

Advantages:
a) cost savings;
b) time-to-market, as CADD's predictive power aids in the identification of prospective lead candidates, reducing time spent on dead ends.
c) Assists scientists in reducing the amount of time and money spent on synthetic and biological testing by focusing solely on the most promising substances.

Disadvantages –
a) Targeted systems are cleared quickly.
b) Immune reactivity to carrier systems given intravenously.
b) Inadequate targeting of targeted systems within tumor cells.
d) Drug release diffusion and redistribution
e) Formulation necessitates exceedingly advanced technologies.
f) Manufacturing, storage, and administration skills are required.
g) Toxicity symptoms may result from drug accumulation at the target site.
h) It's difficult to keep the dosage form stable.[3]

Drug

A drug is a chemical substance that affects the mind or body's functions and is used to diagnose, treat, or prevent disease or other abnormal conditions.

Drug design

Drug design is the process of coming up with novel treatments based on a biological target's information.
Designed molecules should be:
1) Organic small molecule
2) Shape-wise, complementary to the aim.
3) Charge the bimolecular target in the opposite direction.

Types of Computer aided drug design

Drug design -
1) Ligand bases
2) Structural bases

Computer-aided drug design based on ligands -

Drug development based on ligands Potency and other critical qualities are increased by building appropriate analogs based on knowledge of structure-activity correlations (SAR). Ligand-based drug development starts with either a single chemical or a series of compounds known to be potent against a target. The Topliss approach or a simple analog design based on structural similarity or attributes can be used to design.
Computational techniques such as pharmacophore models and compound shapes are frequently beneficial for design objectives. Once a large dataset with a wide variety of potencies is available, a Quantitative Structure-Activity Relationships (QSAR) model can be tried and used if the models are strong enough for prediction. Machine-learning-based models can also be used if the target is well-known and has a large number of compounds already identified in public literature or databases. They can be used for filtering design ideas, virtual screening, or scaffold-hopping hits if the machine-learning models are robust enough. Jubilant has developed clinical candidate molecules for a number of targets for which the target structure was unknown at the time. To operate the projects involving LBDD efforts, the computational chemistry team collaborates closely with the medicinal chemistry team.

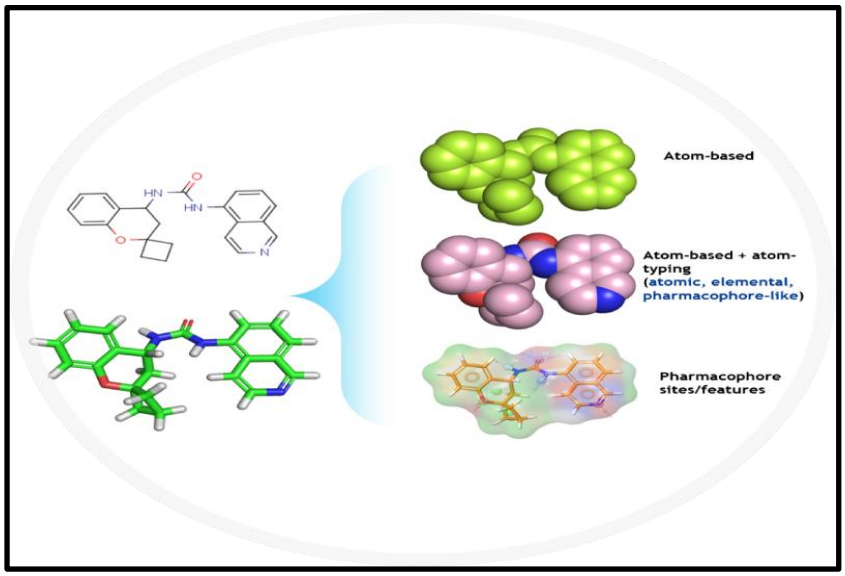

Fig - 2 Ligand base computer aided drug design

If the target structure is unknown but its closest homologues' structures are, a homology-based model can be constructed using the experimental coordinates of the closest homologue's structure. A structure-based design technique can be used if the homology model is good enough [4]

DRUG DESIGN BASED ON LIGANDS

1) Relationship between structure and activity on a quantitative scale (QSAR)
2) CoMFA
3) CoMSIA (Commonwealth of Massachusetts Institute of Technology)

1) QUANTITATIVE STRUCTURE-ACTIVITY Link - Investigates the relationship between the structures of ligands and their related effects using statistics and analytical methods. To describe, mathematical models are created based on structural factors. Previously, 2D-QSAR was used, but 3D-QSAR has been accepted. 3D-QSAR techniques include CoMFA and CoMSIA.

2) Comparative molecular field analysis (CoMFA) The biological activity of a molecule is influenced by the molecular fields that surround it (Steric and electrostatic fields) Has a number of issues

3) Comparative molecular similarity index analysis (CoMSIA) Additional field attributes are included. Hydrogen bond donor, Hydrogen bond acceptor, Steric, Electrostatic, Hydrophobic Compared to CoMFA , can provide a more accurate structural-activity connection.[5]

Drug design based on structure:

Relies on understanding of the biological target's three-dimensional structure, which can be achieved by:

- **X-ray crystallography is one type of x-ray crystallography.**
- **Spectroscopy using NuclearMagnetic Resonance** (NMR). NMR spectroscopy is a technique for determining the chemical composition of a X-ray crystallography is a technique for determining the structure of a substance. Drug development based on structure If a target's experimental structure isn't accessible, a homology model of the target based on the experimental structure of a comparable protein might be conceivable. Building an atomic-resolution model of the "target" and an experimental three-dimensional structure of a comparable homologous protein is referred to as homology modeling, also known as comparative modeling of proteins (the "template"). Using interactive visuals and the intelligence of a medicinal chemist, prospective medications that are projected to bind with high affinity and selectivity to the biological target can be created. New drug candidates may be suggested using a variety of automated computational approaches. 6

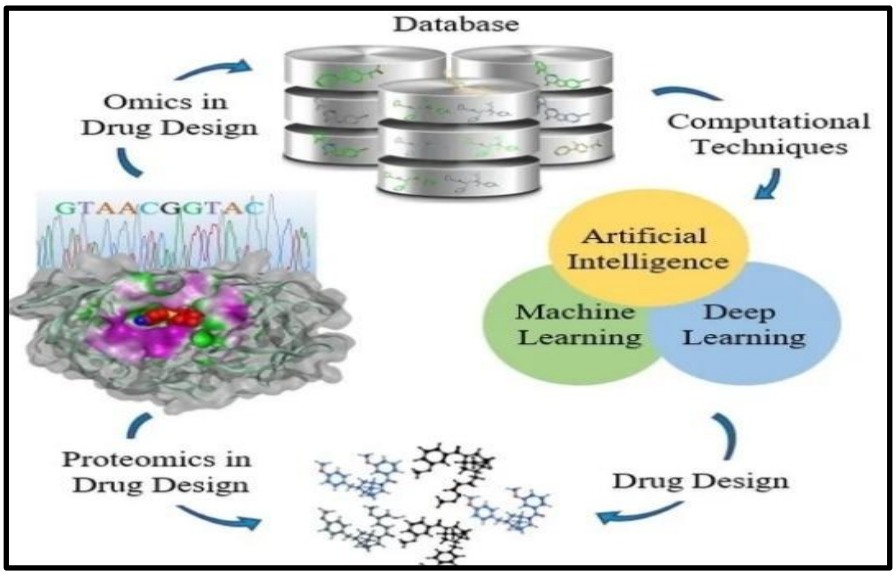

Fig. 3: Computer-aided medication design based on structure

Method -

1) Virtual screening
2) New ligand design from scratch
3) Improvement of a known ligand

1) Virtual screening (VS) is a computational technique used in drug development to scan libraries of small compounds for structures that are most likely to bind to a therapeutic target, which is often a protein receptor or enzyme.[7]

The term "virtual screening" refers to the process of "automatically analyzing very vast libraries of chemicals" with the help of computer algorithms.8 As this characterization implies, VS has essentially been a numbers game, with the goal of narrowing down the vast chemical space of over 1060 possible molecules [9] to a manageable number that can be synthesized, acquired, and tested. Although scanning the entire chemical universe is an intriguing theoretical topic, more realistic VS scenarios focus on developing and optimizing focused combinatorial libraries and augmenting libraries of accessible compounds from in-house compound repositories or vendor offers. Virtual screening has become an important aspect of the drug discovery process as the method's accuracy has improved. 10 Virtual Screening can be used to choose compounds for screening from within the company's database, chose compounds that can be acquired outside, and decide which molecule should be synthesized next. [11]

Virtual screening based on structure - The drug development process is a huge problem in the pharmaceutical industry since it takes a long time and a lot of money to complete all of the stages of generating a new drug. Computer-aided drug design is one of the most widely utilized methods for reducing medication development costs and time (CADD). CADD enables for improved experiment focus, which can cut down on the time and cost of medication development. Structure-based virtual screening (SBVS), one of the most promising in silico tools for drug research, is resilient and useful in this context. SBVS uses scoring functions to evaluate the force of non-covalent contacts between a ligand and a molecular target, and it tries to anticipate the optimum interaction mode between two molecules to form a stable complex. As a result, the success or failure of SBVS software is mostly determined by scoring functions. Many software packages are used to perform SBVS, and because they all employ various algorithms, different software can produce different results when given the same input. In the last decade, some research have adopted a novel SBVS technique termed consensus virtual screening (CVS) to improve SBVS accuracy and reduce the number of false positives produced in these tests. The presence of a 3D structure of the target protein is an absolute requirement for SBVS to work. Virtual databases have been built to store 3D structures of molecules, such as the Protein Data Bank. However, it is not always possible to obtain the 3D structure experimentally. In this case, homology modeling allows for the

prediction of a protein's 3D structure based on its amino acid sequence. This paper provides an overview of the problems of using CAD to perform SBVS, the areas where CAD tools help SBVS, a comparison of the most often used tools, and the strategies currently being employed to try to minimize time and cost in the drug development process. Finally, the final thoughts highlight the significance of SBVS in the drug development process.[12]

1) Protein Preparation Schemes for SBVS- The effectiveness of an SBVS campaign is heavily reliant on suitable protein and ligand starting structures. If the input structure is an X-ray structure, a typical PDB structure file contains just heavy atoms and may also contain water molecules, cofactors, activators, ligands, and metal ions, as well as numerous protein subunits. Furthermore, the structure lacks information on bond ordering, topologies, or formal atomic charges in general. Because X-ray structures can't tell the difference between O and NH2 groups, terminal amide groups and asparagine residues may be misplaced. In most situations, ionisation and tautomeric states are unassigned, and residue side chains or longer loops may be missing due to low resolution of a specific protein area, as well as steric conflicts. Several protein preparation strategies have been presented to effectively solve the structural difficulties discussed above. [13,14,15]

2) When the binding site is unknown or new allosteric modulators of protein activity are required, an additional prerequisite for SBVS is often binding site discovery. The target binding site should ideally be a pocket, often concave, with a range of hydrogen bond donors and acceptors as well as hydrophobic properties. There are currently four methods for identifying putative binding sites in the literature: 1) Static techniques, in which chemical probes (small organic compounds) are used to discover binding hot spots on a 3D structure via computational solvent mapping (from Xray, MD, etc). These methods identify druggability hotspots and provide data for drug development. SiteMap 16 is one example of such an approach.

3) Preparation of a compound database

The next critical phase in the SBVS process is the creation of compound databases. SBVS databases contain drug-like small molecules that are often freely available or can be purchased or synthesized and have desirable properties like aqueous solubility, the presence of appropriate functional groups to interact with biological targets, and the absence of toxic and undesirable moieties. To ensure 'drug-likeness,' several rules have been applied, the most popular of which is the "Lipinski Rule of Five,"17 which states that drug-like compounds should have a molecular weight of less than 500, a lipophilicity (logP) of less than 5, less than five hydrogen bond donors, and less than ten hydrogen bond acceptors. As more compounds break parts of these constraints and enter the market (for example, natural product medications and 50% of marketed drugs do not conform with the "Rule of Five"), 18 attempts to improve drug likeness prediction have created a slew of extensions to the Lipinski Rule of Five. Finally, preprocessing compound datasets in realistic 3D representations is recommended. Because bond lengths and angles may not vary during docking, the compound set utilized for SBVS should have realistic bond lengths and angles. All compounds must have assigned bond order and filled valances, partial charges, a suitable protonation state at physiological pH or at the pH of interest, and proper tautomeric states, and they must be free of surrounding fragments such as counter-ions, metals, and solvent molecules. 19,20

4) Library Design - While many drug-like compound libraries are freely available online [1, 5], users may need to construct a bespoke library in some cases. Libraries are classified as follows: a) generic virtual high throughput (vHTS) libraries, which contain large sets of compounds; b) diversity-oriented libraries, which contain highly chemically diverse compounds; c) target-oriented libraries, which are designed with a specific target in mind; d) molecular property diversity libraries, which are designed with specific molecular property profiles (i.e. solubility, lipophilicity, etc.); and e) natural product libraries. When examining underexplored targets with few known ligands, libraries with inherent chemical diversity, such as those described in Ref. [78], may be desirable. However, in order to locate hits with increased potency, targeted libraries based on features of known ligands may be required. Based on a benzoxazole template generating conserved hydrogen bonds with the catalytic machinery of sEH, Xing et al. created combinatorial libraries to hunt for novel soluble epoxide hydrolase (sEH) inhibitors, [21]

5) Docking & Scoring- Docking involves predicting the protein-ligand complex structure, which is then followed by SBVS scoring to rank the compounds. In order to explore the ligand conformational space, docking algorithms use a variety of conformational search methods, which are classified as follows: a) Systematic methods, which place ligands in the predicted binding site after accounting for all degrees of freedom, b) Random or stochastic torsional searches about rotatable bonds, such as Monte Carlo and genetic algorithms to "evolve" new low energy conformers, and c) Molecular Dynamics simulation methods and energy minimization to explore the energy landscape of a molecule.[22]

Docking tools use scoring functions to estimate the free energy of binding of a ligand to a certain target based on a generated docked pose after docking different ligands from a database in order to rank compounds. To date, a number of scoring functions have been established. The following are some of the most commonly used scoring functions: (a) Force field-based functions that total the strength of intermolecular van der Waals, electrostatic contacts, and hydrogen bonding between all atoms of the two binding partners in the complex to estimate the binding free energy. Contributions from solvation and entropy are also taken into account. (b) Empirical scoring functions based on counting the number of different types of interactions between the two binding partners, such as hydrophobic contacts, hydrogen bonds, and immobilized rotatable bonds in complex formation. For many protein-ligand complexes, these activities have proven to be effective.

6) Improving Pose/Compound Selection (Post-processing) After Docking-

The need for a computational chemist specialist to post-process compounds that come from a VS/docking operation before picking the ones that will advance to the experimental test phase is generally a rate-limiting step in SBVS. Realistic poses, intra-ligand steric conflicts, twisted amides, E/Z esters, an incomplete hydrogen-bonding network, and poses based on shape complementarity can all result from the use of simplified scoring functions and occasionally insufficient sampling of the conformational space for the ligand. These positions may result in an excessively high score and should be avoided. As a result, a medicinal chemist's visual assessment of thousands of docking positions is usually required in order to pick the proper compound

set for assaying. To that end, major efforts have been made to improve compound selection efficiency and quality. [23,24]
Rescoring may be used as part of the post-processing of the results. Malmstrom et al. investigated a set of known binders and non-binders of L99A T4 lysozyme using both free energy of binding (FEB) rescoring and other empirical docking scores to examine the reliability of VS results without post-processing, and concluded that FEB rescoring may assist lead identification resulting from an SBVS exercise 25.

Efficiencies of the SBVS have improved.

Ensemble (ED)-The first step in the SBVS process is to choose the ideal crystal structure of a receptor target. Unfortunately, crystal structures only show a single conformation of the protein, which is influenced by crystallisation conditions, and do not provide information on protein dynamics. Furthermore, ligand interaction has a significant impact on crystal structures, resulting in conformational changes in both the protein and the ligand. When a ligand binds to a protein, it can cause induced fit effects, in which the protein structure alters dramatically. As a result, while crystal structures are a good place to start for SBDD, they might be misleading in some circumstances. As a result, various efforts have been made to incorporate receptor flexibility into docking systems, as this provides a more accurate representation of the modelled [26].
Consensus Induced-Fit Docking (cIFD) is a docking method that allows the protein binding site to adapt to various ligands during SBVS. Kalid et al. used this methodology to validate the cIFD protocol on COX-2, the oestrogen receptor, and HIV reverse transcriptase, which had previously been shown to be difficult for docking programs, and then to demonstrate the utility of cIFD in discovering novel irreversible Crm1 inhibitors [27, 28].

Ligand-based virtual screening - Ligand-based virtual screening methods identify and optimize leads based on information found in known active ligands rather than the structure of a target protein. When no 3D structure of the target protein is available, ligand-based approaches are used. This is frequently the case with GPCR targets2 or protein structures determined in the apo state, for example. 3 In practice, even if you don't know the protein structure of the target of interest, you can usually tell that a group of ligands is active against it. As a result, ligand-based virtual approaches, such as finding new ligands by comparing candidate ligands to known active compounds, can be used. 29 The known active chemicals are collected using a ligand-based technique in order to select a query for virtual screening or alignment in ligand-based design. An effective similarity measure and a trustworthy scoring system are two crucial components of a ligand-based computational technique. Furthermore, the computational technique should be capable of accurately and quickly screening a large number of candidate ligands.
As a result, the similarity measurements are made up of geometrical data from arbitrary objects defined on the structures. The classification of an object varies depending on the approach used, however it may be divided into three categories: pharmacophores, molecular shapes, and molecular fields. **Pharmacophore-**based approaches build patterns of distances between predetermined molecular features such as aromatic systems or hydrogen-bond acceptors/donors5 and use a comparison of the corresponding patterns to calculate the similarity value. The goal of molecular shape techniques is to maximize shape overlap and calculate a similarity value based on that overlap. Ballester et al. developed Ultrafast Shape Recognition, a non-superposition comparison technique for molecular forms that they used in virtual screening trials. [30]
During the ranking phase, a scoring technique for ligand-based screening should effectively distinguish active compounds from inactive compounds and be able to quickly select a small number of active compounds from a library with a high number of inert compounds.[31]

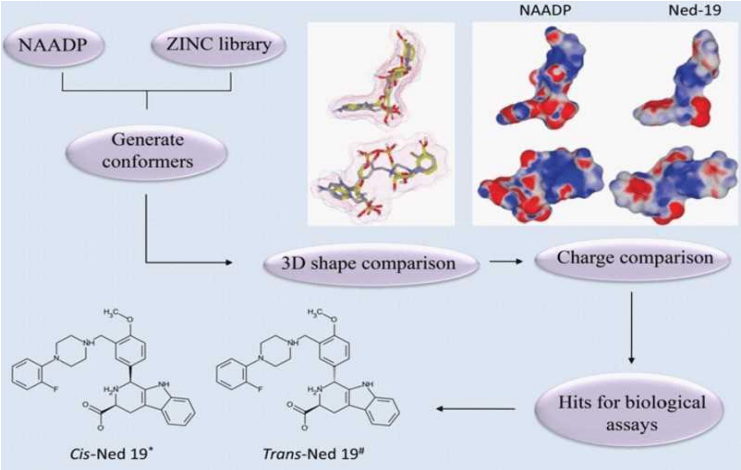

Figure 4: Computer-aided medication design based on ligands

General strategy

This procedure is carried out for each candidate structure in the database, and a new database containing "reduced" candidate structures is created.

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Procedure for overlapping shapes

This strategy allows us to explore the entire 3D space with the fewest iterations possible during the shape overlapping and optimization procedures,

resulting in fewer false-positive overlaps. Furthermore, by using this method, the CPU time required for the shape overlapping process can be greatly reduced.

Finally, the steepest descent method is used to refine the position and orientation of molecule B in relation to the rigid-body translations and rotations of the coordinates.[32]

Scroning- A ligand-based screening scoring method that effectively distinguishes active compounds from inactive compounds during the ranking phase and can be used to quickly discover a limited number of active compounds from a library with a large number of inactive compounds. for a look at how molecular similarity approaches work.

Model of molecular shape-density

According to Grant et al., the molecular electron density function can be approximated as a superposition of atom-centered Gaussian functions. The Gaussian function is used to calculate the molecular shape-density of a ligand.

Validation

The aforementioned approach, which uses the HWZ or Tanimoto scoring function, has been developed as a standalone module in Fortran90 (dubbed SABRE for "Shape-Approach-Based Routines Enhanced" for ease of usage in our lab). The implementation allowed us to calibrate and validate the scoring function, i.e. Validation of our technique was based on the proper usage of the DUD database 33 of annotated active chemicals and decoys. The DUD is a publicly accessible virtual screening test database, and it is Cross 34's second data set.

Drug development from the ground up

De novo meaning "from the beginning," "from the beginning," "from the beginning," "from the beginning," "from the beginning," "from the beginning," "from the beginning," It's a method of designing new molecules based on the receptor's 3D structure. It entails using molecular modeling tools to determine the structural properties of the lead target complexes and to modify the lead. There is information regarding target receptors, but no existing leads that can interact with them.

De-Novo Drug Design Principles- Assembling potential molecules and assessing their quality. • Looking for novel structures with drug-like characteristics in the sample space. Create a model of the protein structure of a binding site [35].

Known ligand optimization

An optimization approach is used in protein-ligand docking to discover the optimum binding posture of a ligand against a protein target. This algorithm is crucial in assessing the precision of docking. We conducted a comparative study on six efficient optimization algorithms, including two evolutionary algorithm (EA)-based optimizers (LGA, DockDE) and four particle swarm optimization (PSO)-based optimizers (SODock, varCPSO, varCPSO-ls, FIPSDock), which were implemented into the protein-ligand docking program AutoDock, to evaluate the relative performance of different optimization algorithms and provide guidance for real-world applications. We harmonized the objective functions by using the same scoring function, and we created a new fitness accuracy criteria that integrates optimization accuracy, robustness, and efficiency as the assessment criterion. [36]

Computational tool for drug designing

1) Database

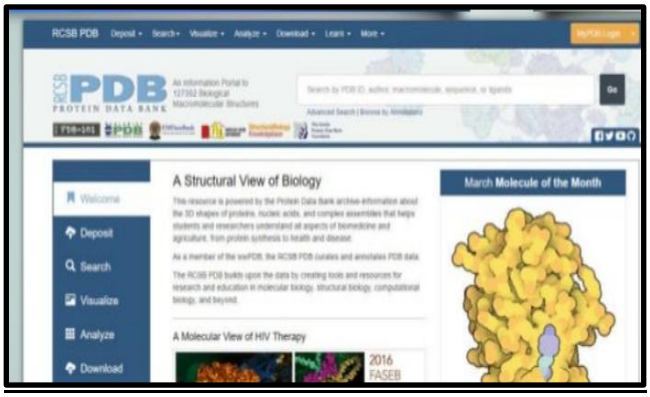

Fig - 5 Database

A database is an organized collection of data that is stored and retrieved electronically in computing. Large databases are housed on computer clusters or cloud storage, whereas small databases can be stored on a file system.

2) Medchem -

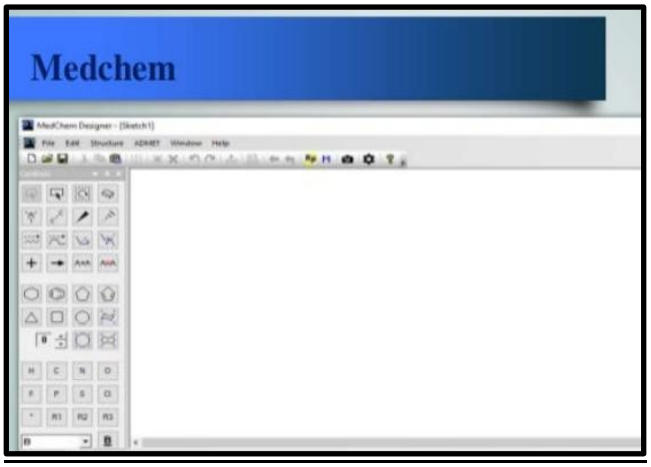

Fig - 6 Medchem

Medicinal chemistry is a field that combines chemistry, particularly synthetic organic chemistry, with pharmacology and other biological disciplines to work on the design, chemical synthesis, and development of pharmacological agents, or bio-active compounds, for the market.

3) HyperChem-

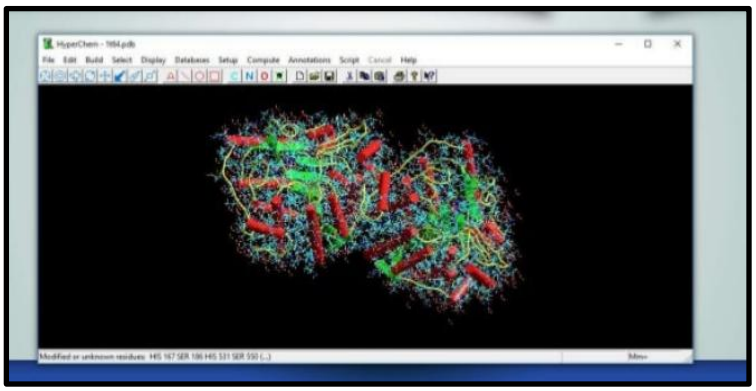

Fig - 7 HyperChem

HyperChem is a sophisticated molecular modeling environment noted for its quality, flexibility, and ease of use. Release 8.0 adds even more powerful computational chemistry capabilities, as well as support for various third-party programs.

Limitations of CADD

Despite the emergence of the several pioneering methodologies outlined above, drug design and development remains an inherently risky enterprise with high input costs and a poor success rate. In general, just one out of every 1000 lead compounds makes it to phase 1 clinical trials, and only one out of every five pharmaceuticals makes it to the market from phase 1 studies (Wishart, 2006). Some computer-aided drug design techniques take a long time, especially when seeking for the right lead component (Jorgensen, 2004). Because most of the available scoring functions are classical approximations of events governed by quantum physics, current molecular docking algorithms do not assess the absolute energy associated with the intermolecular interaction with sufficient accuracy. Furthermore, there is a scarcity of correct experimental data, which stymies CADD's progress.[37]

Conclusion -

CADD can help with 3D structure prediction, compound design, druggability prediction, and in silico ADMET prediction in pharmaceutical development. However, it's important to remember that computational predictions must be combined with experimental approaches for successful drug discovery and development. Computer-Assisted Drug Design is a natural evolution of theoretical chemistry. It is critical to rational drug design, contributes to the selection and synthesis of novel materials, and directs catalyst design. The development of high-quality datasets and designs that can be optimized for molecular similarity has resulted from the quest for new molecular entities.

Reference -

[1] The Significance of Discovery Screening and Structure Optimization Studies

[2] Odilia Osakwe, in Social Aspects of Drug Discovery, Development and Commercialization, 2016.

[3] Drug Development Strategies,Awanish Kumar Ph.D, Anubhuti Jha, in Anticandidal Agents, 2017.

[4] Computer aided drug designing for targeted drug delivery System. Presented by: Mahmudur Rahman Saad Rafiul Bashar Rabby Mehedi Hasan.

[5] Jubilant Biosys is a Contract Research Organisation in India providing comprehensive drug discovery and contract research services in partnership with leading healthcare companies worldwide.

[6] Structure based and ligand based drug designing, Vysakh Mohan M.

[7] Computer aided drug design By Dr Sameh Ahmad M- Abdelghany

[8] Rester U (July 2008). "From virtuality to reality - Virtual screening in lead discovery and lead optimization: a medicinal chemistry perspective". Current Opinion in Drug Discovery & Development. 11 (4): 559–68.

[9] Rollinger JM, Stuppner H, Langer T (2008). "Virtual screening for the discovery of bioactive natural products". Natural Compounds as Drugs Volume I. Progress in Drug Research. Fortschritte der Arzneimittelforschung. Progrès des Recherches Pharmaceutiques. Progress in Drug Research. 65. pp. 211, 213–49

[10] Walters WP, Stahl MT, Murcko MA (1998). "Virtual screening – an overview". Drug Discov. Today. 3 (4): 160–178.

[11] Bohacek RS, McMartin C, Guida WC (1996). "The art and practice of structure-based drug design: a molecular modelling perspective". Med. Res. Rev. 16 (1): 3–50.

[12] McGregor MJ, Luo Z, Jiang X (June 11, 2007). "Chapter 3: Virtual screening in drug discovery". In Huang Z (ed.). Drug Discovery Research. New Frontiers in the Post-Genomic Era. Wiley-VCH: Weinheim, Germany. pp. 63–88.

[13] Abagyan, R., Totrov, M., and Kuznetsov, D. (1994). ICM - a new method for protein modelling and design: applications to docking and structure prediction from distorted native conformation. J. Comput. Chem. 15, 488–506.

[14] 5. Cheng T, Li Q, Zhou Z, Wang Y, Bryant S.H. Structure-based virtual screening for drug discovery: a problem-centric review. AAPS J. 2012;14(1):133–141.

[15] Sastry G.M, Adzhigirey M, Day T, Annabhimoju R, Sherman W. Protein and ligand preparation: parameters, protocols, and influence on virtual screening enrichments. J. Comput. Aided Mol. Des. 2013;27(3):221–234.

[16] Pitt W.R, Calmiano M.D, Kroeplien B, Taylor R.D, Turner J.P, King M.A. Structure-based virtual screening for novel ligands. Methods Mol. Biol. 2013;1008:501–519.

[17] SiteMap, Schrodinger, LLC, 2013.

[18] Lipinski C.A, Lombardo F, Dominy B.W, Feeney P.J. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv. Drug Deliv. Rev. 2001;46(1-3):3–26.

[19] Zhang M.Q, Wilkinson B. Drug discovery beyond the ‘rule-of-five’ Curr. Opin. Biotechnol. 2007;18(6):478–488.

[20] Kalliokoski T, Salo H.S, Lahtela-Kakkonen M, Poso A. The effect of ligand-based tautomer and protomer prediction on structure-based virtual screening. J. Chem. Inf. Model. 2009;49(12):2742–2748.

[21] Sadowski J, Rudolph C, Gasteiger J. The generation of 3D-models of host-guest. Anal. Chim. Acta. 1992;265:233–241.

[22] Baell J.B. Broad coverage of commercially available lead-like screening space with fewer than 350,000 compounds. J. Chem. Inf. Model. 2013;53(1):39–55.

[23] Xing L, McDonald J.J, Kołodziej S.A, Kurumbail R.G, Williams J.M, Warren C.J, O’Neal J.M, Skepner J.E, Roberds S.L. Discovery of potent inhibitors of soluble epoxide hydrolase by combinatorial library design and structure-based virtual screening. J. Med. Chem. 2011;54(5):1211–1222.

[24] Guido R.V, Oliva G, Andricopulo A.D. Virtual screening and its integration with modern drug design technologies. Curr. Med. Chem. 2008;15(1):37–46.

[25] Athanasiadis E, Cournia Z, Spyrou G. ChemBioServer: a web-based pipeline for filtering, clustering and visualisation of chemical compounds used in drug discovery. Bioinformatics. 2012;28(22):3002–3003.

[26] Waszkiewicz B. Towards improving compound selection in structure-based virtual screening. Drug Discov. Today. 2008;13(5-6):219–226.

[27] Malmstrom R.D, Watowich S.J. Using free energy of binding calculations to improve the accuracy of virtual screening predictions. J. Chem.

Inf. Model. 2011;51(7):1648–1655.

[28] Korb O, Olsson T.S, Bowden S.J, Hall R.J, Verdonk M.L, Liebeschuetz J.W, Cole J.C. Potential and limitations of ensemble docking. J. Chem. Inf. Model. 2012;52(5):1262–1274.

[29] Kalid O, Toledo Warshaviak D, Shechter S, Sherman W, Shacham S. Consensus Induced Fit Docking (cIFD): methodology, validation, and application to the discovery of novel Crm1 inhibitors. J. Comput. Aided Mol. Des. 2012;26(11):1217–1228.

[30] Tresadern G, Bemporad D, Howe T. A comparison of ligand based virtual screening methods and application to corticotropin releasing factor 1 receptor. J Mol Graphics Modell. 2009;27(8):860–870.

[31] Ballester PJ, Finn PW, Richards WG. Ultrafast shape recognition: Evaluating a new ligand-based virtual screening technology. J Mol Graphics Modell. 2009;27(7):836–845.

[32] Lemmen C, Lengauer T. Computational methods for the structural alignment of molecules. J Comput-Aided Mol Des. 2000;14(3):215–232.

[33] Vand V. A SIMPLIFIED METHOD OF STEEPEST DESCENTS. Acta Crystallographica. 1951;4(3):285–286

[34] Huang N, Shoichet BK, Irwin JJ. Benchmarking sets for molecular docking. J Med Chem. 2006;49(23):6789–6801.

[35] Cross JB, Thompson DC, Rai BK, Barber JC, Fan KY, Hu YB, Humblet C. Comparison of Several Molecular Docking Programs: Pose Prediction and Virtual Screening Accuracy. J Chem Inf Model. 2009;49(6):1455–1474

[36] Denovo Drug Design By, Somasekhar gupha, 24 april 2015

[37] A comparison of various optimization algorithms of protein-ligand docking programs by fitness accuracy Liyong Guo et al. J Mol Model. 2014 Jul.

[38] Small Molecule Drug Design Vartika Tomar, Meena K. Sakharkar, in Encyclopaedia of Bioinformatics and Computational Biology, 2019