IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

COMPUTER AIDED DRUG DESIGN: A COMPUTATIONAL METHOD FOR DRUG DISCOVERY AND DEVELOPMEN

Mr.Tushar khore[1], Ms.Sonali kalam[2],Dr.Gajanan Sanap[3]
Student[1], Assistant professor[2], Principal[3]

1. Abstract : Computational approaches in medicine design, discovery and admiration. Generally, medicine discovery takes a long duration of time period about 12 time and billon of capital. It includes the creating of new motes, docking motes to target protein, assaying molecular commerce, estimating binding strength and medicine parcels. Computer backed Drug Designing(CADD) is cost effective and free of some natural trials. Structure grounded medicine design(SBDD) and ligand grounded medicine design(LBDD) are the two general types of computer- backed medicine design(CADD) approaches in actuality. SBDD styles dissect macromolecular target 3- dimensional structural information, generally of proteins or RNA, to identify crucial spots and relations that are important for their separate natural functions. LBDD styles concentrate on known antibiotic ligands for a target to establish a relationship between their physiochemical parcels and antibiotic conditioning appertained to as a structure- exertion relationship(SAR),information that can be used for optimization of known medicines or guide the design of new medicines with advanced exertion.

Keywords : Computer aided drug design, insilico design, ligand, drug discovery

3.Introduction : Several antibiotic capsules are available and were mechanically used amiles longer time than maximum other capsules, the fight between human beings and the encircling micro organism accountable for infections are ongoing and might be so for the foreseeable destiny. Contributing to this is the consistent upward thrust of antibiotic drug resistance leading to the need for brand spanking new antibiotics(1,2).closer to the design of Recent antibiotics, computer-aided drug layout (CADD) can be combined with wet-lab strategies to clarify the mechanism of drug resistance, to search for new targets and to layout novel antibiotics for each recognised and new targets. An vital opportunity to resolve the antibiotic resistance issue is the identification of recent antibiotic objectives that can constitute novel mechanisms vital for bacterial survival. as an instance, researchers bioinformatics tactics to display numerous databases computationally and recognized seven enzymes involved in bacterial metabolic pathways in addition to 15 non-homologous proteins positioned on membranes in gram nice bacterium Staphylococcus aureus (SA), thereby indicating them as potential objectives three. Such findings may also help to overcome the resistance of this bacterium common antibiotics such as methicillin, fluoroquinolones and oxazolidinones. An example of a these days diagnosed novel antibiotic target is the protein heme oxygenase, involved within the metabolism of heme by bacteria as required to get admission to iron .
have efficiently applied CADD techniques to discover inhibitors of the bacterial heme oxygenases from Pseudomonas aeruginosa and Neisseria meningitides, therebyconfirming the potential position of heme oxygenases as a antimicrobial objectives(4,5).

4.Computer aided drug design (CADD) : The use of computer-aided drug design (CADD) reduces the cost and duration of drug research and development by offering a variety of tools and approaches to assist in different stages of drug design. The process of finding new drugs and developing them is a protracted, intricate, expensive, and extremely dangerous one with few parallels in the business world. For this reason, the pharmaceutical industry frequently uses computer-aided drug design (CADD) techniques to speed up the process.

Using computational methods during the lead optimisation stage of drug development provides a significant financial benefit. Pharmacological research laboratories invest a great deal of money and effort in the many stages of drug discovery, beginning with the identification of therapeutic targets. The process of Computer Aided Drug Designing (CADD) is economical and does not require any biological experiments.

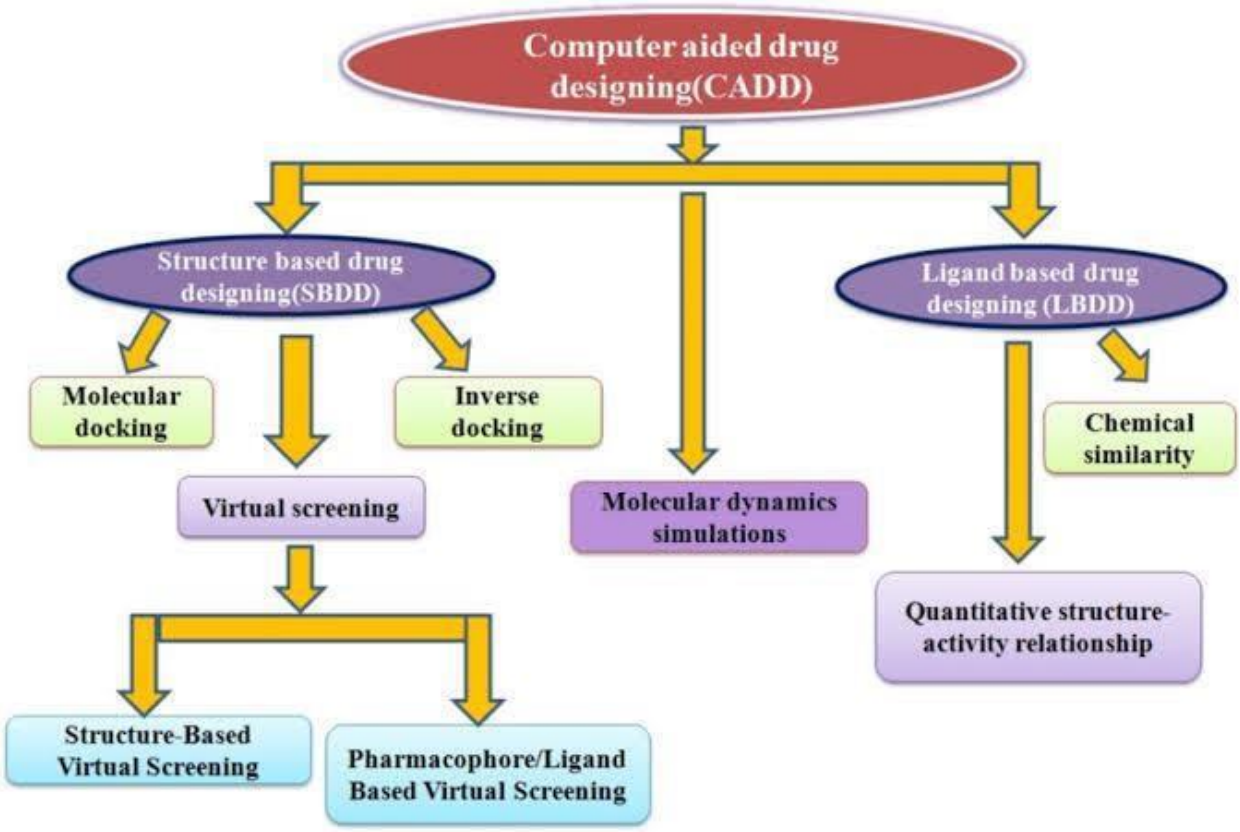

Fig1:Computer Aided Drug Design

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.

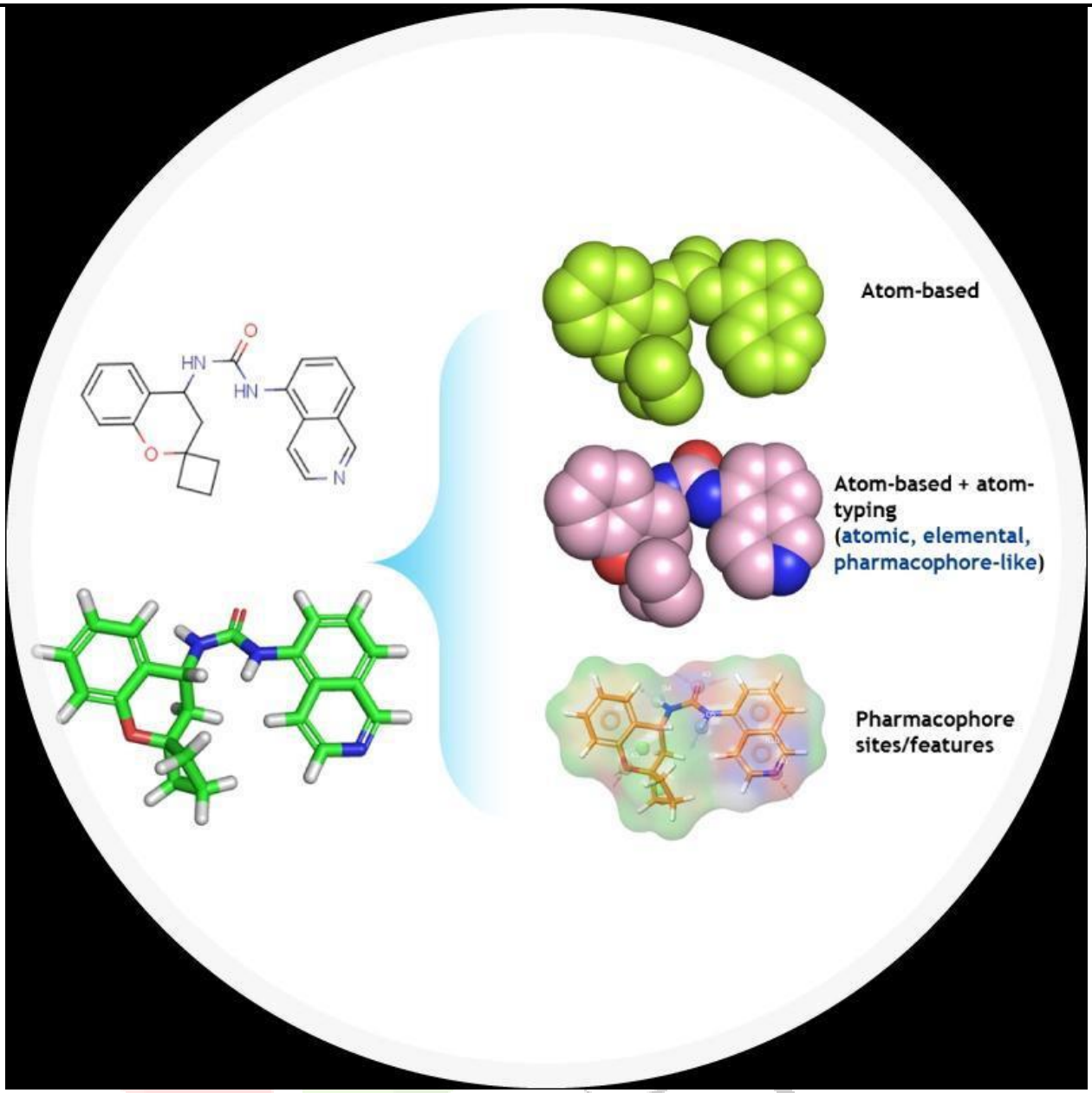

Fig – 2 Ligand base computer aided drug design

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 (17).

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 3DQSAR 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.(18).

5.Structure based drug design (SBDD) :

The two main categories of computer-aided drug design (CADD) methodologies that are now in use are structure-based drug design (SBDD) and ligand-based drug design (LBDD). Using 3-dimensional structural data from macromolecular targets (mostly proteins or RNA), SBDD approaches uncover critical locations and interactions that are crucial for the biological functions of the target molecules.

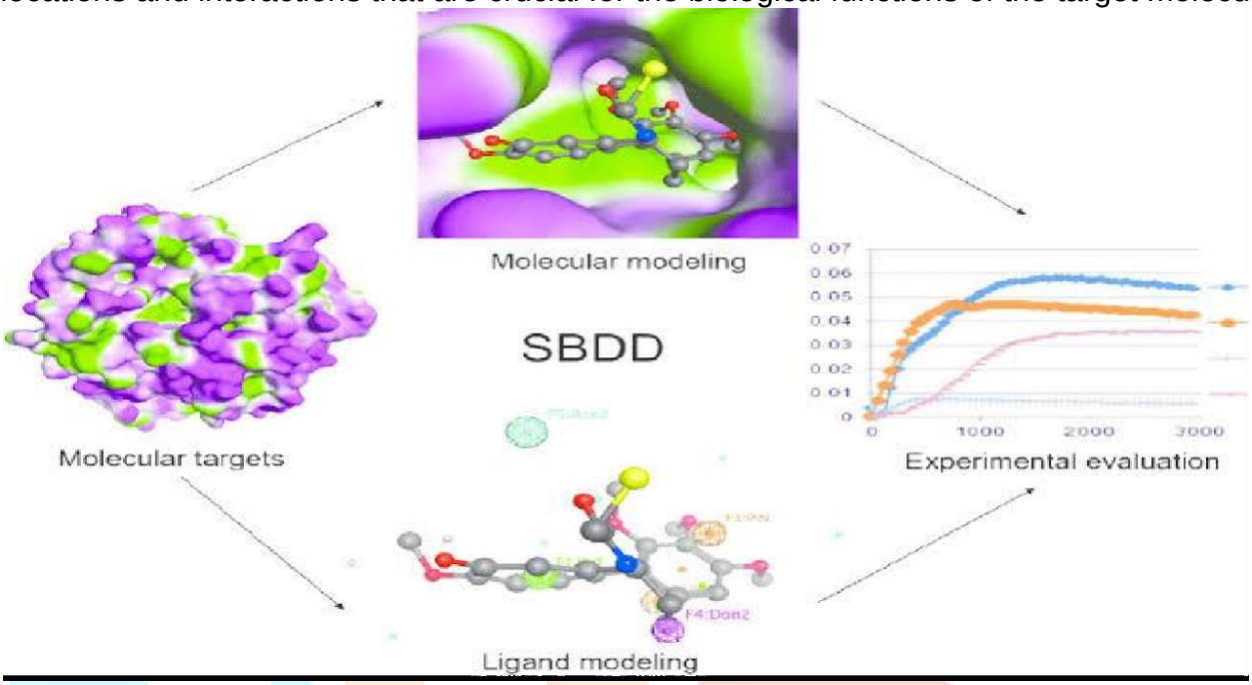

Fig.2:Strucure Based Drug Design

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. (19)

6.Steps Involved In Structure Based Drug Design:

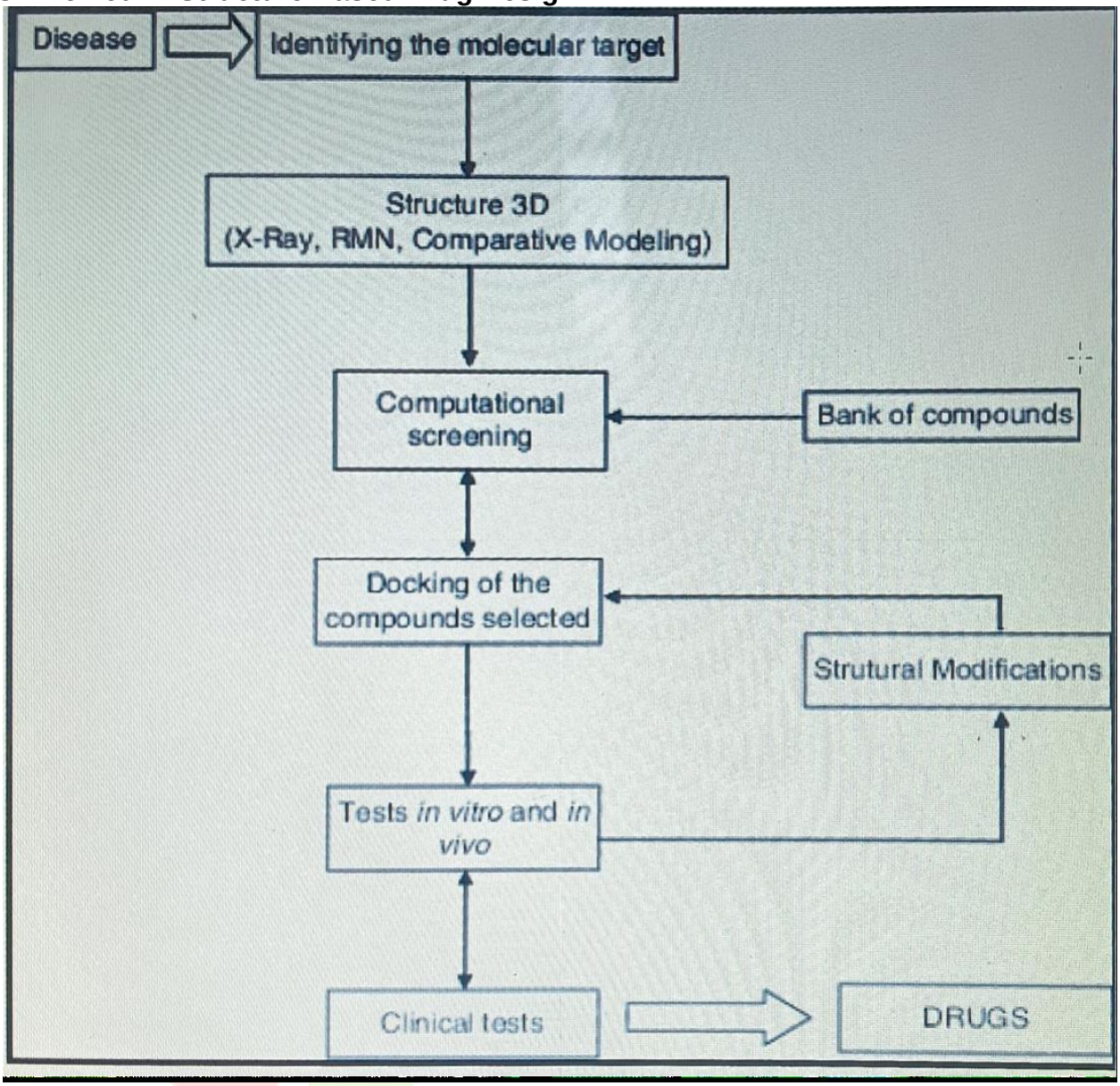

Fig.3:Steps Involved In Structure Based Drug Design

In LBDD, 3D structure of the target protein is not known but knowledge of ligands which binds to the desired target site is known. These ligands can be used to develop a pharmacophore model or molecule which possesses all necessary structural features for bind to a target active site(10,11). Put another way, using the information about what binds to the biological target, a model of the target could also be created. This model could then be used to create new molecular entities that interact with the target. Alternatively, a quantitative structure-activity relationship (QSAR), which establishes a connection between the features of molecules calculated by experimentation and their Additionally, biological activity could be derived(12). The activity of the most recent analogues might likewise be predicted sequentially using these QSAR correlations. In ligand-based drug design, a sequence of molecules with discernible smart activity is selected and processed by tools such as Sybyl.

With the advent of genomics, bioinformatics, proteomics, and efficient technologies like combinatorial chemistry, virtual screening, high throughput screening (HTS), de novo drug design, in vitro studies, and in silico studies for pharmacokinetic screening as well as for structure-based drug design, the process of drug discovery has undergone significant changes(13).

The In silico procedures are veritably useful in relating medicine targets via bioinformatics tools similar as computer software programs. Further it's used to examine the supereminent structures for implicit list or active spots, produce structurally analogous motes, vindicating for its medicine likeness parcels, dock these active motes(ligands) with the target enzyme, arrange them according to their list lodestones , and eventually optimize the lead motes for to enhance its list parcels. Quantitative structure exertion relationship is defined that a correlation between advised parcels of the motes and it ' s experimentally determined natural exertion was deduced. QSAR studies are used to prognosticate the exertion of patch Computer- backed medicine design(CADD) ways are used for the rapid-fire assessment of chemical libraries in order to guide and speed up the early- stage development of new active composites. CADD entails a vast number of computational methodologies like virtual webbing, virtual library design, lead optimization, de novo design, and so forth. Because of the proven capability of computational ways to guide the selection of new megahit composites, computational chemistry and chemo informatics are still scientific disciplines in full bloom and, in particular(16).

7.Method of CADD :

1.Structure-Based Drug Design (SBDD):

Molecular Docking: This method involves the prediction of the preferred orientation of one molecule to a second when bound together to form a stable complex. Docking programs analyze how well a ligand (potential drug) fits into a binding site on a target protein, predicting the binding affinity and interactions.

Virtual Screening: In virtual screening, large databases of chemical compounds are computationally screened to identify potential drug candidates that could interact with a target of interest. It helps prioritize compounds for further testing.

2.Ligand-Based Drug Design (LBDD):

Quantitative Structure-Activity Relationship (QSAR): QSAR models correlate the biological activity of a set of compounds with their chemical structure. These models can then be used to predict the activity of new compounds with similar structures.(20).

Pharmacophore Modeling: A pharmacophore is the three-dimensional arrangement of features that is necessary for a molecule to interact with a specific biological target. Pharmacophore modeling helps identify key structural and chemical features required for biological activity.(20)

3.Drug - Receptor Interaction Analysis through CADD: For information about drug-receptor interaction and the search for new active compounds, experimental work, analysis, and computer simulation are used. They all collaborate since analysis requires information of 3-D structure of molecules involved. Bio molecular docking is the process of confirming and orienting 'pose' of small molecule (ligand) in the cavity (active site) of a target protein after gaining knowledge of bio molecular structure (21).

4.Multi-target Drug Searching and Designing Through CADD: With the help of the CADD technique, it is possible to search for drugs against a variety of targets and create hits for each target. When searching for multi-target searching for enrichment, 60, 61 and 62 the true -hits rate should be higher than False -hits rates against the target (22)

5.Quantitative Structure Activity Relationship (QSAR) Studies through CADD: QSAR provides information in the form of a mathematical expression on the relationship between chemical structure and biological activity. The primary benefits of the QSAR method are the properties of novel chemical compounds that can be identified without the necessity for their manufacture or testing. Additionally, studies link each of them to physiological characteristics, biological activities, and structural descriptors of substances (23).

8.Application of CADD

1. CADD can avoid a certain degree of blindness in the previous research process and enable intuitive design to guide people todevelop new drugs purposefully (24)
2. It gives the most promising drug candidate by eliminating the compounds with undesirable properties through in silico filters.
3. It reduces the synthetic & biological testing efforts.
4. It is quick, automatic, efficient with money, and saves time.
5. It knows the drug receptor interaction pattern (25)
6. The approaches minimize the chances of failures in the final phase.
7. It gives compounds with high hit rates through searching huge libraries of compounds in silico in comparison to traditional high throughput screening (26).
8. (CADD) is the use of computer modeling techniques for drug development. A new drug's introduction to the market is an extremely difficult, expensive, and risky procedure in terms of resources like time, money, and labor and it takes 10-15 years to develop in terms of esteemed amount (27,28)
9. CADD may be used to the majority of drug development stages, including preclinical research, lead optimization, target validation, and target selection and it is predicted that CADD might cut the price of medication development by as much as 50% (29,30).
10. The basic components of CADD include homology modeling, molecular docking, virtual screening (VS) or virtual high-throughput screening (vHTS), quantitative structure-activity relationship (QSAR), and often three-dimensional (3D) pharmacophore Mapping (31).

11. Anticancer agent

Sequencing the human genome is one of the major scientific efforts of aspect. This major aspect, by using this information is the provision of small molecules that recognize selected sequences possibly for the purpose of switching off specific genes, such as cancer chemotherapy. For some time, antibiotics such as netropsin have been known to bind especially to sequences rich in A-T pairs. Therefore, we may consider ligands that can exist in two forms, oxidized and reduced, and it may be appropriate that the redox potential is oxidized in normal tissues but decreased in tumors.

12Target Enzyme

When the structure of the enzyme is already identified then is easy to design inhibitors that can block in vitro activities. The free energy of binding of the inhibitor to the enzyme is an important amount for which strong binding is essential.

13.Drug Transport

Transport across biological membranes is essential. The compound needs to dissolve in the lipid and enter the membrane, but it must not dissolve and stay there. The partition coefficient between water and n-Octanol is used as membrane transport. A free energy perturbation method useful for calculating partition coefficients. However, it is probable to model biological membranes. Starting with the crystal structure of a membrane containing DMPC (1,2-dimyristoyl-snglycero-3phosphorychloro), a very

realistic simulation involving a hydrated lipid bilayer is possible. The membrane is involved in lead separation and diffusion.

14.Structure determination of protein

The three-dimensional structure of a protein is determined from primary to tertiary structure and increases from a few cases to thousands, depending on the drug target whose binding site structure is known. The currently favored and only successful methods are all based on finding similarities and homologies between proteins of known topology but of unknown topology and known structure from 3D databases.

14.Biochemical Transformation

Computer-aided design methods can be used even if there is no knowledge of detailed polymer targets at the atomic level. A popular and ideal approach is to calculate the energy profile of the biochemical transformation that it is desirable to inhibit. It acts as an inhibitor, identifying transition states or intermediates, creating stable mimetics of these unstable transients recognized by enzymes that catalyze the reaction.

15.Molecular similarity

Even more striking is the achievement of structureactivity relationship and quantitative structure-activity relationship similarity measurement for example, steroids which gives comparative molecular field threedimensional structure activity studies for which binding affinity data are available [44].

15.RECEPTOR SITE BY HOMOLOGY:

In a number of cases of therapeutic interest, the amino acid sequence of the target protein is known and homologous proteins exist whose three dimensional structure has been determined. Computer modeling has been used to transform the known structure into the target by a combination of sidechain replacement and energy minimization. Obviously, when the structure of the target protein is close to the known structure, one has. a greater chance of success. Aspartyl proteases are probably most widely studied. With these structures, renin inhibitors are the target (32). Several investigators have attempted to evaluate the likelihood of success of such studies. The Alberta group (33) made the most critical evaluation. They determined the crystal structure of an enzyme that had previously been modeled by homology. Drug design usually focuses on the active site; specificity for the particular enzyme is a design goal. Unfortunately, it is the residues that differ between the two proteins that cause the specificity. The successful design of renin inhibitors that resulted from this approach may be due to the same medicinal chemical logic that inspired so many angiotensin-converting enzyme (ACE) inhibitors in the absence of three-dimensional information. In that case, mechanistic arguments generated a framework on which to base designs, as the sequence of ACE was not available-even though the structures of carboxypeptidase A and thermolysin might have served as a rough template (34).

16.RECEPTOR SITE BY INDUCTION

With the advent of DNA sequencing, determining the sequence of proteins by inference has become routine, and a project to sequence the entire human genome is under consideration. Unfortunately, knowing the sequence of the therapeutic target does not aid the medicinal chemist. Progress in understanding the process of protein folding continues at an enhanced rate, with genetic engineering techniques offering a powerful experimental adjunct to theoretical studies. What hope do we have of predicting the three-dimensional structure based on sequence information alone? Whereas it is clear the tertiary information resides in the sequence, the translation rules have defied definition. Predictive methodology based strictly on statistical approaches is only approximately 60% accurate in secondary structure prediction (35). Even if one could correctly predict secondary structure, the correct folding is a combinatorial problem whose complexity should not be underestimated. A heuristic approach by Cohen et al (36) claims a high success rate (approximately 90%) in tum prediction. Sheridan et al (37, 38) have correlated amino acid composition and hydrophobicity patterns with the structure of protein domains.

Their results may allow the prediction of the structural class with some degree of certainty and offer increased hope that such methodology may allow systematic exploration of possible folded structures by energy minimization. The same caveats expressed with regard to force fields, entropy, solvation, and local minima apply, of course, and become even more dominant due to the size of the structures considered.

17.RECEPTOR SITE BY DEDUCTION

The problem most familiar to the medicinal chemist is the one in which the therapeutic target (the receptor) can by inferred only by binding studies or pharmacological studies. Systematic variation of the chemical structure leads quickly to the conclusion that some parts of the molecule are critical for activity, whereas others can be changed, causing only minor variations in affinity. These qualitative differences in results led to the concept of the pharmacophore at the tum of the century. The inherent conformational freedom associated with most drugs hampered efforts to interpret structure-activity information in a three-dimensional framework. The work of Hansch and others in developing the QSAR para digm showed that a common frame of reference based on a congeneric series offered a basis for rational interpretation. Comparison of binding modes at known active sites with the correlation equations developed with QSAR show clearly that the coefficients of the parameters can be interpreted with some degree of assurance in terms of the binding site (39,40). While this approach is essentially topological, a topographical, or three-dimensional, equivalent must exist. This realization led Marshall and his coworkers (41,42,43) to develop the Active Analog Approach in which the pharmacophore provides the frame of reference analogous to the congeneric framework as a basis for comparison of molecules.

9.Advantages Of CADD :

1) Through it we can reduce the synthetic and biological testing efforts(9,10).

2) It gives the most promising drug candidate by eliminate the compounds with undesirable properties (poor efficacy, poor ADMET etc.) through in silico filters (10).

3) It is a Cost-effective, time saving, Rapid and automatic process11. · Through it we can know about the drug-receptor interaction pattern.

4) It gives compounds with high hit rates through searching huge libraries of compounds in silico in comparison to traditional high throughput screening

5) These approaches minimize chances of failures in the final phase.

10.Future Of CADD :

In the field of drug discovery and development, computer-aided drug design is a useful technology that allows us to quickly and affordably identify the most promising therapeutic candidate. It consistently offers hope for advancements in the field of medication discovery. Computer-aided drug design has made many impressive scientific discoveries in recent years, and given its current accomplishments, it is expected to play a significant role in the near future. It also has a bright future ahead of it, helping to discover many more cures through drug discovery (12,13, 14)

List Of Abbreviations

Sr.No.	Abbreviation	Meaning
1	CADD	Computer Aided Drug Designing
2	SBDD	Structure Based Drug Design
3	LBDD	Ligand Based Drug Design
4	SAR	Structure-Activity Relationship
5	QSAR	Quantitative Structure-Activity Relationship
6	HTS	High Throughput Screening
7	SILCS	Site Identification By Ligand Competitive Saturation
8	VS	Virtual Screening

11Conclusion : Computer aided drug design (CADD) is a multidisciplinary field attracting the researchers from information technology, medicine, pharmacology etc. to discover new tools and techniques or enhance the available tools and techniques to assist in drug discovery process. These techniques proved to be effective in various stages of drug discovery process thus reducing both cost and time taken for developing a drug than conventional methods.

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