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COMPUTER AIDED DRUG DESIGN (CAAD) AND IT'S IMPLICATIONS IN DRUG DISCOVERY AND DEVELOPMENT PROCESS.

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Abstract:

Computer Aided drug design(CADD) provides a variety of tools and ways that help in the colorful stages of medicine design, thereby reducing the cost of medicine exploration and development time. medicine discovery and the development of a new medicine is a long, complex, expensive and largely parlous process that has no equal in the marketable world. thus, computer Aided drug design(CADD) approaches are extensively used in the pharmaceutical assiduity to speed up the process. The cost advantage of using computational tools in the lead optimization phase of medicine development is significant. The cost and time invested by pharmacological exploration laboratories are heavy at colorful stages of medicine discovery, starting from remedial target setting seeker medicine discovery to assessing the efficacity and safety of recently developed medicines, medicine optimization through preclinical and expansive clinical trials. Major pharmaceutical companies have invested heavily in routine ultra High Outturn Webbing(uHTS) of large figures of medicine- suchlike motes. In resemblant, medicine design and optimization are decreasingly using computers for virtual webbing. Recent advances in DNA microarray trials are discovering that thousands of genes involved in a complaint can be used to gain in- depth information about complaint targets, metabolic pathways, and toxin of medicines. Theoretical tools include empirical molecular mechanics, amount mechanics, and more lately statistical mechanics. This rearmost advance allowed the addition of overt solvent goods. All this is largely the vacuity of high- quality computer plates supported on workstations

KEYWORDS:

Computer aided drug discovery, structure based drug design , ligand based drug design, virtual screening and molecular dooking.

INTRODUCTION:

Computer Aided drug design(CADD) provides a variety of tools and ways that help in the colorful stages of medicine design, thereby reducing the cost of medicine exploration and development time. medicine discovery and the development of a new medicine is a long, complex, expensive and largely parlous process that has no equal in the marketable world. thus, computer Aided drug design(CADD) approaches are extensively used in the pharmaceutical assiduity to speed up the process. The cost advantage of using computational tools in the lead optimization phase of medicine development is significant. The cost and time invested by pharmacological exploration laboratories are heavy at colorful stages of medicine discovery, starting from remedial target setting seeker medicine discovery to assessing the efficacity and safety of recently developed medicines, medicine optimization through preclinical and expansive clinical trials. Major pharmaceutical companies have invested heavily in routine ultra High Outturn Webbing(uHTS) of large figures of medicine- suchlike motes. In resemblant, medicine design and optimization are decreasingly using computers for virtual webbing. Recent advances in DNA microarray trials are discovering that thousands of genes involved in a complaint can be used to gain in- depth information about complaint targets, metabolic pathways, and toxin of medicines. Theoretical tools include empirical molecular mechanics, amount mechanics, and more lately statistical mechanics. This rearmost advance allowed the addition of overt solvent goods. All this is largely the vacuity of high- quality computer plates supported on workstations.

DISCUSSION:

A Brief History of CADD In 1900, the concept of receiver and lock-key was given by P.Ehrich (1909) and E. Fisher. In the 1970s the concept of Quantitative structure-activity relationships (QS-AR) was established, It had limitations: 2-Dimensional, retrospective analysis; In the 1980s, CADD Molecular Biology, X-ray crystallography, multidimensional NMR along with computer graphics started the era of molecular modeling. In the 1990s, more modern techniques such as Human genome Bioinformatics were introduced in the Innovative world of medical science along with Combinatorial chemistry and High throughput screening.

DRUG DISCOVERY PROCESS :

From the original idea to the launch of a finished product, developing a new drug is a complex process that can take 12-15 years and costs more than USD 1 billion. A goal idea can come from a variety of sources, including academic and clinical research, and the commercial sector. It may take many years to generate supporting evidence before choosing a target for an expensive drug discovery program. Once a target has been selected, the pharmaceutical industry and, more recently, some academic centers streamlined a series of early processes to identify molecules with properties suitable for making acceptable drugs. Product Characterization.

• Formulation, Delivery, Packaging Development.
• Pharmacokinetics and Drug Disposal.
• Preclinical Toxicology Test and IND Application.
• Bioanalytical Test.
• Clinical trials.

VARIOUS STAGES OF DRUG DESIGN:

- Choose a disease
- Choose a drug target

- Define a bioassay
- Find a precursor compound
- Isolate and purify lead compound if necessary
- Determine the structure of the lead compound
- Define the structure Activity relationship
- Identify the pharmacophore
- Improve target interaction.

Commonly Used Methods in Drug Design:

TYPES OF DRUG DESIGN:

A. Ligand based drug design
B. Structure based drug design

A. Ligand-based drug design (LBDD):

Ligand based drug design is an approach used in the absence of receptor 3D information and relies on knowledge of motes that bind to the natural target of interest. 3D quantitative structure exertion connections(3D QSAR) and pharmacophore modeling are the most important and extensively used tools in ligand- grounded medicine design. They can give applicable prophetic models for lead identification and optimization. Ligand-grounded medicine design is an approach used in the absence of receptor 3D information and relies on knowledge of motes that bind to the natural target of interest. a) Ligand- Grounded Drug Design consists of the information of motes that bind to the asked target point. b) These motes can be used to decide a Pharmacophore model. c) A pharmacophore model is defined as a patch with the necessary structural capacities to bind to a asked target point. d) Once the Pharmacophore is linked, it's determined whether it's suitable for the receptor, else the Pharmacophore is further modified to make a implicit medicine.

Important tools used in ligand-based drug design-

1. Quantitative structure-activity relationships (QSAR)

Quantitative structure- exertion relationship models are retrogression or bracket models used in the chemical and natural lores and engineering. Like other retrogression models, QSAR retrogression models relate a number of" prophetic " variables with energy. response variable(Y), while the bracket QSAR models relate the estimator variables are converted to a categorical value of the response variable. In order to place 10 different groups at the 4 positions of the benzene ring, the number of composites needed for conflation is 10. result Synthesize a small number of composites and decide from theirdata.rules for prognosticating the natural exertion of other composites. A) VEGA platform(https//www.vegahub.eu/portfolio-item/vega-qsar/)Using the VEGA platform, you can pierce a range of QSAR models for nonsupervisory purposes or develop your own for exploration purposes. QSAR models can be used to prognosticate the property of a chemical emulsion using information from its structure. B) DEMETRA(http//www.demetra-tox.net/)DEMETRA is an EU funded design. The end of this design was to develop prophetic models and software that give a quantitative estimate of the toxin of a patch, specifically fungicide motes, seeker fungicides and their derivations. The input is the chemical structure of the emulsion. software algorithms use " Quantitative Structure- exertion connections "(QSARs). The DEMETRA software tool can be used for toxin estimation of fungicide motes and related composites. DEMETRA Models are freely available. Five models were developed to prognosticate toxin to trout, daphnia, quail and notions. The software is

grounded on the homogeneous integration of the knowledge acquired in the DEMETRA EU design, using the stylish algorithms attained as the base for mongrel combination models to be used for vaticination purposes. C)T.E.S.T(https//www.epa.gov/chemical-research/toxicity-estimation-software-tool-test)The toxin Estimation Software Tool(T.E.S.T.) will allow druggies to fluently estimate acute toxin using the below QSAR methodologies. D) OCHEM(https//ochem.eu/ home/show.do) OCHEM is an online database of experimental measures integrated with the modeling terrain. Submit your experimental data or use data uploaded by other druggies to produce prophetic QSAR models for physical- chemical or natural parcels. E)E-DRAGON(http//www.vcclab.org/lab/edragon/)E-DRAGON by Milan Chemometrics and QSAR Research Group byProf. It's an electronic remote interpretation of the well- known software DRAGON, an operation for the computation of molecular descriptors developed byR. Todeschini. These descriptors can be used for molecular structure- exertion or structure- property connections as well as similarity analysis and high- outturn webbing of the patch database. F) SeeSAR(https//www.biosolveit.de/SeeSAR/)SeeSAR is a software tool for interactive, visual compound prioritization and compound elaboration. Structure-grounded design work immaculately supports amulti-parameter optimization to maximize the probability of success rather than similarity alone. One of SeeSAR's strengths is that the applicable parameters are at hand, along with real- time visual computer backing in 3D. G) Dragon(https//chm.kode-solutions.net/products_dragon.php)Dragon calculates 5,270 molecular descriptors covering utmost of the colorful theoretical approaches. The list of descriptors includes the simplest types of tittles, functional groups and part counts, topological and geometric descriptors, three- dimensional descriptors, as well as several property prognostications(similar as logP) and medicine- suchlike and supereminent- suchlike stimulants(similar as Lipinski's). Alarm). H) PaDEL- Descriptor(http//www.yapcwsoft.com/dd/padeldescriptor/)A software to calculate molecular identifiers and fingerprints. The software presently calculates 1875 identifiers(1444 1D, 2D identifiers and 431 3D identifiers) and 12 types of fingerprints(16092 bits total). Identifiers and fingerprints are calculated using The Chemistry Development Kit, which has fresh identifiers and fingerprints similar as snippet type electrotopological state descriptors, Crippen logP and MR, extended topochemical snippet(ETA) descriptors, McGowan volume, molecular direct free energy relationship descriptors, ring figures. The number of chemical substructures and double fingerprints linked by Laggner and the number of chemical substructures linked by Klekota .
Identifiers and fingerprints are calculated using The Chemistry Development Kit, which has additional identifiers and fingerprints such as atom type electrotopological state descriptors, Crippen logP and MR, extended topochemical atom (ETA) descriptors, McGowan volume, molecular linear free energy relationship descriptors, ring numbers. The number of chemical substructures and binary fingerprints identified by Laggner and the number of chemical substructures identified by Klekota and Roth.

2. PHARMACOPHOR

Molecular similarity-based search is the simplest LBDD technique to identify desired small molecules. Molecular similarity-based searching is both an independent and integral part of other LBDD and SBDD techniques, where small molecule libraries are searched using molecular identifiers. Molecular descriptors are characteristic numerical values that represent small molecules and range from simple physicochemical properties to complex structural properties. Examples of molecular descriptors include molecular weight, atom types, bond distances, surface area, electro-negativities, atomic distributions, aromaticity indices, solvent properties, and others. Molecular descriptors are derived through experiments, quantum-mechanical tools, or prior knowledge. Depending on the "dimensionality", molecular identifiers can be 1D, 2D or 3D identifiers. 1D descriptors are scalar physicochemical properties of a molecule, such as molecular weight, logP values, and molar refraction. 2D identifiers are derived from molecular structure or configuration and include topological indexes and 2D fingerprints. 3D descriptors are derived from the conformation of molecules. 3D descriptors can identify 3D fingerprints, dipole moments, highest occupied molecular

orbital/lowest unoccupied molecular orbital energies, electrostatic potentials, etc. includes. A list of software that predicts molecular annotation

B. **Structure-based drug design (SBDD):**

Structure-based drug design (SBDD) is the process that includes virtual screening and de novo drug design. These methods are a highly efficient and alternative approach to the discovery and development of the drug design course. In virtual scanning, drug chemical compounds are computationally screened against known target structure [5,6]. In classical or advanced pharmacology or legacy drug design and development, rational drug design is very costly and efficient. The first step in rational drug design method or reverse pharmacology is sto identify promising target proteins used for screening small molecule libraries. Structure-based virtual scanning (SBVS), molecular docking and molecular dynamics (MD) are methods used in SBDD, a more specific, efficient and rapid process for lead discovery and optimization, because they are approximately related to the 3D structure of a Target protein. analysis of disease and binding energies at the molecular level, ligand protein interaction induction insertion process.[5,6] There are many drugs identified by SBDD with the help of some techniques such as thymidylate synthase inhibitor, raltitrexed and potential HIV protease inhibitor. these were discovered by MD simulation and the antibiotic norfloxacin [7,8,9,10]. The three-dimensional (3D) structure of proteins (more than 100,000) is provided in SBDD.

1] Identification of target protein and binding site:

Target protein identification is the key step in the SBDD process. It provided clear information on the binding site of the target macromolecule, protein-ligand interaction, post-docking dynamics, as well as hydrogen bond formation, which helped to calculate the best pharmacophores of the 'new' ligand. The binding sites determined experimentally by integrative structural biology techniques in the 3D structure of the target macromolecule such as NMR, X-ray crystallography. The next step is to identify the binding pocket after the target protein is resolved. It is a very small space where the ligand binds and also exerts its therapeutic or desired effect. These methods provide information on energy interaction and Van der Waals (vdW) forces for binding site mapping. There are many methods developed by energy interaction calculations for binding site mapping specifically for SBDD, and these methods identify specific regions of the target protein that interact with appropriate functional groups on drugs. These identify with the protein Q-site Finder [11][12][13][14]

2] Molecular docking

Molecular docking is a virtual simulation technique used to model the interaction between a small molecule and a protein at the atomic level. This technique is also used to characterize the behavior of small molecules at the binding site of the target protein The insertion process involves two basic steps - the estimation of ligand conformation and the second is the binding of the ligand within the target active site with accuracy, so this technique is widely used in structure-based drug design (SBDD).

3] Scoring function

The scoring function assists an insertion program into the ligand binding site. The scoring function also helps calculate the binding affinity between protein and ligand functions. Scoring functions are divided into force field, empirical, knowledge-based, and machine learning.

An early general-purpose empirical scoring function was developed by Bohm to describe the binding energy of ligands to receptor.

CADD IN THE DRUG DISCOVERY:

CADD can be combined with wet laboratory techniques to elucidate and accelerate the drug discovery process to design new drugs (eg antibiotics) for both known and novel targets. CADD simplifies the drug design process by minimizing time and cost.[15[16][17]

ADVANTAGES:

1. A cost-effective, time-saving, fast and automated process.
2. It give an idea about the drug-receptor interaction pattern.
3. Minimize synthetic and biological testing efforts.
4. Minimize the possibility of failure in the final stage.

CONCLUSION:_

- Structure-based and ligand-based drug style kind 2 branches of the computer-aided drug discovery method which plays a big role within the style and identification of drug molecules in reduced time and value. the rise in the number of positive cases and deaths from COVID-19 and the lack of approved medicine and vaccines still be a matter of worldwide health concern that necessitates the urgent discovery of medicine for the hindrance and cure of the disease. The structural elucidation of pharmacologic targets of SARS-CoV-2 has helped the researchers within the structure-based virtual identification of inhibitors, and therefore the discovery of few lead molecules against COVID-19 has diode to the employment of scaffolds which will be optimized through ligand-based drug design. Realizing the doable changeability of this polymer virus and the emergence of drug resistance issues, it is, therefore, necessary to require a step any and take into account targeting multiple drug targets which will be simpler and may help in overcoming drug resistance barriers.

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