Review Article on Rational Drug Design

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***Abstract*—Currently, combination of classical QSAR and other computational techniques at three-dimensional level is of greatest interest and generally used in the process of modern drug discovery and design. A computational technique called QSAR is used in rational drug design to determine mathematical relationship between the chemical structure of a molecule and its biological activity or function. These models assess molecular characteristic that affect pharmacological potency and selectivity allowing for the predication and optimization of novel drug candidates. The predication power and scope of QSAR have been greatly increased by development in machine learning, large data, computing power making it a virtual component of contemporary drug design. Together these methods enhance drug discovery by reducing time. Cost and experiment uncertainly while improving the precision and success rate of developing safe and effective therapeutic agent. The aim of this review is to give an overview on the rational drug design approaches with a case study on drug discovery for Influenza A virus, cancer and Antifungal. A significant amount of data has been generated and collected because of advancements in computational resources and the ability to solve numerical problems. Finding intelligible patterns in these massive silica databases is extremely difficult, though. All things considered, this paper emphasizes the advantages and potential of creating drug discovery tools.**

***Index Terms*—QSAR, Rational drug design, structure activity relationship, 2D-QSAR, 3D-QSAR, molecular descriptors, pharmacophore modelling.**

I. INTRODUCTION

QSAR is a method for building computational or mathematical models by identifying a statistically significant correlation between structure and function using chemometric techniques. It aims to optimize existing leads and predict the biological activities of untested compounds and is widely used in various situations.

The QSAR method is utilized in medicinal chemistry, drug design, and predicting biological activity of chemical compounds based on their chemical structure. Computer-aided drug design is widely accepted for its efficiency in designing new compounds and optimizing lead compounds, saving time and cost.

History of QSAR

The QSAR technique, developed by Hansch and Fujita, relates a molecular system's properties and biological activity mathematically. It was first proposed in 1868 by Crum Brown and T.R. Fraser. Other researchers like Brown and Fraser investigated Qatarized strychnine derivatives, Richardson noted narcotic action based on molecular weight, Richet demonstrated solubility in water's toxicities, Meyer and Overton discovered compound potencies using LogP, Traube discovered a linear relationship between narcosis surface, and Fujita and Hammett equation in 1964.

Free and Wilson conducted a QSAR in 1964, leading to the development of 2D, 3D, and virtual screening techniques. A well-defined end point, algorithm, and application area are essential for a good QSAR model. These techniques have been used to predict chemical characteristics and optimize compounds.

Rational drug design

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RDD employs scientific understanding of molecular biology, biochemistry, and computer technologies to create targeted and efficient medications rather than solely depending on trial-and-error techniques. Researchers can create therapeutic compound that precisely interact with target to alter its activity by three-dimensional structure, binding location, and molecular mechanisms. This raises the possibility of

creating medication that are safer, more efficacious and selective.

History of rational drug design Rational drug design, developed in the 1950s, gained prominence in the 1980s, leading to significant medication development like captopril and lovastatin, and was bolstered by Hitchings Elion's 1988 Nobel prize.

II. FUNDAMENTALS OF QSAR

Molecular descriptor.

Molecular descriptors are crucial physicochemical characteristics of molecules, including constitution, electronic, geometric, hydrophobic, lipophilic, solubility, steric, quantum mechanical, and topological properties, used for QSAR development.

QSAR investigates biological and chemical characteristics of molecules, including bio composition, chromatographic retention, carcinogenicity, dielectric constant, drug clearance, metabolism, coefficient of diffusion, inhibitor reactivity, mutagenicity, solubility, and consistency.

Structure activity relationship:

SAR examines the relationship between a molecule's biological activity and its chemical or dimensional structure, examining how structure changes impact biological effects.

Important

SAR, specifically QSAR link, aids in determining chemical groups and biological impacts, aiding in the development of new drugs and pharmaceutical agents by analyzing structure-function relationships.

Functional groups, substituents, and structure modifications in compounds can enhance their binding capacity, pharmacokinetics, and effectiveness. SAR aids in designing safer, more effective drugs in less time and cost.

Parameters

Parameters play a crucial role in determining the intermolecular forces underlying drug receptor interactions, with electronic, hydrophobicity, and steric being the three major types initially suggested.

Hydrophobicity parameter:

The hydrophobicity parameter measures a molecule's ability to dissolve in a nonpolar environment versus a polar one, often using the logarithm of the octanal-eater partition coefficient.

Electronic parameter

The electronic parameter quantifies the effects of substituents on a molecule's biological activity, such as the Hammette substituent constant. These parameters are crucial as they can affect a drug's polarity, cell membrane cross ability, and binding affinity to biological targets. Other parameters include pKa value, inductive effect constants, Taft's substituent constants, and quantum chemical parameters.

Steric parameter

Steric parameter measures a molecule's size and shape, affecting its interaction with a receptor. It's harder to measure than electronic factors like Taft's steric factor and molar refractivity. It also describes steric hindrance.

Types of QSAR

2D QSAR: 2D QSAR is a method for analyzing chemical structure and experimental results, focusing on data quality, statistical techniques, and correlations. It's commonly used for optimizing chemical series for clinical trials and will become a stand-in for experimental observation as more research is conducted.

2D QSAR aids in predicting biological activity properties, designing effective drugs, and reducing experimental testing costs by facilitating virtual screening of large compound libraries.

3D QSAR:

3D QSAR uses 3D ligand characteristics to predict biological activities using chemometric techniques like PLS, G/PLS, and ANN. It compares molecular structures and establishes a representative structural group as the pharmacophore.

Cramer et al.'s CoMFA and CoMSIA techniques are popular 3D-QSAR models used in drug design. These techniques help visualize ligand-receptor interactions, aiding in the design of more potent inhibitors. This review focuses on the combination of classical QSAR and 3D QSAR.

Types of rational drug design

- Structure based drug design- relies on finding new medication based on the knowledge of the target. Also known as Direct Drug Design.
- Ligand based drug design- relies on knowledge of other molecules that bind to the biological target of interest. Also known as Indirect Drug Design.

Rational drug design Approaches

- Anti-fungal
- Cancer
- Influenza A virus

ANTI FUNGAL: 2-aryl-4-chromanones, flavonoid derivatives, are phytoalexins that inhibit biological functions. Synthetic models for antifungal development have been proposed, but the binding model and fungicidal effect mechanism are not fully understood. A bioisosterism technique was used to design and synthesize new analogues.

CANCER: QSAR techniques are used in medicinal chemistry to understand the structural prerequisites for compounds to interact with target biomolecules. 3D-QSAR models use a small number of descriptors, including topological indices, geometrical, constitutional, and physicochemical descriptors. Constitutional descriptors represent molecular composition, while 2D molecule structure is used for physicochemical characteristics. 3D geometrical descriptors require geometry optimization due to conformation-sensitive information.

INFLUENZA A VIRUS: The H1N1 swine influenza pandemic, affecting nearly every country between 2009 and 2010, caused a significant global outbreak. Around 60.8 million cases of H1N1 virus infection occurred, causing 12,469 fatalities and 274,304 hospitalizations, and affecting 62.9 million people globally.

III. APPLICATION OF THE RATIONAL DRUG DESIGN

HIV Protease Inhibitors:

The drug, designed to inhibit HIV protease enzyme, has been developed through detailed structure studies and docking simulations, resulting in precise target binding and minimal side effects.

Kinase Inhibitors (e.g., Imatinib):

Imatinib, a cancer treatment, targets abnormal kinases, such as the BCR-ABL kinase, to inhibit cancer cell growth.

Antiviral and Anticancer Agents:

Rational design has significantly contributed to the development of selective COX-2 inhibitors, antipsychotics, integrase inhibitors, and enzyme-specific drugs like dorzolamide for various diseases.

Personalized Medicine:

Understanding patient molecular variations allows for rational drug design, enabling tailored therapies that improve efficacy and safety.

IV. FUTURE PERSPECTIVE IN DRUG DESIGN

Artificial intelligences [AI]and Machine Learning:

Al will be central to all stages of drug discovery, from target identification and molecule screening to clinical trial design. Al-driven tools can Analyse massive datasets quickly, predict drug interactions, and personalize treatments, significantly shortening drug development timelines and reducing costs. Over 80% of drug discovery processes will integrate Al by 2030

Biologics and Gene Therapies:

These therapies will dominate new drug approvals, comprising over 60% of future drug launches. They offer high precision and effectiveness for complex and rare diseases. Investment in biomanufacturing and biotech partnerships will become increasingly crucial.

3D Bioprinting:

This technology will revolutionize drug testing and personalized medicine by enabling the production of biologically relevant models and potentially lab-grown organs. It will improve the precision and speed of preclinical testing

Digital Therapeutics:

Software-based interventions, such as Al-driven apps and virtual coaching, will emerge as complementary or alternative treatment options for chronic and mental health conditions. This field will grow to a $25 billion industry by 2030

Nanomedicine:

Targeted drug delivery using nanotechnology will enhance bioavailability and reduce side effects

Quantum Computing:

Expected to substantially accelerate molecular simulations and drug discovery processes, quantum computing will enable the rapid design and analysis of new drug candidates at a scale previously impossible.

Factors affecting drug design

1. Researchers and the pharmaceutical industry seek to clarify the medicinal objectives of drug development, as specificity in purpose increases the chances of success. For instance, developing a pain reliever is generally easier than creating a functional proton-pump inhibitor, indicating that medical requirements significantly impact the drug discovery process.

2. The medicinal chemist is essential in drug development, focusing on identifying and preparing therapeutic compounds and evaluating the safety and effectiveness of Structure-Activity Relationships (SARs).
3. To identify effective therapeutic molecules swiftly, it is essential to have a comprehensive knowledge of biomolecule screening and rapid mass screening procedures.
4. The drug development process necessitates a modern facility that supports interdisciplinary collaboration among biology, chemistry, and pharmaceutical researchers.

Advantages of drug design

- It allows for the development of drugs with greater potency and selectivity. By knowing the structure of the biological target, drugs can be designed to interact optimally and specifically, minimizing undesired effects.
- Rational drug design aims to reduce side effects because the drugs are tailored to fit the target more precisely than drugs discovered by traditional trial-and-error methods.
- The process is more efficient and cost-effective, saving time in drug development by focusing on compounds that are predicted to be effective through structural and molecular knowledge rather than random screening.
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- It facilitates the optimization of drug properties such as pharmacokinetics (absorption, distribution, metabolism, excretion) and pharmacodynamics, enhancing drug safety and efficacy.
- The approach can incorporate computational methods and techniques like X-ray crystallography and NMR to better understand target structures, improving drug candidate selection.

Disadvantages of drug design

- It requires detailed knowledge of the biological target's structure, which is often unavailable or incomplete for many diseases, limiting the applicability of this approach.
- The molecular complexity and flexibility of drug targets make it challenging to design a perfectly complementary drug molecule, which can lead to more trial and error despite a rational approach.
- Rational drug design can be expensive and time-consuming due to the need for advanced computational resources and experimental techniques like X-ray crystallography or NMR for target characterization.
- Designing drugs that are too closely aligned with disease gene targets might increase the incidence of side effects, as very close network distances between targets and disease genes can be associated with higher adverse effects.
- The scoring functions and computational predictions used in rational drug design are not always fully accurate, sometimes failing to account for all molecular interactions, which can lead to less effective drug candidates

V. CONCLUSION

QSAR (Quantitative Structure-Activity Relationship) is a crucial tool in rational drug design, significantly transforming the pharmaceutical discovery process. Originating in the early 1960s, drug discovery involved screening numerous compounds for biological activity. The integration of molecular biology, protein crystallography, and computational chemistry since the 1980s facilitated the advent of rational drug design, which effectively predicts binding affinity. QSAR has proven essential in discovering cancer and antifungal agents, improving the prediction and diagnosis of structure-activity relationships. Thus, QSAR plays a pivotal role in developing safer and more effective drug candidates within computational chemistry and biomedical research.

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