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# THE USE OF COMPUTATION IN DRUG DISCOVERY AND DEVELOPMENT

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**ABSTRACT:**

**Background:** Drug development is a complex and expensive process involving multiple scientific disciplines. The integration of computational methods has become essential in this multifaceted endeavour.

**Objective:** To explore the contributions and challenges of computational methods in the drug development process and highlight the importance of teaching these methods in medicinal chemistry courses.

**Methods:** This study reviews the deployment of computational methodologies based on available system information and specific project objectives. It examines the contributions of these methods to data analysis, compound filtering for experimental screening, hypothesis generation for drug mechanisms, and the creation of new chemical structures. Additionally, the study discusses the impact of computational methods on currently used clinical medications.

**Results:** Computational methods have significantly improved efficient data analysis, facilitated the selection of molecules for experimental screening, generated hypotheses for understanding drug mechanisms, and aided in creating new chemical structures. These methods have also contributed substantially to the development of medications in clinical use. However, several challenges remain, including data quality, computational resource limitations, and methodological constraints.

**Conclusion:** Computational methods play a crucial role in drug development, enhancing efficiency and innovation. Addressing existing challenges will further refine these approaches and support the interdisciplinary efforts in medicinal chemistry education and drug production.

**KEYWORDS:** Drug discovery, molecular modelling, chemoinformatics, and structure-activity connections are some of the topics that are covered in molecular docking.

## INTRODUCTION:

The process of developing medicines is a complex one that starts with the identification of chemicals that are mixed with a white substance that is used in therapy or that demonstrate biological activity in a tamale test (Sliwoski et al., 2014). This is the first step in the progression of the pharmaceutical industry (Hung & Chen, 2014). The compounds that display biological action are referred to as hits. As molecules that exhibit activities, hits are referred to as hits (Ou-Yang et al., 2012). The third step is to discover compounds that exhibit acceptable features in the field of pharmaceuticals. These compounds should have properties such as low toxicity and adequate solubility for oral administration, among other desirable properties in the field of pharmacology (Materi & Wishart, 2007). One of the names that is commonly used to describe this kind of collection is "líderes or cabezas de serie." In most cases, the hits are found by a procedure known as tamale, which includes the modification of a significant number of molecules (Balasubramanian, 2018). On the other side, the "cabezas de serie" are created by employing chemical alterations to begin with the hits as a beginning point to produce the series. Taking into consideration the fact that the number of organic molecules that can be factually determined with a high degree of certainty falls somewhere in the range of 1020 to 1024 (Ertl, 2003) (Prada-Gracia et al., 2016), It is the creation of drugs that are directed against epigenetic domains that are the focus of these applications (Baldi, 2010). In the article that was published in 2015, the focus is on four distinct lines of investigation and individual cases of research. It is vital to highlight that this is the primary topic of the essay (Wu et al., 2020).

**Creating new medications and developing new pharmaceuticals.** The vast majority of the pharmaceuticals that are currently being used in clinical settings are the result of an inquiry procedure that is quite complicated (Kapetanovic, 2008). This is the case for the majority of the medications (Pathak et al., 2020). To phrase it another way, it is very necessary to integrate the efforts of several different scientific disciplines to discover and produce drugs that have favourable clinical effects while having minimum undesirable effects (Kumar et al., 2006). Even though the discovery and development of medicines have been carried out over a considerable period using only experimental methods, it is (Kapetanovic, 2008) anticipated that the process will be accelerated through the utilization of computational methods, also known as in silico methods, which enable the codification of theoretical models with precision and are capable of processing these models (Lipinski et al., 2012). In addition, the utilization of in silico methods will allow for the processing of these models. It is possible to find a tremendous amount of information (Cox & Gupta, 2022). The application of models that are developed in silico also adds to the study of the mechanisms of action of the fundamental active characteristics of the drugs or to the enhancement of the properties of the medications themselves in a variety of projects that are being undertaken (Hecht, 2011). As an illustration, one suitable example is the optimization of medications that are derived from natural or organic sources (Cao et al., 2018). Efforts are currently being made to improve the qualities of these treatments, such as reducing the likelihood of potential bad effects or looking for biochemical activities that have the potential to be separated from natural sources (Medina-Franco, 2013). These efforts are currently being made (Lin et al., 2020). **One of the stages in the process of developing drugs** In Figure 1, we have an illustration of the major stages that are involved in the process of developing a conventional model for the design of a pharmaceutical product. An initial phase in the procedure is the examination of the factors that lead to the development of a disease (Nag et al., 2022). There is a possibility that this inquiry will result in the identification of one or more chemical molecules that are connected to the disease in certain circumstances (Vamathevan et al., 2019). One of the ensuing processes is the identification of active compounds with the molecular Diana, and the other step is the optimization of the biological activity of these compounds. Molecular whites that have been extracted from the cells are used in every one of these tests, which are conducted in vitro

(Hasan et al., 2022). Many different kinds of experimental evaluations are carried out on Los Compuestos activos (Kiriiri et al., 2020).

**Table 1: Stages in Pharmaceutical Development**

| Step | Description | Reference |
|---|---|---|
| Identification of Chemicals | Begins with identifying chemicals mixed with a white substance used in therapy or showing biological activity in a tamale test. | Sliwoski et al., 2014; Hung & Chen, 2014 |
| Discovery of Hits | Compounds showing biological action are referred to as hits. | Ou-Yang et al., 2012 |
| Optimization of Compounds | Compounds with acceptable pharmaceutical properties like low toxicity and adequate solubility for oral administration are identified. These are termed as "líderes or cabezas de serie". | Materi & Wishart, 2007; Balasubramanian, 2018 |
| Drug Development Focus | Creation of drugs directed against epigenetic domains, highlighting four distinct lines of investigation. | Baldi, 2010; Wu et al., 2020 |

**Table 2: Integration of Scientific Disciplines**

| Aspect | Details | Reference |
|---|---|---|
| Complexity of Drug Development | The process involves integrating multiple scientific disciplines to discover and produce effective drugs. | Kapetanovic, 2008; Pathak et al., 2020; Kumar et al., 2006 |
| Use of Computational Methods | Anticipated to accelerate drug discovery and development through in silico methods, which process theoretical models with precision. | Kapetanovic, 2008; Lipinski et al., 2012 |
| In Silico Models | Aid in studying drug mechanisms or enhancing drug properties in various projects. | Cox & Gupta, 2022; Hecht, 2011 |
| Optimization of Natural Source Drugs | Efforts to improve drug properties and reduce adverse effects, searching for new biochemical activities. | Cao et al., 2018; Medina-Franco, 2013; Lin et al., 2020 |

**Table 3: Major Stages in the Drug Development Process**

| Stage | Details | Reference |
|---|---|---|
| Examination of Disease Factors | Identifying chemical molecules related to diseases. | Nag et al., 2022; Vamathevan et al., 2019 |
| Identification of Active Compounds | Finding and optimizing compounds with biological activity. | Hasan et al., 2022 |
| Experimental Evaluations | Tests on cellular lines, animals, and humans for active compounds. | Kiriiri et al., 2020 |
| Regulatory Approval | Compounds passing all evaluation stages are approved by agencies like the FDA (USA) and COFEPRIS (Mexico). | - |

These evaluations include tests carried out on cellular lines, testing carried out on animals, and clinical studies carried out on humans. A couple of examples of regulatory agencies that have approved the use of compuestos that have passed through all stages of analysis with a satisfactory level of approval include the Administración de Alimentos y Medicamentos (FDA) in the United States and the Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS) in Mexico. Both of these agencies are located in Mexico.


**Figure 1 displays the primary steps involved in the development of a conventional medication.**

**Probabilities of making a profit** When it comes to the development of pharmaceuticals, the majority of the compounds that demonstrate activities in vitro with molecular dianas fail the following tests. In many cases, this is because they have poor properties in terms of their pharmacological toxicity. To put it another way, in addition to the fact that a compound is active with the desired molecular whites, it also affects other physiological processes and cannot be used safely in human beings. It is estimated that just one out of every nine thousand biologically active molecules has a clinical use. Even if the methodology for the development of pharmaceuticals depicted in Figure 1 continues to be successfully implemented, it is not necessarily the most effective one. Every time there is more evidence that a drug interacts with a variety of different white molecular substances, the evidence grows. The clínic effect can be attributed to the interaction with many dianas, which is where the notion of polifarmacología originates. This occurs in several different cases. As a result of this, the polifarmacología is undergoing a paradigm shift in the design of pharmaceuticals, shifting from a design directed at a single day to a design directed simultaneously towards multiple white pharmaceuticals. This strategy is being referred to as a multi-objective design, and one of the goals is to design a "master llave" that will be applied selectively to a series of molecular whites that will result in the desired clinical response. A visual representation of the polifarmacología and the design of pharmaceuticals that function as "llaves maestras" can be found in Figure 2.


The second illustration illustrates the idea of polypharmacology as well as the process of developing "master keys."

**Estimated time and money resources** According to estimates, the process of developing a medicine takes around ten to fifteen years and requires an average investment of eight hundred

million dollars. The most expensive and time-consuming part of the process is conducting clinical trials at the human level. One of the primary reasons for the significant amount of time and money required for drug development is the vast number of compounds that are unsuccessful in one or more stages of the process.

**Approaches to the identification of lead compounds** Identifying active molecules that are deemed to be leaders in the implementation of an optimization program can be accomplished by a variety of experimental and/or computational methodologies, including the following: Drugs that have already been approved for clinical usage undergoing optimisation. The term "optimization" can refer to either the enhancement of the medication's efficacy or the reduction of its adverse interactions. Testing of compound collections using a systematic biological approach. The high-throughput biological testing (HTS) method is an example of a common instance. Robots are utilized in HTS to evaluate sample collections consisting of thousands or millions of molecules in a matter of hours. Make use of the biological information that is accessible. If the mechanism of action of a substrate is known, for instance, compounds that are developed with the expectation that they will follow the same mechanism of action are created. DIFAC stands for computer-aided drug construction. A number of the methods that are going to be covered in the next part are going to be utilized in this strategy.

**Computer-aided drug design (CAD)** According to Medina-Franco et al. (2006), the DIFAC's guiding premise is to get an understanding of the interaction between the structure and the biological or pharmacological activity of chemicals.

**Objectives of the DIFAC** It is possible to categorize the goals of DIFAC into three sets: Developing novel chemicals or determining their identities. For example, the creation of novel structures that have a biological effect and fall into a therapeutic category that is wanted. A different approach would be to look for molecules that possess a particular biological activity within collections of substances that already exist. Pick out the candidates. For example, procurement, synthesis, and biological evaluation are all examples of areas that can benefit from the application of computational approaches, which assist in distinguishing the molecules on which experimental testing should be concentrated first. Computational methods, on the other hand, are not a suitable replacement for experimentation. The leaders should be optimized to improve the desirable qualities and reduce the negative impacts.

**DIFAC is an amalgamation of many approaches.** DIFAC is comprised of several different study fields, some of which are chemo-informatics, bio-informatics, molecular modelling, theoretical chemistry, and data visualization. Every one of them consists of approaches that are utilized by the characteristics of the system, the experimental knowledge that is readily available, and the particular goals that are being pursued by the project.

**Expectations devoid of reality from DIFAC** There is a common misconception that the idea of "computer drug design" is associated with unrealistic expectations. This table provides a summary of the cases that are explained in more detail below.

**Table 1: Typical DIFAC erroneous expectations and realistic vision.**

| delusional anticipation<br>Drugs can be designed by computers. | The vision of reality<br>Computational approaches are not used in the design of medications on their own; rather, they are a component of an endeavour that involves multiple disciplines to accomplish an incredibly difficult goal. |
|---|---|
| Evidence of drug-molecular target binding can be demonstrated through the use of a theoretical | Quantitative molecular docking simulations provide hypotheses and offer binding models; these |

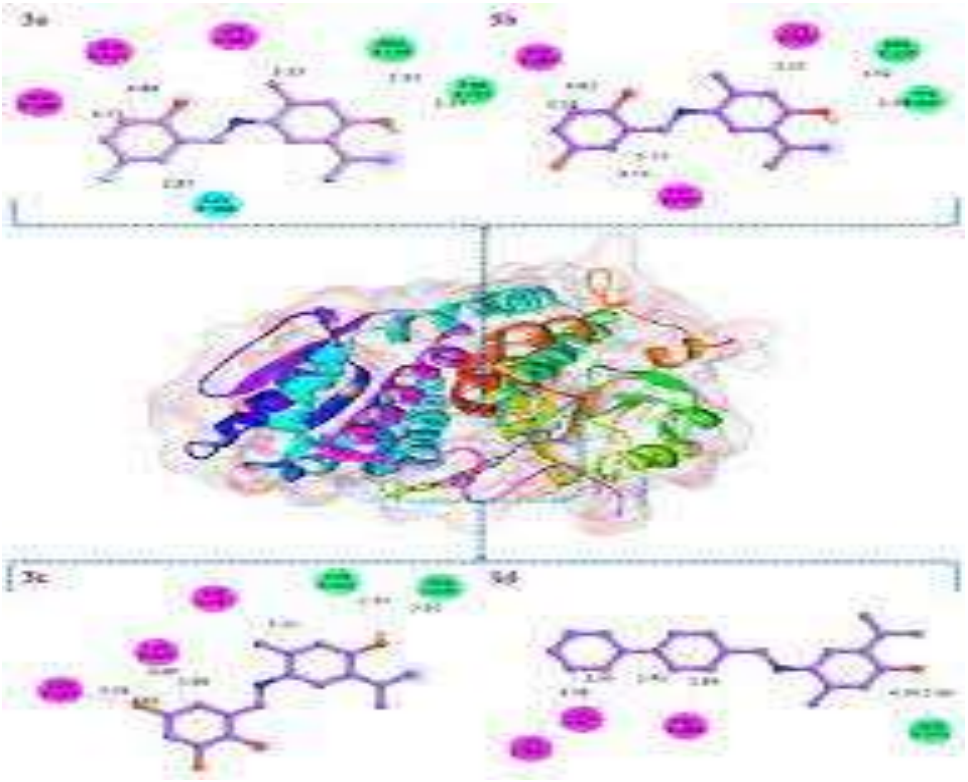
| | |
|---|---|
| calculation, such as molecular docking. | calculations are utilized as support for studies that demonstrate the union of molecules. |
| By pressing buttons, it is possible to design drugs (also known as "push-a-bottom drug discovery"). | The DIFAC is a procedure that necessitates a significant amount of preparation, analysis, and interpretation of the data that are produced from the computer. |
| The DIFAC is quick because it is performed by computers. | The preparation of data and the interpretation of results, both of which are essential components of DIFAC, are processes that demand time and can extend for several months depending on the circumstances. |

It is a mistake to believe that computers are capable of independently designing pharmaceuticals. The question of whether or not any medicine has been designed using computational methods is frequently raised as a result of this view. The design of drugs is not automatically accomplished by computational methods. For theoretical models to be useful, they need to be incorporated as evidence from biological or biophysical sources. The computational approaches are a component of a multidisciplinary endeavour that also includes other fields, such as organic synthesis, natural products, and HTS. Calculations performed on a computer, for instance, do not demonstrate that a molecule is capable of binding to an enzyme. The calculations "assist" in predicting the binding mode of a molecule with a molecular target, but they do not demonstrate such binding. This will become clear when discussing automated molecular docking. On the other hand, the calculations do not demonstrate such binding. Other erroneous assumptions include the notion that synthetic pharmaceuticals may be created by "pushing buttons" and that computational analyses can be completed quickly. If it is true that the processing of data is quick (varying according to the kind of computation, the computer equipment, and the system that is being investigated), then the analysis and interpretation of data are tedious. It is necessary to validate the computational methods in a manner that is analogous to an experimental test, and it is also necessary to locate the ideal parameters to ensure that the calculations are as accurate as possible.

**METHOD:**

As was indicated before, the process of developing a medicine encompasses several stages, beginning with the discovery of molecular targets and ending with clinical phases (Fig. 1). In the majority of the traditional DIFAC procedures, the initial stages are the primary focus. In this section, we will examine three techniques that are widely utilized in the process of identifying lead compounds and optimizing their performance.

**Computerized molecular docking system** Automated molecular docking, often known as molecular docking in English, is a process that involves searching for the best shape and position of a ligand (for instance, a small organic molecule) within a molecular target (for instance, an enzyme, an ion channel, or a receptor). Linked to the G protein). A docking model of the BRD4 (BET family bromodomain) isoform, which is an epigenetic target, is depicted in Figure 3. The conformation of the proposed ligand is indicated in purple, which is comparable to the orientation of the cocrystallized ligand (A). This was discovered using molecular similarity searches, which led to the discovery that pentoxifylline has the potential to act as a BRD4 inhibitor. Why should we have faith in the outcome? This is accomplished by using the same algorithm to the cocrystallized ligand to determine whether or not it is capable of retrieving the conformer (B) that was seen through experimentation.



The coupling model of pentoxifylline (carbon atoms in purple) about the cocrystallized ligand (yellow) is shown in Figure 3. Docking model of the epigenetic target BRD4 (PDB 3P5O) is shown in Figure 3. The conformation shown in blue represents the prediction made by the docking algorithm. This pertains to the validation of the docking procedure.

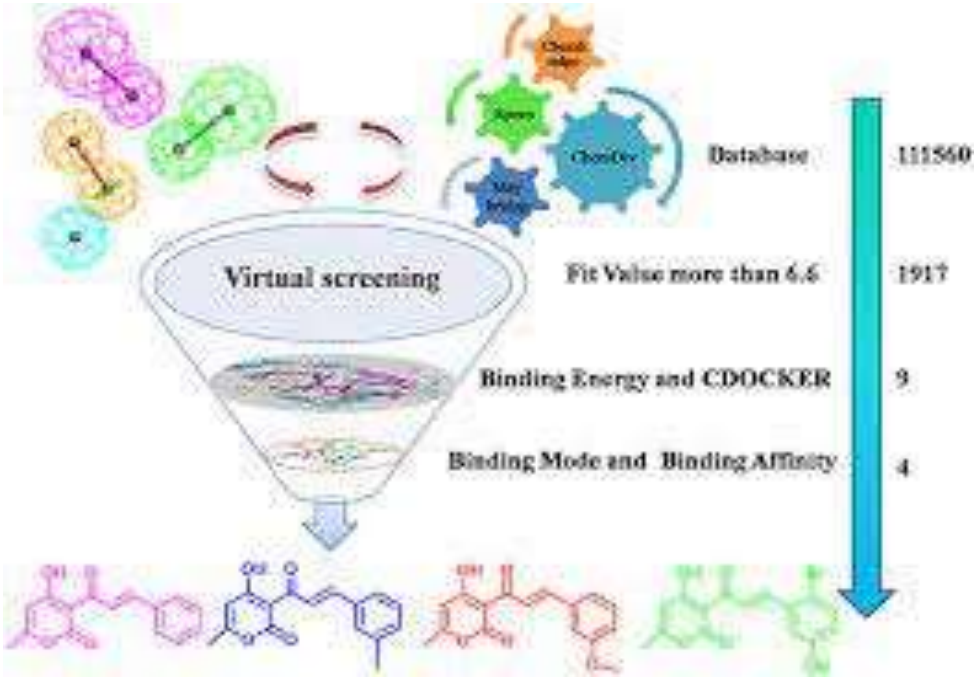
There is the possibility of performing molecular docking in an automated fashion between two macromolecules, such as two proteins. When taking into account the adaptability of the molecules, the number of potential conformations might grow to an extremely high level. When the cavity of the receptor site is large and/or flexible, it is more difficult to determine the position and orientation that the small molecule will have within the receptor. This is because the cavity is more likely to be occupied by the small molecule. The utilization of computers, thus, contributes to the acceleration of the search process and provides union models.

Two components make up automated molecular docking: a) docking, which is the process of looking for the conformation and orientation of the molecules, and b) scoring, which is the process of providing a value or score that measures the interaction between the two structures. The second stage is the one that is the most challenging to compute precisely and in a short amount of time. It is for this reason that molecular docking is currently very beneficial for developing binding models; yet, they are still not very dependable for precisely measuring the contact energy. Because of the enormous number of approximations that are made to calculate the interaction energy in a short amount of time, this is the result. As an illustration, the molecular target's flexibility and solvation are not taken into consideration in such a comprehensive manner. To find a solution to this issue, the models that were created through molecular docking are put through additional calculations that are more refined and are calculated using high levels of theory.

**The modelling of pharmacophores** Another computational tool that is commonly utilized is known as the "pharmacophore" model. Specifically, this is described as a three-dimensional arrangement of the bare minimum of steric and electronic features that are required to guarantee good interactions with a particular pharmacological target, which will either trigger or prevent a biological response. It is essential to have a clear understanding that a pharmacophore does not represent a genuine molecule or a true combination of functional groups, even though the visual representation of a pharmacophore might be either two-dimensional or three-dimensional. An

abstract idea known as a pharmacophore model demonstrates the shared molecular interaction capability of a set of chemicals that are oriented toward a particular pharmacological target. To put it another way, the pharmacophore can be thought of as the element that is shared by all of the active compounds in a group.

**Screening in Virtual Reality** According to Scior et al. (2012), virtual screening is a computational (in silico) filtering of molecules that selects candidates, also known as computational hits, for experimental evaluation (Fig. 4). Through this method, the number of biological tests that would be carried out in the absence of compound selection is greatly cut down by the utilization of virtual screening services. Nevertheless, it is a predictive method that needs to be combined with experimental tests to validate the predictions that were made by the in silico tests.




A diagrammatic illustration of the process of virtual screening is shown in Figure 4.
To carry out virtual screening, several filters are utilized, and the specific filters that are utilized can change based on the complexity of the database and the experimental information that is provided. The structure-based screening method, also known as molecular docking, is recommended, for instance, if the three-dimensional (3D) structure of the receptor is already known. When just the active molecules are known, but not the receptor, the search is conducted based on the ligand, which is a term that refers to the molecular similarity between the two. Molecular descriptors and pharmacokinetic features are two examples of filters that can be combined to make the search process easier. If the three-dimensional structure of the receptor and the active molecules is already known, then the search can be made easier. It is dependent on the information that is available in the system as to the techniques that are used for virtual screening.Virtual screening using molecular docking has been utilized by our research team to discover new inhibitors of the AKT-2 and DNA methyltransferase enzymes (Kuck, Singh, Lyko, & Medina-Franco, 2010; Medina-Franco et al., 2009). They have been successful in their hunt for these inhibitors. Both of these are molecular targets that can be used in the development of medicines that fight cancer. It has been shown that experimental hits have been used as beginning points for optimization programs (Hernández-Campos et al., 2010; Medina-Franco, Fernández-de-Gortari, and Naveja, 2015).

**The process of repositioning pharmaceuticals through virtual screening of licensed drugs**The process of identifying a new therapeutic application for a medicine that is distinct from the one for which it was originally developed and that does not necessarily require the utilization of the same

dosage is known as drug repositioning. One of the goals of this technique is to cut down on the amount of time and money spent on research. More recently, there has been a discussion on successful cases of pharmacological repositioning, as reported by Navija, Dueñas-González, and Medina-Franco (2016).Several computational algorithms have been implemented with the intention of repositioning pharmaceuticals. These approaches are based on the concept that "similar molecules have similar properties." As an illustration, there is an endeavour to reposition olsalazine as an anticancer medication. Clinical usage of the anti-inflammatory medication olsalazine has been authorized. It was through the use of computer-assisted similarity searches in DrugBank that olsalazine was recognized as a hypomethylating drug (Méndez-Lucio, Tran, Medina-Franco, Meurice, & Muller, 2014).

**The field of chemoinformatics**The field of chemoinformatics is a tool that is utilized in the management, visualization, and systematic analysis of chemical information. It is a product of the merging of computer resources with chemical data. Using this program, you will be able to analyze hundreds of data effectively. Information can be managed and organized, chemical space can be visualized, data mining can be performed, and mathematical correlations between structure and activity may be established through the use of cheminformatics tools. A well-known illustration of this is the quantitative structure-activity relationship, sometimes known as QSAR.

**Databases accessible to the public** applications of cheminformatics that are particularly useful include the maintenance and analysis of molecular databases. Collections such as ZINC, DrugBank, ChEMBL, Binding Database, and PubChem are examples of collections that are frequently utilized in the process of drug development. Information that can be used to do virtual screening, chemogenomics, structure-activity analysis, and medication repositioning is contained within these collections, which are covered in other works (Nicola, Liu, and Gilson, 2012; Scior, Bernard, Medina-Franco, and Maggiora, 2007).

**Computational Analysis Conducted Online?**Using resources that are included in the same database, it is possible to analyze the information that is stored in public databases. One platform that falls under this category is the PubChem BioAssay Database, which may be accessed at http://pubchem.ncbi.nlm.nih.gov. Clustering and structure-activity connection analysis are two examples of the types of tools that are included in PubChem that enable the study of any data.

**Relationships between structure and behaviors**Ligand-based approaches are utilized in situations when the structure of the receptor is unknown. These methods are dependent on the information that is available for chemical compounds that have been shown to have known biological action. Both qualitative and quantitative approaches, known as SAR and QSAR research, are frequently used.

**Frequent methods and QSAR**QSAR approaches can be broken down into three distinct categories, each of which is determined by the origin of the molecular descriptors that are utilized in the calculations. One of them makes use of a very limited number of descriptors to describe various effects, such as hydrophobic, steric, and electrostatic effects of the substance. The features that are derived from the molecular connection system provide the basis for another category. These techniques are referred to as 2-dimensional QSAR studies or 2D-QSAR. This is possible because the structural formulas are two-dimensional. A third category of approaches is known as QSAR in three dimensions or QSAR-3D for short. These methods are developed based on the descriptors that are generated from the three-dimensional representation of the structures. The comparative molecular field analysis (also known as CoMFA) is certainly one of the most well-known examples of QSAR-3D. It is also possible to categorize QSAR investigations according to the type of correlation approaches that were utilized. These methods might be linear, such as linear regression or multiple linear regression, or they can be nonlinear, specifically regression.

**Summary of the activities** The purpose of activity landscape modelling is to provide a methodical description of how changes in chemical structures are connected with changes in biological activity. The identification of instances in which very minor structural alterations are linked to significant alterations in biological activity is one application of this technique. According to Medina-Franco et al. (2013), these conditions, which are referred to as "activity cliffs," are exceptions to the "similarity principle" and have a significant influence on the design of pharmaceuticals. **Successful cases** The research of compounds that are currently being used in clinical settings has been significantly aided by the application of large computational calculations. DIFAC, for instance, has already made significant contributions to the treatment of glaucoma, acquired immunodeficiency syndrome, and influenza virus infections (Medina-Franco, 2007; Talele, Khedkar, and Rigby, 2010). These are just a few examples. The following table provides a summary of some recent examples of successful endeavours.

**Table 2: Recent examples of medications that were produced with the assistance of computational approaches**

| The drug | The application | Techniques based on computation | The pharmaceutical industry |
|---|---|---|---|
| The drug crizotinib | chemical that inhibits the growth of lung cancer | The docking of molecules | "Pfizer" |
| The drug rilpivirine | antiviral medication (treatment for HIV infection) | The process of molecular docking | Pharmaceuticals manufactured by Janssen |
| A. Zelboraf | Malignant melanoma is an anti-cancer agent. | An examination of the molecular interaction and the substructure | A Roche |

For the treatment of patients diagnosed with non-small cell lung cancer (NSCLC), the Food and Drug Administration (FDA) approved crizotinib (Xalkori; Pfizer) in August 2011. It was via research that researchers were able to identify powerful drug-like inhibitors of MET receptor tyrosine kinase that crizotinib was found. Subsequently, it was discovered that it would also be an effective inhibitor of ALK. The discovery was made through the use of molecular docking studies and biological testing. It has been observed that acquired resistance to crizotinib is developing at present. One of the mechanisms that has been identified is the acquisition of secondary resistance mutations within the tyrosine kinase domain of ALK. These mutations can also be studied through molecular docking studies and molecular dynamics (Cui et al., 2011).

## Conclusions

Advances in a variety of fields, including molecular biology, theoretical chemistry, chemoinformatics, computer science, and technology advancements, have contributed to the exceptional growth that DIFAC has experienced in recent years. The development of medications that are currently being used in clinical settings is a direct result of the introduction of computational approaches into the interdisciplinary effort that is engaged in the process of drug development. Additionally, computational approaches make consistent contributions to research efforts, allowing for the quick analysis of data and the formulation of valuable hypotheses that direct the development of new pharmaceutical materials. One might anticipate a growth in both the quantity and the quality of the advantages that in silico approaches provide to the process of drug design.

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