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In Silico Drug Discovery: Navigating the Landscape of Modern Therapeutics

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ABSTRACT
In silico drug discovery and development leverages computational tools and databases to expedite and optimize the identification and design of novel therapeutic agents. This approach encompasses a range of methodologies, including virtual screening, molecular docking, pharmacophore modeling, quantitative structure-activity relationship (QSAR) analysis, and molecular dynamics simulations. By simulating biological systems and molecular interactions, in silico methods can predict drug efficacy, toxicity, and pharmacokinetic properties, thereby reducing the need for extensive experimental screening and animal testing. This abstract highlight the key principles and applications of in silico techniques in streamlining the drug discovery pipeline, from target identification and lead optimization to preclinical evaluation, ultimately accelerating the delivery of effective and safe medicines.

Keywords: *In silico, virtual screening, molecular docking, pharmacophore modelling, toxicity, preclinical, pharmacokinetic.*

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I. INTRODUCTION

The need for novel drugs with increased efficacy and decreased toxicity is always present. Nevertheless, the process of finding and developing new drugs is costly, time-consuming, and fraught with difficulties. Clinical trials usually have a high failure rate, which is commonly ascribed to poor pharmacokinetics, low efficacy, and excessive toxicity levels, notwithstanding the difficulties in target validation and hit identification (1, 2).

Wong et al.'s study, which looked at 406,038 trials between January 2000 and October 2015, found that the overall success rate for all medications—both those that were on the market and those that were still in development—was only 13.8% (3). Finding possible targets is the first step in the drug discovery process, which is followed by target validation. Preclinical or clinical development, lead optimization, and hit identification come next. If these stages are successful, the drug candidate moves into the development phase, undergoing various clinical trial phases before being submitted for market approval (4).

Flow chart 1: Drug discovery process

Creating and utilizing computational models of biological targets (such as proteins and enzymes) and potential pharmacological substances is the main concept behind in silico drug development. These models make it possible to optimize lead compounds, forecast drug-target interactions, and virtually screen enormous chemical libraries. Before producing and testing drug candidates in vitro or in vivo, researchers can gain important insights into their behavior by simulating molecular docking, pharmacokinetics, and pharmacodynamics.

FUNDAMENTALS OF IN SILICO METHODS FOR DRUG DISCOVERY

- **Virtual Screening:** Rapidly evaluating large chemical libraries to identify potential drug candidates (5).

- **Molecular Docking:** Predicting the binding affinity and orientation of a ligand (drug molecule) to a target protein (7).
- **Pharmacophore Modeling:** Identifying the essential structural features of a molecule that are responsible for its biological activity.
- **Quantitative Structure-Activity Relationship (QSAR) Modeling:** Developing mathematical models to predict the biological activity of compounds based on their chemical structure.
- **ADMET Prediction:** Assessing the absorption, distribution, metabolism, excretion, and toxicity of drug candidates (6).
- **Molecular Dynamics Simulations:** Studying the dynamic behavior of molecules over time to understand their interactions and conformational changes

3. A Structure-Based Drug Discovery Paradigm:

The creation of new medications with possible interactions with therapeutic targets is a crucial step in the drug discovery process. Experimental high-throughput screening (HTS) is the traditional method for identifying potential leads, but it is costly and time- consuming [8]. From target selection to FDA approval, a typical drug discovery cycle can take up to 14 years [9] and cost about 800 million dollars [10]. However, failure at various stages of clinical trials has recently resulted in fewer new medications becoming available on the market [11]. A study to calculate the overall cost of pivotal trials for the creation of new FDA-approved medications was carried out in November 2018. $19 million. Thus, it is important to overcome limitations of the conventional drug discovery methods with efficient, low-cost, and broad-spectrum computational alternatives. Unlike the conventional approach to drug development, known as forward pharmacology or classical pharmacology, rational drug design is cost-effective and efficient. Because promising target proteins are first identified and subsequently employed for small- molecule library screening, the rational drug design process is often referred to as reverse pharmacology (12).

Along with developments in biomolecular spectroscopy structure determination techniques, remarkable strides have been made in structural and molecular biology. More than 100,000 proteins' three-dimensional (3D) structures have been made available by these techniques [13]. There has been a lot of excitement surrounding the creation of advanced and reliable computing methods in tandem with the storage (and organization) of such data. The availability of a vast number of target proteins following the completion of the Human Genome Project and bioinformatics advancements accelerated the pace of medication development. The basis for structure-based drug design (SBDD) has been established by the availability of 3D structures of therapeutically significant proteins, which facilitate the discovery of binding cavities. Industrial drug development programs are increasingly including this as a key component. Because SBDD works with the 3D structure of a target protein and information about the disease at the molecular level, it is a more focused, effective, and quick procedure for lead discovery and optimization [14]. The most popular computational approaches for SBDD include molecular docking, molecular dynamics (MD) simulations, and structure-based virtual screening (SBVS).

[15] These techniques are widely used in the study of ligand-protein interactions, binding energetics, and the assessment of conformational changes that take place during the docking process [16]. A huge increase in software packages for effective drug discovery procedures has propelled advancements in the software sector in recent years. [17] However, selecting exceptional packages is crucial for a successful SBDD procedure [18].

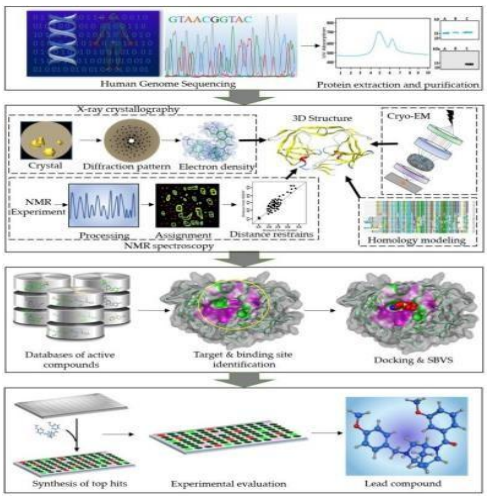
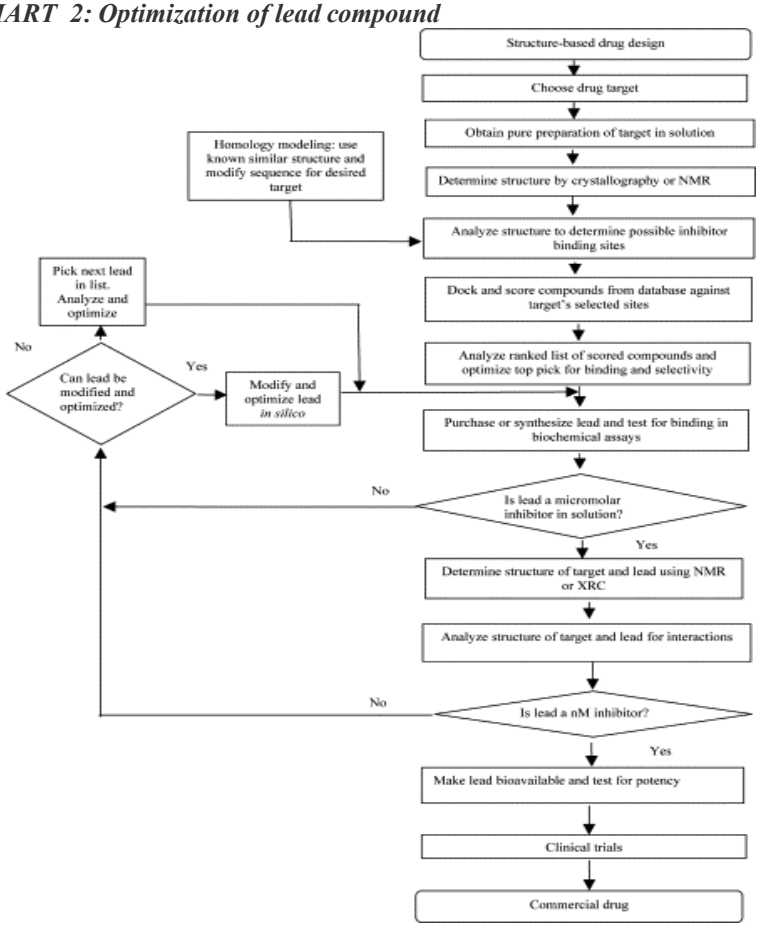


FIGURE 1: A workflow diagram of the structure-based drug design (SBDD) process.

The first panel shows the human genome sequencing followed by extraction and purification of the target proteins. The second panel represents the structure determination of the therapeutically important proteins using integrative structural biology approaches. The third panel represents the database preparation of the active compounds. The next step is identification of the druggable target protein and its binding site. Subsequently, the databases of active compounds are screened and docked into the binding cavity of the target protein. In the last panel, the identification of the potent lead compound is shown. The top hit compounds obtained as a result of virtual screening and docking are synthesized and tested in vitro. Further modifications can be done for optimization of the lead compound.

Process: ***FLOW CHART 2: Optimization of lead compound***

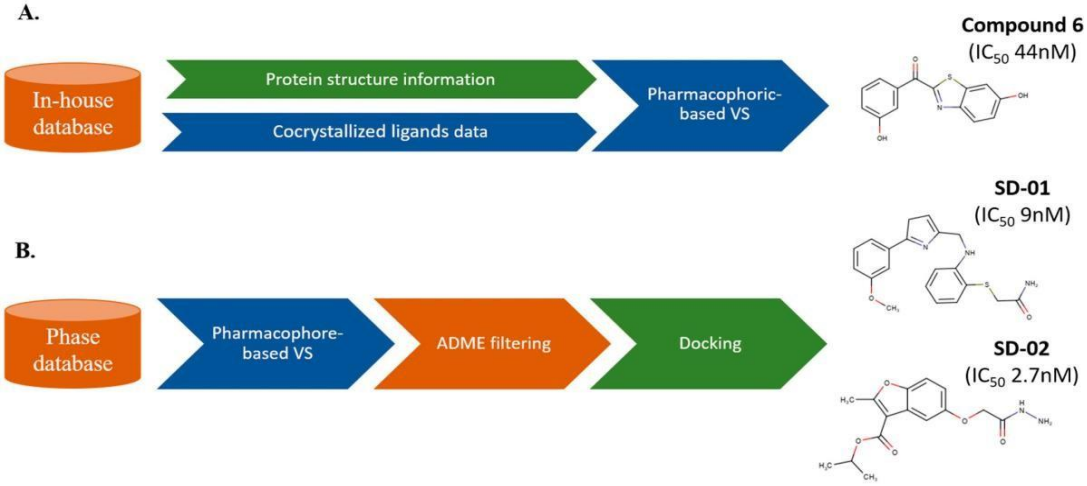


4. Ligand-based drug delivery systems (LBDDS)

When ligands and data on the biological activities of those ligands are the only information available for drug development, computer-aided ligand-based drug design (LBDD) (19) is an effective method to extend the knowledge of the known ligands to design compounds with improved biological activity. The fact that over half of currently approved FDA-approved medications target membrane proteins, including nuclear receptors, transporters, and G protein-coupled receptors (GPCRs) (20), for which three- dimensional (3D) structures are frequently unavailable—a prerequisite for target-based drug design approaches—highlights the significance of LBDD. Drug development is expected to be significantly impacted by LBDD techniques for some time to come, given the challenges in figuring out the 3D structure of membrane-associated proteins (21).

Usually, certain interactions between drugs and their target proteins produce their pharmacological effects. Based on the intrinsic chemical structure of molecules, their dynamic conformational features, and how those two affect the receptor, these special interactions have been referred to as “lock-and-key"(22)"induced-fit” “conformational selection," or "population shift" hypotheses (23). Thus, establishing a structure-activity relationship (SAR), which is the term used to describe any causality or link between structures and activities, could be useful for designing ligands. LBDD-based SAR finds similarities and/or differences in a compound's structural or physicochemical properties and links them to activity, such as pharmacokinetics (ADME) (24), drug-drug interactions, affinity (e.g., Ki), selectivity (e.g., Ki, isoform 1/Ki, isoform 2), efficacy (e.g., activation or stimulation of receptors, Vmax of enzymes), or any biological properties of interest.

Through a variety of statistical techniques, such as regression, classification, dimension reduction, variable selection, etc., different ligand descriptors are linked to biological activities. From these, key characteristics of the ligands that cause activity are found and utilized to create new leads or improve existing ligands. Three major categories of LBDD are quantitative structure activity relationship (QSAR) (25), pharmacophore modeling and similarity searching Over several decades, statistics, computational algorithms, and descriptors comprising the three categories and their pipelining have led to significant improvements both in efficiency and accuracy. (26) Programs can deal with 100∼1000s of molecules to build models or search molecular properties against databases of millions of compounds in a short period of time.



FLOW CHART 3 : Merging ligand -based and structural-based ligand methods

5. Virtual Screening: Accelerating Lead Identification

Virtual screening can be defined as a set of computational methods that analyzes large databases or collections of compounds in order to identify potential hit candidates. This search can be performed on corporate libraries and/or on virtual libraries. These in silico experiments can complement HTS (and are indeed often combined with the screening campaigns); they can also be performed prior to experimental screening or after HTS to rescue some compounds potentially missed by the in vitro readouts (so-called latent hits). Virtual screening methods can be classified into two major groups: (a) ligand-based methods, which rely on the similarity of the compounds of interest with active compounds, and (b) receptor-based methods, which focus on the complementarity of the compounds of interest with the binding site of the target protein. (27) In recent decades, the identification of new lead compounds in the early stages of drug discovery has been greatly aided by high-throughput screening (HTS), which is the experimental screening of huge chemical libraries against a biological target. However, HTS depends on the size of the compound library and necessitates costly facilities and equipment. The creation of in silico virtual screening (VS) has been prompted by the high expense and low hit rate of HTS. (28)

A computational method called virtual screening looks through libraries of small molecules to find the structures that have the highest chance of attaching to a therapeutic

target. Its distinct advantages over experimental HTS have made it an essential step in early-stage drug development today: related to the medication target, the low success rates of early HTS experiments and the real costs associated with testing large numbers of samples have meant that the emphasis is now on quality rather than quantity, with screening sets being carefully designed in order to increase the chances of finding good hits. (29) Virtual screening includes a broad range of computational methods, with the specific method used based on the biological endpoint's information and the screening set's intended purpose. The methods can be separated into two categories: structure-based virtual screening, which uses the biological target's 3D structure to find compounds that might bind to it, and ligand-based virtual screening, which is employed when the biological target's 3D structure is unknown (30). Three distinct ligand-based virtual screening scenarios are described by Wilton and colleagues. Similarity searching is the most widely utilized method in the early stages of a drug discovery program, when little is known about the target but an active chemical, such as a compound from the literature, is available. (31) Pharmacophore elucidation and database searching can be employed when several activities are known but no inactive ones are available (32).

6. The Rise of Machine Learning and Artificial Intelligence in Drug Discovery:

AI Contribution to Drug Development and Research. AI can be used to enhance nanosystem design, expand the

present drug testing modeling system, and increase the accuracy of parameter and factor selection in drug design, drug discovery, and drug repurposing methods. It also helps to better understand the mechanism of membrane interaction with the modeled human environment by studying drug permeation, simulation, human cell targets, etc.

It has revolutionized drug research and discovery in numerous ways. Some of the key contributions of AI in this domain include the following:

1. **Target Identification**

AI systems can analyze diverse data types, such as genetic, proteomic, and clinical data, to identify potential therapeutic targets. By uncovering disease-associated targets and molecular pathways, AI assists in the design of medications that can (33) modulate biological processes.

2. **Virtual Screening**

AI enables the efficient screening of vast chemical libraries to identify drug candidates that have a high likelihood of binding to a specific target. By simulating chemical interactions and predicting binding affinities, (34) AI helps researchers prioritize and select compounds for experimental testing, saving time and resources.

3. **Structure-Activity Relationship (SAR) Modeling**

AI models can establish links between the chemical structure of compounds and their biological activity. This allows researchers to optimize drug candidates by designing molecules with desirable features, such as high potency, selectivity (35), and favorable pharmacokinetic profiles.

4. **De Novo Drug Design**

Using reinforcement learning and generative models, AI algorithms can propose novel drug-like chemical structures. By learning from chemical libraries and experimental data, AI expands the chemical space and aids in the development of innovative drug candidates. (36)

5. **Optimization of Drug Candidates**

AI algorithms can analyze and optimize drug candidates by considering various factors, including efficacy, safety, and pharmacokinetics. This helps researchers fine-tune therapeutic molecules to enhance their effectiveness while minimizing potential side effects. (37)

6. **Drug Repurposing**

AI techniques can analyze large-scale biomedical data to identify existing drugs that may have therapeutic potential for different diseases. By repurposing approved drugs for new indications, AI accelerates the drug discovery process and reduces costs. (38)

7. **Toxicity Prediction:**

By examining the chemical makeup and properties of molecules, artificial intelligence (AI) algorithms are able to forecast the toxicity of drugs. Toxicological databases can be used to train machine learning algorithms that can detect dangerous structural characteristics or predict negative effects. This aids scientists in prioritizing safer compounds and reducing the possibility of negative clinical trial reactions. (39) All things considered, AI-driven methods in drug research and development have the potential to simplify and accelerate the process of finding, refining, and creating new therapeutic candidates, which will ultimately result in more effective and efficient drugs.

7. In silico prediction of ADMET properties:

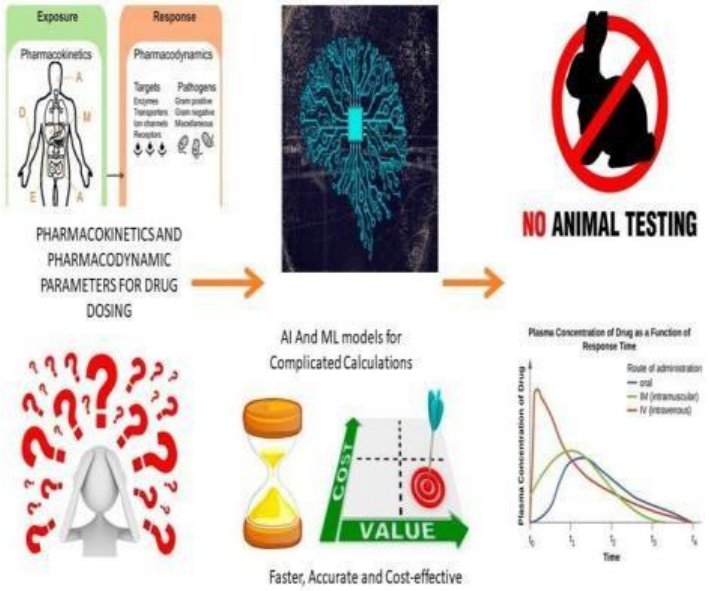


FIGURE 2 : Role of AI in PK/ PD studies.

Pharmacokinetic studies include absorption (A), distribution (D), metabolism (M), and excretion (E) studies. A pharmacodynamic study includes the drug's effect on the target. Understanding the effect of drug molecules and their distribution requires a large number of calculations. A smaller miscalculation or missed dataset may lead to a huge error that may be critical. AI helps to accelerate complicated calculations without missing datasets and provides more accurate, faster, and cost-effective results. It converts complicated data into easily understandable and representable graphs, which might help to identify the root cause of the problem. It can also help to minimize animal studies by calculating the impact of different conditions, such as enzymes, diseased conditions, dosing differences, patient data, etc., in different animals and reduce the number of animals required for clinical trials. Drug discovery, preclinical research, clinical trials, and regulatory approval are all steps in the intricate process of developing new drugs.

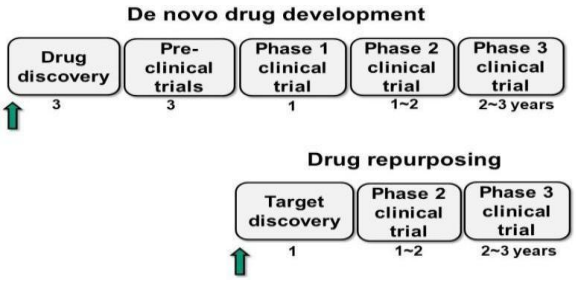
Because they establish the ideal dosage, mode of administration, and safety of a medicine in the body, pharmacokinetics and pharmacodynamics are essential components of drug development. Pharmacokinetic and pharmacodynamic investigations using traditional experimental methods can be costly and time-consuming, and they might not always yield reliable forecasts of a drug's safety and efficacy (40)**.** These methods use statistical and learning approaches, molecular descriptors and experimental data to model complex biological processes (e.g. oral bioavailability, intestinal absorption, permeability and mutagenicity(41). The well-known guidelines for drug-likeness, lead-likeness, or metabolite-likeness (42) that are based on basic physicochemical characteristics are also used in openly accessible and commercially available packages (43). All of these methods have drawbacks, though, including the infrequent availability of high-quality experimental data and their propensity to overlook direct structural information about the ADMET proteins. As a result, in silico methods based on the three- dimensional structures of these proteins might be a desirable substitute or addition to ADMET data-modeling methods about ten years ago the first attempts to predict ADMET based on atomic-level protein structures began with the early homology models of human cytochrome p450 cyp(44) recently a number of novel studies have been published that take advantage of molecular docking the 3d structures of ADMET proteins and various approaches to account for protein flexibility during the procedure all of them emphasize how challenging it is to study these proteins partly due to their huge flexible ligand-binding cavities that can interact with a variety of ligands the majority of these studies concentrate on cyp and other phase i metabolizing enzymes see to refs (45,46)for recent significant reviews.

8. In Silicon Approaches to Drug Repurposing:

A strategy known as "drug repurposing" (or "drug repositioning"), which was initially presented by Ashburn and Thor in 2004[2], has started to bridge the gap left by the inefficiency of traditional drug development in this setting by identifying new indications and targets for already marketed medications. [47] The main benefit of drug-repurposing strategies is that they lower the development risk because preclinical data and clinical profiles (pharmacokinetic, pharmacodynamic, and toxicity) are already accessible for an existing medicine. As a result, the therapeutic compound can quickly move into late-stage clinical trials, cutting down on time and expense associated with research. [48] Thus, it should come as no surprise that over 30% of recently authorized medications in the United States are repositioned medications. Repurposing drugs can be

done computationally or empirically. The latter strategy, which falls under the field of computational pharmacology, is also known as "in silico drug repurposing" [49]. Finding new uses for an existing drug (drug-centric) and finding effective drugs for an illness (disease-centric) are two categories of in silico drug repurposing. Both use the similarity evaluation method between drugs and/or diseases. [50] A review of different computational repurposing techniques was conducted by Jin and Wong. [51].

The following two technological trends have enabled the creation of in silico drug repurposing and its widespread application today. [52] The first trend is the generation and accumulation of high-throughput data from multiple sources, such as proteomics, chemo-proteomics, phenomics, and genomes. This has led to the availability of complete pathway maps in addition to information describing disease characteristics and medication profiles. The second is that repurposing algorithms, retrospective analysis, and database management for experimental data have all been made possible by developments in computational and data sciences. [53].



FLOW CHART 4: de novo drug development and drug repurposing

Conceptual diagram of de novo drug development and drug repurposing; the arrow denotes the initiation time in each scenario and the number denotes a period of time in years. In this figure, the objective of drug repurposing was assumed to be to identify or discover new targets for a drug marketed. Note that drug repurposing begins with target discovery for an existing drug, directly followed by phase 2 and 3 clinical trials, while animal and phase 1 clinical studies were not conducted as results for these studies are already available for an existing drug.

Drug repurposing strategies

1. Knowledge-based repurposing

In this repurposing strategy, utilizing the drug-related information, including drug targets, chemical structures, pathways, adverse effects, etc., models are built to predict unknown targets, bio-markers or mechanisms for diseases.[54] This strategy includes target-based, pathway-based, and target mechanism-based drug-repurposing**.**

2. Target-based drug-repurposing

Given proteins or biomarkers of interest, target-based drug-repurposing comprises high-throughput and/or high-content screening (HTS/HCS) of drug compounds,[55] followed by in silico screening of drug compounds from drug libraries, such as ligand-based screening or docking.[56] Compared with blinded search or screening which does not use biological or pharmacological information when screening, target-based repurposing directly links targets with disease mechanisms and therefore the likelihood of drug discovery significantly improves. The advantage of the target-based approach lies in its ability to screen nearly all drug compounds with known chemical structure. However, target-based methods cannot identify unknown mechanisms beyond the targets already known.

3. Pathway-based drug-repurposing

Pathway-based drug-repurposing utilizes metabolic pathways, signaling pathways, and protein-interaction networks information to predict the similarity or connection between disease and drug. For example, using omics data processed from human patients or animals, disease-specific pathways are reconstructed to serve as new targets for repositioned drugs [57].

4. Target mechanism-based drug-repurposing

Target mechanism-based drug repurposing integrates signaling pathway information, treatment omics data, and protein interaction networks to discover new mechanisms of action for drugs.

[58] The necessity of precision medicine, which has been increasingly important, motivates such drug-repurposing approaches. The advantage of these repurposing approaches is that they aim to discover the mechanisms related not only to diseases or drugs but also to drug treatments for specific diseases.

5. Signature-based repurposing

In signature-based repurposing, gene signature information obtained from disease omics data [59] is used to discover new off-targets or mechanisms of disease. This approach searches inverse drug–disease relationships by comparing gene expression profiles between drug and disease. In the work by Dudley et al. [60], potential drug–disease pairs were investigated for inflammatory bowel disease (IBD), where gene expression profiles obtained from the Gene Expression Omnibus database [61] were compared with gene expression profiles comprising 164 drug compounds obtained from the Connectivity Map.As a result, unknown drug–disease pairs were discovered, with one pair validated in preclinical models. The advantage of these approaches is that they identify new mechanisms of action for drugs. Also, unlike knowledge-based methods, more molecular- and/or genetic-level mechanisms are involved in these methods.

6. Phenotype-based repurposing

The phenotypic information has become available as a new source of drug repositioning. In recent years, this type of information has been increasingly used by systems approaches to detect genetic traits associated with human diseases. Natural language processing skills applied to electronic health records (EHRs) can reveal additional adverse drug events that were not observed during drug development. For example, mining EHRs helped in identifying that metformin can be repurposed for cancer treatment.

9. Integration of In Silico and Experimental Approaches: A Synergistic Paradigm

The human epidermal growth factor receptor 2 (HER2) is a receptor that spans the cell membrane and acts as a tyrosine kinase, playing a crucial role in cell growth, survival, and differentiation. Its expression levels significantly influence cell behavior, with overexpression occurring in 30% of breast cancer cases. Additionally, this overexpression is linked to increased tumor aggressiveness and a higher likelihood of relapse. (62) Trastuzumab is the most commonly used medication for targeting HER2; it is a humanized monoclonal antibody that binds to an extracellular domain of HER2, effectively inhibiting its functions and reducing the growth and survival of cancer cells. Recent advancements in recombinant antibody technology have significantly enhanced the ability to genetically manipulate antibody (63) fragments. Putative target, falling into the category of the so-called targeted therapies.

Additionally, nanoparticles opened up new perspectives for the next generation of targeted therapies due to their recognized ability to improve drug packaging, delivery and targeting efficiency [3]. Among others, the viral nanoparticles (VNP) appear as promising and exciting nanoplatforms to be used as drug delivery systems due their biocompatibility and biodegradability. Taken all together, our main aim was the design and production of a biomimetic vector containing thesc Fvoftrastuzumab, a well-known anti-HER2 antibody, as a targeting fused with HIV viral protein gp41. HIV-based VNPs show strong invivo immunogenicity [64] and have been amplified in clinical environment [65]. Docking studies were performed in order to select the most favorable residue in the viral protein to be considered to fuse with as Fvofrtrastuzumab, after which DNA plasmid was produced. Here, we intended to provide an ovel approach to constructing a new recombinant protein from two separate ones. This undocumented approach can provide a new strategy for targeted therapy using recombinant proteins to be expressed into NPs that will be designed in silico method (66).

10. Case Studies and Success Stories Of In Silico Drug Discovery:

In silico experiments, essentially "experiments on a computer," are revolutionizing how we approach scientific research. Think of it as using the power of computational modeling and simulation to explore biological, chemical, and even physical systems.

a. Case Study: Accelerating Drug Discovery for Fibrosis

Insilico Medicine, a company specializing in artificial intelligence for drug discovery, used its in silico platforms, PandaOmics and Chemistry42, to tackle fibrosis. Traditionally, bringing a drug from target identification to validation can take years and cost a fortune.

However, by leveraging AI and machine learning on vast datasets, Insilico was able to:

* Rapidly identify promising drug targets: PandaOmics sifted through millions of data points to pinpoint key biomarkers associated with fibrosis.

* Design novel drug candidates: Chemistry42 then used this information, along with experimental data and physics-based methods, to design specific small molecule modulators.They were able to bring a fibrosis drug candidate from target discovery to compound validation in under 18 months for just $2.6 million. This is a stark contrast to the average of 4.5 years and $674 million using conventional methods!

insightful:

* Speed and Efficiency: In silico methods drastically cut down the time and cost associated with traditional lab-based research. You can test countless hypotheses and compounds virtually before even stepping into a wet lab.

* Targeted Approach: These experiments allow for a much more focused approach, identifying the most promising avenues for further investigation.
* Ethical Considerations: By reducing the reliance on animal testing and optimizing clinical trial design, in silico methods also contribute to more ethical research practices.

Vibrant Connections:

* This isn't just about drug discovery! In silico experiments are being used in diverse fields, from understanding disease mechanisms (like cancer) to optimizing bioprocesses and even designing new materials.
* The integration of AI and machine learning is a game-changer, allowing us to analyze complex biological data in ways never before possible.

Straightforwardly Speaking:

* In silico doesn't replace traditional research entirely. It's a powerful tool that complements and enhances it. The findings from computer simulations still need to be validated through in vitro (in the lab) and in vivo (in living organisms) experiments**.**

b. Case Study: Rapid Identification of a Novel Drug Candidate for Hepatocellular Carcinoma (HCC)

Hepatocellular carcinoma (HCC), a type of liver cancer, has a poor prognosis and limited treatment options. Recognizing the urgent need for new therapies, researchers embarked on a project leveraging the power of both protein structure prediction and AI-driven drug design.

In silico methods played a pivotal role:

* Target Identification with AI: Insilico Medicine's AI-powered target discovery engine, PandaOmics, analyzed vast amounts of biological data to identify a promising protein target, Cyclin-Dependent Kinase 20 (CDK20), implicated in HCC progression. Notably, at the time, there was limited structural information available for this target.
* Structure Prediction with AlphaFold: DeepMind's groundbreaking AlphaFold technology stepped in to predict the 3D structure of the CDK20 protein with remarkable accuracy. This predicted structure provided crucial insights into potential binding sites for drug molecules.
* Generative AI for Drug Design: Insilico's Chemistry42 platform, a generative chemistry engine, utilized the predicted CDK20 structure to design novel small molecule inhibitors. This involved virtually screening and optimizing a vast library of potential drug candidates to find molecules that could effectively bind to and inhibit CDK20.
* Rapid Hit Identification: The integration of Alpha Folds structural information with Chemistry42's design capabilities allowed the researchers to rapidly identify a promising "hit" compound with nanomolar potency in just 30 days after selecting the target.
* Further Optimization: The initial hit compound served as a starting point for further rounds of in silico design, synthesis, and testing, leading to the identification of even more potent and selective drug candidates.

Insightful Highlights:

* Synergy of AI Tools: This case beautifully illustrates the power of combining different in silico approaches—AI for target discovery and generative AI guided by AI- predicted protein structures for drug design.
* Addressing "Dark Targets": AlphaFold's ability to accurately predict the structure of proteins with limited experimental data opens up new possibilities for targeting previously undruggable or poorly understood proteins.
* Accelerated Timeline: The ability to go from target identification to a potent hit compound in just one month showcases the dramatic time savings offered by these technologies.

Vibrant Connections:

* This success highlights the growing importance of publicly available resources like the AlphaFold Protein Structure Database in accelerating scientific discovery.
* The integration of AI with robotics and automation in high-throughput screening further amplifies the speed and efficiency of the drug discovery process.

Straightforwardly Speaking:

* While this case demonstrates a significant acceleration in the early stages of drug discovery, the identified drug candidates still need to undergo rigorous preclinical testing and clinical trials to confirm their safety and efficacy in treating HCC.

Warm Reflection:

This collaboration between AI-driven target discovery and AI-powered protein structure prediction represents a

significant leap forward in our ability to rapidly identify potential drug candidates for challenging diseases like liver cancer. It offers a compelling vision of a future where computational tools play an increasingly central role in the fight against diseases.

Challenges and Limitations of Current In Silicon Method:

Because of their many benefits, the pharmaceutical industry is constantly researching tiny molecules to provide better products and increase customer happiness. While the preparation of synthetic derivatives is cost-effective, the chemical synthesis process is straightforward. Therefore, the pharmacy industry has a wide variety of stable and effective small-molecule-loaded formulations. With the exception of rare disease treatments, generic molecules compete with numerous novel small molecules, and their introduction necessitates complicated data and clinical trials. These procedures put more financial pressure on businesses to innovate more. To make up for the problem brought on by the small molecular size and the inadequate distribution of research and inventions, the biomolecular medication business is nevertheless expanding quickly

The spatial conformation and supramolecular sequence also affect their stability and function [68]. Adalimumab and insulin are two examples of biomolecules that have achieved great success. Since infusion is the most practical and preferred method of administering these macromolecules, their pharmacokinetic characteristics are complicated. Important facets of nucleic acid-based research include molecular stability and pharmacokinetic regulation. Enhancement and pharmacokinetic exposure of these molecular forms are important objectives. To overcome these obstacles and resolve associated problems, new technical developments could be beneficial [68,69] AI has enormous potential for improving medicine delivery and discovery, but it also has significant drawbacks that eventually necessitate human intervention or experts to decipher the intricate outcomes.

The datasets provide the basis of AI predictions, but because of the gray area, human intervention is necessary to interpret the results and arrive at the right conclusion. When it comes to processing data for predictions and evaluating hypotheses, AI may encounter problems with algorithm bias. Furthermore, inactive molecules are frequently found using docking simulations [70]. To rule out system bias issues, a critical review of these characteristics still necessitates human involvement for efficient decision-making and cross-verifications. However, AI has enormous potential for use; therefore, a lot of effort could be made to lessen its drawbacks and make it more dependable and efficient [70].In terms of AI, the approach used makes use of machine learning or its subsets, including natural language processing and deep learning. Both supervised and unsupervised learning are possible, and the kind of algorithm used is also very important. Unlike unsupervised learning, which works with unknown outcomes, supervised learning is a machine learning process that uses known inputs (features) and outputs (labels or targets). Using a variety of inputs or attributes, the supervised technique predicts output, such labels or targets. Conversely, the goal of unsupervised classification is to form feature- homogeneous groupings [71].

Lack of Clinical Expertise

While AI can identify correlations, it is essential to recognize that individual patient therapies can vary despite these correlations. AI algorithms typically operate on a statistical framework, which may limit their comprehension of the intricate factors and the profound effects certain parameters can have. The complex nature, where treatment decisions are influenced by various individualized factors, poses a challenge for AI models primarily focused on statistical associations [75]. Therefore, the ability of AI to fully capture the critical aspects and implications of specific parameters may be limited. [76]

11. Future direction and Perspectives

Future Perspectives:

* Shifting from Prediction to Design: In silico methods will increasingly move beyond simply predicting the properties of existing molecules to actively designing novel molecules with desired characteristics from the outset.Accelerating Drug Discovery Timelines: The integration of advanced in silico tools has the potential to significantly shorten the drug discovery and development timeline, bringing new therapies to patients faster and more cost-effectively.
* Addressing Neglected Diseases and Pandemic Preparedness: In silico approaches can be rapidly deployed to identify potential drug candidates for neglected diseases or emerging infectious threats, as demonstrated during the COVID-19 pandemic.
* Reducing Reliance on Animal Testing: More accurate and predictive in silico models can contribute to the "3Rs" principles (Replacement, Reduction, Refinement) in animal research by reducing the need for animal testing in early drug development.
* Democratization of Drug Discovery: User-friendly in silico platforms and open- access databases

could empower a wider range of researchers and institutions to participate in drug discovery efforts.

* Convergence with Other Technologies: The synergy between in silico methods and other technologies like CRISPR-Cas9 gene editing and synthetic biology will open up new avenues for therapeutic development.

II. CONCLUSION:

In conclusion, in silico drug discovery has evolved into a powerful and indispensable paradigm in pharmaceutical research. By integrating computational methodologies like SBDD, LBDD, virtual screening, and ADMET prediction alongside the burgeoning influence of machine learning and AI, the field offers significant advantages in accelerating lead identification, optimizing drug candidates, and reducing development costs. While challenges and limitations remain, the synergistic integration of in silico and experimental approaches, as evidenced by successful case studies, underscores its potential to revolutionize the drug discovery pipeline and pave the way for more efficient and targeted therapeutic interventions in the future.

REFERENCES:

[1]. Wouters O.J., McKee M., Luyten J. Estimated research and development investment needed to bring a new medicine to market, 2009–2018. Jama. 2020;323:844–853.
[2]. Wong C.H., Siah K.W., Lo A.W. Estimation of clinical trial success rates and related parameters. Biostatistics. 2019;20:273–286.
[3]. Paul S.M., Mytelka D.S., Dunwiddie C.T., Persinger C.C., Munos B.H., Lindborg S.R.,
[4]. Schacht A.L. How to improve R&D productivity: The pharmaceutical industry's grand
[5]. challenge. Nat. Rev. Drug Discov. 2010;9:203–214.
[6]. Schneider, G. (2010). Virtual screening: an endless staircase**?** Nature Reviews Drug Discovery, 9(1), 27-39.
[7]. Lipinski, C. A. (2004). Lead-and drug-lik**e** compounds: the rule of five ten years after. Drug discovery today, 9(7), 337-341.
[8]. Kitchen, D. B., Decornez, H., Furr, J. R., & Bajorath, J. (2004). Docking and scoring in drug discovery: methods and applicat**i**ons**.** Nature reviews drug discovery, 3(11), 935- 949.
[9]. Cheng, T.; Li, Q.; Zhou, Z.; Wang, Y.; Bryant, S.H. Structure-based virtual screening for drug discovery: A problem-centric review. AAPS J. 2012, 14, 133–141.
[10]. Song, C.M.; Lim, S.J.; Tong, J.C. Recent advances in computer-aided drug design. Brief. Bioinform. 2009, 10, 579–591
[11]. 9,10. Lavecchia, A.; di Giovanni, C. Virtual screening strategies in drug discovery: A critical review. Curr. Med. Chem. 2013, 20, 2839–2860
[12]. Lavecchia, A.; Cerchia, C. In silico methods to address polypharmacology: Current status, applications and future perspectives. Drug Discov. Today 2016, 21, 288–298.
[13]. Moore, T.J.; Zhang, H.; Anderson, G.; Alexander, G.C. Estimated costs of pivotal trials for novel therapeutic agents approved by the US food and drug administration, 2015– 2016. JAMA Intern. Med. 2018, 178, 1451–1457Swinney, D.C.; Anthony, J. How were new medicines discovered? Nat. Rev. Drug Discov. 2011, 10, 507–519.
[14]. Ferreira, L.G.; dos Santos, R.N.; Oliva, G.; Andricopulo, A.D. Molecular docking and structure-based drug design strategies. Molecules 2015, 20, 13384–13421.
[15]. Anderson, A.C. The process of structure-based drug design. Chem. Biol. 2003, 10, 787–797
[16]. Lionta, E.; Spyrou, G.; Vassilatis, D.K.; Cournia, Z. Structure-based virtual screening for drug discovery: Principles, applications and recent advances. Curr. Top. Med. Chem. 2014, 14, 1923–1938
[17]. Kaliyamoorthy, S.; Chen, Y.P. Structure-based drug design to augment hit discovery. Drug Discov. Today 2011, 16, 831–839
[18]. Searls, D.B. Data integration: Challenges for drug discovery. Nat. Rev. Drug Discov. 2005, 4, 45–58.
[19]. Young DC. Computational drug design: a guide for computational and medicinal chemists. Wiley-Interscience; 2009
[20]. Overington JP, Al-Lazikani B, Hopkins AL. Nat Rev Drug Discov. 2006;5:993–996.
[21]. Costanzi S, Tikhonova IG, Harden TK, Jacobson KA. Journal of Computer-Aided Molecular Design. 2009;23:747–754.
[22]. Fischer E. Bericht der Deutschen Chemischen Gesellschaft.1894;27:2985–29:93.
[23]. Gillet VJ, Willett . Compound selection using measures of similarity and dissimilarity In Comprehensive medicinal chemistry II. Elsevier; 2007.
[24]. Strategies in the Search for New Lead Compounds or Original Working HypothesesG. Chemoinformatics
[25]. Lavecchia A, Di Giovanni C. Virtual screening strategies in drug discovery: a critical review. Curr. Med. Chem. 2013;20(23):2839–2860.
[26]. Andricopulo A.D, Salum L.B, Abraham D.J. Structure-based drug design strategies in medicinal chemistry. Curr. Top. Med. Chem. 2009;9(9):771–790
[27]. Ananda Krishnan R, Aguilar B, Onufriev A.V. Onufriev, A.V. H++ 3.0: automating pK prediction and the preparation of biomolecular structures for atomistic molecular modeling and simulation. NucleicAcidsRes.2012;40:W537-41–W541
[28]. Mattos C. Protein-water interactions in a dynamic world. Trends Biochem. Sci. 2002;27:203–208
[29]. Shah H., Chavda V., Soniwala M.M. Bioinformatics Tools for Pharmaceutical Drug Product Development. Wiley; Hoboken, NJ, USA: 2023. Applications of Bioinformatics Tools in Medicinal Biology and Biotechnology; pp. 95–116
[30]. Jenkins J.L., Bender A., Davies J.W. In Silico Target Fishing: Predicting Biological Targets from Chemical Structure. Drug Discov. Today Technol. 2006;3:413–421
[31]. to Target Prediction Taking Ligand Promiscuity into Account. J. Cheminform. 2015;7:24
[32]. Wang L., Xie X.-Q. Computational Target Fishing: What Should Chemogenomics Researchers Expect for the Future of in Silico Drug Design and Discovery? Future Med. Chem. 2014;6:247–249
[33]. Iorio F., Bosotti R., Scacheri E., Belcastro V., Mithbaokar P., Ferriero R., Murino L., Tagliaferri R., Brunetti-Pierri N., Isacchi A., et al. Discovery of Drug Mode of Action and Drug Repositioning from Transcriptional Responses. Proc. Natl. Acad. Sci. USA. 2010;107:14621–14626.
[34]. Begam B.F., Kumar J.S. A Study on Cheminformatics and Its Applications on Modern Drug Discovery. Procedia Eng. 2012;38:1264–1275Lomenick B., Olsen R.W., Huang J. Identification of Direct Protein Targets of Small Molecules. ACS Chem. Biol. 2011;6:34– 46.
[35]. Pushpakom S., Iorio F., Eyers P.A., Escott K.J., Hopper S., Wells A., Doig A., Guilliams T., Latimer J., McNamee C., et al. Drug

Repurposing: Progress, Challenges and Recommendations. Nat. Rev. Drug Discov. 2019;18:41–58.
[36]. Zhuang X., Lu C. PBPK Modeling and Simulation in Drug Research and Development. Acta Pharm. Sin. B. 2016;6:430–440
[37]. Healthcare Artificial Intelligence, Causal Machine Learning & Data Analytics—GNS Healthcare. [(accessed on 5 May 2023)].
[38]. Jones H., Rowland-Yeo K. Basic Concepts in Physiologically Based Pharmacokinetic Modeling in Drug Discovery and Development. CPT Pharmacomet. Syst. Pharmacol. 2013;2:63.
[39]. Obrezanova O. Artificial Intelligence for Compound Pharmacokinetics Prediction. Curr. Opin. Struct. Biol. 2023;79:102546.
[40]. Mhatre S., Shukla S., Chavda V.P., Gandikota L., Patravale V. Bioinformatics Tools for Pharmaceutical Drug Product Development. Wiley; Hoboken, NJ, USA: 2023. AI and ML for Development of Cell and Gene Therapy for Personalized Treatment; pp. 371–400.
[41]. Chou W.-C., Lin Z. Machine Learning and Artificial Intelligence in Physiologically Based Pharmacokinetic Modeling. Toxicol. Sci. 2023;191:1–14
[42]. Van Tran T.T., Tayara H., Chong K.T. Artificial Intelligence in Drug Metabolism and Excretion Prediction: Recent Advances, Challenges, and Future Perspectives. Pharmaceutics. 2023;15:1260.
[43]. Munos BH, Chin WW. How to revive breakthrough innovation in the pharmaceutical industry. Sci Transl Med. 2011;3:89cm16.
[44]. Novak N. Challenges and opportunities of drug repositioning. Trends Pharmacol Sci. 2013;34:267–272.
[45]. Shim JS, Liu JO. Recent advances in drug repositioning for the discovery of new anticancer drugs. Int J Biol Sci. 2014;10:654–663
[46]. Jin G, Wong ST. Toward better drug repositioning: Prioritizing and integrating existing methods into efficient pipelines. Drug Discov Today. 2014;19:637–644
[47]. Hodos RA, Kidd BA, Shameer K, Redhead BP, Dudley JT. In silico methods for drug repurposing and pharmacology. Wiley Interdiscip Rev Syst Biol Med. 2016;8:186–210.
[48]. Emig D, Ivliev A, Pustovalova O, Lancashire L, Bureeva S, Nikolsky Y, et al. Drug Target Prediction and Repositioning Using an Integrated Network-Based Approach. PLoS ONE. 2013;8:e60618.
[49]. Swamidass SJ. Mining small-molecule screens to repurpose drugs. Brief Bioinform. 2011;12:327–335
[50]. Doman TN, McGovern SL, Witherbee BJ, Kasten TP, Kurumbail R, Stallings WC, et al. Molecular docking and high-throughput screening for novel inhibitors of protein tyrosine phosphatase-1B. J Med Chem. 2002;45:2213–2221.
[51]. Jadamba E, Shin M. A Systematic Framework for Drug Repositioning from Integrated Omics and Drug Phenotype Profiles Using Pathway-Drug Network. BioMed Res Int. 2016;2016:7147039.
[52]. Jin G, Fu C, Zhao H, Cui K, Chang J, Wong ST. A novel method of transcriptional response analysis to facilitate drug repositioning for cancer therapy. Cancer Res. 2012;72:33–44
[53]. Haeberle H, Dudley JT, Liu JT, Butte AJ, Contag CH. Identification of cell surface targets through meta-analysis of microarray data. Neoplasia. 2012;14:666–669.
[54]. Barrett T, Suzek TO, Troup DB, Wilhite SE, Ngau WC, Ledoux P, et al. NCBI GEO: mining millions of expression profiles—database and tools. Nucleic Acids Res. 2005;33:D562–D566
[55]. Lamb J, Crawford ED, Peck D, Modell JW, Blat IC, Wrobel MJ, et al. The Connectivity Map: using gene-expression signatures to connect small molecules, genes, and disease. Science. 2006;313:1929–1935.
[56]. Dudley JT, Sirota M, Shenoy M, Pai RK, Roedder S, Chiang AP, et al. Computational repositioning of the anticonvulsant topiramate for inflammatory bowel disease. Sci Transl Med. 2011;3:96ra76. Hebbring SJ. The challenges, advantages and future of phenome-wide association studies. Immunology. 2014;141:157–165.
[57]. Holliger,P.;Hudson,P.J.EngineeredAntibodyFragmentsandtheRiseofSingleDomains.Na t.Biote chnol.2005,23,1126–1136.
[58]. Monnier,P.;Vigouroux,R.;Tassew,N.InVivoApplicationsofSingleChainFv(VariableDom
[59]. ain)(Sc Fv)Fragments.Antibodies 2013,2,193–208,
64.Gulati,N.M.;Stewart,P.L.;Steinmetz,N.F.BioinspiredShieldingStrategiesforNanoparticle Drug DeliveryApplications.Mol.Pharm.2018,15,2900–2909.
[60]. Steinmetz,N.F.ViralNanoparticlesasPlatformsforNext- GenerationTherapeuticsandImagingDe
[61]. vices.Nanomed.Nanotechnol.Biol.Med.2010,6,634 -- 641.
[62]. Watkins,J.;Marsh,A.;Taylor,P.C.;Singer,D.R.J.PersonalizedMedicine:TheImpactonChe mistry. Ther.Deliv.2010,1,651–66
[63]. Caravella,J.;Lugovskoy,A.DesignofNext- GenerationProteinTherapeutics.Curr.Opin.Chem.Bi
[64]. ol.2010,14,520–528.
[65]. Wise J., Möller A., Christie D., Kalra D., Brodsky E., Georgieva E., Jones G., Smith I., Greiffenberg L., McCarthy M., et al. The Positive Impacts of Real-World Data on the Challenges Facing the Evolution of Biopharma. Drug Discov. Today. 2018;23:788–801.
[66]. Taylor D., Bowden S.G., Knorr R., Wilson D.R., Proudfoot J., Dunlop A.E. The Pistoia Alliance Controlled Substance Compliance Service Project: From Start to Finish. Drug Discov. Today. 2015;20:175–180.
[67]. Lee C.K.H., Choy K.L., Chan Y.N. A Knowledge-Based Ingredient Formulation System for Chemical Product Development in the Personal Care Industry. Comput. Chem. Eng. 2014;65:40–53.
[68]. Sarker I.H. AI-Based Modeling: Techniques, Applications and Research Issues Towards Automation, Intelligent and Smart Systems. SN Comput. Sci. 2022;3:158.
[69]. .Dara S., Dhamercherla S., Jadav S.S., Babu C.M., Ahsan M.J. Machine Learning in Drug Discovery: A Review. Artif. Intell. Rev. 2022;55:1947–1999
[70]. Wang N., Sun H., Dong J., Ouyang D. PharmDE: A New Expert System for Drug- Excipient Compatibility Evaluation. Int. J. Pharm. 2021;607:120962
[71]. Zarrinpar A., Lee D.-K., Silva A., Datta N., Kee T., Eriksen C., Weigle K., Agopian V., Kaldas F., Farmer D., et al. Individualizing Liver Transplant Immunosuppression Using a Phenotypic Personalized Medicine Platform. Sci. Translate. Med. 2016;8:333.
[72]. 220.Sarmadi A., Hassanzadeganroudsari M., Soltani M. Bioinformatics Tools for Pharmaceutical Drug Product Development. Wiley; Hoboken, NJ, USA: 2023. Artificial Intelligence and Machine Learning Applications in Vaccine Development; pp. 233–253.
[73]. Uddin M., Wang Y., Woodbury-Smith M. Artificial Intelligence for Precision Medicine in Neurodevelopmental Disorders. NPJ Digit. Med. 2019;2:112