ijlpr 2023; doi 10.22376/ijlpr.2023.13.5.P130-P148

International Journal of Life science and Pharma Research

ISSN 2250-0480

Review Article

Silico Drug Design for Anticancer Drugs

Techniques and Tools for *in Silico* Drug Design for the Development of Anticancer Drugs

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Abstract: This review focuses on different techniques used in the in-silico drug design, such as molecular modeling, molecular docking, pharmacophore mapping, QSAR, and more, and also highlights and looks at how these techniques are being used to create new potential anticancer drugs for their effective cancer treatments. Most of the article studies focus on In-silico approaches only but rarely on the In-silico approach used to develop anticancer drugs with effective targets. Cancer, which is caused by pathophysiological changes in the normal process of cell division, has become a serious disorder that kills a lot of people every year all over the world. Recently, more than 19.3 million (19,300,000) new instances of cancer were identified and reported; based on the available data, this will result in almost 10 million fatalities in 2020. The necessity and desire for powerful medications to treat various malignancies have been sparked by the persistently rising occurrences of cancer worldwide, resulting in millions of deaths each year. Developing new anticancer drugs is a high priority for researchers and medical professionals, and designing these anticancer drugs is challenging, expensive, and time-consuming. In-silico drug design, also known as computer-aided drug discovery/design (CADD) approaches, have been created to get around these restrictions and manage massive amounts of emerging data. It is possible to use computational tools to aid in the design of experiments and, more crucially, to clarify the links between structure and activity that underlie drug discovery and lead optimization techniques. To design effective new drugs, one should understand the molecular processes that cause cancer on the molecular level. In Silicodrug design is a powerful tool for understanding these molecular processes and developing new and effective anticancer drugs.

Keywords: In Silico, Cancer, Drug design, Docking, Pharmacophore, Quantitative Structure-Activity Relationship, and Virtual screening.

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Received On 30 January, 2023

Revised On 6 June, 2023

Accepted On 27 June, 2023

Published On 1 September, 2023

Funding This research did not receive any specific grant from any funding agencies in the public, commercial or not for profit sectors.

Citation K. Masilamani, B. Senthilnathan, M. Manoyogambiga, R. Gowri, M. Vigneshwar, R. Sathiyasundar, and K. Rajaganapathy , Techniques and Tools for in Silico Drug Design for The Development of Anticancer Drugs.(2023).Int. J. Life Sci. Pharma Res.13(5), P130-P148 http://dx.doi.org/10.22376/ijlpr.2023.13.5.P130-P148

1. INTRODUCTION

One of the biggest causes of morbidity and mortality in the globe is cancer. Based on the impacted cell type, there are approximately 200 different forms of cancer.[1] The Food and Drug Administration (FDA) authorized drugs, causes of each type of cancer, treatments, and other information are all provided in the National Cancer Institute (NCI) database.[1] The most likely cancers in 2022, according to NCI reports, will be melanoma of the skin, non-Hodgkin lymphoma, pancreatic cancer, prostate cancer, thyroid cancer, bladder cancer, breast cancer, colon and rectum cancer, endometrial cancer, kidney and renal pelvis cancer, leukemia, lung and bronchus cancer, and thyroid cancer. At first, cancer was thought to be caused by uncontrolled cell proliferation and division. Therefore, finding antiproliferative drugs was the focus of all research efforts. In contrast to slowly developing solid tumors, the success rates tend to be higher in lymphoid malignancies.[2] The researchers modified the pre-screening and screening procedures to account for all the various cell lines and cancer types. The prevention, identification, and treatment of cancer are all receiving significant financial support on a global scale. The development of anticancer agents is the main focus of several pharmaceutical industries and governmental and non-governmental organizations, including the British Cancer Research Campaign (CRC), the European Organization for Research and Treatment of Cancer (EORTC), and the US National Cancer Institute (NCI). The search for anticancer drugs began in 1937 by screening more than 3000 substances in a mouse S37 model.[3,4] Cytotoxic compounds, which date back to the 1950s, was recognized as the first generation of anticancer medications. In the drug development, substances with strong cytotoxic or cytostatic activity on cancer cell lines and inhibited tumor growth in murine tumor allografts or xenografts were chosen.[5] Most cytotoxic substances have been discovered by accident or purposefully targeting biological pathways important for cell division. The first anticancer medication created in 1949 and approved by the FDA was mechlorethamine (Mustargen), and this drug is highly producing mutagenic analogs of mustard gases. Since the 1990s, anticancer medication development has accelerated. More than 190 oncology treatments have received FDA approval in the last two decades. The FDA data indicates that a total of seven oncology medications have already been approved for use in 2016. (until April 25).[6,7] Additionally, it has been stated that the FDA has authorized nearly 300 indications for oncology medications, covering an average of 4.4 indications annually. Recent years have seen many new oncology drug approvals, giving patients new therapy alternatives. Oncology, though there is a robust level of pipeline activity, is still a difficult field for research and development. Anticancer medication discovery and design are challenging, expensive, and time-consuming processes. In-silico drug design, also known as computer-aided drug discovery/design (CADD) approaches, have been created to get around these restrictions and manage massive amounts of emerging data.[7,8] It is possible to use computational tools to aid in designing experiments and, more crucially, to clarify the links between structure and activity that underlie drug discovery and lead optimization techniques. The most widely used CADD techniques are those based on structure and ligand. Even more remarkable is the assimilation that these two complementary techniques provide. The rapid development of new anticancer therapies shows significant potential when combined with experimental and computational methods.[8] In Silicodrug design, homology modeling, molecular docking, and pharmacophore mapping are all molecular modeling techniques used to model and study the 3D structure of molecules. Homology modeling is a method of predicting the 3D structure of a molecule based on an existing sequence of related molecules. Molecular docking is a method of predicting the affinity of a molecule by understanding how it fits into a target molecule, especially an anticancer target.[9,10,11] Pharmacophore mapping is a method of understanding the requirements of a molecule to interact with a biological target, particularly cancer. These techniques are used in many areas of molecular research, such as drug discovery, protein structure prediction, and analysis. Together, they provide important insights into the structure and function of molecules, which are essential for developing new drugs and understanding their effects. They are also used in structure-based drug design and quantitative structure-activity relationships (QSAR) studies[12]. Another method indicating structure-based methods is a fragment-based drug design; the discovery of fragments or low molecular weight compounds that typically bind to the target of interest with limited affinity is the first step in the fragment-based drug design process. The fragments that produce high-quality contacts are further refined to create compounds with high affinity and selectivity. Most review studies focus on In-silico approaches only but rarely on In-silico approaches for anticancer drug development. Hence, in this review, we will explore the different techniques used in Silicodrug design, such as molecular modeling, molecular docking, pharmacophore mapping, QSAR, and more, and explore current macromolecular targets for anticancer drugs and highlights to look at how these techniques are being used to create new and effective treatments for cancer. Any medication that successfully treats malignant or cancerous disease is called an anticancer drug, often known as an antineoplastic drug[13]. Alkylating agents, antimetabolites, natural products, and hormones are a few of the main classifications of anticancer medications shown in Figure 1 Shown Figure-1. Moreover, various medications that do not belong to such classes yet have anticancer action are utilized to treat malignant diseases. Although it is more true to say that chemotherapy refers to the use of chemical substances to treat disease in general, chemotherapy is usually used synonymously with anticancer medications.

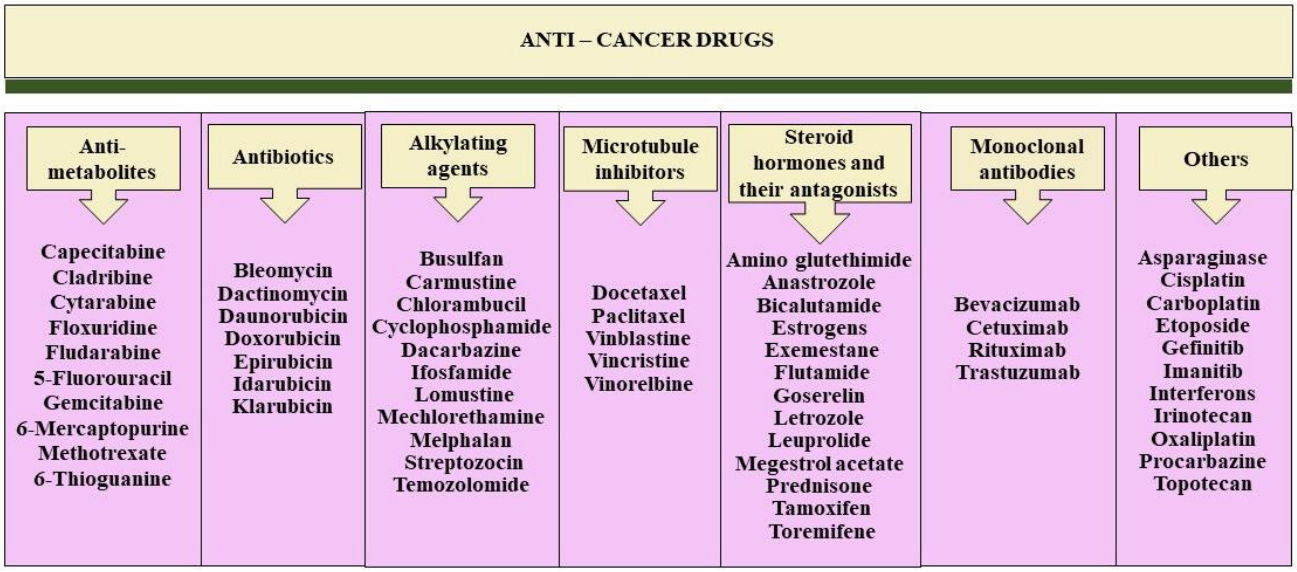

Fig 1: Flowchart for Anticancer drug classification[13,14]

Cancer cells become resistant to anticancer medications when we use them for a long time[14]. The following is a description of the mechanism through which this resistance arises:

1. A decrease in the number of drugs that cancer cells uptake: Cancer cells change how drugs enter their cells, lowering drug uptake. Consider the drug methotrexate[14].
2. An increase in medication evacuated by cancer cells: Cancer cells produce more reflux proteins, such as glycoprotein transporters, that expel medication from the cell. Vinblastine, Doxorubicin, Bleomycin, and Etoposide are a few examples [14].
3. A decrease in or change in the target molecule's sensitivity: The medicine uses a target molecule to pinpoint the cells in the body. Sometimes cancer cells alter these target molecules structurally or reduce their production so that medications do not recognize them. Take methotrexate, mercaptopurine, and doxorubicin as examples.
4. Cells' ability to repair DNA damage by producing more DNA repair enzymes: Several drugs function by causing DNA damage to cells. The medication loses its effectiveness when cancer cells make additional DNA repair enzymes. Alkylating agents, for instance, lose their effectiveness over time when used extensively[14].

A significant problem in cancer therapy is the highly complicated nature of the disease and the non-specificity of anti-cancer medications. The field of drug discovery in cancer research has undergone a radical transformation thanks to the development of high-speed processing units and advanced molecular modeling software. This review focuses on the value and most recent developments in Silicomodeling for creating new, effective anti-cancer medications. Although in Silicotechnologies have revolutionized the development and design of small molecule anti-cancer therapies, difficulties, including acquired resistance and intra-tumor heterogeneity, still need to be addressed. Moreover, the "Multi Target Drug Ligands" (MTDL) method for drug creation for the treatment of cancer is replacing the "One Ligand-One Target" strategy[14]. In-silico drug design, also known as computer-aided drug discovery/design (CADD) techniques, was developed to overcome these limitations and handle enormous volumes of developing novel anticancer drugs. It is possible to employ computational tools to support experiment design and, more importantly, to elucidate the relationships between structure and activity that underlie lead optimization and drug discovery methods. Understanding the molecular mechanisms that lead to cancer at the molecular level is necessary for developing novel treatments with high efficacy. A useful method for comprehending these molecular processes and creating novel, potent anticancer medications by using in Silicodrug design techniques and tools. Hence, the present review focused on developing anticancer drugs by utilizing the techniques and tools of in-silico drug design.

2. COMPUTER-AIDED DRUG DESIGN OR IN-SILICO DRUG DESIGN

A large number of proteins have been solved either by X-ray or by nuclear magnetic resonance (NMR) spectroscopy and are available at open-access protein databases (http://www.rcsb.org) since the invention of the X-ray diffraction to reveal the chemical composition and three-dimensional (3D) geometry of a small organic molecule in 19327. With the aid of this knowledge, scientists can now comprehend and describe various physiological processes that depend on interactions between proteins or between proteins and tiny molecules (ligands), as in the instance of drug-target binding[15]. Max Perutz and John Kendrew received the Nobel Prize in Chemistry in 1962 for figuring out the first high-resolution protein structure (myoglobin). Up until the most recent Nobel Prize in Chemistry (2012), which was given jointly to Brian Kobilka and Robert Lefkowitz for their structural and functional studies on G-protein-coupled receptors, several prior works in the crystallographic determination of protein structure had received the honor (GPCRs) [15].The search for hit molecules that may act as drugs have changed significantly as a result of the chemical makeup and 3D relative positions of each atom in a target: from a blind screening process that hoped to find molecular hits primarily by fate to an approach frequently referred to as "rational" drug discovery and design[15]. The first medicine to be optimized using structural data was the angiotensin-converting enzyme (ACE) inhibitor Capoten (captopril), developed in the 1980s. Nelfinavir mesylate (Viracept), an HIV protease inhibitor, was

the first medicine authorized for the US market whose design was entirely determined by the structure of the target. These findings were just the start of a frenzied career spent looking for new, quicker, and less expensive approaches and computational algorithms and procedures for creating and designing new medications. Also, to sample more compounds from the target (screening procedure) in less time and to gain important knowledge and experience beforehand to create a library of chemical compounds for subsequent screening more precisely. The relevant revolution occurred when computational models based on basic physical laws could replicate the interactions between organic molecules, atom by atom, following the high-resolution solution of protein structures. The van der Waals radii of the atoms, the parameters of covalent bonds, torsions, and dihedral angles were taken into account in addition to the 3D structure of a molecule[15,16]. With computational tools like powerful workstations or supercomputers, scientists may now simulate or conduct in Silicoexperiments to simulate genuine systems. This development laid the foundation for a more rational approach to the search for effective, selective medications with fewer side effects while also making the procedure more affordable and efficient [15,16]. Nowadays, these methods allow quicker and less expensive screening of more chemicals (virtual screening). Researchers have advanced in Silicothanks to the Computer-Aided Drug Discovery and Design (CADDD) era, where computer simulations of chemical systems have sparked the potential in this discipline. Among these developments include computer models to resolve 3D structures, the optimization and design of new compounds, and the knowledge of the characterization of the atomic mechanisms of earlier medications or naturally occurring molecules. Breaking the mold of orthosteric medications (drugs binding to the target at a specific active site) has also led to the discovery of allosteric modulators and bitopic pharmaceuticals in the search for therapeutic compounds [15,16.]

3. CURRENT MACROMOLECULAR TARGET FOR ANTICANCER DRUGS

Medications or other substances that specifically influence the molecular targets involved in the onset, progression, and dissemination of a particular tumor are known as molecularly targeted anticancer therapy. Contrarily, most conventional chemotherapeutics operate on both malignant and healthy cells that are rapidly multiplying.[17] Target anticancer medications function cytostatically rather than cytotoxically like traditional chemotherapeutics since they are created with a specific goal. More than 300 biological molecular targets have currently been discovered. Receptor proteins, signal transduction proteins, mRNA thread matrix synthesis proteins engaging in neoplastic transformation, cell cycle control proteins, and functional and structural proteins are just a few of the proteins involved in cellular metabolism. Epithelial growth factor receptor (EGFR), platelet-derived growth factor receptor (PDGFR), and vascular endothelial growth factor receptor are the receptor proteins that anticancer medications now in use target (VEGFR).[17] Target anticancer medications may impact intracellular or extracellular receptor domains (antibodies) (tyrosine kinase inhibitors). Another molecular target of anticancer medications is the inhibition of the mRNA thread carrying data about the shape of oncogenes (signal transduction proteins).[17] Clinical trials are being conducted for this kind of therapy, also known as antisense therapy. The transition to the following phase of the cycle is typically impeded when the synthesis of genetic material is interrupted. Cyclines and cyclin-dependent kinases are the main proteins causing the blockage (CDK). Clinical trials are concentrated on using organic and synthetic compounds that can block different CDKs.[17]

3.1. Kinases as Targets for Developing Anticancer Drugs

The broad family of enzymes known as kinases is responsible for transferring the high-energy phosphate group from adenosine triphosphate (ATP) to a variety of substrates, including proteins, lipids, carbohydrates, nucleic acids, and serine-threonine-specific kinases. Several physiological reactions are brought on by the substrate's phosphorylation, which modifies its activity and interactions with other molecules. Protein kinases are important for practically all aspects of cellular function, including cell development, proliferation, apoptosis, and signal transduction. It is believed that 50% of all proteins are constantly undergoing reversible phosphorylation and dephosphorylation [17,18]. Several disorders, including cancer, have protein kinases that are dysregulated, overexpressed or have mutations. Over the past 20 years, these protein kinases have been widely studied as potential targets for creating new antineoplastic medicines. Almost 200 potential inhibitors are undergoing various stages of clinical studies globally, with 53 kinase inhibitors (KIs) already licensed by the FDA (FDA, 2019) were shown in Figure 2. The majority of the medications that have been approved work against different types of cancer when taken orally[17,18]. Several protein kinases frequently elevated in cancer cells are the focus of PTK inhibitors. The key target for medications like erlotinib and gefitinib is the epidermal growth factor receptor (EGFR), a member of the ErbB family of tyrosine kinase receptors that are overexpressed or mutated in non-small cell lung cancer (Bethune et al., 2010)[17-19]. Lapatinib and neratinib bind to the intracellular domain of HER2/neu, a different member of the ErbB tyrosine kinases that is increased in about 20–30% of breast tumors . Imatinib has been linked to the pathogenesis of nearly all cases of chronic myeloid leukemia (CML) and acute lymphoblastic leukemia with the Philadelphia chromosome due to its activity against non-receptor breakpoint cluster region (Bcr)-Abelson leukemia virus (Abl) tyrosine kinase. Imatinib has been approved for this indication even though it is a relatively specific Bcr-Abl inhibitor and inhibits the CD117 tyrosine kinase linked to gastrointestinal stromal tumors. The tyrosine kinase domain of the vascular endothelial growth factor family of receptors (VEGFR) can activate signaling pathways that control cell survival, proliferation, and the development of tumor angiogenesis. Lenvatinib, sorafenib, and vandetanib are the VEGFR-targeting medications widely used to treat thyroid cancer. BRAF is a serine/threonine protein kinase targeted by vemurafenib, dabrafenib, and encorafenib. About 50–60% of cutaneous melanomas express this mutation, which results in ongoing activation of the mitogen-activated protein kinase (MAPK) pathway and unchecked proliferation of cancer cells.

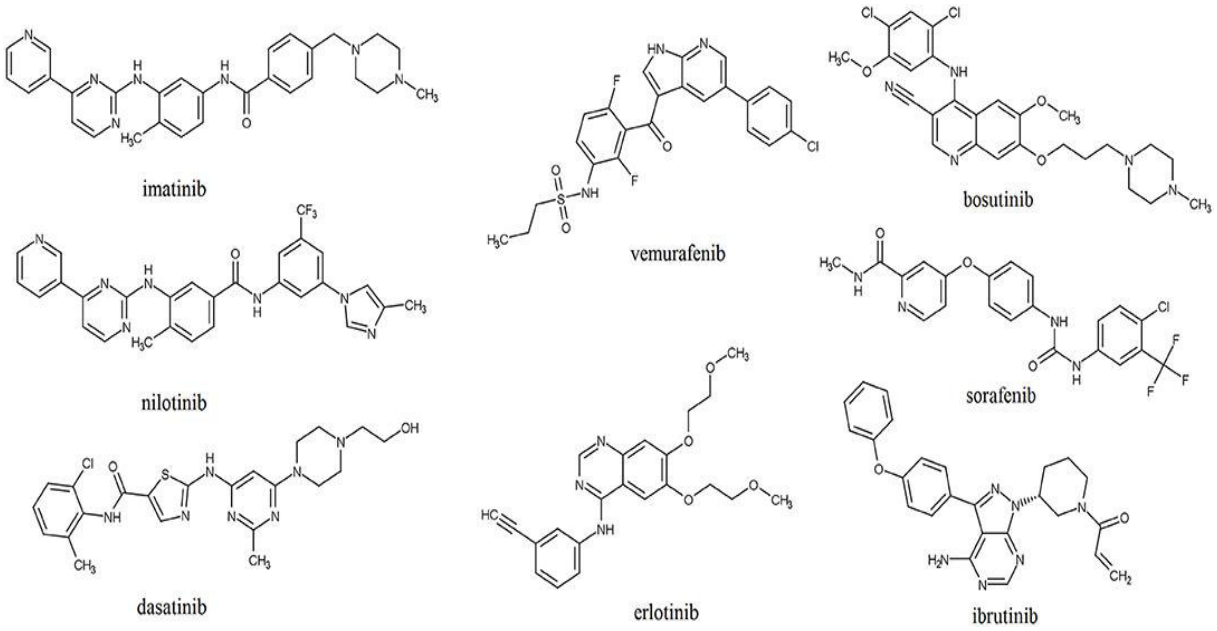

Fig 2: Chemical Structures of Clinically Approved PTK-Inhibitors[17,18,19].

4. DRUG REPOSITIONING

Pharmaceutical companies spend around $2.6 billion developing a drug through market approval. Drug repositioning identifies new indications for known drugs to minimize risk and development time. Drug repositioning moves experimental or approved drugs to new indications; there are several examples of repositioning success stories, such as sildenafil, which was originally developed for heart disease and was repurposed for erectile dysfunction, the sedative thalidomide, which is now approved for the treatment of multiple myeloma and leprosy[20], or the cytotoxic anti-cancer agent gemcitabine, which was originally developed as an antiviral [20]. Computational approaches have been applied to the drug- repositioning pipeline. In Silicodrug target identification, which involves numerous distinct algorithms for identifying disease-associated genes and proteins, is the first step in the drug discovery pipeline (Liu et al., 2010)[67]. Reverse docking, first proposed in 2001, refers to the computational docking of a specific small molecule of interest to a protein structure database (Chen, Zhi, 2001)[20].

4.1. Activity Based Vs. Drug Repositioning

Several examples of successful drug repositioning have drawn attention to the existing drug market's potential for off-target effects that could help treat diseases like cancer. As existing medications have already been administered to humans, they have well-established dosage regimens, acceptable pharmacokinetics (PK), pharmacodynamics (PD), and manageable side effects, making them valuable sources for developing novel anticancer medications. The Johns Hopkins Drug Library (JHDL), a novel project to compile a library of pre-existing medications, was introduced in the early 2000s[20,21]. Around 2,200 of JHDL's medications have received FDA approval in the US or from international counterparts, and about 800 unapproved drug candidates have begun various stages of human clinical trials. We point out that the NCGC Pharmaceutical Collection (NPC), recently developed by the NIH Chemical Genomics Center (NCGC), contains 2,400 small molecular entities that have received clinical use approval from the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), the Japan National Health Insurance Agency (NHI), and the Health Canada (HC)[10, 11]. These are just some of the clinical medication collections that are now offered commercially. These clinical drug collections have proven to help identify novel uses for already-approved medications [20,21]. The use of actual medications for screening is referred to as "activity-based drug repositioning" in this review. Comparatively, "in Silicodrug repositioning" uses open-access databases and bioinformatics tools to find interaction networks between medications and protein targets [21] comprehensively. Due to the development of bioinformatics and computational science over the past few decades, a wealth of knowledge on the structure of proteins and pharmacophores has been gathered, making the latter method successful. Most pharmaceutical firms have previously adapted in Silicodrug development models from other chemical domains. In Silicomedication repositioning, a potentially potent approach, offers some benefits over activity-based drug repositioning, including faster processing times and lower costs. Due to the need for high-resolution structural information on targets, it does have significant drawbacks. When a screen does not include protein targets, additional information such as disease/phenotype details or drug-gene expression patterns are needed. In contrast, protein target-based and cell/organism-based screens can be used in activity-based medication repositioning without needing a database or structural knowledge about the target proteins. Thus, activity-based and in Silicodrug repositioning constitute two distinct and complimentary methods for discovering novel drugs (Shown Table 1) [20,21]. The various tools used for drug repositioning are shown in Table 2 [20,21].

Table-1: Activity-Based and In-silico Approaches for the Development of Drug-Repositioning for Anticancer Drug

Approaches	Pros	Cons
Activity Based Drug-Repositioning	No limitation to the screening of target-based and cell-based assays Easy to validate screening hits Lower rate of false positive hits during the screening	Time and labor efficient Requires an entire collection of existing drugs Need to develop a screening assay
In-silico Drug Repositioning	Which executes Time and labor efficient No need for an entire collection of existing drugs No need to develop a screening assay	Limitation for target-based and cell-based screenings (requires structural information of target proteins and drug-induced cell/disease phenotype information) Higher rate of false positive hits during the screening

Table-2: Tools to be used for Reverse Docking for Drug Repositioning

S.No	Tools used for Reverse Docking for Drug Repurposing	Description
1.	*SurflexDock*	A program designed to predict interactions between a target protein and compounds from a database by fitting them together with their surfaces to create plausible complexes.
2.	*Raccoon2*	Tool for virtual reverse screening providing support for database queries along with feature enrichment analysis capabilities
3.	*SybylX Suite*	Includes three modules designed specifically for virtual reverse screening: High Throughput Searching (HTS) module, Lead Optimization (LO) module, and Super Screening (SS) module
4.	*Glide XP*	A module of Schrödinger Suite optimized specifically for reverse virtual screening scenarios involving thousands or millions of compounds through highly parallelized searches executed on GPUs or CPUs clusters.
5.	*ICM Explorer*	Integrated into Accelrys Discovery Studio software suite, which includes, among others, a de novo library building tool focused on synthesis protocols design automation features.; - SYBYL X by Tripos is an advanced Software Tool used in Reverse Docking Studies
6.	AutoDock Vina	Reverse docking software

5. TYPES OF IN-SILICO DRUG DESIGN

The phrase "in Silicodrug design" refers to "computer-aided molecular design," which means that pharmaceutical drugs are rationally designed or discovered utilizing a wide range of computational techniques. Recently, there has been a noticeable increase in the use of in-silico chemistry and molecular modeling for computer-aided drug design fields of nanotechnology, molecular biology, biochemistry, etc., all use in-silico drug creation techniques[22]. The fundamental advantage of in-silico drug design is that it makes medication research and development more affordable. This creative process of discovering novel pharmaceuticals based on understanding a biological target is known as drug design, sometimes known as rational drug design or simply rational design. A protein, for example, is a common example of a biomolecule whose function is activated or inhibited by the medicine, which benefits the patient therapeutically. In its most basic sense, drug design creates compounds that interact with and bind to biomolecular targets that are complementary to one another in shape and charge. Computer modeling methods are commonly but only sometimes used in drug design[22]. Computer-aided drug design is another name for this kind of modeling. The term "structure-based drug design" refers to drug development based on understanding the biomolecular target's three-dimensional structure. In addition to small molecules, biopharmaceuticals, including peptides and therapeutic antibodies, are a growingly significant class of medications. Computational techniques have also been developed to enhance the affinities, selectivities, and stabilities of these protein-based therapeutics[22,23]. In Silicomethods Shown in Figure-3[24] are classified into 1) Structure-Based Drug Design, which includes Molecular Modelling and Homology Modelling, Molecular Docking, Pharmacophore generation and mapping, and Molecular Dynamic Simulations., Integrated methods and In-silico target prediction 2) Ligand Based Drug Design, which includes Quantitative Structure-Activity Relationship (QSAR) Studies, fragment based-descriptors, Artificial Intelligence Based Drug Design, Virtual Screening, and High-throughput screening (HTS)-Virtual Screening. And Lead optimizations 3) Multi-Targeted Drug Design strategies [22-24]. A critical molecule participating in a certain metabolic or signaling pathway linked to a particular disease condition or pathology or to the infectivity or survival of a microbial pathogen is known as a biomolecular target (most frequently a protein or a nucleic acid). Prospective pharmacological

targets must, by definition, be capable of treating or preventing disease. Small compounds may occasionally be made to either boost or inhibit the target function in a particular disease-modifying pathway. Small compounds complementary to the target's binding site will be created, such as receptor agonists, antagonists, inverse agonists, or modulators; enzyme activators or inhibitors; or ion channel openers or blockers[22-24]. As medication interactions with off-target molecules may result in negative side effects, small molecules (drugs) can be created so as not to affect any other significant "off-target" molecules (commonly referred to as anti-targets). Closely related targets discovered by sequence homology have the highest likelihood of cross-reactivity and, thus, the biggest side effect potential because of similarity in binding sites. Drugs are typically small organic molecules made by chemical synthesis. However, biopolymer-based medications (biopharmaceuticals) made through biological processes are more widespread. Moreover, therapeutic uses for mRNA-based gene silencing technologies are possible [22-24].

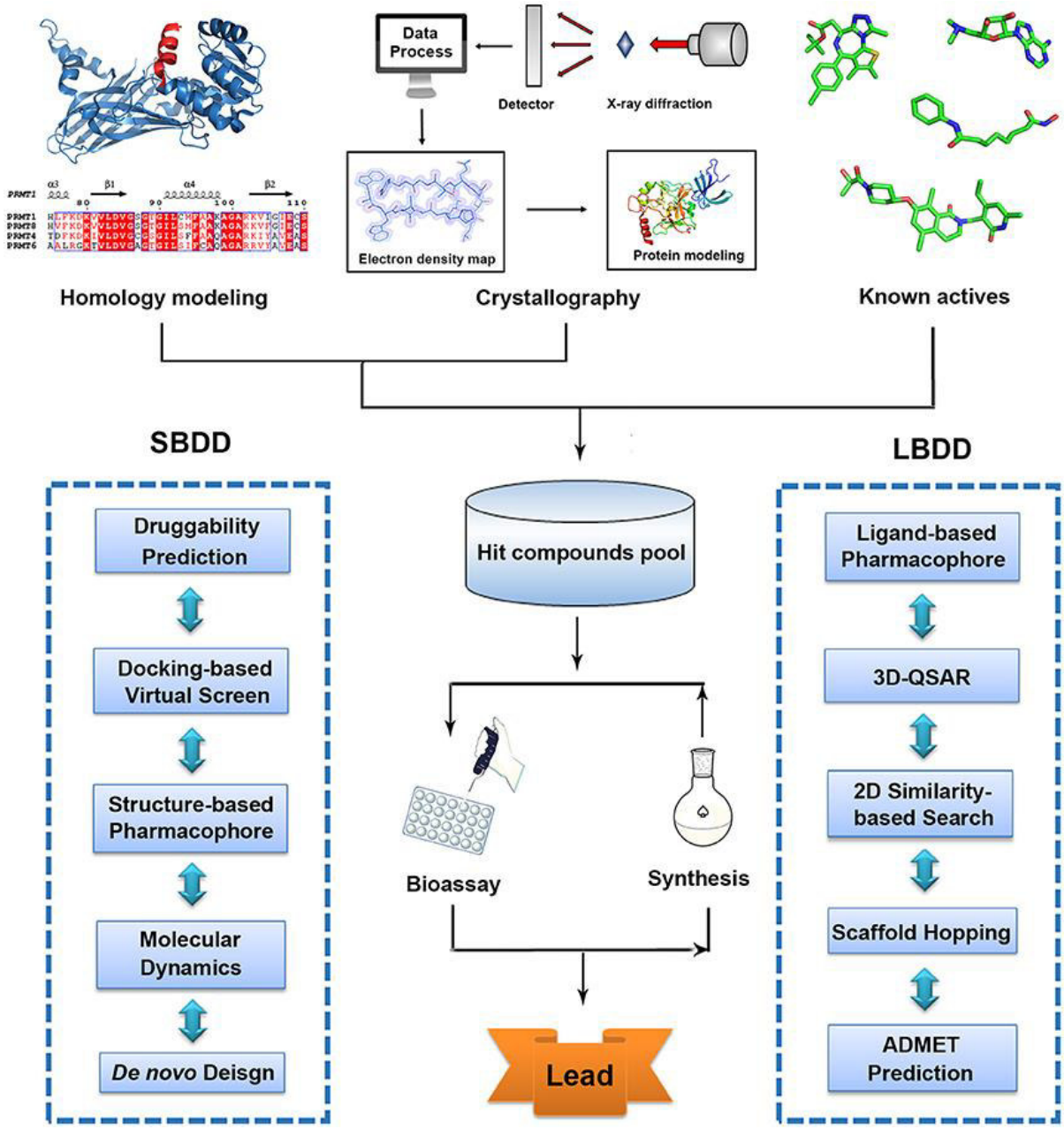

Fig 3: Types and Methods of In-silico Drug Design[24]

6. STRUCTURE-BASED DRUG DESIGN

Structure-based drug design involves using 3D models of biological systems to predict which chemical structures would best bind to their targets, making them more likely to be successful as drug candidates. By analyzing the structures of proteins, nucleic acids, and other cellular components at atomic resolution, it is possible to construct 3D models of how the target interacts with ligands.[24] These 3D models can then be used to virtually screen databases of chemical compounds to identify candidates with optimal binding affinities. Structure-based drug design uses 3D computer modeling to simulate interactions between proteins and small molecules. It seeks to identify molecules with the best fit in terms of size and shape, charge, hydrophobicity, and other properties that enable them to interact effectively with target proteins. The most effective hits from these simulations can be further explored as leads for developing new cancer therapies[24].

6.1. Molecular Modelling and Homology Model

Molecular and homology modeling are two computer-assisted methods to develop new anticancer drugs. Molecular modeling, also known as molecular simulation, is a computational method that uses mathematical algorithms, physical laws, and empirical data to generate 3D images of molecules.[25] This simulation can identify suitable drug candidates and predict their properties, such as stability and solubility. Homology modeling, on the other hand, is a technique used to reproduce the 3-dimensional structure of proteins accurately. Homology models use existing data of known proteins to create structures of unknown proteins. This method can generate 3D structures of target proteins to identify suitable binding sites for drug molecules. Both molecular modeling and homology modeling can be used in developing new drugs for treating various diseases, including cancer. Another method of Molecular modeling used for Protein Modeling involves building 3D models of proteins based on the amino acid sequence, which is then used to study the protein's interactions with different compounds and drugs.[25]

6.2. Molecular Docking

Molecular docking is an in-silico technique that allows for the simulation of protein-ligand interactions and the prediction of binding modes and affinities between ligands and a target receptor.[26] This technique, including anticancer drugs, is widely used to aid drug discovery. 3D structures of both the receptor and the potential ligands are modeled during the process. Molecular docking is based on finding optimal fit by exploring all possible orientations and positions of the ligand molecule relative to the target molecule (receptor) shown in Figure 4-5. Once identified, the docking results provide information about key interactions between receptor and ligand, such as hydrogen bonding or Van der Waals forces. It can then be used to guide further design optimization or help elucidate mechanisms of action. Molecular docking is an essential step in drug design, involving ligands' virtual binding to receptors. Recent developments in this area have revolutionized the field of drug discovery, allowing for more rapid and accurate drug design. To take advantage of these advancements, a revolutionary study of molecular docking techniques was conducted to assess their ability to identify small molecule ligands that could be used to treat cancer. Another docking method enabled by in-silico docking uses a computer program to search through databases (Shown Table-3) of compounds and determine which compounds could have the highest potential binding affinity to the desired target protein or enzyme based on their structural characteristics.[26]

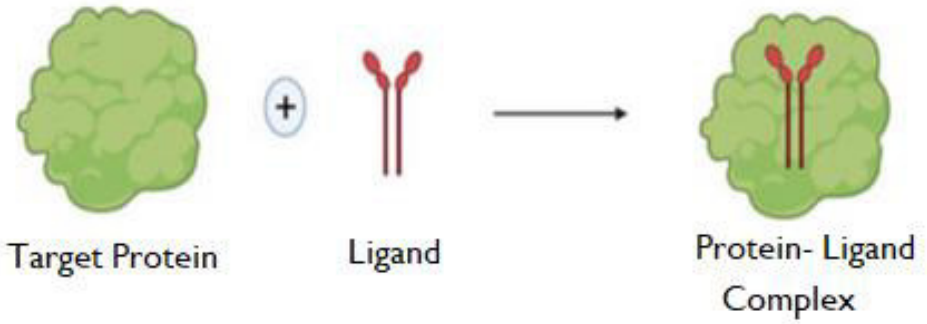

Fig 4: Illustration of Molecular Docking

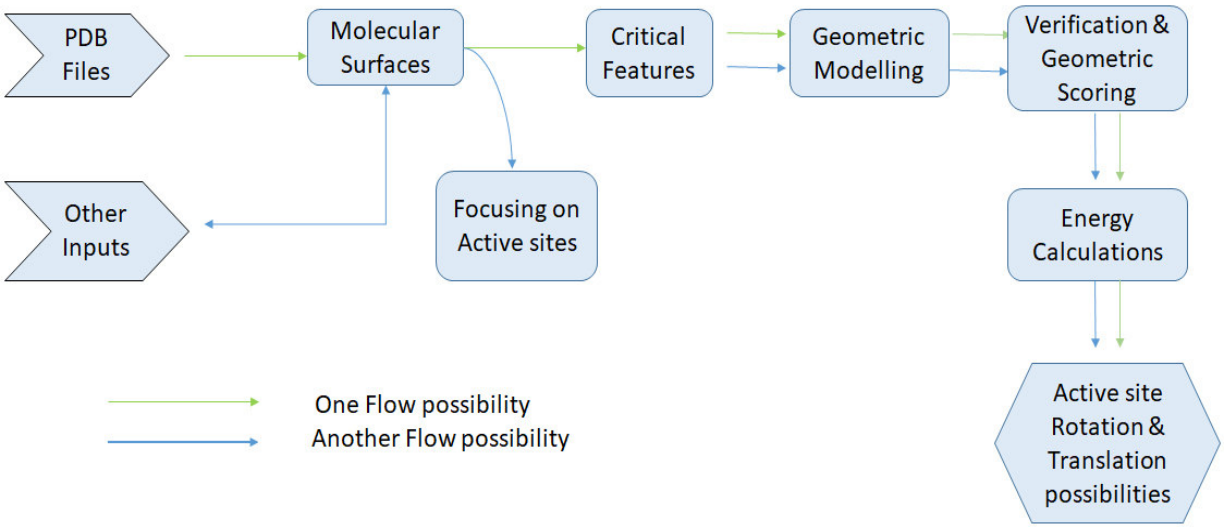

Fig 5 Flowchart for the Docking and Scoring Features

Table-3: Tools Used for Molecular Docking

S.No	Tools Used for Molecular Docking	Description
1.	Autodock Vina	It's one of the fastest and most widely used open-source docking engines. It is a turnkey computational docking program based on a simple scoring function and quick gradient-optimization conformational search.
2.	Maestro Suite	It's a streamlined portal for structural visualization and access to advanced predictive computational modeling and machine-learning workflows for small molecule drug discovery.
3.	PLANTS	Parallel Molecular Docking using PLANTS software
4.	Glide	Glide offers the full range of speed vs. accuracy options, from the HTVS (high-throughput virtual screening) mode for efficiently enriching million compound libraries to the SP (standard precision) mode for reliably docking tens to hundreds of thousands of ligands with high accuracy to the XP (extra precision) mode where further elimination of false positives is accomplished by more extensive sampling and advanced scoring, resulting in even higher enrichment.
5.	OpenEye Omega	OMEGA was designed with the large libraries required for computer-aided drug design. It generates multi-conformer structure databases with high speed and reliability. OMEGA performs rapid conformational expansion of drug-like molecules, yielding a throughput of tens of thousands of compounds per day per processor.
6.	SMINA	Docking with Smina is done from the command line and is very easy to script, thanks to the possibility of calculating the box from an existing ligand. The –autobox_ligand and –autobox_add switches define a docking box that is 8Å greater than the ligand specified. The –exhaustiveness 16 switch tells Smina to spend more time finding the best scoring binding mode of the ligand in the binding site; the default is 8.
7.	GOLD	GOLD is the validated, configurable protein–ligand docking software for expert drug discovery.
8.	Discovery Studio (Catalyst)	Discovery Studio is a software suite for simulating small molecule and macromolecule systems.

6.3. Pharmacophore Mapping

Pharmacophore mapping is a technique used to compare active drug compounds to find structural similarities or differences to gain insight into the molecular interactions responsible for their biological activity. This process involves building 3D models of chemical structures using tools such as "pharmacophore databases," which store different active compounds, structural features, and pharmacological properties.[27,28] Once a pharmacophore map is created, scientists can analyze the information and search for novel compounds with similar effects to existing drugs but with improved activity.

Table-4: Tools Used for Pharmacophore Mapping

S.No	Software used for Pharmacophore Mapping	S.No	Software used for Molecular Docking Mediated Pharmacophore Mapping
1.	Schrodinger Suite	1.	AutoDock Vina - An open-source software program used for protein-ligand docking simulations
2.	Discovery Studio	2.	Schrodinger Suite – A software package for macromolecular structure determination, including molecular docking and pharmacophore mapping tools
3.	Ligand Scout 4	3.	Glide - Software application from Schrodinger used for molecular docking simulations and pharmacophore mapping
4.	CS Chem Space Analyzer Toolbox	4.	MOE – Molecular Operating Environment - All-inclusive integrated modules that combine 3D visualization and modeling, chemistry, high-performance computing, informatics, and collaboration tools.
5.	Hyper Chem HL Chem	5.	PyRx for Visualization
		6.	Autodock Vina for Protein-Ligand Docking
		7.	Schrodinger Maestro for Preparing 3D Structures
	----------	8.	LigandFit from Tripos Sybyl for Docking Studies

6.4. Molecular Dynamics Simulation

It is a computer simulation technique used to model the movements of molecules in time, which can be used to understand their interactions better and inform reverse docking strategies for drug target identification.[27,28]

6.5. Integrated Methods

Structure- and ligand-based approaches, which leverage the knowledge of the protein's structure or the biological and physicochemical characteristics of bound ligands, respectively, are increasingly being combined. By merging pertinent data

from the ligand and the protein, it is intended to increase the dependability of computer-aided drug design methodologies. The simplest combined strategy is creating a 3D pharmacophore to identify possible ligands and conducting additional docking studies on the target[29]. These integrated methods can be divided into two categories: methods based on interaction and methods based on docking similarity. Using the physicochemical information, interaction-based approaches pinpoint the crucial interactions between the protein and ligand. Then, small molecule libraries are screened for compounds that can create such an interaction profile using these interactions. Comparatively, ligand and structure-based docking approaches are combined in docking similarity-based methods. Virtual screening is incredibly effective using these pairings and enables the exploration of libraries containing up to 106 small compounds[29].

6.6. In-silico Target Prediction

SARS (severe acute respiratory syndrome) broke out in China in the spring of 2003. A serotonin antagonist known as cinanserin was found to be a possible inhibitor of the 3C-like (3CL) protease of SARS, which is crucial for processing the coronavirus replicase polyprotein, according to docking-based.'s VS analysis. According to the subsequent laboratory testing, cinanserin can inhibit 3CL protease at nontoxic drug concentrations (IC50 = 5 mM) and may also be able to inactivate the SARS virus. The scientists concluded that cinanserin might be stored in case of future SARS pandemics or utilized as an emergency treatment because it was an old, affordable medicine with a proven safety record[29]. Another in Silicotarget prediction case study was carried out by merging a human-reconstructed signaling network with microarray gene expression data, these authors developed a system biology technique to examine drug-target interactions and offer novel insights into the torcetrapib side effects that are not intended to be seen. The findings revealed that detrimental effects were very relevant to the platelet-derived growth factor receptor (PDGFR), interleukin-2 (IL-2), hepatocyte growth factor receptor (HGFR), and epidermal growth factor receptor (ErbB1) tyrosine kinase. Torcetrapib's acquired potential off-targets were also discovered using the reverse docking approach[29]. Another case study focused on fibroblast growth factor receptors (FGFRs), which are targets for the treatment of various human cancers and consist of an intracellular domain with tyrosine kinase activity, three immunoglobulin-like domains, and an extracellular ligand domain composed of a single transmembrane helix domain. Applied the reverse pharmacophore mapping approach to finding potential targets for an active substance that they had previously synthesized and demonstrated strong in vitro antiproliferative properties. Tyrosine kinases may be the representative compound's possible targets, according to in Silicotarget prediction. Following structural optimization, acenaphtho[1,2-b] pyrrole carboxylic acid esters were found to be potent inhibitors of FGFR1, with IC50 values ranging from 19 to 77 nM, and to exhibit favorable growth inhibition properties against FGFR-expressing cancer cell lines. It was shown by the structure-activity relationship (SAR) analysis assisted by molecular docking simulation in the ATP-binding site[29].

7. LIGAND-BASED DRUG DESIGN

Ligand-based drug design utilizes pharmacophore modeling, chemometric analysis, and machine learning algorithms to quickly analyze huge amounts of data regarding known active sites on receptors or enzymes to identify new compounds with the potential to bind or inhibit their targets.[29] These new compounds can then be further tested and refined in Silicobefore progressing onto further stages of drug development. Ligand-based drug design utilizes a library of known small molecules with known binding activity for a target protein or other macromolecule of interest. By matching the three-dimensional shape of the known ligand(s) to that of the unknown compound, computer modeling techniques are used to assess their binding ability with potential cancer targets[29-31]. In this way, lead compounds can be identified that exhibit favorable properties for effective drug delivery and maximum efficacy against cancer cells[29-31].

7.1. QSAR

Quantitative structure-activity relationships (QSAR) are a powerful predictive tool for discovering novel compounds based on established relationships between chemical structures and biological activities. This method utilizes various statistical techniques to measure the relationship between various physicochemical parameters of a molecule (e.g., its size, shape, surface charge, and hydrophobicity) and its biological activity to predict the behavior of other molecules with similar structures.[30-35] This type of analysis can provide valuable insight into structure-activity relationships, aiding in the design of new drugs with enhanced efficacy and specificity. Another method indicating 3-D QSAR modeling: is used to predict how changes in molecular structure can influence activity. They utilize physical parameters like size and shape and properties like electronegativity and charge density. It can be useful for predicting the binding affinity of small molecules for given drug targets without physically synthesizing each one for testing.[36-38] The various tools for studying QSAR models are shown in Table-5.

Table-5: Tools Used for QSAR Studies

S.No	Tools	Description
1.	DRAGON	Descriptors, Alignments, and Statistics for Genetic Optimization of Responses
2.	RD Kit	Rational design kit for QSAR
3.	CORAL	Comprehensive Organically Regulated Active Library
4.	Amber tools package	Parameter for QSAR descriptors studies
5.	WEKA	Machine learning algorithm with extensive capabilities for data pre-processing, model construction, evaluation, and optimization
6.	ChemMine Tools	A suite of machine learning models and applications to process bioactivity data, such as clustering or virtual screening results

7.	CatRAPID	An automated framework developed to support the design of selective inhibitors targeting small molecules using the CatRAPID algorithm
8.	OPUSQSAR	Framework based on linear methods (multiple linear regression), developed to allow easy data curation, development, and validation of QSAR models.
9.	DockMaster Pro	An advanced tool for efficient comparison of binding sites within multiple ligand structures with enhanced 3D search capabilities for exploring non-active site drug discovery
10.	SMILE	(Structure Modeling Interface & Library Extension) Toolbox to Generate the QSAR Model Parameters
11.	KNIME	To Construct Models by Connecting Nodes and Linking Tools Together
12.	Cheminformatics Suite of Chemical Computing Group Inc. (CCG)	For Analyzing Structure-Property Relationships

7.2. Fragment based-Descriptors

The number of molecular descriptors is exploding for application in chemoinformatics; more than 4000 of these structural variables have been documented in the literature, such as functional group counts (FGC) and atom-centered fragments as descriptors (ACF).[38] Several QSAR research have successfully used these descriptors. They offer a wealth of important knowledge about certain molecular fragments or functional groups, their capacity to engage in hydrophobic and dispersive interactions, or their capacity to display a specific chemical reactivity. The variables utilized in a Free-Wilson analysis share some characteristics with the previously described fragment-based descriptors. The spectral moments of the bond adjacency matrix (lk), the cornerstone of the TOPS-MODE (topological substructural molecular design) approach, were another set of fragment-based descriptors. These descriptors have been used often in QSAR studies,[33–35], and for evaluating various toxicological profiles.[38-41]

7.3. Artificial Intelligence (AI) Based Drug Design

Artificial intelligence is being utilized to create deep learning models that can be used to discover novel molecules with desirable features and optimize existing compounds by selecting ideal combinations of atom types or substituents known to produce higher affinities or greater bioactivity against desired targets.[42,43]

7.4. Virtual Screening (VS)

Virtual Screening (VS): Virtual screening is an in Silicotechnique used to quickly and cost-effectively identify potential drugs by comparing them against a target drug molecule, such as a specific enzyme or receptor site. It allows researchers to rapidly explore thousands of different structures, each with its chemical properties, to narrow their focus to molecules with the most promising properties.[44,45]

7.5. High Throughput Screening: High throughput screening (HTS)

HTS techniques are automated processes that are used to quickly evaluate large numbers of compounds to identify those that may be suitable candidates for drug development or target identification using reverse docking.[44,45]

7.6. HTS-Virtual screening

It's a high-throughput screening technique used for drug discovery and development. This technology uses computational tools such as virtual libraries, QSAR (quantitative structure-activity relationships), 3D-QSAR, and protein-ligand docking to quickly screen thousands of potential drug molecules and identify those with the most promise for further study and development.[46-48] It also allows exploring large databases of chemical compounds to find novel drugs with optimal binding affinity. HTS-Virtual screening is a drug discovery process that combines high throughput and virtual screening approaches to identify promising compounds for developing new anticancer drugs.[46-48] This process typically involves rapidly screening large libraries of compounds using computer algorithms before making a more informed decision on which compounds should progress further in the drug development pipeline. Structure-based drug design is used within HTS-Virtual screening, where the 3D structures of proteins involved in disease processes are studied to understand their interactions with small molecules.[47,48] This information can be used to predict and optimize new molecules as potential therapeutic agents. Ligand-based drug design takes this one step further, focusing on identifying and validating the relationship between biological activities of potential therapeutics and specific binding sites in a target molecule. These approaches can provide valuable insights into how potential new anticancer drugs interact with their targets and thus form an essential part of modern drug discovery strategies. The HTS-Virtual screening approach has been used in drug discovery and the development of potential new anticancer treatments. It involves utilizing high throughput screening (HTS) methods and computational models to identify novel compounds that may have therapeutic effects against cancer cells. HTS-Virtual screening leverages various technologies such as cheminformatics, structure-based design, pharmacophore searches, similarity searching, ligand-based design, and more to identify candidates from large libraries of available compounds.[47,48]

7.7. Lead Optimization

The discovery of effective new treatments for cancer continues to be a major challenge for the medical community. With the development of more sophisticated technologies and approaches, it is possible to identify promising leads for anticancer drug discovery. Lead discovery and optimization is a complex scientific process involving identifying, testing, and refining potential drug candidates[49].

7.7.1. Steps for lead optimization

Lead optimization is a key step in anticancer drug discovery. It involves selecting candidate compounds that show promising

results in preclinical studies and then modifying them to improve their efficacy, safety, and bioavailability. Lead optimization techniques involve a series of steps divided into three main categories: assessing the target, analyzing the candidate compounds, and modifying the compounds [49-51]. The first step in lead optimization is to assess the target. It means understanding the characteristics of the target protein or enzyme and how it functions in the disease. It will help identify the best compounds to target and provide insight into how they should be modified[49-51]. The next step is to analyze the candidate compounds. It includes testing the compounds in preclinical studies and evaluating their efficacy. It will help identify which compounds have the potential to be effective anticancer drugs[49-51]. Finally, compounds promising in preclinical studies must be modified to improve their efficacy, safety, and bioavailability. It may include chemical modifications, such as changing the molecule's structure, or using other techniques, such as conjugation or adding functional groups. By making these modifications, the drug can be more effective in treating cancer[52,53].

7.7.2. Lead Optimization for anticancer drug discovery

Lead optimization for anticancer drug discovery is important in developing effective cancer therapies. It involves identifying and selecting compounds that interact with the target protein, optimizing their structures, and testing their efficacy in animal and human models[52,53]. Lead optimization involves applying computational and chemical techniques to improve the drug's activity and specificity for the target protein. It can include the introduction of modifications to the drug's chemical structure, the application of bioinformatics to analyze the structure-activity relationships, as well as the use of high throughput screening techniques to identify active molecules[52,53]. Lead optimization is essential to improve the efficacy and safety of anticancer drugs. It helps identify new drug candidates that are specific and selective for the target protein and possess improved properties such as greater stability, bioavailability, and selectivity. It leads to more effective and safer anticancer drugs, which can help to improve the outcomes of cancer patients[52,53]. Lead optimization and discovery are critical steps in developing anticancer drugs. Lead optimization and discovery aim to find the most promising chemical compounds with the highest potential to become effective drugs. The process involves identifying, optimizing, and testing structural leads to develop the most promising candidate compounds[52,53]. Lead optimization involves the modification of existing chemical compounds to maximize their potential efficacy and safety. It can involve changing the chemical structure or how the compound binds to its target. The optimization process also includes testing the candidate compounds on cellular and animal models to assess the safety and efficacy of the compounds. Lead discovery involves the identification of new chemical compounds that have the potential to be effective drugs. It can be done through high throughput screening of libraries of compounds or the exploration of natural products. The discovery process also includes testing the compounds on cellular and animal models to assess their safety and efficacy[52,53]. In-silicoLead optimization and discovery are essential steps in developing any anticancer drug. By optimizing and discovering new compounds, researchers can identify the most promising candidates for further development into effective drugs through In-silico docking, Pharmacophore mapping, and QSAR studies[52,53].

7.7.3. Tools Used for Lead Optimizations

The tools and software programs used for lead optimization are the Schrodinger-Phase program, mainly focused on lead optimization by structure-activity relationships, auto dock vina for drug repurposing and optimization, and Discovery Studio-Catalyst[52,53].

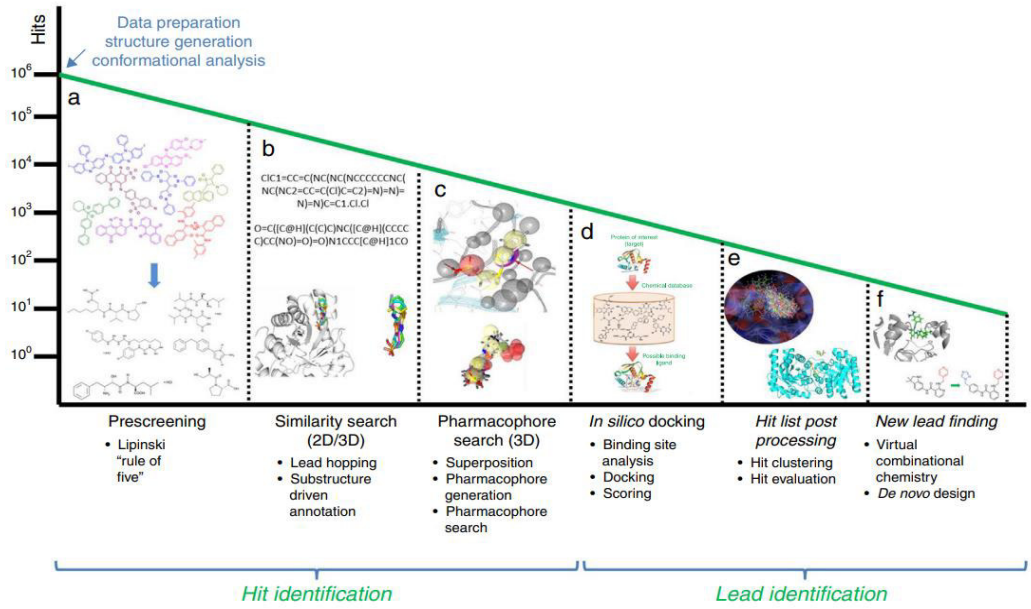

Fig-6: Flow Chart for hit identification followed by Lead Identification and Optimization[54]

Via data preparation to find new leads. (A) The standard in Silicodrug design cycle consists of docking, scoring, and ranking initial hits based on their steric and electrostatic interactions with the target site, commonly called virtual screening. Generally, ligand-based virtual pre-screening has been utilized without structural information of a receptor protein, enzymes,

or signal transductors and when one or more bioactive compounds are available. This pre-screening method is carried out by similarity search. The basic principle behind similarity searching is to screen databases for similar compounds, which is based on the backbone of the structural features of lead molecules. (B) In many situations, 2D similarity searches of databases use the chemical features of the first-generation hits. (C) One alternative approach employs a ligand-based pharmacophore strategy often partnered with structure-based docking that uses a more stringent scoring matrix to determine the relative score by matching two characters in a sequence alignment. It enhances the enrichment of initial hits and identifies the best compounds for computational evaluation: the second-generation hits. (D) Based on the molecular interactions between the target (Receptors, proteins, or enzymes) and hits (Identified active molecules), the second phase often identifies ligand-based sites for optimizing these metrics for a unique molecular chemotype. (E) Computer algorithms, compounds, or fragments of compounds from a database are positioned into a selected region of the structure (docking). These compounds are scored and ranked based on their steric features and electrostatic interactions between their target sites. (F) Structure determination of the target in complex with a promising lead from the first cycle reveals sites on the compound that can be optimized to increase potency.

8. MULTI-TARGETED DRUG DESIGN FOR ANTICANCER DEVELOPMENTS

Three different steps can be used to separate the multi-targeted drug design strategies: The first phase in developing a multi-targeted medicine is choosing a target and combination; the second is discovering the pharmacophore against different targets; and the last step is combining the identified pharmacophore. Network pharmacology analytic methods and coordinated high-throughput screening (HTS) are used to choose target combinations while designing multi-targeted anticancer drugs.[55,56,57] Network pharmacology provides helpful information regarding target/drug combinations that have synergistic effects and likely routes for many substances at the systemic level by investigating complex and multi-layered networks. After choosing a target combination, identifying the pharmacophore versus individual targets was done rationally and computationally using shape-based pharmacophore matching, 3D QSAR analysis, molecular docking, and combinations of these methods.[55,56,57] To create multi-targeted anticancer medicines, the identified pharmacophore can be combined with merged, fused, linked with a cleavable or non-cleavable linker, and so on. A suitable strategy should be employed to create multi-targeted medications because the methodology for the combination is based on the characteristics of important pharmacophore elements and scaffold architectures.[55-57] The multi-targeted anticancer agent's developed molecule should sustain its interaction with the primary target while being acceptable to secondary targets. De novo designing (fragment-based drug designing), multi-target virtual ligand screening (VLS), structure-based drug design (SBDD), ligand-based drug design (LBDD), and combinations of these methodologies are computational methods that are used to design dual or multi-targeted anticancer drugs with remarkable methods to speed up the process.[55-57]

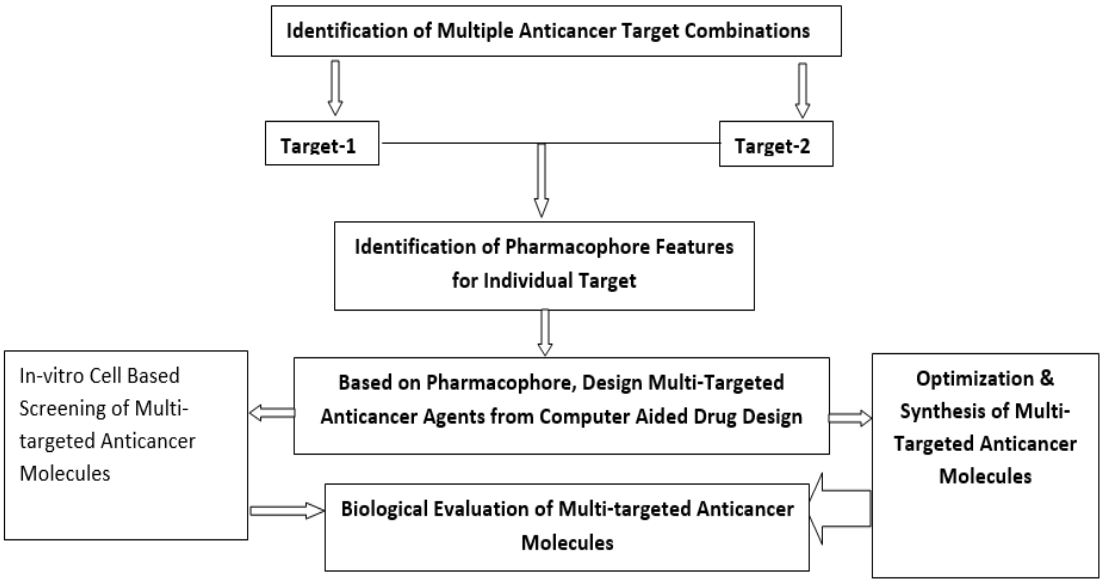

Fig 7: Flow Chart for Development of Multi-Targeted Anticancer Drugs

9. CASES OF LEAD DISCOVERY AND OPTIMIZATION

The desired activity of a lead chemical was discovered during screening; however, further testing is required to confirm this activity. One of the most used techniques for lead discovery is docking, which includes predicting ligand shape and orientation within a particular binding site. Docking is typically integrated into the workflow of various in Silicoprocedures. Modern drug development relies heavily on identifying tiny compounds and turning them into lead series with high content [54-,57]. Zanamivir, dorzolamide, and captopril are three of the best instances of lead optimization and discovery compounds. A neuraminidase inhibitor called zanamivir (Relenza®, Gilead Sciences) is used to prevent and treat influenza brought on by influenza A and B viruses. The architecture of the active site of the influenza neuraminidase protein was revealed by X-ray crystallography, enabling for the first time the creation of an inhibitor to stop

the virus from exiting its host cell and infecting other cells [54-,57]. A drug design method focused on structure was used to attain this success. An array of sialic acid analogs was created using computer-assisted active site modeling. [47] However, dorzolamide (Trusopt®, Merck), a carbonic anhydrase inhibitor that reduces the production of aqueous humor and is used to treat glaucoma, was the first medication used in human therapy that was created using structure-based drug design and ab initio calculations. The project's incorporation of two ideas that the prototype molecule produces two enantiomers and that the active-site cavity is amphiphilic was essential for the successful design of dorzolamide. A last example of the early efforts and triumphs of structure-based and ligand-based drug design is the antihypertensive medication captopril (Capoten®, Bristol-Myers-Squibb), an ACE inhibitor used to treat some kinds of congestive heart failure and hypertension. The understanding that the enzymatic mechanism of ACE was comparable to that of carboxypeptidase A with the distinction that ACE cleaves off a dipeptide, whereas carboxypeptidase A cleaves a single amino acid residue from the carboxyl terminus of the protein, was important for the design of captopril. The development of captopril 4 (IC50 = 23 nM) was heavily influenced by structure-activity relationship (SAR) research [54,-57].

10. INCREASE IN BIOLOGICAL DATA ON CHEMICAL MOLECULES FOR DRUG DISCOVERY

By biological screening, enormous amounts of data have been gathered over the past few decades on hundreds of thousands of tiny molecules. This data has been pooled in online repositories that are open to inquiry. For instance, large-scale studies including more than one million compounds have been produced due to developments in HTS methodology. Information is also growing quickly due to improvements in chemical synthesis and HTS methods. This biological assay data has also been aggregated in chemical library databases. The development of machine learning models and contemporary in Silicodrug discovery have been made possible by accumulating data and its availability to the general public. Prioritizing drug candidates according to their pharmacological characteristics and potential adverse effects can be done in the early phases of drug discovery using conventional prediction techniques like quantitative structure-activity relationship (QSAR) models. Several machine learning-based prediction techniques have been created recently due to increased public resources to forecast drug-target interactions, the permeability of substances across the blood-brain barrier, and the ADMET-Tox characteristics of therapeutic candidates. CADD techniques may find a new path forward by incorporating machine learning algorithms and accumulating data. Table 6 provides a list and summary of the public databases, which contain both chemical and biological databases that are accessible, and Table-7 shows a list of ligand site prediction tools[56,57,58.]

Table-6: Currently Available Chemical and Biological Databases for In-silico Drug Design

Database	Website	Information for In-silico Drug Design
PubChem	https://pubchem.ncbi.nlm.nih.gov	Chemical structure, identification, physical and chemical properties, biological activities, patents, safety, toxicity
PDB	www.rcsb.org	Macromolecules, proteins, Enzymes, Receptors, and 3D structures
ChEMBL	www.ebi.ac.uk/chembl	2-D structures, log P, mol weight, Lipinski parameters, binding constants, pharmacology, and ADME
Binding DB	www.bindingdb.org	binding affinities for drug-like compounds that interact with proteins (therapeutic targets). It has 1,454,894 binding records for 652,068 small molecules and 7,082 protein targets
ZINC	https://zinc.docking.org	substances for purchasing commercially for structure-based virtual screening. 90 million chemicals available. Ready-to-dock, 3D configurations with molecules depicted in biologically appropriate shapes
ChemSpider	www.chemspider.com	structure searches for more than 63 million compounds
Drug Bank	www.drugbank.ca	11,652 drug entries are included in it, including 5,485 experimental pharmaceuticals and 2,602 authorized small molecule drugs, as well as 1,075 approved biotech drugs
GRAC	www.guidetopharmacology.org	summaries of the salient characteristics and available tool compounds and selective ligands. Information on the pharmacological, physiological, structural, genetic, and pathophysiological characteristics of each target
ChemBridge	www.chembridge.com	chemical compounds like small molecules and target-focused screening compounds over 14,000 chemical building blocks
Maybridge	www.maybridge.com	chemistry products and services for the drug

		discovery and biotechnology sector.
ChemDiv	www.chemdiv.com	It offers a shelf-available set of over 1.5M individual solid screening compounds
Life Chemicals	www.lifechemicals.com	It offers over 1,350,000 drug-like and lead-like screening compounds for HTS
Specs	www.specs.net	ordering system for Screening compounds, Building blocks, and Natural products gives you FREE secured access to its entire available compound library of over 240.000 true novel compounds.
Enamine	www.enamine.net	It distributes data about structures of offered compounds in MDL SD Files
ZincPharmer	https://zincpharmer.csb.pitt.edu	Free pharmacophore search software.
Procheck	https://www.ebi.ac.uk/thornton-srv/software/PROCHECK/	Protein, Macromolecule verification server
Uniport/Swiss-Prot	https://www.expasy.org/resources/uniprotkb-swiss-prot	UniProtKB/Swiss-Prot is the expertly curated component of UniProtKB (produced by the UniProt consortium). It contains hundreds of thousands of protein descriptions, including function, domain structure, subcellular location, post-translational modifications, and functionally characterized variants.
Swiss-model	https://swissmodel.expasy.org/	Protein, macromolecules structure prediction, and Homology modeling
Blast	https://blast.ncbi.nlm.nih.gov/Blast.cgi	Protein/receptors/enzymes/ Nucleotides sequence analysis
CASTp	http://sts.bioe.uic.edu/castp/index.html?3igg	Computed Atlas of Surface Topography of Proteins and protein-ligand active site prediction
Q-Site finder	https://dl.acm.org/doi/10.1093/bioinformatics/bti315	An energy-based method for the prediction of protein-ligand binding sites

Table-7: List of ligand binding site prediction tools.

ligand binding site prediction tools	Link	Description	References
CASTp	http://sts.bioe.uic.edu/castp/index.html?3igg	Computed Atlas of Surface Topography of Proteins and protein-ligand active site prediction	59
Q-Site finder	https://dl.acm.org/doi/10.1093/bioinformatics/bti315	An energy-based method for the prediction of protein-ligand binding sites	60
Meta-PPISP	https://pipe.rcc.fsu.edu/meta-ppisp.html	meta-PPISP: a meta web server for protein-protein interaction site prediction also ligand binding site	61
3DLigandSite	http://www.sbg.bio.ic.ac.uk/3dligandsite/advanced.cgi	3DLigandStie is an automated method for the prediction of ligand binding sites.	62

11. SUCCESSFUL APPLICATIONS IN CANCER DRUG DISCOVERY

Creating new anticancer medications is exceedingly complex, expensive, and time-consuming. Given the benefit of requiring far less investment in technology, resources, and time, CADDD is gaining importance. Computational techniques are now being incorporated at nearly every stage of the drug discovery and development process due to the dramatically increased information on genomes, small compounds, and protein structures that is now readily available. Chemical compounds may have a higher affinity for their target when they are developed logically with the aid of computational tools, given the 3D structure of a target molecule. Several effective uses of structure-based medication design have been documented in recent years [63,64.] The discovery of the p53 upregulated modulator of apoptosis (PUMA) inhibitors is an intriguing example of structure-based pharmacophore modeling. A proapoptotic protein belonging to the Bcl-2 protein family, PUMA. The tumor suppressor p53 is in charge of controlling its expression. PUMA suppression or ablation results in a lack of apoptosis, which increases the likelihood of cancer formation and therapeutic resistance. By interacting with every member of the known anti-apoptotic Bcl-2 family, this cancer therapeutic target plays a key role in mitochondria-mediated cell death. Many methods have been used to find small compounds that can modify the interactions between BH3-only proteins and Bcl-2-like proteins, suppressing apoptosis. Most of the work has gone into creating Bcl-2 family inhibitors that replicate the effects of BH3 domains, which promote apoptosis. These substances have been found using computational modeling, structure-based design, and high-throughput screening of libraries of synthetic and natural products [63,64]. In contrast, Liu et al[67]. published a combinatorial

computational method for identifying possible inhibitors against the insulin-like growth factor-1 receptor (IGF-1R), which has been linked to a number of malignancies, including breast, prostate, and lung cancer. The tyrosine kinase family member IGF-1R is essential for the signaling pathway that controls cell growth, proliferation, and death. A focused library was created using the initial hit from hierarchical VS as the query scaffold for the substructure search. The library was subjected to an internal pharmacophore-constrained docking procedure for IGF-1R screening. Ultimately, enzymatic testing revealed inhibitory action in 15 out of 39 compounds. Surprisingly, the two strongest inhibitors showed significant selectivity over the insulin receptor (IR), similar to the IGF-1R, and great inhibitory activity (IC50 = 57 and 61 nM, respectively). The scientists concluded that the prospective selective IGF-1R inhibitors might be studied as molecular probes to distinguish between the biological activities of IGF-1R and IR in addition to being possible anticancer medicines [63,64]. Tubulin inhibitors are a further successful example of small compounds created employing a ligand-based strategy. A key target for cancer treatment is tubulin polymerization, a crucial step in cell cycle progression and cell division. Several antimitotic drugs, including paclitaxel, colchicine, and the vinca alkaloids, have been identified and are used in medicine. Still, they frequently exhibit high toxicity levels, poor bioavailability, quickly developing resistance, and overexpression of drug-resistant pumps that expel these mitosis inhibitors from the cell. Since it is thought that antimitotic drugs might operate to reduce the blood supply to malignant tumors, researchers have spent a lot of time and energy trying to find new agents with more palatable and effective qualities. Liu et al[67]. used structure-activity relationship (SAR) analysis to power their model generation based on 21 indole derivatives first created for potential tubulin inhibition. These substances were chosen so that the range of their inhibitory IC50 values, from 1.2 nM to 6M, covered three orders of magnitude. Based on the same chemical properties of these compounds, the authors decided to build a chemical library using four common pharmacophoric features: a hydrophobic group, a hydrophobic aromatic group, a hydrogen bond donor, and a hydrogen bond acceptor. A human oral squamous carcinoma cell line was then used to test 142 substances (KB) physiologically. Four of these 142 biologically investigated substances were discovered to inhibit the KB cell line, with corresponding IC50 values of 187 nM, 2.0 M, 3.0 M, and 5.7 M. With IC50 values of 236 nM, 285 nM, and 319 nM, respectively, the most potent substance of these four active molecules was also discovered to inhibit the growth of other cancer cell lines like SF-268 (human central nervous system cancer), NCI-H460 (human non-small-cell lung cancer), and MCF-7 (breast cancer). The I-Kappa-B Kinase (IKK-) inhibitors are another instance of small compounds created utilizing a computational technique. In addition to inflammation, 59 IKK-, a crucial component of the NF- B signaling cascade, is yet another potential target for cancer therapy. To find novel drugs with affinity to IKK-, Noha et al.[70] opted to apply ligand-based pharmacophore modeling in 2011. To create an IKK- inhibitor-specific pharmacophore model, the ligand-based pharmacophore model for this investigation was based on a group of five drugs with high activity (IC50 values of 100 nM or less) and at least a few-fold difference in selectivity for IKK- over NF B [45,46]. The model was further improved using a dataset taken from the literature that included 12,775 different random decoy compounds, 128 active compounds, and 44 physiologically inactive compounds. The top 10 high-scoring substances underwent in vitro testing. The most effective compound NSC-719177 had an IC50 value of roughly 6.95 M and could inhibit IKK-. The capacity of compound NSC-719177 to suppress NF B activation in HEK293 cells that had been transfected and contained a luciferase reporter gene activated by a promoter made up of several copies of the NF- B response element was also tested by cell-based analysis. In a cell-based experiment, compound NSC-719177 was discovered to have an IC50 value of roughly 5.85M and to show dose-dependent efficacy in suppressing TNF-induced luciferase activity. As a result, Noha et al.[70] showed the effective use of ligand-based methods for discovering low micromolar inhibitors of IKK. The utilization of high-throughput X-ray crystallography for a target alone or in complex with small compounds and the advancement of much more advanced molecular modeling tools has made rational drug design methodologies an essential tool for creating target-based therapeutics. The Selected anticancer drugs/inhibitors developed with computational chemistry and rational drug design strategies are Shown in Table-8.

Table-8: Selected anticancer drugs/inhibitors developed with computational chemistry and rational drug design strategies

Molecule/Drug Name	Pharmacological Area	Pharmacological Function	References
Gefitinib	NSCLC	EGFR kinase inhibitor	65
Erlotinib	NSCLC pancreatic cancer	EGFR kinase inhibitor	66
Sorafenib	Renal cancer, Liver cancer, Thyroid cancer, HDACi	VEGFR kinase inhibitor	67
Lapatinib	ERBB2- positive breast cancer	EGFR inhibitor	68
Abiraterone	Metastatic castration-resistant prostate cancer or hormone-refractory prostate cancer	Androgen synthesis inhibitor	69

12. CONCLUSION

Cancer is one of the leading causes of death worldwide, making it urgently necessary to find new ways to treat the disease. In Silicodocking and pharmacophore mapping are powerful approaches to developing anticancer drugs. These tools are used to investigate the interactions of a drug molecule with its receptor and predict its pharmacological effects. In this concern, we have discussed the revolutionary study for in Silicostructure-based and ligand-based methods, which include docking and pharmacophore mapping, Molecular modeling, Homology modeling, HTS-Virtual screening, drug repositioning & repurposing, and Multi Targeted Drug strategies for the development of anticancer drugs. We also demonstrated how these methods were used to identify effective drugs for treating cancer. Finally, These In-silico drug design approaches have the importance of this innovative research for advancing the fight against cancer.

13. AUTHORS CONTRIBUTION STATEMENT

Dr. K. Rajaganapathy provided the written direction and guidance for the current review. Dr. K. Masilamani has revised and formatted the manuscript. The manuscript was edited by Dr. B. Senthilnatan, Dr. R. Gowri, Dr. R. Sathiyasundar, and M. Vigneshwar, who also collected the literature.

14. CONFLICT OF INTEREST

Conflict of interest declared none.

15. REFERENCES

1. Basith S, Cui M, Macalino SJY, Choi S. Expediting the design, discovery, and development of anticancer drugs using computational approaches. Curr Med Chem. 2017;24(42):4753-78. doi: 10.2174/0929867323666160902160535, PMID 27593958.
2. Sun J, Wei Q, Zhou Y, Wang J, Liu Q, Xu H. A systematic analysis of FDA-approved anticancer drugs. BMC Syst Biol. 2017 Oct 3;11;Suppl 5:87. doi: 10.1186/s12918-017-0464-7, PMID 28984210.
3. Pacheco C, Baião A, Ding T, Cui W, Sarmento B. Recent advances in long-acting drug delivery systems for an anticancer drug. Adv Drug Deliv Rev. 2023;194(Mar):114724. doi: 10.1016/j.addr.2023.114724, PMID 36746307.
4. Olgen S. Overview on anticancer drug design and development. Curr Med Chem. 2018;25(15):1704-19. doi: 10.2174/0929867325666171129215610, PMID 29189124.
5. Wang L, Song Y, Wang H, Zhang X, Wang M, He J, Li S, Zhang L, Li K, Cao L. Advances of Artificial Intelligence in Anti-Cancer Drug Design: A Review of the Past Decade. Pharmaceuticals. 2023 Feb 7;16(2):253.
6. Kumar B, Singh S, Skvortsova I, Kumar V. Promising targets in anti-cancer drug development: recent updates. Curr Med Chem. 2017;24(42):4729-52. doi: 10.2174/0929867324666170331123648, PMID 28393696.
7. Cui W, Aouidate A, Wang S, Yu Q, Li Y, Yuan S. Discovering anti-cancer drugs via computational methods. Frontiers in pharmacology. 2020 May 20;11:733.
8. Gagic Z, Ruzic D, Djokovic N, Djikic T, Nikolic K. In SilicoMethods for Design of Kinase Inhibitors as Anticancer Drugs. Front Chem. 2019;7:873. doi: 10.3389/fchem.2019.00873, PMID 31970149.
9. Raval K, Ganatra T. Basics, types and applications of molecular docking: a review. IJCAAP. 2022;7(1):12-6. doi: 10.18231/j.ijcaap.2022.003.
10. Wang X, Song K, Li L, Chen L. Structure-based drug design strategies and challenges. Curr Top Med Chem. 2018;18(12):998-1006. doi: 10.2174/1568026618666180813152921, PMID 30101712.
11. Ismail FMD, Nahar L, Sarker SD, Chapter 6. High-throughput screening of phytochemicals: application of computational methods. In: Sarker SD, Nahar L, editors. Computational. Phytochemistry Elsevier; 2018. p. 165-92.
12. Song CM, Lim SJ, Tong JC. Recent advances in computer-aided drug design. Briefings in bioinformatics. 2009 Sep 1;10(5):579-91.
13. Lu D-Y, Lu T-R. Anticancer drug development, challenge and dilemma. Nurse Care Open Access J. 2020;7(3):72-5. doi: 10.15406/ncoaj.2020.07.00222.
14. Dr. Da-Yong Lu, Dr. Bin Xu and Dr. Ting-Ren Lu. Anticancer drug development, pharmacology updating. EC pharmacology and toxicology SI.02., 2020: 01-6.
15. Surabhi SBK, Singh B. Computer-aided drug design: an overview. J Drug Deliv Ther. 2018;8(5):504-9. doi: 10.22270/jddt.v8i5.1894.
16. Ece A. Computer-aided drug design. BMC Chem. 2023;17(1):26. doi: 10.1186/s13065-023-00939-w, PMID 36964610.
17. Zajac M, Muszalska I, Jelinska A. New molecular targets of anticancer therapy - current status and perspectives. Curr Med Chem. 2016;23(37):4176-220. doi: 10.2174/0929867323666160814002150, PMID 27528054.
18. Kumar R, Lal N. PET in anti-cancer drug development and therapy. Recent Patents on Anti-Cancer Drug Discovery. 2007 Nov 1;2(3):259-63..
19. Kinch MS. An analysis of FDA-approved drugs for oncology. Drug discovery today. 2014 Dec 1;19(12):1831-5..
20. Jarada TN, Rokne JG, Alhajj R. A review of computational drug repositioning: strategies, approaches, opportunities, challenges, and directions. J Cheminform. 2020;12(1):46. doi: 10.1186/s13321-020-00450-7, PMID 33431024.
21. Oprea TI, Overington JP. Computational and practical aspects of drug repositioning. Assay Drug Dev Technol. 2015 Jul-Aug;13(6):299-306. doi: 10.1089/adt.2015.29011.tiodrrr, PMID 26241209.
22. Shaker B, Ahmad S, Lee J, Jung C, Na D. In Silicomethods and tools for drug discovery. Comput Biol Med. 2021 Oct;137:104851. doi: 10.1016/j.compbiomed.2021.104851, PMID 34520990.
23. Makrynitsa GI, Lykouras M, Spyroulias GA, Matsoukas M-T. In SilicoDrug Design. In: eLS. Chichester: John Wiley & Sons, Ltd; Aug 2018. doi: 10.1002/9780470015902.a0028112.
24. Lu W, Zhang R, Jiang H, Zhang H, Luo C. Computer-aided drug design in epigenetics. Front Chem. 2018;6:57. doi: 10.3389/fchem.2018.00057, PMID 29594101.
25. Muhammed MT, Aki-Yalcin E. Homology modeling in drug discovery: overview, current applications, and future perspectives. Chem Biol Drug Des. 2019;93(1):12-20. doi: 10.1111/CBD.13388, PMID 30187647.
26. Dar AM, Mir S. Molecular docking: approaches, types, applications, and basic challenges. J Anal Bioanal Tech. 2017;08(2):356. doi: 10.4172/2155-9872.1000356.
27. Zhou Y, Di B, Niu MM. Structure-based pharmacophore design and virtual screening for novel tubulin inhibitors with potential anticancer activity.

Molecules. 2019 Sep 1;24(17):3181:1-10. doi: 10.3390/molecules24173181, PMID 31480625.
28. Meshram RJ, Baladhye VB, Gacche RN, Karale BK, Gaikar RB. Pharmacophore mapping approach for drug target identification: A chemical synthesis and in Silicostudy on novel thiadiazole compounds. J Clin Diagn Res. 2017 May;11(5):KF01-8. doi: 10.7860/JCDR/2017/22761.9925, PMID 28658808.
29. Prada-Gracia D, Huerta-Yépez S, Moreno-Vargas LM. Application of computational methods for anticancer drug discovery, design, and optimization. Bol Med Hosp Infant Mex. 2016;73(6):411-23. doi: 10.1016/j.bmhimx.2016.10.006, PMID 29421286.
30. Kim E, Yang C. Application of quantitative structure-activity relationship models for virtual screening drug libraries: an overview of state-of-the-art methodologies and strategies. Drug Des Rev. 2020;6(2):75-88.
31. Thafar M, Raies AB, Albaradei S, Essack M, Bajic VB. Comparison study of computational prediction tools for drug-target binding affinities. Frontiers in chemistry. 2019 Nov 20;7:782..
32. Sharan S, Swaminathan PN. Exploring new avenues using pharmacophore mapping. Int J Pharm Sci Res. 2020;11(11):5270-9.
33. Yadav M, Eswari JS. Modern paradigm towards potential target identification for antiviral (SARS-nCoV-2) and anticancer lipopeptides: A pharmacophore-based approach. Avicenna J Med Biotechnol. 2022 Jan-Mar;14(1):70-8. doi: 10.18502/ajmb.v14i1.8172, PMID 35509362.
34. Villoutreix BO, Bismuth E, Corpet F. Molecular docking studies in drug discovery. Nat Rev Drug Discov. 2000;1(1):51-60.
35. Prabhakar A, Lee SK. Molecular docking techniques: fundamentals and recent advances in drug discovery. Asian J Pharm Clin Res. 2015;8(6):136-43.
36. Rane M, Pateriya A, Makwana H, Pradhan A. A comprehensive review on Molecular Docking Approach for Drug Discovery Process. Int J Res Technol. 2017;6(7, Jul):111-8.
37. Prieto-Martínez FD, Arciniega M, Medina-Franco JL. Molecular docking: current advances and challenges. TIP. Revista especializada en ciencias químico-biológicas. 2018;21.
38. Bell N. An overview of pharmacophore modeling and computer-aided drug design in lead identification for cancer therapy. World J Clin Oncol. 2011;2(2):33-40.
39. Varma DA, Singh M, Wakode S, Dinesh NE, Vinaik S, Asthana S, Tiwari M. Structure-based pharmacophore mapping and virtual screening of natural products to identify polypharmacological inhibitor against c-MET/EGFR/VEGFR-2. Journal of Biomolecular Structure and Dynamics. 2023 May 3;41(7):2956-70.
40. Agarwal S, Mishra M, Mishra VK, Vinod D, Verma E, Kashaw SK. In-silico pharmacophore mapping and docking studies of indole/benzoximidazole-5-carboximidine derivatives as anti-cancer agents. International journal of pharmaceutical sciences and research. 2016 Aug 1;7(8).
41. Khedkar SA, Malde AK, Coutinho EC, Srivastava S. Pharmacophore modeling in drug discovery and development: an overview. Med Chem. 2007 Mar;3(2):187-97. doi: 10.2174/157340607780059521, PMID 17348856.
42. Zeng X, Dong W, Gong H. QSAR modeling: A novel tool for drug discovery against cancers. Comp Struct Biotechnol J. 2015;13(1):85-90.
43. Subramani AK, Sivaperuman A, Natarajan R, Bhandare RR, Shaik AB. QSAR and molecular docking studies of pyrimidine-coumarin-triazole conjugates as prospective anti-breast cancer agents. Molecules. 2022 Mar 11;27(6):1845. doi: 10.3390/molecules27061845, PMID 35335208.
44. Perkins R, Fang H, Tong W, Welsh WJ. Quantitative structure-activity relationship methods: perspectives on drug discovery and toxicology. Environ Toxicol Chem. 2003 Aug;22(8):1666-79. doi: 10.1897/01-171, PMID 12924569.
45. Speck-Planche A, Kleandrova VV, Luan F, Cordeiro MN. Rational drug design for anti-cancer chemotherapy: multi-target QSAR models for the in Silicodiscovery of anti-colorectal cancer agents. Bioorg Med Chem. 2012;20(15):4848-55. doi: 10.1016/j.bmc.2012.05.071, PMID 22750007.
46. Zhao L, Teng Q, Liu Y, Chen H, Chong W, Du F, Xiao K, Sang Y, Ma C, Cui J, Shang L. Machine learning-based identification of a novel prognosis-related long noncoding RNA signature for gastric cancer. Frontiers in Cell and Developmental Biology. 2022 Nov 11;10:1017767.
47. Storchi L. Computational tools used in modern medicinal chemistry for drug discovery. Curr Top Med Chem. 2018;18(4):441-68.
48. Gupta SP. Quantitative structure-activity relationship studies on anticancer drugs. Chemical reviews. 1994 Sep;94(6):1507-51.
49. Maruca A, Ambrosio FA, Lupia A, Romeo I, Rocca R, Moraca F, Talarico C, Bagetta D, Catalano R, Costa G, Artese A. Computer-based techniques for lead identification and optimization I: Basics. Physical Sciences Reviews. 2019 Jan 11;4(6):20180113.
50. Vaishnaw A. Multi-targeted anticancer drugs: Design strategies and recent development. International Journal of Green Pharmacy (IJGP). 2022;16(4).
51. Lu DY, Xu B, Lu TR. Anticancer Drug Development, Pharmacology Updating. EC Pharmacology and Toxicology SI.02., 2020: 1-6.
52. Lu DY, Xu B, Ding J. Antitumor effects of two bisdioxopiperazines against two experimental lung cancer models in vivo. BMC Pharmacol. 2004: 24;4:32. doi: 10.1186/1471-2210-4-32, PMID 15617579.
53. Belete TM. Recent updates on the development of deuterium-containing drugs for the treatment of cancer. Drug design, development and therapy. 2022 Jan 1:3465-72.
54. Xiao Z, Morris-Natschke SL, Lee KH. Strategies for the optimization of natural leads to anticancer drugs or drug candidates. Medicinal research reviews. 2016 Jan;36(1):32-91..
55. Fu RG, Sun Y, Sheng WB, Liao DF. Designing multi-targeted agents: an emerging anticancer drug discovery paradigm. Eur J Med Chem. 2017 Aug 18;136:195-211. doi: 10.1016/j.ejmech.2017.05.016, PMID 28494256.
56. Talevi A. Multi-target pharmacology: possibilities and limitations of the skeleton key approach from a

medicinal chemist perspective. Front Pharmacol. 2015;6205:1-7.
57. Pradhan T, Gupta O, Singh G, Monga V. Aurora kinase inhibitors as potential anticancer agents: Recent advances. European Journal of Medicinal Chemistry. 2021 Oct 5;221:113495..
58. Shim JS, Liu JO. Recent advances in drug repositioning for the discovery of new anticancer drugs. Int J Biol Sci. 2014;10(7):654-63. doi: 10.7150/ijbs.9224, PMID 25013375.
59. Tian W, Chen C, Lei X, Zhao J, Liang J. CASTp 3.0: computed atlas of surface topography of proteins. Nucleic Acids Res. Jul 2 2018;46(W1):W363-7. doi: 10.1093/nar/gky473, PMID 29860391.
60. Laurie ATR, Jackson RM. Q-SiteFinder: an energy-based method for the prediction of protein–ligand binding sites. Bioinformatics. 2005;21(9, May):1908-16. doi: 10.1093/bioinformatics/bti315, PMID 15701681.
61. Qin S, Zhou HX. meta-PPISP: a meta web server for protein-protein interaction site prediction. Bioinformatics. 2007;23(24):3386-7. doi: 10.1093/bioinformatics/btm434, PMID 17895276.
62. McGreig JE, Uri H, Antczak M, Sternberg MJE, Michaelis M, Wass MN. 3DLigandSite: structure-based prediction of protein-ligand binding sites. Nucleic Acids Res. 2022 Apr 12;50(W1):W13-20. doi: 10.1093/nar/gkac250, PMID 35412635.
63. van Hasselt JG, van Eijkelenburg NK, Beijnen JH, Schellens JH, Huitema AD. Optimizing drug development of anti-cancer drugs in children using modelling and simulation. British Journal of Clinical Pharmacology. 2013 Jul;76(1):30-47..
64. Bajorath J, editor. Chemoinformatics: concepts, methods, and tools for drug discovery. Springer Science & Business Media; 2008 Feb 4..
65. Sim EH, Yang IA, Wood-Baker R, Bowman RV, Fong KM. Gefitinib for advanced non-small cell lung cancer. Cochrane Database Syst Rev. 2018 Jan 16;1(1):CD006847. doi: 10.1002/14651858.CD006847.pub2, PMID 29336009.
66. Chelli SM, Gupta P, Belliraj SK. An in Silicodesign of bioavailability for kinase inhibitors evaluating the mechanistic rationale in the CYP metabolism of erlotinib. J Mol Model. 2019 Feb 14;25(3):65. doi: 10.1007/s00894-018-3917-z, PMID 30762124.
67. Liu T-P, Hong YH, Yang PM. In Silicoand in vitro identification of inhibitory activities of sorafenib on histone deacetylases in hepatocellular carcinoma cells. Oncotarget. 2017 Sep 16;8(49):86168-80. doi: 10.18632/oncotarget.21030, PMID 29156785.
68. Medina PJ, Goodin S. Lapatinib: a dual inhibitor of human epidermal growth factor receptor tyrosine kinases. Clin Ther. 2008 Aug;30(8):1426-47. doi: 10.1016/j.clinthera.2008.08.008, PMID 18803986.
69. Hoy SM. Abiraterone acetate: a review of its use in patients with metastatic castration-resistant prostate cancer. Drugs. 2013 Dec;73(18):2077-91. doi: 10.1007/s40265-013-0150-z, PMID 24271422.
70. Noha SM, Atanasov AG, Schuster D, Markt P, Fakhrudin N, Heiss EH, Schrammel O, Rollinger JM, Stuppner H, Dirsch VM, Wolber G. Discovery of a novel IKK-β inhibitor by ligand-based virtual screening techniques. Bioorganic & medicinal chemistry letters. 2011 Jan 1;21(1):577-83.