Comprehensive Study on Drug Designing and Process Chemistry: Where we are now and What lies ahead

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Abstract-

Drug designing is an integrated developed discipline. Which predicts an era of 'tailored'. Drug designing and discovery in the present scenario significantly reduces the time and cost required for developing novel drugs with the advancement of technology and growth, numerous deep learning-based methodologies are emerging at all steps of drug development process. The major challenges are prediction of interaction between drugs and druggable target and generation of novel molecular structures suitable for a target of interest in the present review deals with the advancement of drug designs which provide stimulus to the imagination of a new molecules.

Keywords- Endogenous Ligand, De novo design, Pharmacophore, Lead Compounds, Drug design.

Introduction

Drug design methodologies and tactics have evolved over time, utilizing and promoting new technology advancements to address the various, challenging roadblocks that arise during the drug development process. In addition to experimental methods, numerous computer tools have been used at various echelons of rational design practice Initial level of these methodologies concentrated on limiting the number of potential ligands, whereas future models, through lead optimization, focus is toward lowering trial expenses and shortening the research process (1). One such computational strategy is structure-based drug design (SBDD), This may be applied alongside crucial steps in the drug development process including "hit identification" as well as "hit-to-lead." Detection of a catalog of molecular entities, or "hits," that typically exhibit some level of strength and specific toward the target, constitutes the first step in the procedure. The other assesses the scanned hits to identify the prospective lead substances before to continuing with a huge lead optimization (2)(3). Such methods frequently produced multidimensional results that paved the path for retracing the fundamental ideas and fostering novel ideas including receptor elasticity (4), numerous conformational answerability (5), and Virtual screening using pharmacophores (6). The time, money, and labor invested at SBDD are very small, yet it can have a significant impact on the search for novel medications (7). As a result, SBDD is now universally acknowledged as being crucial to the study of drugs. Fig.1 displays the SBDD flowchart that is most frequently used. The variety of programming bundles that may assist in efficiently completing the different SBDD stages has grown significantly over the past few decades. Even though SBDD can benefit greatly from these computational capabilities, selecting effective amalgamations of tactics and gears intended for effective lead detection has become increasingly difficult (8). Therefore, in the sections that follow, we will examine the various computational methods and protocols that are employed in Insilco hit finding.

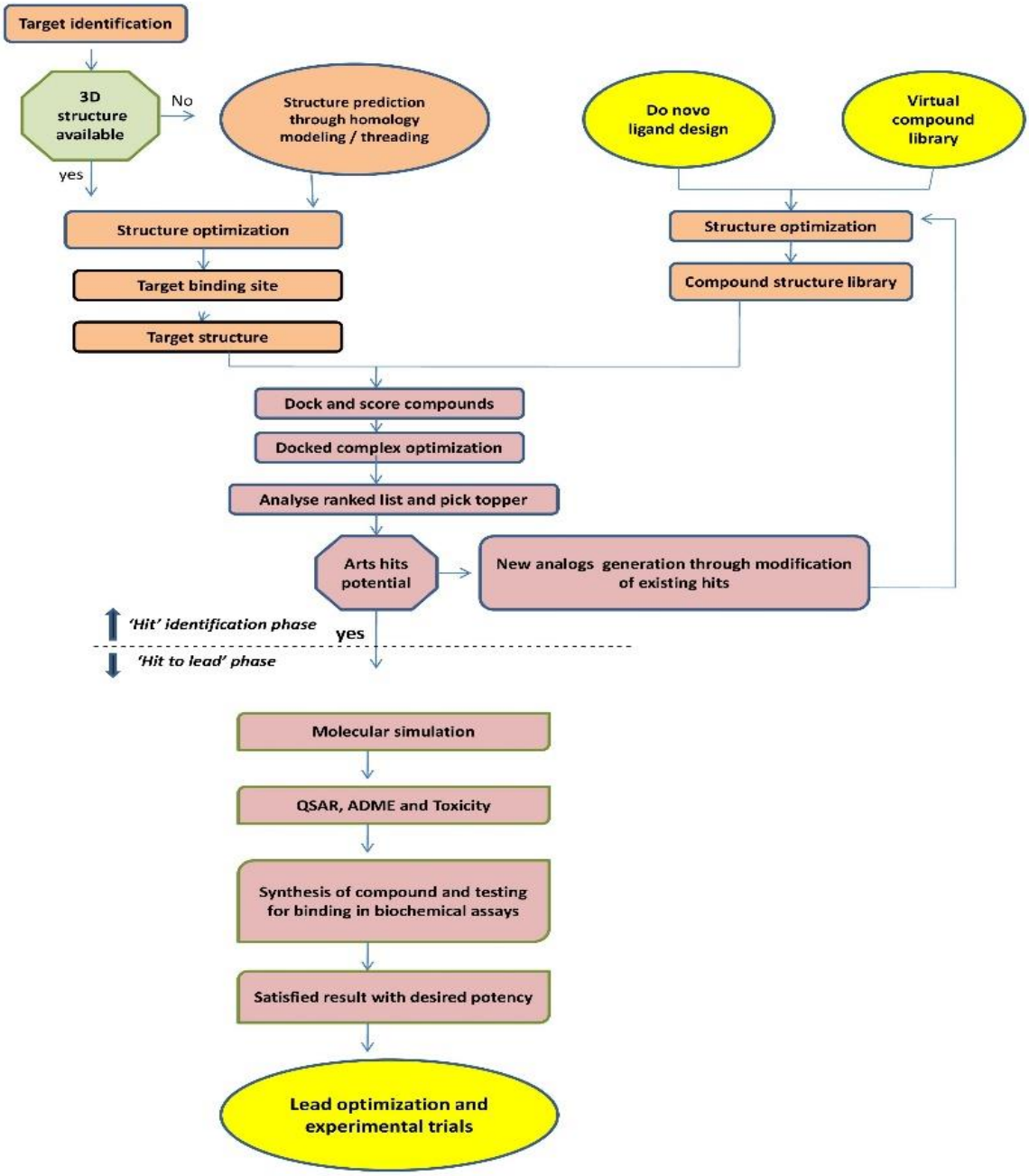


Figure1: Process flow for the 'hit identification' phase and 'hit-to-lead' phase – the structure-based drug design (SBDD) approach. (a) Target structure preparation and binding-site analyses; (b) compound library preparation; (c) docking of compounds against the target binding pocket and analyses.

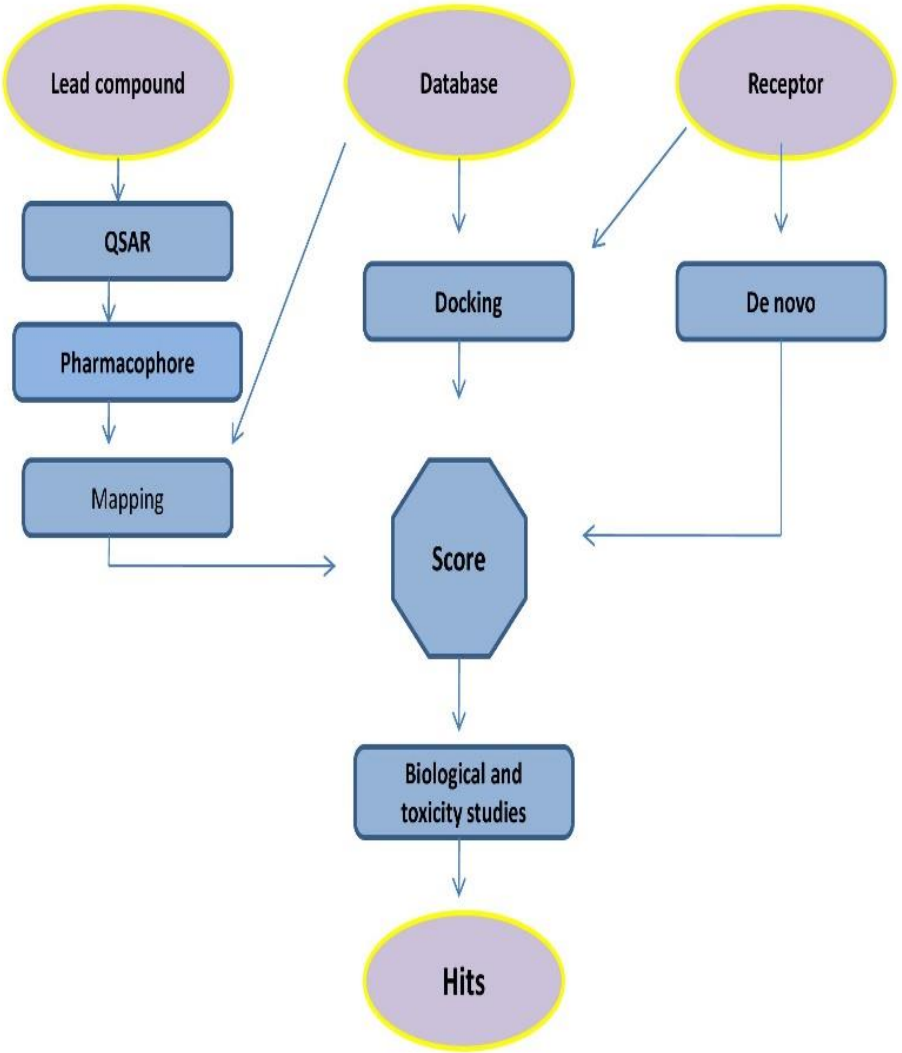


Figure 2: Schematic representation of drug design with the help of tools

Target Identification

Two key factors contribute to medication failure in clinical trials: first, therapeutic efficacy, and second, toxicity profile. corollary, choosing and validating the right targets is an important step in creating new medicines. A large group of biological components, including proteins, genomes, and RNA, are referred to as "targets." Effective, secure, suitable for clinical and commercial aims, and most significantly, "druggable" are all requirements for a good target. Both in vitro and in vivo biological reactions may be seen when a prospective medication molecule connects to a target, as to if it be a small biological entity or a larger biological molecule. This target is known as a "druggable" target. Presently, it is known that immunoglobulins are successful in preventing protein/protein interactions, although some target categories, such as G-protein-coupled receptors (GPCRs), seem to be more amenable to small molecule drug development. Suitable target characterization and confirmation allow us to increase our trust in the relationship among both the target and the disease and to determine if changing the target would have any associated health hazards. As an outcome of data mining the available biological data, target identifying has considerably increased. The adoption of a bioinformatics strategy known as data mining in this scenario is intended to help with not only discovering rather additionally picking and ranking potential disease targets(9)

Binding site recognition

A binding position is a constrained area, such as a pouch or a set of bumps, whereby ligand units can fit or bind most effectively to stimulate that receptor and/or target and have the anticipated effect. Therefore, in SBDD, it is crucial to identify the binding pocket or the active site regions in the target sequence. Recognizing the precise binding site regions is challenging since proteins can experience conformational changes; yet, there are only a few computational algorithms, like Ligsitecsc (10), Qsitefinder (11) and CASTp (12), that can correctly identify every residue at the binding location. In contrast to CAST, It maps the surface gaps using dynamically labeled molecules, Vander Waal's probe and interface energies are used by Qsitefinder to identify and group the optimal binding sites. As a result, by the software package for SBDD at our disposal, more accurate active spot forecasts can be made. Hit identification, which often probably results in a library of compounds that can interact with the target once the targets and their binding sites have been found, is the next crucial stage in SBDD. It is widely acknowledged that successful lead optimization in the

latter stages of drug development depends on the early selection of bioactive molecules with limited potency and specificity (13). Thus, the major objective of pharmaceutical chemistry continues to be the search for novel chemical entities having therapeutic utility. HTS has been acknowledged as the primary method for hit recognition up to this point Regardless of the fact that this method is particularly efficient and powerful for screening molecules of concern, it is time- and money-consuming to perform empirical study for a vast complex space. Furthermore, the effectiveness of HTS tends to decline as a screening library's size increases (14).

Virtual screening

Even though the quest for a "new recipe" for a drug is a method of constant selection, investigators attempt to narrow down the millions of candidate chemicals to the most potent selection possible. Virtual screening (VS), commonly referred to as vHTS, has gained recognition as a competitive HTS replacement on a global level. vHTS computationally searches through enormous chemical databases for substances that complement the targets. Using docking calculations, substances are screened in vHTS and filtered according to how strongly they attach to the target (15), (16).

Because the majority of these screening methods rely on data, data accessibility is still very important. Over the past 10 years, the significance of biochemical resources that serve as knowledge bases for efficient VS has increased (17). a few well-known unique molecular resources with millions of publicly accessible chemical information are highlighted. Additionally, many chemical vendors provide free entry to their libraries of compounds, which may be used for scanning (18). The pace at which drug candidates can now be identified and assessed has increased because to more powerful and reasonably priced computer clusters (19).

De novo designs

The process of creating new lead compounds from scratch is known as de novo design. This method combines vHTS with HTS in terms of hit finding. The fundamental concept of de novo design is to construct simple synthetic compounds that are optimal for the target space (20). Two alternative approaches receptor-target based design and ligand-based design—can be used to accomplish this, with the former being used more frequently than the latter. For receptor-based de novo design, protein rich constructions and their related interaction regions

are essential because the hits are made by introducing tiny pieces into the proteins' essential interaction areas, which are constructed based on the target structures. The programme can put the fragments or they can be pre-docked with framework (21).

Docking and scoring functions

SBDD's ability to accurately depict the empirical binding interactions of a tiny molecule linked to the targeted molecule is its main advantage. Docking, which includes figuring out the ligand geometry and positioning inside the test model, is a critical step in SBDD. The finest illustration of the interactions or compatibility among both the ligand as well as protein design is the "hand and glove" concept(22).

Target validation

Furthermore, after being located, the target should be thoroughly investigated. Medicines can be validated using a variety of methods, including in vitro tools, complete experimental animals, and modifying a target in diseased patients. Even although each technique is good all by itself, a multi-validation approach significantly increases assurance in the reported result. Antisense technique has the ability to be highly productive since it employs chemically altered oligonucleotides that mimic RNA and are meant to enhance a particular region of a target mRNA unit (23). By inhibiting the translational mechanism for binding towards the targeted mRNA, the antisense oligonucleotide prevents the creation of the encoded proteins. In order to demonstrate the effectiveness of antisense technology, Abbott Laboratories research scientist proposed antisense probe for the rat P2X3 receptor (24).

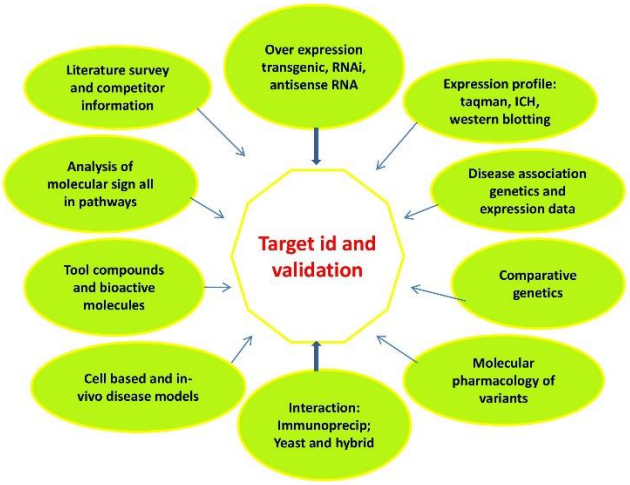


Figure:3 Target ID and validation is a multifunctional process. IHC,immunohistochemistry

The Hit Discovery Process

In the phase of drug development known as hit recognition and lead identification, which follows after the target confirmation procedure, molecule screening techniques are developed. A hit molecule is one in which functionality in a compound screening is confirmed after retesting for the purposes of this evaluation. The term "hit" can signify different things to different researchers. There are numerous screening paradigms available to find hit compounds. HTS comprises examining the complete component library against the target molecule either instantly or through a quite challenging assay strategy, like a cell-based method, whose action depends on the target which requires secondary analyses to identify the molecules' sites of activity (25). Despite using modern laboratory automation, this screening strategy makes no presumptions on the traits of the chemotypes which are most probable to interface with target molecule. Intensive or experience and understanding vetting involves choosing from the compound library smaller subsets of substances that are most likely to act at the target protein in accordance with information about the target protein and literary criticism or patent procedural rules for the groups of compounds likely to have activity at the

target molecule (26). This sort of information has more lately led to premature finding standards that conduct virtual screening of chemical databases utilising pharmacophores and molecular modelling (27). Fragment screening is the creation of libraries of extremely tiny molecules that are screened at high concentrations. Typically, this process is combined with the creation of protein structures to facilitate compound development (28). Physiological screening is a more specialized, targeted strategy that can also be employed. Instead of focusing on a single molecular element, this tissue-based strategy seeks a response that is more in line with the anticipated in vivo outcome. HTS and other chemical computer observes are designed and carried out in order to discover compounds that interact with the therapeutic target. The efficiency, selectivity, physical and chemical characteristics of the compound are then improved using chemistry programmes. Additionally, data is being gathered to back up the assertion that the disease condition would respond well to treatment focused on the pharmacological target. To find candidate molecules for clinical development, this set of actions is the focus of significant research in the pharmaceutical business and increasingly in academia.

Assay development

Although there have been more findings in recent years characterizing the use of primary cell systems for compound screening, most of the industry's assays presently, which were evolved during the age of recombinant proteins, rely on the advancement of stable mammal-cell-lines that overexpress the point of interest. (29). Target classes including receptor molecules, ion channels, and nuclear receptors have classically been tested using cell-based assays, which often result in a functional read-out as a result of drug action (30). In contrast, biochemical tests, which have been used to identify targets for receptors and enzymes, frequently just quantify the test substance's affinity for the target protein. There has been much discussion and examination of the relative benefits of biochemical and cell-based tests (31). It has been effective to find hit and candidate compounds using both assay paradigms. The following criteria must be taken into account regardless of the test format that is chosen:

1. **The assay's pharmacological significance**:- Research must be executed by means of recognized ligands with action at the target during research, if they are accessible, to identify if the assay pharmacology is indicative of the clinical condition and to demonstrate that the test is proficient of discovering molecules with the appropriate strength and MOA.

2. Reproducibility of the assay :- In a molecule screening atmosphere, the assay must be reproducible across assay plates, through screening sessions, and, in a project that may extend for numerous ages, over the course of the whole remedy advancement program.

3. Assay costs:- (CSA)Compound screening assays commonly employ microtiter plates. Assays in theoretical or for relatively small quantities of chemicals are frequently formatted on 96-well or 384-well microtiter plates, but assays in industrial field or for HTS purposes are frequently produced in 384-well or 1536-well microtiter plates with assay volumes likely few microliters. To reduce costs, the test chemicals and volume are selected each time.

4. Assay quality:- The assay quality is frequently assessed using the Z' factor (Zhang et. al., 1999). This analytic metric takes into account both the variation surrounding the assay's strong and weak signals in addition to the test's signal window. For assessing the assay integrity plate by plate, The Factor has evolved into the industrial norm. Although many organizations prefer to utilize assays with a Z factor of greater than 0.6, an assay with a Z factor of bigger than 0.4 is thought to be adequately reliable for compound screening. The Z factor goes from 0 to 1. Each test contains pharmacological controls in addition to the Z factor to assist assure its high quality.

5. Effects of compounds in the assay:- The majority of the time, organic solvents like ethanol or dimethyl sulfoxide are used to store chemical libraries (DMSO). Tests must thus be designed so that they are impervious to the solvent concentrations that are used. Biochemical experiments may be carried out at eluent levels of up to 10% DMSO, but cell-based tests are usually sensitive to doses greater than 1%. The test's false negative and false positive hit ratios are also investigated. The test has to be changed if these values are really high. Another factor to consider is the screening concentration. Compounds are typically used in assays for identifying hits at concentrations between 1 and 10 mM. At this dose, compounds with activity up to 40 mM can be discovered. You can change the test concentration to hunt for substances with a greater or lesser potency. One HTS approach used to locate hit compounds with action at GPCRs is the aequorin test (32).

6. Defining a hit series

Compound reference library have been constructed to include tiny compounds that adhere to Lipinski's Rule of Five (33) and more commonly have molecular weights of 500 Dalton or less, log P values of no more than 5, and no more than 5 hydrogen bond donors and 10 OH bond acceptors (a lipophilicity index that influences how well drugs are absorbed by the body). Molecules with these properties are denoted to as "drug-like" entities since the

majority of commercially available medicines have a molecular mass of less than 350 and a cLog P of under 3. It is essential to begin a drug discovery effort with a tiny, modest compound as the lead optimization in order to maximize strength and selectivity.

Hit-to-lead phase

During this phase of the project, it is planned to make improvements to each successful series in order to generate more powerful and selective molecules with sufficient PK characteristics to evaluate their efficacy in any accessible in vivo assays. Measuring the amount of selectivity and activity of each chemical is now standard procedure in this kind of investigation, which involves in-depth SAR research. This must be done carefully, and if the target's structural information is known, structure-based drug design methodologies using molecular modelling and technologies like X-ray crystallography and NMR may be used to create the SAR more rapidly and precisely. These procedures frequently result in the discovery of new binding upon those targeted proteins.

Lead Discovery

Choosing promising lead compounds, as was mentioned in the drug discovery overview, is the first step in lead optimization, which entails modifying leads to achieve the required potential and tunability as well as the desired ADME and IP rights (patent) position. Given the difficulties usually presented by these many and diverse purposes, locating the appropriate lead compounds might be essential to the overall viability of a drug development programmed. Every known ligand (a smaller molecule that binds to a receptor) for the target will often be taken into consideration in the lead identification strategy used in a specific drug discovery programmed. On the other hand, if there are already commercially accessible drugs for a particular target, lead compounds could be readily available; nonetheless, in this case, the main challenge might be obtaining a strong IP position. The indigenous ligand for a novel biological target, on the other hand, may not be well characterized or might not be suitable as a lead chemical when the endogenous ligands have created potent lead structures for multiple projects (34). It may not be wanted as a lead if, for instance, an endogenous ligand is a complex molecule that is challenging to change synthetically or has other unfavorable characteristics that are not easily addressed, in which case additional lead seeking strategies must be taken into consideration (35).

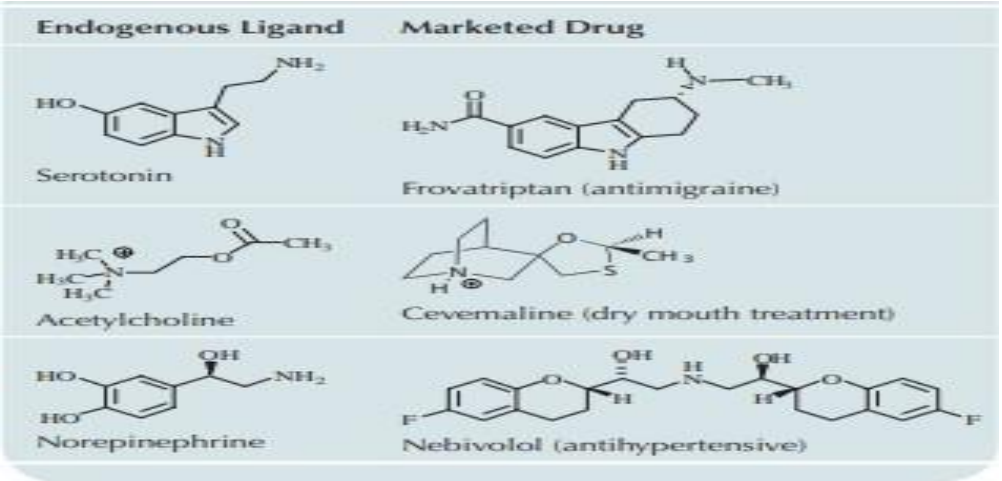
Sources of Lead Compounds

Lead compounds can be found by screening substances, include natural remedies and various chemical library resources, randomly or intentionally. Other known ligands, such as available on the market drugs, molecules isolated in studies of biotransformation, and substances used in clinical testing, are also resource of lead molecules (36).

Endogenous Ligand

Leading discovery often takes logical techniques. Finding the disease's underlying cause is the first step. Many illnesses, or at least their symptoms, are brought on by chemical imbalances in the body (either an excess or a deficiency), invasions by alien organisms, or abnormal cell proliferation. We'll go through several examples of drugs whose chemical makeup was inspired by endogenous transmitters includes serotonin, acetylcholine, and norepinephrine. Hormones are a large group of naturally occurring chemicals that have served as model substances for the creation of novel medications. Similar to neurotransmitter, hormones are made by cells, where they also interact with other cells' receptor. Neurotransmitter receptors are present close to the location of neurotransmitter secretion, but hormone receptors may be quite a distant from the region of hormone secretion. As a result, hormones must travel through the circulation to reach their site of action. One significant class of hormones are steroids, and lead compounds are contraceptives (37).

Typical Endogenous Neurotransmitter Ligands Used as Lead Compounds in Drug Discovery

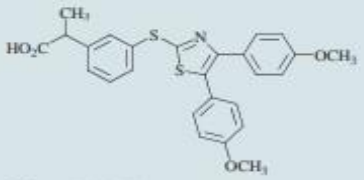
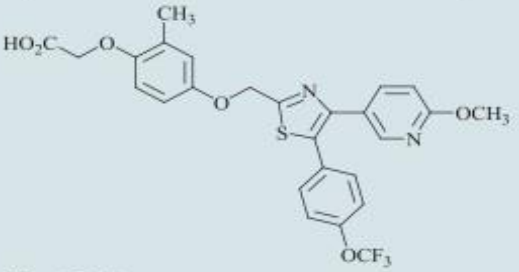
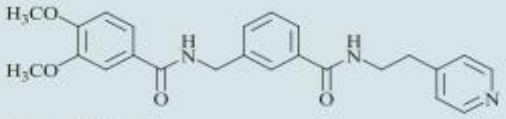
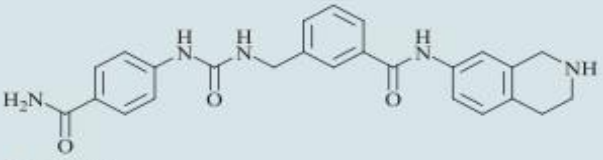
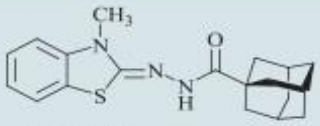
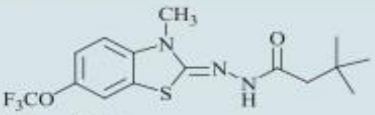
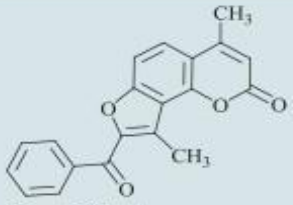
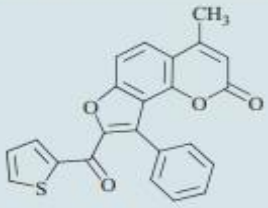


Screening of Compounds

It's possible that a target of interest lacks recognized endogenous or external ligands. Alternatively, it's likely that when looking for drugs with the required properties, starting with the known ligands for a target is not the ideal place to start. In the search for an oral medicine, for instance, many indigenous compounds are big proteins, which are frequently poor leads. Due to these reasons, lead generation screening has long been an important step in the drug discovery process, despite the fact that technological developments over the past 20 years have significantly changed the process of lead generation screening. Researchers must first devise a method to test substances for a certain biological activity in order to establish if a molecule is active. A bioassay, often referred to as a screen, can be performed in a biological system to ascertain whether a compound has the necessary activity and, if so, how powerful it is when compared to a control substance. Remember that "activity" and "potency" are two distinct concepts. In order to characterize various biological or pharmacological effects, the terms "activity" and "potency" are utilized (such as antibacterial or anticonvulsant activity). Wong, Pompliano, and colleagues developed a novel method for screening compounds that may engage including an enzyme in a metabolism to find possible lead compounds that interfere with the synthesis of bacterial cell walls. (as possible antibacterial medicines) (38).

Compound screening can also be done using nuclear magnetic resonance (NMR) spectroscopy, for which Kurt Wüthrich and Richard Ernst, respectively, got Nobel Prizes in 1991 and 2002, and electrospray ionization mass spectrometry (MS)(10), for which John Fenn won the prize in 2002 [11]. The mass spectrum can reveal tightly bound non-covalent complexes of substances with a macromolecule (such a receptor or enzyme). By adjusting the collision energy and calculating the energy at which the complex dissociates, the affinity of the ligand may be calculated. High-throughput screening (HTS)(39), from which more than two-thirds of drug discovery programmes now stem (40), was first established in the late 1980s using extremely quick and sensitive invitro screens that could be performed robotically. In a large pharmaceutical business, approximately 200,000 compounds were assayed annually in the early 1990s, increasing to 5-6 million in the middle of the decade, and then to >50 million by the end of the decade, according to Drews (41). On small (sub microgram) amounts of chemical, HTS can be performed robotically in 1536 or 3456 well titer plates (dissolved in sub microliter volumes). With these ultra-high throughput screening techniques from the early 21st century (42).

Examples of HTS and Analog Hits as a Result of Further Optimization Efforts

Biological Target	HTS Hit	Representative Structure after Initial or Full Optimization
Peroxisome proliferator-activated receptor (PPAR) δ (target class: nuclear hormone receptor)	 EC_{50} = 3200 nM	 EC_{50} = 17 nM
Rho kinase (target class: enzyme)	 IC_{50} = 2300 nM	 IC_{50} = 4 nM
KCNQ2/Q3 potassium channels (target class: ion channel)	 EC_{50} = 27 nM	 EC_{50} = 49 nM Significantly increased oral efficacy
Influenza A (H1N1) virus	 IC_{50} = 4500 nM	 IC_{50} = 70 nM

Sources of Compounds for Screening

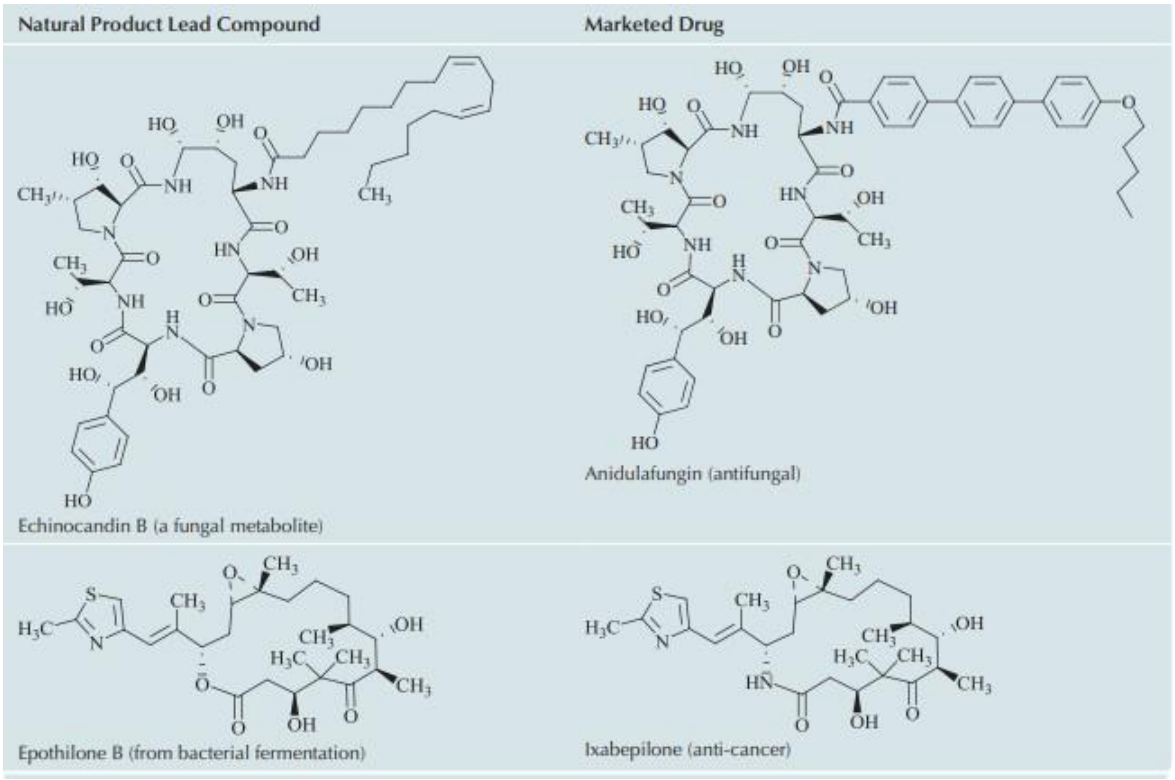
A significant second criterion for HTS is a great variety of eligible molecules for vetting, in addition to a high-throughput assay, as was already mentioned. The main chemical sources for HTS are covered in the following set of subsections. Over the last ten years, significant changes have been made to the guidelines for selecting molecules to be added to a general scanning dataset and for enhancing the selection of particular compounds for a certain screen. A major goal for a business that conducts several HTS campaigns on diverse biological target types will be the development of a screening library of chemical compounds with a variety of structural features. Similar biological activities are predicted for molecules with similar structural features, while varied biological behaviors are predicted for compounds with different structural qualities. This is generally true, but caution should be exercised when drawing inferences from such generalizations. Dixon and Villar showed that proteins have

the capacity to bind a wide range of molecules with varying structural complexity with similar strong binding affinities, while analogues that are nearly linked to these substances can occasionally have very weak binding. (43)

Natural Products

Even now, nature is still abounded in drug precursors and actual narcotics. The present category is intended to contain items made by non-mammalian natural sources, such as plants, marine creatures, bacteria, and fungi. Although strictly speaking endogenous ligands, which were also discussed previously, are also natural products. Among the roughly half of new treatments that were authorized between 1994 and 2007 that are based on natural goods, 13 medications connected to natural products were approved between 2005 and 2007. When biologicals, such as antibodies and genetically modified proteins, and vaccines are eliminated, the percentage of anticancer and anti-infective medications that originated from or were derived from natural sources between 1981 and 2006 climbs to 73% (44).

Examples of Lead Compounds from Natural Products and Marketed Drugs Derived from Them



Computational methods in lead discovery, virtual screening, and targeted (or focused) screening

It is possible to reduce a huge vetting library to a smaller collection of compounds that may be more likely to hit the target, lowering vetting efforts, by using knowledge to one or more recognized ligand for a target or about the structure of the target itself. As contrast to the stochastic process mentioned in the previous section, the screen is consequently viewed as being targeted or focused. Virtual screening is the most popular computational technique for selecting compounds. It entails quickly evaluating vast libraries of chemical structures using Insilco (by computer) to find those structures that are most likely to bind to a therapeutic target, such as a protein receptor or enzyme. Finding new scaffolds is the aim, particularly any that might already be in the collection. The technique, taken in its widest meaning, can be used to define virtual screening.

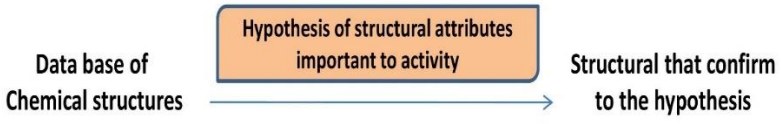
Two variables are required:

(1) An assortment of structures that may be computationally evaluated to determine their structural characteristics.

(2) A hypothesis or representation of the structural characteristics crucial for activity.

For instance, a hypothesis regarding the size and charge distribution of a binding pocket that establishes the characteristics a complementary ligand structure should have may also include other substances that could be viewed as being appropriately accessible. For instance, compounds assumed to be easily synthesizable may be found in a virtual screening database. Members of combinatorial libraries with generic synthesis techniques described in the literature, as well as chemicals that have previously been synthesized inside the organization and for which specific methodologies are known, may fall into this category (45).

Finding compounds that meet a hypothesis defining qualities (visible from a compound's structure) required for activity through virtual screening



Virtual Screening Database

One of the most important requirements for the structures that will be digitally screened is the availability of physical samples of the compounds, should the virtual screen identify them as compounds of interest. These criteria would normally support the inclusion of both drugs that

are available for sale commercially and chemicals that are part of an organization's corporate collection. In a virtual screen for fatty acid amidohydrolase inhibitors, this criterion used two databases of structural data, one representing compounds in the Lead Quest collection made available for sale commercially by Tripos (St. Louis, MO, USA), and another screening collection made available for sale commercially by May Bridge (Cornwall, England, UK). There are databases that gather compounds from the catalogues of several suppliers, in addition to the free "ZINC" database, which contains about 19 million commercially available compounds, 4 million compounds that resemble lead, and more than 13 million compounds that resemble drugs. Nearly 4 million compounds are present in the commercial Accelrys ACD. (46)

Virtual Screening Hypothesis

Numerous techniques have been developed to characterize the characteristics that may be used to evaluate a compound's potential to interact with a certain target. This led to the development of computational techniques that were more complex than the substructure approach. The following models may be used to broadly classify these techniques:

1. 2D similarity models

2. 3D-QSAR models

3. Computational docking and structure-based pharmacophore models

Two-dimensional similarity models Researchers frequently establish a set of so-called 2D descriptors and then assess how each description is satisfied by a particular molecule in order to compare two molecules that are comparable to one another. (2D) due to the way they imitate the similarities between flat buildings as they are drawn on paper. There are many different types of descriptors that are utilized. (47)

Three-dimensional quantitative structure–activity relationships It is possible to correlate diverse chemical structure series with their biological function at a particular target through the analysis of quantitative structure-activity relationships (QSARs) in three dimensions (3D-QSARs). There have been various QSAR methods developed throughout the last century. For the development of medication candidates, these strategies have shown to be helpful

predictive tools. A description of the conventional 2D QSAR techniques, which only considered 2D structures, is included in the historical history of computational approaches in lead modification. Several computer-based methodologies have been used to investigate the link between molecule structure and receptor binding and, subsequently, activity. While some are discussed here, others are cited in the General References section at the chapter's end (48

A pharmacophore model is a three-dimensional depiction of the ligand areas thought to be involved in interactions with biological targets. A pharmacophore model is a three-dimensional depiction of the ligand areas thought to be involved in interactions with biological targets. Using known ligands for the target, a ligand-based pharmacophore model was developed (in contra sttoa structure-based pharmacophore model, which is based on knowledge of the receptor structure, see below). With the aid of computer programmes like Catalyst (Accelrys, Inc., San Diego, CA, USA), DISCO (Tripos, Inc., St. Louis, MO, USA), Ligand Scout (Inteligand, Wien, Austria), Phase (Schrodinger, Portland, OR, USA), or MOE, one or more models can be produced from the structures of a group of known ligands (Chemical Computing Group, Montreal, Canada). This technique is known as receptor mapping (49).

Conclusion-

Complex and difficult medication development is one of the most challenging aspects of pharmaceutical research and development. There is a lot of money and time invested in the development of novel medicinal medicines. A medication’s action is influenced by several aspects, including its bioavailability, toxicity and metabolism making rational drug design a long-held dream. Reasonable drug design has lately become a reality because to recent development in fields like structural characterization of biomacromolecules, computer science and molecular biology. In the past, CADD was seen as only a promising method. It’s a realistic and useful technique to assist the pharmacist. However, as a thinking help and a guide for synthesis this method is more useful than it is as a source of pharmacological novelty on its own. Although computationally generated and tested medications may give a clear molecular basis and most all a stimulus to the imagination, they are not without their limitation.

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