

## RECENT TRENDS IN PHARMACEUTICAL CHEMISTRY FOR DRUG DISCOVERY

Sathyaraj A

Department of Chemistry, Krishna University, Machilipatnam, Andhra Pradesh, India.

\*Corresponding Author: [arsathya.pharma@gmail.com](mailto:arsathya.pharma@gmail.com)

### ABSTRACT

Pharmaceutical chemistry is used to the development and assessment of therapeutic compounds. And the Pharmaceutical chemistry encompasses drug design, drug **synthesis**, and the evaluation of drug efficacy (how effective it is in treating a condition) and drug safety. Drug discovery is the core of pharmaceutical chemistry. The drug discovery process includes all the stages of drug development, from targeting a disease or medical condition to toxicity studies in animals, or even, by some definitions, testing the drug on human subjects. The field of pharmaceutical chemistry is diverse and involves many areas of expertise. Natural-product and analytical chemists isolate and identify active components from plant and other natural sources. Theoretical chemists construct molecular models of existing drugs to evaluate their properties. These computational studies help medicinal chemists and bioengineers design and synthesize compounds with enhanced biological activity. Pharmaceutical chemists evaluate the bioactivity of drugs and drug metabolites. Toxicologists assess drug safety and potential adverse effects of drug therapy. When a drug has been approved for human studies, clinicians and physicians monitor patients' response to treatment with the new drug. The impact of pharmaceutical chemistry on the normal human life span and on the quality of life enjoyed by most people is hard to overestimate.

**Keywords:** Drug Design, Drug Synthesis, Evaluation of Drug Efficacy and Drug safety.

### INTRODUCTION

Pharmaceutical chemists are involved in the development and assessment of therapeutic compounds. Pharmaceutical chemistry encompasses drug design, drug **synthesis**, and the evaluation of drug efficacy (how effective it is in treating a condition) and drug safety. Prior to the nineteenth century, schools of pharmacy

trained pharmacists and physicians how to prepare medicinal remedies from natural organic products or inorganic materials. Herbal medications and folk remedies dating back to ancient Egyptian, Greek, Roman, and Asian societies were administered without any knowledge of their biological mechanism of action. It was not until the early 1800s that

scientists began extracting chemicals from plants with purported therapeutic properties to isolate the active components and identify them. By discovering and structurally characterizing compounds with medicinal activity, chemists are able to design new drugs with enhanced potency and decreased adverse side effects.

### Pharmaceutical Chemistry in Drug Discovery and Novel Drug Delivery System

Drug discovery is the core of pharmaceutical chemistry. The drug discovery process includes all the stages of drug development, from targeting a disease or medical condition to toxicity studies in animals, or even, by some definitions, testing the drug on human subjects. Typically, conditions that affect a larger percentage of the population receive more attention and more research funding. Antiulcer drugs and cholesterol-reducing agents are currently the therapeutic areas of greatest emphasis. To develop a drug to target a specific disease, researchers try to understand the biological mechanism responsible for that condition. If the biochemical pathways leading up to the diseases are understood, scientists attempt to design drugs that will block one or several of the steps of the disease's progress. Alternatively, drugs that boost the body's own defense mechanism may be appropriate.

How do chemists "discover" drugs? Often there is an existing remedy for a condition, and scientists will evaluate how that drug exerts its actions. Once the drug's structure is known, the drug can serve as a prototype or "lead compound" for designing more effective therapeutic agents of similar chemical structure. Lead compounds are molecules that have some biological activity with respect to the condition under investigation. However, the lead compound may not be effective in combating the disease, or it may produce undesirable side effects. Lead optimization involves chemical modifications to the lead compound to produce a more potent drug, or one with fewer or decreased adverse effects.

Computers have transformed the drug discovery process. Rational drug design involves computer-assisted approaches to designing molecules with desired chemical properties. Rational drug design is based on a molecular understanding of the interactions

between the drug and its target in biological systems. Molecular modeling software depicts three-dimensional images of a chemical. Mathematical operations adjust the positions of the atoms in the molecule in an attempt to accurately portray the size and shape of the drug, and the location of any charged groups. Chemists can vary the atoms or groups within the model and predict the effect the transformation has on the molecular properties of the drug. In this way, new compounds can be designed.

Advances in technology have made it possible for medicinal chemists to synthesize a vast number of compounds in a relatively short time, a process referred to as *combinatorial chemistry*. In this technique, one part of a molecule is maintained, as different chemical groups are attached to its molecular framework to produce a series of similar molecules with distinct structural variations. Combinatorial libraries of these molecular variants are thus created.

Every chemical that is synthesized must be tested for biological activity. *In vitro* testing involves biological assays outside a living system. For example, if the desired effect of a drug is to inhibit a particular enzyme, the enzyme can be isolated from an organ and studied in a test tube. New technologies have made it possible to assay large numbers of compounds in a short period. High-throughput drug screening allows pharmaceutical chemists to test between 1,000 and 100,000 chemicals in a single day! A compound that demonstrates some biological activity will undergo further tests, or it may be chemically modified to enhance its activity. As a consequence, chemical libraries consisting of potentially therapeutic compounds are developed. Each of these compounds can then serve as leads for the development of new drugs to be screened.

Once a drug shows promise *in vitro* as a therapeutic agent, it must also be screened for toxic properties. Adverse drug side effects are often due to the interaction of the drug with biological molecules other than the desired target. It is very rare that a drug interacts with only one type of molecule in a living system. Drug selectivity refers to the ability of the compound to interact with its target, not with other proteins or enzymes in the system. To investigate drug toxicity, animal studies are

performed. These studies also estimate mutagenicity, that is, whether the compound under investigation damages genetic material.

Rarely does a drug pass through a biological system unchanged. Most drugs undergo chemical transformations (in a process known as drug metabolism) before they are **excreted** from the body. The drug transformation products (metabolites) must be identified so that their toxicological profiles can be determined.

Since the 1970s more attention has been given to drug formulation and methods of drug delivery. Historically, drugs have been administered orally, as a pill or a liquid, or in an injectable form. The goal of drug-delivery systems is to enable controlled and targeted drug release. Today, many medications are commonly introduced as inhalants or in a time-release formulation, either encapsulated in a biodegradable polymer or by means of a transdermal patch.

### Pharmaceutical Chemistry in Clinical Trials

Once scientists and government regulatory agencies have determined the drug candidate to be relatively safe, it can enter into clinical trials. The clinical stage involves four phases of testing on human volunteers. Animal studies and in vitro testing continue during clinical investigations of a drug. Drug-therapy evaluation is very costly and time consuming. *Phase I* clinical trials evaluate drug tolerance and safety in a small group of healthy adult volunteers. *Phase II* trials continue to assess the drug's safety and effectiveness in a larger population. Volunteers participating in phase I trials understand that they are receiving experimental therapy. While those patients involved in phase II clinical trials are made aware of the medication and any known side effects, some of the volunteers may be administered a placebo (a compound with no pharmacological activity against the condition being treated) rather than the drug being studied. In a blind study, only the physician administering therapy knows whether the patient is receiving the drug or a placebo. Both groups of patients are monitored, and physicians or clinicians evaluate whether there is significant improvement in the condition of the group receiving the experimental drug, compared with those individuals who were

administered a placebo. In a double-blind study, neither the physician nor the patient knows whether the drug, a placebo, or a related remedy has been administered. Therapy is monitored by an outside group.

Phase III and phase IV clinical trials involve larger populations. During phase III trials, which can last two to eight years, a drug is often brought to market. Phase IV studies continue after the drug is being marketed.

### Combinatorial Chemistry in Drug Discovery

Combinatorial chemistry is a sophisticated set of techniques used to synthesize, purify, analyze, and **screen** large numbers of chemical compounds, far faster and cheaper than was previously possible. The direct precursor of combinatorial chemistry was the solid-phase synthesis of **polypeptides** developed by American biochemist Robert Bruce Merrifield in the 1960s, followed by the advances in laboratory automation since then. Initial development of the field has been led by the pharmaceutical industry in the search for new drugs, but its applications are spreading into other fields of chemistry. Other terms associated with this field are *parallel array synthesis* and *high-throughput chemistry*.

Whereas classical synthetic chemistry involves the stepwise synthesis and purification of a single compound at a time, combinatorial chemistry makes it possible to synthesize thousands of different molecules in a relatively short amount of time, usually without the intermediate separation of compounds involved in the synthetic pathway, and with a high degree of automation. Such procedures result in the production of new compounds faster and in greater numbers than is possible with standard synthetic methods. The first and still the most common type of combinatorial synthesis involves attaching a molecular species onto a macroscopic substrate such as a plastic bead and performing one or several well-characterized chemical reactions on the species. After each reaction, the product mixture can be split among several reaction containers and then recombined after the reaction (a procedure called *mix and split*), or else carried out in parallel containers. The resulting mixture of compounds is referred to as a *molecular library* and can contain many thousands of individual compounds. The

analysis, or *screening*, of these libraries to identify the compounds of interest, along with their subsequent isolation and identification, can be completed by a variety of methods. One example is *iterative deconvolution*; it involves the successive identification of each of the units backward along the chain of synthesized units. Another, called *positional scanning*, requires the multiple synthesis of a library, each time varying the location of a known unit along the chain and comparing the activities of the resulting libraries. More recent advances in library screening involve the "tagging" of a substrate with tiny radio frequency transmitters or unique two-dimensional barcodes. Another important recent advance by researchers allows combinatorial syntheses to be carried out in solution, which further extends the scope and utility of this field.

Although the initial applications of combinatorial and high-throughput chemistry have occurred in the pharmaceutical field, the same techniques are now being used successfully to aid in the discovery of new catalysts, polymers, and high temperature superconductors.

### Pharmaceutical Chemistry for Drug Discovery

**Significance of Recent Trends** reviews the state of the art and aims to determine the significance of technology and market trends in pharmaceutical chemistry for advancing productivity in drug discovery. Although the fundamental task of medicinal chemists has not changed drastically over time, the chemical and computational tools and perspectives at their disposal have advanced significantly. One in particular, fragment-based drug design, stands out as promising major improvements in research productivity.

We examine pharmaceutical chemistry-related approaches and methodologies that drug discovery organizations employ in an effort to increase productivity in early drug discovery and decrease attrition at later pipeline stages. Key topics considered include structure-based drug design, fragment-based drug design, natural products-based drug design, diversity-oriented synthesis, and chemogenomics. An overall assessment of the current and potential value of these approaches is presented. Various flavors of computer-aided drug design are also

considered, as the complexity and limitations of drug discovery programs that are based on biochemical screens of large compound collections have been major factors in stimulating the growth of this modality.

### CONCLUSION

The field of pharmaceutical chemistry is diverse and involves many areas of expertise. Natural-product and analytical chemists isolate and identify active components from plant and other natural sources. Theoretical chemists construct molecular models of existing drugs to evaluate their properties. These computational studies help medicinal chemists and bioengineers design and synthesize compounds with enhanced biological activity. Pharmaceutical chemists evaluate the bioactivity of drugs and drug metabolites. Toxicologists assess drug safety and potential adverse effects of drug therapy. When a drug has been approved for human studies, clinicians and physicians monitor patients' response to treatment with the new drug. The impact of pharmaceutical chemistry on the normal human life span and on the quality of life enjoyed by most people is hard to overestimate.

Each of the aforementioned technological modalities is viewed in terms of practical examples and commercial activity. Outsourcing arises as a prominent theme in the applications realm, with special emphasis on companies with primary operations in countries with developing economies, notably China, India, and Russia. Among 32 companies considered, structure-based drug design is the most prevalent activity with most players emphasizing the fragment-based variation. Virtual screening is the second-most prevalent modality, whereas natural products, diversity-oriented synthesis, and chemogenomics appear in only a small minority of cases.

A thorough analysis of recent trends in pharmaceutical chemistry and evaluation of their significance for advancing productivity in drug discovery is presented.

This report includes:

1. A critical evaluation of chemical and computational technological modalities, their current and potential value, and their commercial manifestations.

2. A consideration of market dynamics with an emphasis on outsourcing and user views on the implications of current practices in drug discovery organizations.
3. Insights gleaned from an extensive literature review, discussions with industry experts, and an opinion survey of personnel active in pharmaceutical chemistry for drug discovery.

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