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# A Review on Drug Design

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## ABSTRACT

'Human life is more precious than any other thing' so to take care of it there is ultimate requirement of better drug treatment, hence there is the birth of drug design & new invention in drug development takes place in the pharmaceuticals. In present scenario the drug demand in the pharmaceutical market is increasing day by day, hence various methods of drug design are being developed to create a new drug with less cost, less efforts, less time and maximum efficiency. There is a observation that, various methods and approaches are use to design a drug, like Molecular modeling, Quantitative structure activity relationship, Combinatorial chemistry, Structure based drug designing, Computational chemistry, In silico drug designing, Synthone approach. But in the above mentioned methods all are not used routinely. The most convenient methods to be used according to my study and observations are Molecular modeling and computational chemistry. In this method we can save the time by structure activity relationship or mechanism of action of a compound without performing experimental work, but by changing the molecular structure or by use of different computer software. Hence these methods are time saving, economic to gives better results.

**Keywords:** Drug design, Molecular modeling, Computational, chemistry, Synthone approach.

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## INTRODUCTION

The lifestyle of human being is changing drastically. Because of unaware of health, they are very much prone to disease. When such conditions happen they require the medical treatment, there is no panacea. This leads to development of new moieties and designing of new drug. As drug designing is a challenging job involving efforts of scientists for several years still more is a need to select appropriate scheme to design drug. As far as 'human life is more precious than any other thing' so to take care of it there is ultimate requirement of better drug treatment & hence there is the birth of drug design & new invention in drug development takes place in the pharma market place. A drug is defined as an agent intended for use in the diagnosis, mitigation, treatment, cure, or prevention of disease in humans or in other animals[1]. The development of a new logical and scientific approach in discovery of a new drug which is known as 'drug design'[2].

## Designing of Drug[3]

The shortcoming of traditional drug discovery; as well as the allure of a more deterministic approach to combating disease has led to the concept of "Rational drug design".

**Drug Design** is the approach of finding drugs by design, based on their biological targets. Typically a drug target is a key molecule involved in a particular metabolic or signaling pathway that is specific to a disease condition or pathology, or to the infectivity or survival of a microbial pathogen. Drugs may be designed that bind to the active region and inhibit this key molecule. However these drugs would also have to be designed in such a way as not to affect any other important molecules that may be similar in appearance to the key molecules. Sequence homologies are often used to identify such risks. Other approaches may be to enhance the normal pathway by promoting specific molecules in the normal pathways that may have been affected in the diseased state. The structure of the drug molecule that can specifically interact with the biomolecules can be modeled using computational tools. These tools can allow a drug molecule to be constructed within the biomolecule using knowledge of its structure and the nature of its active site. Construction of the drug molecule can be made inside out or outside in depending on whether the core or the R-groups are chosen first. However many of these approaches are plagued by the practical problems of chemical synthesis. Newer approaches have also suggested the use of drug molecules that are large and proteinaceous in nature rather than as small molecules. There have also been suggestions to make these using mRNA. Gene silencing may also have therapeutically applications[4].

**Factors Governing Drug Design**[5]

A few cardinal factors governing the efficacy towards the evaluation of drug design include:

1. The smaller the expenditure of human and material resources involved evolving a new drug of a particular value, the more viable is the design of the programme.
2. Experimental animal and clinical screening operations of the new drugs.
3. Relationship between chemical features and biological properties need to be established retrospectively.
4. QSAR vary to an appreciable extent in depth and sophistication based on the nature of evaluation of structure or activity. A purposeful relation of structural variables must include steric factors, electronic features of component functional groups and, in general, the molecule as a whole.
5. The trend to synthesize a huge number of newer medicinal compounds indiscriminately for exploratory evaluation still prevails which exclusively reflects the creative genuineness and conceptual functions of a highly individualized expression of novelty by a medicinal chemist.
6. Introduction of functional group in a molecule that need not essentially resemble metabolites, but are capable of undergoing bonding interactions with important functional groups of biochemical components of living organisms affords an important basis for exploration.
7. Disease etiologies and various biochemical processes involved prove useful.

**Design of a drug**

In the real work, the researchers will exploit all of the possible approaches to design or find good candidates for drug. The following figure briefly shows the flowing of drug design. Again almost nobody could design a drug without any assistance of computer tools, even after knowing the detail information of the target molecule, as shown in figure 1.

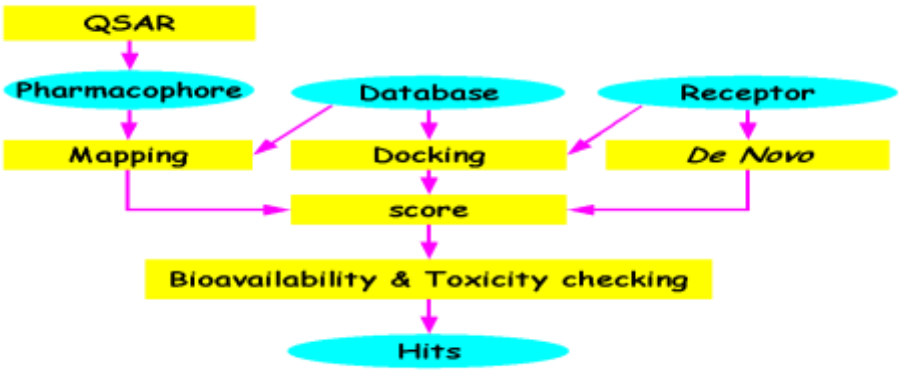



**Figure 1: QSAR Type Drug Design**

**Methods of lead discovery**[2]

**Concept of Lead**

Drug design is a vital process of envisioning and preparing specific new molecules that can lead more efficiently to useful drug discovery. This may be considered broadly in terms of two types of investigational activities,

- Exploration of lead, which involves the search for a new lead.
- Exploration of lead that requires the assessment, improvement and extension of the lead.

There are several approaches which can be employed for lead identification. In order to identify a lead nucleus in a given series, the whole series should be analyzed for a particular biological activity. Once the lead is identified, it can be structurally modified to improve the potency. Following are some of the important methods which can be used for lead identification: Random Screening, Non-random Screening, Drug Metabolism Studies, Clinical Observations.

**Rational Approaches to Lead Discovery**

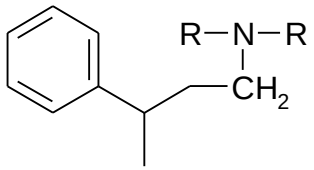
The knowledge about the receptors and their mode of interaction with drug molecules plays an important role in drug design. This knowledge may be used to develop conformationally bioactive skeletons having exact three dimensional complementarily to a receptor. Greater potency high selectivity and less adverse effects are expected by reducing the flexibility of the drug structure. For example, replacement of a terminal N, N-diethyl amino group by piperidino exploits the decreasing valency angle at tertiary nitrogen of the latter so that access of the basic group to anionic site might be improved. This modification leads to development of major tranquilizers, local anesthetics, antihistaminic and spasmolytics. Incorporating a rigid ring leads to altered pharmacokinetic and pharmacodynamic features due to altered pKa of the amine and lipophilicity of the molecule.

**Optimization of the Lead**

Once the lead nucleus is identified, it is easy to exploit. This process is rather straight forward. Various approaches are employed in order to improve the desired pharmacological properties of the lead nucleus. Important amongst them are:

**Identification of the Active Part (The Pharmacophore)**

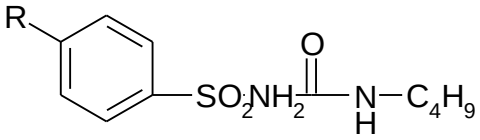
Once such pharmacophore is identified, structural modifications can be done to improve pharmacokinetic properties of the drug. For example, the presence of the phenyl ring, asymmetric carbon, Ethylene Bridge and tertiary nitrogen are found to be minimum structural requirement for a narcotic analgesic to become active.




Pharmacophore for narcotic drug

**Functional group optimization**

The activity of a drug can be correlated to its structure in terms of the contribution of its functional groups to the lipophilicity, electronic and steric features of the drug skeleton. Hence, by selecting proper functional group, one can govern the drug distribution pattern and can avoid the occurrence of side effects. For example, the amino group of carbutamide (antibacterial agent) was replaced by the methyl group to give tolbutamide (antidiabetic agent).

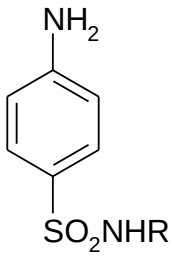



Carbutamide: R=$NH_2$

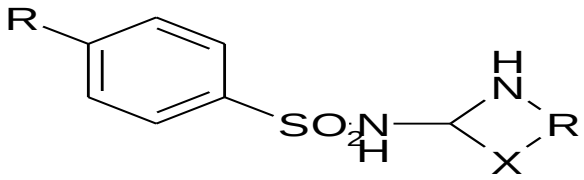
Tolbutamide: R=$CH_3$

**Structure Activity Relationship Studies**

The physiological action of a molecule is a function of its chemical constitution. This observation is the basis of SAR-studies. SAR studies usually involve the interpretation of activity in terms of the structural features of a drug molecule. Generalized conclusions then can be made after examining a sufficient number of drug analogues. For example, sulfonamides are found to be associated with diuretic and antidiabetic activities in addition to their antibacterial activity. The generalized structure needed for individual activity is represented below:

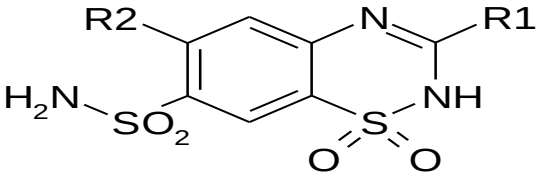



Antibacterial sulphonamide



Antidiabetic sulphonamide

(X = O,S or N)



Diuretic sulphonamide

**Bioisosterism**

The purpose of molecular modification is usually to increase potency, selectivity, duration of action and reduce toxicity. Bioisosteres are substituents or groups that have similar physical or chemical properties and hence similar biological activity pattern. **Classical bioisosters:** Univalent atoms and groups, Biovalent atoms and groups, Trivalent atoms and groups, Tetravalent atoms, Ring equivalents. **Non-classical bioisosters:** Halogens, Ethers, Carbonyl group, Carboxylic acid group, Hydroxyl group, Catechol, Thiourea, Spacer group, Ionizing analogs.

**Prodrug Designing**

Prodrug is a chemically modified form of a drug which has superior delivery properties. The term prodrug was coined by Albert. Prodrug may be considered as drug containing specialized non toxic protective group utilized in a transient manner to alter or eliminate undesirable properties in the parent drug. Prodrug designing is required to overcome many formulation pharmacokinetic or pharmacodynamic drawbacks. The prominent drawbacks include:

1. Unpleasant taste or odor (gastric irritation)
2. A wide range of adverse effects
3. Shorter duration of action
4. Instability
5. Site non-specific
6. Poor absorption or distribution
7. Poor water solubility
8. Some compounds are more active but unable to reach the site of action (e.g. GABA).

**ADME Property Prediction**[6]

Drug discovery needs the study of what the drug does on the body (pharmacodynamics), curing the disease without causing harmful side effects, and of what the body does on the drug (pharmacokinetics), namely ADME (absorption, distribution, metabolism, and excretion) of the drug. For clinical trials in the USA, a drug candidate has to be filed as an Investigational New Drug (IND), and in fact 90% of such New Chemical Entities (NCEs) applied for IND fail in the clinical trials due to ADME and/or toxicity defects.

**Rational Drug Designing**

Rational drug designing is a process used in the biopharmaceutical industry to discover and develop new drug compounds. RDD uses a variety of computational methods to identify novel compounds, design compounds for selectivity, efficacy and safety, and develop compounds into clinical trial candidates. These methods fall into several natural categories-structure-based drug design, ligand based drug design, de novo design and homology modeling- depending on how much information is available about drug targets and potential drug compounds.

**Rational Approach**

The rational approach to drug design may be viewed from different angles, namely:

- Quantum mechanical approach
- Molecular orbital approach
- Molecular connectivity approach
- Linear free-energy approaches

**Advantages of Drug Design**

- At least one new compound of known activity is found.
- The new structural analogues even if not superior may be more economical.
- Identical chemical procedure is adopted and hence, considerable economy of time, library and laboratory facilities.
- Screening of a series of congener (i.e., member of the same gene) gives basic information with regard to pharmacological activity.
- Similar pharmacological technique for specific screening may be used effectively.

The cardinal objectives of the method of variation are:

- To improve potency
- To modify specificity of action
- To improve duration of action

- To reduce toxicity
- To effect ease of application or administration or handling
- To improve stability
- To reduce cost of production

## METHODS OF DRUG DESIGN

### Molecular Modeling[7, 8, 9, 10]

Molecular modeling used in several different research areas, and therefore the term does not have rigid definition.

The term molecular modeling comprises a variety of computer based methods which are used to construct three dimensional models of chemical compounds and to calculate different properties for these compounds

### Molecular Modeling Strategies

Currently, two major strategies are used for the conception of new drugs.

- Direct drug design
- Indirect drug design

### Molecular Mechanics[11, 12]

The term molecular mechanics refers to the use of Newtonian mechanics to model molecular systems. The potential energy of all systems in molecular mechanics is calculated using force fields. Molecular mechanics can be used to study small molecules as well as large biological systems or material assemblies with many thousands to millions of atoms, as shown in figure 2.

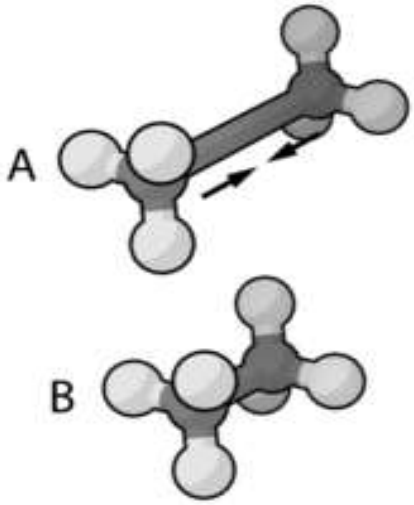



**Figure 2: Simulated using a "bead" model that assigns two to four particles per amino acid a force field is used to minimize the bond stretching energy of this ethane molecule**

All-atomistic molecular mechanics methods have the following properties:

- Each atom is simulated as a single particle
- Each particle is assigned a radius (typically the van der Waals radius), polarizability, and a constant net charge (generally derived from quantum calculations and/or experiment)
- Bonded interactions are treated as "springs" with an equilibrium distance equal to the experimental or calculated bond length

The interactions between atoms are divided into bonded and nonbonded classes. Molecular Design, Drug Discovery, Biomaterials and Nanotechnology**.**

**Nucleotide and protein sequences and variation**

- associations of homologous sequences
- genetic maps
- gene/protein/disease associations
- gene to metabolic pathway associations
- gene and protein expression data
- protein structural information
- function prediction from sequence and structure
- species/taxonomic distribution

**Nanobiology**, a sub-specialty of nanotechnology, offers the possibility of advancement in biology and medicine. Nanobiology applications include technologies and applications in biomolecular components development and biocompatible surfaces integrated into microscale systems, implantable biochip devices, synthetically engineered quasi-viral components, modified DNA, structured proteomics, pseudoproteins, biomolecular "devices".

**Quantum Mechanics**[12, 13]

One of the great theoretical accomplishments of the 20$^{th}$ century was the development of quantum mechanics. The philosophical interpretations of quantum mechanics may be considered weird from the standpoint of our practical everyday experiences in the macroscopic world. Quantum mechanical methods offer the most detailed description of the molecules chemical behavior.

**Quantitative Structure Activity Relationship**[14]

Quantitative structure-activity relationship (QSAR) is the process by which chemical structure is quantitatively correlated with a well defined process, such as biological activity or chemical reactivity. For example, biological activity can be expressed quantitatively as in the

concentration of a substance required to give a certain biological response. The mathematical expression can then be used to predict the biological response of other chemical structures.

**QSAR's most general mathematical form is**

Activity = *f* (physiochemical properties and/or structural properties). The basic assumption for all molecule based hypotheses is that similar molecules have similar activities. This principle is also called **Structure-Activity Relationship (SAR).**

**3D-QSAR: 3D-QSAR** refers to the application of force field calculations requiring three-dimensional structures, e.g. based on protein crystallography or molecule superposition. It uses computed potentials, rather than experimental constants and is concerned with the overall molecule rather than a single substituent. It examines the steric fields (shape of the molecule) and the electrostatic fields based on the applied energy function.

**Combinatorial Chemistry[15]**

Combinatorial chemistry is defined as 'the systematic and repetitive, covalent connection of a set of different building blocks of varying structures to yield a large array of diverse molecular entities'.

**Combinatorial synthesis**

The solid phase technology used in a combinatorial library can be broken down into three major compounds.

1. First is the solid support tat should be stable to a wide range of organic solvents in reagents.
2. Second is the linker, which connects the support to the scaffold or target molecule.
3. Tired is the target molecule or scaffold, which should be synthesized in high yield purity. Solution phase method-

**Biological source as method**

A variety of biological systems are available for library construction, phage particles, polysomes plasmids, bacteria etc., however, choosing the appropriate system depends; on the desirability of the features characteristic of that particular type library.

**Combinatorial approach has two phases**

1. Creating chemical libraries
2. Identification of active ingredient

**Creating chemical libraries**

Chemical library is defined as the set of compounds or collections of different molecules prepared either synthetically or biosynthetically. Combinatorics has two basic techniques and their disposal to creating chemical libraries.

i) Split and Mix Synthesis

ii) Parallel synthesis

**Identification of active ingredient**-The ultimate goal of producing combinatorial libraries is to discover compounds that have some desired behavior and associated with this behavior to serve as a drug.

**Application of Combinatorial Chemistry**

Various applications of combinatorial chemistry are,

1) Finding the right combination of drug molecules.
2) Combinatorial chemistry provides fresh and promising leads for medicinal chemistry.
3) Synthesis of small molecule libraries.
4) Application of antibody libraries obtained by combinatorial chemistry.
5) Discovery of enzyme inhibitors through combinatorial chemistry.
6) This is the tool for lead optimization.
7) Combining structure based drug design and combinatorial chemistry for rapid lead discovery.
8) Small peptide can mimic erythropoietin.
9) Combinatorial methods net a thin film dielectric discovery.
10) Combinatorial chemistry introduces new software systems to manage flood of information.
11) A qualitative and quantitative characterization of known drug database through combinatorial libraries[18].

**Combinatorial Chemistry: A Strategy for the Future**[16]

Combinatorial chemistry is one of the important new methodologies developed by academics and researchers in the pharmaceutical, agrochemical, and biotechnology industries to reduce the time and costs associated with producing effective, marketable, and competitive new drugs. The field represents a convergence of chemistry and biology, made possible by fundamental advances in miniaturization, robotics, and receptor development.

**Structure-Based Drug Design**[17, 18]

Structure-based design is one of the first techniques to be used in drug design. Structure-based design refers specifically to finding and complementing the 3D structure (binding and/or active site) of a target molecule such as a receptor protein. Chemists may be guided to subsets of compounds with desired features to complement 3-dimensional shape of the site. From the geometry and functional features of the binding site, complementary structures of a compound (ligand) are so designed as to have high binding affinity with the target molecule. It is a powerful technique to design a corresponding ligand specifically interacting with the target, particularly

for the development of a novel therapeutic through stimulation or inhibition of the receptor protein, as shown in figure 3.

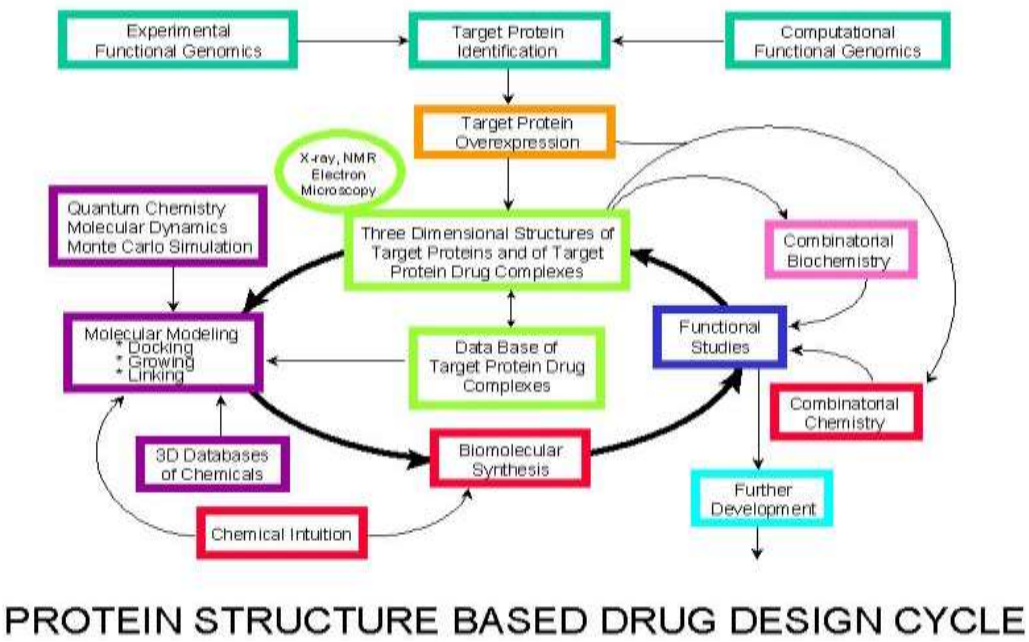



**Figure 3: Protein Structure Based Drug Design**

**Structure Guided Drug Design**[19]

The report STRUCTURE-GUIDED DRUG DESIGN goes beyond the concept of structure-based drug design and its limited application to targets with a known 3D structure. STRUCTURE-GUIDED DRUG DESIGN has a broader remit and argues for the overriding importance of structure for the whole of the drug discovery process, from indication selection to market entry and beyond.

**Computational Chemistry**

The current roles of the computer in drug design

- Storing and retrieving information
  - Structures determined experimentally by X-Ray crystallography for biological targets (enzymes) and drug molecules
  - Molecules and activities testing the affect of small structural changes on biological activity
  - Information about toxicity and its relationship to structure
- Visualizing molecules
  - Similarities/differences between drugs acting in the same way
  - Interaction between drugs and receptors
- Calculations

- Interaction strengths
- Motion (dynamics)

**In silico drug design: ADME/Toxicity prediction**[18]

The phrase "drug-like" generally means molecules which contain functional groups and/or have properties consistent with the majority of known drugs. Lead structures are ligands that typically exhibit suboptimal target binding affinity. Studies have shown that there exists a difference between leads and drugs which can be expressed as follows: Lead structures exhibit, on average, less molecular complexity (less molecular weight, less number of rings and rotatable bonds), are less hydrophobic (lower ClogP and LogD74) and have lower polarizability (less CMR). Leads should display the following properties to be considered for further development in the drug discovery process or to be called as "drug-like":

**SYNTHON APPROACH**

**Disconnection**

An operation which involves breaking a bond between two atoms. Disconnection is the reverse of synthetic step of reactions and we disconnect only when we have a reliable reaction in mind.

**Synthon**

An idealized fragment usually an ion (positive/negative) or a radial (neutral) obtained by disconnection. An idealized fragment which may not be involved in reaction but which help us to work out which reagent to be used.

**Functional Group Interconversion (FGI)**

The process of converting an functional group into another by substitution, addition, elimination, oxidation or reduction and the reverse operation used in analysis.

**Target molecule (TM)** -the molecule to be synthesized.

**Reagent** - the compound used in practice for synthon.

**Analysis/ Retro synthetic analysis** - the process of breaking down a target molecule in available starting material by FGI and disconnection.

**Supermolecular Synthon Approach** [29]

The supramolecular synthon approach to crystal structure prediction (CSP) takes into account the complexities inherent in crystallization. The synthon is a kinetically favored unit, and through analysis of commonly occurring synthons in a group of related compounds, kinetic factors are implicitly invoked. The working assumption is that while the experimental structure need not be at the global minimum, it will appear somewhere in a list of computationally generated structures so that it can be suitably identified and ranked upward using synthon information.

**Pre clinical studies**

Pre-clinical studies involve *in vitro* (*i.e.*, test tube or laboratory) studies and trials on animal populations.

**Phase 0:**

Phase 0 is a recent designation for exploratory, first-in-human trials conducted in accordance with the U.S. Food and Drug Administration's (FDA) 2006 Guidance on Exploratory Investigational New Drug (IND) Studies. Phase 0 trials are designed to expedite the development of promising drugs or imaging agents by establishing very early on whether the drug or agent behaves in human subjects as was anticipated from preclinical studies. Distinctive features of Phase 0 trials include the administration of single subtherapeutic doses of the study drug to a small number of subjects (10 to 15) to gather preliminary data on the agent's pharmacokinetics (how the body processes the drug) and pharmacodynamics (how the drug works in the body).

**Phase I:**

Phase I trials are the first stage of testing in human subjects. Normally, a small (20-80) group of healthy volunteers will be selected. This phase includes trials designed to assess the safety (pharmacovigilance), tolerability, pharmacokinetics, and pharmacodynamics of a drug. These trials are often conducted in an inpatient clinic, where the subject can be observed by full-time staff. The subject who receives the drug is usually observed until several half-lives of the drug have passed. Phase I trials also normally include dose-ranging, also called dose escalation, studies so that the appropriate dose for therapeutic use can be found. The tested range of doses will usually be a fraction of the dose that causes harm in animal testing. Phase I trials most often include healthy volunteers; however, there are some circumstances when real patients are used.

**Phase II:**

Once the initial safety of the study drug has been confirmed in Phase I trials, Phase II trials are performed on larger groups (20-300) and are designed to assess how well the drug works, as well as to continue Phase I safety assessments in a larger group of volunteers and patients. When the development process for a new drug fails, this usually occurs during Phase II trials when the drug is discovered not to work as planned, or to have toxic effects.

**Phase III:**

Phase III studies are randomized controlled multicenter trials on large patient groups (300–3,000 or more depending upon the disease/medical condition studied) and are aimed at being the definitive assessment of how effective the drug is, in comparison with current 'gold standard'

treatment. Phase III trials are the most expensive, time-consuming and difficult trials to design and run, especially in therapies for chronic medical conditions.

**Phase IV:**

Phase IV trials involve the safety surveillance (pharmacovigilance) and ongoing technical support of a drug after it receives permission to be sold. Phase IV studies may be required by regulatory authorities or may be undertaken by the sponsoring company for competitive (finding a new market for the drug) or other reasons (for example, the drug may not have been tested for interactions with other drugs, or on certain population groups such as pregnant women, who are unlikely to subject themselves to trials). The safety surveillance is designed to detect any rare or long-term adverse effects over a much larger patient population and longer time period than was possible during the Phase I-III clinical trials. Harmful effects discovered by Phase IV trials may result in a drug being no longer sold, or restricted to certain uses: recent examples include cerivastatin (brand names Baycol and Lipobay), troglitazone (Rezulin) and rofecoxib (Vioxx).

**Major tasks and concerns in drug development.**

1. Characterize medical condition and determine receptor targets.
2. Achieve active site complementarily: steric, electrostatic, and hydrophobic.
3. Consider biochemical mechanism of receptor.
4. Adhere to laws of chemistry.
5. Synthetic feasibility.
6. Biological considerations.
7. Patent considerations.

## CONCLUSION

In present scenario the drug demand in the pharmaceutical market is increasing day by day, hence various methods of drug design are being developed to create a new drug with less cost, less efforts, less time and maximum efficiency.

From the above literature study of drug designing, there is a observation that, various methods and approaches are use to design a drug, like

- Molecular modeling
- Quantitative structure activity relationship
- Combinatorial chemistry
- Structure based drug designing
- Computational chemistry
- In silico drug designing
- Synthone approach

But in the above mentioned methods all are not use routinely. The most convenient methods to be used according to my study and observations are Molecular modeling and computational chemistry in which structure activity relationship or mechanism of action of a compound without performing experimental work, but by changing the molecular structure or by different computer software. These methods are time saving, economic and requires less efforts and gives better results.

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