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Drug Design: An Overview

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Abstract

Drug discovery is the process where new medicines are identified with respective to various fields like chemistry, pharmacology and biology. With the involvement of some newer techniques the practice of the drug discovery process has been revolutionized. Target based drug design is more advantageous, effective and time consuming. With the use of High Throughput Screening (HTS) technique a large number of compounds screened for their biological activity with the discovered target, which are synthesized by combinatorial chemistry, they are called hits. Quantitative Structure Activity Relationships (QSAR) constitutes immense importance in discovering new drug candidate called analogues which shows high affinity with the target. Various advanced techniques and Modern research disciplines such as metabolomics, chemogenomics, genomics, proteomics, and others improve the quality of the drug discovery process. The main objective of this article is to highlight the steps and trends followed in drug discovery process and methodology applied in drug designing.

Keywords: Drug Designing; QSAR; Physicochemical Parameters; Pharmacophore Modeling; Docking Techniques; Combinatorial Chemistry

Abbreviations: HTS: High Throughput Screening; QSAR: Quantitative Structure Activity Relationships; SAR: Structure Activity Relationship; SEA: Similarity Ensemble Approach; MLR: Multiple Linear Regressions; BR: Biological Response; MNPs: Manufactured Nanoparticles; AMPs: Antimicrobial Peptides; CoMFA: Comparative Molecular Field Analysis; CSD: Cambridge Structural Database; HTS: High Throughput Screening; SPS: Solid Phase Synthesis; GPS: Gel Type Polystyrene.

Introduction

The most difficult aspect of drug discovery is that of lead discovery. Until the late 19th century, the development of new chemical entities for medicinal purposes was achieved primarily through the use of natural products, generally derived from plant sources. Salicylic acid was isolated from the bark of willow trees after learning that Native Americans brewed the bark to treat inflammatory ailments. Structural optimization of this lead compound (salicylic acid) by the Bayer Corporation of Germany resulted in acetylsalicylic acid, or aspirin, the first nonsteroidal anti-inflammatory agent [1]. The discovery or design of new drugs requires a design process along with the synthetic techniques, methods of administration, development of tests, and further procedures to establish pharmacodynamics and their toxicological assessment. The diversity in synthetic chemistry is ever increasing as a result of the increase in

the number of chemical compounds, which requires a sequence of screening modules with appropriate time consumption and affidavits little success. These consequences made it necessary to find out the possibilities for the development of new, logical, and scientific approaches in the discovery of new molecules or drugs and came to be known as drug designing. Drug design is an integrated advancing discipline, in which a biologically active molecule is produced by chemical synthesis followed by an evaluation of its activity and toxicological studies with the limitation of trial-and-error screening. In the broader sense, it implies the random evaluation of congeners produced from the lead molecule either by implementing tailor-made techniques or by applying the basic concepts of physicochemical properties to produce an able molecule. Occasionally, new drugs are discovered by accidently, more frequently, they are developed as a part of an organized effort to discover new ways to treat specific diseases. The trial-and-error method usually employed for new drug developments are highly expensive, as they require various predictions, such as pharmacokinetic, pharmacodynamic, and toxic properties before the synthesis of a chemical compound. Finally, after these, it is observed that out of the several thousand compounds synthesized and tested, hardly one, two, or even none clicks. Today, the emphasis is not just finding new ways to treat human disease, but also on improving the quality of life in general. Computer-based drug design techniques have the ability to accomplish both these goals and improve the efficiency of the process as well. The drug discovery and lead optimization process is currently dominated by developments in two fields, a rational design based on structural information and sophisticated computational methods to elucidate the structural prerequisites that are important for binding to a particular target. The rational drug design processes have changed the way in which potential new drugs are discovered which includes QSAR studies [2-7]. The rational drug design process starts with an understanding of the fundamental physiological and biochemical aspects of the disease or target, rather than random screening process. One method to bring about cost effectiveness in drug design process is by applying both the knowledge of mechanistic basis of a target disease and molecular characteristics of the compounds to have an effect on diseases state. This approach to therapeutic development is called rational drug design approach.

Various Approaches Used in Drug Design

Drug design is an integrated advancing discipline, in which a biologically active molecule is produced by chemical synthesis followed by an evaluation of its activity and toxicological studies with the limitation of trial-and-error screening. In the broader sense, it implies the random evaluation of congeners produced from the lead molecule either by implementing tailor-made techniques or by applying the basic concepts of physicochemical properties to produce an able molecule. The concept of lead discovery envisages two investigational processes. They are:

- Exploration of leads: search of new molecules.
- Exploitation of leads: assessment, chemical modeling, and extension of leads.

The drug discoveries without a lead are quiet few in number. The most prominent examples include penicillium and Librium. Librium is the first benzodiazepine tranquillizer. A series of quinazoline-3-oxides were synthesized by Leo Sternbach at Roche in a new tranquilizer development program [8]. None of the molecules produced reliable pharmacological activity. One of the molecules that had been missed and identified while laboratory cleanup was happening found to posse's probable activity and chemically it was benzodiazepine-4-oxide. It produced chloromethyl quinazoline-3-oxide with methylamine. This lead identification was further exploited to develop potent analogues such as diazepam, which was found to be 10 times more potent than the lead. The lead identifications require a series of biological evaluation of the lead molecules [9-12]. Once, after the identification, it can be structurally modified, the potency and the activity are improved.

Random Screening

The random screening of synthetic organic compounds approach to the discovery of new chemical entities for a particular biologic action began in the 1930s, after the discovery of the sulfonamide class of antibacterial. All compounds available to the investigator (natural products, synthetic molecules), regardless of structure, were tested in the pharmacologic assays available at the time. This random screening approach was also applied in the 1960s and 1970s in an effort to find agents that were effective against cancer. Some groups did not limit their assays to identify a particular type of biologic activity but, rather, tested compounds in a wide variety of assays. This large-scale screening approach of drug "leads" is referred to as high-throughput screening, which involves the simultaneous bioassay of thousands of compounds in hundreds to thousands of bioassays. These types of bioassays became possible with the advent of computer-controlled robotic systems for the assays and combinatorial chemistry techniques for the synthesis of large numbers of compounds in small

(milligram) quantities. This type of random screening eventually gave way to targeted dedicated screening and rational design techniques. The entire synthesized compounds or any chemical constituents obtained from natural products are evaluated in a series for their biologically active components. Thus, random screening may produce unexpected active medicines. Antibiotics, such as streptomycin, tetramycin, and fungal metabolites, such as lovastatin and cyclosporins, were investigated through this method. This approach needs more manpower, and it is expensive and time-consuming and the success rate is considerably low.

Nonrandom Screening

In this method, only compounds that possess similar structural skeletons were evaluated from their particular properties.

Pharmacokinetic Studies

Biotransformation occurs as the fate by metabolizing enzymes. In order to develop new leads, the metabolites are studied for their properties, and such studies are expected to assess the activity from a comparison with the parent molecule. For example, the discovery of sulphanilamide is reported through the metabolic studies of prontosil.

Pharmacodynamic Studies

The effects apart from the therapeutic actions, that is, side effects may lead to the finding out of a new molecule with some appreciable structural modification. For example, sulphonamide used specifically for the treatment of typhoid, lowered the blood sugar levels drastically. This exerted action led to the finding of aryl sulphonyl thiourea moiety responsible for the lowering of blood glucose level. Amino alkyl derivatives of iminodibenzyl were synthesized as analgesic, sedative, and antihistamines that were found to posse's ant depressive action. This led to the synthesis of many tricyclic antidepressants.

Rational Approach to Drug Design

Rational drug design is a more focused approach that uses greater knowledge (structural information) about the drug receptor (targets) or one of its natural ligands as a basis to design, identify, or create drug "leads." Testing is usually done with one or two models (e.g., specific receptor systems or enzymes) based on the therapeutic target. The drug design component often involves molecular modelling and the use of quantitative structure activity relationships (QSARs) to better define the physicochemical properties and the pharmacophore groups that are essential for biologic activity. The development of QSARs relies on the ability to examine multiple relationships between physical properties and biologic activities. In classic QSAR (e.g., Hansch-type analysis), an equation defines biologic activity as a linear free-energy relationship between physicochemical and/or structural properties. It permits evaluation of the nature of interaction forces between a drug and its biological target, as well as the ability to predict activity in molecules. These approaches are better for the development of a lead compound into a drug candidate than for the discovery of a lead compound. There are many approaches to drug designing in relation with physiochemical parameters and electronic features taken into consideration for designing a drug. These are as follows:

Approach with Quantum Mechanics: This is also called as wave mechanics, comprises the fundamental physical properties of a molecule. These include the properties of protons, neutrons, and electrons, which are explained by quantum mechanics. The basis of drug molecule nature is altered by chemical alterations of the electronic features.

Approach with Molecular Orbital Theory: This approach depicts the change in properties that shall be made by the alteration of orbits. Based on this, the electrons present in the molecules are linked with orbital's to change the electronic feature. The molecular orbital approach is the change on electronic charges, evidenced from the investigation of three volatile inhalation anesthetics, and also on molecular conformation, as studied with respect to acetylcholine, in regard to bond lengths and angles including torsion angle. These interpretations are carried out by computational methods in respect to structure activity relationship (SAR).

Approach with Molecular Connectivity: This is based on the structural features of a molecule. All steric and electronic parameters vary according to their configuration. These include cyclization, unsaturation, presence of heteroatom, skeletal branching, and position in molecules with the aid of numerical indices and the series of functional attachments.

Approach of Linear Free-Energy: Linear free energy approach was based on the selection of physiochemical parameters of a molecule with a specific biological activity. But the biological activity may vary in relation to the physiochemical properties of the drug or molecule

and does not provide a prompt success, but it may reveal some beneficial features regarding the molecule.

Quantitative Structure Activity Relationship (QSAR)

Structure-activity relationship (SAR) and quantitative structure-activity relationship (QSAR) study, collectively referred to as (Q) SAR, are theoretical models that can be used to predict the physicochemical, biological, and environmental fate properties of molecules. Several important studies have been published recently in which QSAR-based predictions have been experimentally confirmed. These studies illustrate how useful and reliable computer-assisted approaches can be in assisting medicinal chemists to design novel compounds with controlled bio profiles. Keiser, et al. [13] developed the Similarity Ensemble Approach (SEA) to compare targets utilizing the overall similarity between their known ligands. The authors applied this approach to prognosticate unknown drug-target interactions for demonstrating the potential use of computational approaches to study and predict drugs polypharmacology. More than 3,600 FDA approved and investigational drugs were analyzed by SEA and thousands of unknown associations were discovered. Out of 30 experimentally tested associations, 23 precedently unknown drug-target interactions were confirmed (five of them characterized by a potency less than 100 nM). Lounkine, et al. [14] conducted a large-scale prediction and testing of drug potency on different side-effect targets. The authors extracted and curate experimental data for 285,000 ligands and 1,500 biological targets from the ChEMBL database. Then, they used the SEA similarity search approach to predict the activity of 656 marketed drugs on 73 unintended 'side-effect' targets. Out of 1,644 significant drug-target associations predicted by SEA, there were 893 that were unknown and never reported before. The authors then conducted experimental tests for confirming these predictions. Out of 694 experimental tests, 478 drug-target associations (68.9%) were disproved and 65 found to be ambiguous. However, significant potencies (less than 30μM) were confirmed for the 151 remaining drug-target associations, especially for 48 compounds with sub-micromolar activities. Interestingly, the authors linked those targets with known side effects and successfully established previously unknown links between drugs and several side effects. This study demonstrated that QSAR-like predictions can successfully prognosticate ligand-target interactions, which can then be confirmed experimentally. Besnard, et al. [15] utilized cheminformatics methods to explore and design compounds with unique polypharmacology (Figure 1).

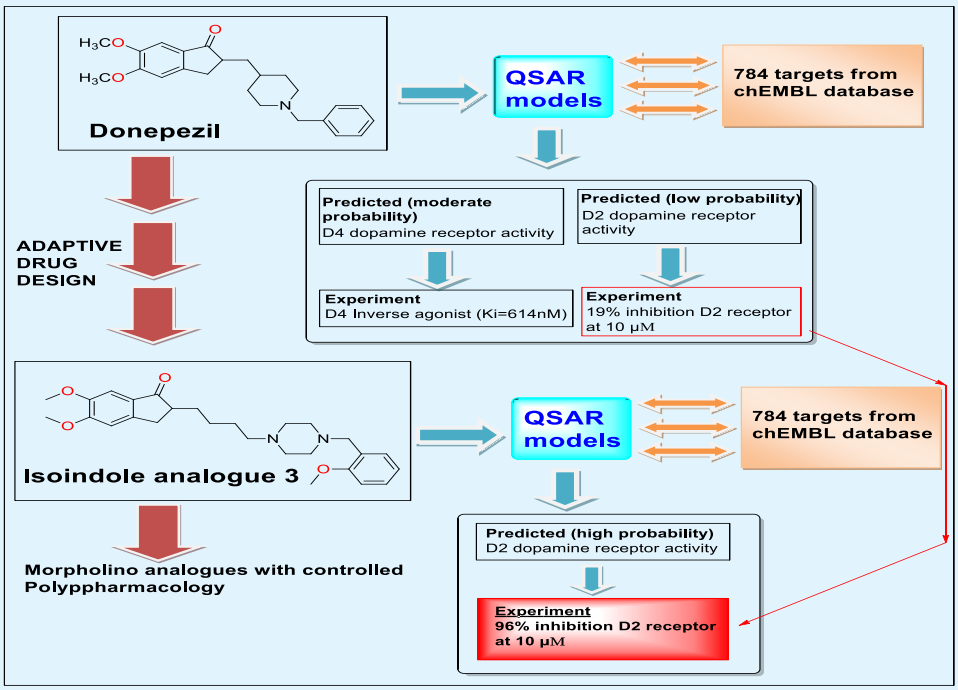


Figure 1: Adaptive drug design for computer-aided generation of compounds with controlled polypharmacology.

As both clinical efficacy and overall safety of a drug is determined by its activity profile towards many biological targets, there is a huge need for approaches capable of predicting and designing drugs with a specific multi-target behavior. The authors developed new methods that:

- Generates one (or several) generation(s) of chemical analogues of a given parent drug with known properties, and
- Predicts their polypharmacology using an ensemble of ligand-based QSAR models.

Then, most interesting compounds with the preferred polypharmacology profiles are synthesized and confirmed experimentally. The authors explored the case study of an approved acetyl cholinesterase inhibitor drug and it's in silico generated analogues, all tested for their specific or promiscuous polypharmacology towards G-protein-coupled receptors. More than 800 ligand-target predictions of prospectively designed ligands were tested experimentally and 75% were confirmed.

Other examples of experimentally validated QSAR-based predictions have been published by the Tropsha group at the UNC. Recently, Hajjo, et al. [16] have developed and validated binary classification QSAR models capable of predicting potential serotonin 5-HT_{2B} actives that are known to cause valvular heart disease. The models were employed to screen the World Drug Index library and 122 compounds were prognosticated to be 5-HT_{2B} actives. Ten of them were tested experimentally and nine were confirmed to be active. These QSAR models can thus be employed for predicting $5HT_{2B}$-related valvulopathy. In summary, a growing number of published QSAR studies include the experimental validation of predicted hits and this critical step should become a standard component of any QSAR investigation.

The aim of QSAR techniques is to develop correlations between any biological property form of activity, frequently biological activity, and their properties, usually, physicochemical properties of a set of molecules, in particular, substituent properties. However, in its most general form, QSAR has been adapted to cover correlations independent of actual physicochemical properties. QSAR started with similar correlations between chemical reactivity and structure. Ideally, the activities and properties are connected by some known mathematical function, F:

Biological activity = F (physicochemical properties)

Biological activity can be any measure of, such as C, Ki, IC50, ED50, and Km.

Physicochemical properties can be broadly classified into three general types such as electronic, steric, and hydrophobic property of biologically active molecules, for which an enormous range of properties and physicochemical parameters have been defined. Ideally, the parameters selected should be orthogonal, that is, have minimal covariance. The relationship or function is usually (but not always) a mathematical expression derived by statistical and related techniques, for example, multiple linear regressions (MLR). The parameters describing physicochemical properties are used as independent variables and the biological activities are dependent variables. In some cases, a function cannot be found, and this reflects the multivariate, nonlinear nature of biological and physical properties. Usage of such data may be possible with neural networks to deduce essential data for biological activities and then using them for prediction. Usually, some data are used to generate a relationship (the training set), while another set of data is reserved as a test set on which predictions using the rule are made. In this manner, a model can be tested for validity. The complete range of techniques used to derive functional relationships between the data is collectively known as chemometrics.

Physicochemical Parameters

The Lipophilic Parameter

Two parameters are commonly used to relate drug absorption and distribution with biological activity, namely, the partition coefficient (P) and the lipophilic substituent constant (π). The former parameter refers to the whole molecule whilst the latter is related to substituent groups.

Partition Coefficients (P): A drug has to pass through a number of biological membranes in order to reach its site of action. Consequently, partition coefficients were the obvious parameter to use as a measure of the movement of the drug through these membranes. The nature of the relationship obtained depends on the range of P values for the compounds used. If this range is small the results may, by the use of regression analysis, be expressed as a straight line equation having the general form:

$$\text{Log } (1/C) = k_1 \log P + k_2 (1)$$

Where, k_1 and k_2 are constants. This equation indicates a linear relationship between the activity of the drug and its partition coefficient. A number of examples of this type of correlation are known (Table 1). Over larger ranges of P values the graph of log (1/C) against log P often has a

parabolic form as shown in Figure 2, with a maximum value (log P_o).

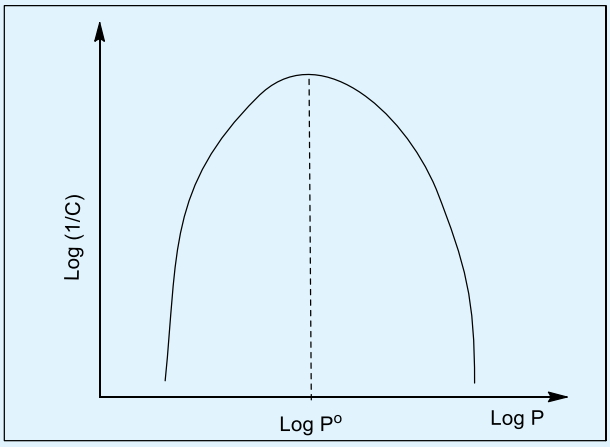


Figure 2: Parabolic curve of log (1/C) vs. log P.

The existence of this maximum value implies that there is an optimum balance between aqueous and lipid solubility for maximum biological activity. Below P_o the drug will be reluctant to enter the membrane whilst above P_o the drug will be reluctant to leave the membrane. Log P_o represents the optimum partition coefficient for biological activity. This means that analogues with partition coefficients near this optimum value are likely to be the most active and worth further investigation. Hansch, et al. [17] showed that many of these parabolic relationships could be represented reasonably accurately by equations of the form:

$$\text{Log } (1/C) = k_1 (\log P)^2 + k_2 \log P + k_3 \quad (2)$$

The values of the constants k_1, k_2 and k_3 in equation (2) are normally determined by either regression analysis or other statistical methods. For example, a study of the inducement of hypnosis in mice by a series of barbiturates showed that the correlation could be expressed by the equation:

$$\text{Log } (1/C) = -0.44 (\log P)^2 + 1.58 \log P + 1.93 \quad (3)$$

Examples	Equation	r^a	n^b	s^c
The binding of miscellaneous neutral molecules to bovine serum	Log (1/C) = 0.75 log P + 2.30	0.96	42	0.16
Toxicity of alcohols to red spiders	Log (1/C) = 0.69 log P + 0.16	0.98	14	0.09
The binding of miscellaneous molecules to haemoglobin	Log (1/C) = 0.71 log P + 1.51	0.95	17	0.16

r^a= Regression coefficient, n^b = Number of compound tested, s^c = Standard deviation

Table 1:Examples of linear relationships between log (1/C) against log P.

This equation has a maximum log P_o at about 2.0. Hansch, et al. [17] showed that a range of non-specific hypnotic drugs with widely different types of structure were found to have log P values around 2. This implies that it is the solubility of these different drugs in the membrane rather than their structures that is the major factor in controlling their activity. On the basis of these and other partition studies, Hansch suggested in the mid-1960s that any organic compound with a log P value of approximately 2 would, provided it was not rapidly metabolized or eliminated, have some hypnotic properties and would be rapidly transported into the CNS. Subsequent practical evidence gives some support to this assertion. The fact that the thiobarbiturates have log P values of about 3.1 suggests that these drugs probably have a different site of action from those of the barbiturates. The larger value also suggests that a more lipophilic receptor is involved. Monitoring the change in log P has been used in drug design. For example, compound I (log P = 2.57) is a cardio tonic agent. However, its use resulted in unwanted CNS side effects in some patients. Replacement of the methoxy group by the approximately same sized but more hydrophilic methyl sulphone residue gave the cardio tonic drug sulmazole with a value of 1.17 for log P. The accuracy of the correlation of drug activity with partition coefficient will also depend on the solvent system used as a model to measure the partition coefficient values. The n-octanol/water system is frequently chosen because it has the most extensive data base. However, more accurate results may be obtained if the organic phase is matched to the area of biological activity being studied. For example, n-octanol usually gives the most consistent results for drugs absorbed in the GI tract whilst less polar solvents such as olive oil frequently give more consistent correlations for drugs crossing the blood–brain barrier. More polar solvents such as chloroform give more consistent values for buccal absorption (soft tissues in the mouth). However, when correlating P values with potency it should be borne in mind that the partition coefficient of a drug is usually only one of a number of parameters influencing its activity. Consequently, in cases where

there is a poor correlation between the partition coefficient and the drug's activity, other parameters must be playing a more important part in the action of the drug.

Electronic Parameter

The distribution of the electrons in a drug molecule will have a considerable influence on the distribution and activity of a drug. In order to reach its target a drug normally has to pass through a number of biological membranes. As a general rule, non-polar and polar drugs in their unionised form are usually more readily transported through membranes than polar drugs and drugs in their ionised forms. Furthermore, once the drug reaches its target site the distribution of electrons in its structure will control the type of bonds it forms with that target, which in turn affects its biological activity.

The Hammett Constant (σ): The distribution of electrons within a molecule depends on the nature of the electron withdrawing and donating groups found in that structure. E.g., benzoic acid is weakly ionised in water as illustrated in Figure 3.

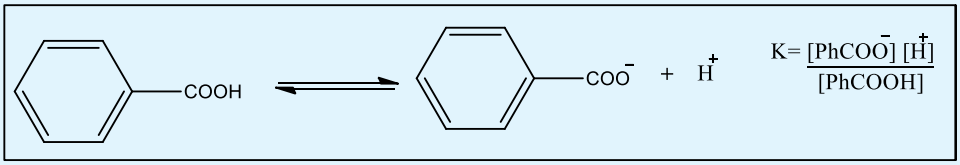


Figure 3: Ionization of benzoic acid.

Substitution of ring hydrogen by an electron withdrawing substituent (X), such as a nitro group, will weaken the O-H bond of the carboxyl group and stabilise the carboxylate anion (Figure 4). This will move the equilibrium to the right which means that the substituted compound is a stronger acid than benzoic acid (K_x>K). It also means that at equilibrium more of the nitro benzoic acid will exist as anions, which could make its transfer through membranes more difficult than that of the weaker less ionised benzoic acid. Conversely, the introduction of an electron donor substituent (X), such as a methyl group into the ring strengthens the acidic OH group and reduces the stability of the carboxylate anion. This moves the equilibrium to the left, which means that the compound is a weaker acid than benzoic acid (K > K_x). This in turn means that it has fewer anions in solution at equilibrium than benzoic acid and so could pass through membranes more easily than benzoic acid. In addition to the effect that changes in the electron distribution have on transfer through membranes, they will also have an effect on the binding of these acids to a target site. These observations show that it is possible to use equilibrium constants to compare the electron distributions of structurally similar compounds. Hammett used equilibrium constants to study the relationship between the structure of aromatic acids and acid strength. In the course of study, he calculated constants known as Hammett substitution constants (σ_x) or Hammett constants [18] for a variety of ring substituents (X) of benzoic acid, using this acid as the comparative reference standard as shown in Table 2.

Substituent	Hammett constants	Inductive constants[a]	Taft constants[b]	Swain-Lupton constants[c]
	$\sigma_m\sigma_P$	σ_1	σ^*	FR
H	0.000.00	0	0.49	0.000.00
CH_3	-0.07-0.17	-0.05	0	0.040.13
OH	0.12-0.37	0.25	-	0.29-0.64

[a]Inductive substituent constants represent the contribution the inductive effect makes to Hammett constants and can be used for aliphatic compounds; [b]Taft substitution constants refer to aliphatic substituents and use the 2-methyl derivative ofpropanoic acid as the reference point; [c]The Swain-Lupton constants represent the contributions due to the inductive (F) and mesomeric or resonance (R) components of Hammett constants.

Table 2: Different electronic substitution constants used in QSAR studies.

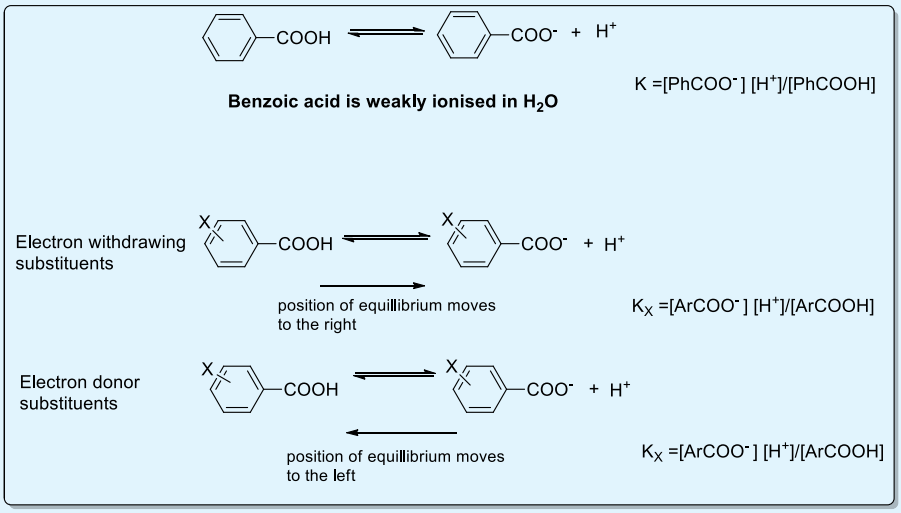


Figure 4: Effect of electron withdrawing and donor groups on equilibrium of substituted benzoic acids.

Hammett constants (σ_x) are defined as:

$$\sigma_x = \log K_X/K$$

i.e.; $\sigma_x = \log K_x - \log K$

$\sigma_x = pK - pK_x$ [as $pK_a = -\log K_a$]

A negative value for σx indicates that the substituent is acting as an electron donor group since K >> K_x. Conversely, a positively value shows that the substituent is acting as an electron withdrawing group as K < K_x. The value of σ_x varies with the position of the substituent in the molecule. This position is usually indicated by the use of the subscripts o, m and p. Where a substituent has opposite signs depending on its position on the ring it means that in one case it is acting as an electron donor and in the other as an electron withdrawing group. This is possible because the Hammett constant includes both the inductive and mesomeric (resonance) contributions to the electron distribution. E.g., the σ_m for the methoxy group of m-methoxybenzoic acid is 0.12 whilst for p-methoxybenzoic acid it is -0.27 as shown in Figure 5. In the former case the electronic distribution is dominated by the inductive (I or F) contribution whilst in the latter case it is controlled by the mesomeric (M) or resonance effect (R) effect.

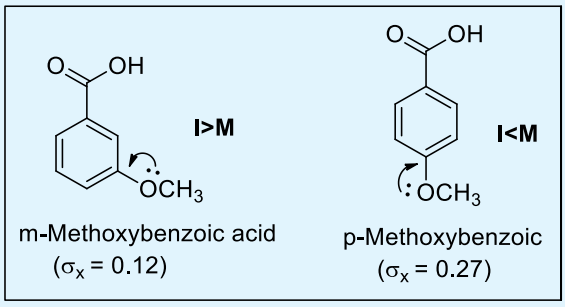


Figure 5: The resonance (mesomeric) and inductive effects of m- & p-methoxy benzoic acid.

Attempt to relate biological activity to the values of Hammett substitution and similar constants have been largely unsuccessful since electron distribution is not the only factor involved. However, a successful attempt to relate biological activity to structure using Hammett constant was the investigation by Fukata and Metcalf into the effectiveness of diethyl aryl phosphates for killing fruit flies. This investigation showed that the activity of these compounds is dependent only on electron

distribution factors. Their results may be expressed by the relationship (equation 4):

$$\text{Log } (1/C) = 2.282\sigma - 0.348 \quad (4)$$

This equation shows that the greater the positive value for σ, the greater the biological activity of the analogue. This type of knowledge enables one to predict the activities of analogues and synthesizing and testing all the possible analogues.

Steric Factor

The bulk, size, and shape of a drug will influence how easily it can approach and interact with a binding site. A bulky substituent may act like a shield and hinder the ideal interaction between a drug and its binding site. Alternatively, a bulky substituent may help to orientate a drug properly for maximum binding and increase activity. Steric properties are more difficult to quantify than hydrophobic or electronic properties. Several methods have been tried, of which 3 are described hereunder.

Taft's Steric Factor (E_s): Taft in 1956 used the relative rate constants of the acid-catalysed hydrolysis of α-substituted methyl ethanoates to define his steric parameter because it had been shown that the rates of these hydrolyses were almost entirely dependent on steric factors. He used methyl ethanoates as his standard and defined E_s as;

$$E_s = \log K_x - \log K_o$$

Where, K_x represent the rate of hydrolysis of substituted ester and K_o represent the rate of hydrolysis of parent ester. It is assumed that the values for E_s obtained for a group using the hydrolysis data are applicable to other structures containing that group.

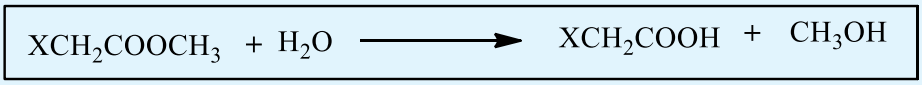


Figure 6: The hydrolysis of α-substituted methyl ethanoates.

The methyl-based E_s values can be converted to H-based values by adding -1.24 to the corresponding methyl-based values. Taft steric parameters have been found to be useful in a number of investigations. For example, regression analysis has shown that the antihistamine effect of a number of related analogues of diphenhydramine was related to their biological response (BR) by equation (5a), where E_s is the sum of the ortho- and meta- E_s values in the most highly substituted ring. Regression analysis also showed that the biological response was related to the Hammett constant by the relationship as shown in equation 5.

$$\text{Log BR} = 0.440\,E_s - 2.204 \quad (n = 30,\ s = 0.307,\ r = 0.886) \quad (5a)$$
$$\text{Log BR} = 2.814\sigma - 0.233 \quad (n = 30,\ s = 0.519,\ r = 0.629) \quad (5)$$

A comparison of the standard deviations (s) for the both the equations (5a, 5) shows that the calculated values for the Hammett constants σ for each of the analogues are more scattered than the values for the corresponding Taft E_s values. Furthermore, although both the r and s values for the former equation (5a) are reasonable, those for the latter equation are unacceptable. This indicates that the antihistamine activity of these analogues appears to depend more on steric than electronic effects. This deduction is supported by the fact that using regression analysis to obtain a relationship involving both the Hammett and Taft constants does not lead to a significant increase in the r and s values. Taft constant suffer from the disadvantage that they are determined by experiment.

Hansch Analysis

Hansch and co-workers in the early 1960s proposed a multiparameter approach to the problem based on the lipophilicity of the drug and the electronic and steric influences of groups found in its structure. They realized that the biological activity of a compound is a function of its ability to reach and bind to its target site. Hansch proposed that drug action could be divided into two stages:

- The transport of the drug to its site of action.
- The binding of the drug to the target site.

He stated that the transport of the drug is like a 'random walk' from the point of administration to its site of action. During this 'walk' the drug has to pass through numerous membranes and so the ability of the drug to reach its target is dependent on its lipophilicity. Consequently, this ability could be expressed mathematically as a function of either the drug's partition coefficient P or the π value(s) of appropriate substituents.

However, on reaching its target the binding of the drug to the target site depends on the shape, electron distribution and polarisability of the groups involved in the binding. A variety of parameters are now used to describe each of these aspects of drug activity, the most common ones being the Hammett electronic σ and Taft Es constants. Hansch postulated that the biological activity of a drug could be related to all or some of these factors by simple mathematical relationships based on the general format:

Log (1/C) = k_1 (partition parameter) + k_2 (electronic parameter) + k_3 (steric parameter) + k_4

Where, C is the minimum concentration required for specific biological response and k_1, k_2, k_3 and k_4 are numerical constants obtained by feeding the data into a suitable computer statistical package. For example, the general equations relating activity to all of these parameters often take the general form:

$$\text{Log } (1/C) = k_1P - k_2P^2 + k_3\sigma + k_4E_s + k_5$$

Where, other parameters could be substituted for P, σ and E_s. For example, π may be used instead of P and MR (Molar Refractivity) for E_s. However, it is emphasized that these equations, which are collectively known as Hansch equations, do not always contain the main three types of parameter as shown in Table 3. The numerical values of the constants in these equations are obtained by feeding the values of the parameters into a suitable computer package. These parameter values are obtained either from the literature (e.g. π, σ, E_s) or determined by experiment (e.g., C, P, etc).

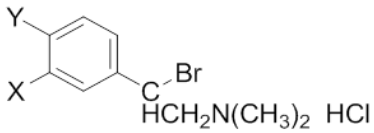
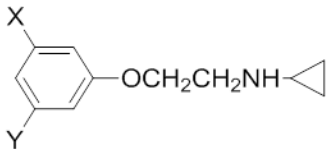
Compound	Activity	Hansch equation
	Antiadrenergic	Log 1/C = 1.22π-1.59σ+7.89(n = 22, s = 0.238, r = 0.918)
	MAO inhibitor (humans)	Log 1/C = 0.398π - 1.089σ + 1.03E_S + 4.541(n = 9, r = 0.955)

Table 3: Examples of simple Hansch equations.

QSAR: Future Trends

Combinatorial chemistry and HTS technologies have been recently extended towards designing novel manufactured nanoparticles (MNPs) [19]. Importantly, a significant portion of these efforts is directed towards the development of "green" products intended to achieve efficient and less polluting energy sources. In this context, QSAR science has a role to play by: (i) facilitating the access, storage, search, and integration of all experimental results currently distributed in literature, databases, and other sources; (ii) achieving externally predictive QSAR models to compute MNPs' properties based on their structural characteristics; and (iii) boosting the development and testing processes by identifying the most promising nanoparticles that require focused experimental investigations. The latter point is especially true due to the concerns about the safety of certain MNPs and the development of Nanomedicine [20]. Thus, computational tools capable of evaluating MNPs for their potential health risk are needed.

In the face of increasing antibiotic resistance by pathogens, AMPs (Antimicrobial peptides) have drawn significant attention as a prospective class of antimicrobial therapeutics [21]. As they hold several notable advantages, including broad range of activity, low toxicity, and minimal development of resistance in target organisms. More than fourteen peptides are currently in development or clinical trials, with two having demonstrated efficacy in Phase III clinical trials [22]. The majority of the previous sequence-based modeling efforts was of qualitative nature and relied on available AMP sequences to (a) discover previously unknown natural peptides, and (b) to modify sequences of known AMPs to improve their therapeutic properties. Fjell, et al. [22] recently reviewed the AMP optimization methods relying on various sequence templates. Such approaches imply systematic change of one or a few amino acids in the

sequences of prominent AMPs such as lactoferricin, cecropin, bactenicin, protegrin and magainin to enhance their antimicrobial activity or reduce toxicity. Such template-based studies (when one changes a part of the molecule, while keeping the rest intact, and records the overall response of the system) has brought the spirit of early-day QSAR into the field of AMP research.

Pharmacophore Modeling and Docking Techniques

Pharmacophore approaches have become one of the major tools in drug discovery after the past century's development [23]. Various ligand-based and structure-based methods have been developed for improved pharmacophore modeling and have been successfully and extensively applied in virtual screening, de novo design and lead optimization. Despite these successes, pharmacophore approaches have not reached their expected full capacity, particularly in facing the demand for reducing the current expensive overall cost associated with drug discovery and development. The three-dimensional structures produced on a computer screen may be manipulated on the screen to show different views of the structures. It is also possible to superimpose one structure on top of another. In other words it is possible to superimpose the three-dimensional structure of a potential drug (ligand) on its possible target site. This process is known as docking. A pictorial representation is shown in Figure 7 [24]. If the structure of a compound is complementary to that of its target site the compound is more likely to be biologically active. Furthermore, the use of a color code to indicate the nature of the atoms and functional groups present in the three-dimensional structures also enables the medicinal chemist to investigate the binding of a drug to its target site.

Figure 7: X-ray study of human serum albumin complexes with Etoposide.

Docking programs operate by placing the ligand in the target area and then attempting to orientate the ligand so that it's binding group's line up with the complementary groups of the target with which they are likely to form bonds. For example, an electron donor group of the ligand lines up with an electron acceptor group of the target site. Not only does the program line up the appropriate complementary groups of the ligand and target site but it also attempts to separate them by a suitable bond distance. The simplest programs use specific conformers of both the ligand and target site, that is, so-called '**locked**' conformations. They do not take into account the fact that the ligand and target site can exist in a number of conformers, in other words, these simple programs does not take into account the flexibility of the structures. This means that when using these molecular modeling programs in drug discovery studies, the medicinal chemist should check the fit of a number of conformers of the potential drug molecule to different conformations of the target. The most used programs treat the ligand as being flexible but regard the target as being a rigid structure. More complex programs that treat both the ligand and target as being flexible are available. However, this type of program does require a considerable amount of computer time and so is not popular. Molecular mechanics also enables the medicinal chemist to calculate the binding energy of a ligand. This is the energy lost when the ligand binds to its target site, that is:

$$E_{binding} = E_{target} + E_{ligand} - E_{target\ plus\ bound\ ligand}$$

All the quantities on the right-hand side of the equation may be calculated using molecular mechanics force fields. However, it should be remembered that in the majority of cases the binding of a drug to its target should be weak because in most cases it has to be able to leave the target after it has activated that site. A major problem with docking and other molecular modeling procedures is that the conformation adopted by a ligand when it binds to its target site will depend on the energy of the molecular environment at that site. This means that although a ligand may have the right pharmacophore, its global minimum energy conformer is not necessarily the conformation that binds to the target site, that is:

Global minimum energy conformer $\longleftrightarrow$ bioactive conformer

However, it is normally assumed that the conformers that bind to target sites will be those with a minimum potential energy. Since molecules may have large numbers of such metastable conformers a number of techniques, such as the Metropolis Monte Carlo method

and Comparative Molecular Field Analysis (CoMFA), have been developed to determine the effect of conformational changes on the effectiveness of docking procedures.

De Novo Design

De novo design is the use of docking programs to design new lead structures that fit a particular target site. Two strategies are normally followed, the first is to use a template structure and the second is to construct a new molecule from component fragments of structure. These approaches both involve fitting fragments of structure into the target site. Consequently, both approaches can only be followed if the structure of the target site is reasonably well established. The *de novo* design methods treat all the structures they use as being rigid, that is, bonds that can exhibit a degree of free rotation are locked into one conformation [25-27]. Consequently, *de novo* programs do not usually take into account the flexibility of molecules and target sites. In other words, the software does not take into account that ligand and the target site can exist in more than one conformation so that those structures used in the program are not necessarily those that they assume in real life. In addition, in fully automated procedures the design is normally limited by the extent of the library of fragments, conformations and links held in the software's data base as shown in Figure 8. *De novo* design is normally used to find new leads. It should be appreciated that the nature of the activities and the ADME characteristics of the leads designed by *de novo* design methods may only be determined by synthesis and testing. Furthermore, the information obtained from the biological tests carried out on the lead will probably indicate that further modification to its structure is necessary. This is most likely to take the form of a SAR investigation.

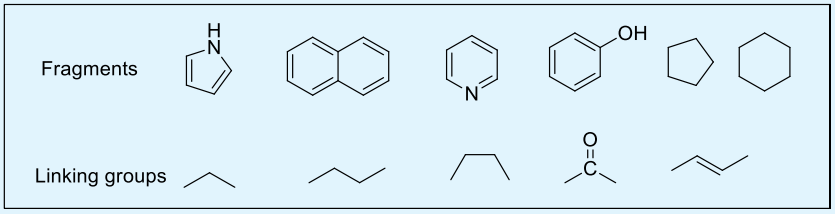


Figure 8: Examples of the types of fragment and linking structures found in de novo software programs.

The Template Method: The template method is based on finding a so-called template structure that approximately fits the target site and modifying that structure to improve its fit and binding characteristics. The method usually starts with a database search for suitable structures to act as a template. Software programs, such as CAVEAT, have been designed to act in conjunction with docking programs, such as DOCK, so that the structures are only listed if they fit the target site. Template structures found in this way are commonly referred to as hits.

The Component Fragment Method: The groups and atoms of the binding site that can form bonds, such as hydrogen bonds and van der Waals' forces of attraction, with a suitable ligand are identified. These fragments are selected on the basis of both their shape and the type of interaction they could have with the target site. The program is used to place the fragments in the target site space at a suitable distance from a complementary group to which they could bind and is used to find the best fit for the fragments by trying different orientations of them in space. In this respect, *de novo* design normally treats all the structures it uses as being rigid, that is, bonds that can exhibit a degree of free rotation are locked into one conformation. The molecular modeler would need to try each of these conformations separately in order to find which one was the most suitable. In order to minimize the conformation problem, programs often contain a number of rigid conformations of the same structure in their data base. Once the fragments have been placed in position they are joined together by suitable linking structures to form a molecule that fits the docking site. This molecule may be further modified by attaching groups that would allow the finished analogue to better fill the target area. Some software programs such as LUDI carry out the complete process automatically once they have had the required criteria loaded into the program. However, it should be appreciated that the activity, its nature and ADME characteristics of the designed molecule may only be determined by synthesis and testing.

Pharmacophore and its Applications

The pharmacophore of a biologically active ligand is the three-dimensional geometric positions of the groups

(pharmacophore centers) of the ligand that form a unique pattern recognizable by the receptor, which is believed to be responsible for the ligand binding to and activating the receptor. These groups may be some distance apart in the structure of the ligand. Pharmacophore are frequently used as a tool for searching data bases for compounds with similar pharmacophores. The coordinates of the pharmacophore and other relevant details are fed into the software program, which searches the appropriate data bases for molecules with similar pharmacophores. Pharmacophore are also used to model binding sites in much the same way that a negative is used to produce a print of a photograph. However, in the case of pharmacophores the process uses a group of structurally different molecules with similar pharmacophores but different activities. These compounds are analyzed using a software program to produce a 'three-dimensional map' of the regions, common to all of the molecules that may be important in their binding to a receptor. This map is obtained using a similar method to that used to obtain three-dimensional QSAR maps. It shows the relative positions of these regions and type of interaction (such as hydrogen bonding, hydrophobic interaction and ionic interaction) found in these areas. This is the so-called negative. It is converted into a model of the receptor site by comparing the types of interactions required for binding with the nature and position of the amino acid residues available in the target receptor. For example, phenylalanine is a candidate for hydrophobic interactions while aspartic acid would be suitable for ionic interactions. These amino acid residues are converted into a molecular model of the receptor site and the validity of the model is checked by examining the docking of molecular models of compounds known to bind to that receptor site. Once validated, the model may be used to discover new leads and drugs. Pharmacophore of active compounds may be found using either high-resolution X-ray crystallography or NMR or obtained from data bases by analysis of a series of compounds with the same type of activity. However, the structure of the pharmacophore is usually a perceived structure, that is, a deduction based on what the researchers think is the most likely three-dimensional shape of the pharmacophore.

High-Resolution X-Ray Crystallography or NMR: The advent of high-resolution X-ray and NMR techniques has allowed the three-dimensional structures of receptors and receptor-ligand complexes to be determined. These structures may be downloaded into molecular modeling programs from data bases such as the Brookhaven National Protein Data Bank in the USA. A study of these receptor and receptor-ligand structures using these molecular modeling programs enables the medicinal chemist to determine the possible nature of the binding of the ligand to its receptor. This allows the medicinal chemist to suggest with a reasonable degree of accuracy which groups of the ligand are involved in this binding and their relative positions, that is, the pharmacophore of the ligand. It also allows the investigator to determine the conformation adopted by the active form of the ligand at the binding site. In addition, a study of the X-ray structures of a receptor and a series of its receptor-ligand complexes involving different ligand will, if available, give a better picture of the shape and electrostatic fields of the target site. Ligand structures may be downloaded from suitable data bases such as the Cambridge Structural Database (CSD) in the UK.

Analysis of the Structure of Different Ligand: Deduction from the analysis of the structures of different ligand is used when there is little or no information available about the target site. This is the most frequently encountered situation in medicinal chemistry. The approach consists of analyzing the three-dimensional structure of a range of active compounds with the same type of activity but different potencies. It is assumed that because the compounds have the same activity they bind to the same receptor. The analysis consists of identifying the binding groups (their three-dimensional orientations in space) and conformations that the structures have in common. Additional information may be obtained from a comparison of active compounds with inactive compounds that are believed to bind to the same receptor. The three-dimensional structures of both the active and inactive compounds selected for the study are either individually modeled or obtained from a data base such as the CSD. The analysis of the structures allows the medicinal chemist to understand (perceive) the structural group and conformation requirements for that type of activity in a drug. The analysis may be made manually using three-dimensional overlays or automatically by the use of specialized software, such as DISCO and Hip Hop. The software usually identifies potential binding groups such as benzene rings, hydrogen bond donor and acceptor groups, acidic and basic groups, etc. in the compound being studied. It records the relative three-dimensional positions of these groups in what is effectively a 'three-dimensional map'. Each compound of the series being studied is treated in the same way. Where the compound being analyzed, it can exist in more than one conformer. The software can usually be used to generate any significant conformers and separately record the new relative three-dimensional positions of the binding groups in each of these new structures. The software compares all the recorded three-dimensional maps and gives a combined visual three-dimensional display of all

the groups it has identified. In essence, it is a three-dimensional map of all the groups identified from all the compounds analyzed by the computer program to produce a three-dimensional map of the pharmacophore. Pharmacophore determined by these methods are referred to as perceived pharmacophores. They are easier to determine for more rigid structures. Once they have been established, data bases are searched using a software program for suitable drug candidates with the same perceived pharmacophores. Some of these programs will also suggest possible alignments (active conformers) for the molecules found by the search with the receptor. These compounds are tested and if any are found to be active they are used as leads in further investigations.

Combinatorial Chemistry

Combinatorial chemistry is a technique through which large numbers of structurally distinct molecules may be synthesized at a time and submitted for high throughput screening (HTS) assay. Combinatorial chemistry is one of the recent methodologies developed by researchers in the pharmaceutical industry to reduce the time and costs associated with producing successful and competitive new drugs. By accelerating the process of biologically active compounds, this method is having a profound effect on all the branches of chemistry, especially on drug discovery. Through the rapidly evolving technology of combinatorial chemistry [28], it is now possible to produce compound libraries to screen for novel bioactivities. This powerful new technology has begun to help pharmaceutical companies to find novel drug candidates quickly, save significant money in preclinical development costs, and ultimately change their fundamental approach to drug discovery.

Principles of Combinatorial Chemistry

The key of combinatorial chemistry is that a large range of analogues are synthesized using the same reaction conditions and the same reaction vessels. In this way, the organic chemist can synthesize hundreds or thousands of compounds at one time instead of preparing only a few by a traditional methodology. For example, compound A would have been reacted with compound B to give product AB, which would have been isolated after reaction, work up, and purification. In contrast to this approach, combinatorial chemistry offers the potential to make every combination of a compound A1 to An with compound B1 to Bn as shown in Figure 9. The range of combinatorial techniques is highly diverse, and these products could be made individually in a parallel or in mixtures, using either solution or solid-phase techniques. Whatever be the technique used, the common denominator is that productivity has been amplified beyond the levels that have been routine for the last hundred years.

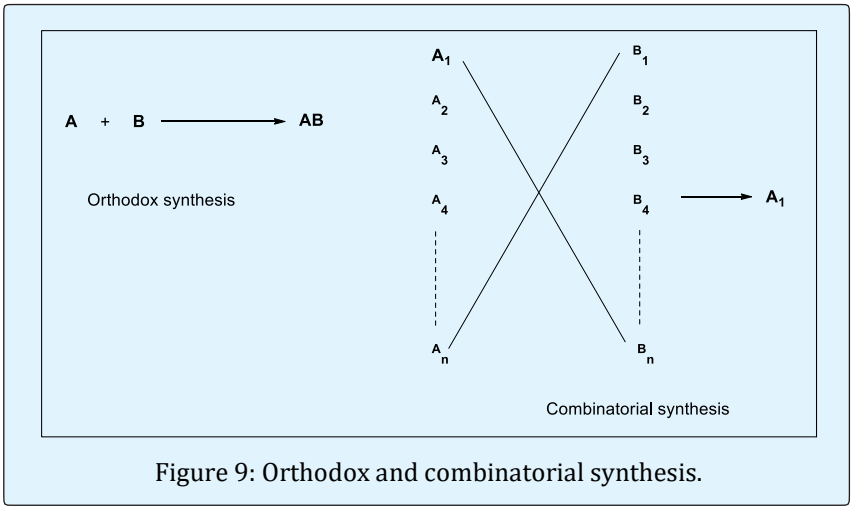


Figure 9: Orthodox and combinatorial synthesis.

Combinatorial Synthesis on Solid Phase

In 1963, Merrifield pioneered the solid phase synthesis (SPS) work, which earned him a Nobel Prize. Merrifield's SPS concept was first applied for a developed biopolymer; recently it has spread in every field where organic synthesis is involved. Nowadays, many academic laboratories and pharmaceutical companies focused on the development of the technologies and chemistry suitable for SPS. This resulted in the impressive outbreak of combinatorial chemistry, which profoundly changed the approach to new drugs, new catalyst, or new natural

discovery. The utilization of solid support for the organic synthesis relies on three interconnected requirements. These are as follows:

- A cross-linked, insoluble polymeric material should be inert to the condition of synthesis.
- The linking substrate (linker) to the solid phase that permits selective cleavage of some or all the products from the solid support during synthesis for analysis of the extent of reaction (s) and ultimately to give the final product of interest.
- The chemical protection strategy must allow selective protection and deprotection of reactive groups.

Advantages and Disadvantages of Solid Support Reagents

Advantages

a. Solid-supported reagents are easily removed from reactions by filtration.
b. Excess reagents can be used to drive reactions to completion without introducing difficulties in purification.
c. Recycling of recovered reagents is economical, environmentally-sound, and efficient.
d. Ease of handling is especially important when dealing with expensive or time-intensive catalysts, which can be incorporated into flow reactors and automated processes.
e. Finely tune chemical properties by altering choice of support and its preparation.
f. Toxic, explosive, and noxious reagents are often more safely handled when contained on solid support.
g. Reagents on solid-support react differently, mostly more selectively, than their unbound counterparts.

Disadvantages

a. Some reagents may not interact well with solid support.
b. Ability to recycle reagents on solid support is not assured.
c. Reactions may run more slowly due to diffusion constraints.
d. Polymeric support materials can be very expensive to prepare.
e. Stability of the support material can be poor under harsh reaction conditions.
f. Side reactions with the polymer support itself may occur.

Resins for SPS: In solid phase synthesis, resin supports for SPS include spherical beads of lightly cross-linked gel type polystyrene (GPS) (1%–2% divinylbenzene) and poly(styrene-oxyethylene) graft copolymers, which are functionalized to allow attachment of linkers and substrate molecules. Each of these materials has advantages and disadvantages, depending on the particular application. There are several types of resins available for different type of reactions, which has been mentioned in Table 4.

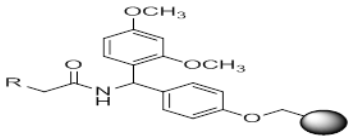
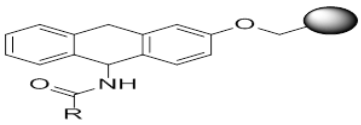
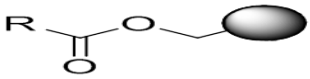
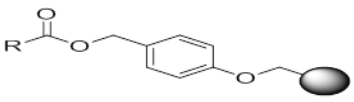
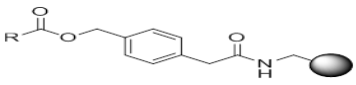
Type of resin	Chemical structure of resin	Protecting group	Deprotecting reagent
Sieber Amide resin		Fmoc	95% TFA
MBHA resin		Boc	HF, TFMSA
Merrifield resin		Boc	HF, TFMSA
Wang resin		Fmoc	95% TFA
PAM resin		Boc	HF, TFMSA

Table 4: Types of resins and reactions.

Combinatorial Synthesis in Solution

Solid phase combinatorial synthesis has a number of inbuilt disadvantages:

a. All the libraries have a common functional group at the position corresponding to the one used to link the initial building block to the linker or bead.
b. Syntheses are usually carried out using the linear approach.
c. Requires especially modified reactions with high yields (>98 percent) if multistep syntheses are attempted.
d. Requires additional synthesis steps to attach the initial building block to and remove the product from the support.
e. The final product is contaminated with fragments (truncated intermediates) of the product formed by incomplete reaction at different stages and often needs additional purification steps.

Many of these disadvantages are eliminated or reduced when combinatorial syntheses are carried out in solution. For example, solution phase combinatorial chemistry does not have to have a common functional group at the position corresponding to the one used to link the synthesis substrate to the linker or bead. Both the linear, template and convergent synthesis routes can be followed. Unmodified traditional organic reactions may be used but multistep syntheses will still require very efficient reactions. However, it does not require additional synthetic steps to attach the initial building block to and remove the product from a solid support. The product is not likely to be contaminated with truncated intermediates but unwanted impurities will still need to be removed at each stage in a synthesis. Solution phase combinatorial chemistry can be used to produce libraries that may contain single compounds or mixtures. Their production is usually by parallel synthetic methods. The main problem in their preparation is the difficulty of removing unwanted impurities at each step in the synthesis. Consequently, many of the strategies used for the preparation of libraries using solution chemistry are directed to purification of the products of each step of the synthesis. These practical problems have often limited the solution combinatorial syntheses to short synthetic routes(Table 5).

Solid phase synthesis	Solution phase synthesis
Purification is easy, simply wash the support	Purification can be difficult
Reagents can be used in excess in order to drive the reaction to completion.	Reagents cannot be used in excess, unless addition purification is carried out.
Automation is easy.	Automation may be difficult.
Scale up is relatively expensive.	Scale up is relatively easy and inexpensive.
Not well documented and time will be required to find a suitable support and linker for a specific synthesis.	Only require time for the development of the chemistry.
Fewer suitable reactions.	In theory any organic reaction can be used.

Table 5: Comparison between solid and liquid phase synthesis.

Conclusion

Rapid advances in molecular and structural biology have provided ample therapeutic targets characterized in three dimensions. Tools to exploit this information are being rapidly developed and several strategies for de novo design of ligands, given an active site, are under investigation. The ultimate goal in comparison of molecules with respect to their biological activity is insight into the receptor and its requirements for recognition and activation. QSAR has done much to enhance our understanding of fundamental processes and phenomena in medicinal chemistry and drug design. The concept of hydrophobicity and its calculation has generated much knowledge and discussion as well as spawned a mini-industry.

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