Chapter

1 Drug Design—A Rational Approach

1. INTRODUCTION

In the past few decades there has been a hiatus in the momentum of research and discovery of **'novel medicinal compounds'.** This particular trend in drug development perhaps is augmented due to **two** vital factors, namely : *first*, strict empirical and rational approach to drug design ; and *secondly*, high standards of safety and therapeutic efficacy together with tremendous increased costs of research and development and finally the clinical trials.

'**Drug design**' or **'tailor-made compound'** aims at developing a drug with high degree of chemotherapeutic index and specific action. It is a logical effort to design a drug on as much a rational basis as possible thus reducing to the minimum the trial and error approach. It essentially involves the study of biodynamics of a drug besides the interaction between drug molecules and molecules composing the biological objects.

Drug design seeks to explain :

(*a*) Effects of biological compounds on the basis of molecular interaction in terms of molecular structures or precisely the physico-chemical properties of the molecules involved.

(*b*) Various processes by which the drugs usually produce their pharmacological effects.

(*c*) How the drugs specifically react with the protoplasm to elicit a particular pharmacological response.

(*d*) How the drugs usually get modified or detoxicated, metabolized or eliminated by the organism.

(*e*) Probable relationship between biological activity with chemical structure.

In short, **drug design** may be considered as an integrated whole approach which essentially involves various steps, namely : chemical synthesis, evaluation for activity-spectrum, toxicological studies, metabolism of the drug, *i.e.*, **biotransformation** and the study of the various metabolites formed, assay procedures, and lastly galenical formulation and biopharmaceutics.

The **'drug design'** in a broader sense implies random evaluation of synthetic as well as natural products in bioassay systems, creation of newer drug molecules based on biologically-active-prototypes derived from either plant or animal kingdom, synthesis of congeners displaying interesting biological actions, the basic concept of isosterism and bioisosterism, and finally precise design of a drug to enable it to interact with a receptor site efficaciously.

In the recent past, another terminology **'prodrugs'** has been introduced to make a clear distinction from the widely used term **'analogues'**. **Prodrugs** are frequently used to improve pharmacological or biological properties. **Analogues** are primarily employed to increase potency and to achieve specificity of action.

2. ANALOGUES AND PRODRUGS

In the course of **drug design** the *two* major types of chemical modifications are achieved through the formation of **analogues** and **prodrugs.**

An **analogue** is normally accepted as being that modification which brings about a carbon-skeletal transformation or substituent synthesis. *Examples :* **oxytetracycline, demclocycline, chlortetracycline, trans-diethylstilbesterol** with regard to **oestradiol.**

The term **prodrug** is applied to either an appropriate derivative of a drug that undergoes *in vivo* hydrolysis to the parent drug, *e.g.,* **testosterone propionate, chloramphenicol palmitate** and the like ; or an analogue which is metabolically transformed to a **biologically active drug,** for instance : **phenylbutazone** undergoes *in vivo* hydroxylation to **oxyphenbutazone.**

3. CONCEPT OF 'LEAD'

Another school of thought views **'drug design'** as the 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. These include :

(*a*) **Exploration of Leads,** which involves the search for a new lead ; and

(*b*) **Exploitation of Leads,** that requires the assessment, improvement and extension of the lead.

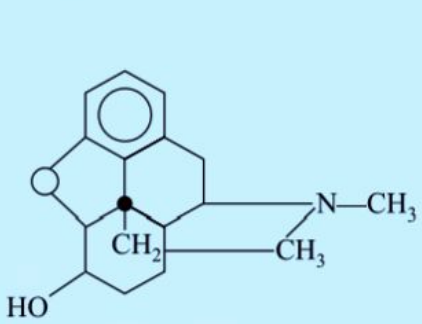
From the practical view-point it is the latter area wherein rational approaches to drug design have been mostly productive with fruitful results.

3.1 Examples

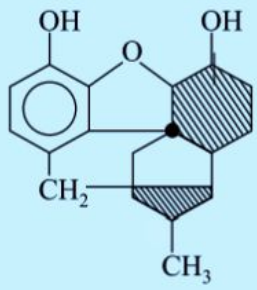
It is worthwhile to look into the right perspective of a few typical and classical examples of **drug design** as detailed below :

(*i*) Narcotic Analgesics

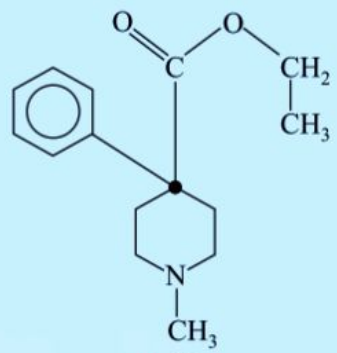
In the year 1939, Schaumann first identified and recognized the presence of a quaternary-carbon-atom in the morphine molecule, which eventually formed an altogether new basis and opened up a new horizon in the field of **drug design** of narcotic analgesics. Intensive research further led to the evolution of **pethidine (meperidine)** which incidentally combines both the properties of **morphine** and **atropine**. It possesses a quaternary carbon-atom and quite astonishingly a much simpler chemical structure to that of **morphine**.



Morphine

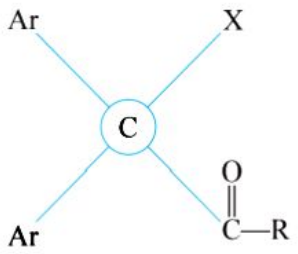


Morphine
(Schaumann's Model)



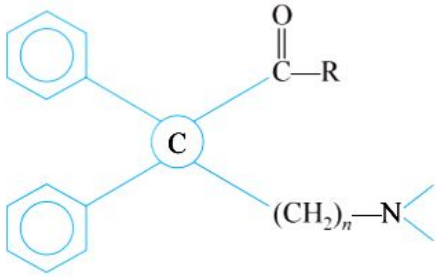
Pethidine
(Meperidine)

Ehrhardt suggested a **general formula** relevant to the analgesic activity in 1949 as stated below :



where, Ar is the aromatic ring, X the basic side chain and (—C—) carbonyl function in the form of an ester, ketone or an amide.

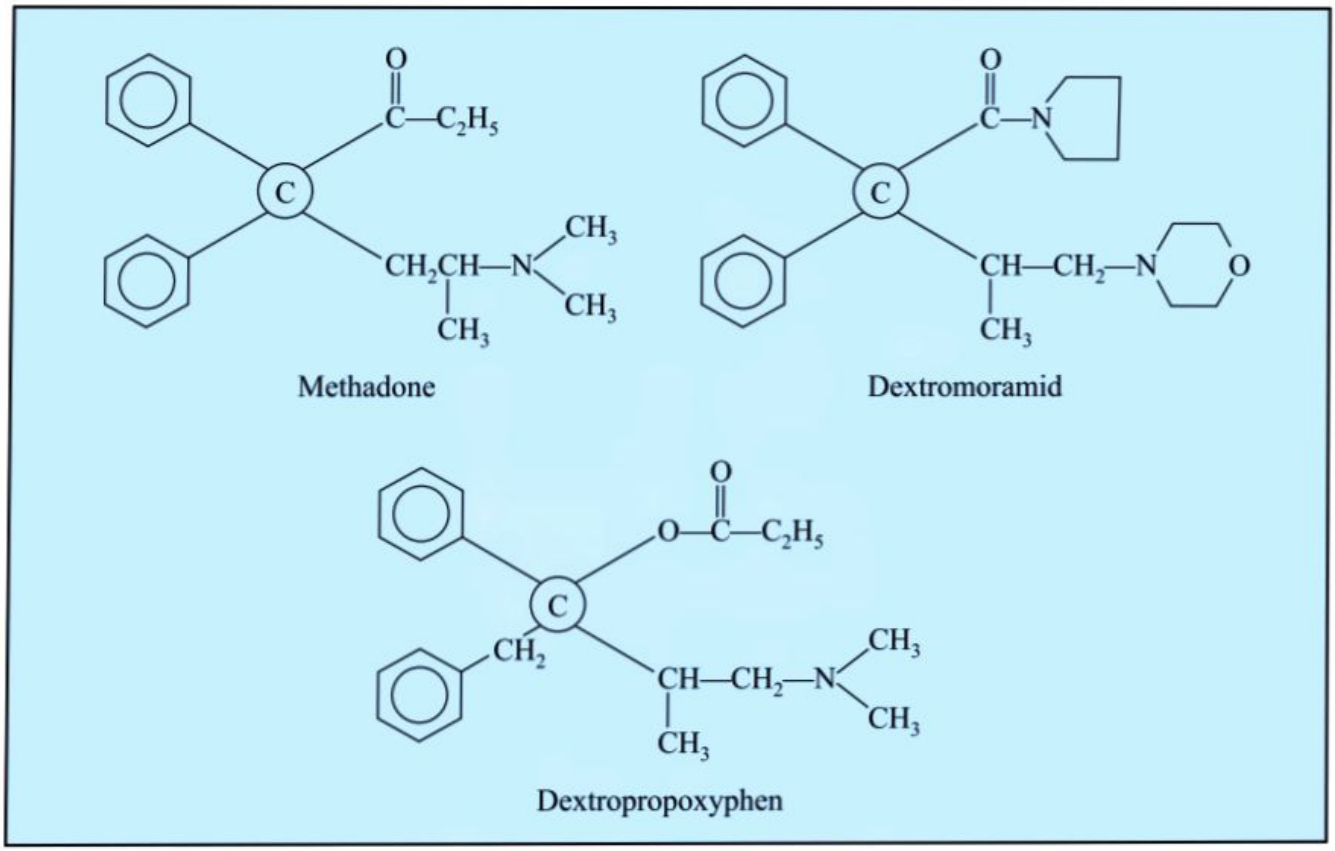
Later on, the above general formula was modified slightly as follows :



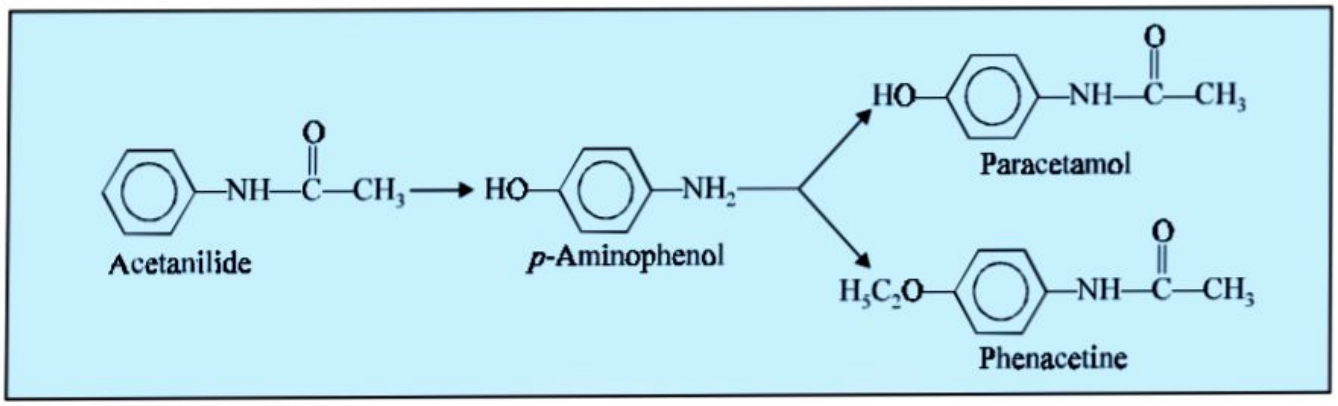
which successfully led to the development of the following *three* **narcotic analgesics,** namely : **methadone, dextromoramid** and **dextropropoxyphen.**

(*ii*) Antipyretic Analgesics

Another fruitful approach in **drug design** is the meticulous screening of the metabolite for probable pharmacological activity. The most interesting example is the bio-oxidation of acetanilide into *para*-aminophenol which subsequently on **chemical manipulation** has yielded better tolerated antipyretic-analgesics like **paracetamol** and **phenacetine.**

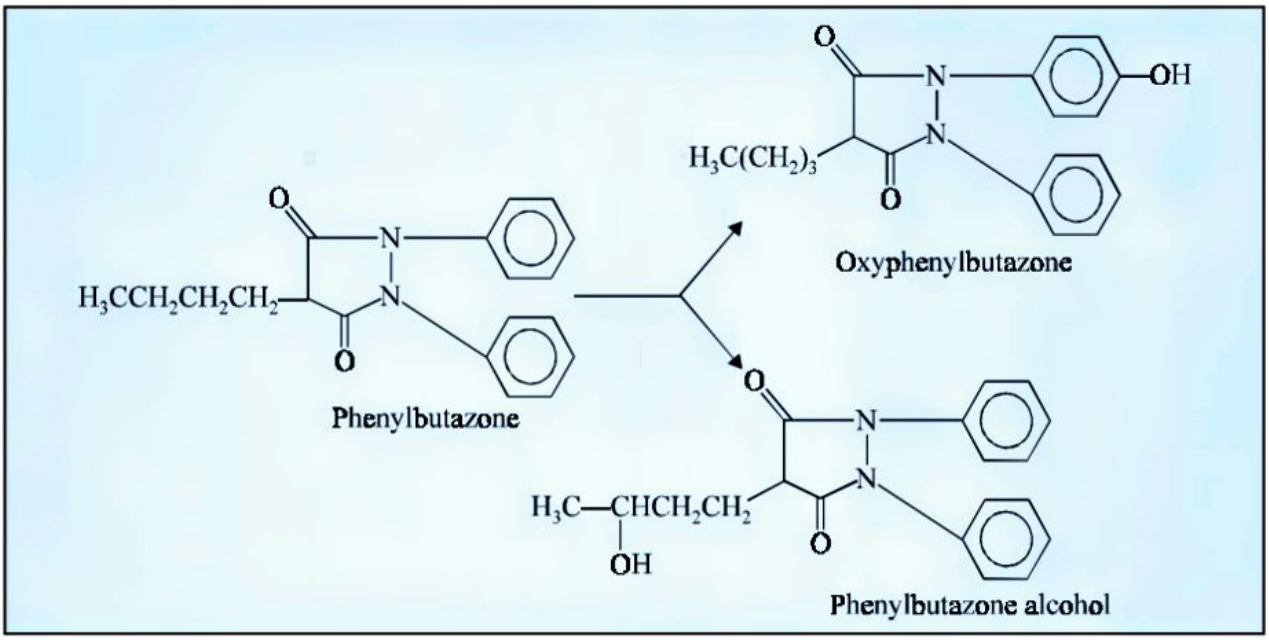


Quite recently **phenacetine** has been withdrawn completely because of its toxic after effects, though it dominated the therapeutic field for over 30 years as a potent antipyretic analgesics.



(*iii*) Antirheumatic Drugs

The study of the metabolite conversion of the antirheumatic drug phenylbutazone resulted in the introduction of a better tolerated drug **oxyphenylbutazone** as an **antirheumatic drug** and **phenylbutazone** alcohol as an **uricosuric agent.**



4. FACTORS GOVERNING DRUG-DESIGN

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

(*a*) The smaller the expenditure of human and material resources involved to evolve a new drug of a particular value, the more viable is the design of the programme.

(*b*) Experimental animal and clinical screening operations of the new drugs.

(*c*) Relationships between chemical features and biolgoical properties need to be established retrospectively.

(*d*) **Quantitative structure-activity relationships (QSARs)** 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.

(*e*) 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.

(*f*) Introduction of functional groups 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.

(*g*) Disease etiologies and various biochemical processes involved prove useful.

5. RATIONAL APPROACH TO DRUG DESIGN

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

5.1. Quantum Mechanical Approach

Quantum mechanics (or **wave mechanics**) is composed of certain vital principles derived from fundamental assumptions describing the natural phenomena effectively. The properties of protons, neutrons and electrons are adequately explained under **quantum mechanics**. The electronic features of the molecules responsible for chemical alterations form the basis of drug molecule phenomena.

5.2. Molecular Orbital Approach

Based on the assumption that electrons present in molecules seem to be directly linked with orbitals engulfing the entire molecule which set forth the molecular orbital theory. The **molecular orbital approach** shows a dependence on electronic charge as evidenced by the study of three volatile inhalation anaesthetics, and also on molecular conformation as studied with respect to acetylcholine by such parameters as bond lengths and angles including torsional angles.

Molecular orbital calculations are achievable by sophisticated computers, and after meticulous interpretations of results the molecular structure in respect of structure-activity analysis is established.

5.3. Molecular Connectivity Approach

This approach establishes the presence of structural features like cyclization, unsaturation, skeletal branching, and the position and presence of heteroatom in molecules with the aid of a series of numerical indices. **For example :** an index was determined to possess a correlative factor in the SAR study of amphetamine-type hallucinogenic drugs.

Molecular connectivity approach has some definite limitations, such as : **electronegativity variance between atoms, non-distinguishable entity of *cis-trans* isomerism.**

5.4. Linear Free-Energy Approaches

This method establishes the vital link between the proper selection of physicochemical parameters with a specific biological phenomenon. However, such a correlation may not guarantee and allow a direct interpretation with regard to molecular structure, but may positively offer a possible clue towards the **selection of candidate molecules for synthesis.**

6. DRUG-DESIGN : THE METHOD OF VARIATION

Under this method a new drug molecule is developed from a **biologically active prototype.** The various **advantages** are as follows :

(*a*) At least one new compound of known activity is found.

(*b*) The new structural analogues even if not superior may be more economical.

(*c*) Identical chemical procedure is adopted and hence, considerable economy of time, library and laboratory facilities.

(*d*) Screening of a series of congener (*i.e.*, member of the same gene) gives basic information with regard to pharmacological activity.

(*e*) 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

In order to obtain a therapeutically potent and better-tolerated drug there exists invariably an apparent conflict of pure scientific objectives and practical objectives. **This may be expatiated by citing the instance of an exceedingly toxic congener (say an anti-neoplastic agent) that possesses a very high degree of specificity and the researcher may have in mind to prepare still more toxic compounds so as to develop the highest possible specificity of action.** On the contrary, absolutely from the practical aspect, the proposed clue may not be pursued solely depending on the policy of the organization and not the individual or group of researchers.

In fact, there are a few generalized approaches utilizing the method of variation. In this particular context, the familiarity with the molecular structure is of the prime importance. The various possible approaches in designing newer drugs by applying variation of a prototype are quite numerous. Once the molecular structure of the compound in question is drawn on the drawing board, one takes into consideration such information as the following :

(*a*) study of the core nucleus of the hydro-carbon skeleton ;

(*b*) variation of functional groups and their proximity to one another ;

(*c*) various probable rotational and spatial configurations ;

(*d*) possibility of steric hindrance between various portions of the molecule in different configurations in space ; and

(*e*) probability of electronic interactions between various portions of the molecule including such matters as inductive and mesomeric effects, hyper-conjugation, ionizability, polarity, possibility of chelation, asymmetric centres and zwitterion formation.

The application of the method of variation, depending on the considerations enumerated above, is exploited in two different manners to evolve a better drug. The two main approaches for this goal can be indicated as :

(*a*) drug design through disjunction ; and

(*b*) drug design through conjunction.

6.1. Drug Design through Disjunction

Disjunction comes in where there is the systematic formulation of analogues of a prototype agent, in general, toward structurally simpler products, which may be viewed as partial or quasi-replicas of the prototype agent.

The **method of disjunction** is usually employed in three *different* manners, namely :

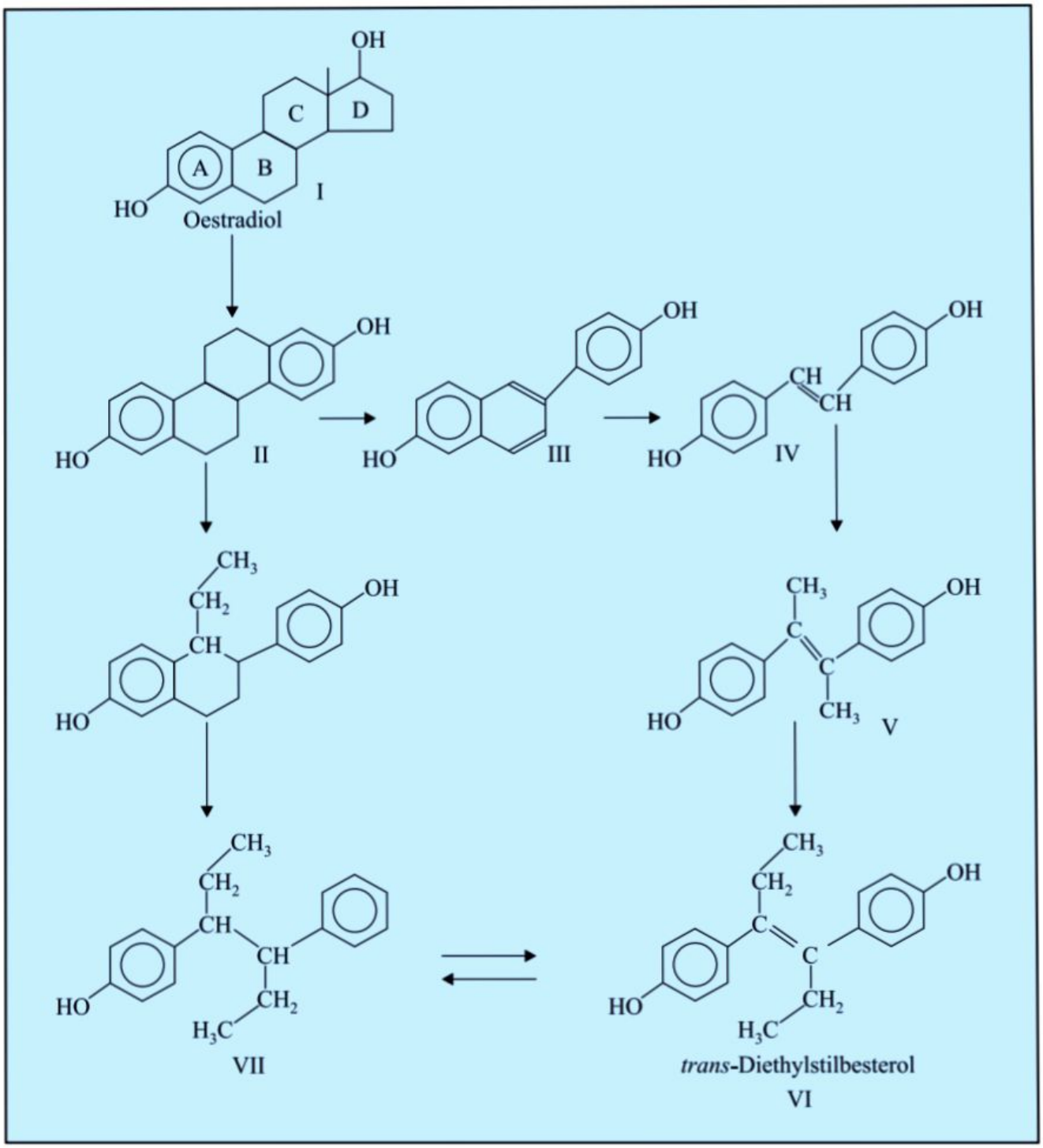
(*i*) unjoining of certain bonds ;

(*ii*) substitution of aromatic cyclic system for saturated bonds ; and

(*iii*) diminution of the size of the hydrocarbon portion of the parent molecule.

Example :

The extensive study on the estrogenic activity of oestradiol *via* drug design through disjunction ultimately rewarded in the crowning success of the synthesis and evaluation of *trans*-diethylstilbesterol. The **flow-sheet of estrogen design** is stated below :



Flow-sheet of Estrogen Design

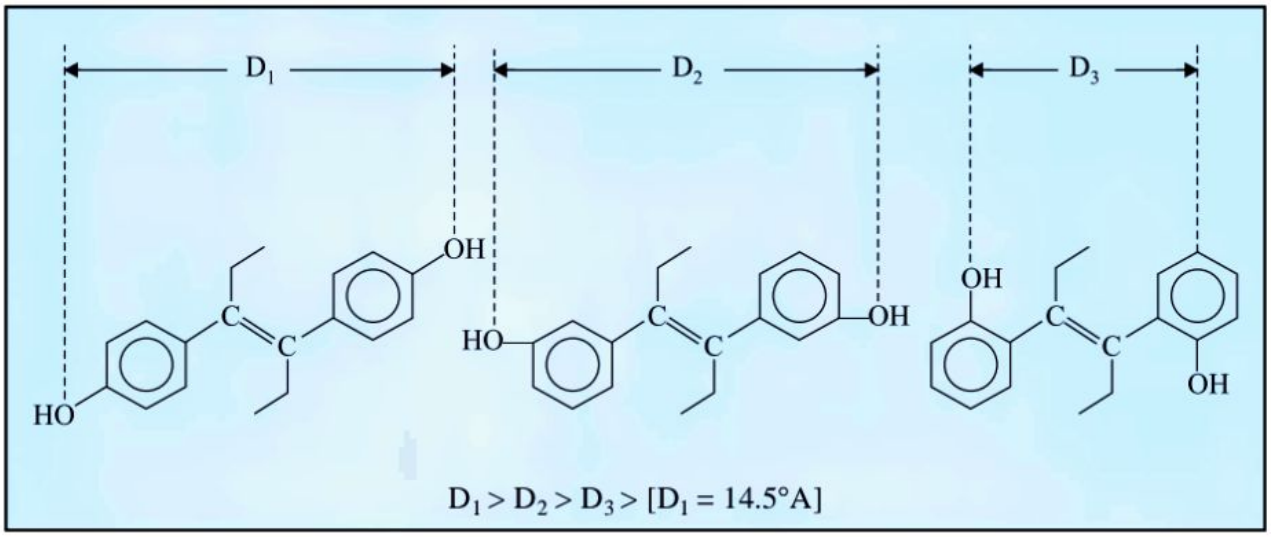
From the above the following *three* observations may be made. They include :

(*i*) Various steps in design of II to III to IV designate nothing but successive simplification through total elimination of the rings *B* and *C* in oestradiol (I).

(*ii*) The above manner of drug design finally led to successively less active products (*i.e.*, II, III, IV).

(*iii*) Upon plotting oestrogenic activity against various structures (I to VII) it was quite evident that the maximal activity in this series was attributed to ***trans*-diethylstilbesterol.**

It is, however, pertinent to mention here that in the following **three** different possible structures of **diethylstilbesterol analogues**, the oestrogenic potency decreases substantially as the distance '*D*' between the two hydroxyl groups decreases.



6.2. Drug Design through Conjunction

This is known as the **systematic formulation of analogues of a prototype agent,** in general, toward structurally more complex products, which may be viewed as structures embodying, in a general or specific way, certain or all of the features of the prototype.

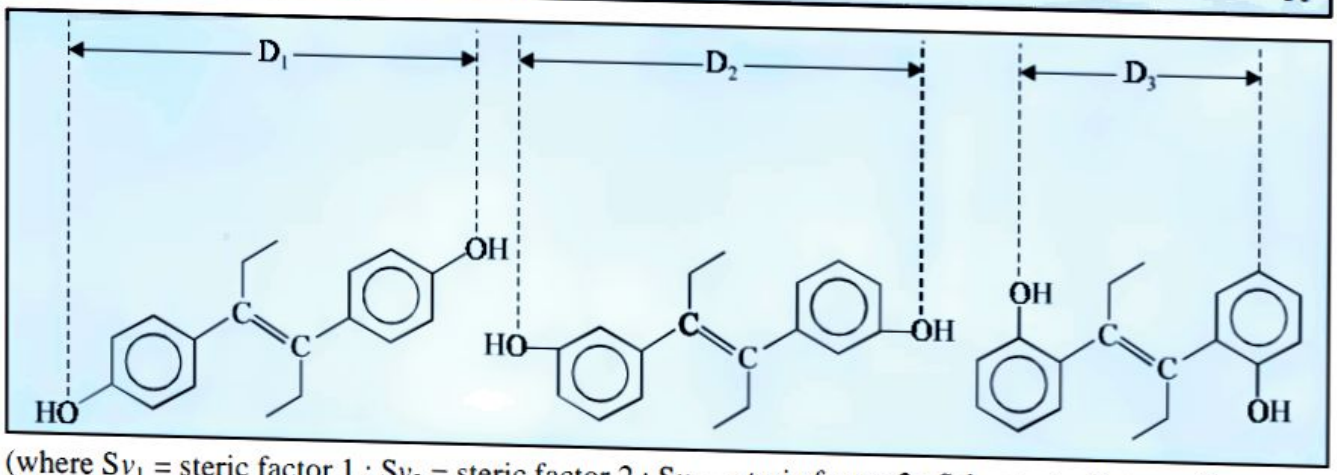
In this type of drug-design, the main principle involved is the **'principle of mixed moieties'.** A drug molecule is essentially made up with two or more pharmacophoric moieties embedded into a single molecule.

Example :

Ganglionic blocking agent—its development based on the principle of mixed moieties.

The principle of mixed moieties actually involve the conjunction of two or more different types of pharmacophoric moieties within a single molecule.

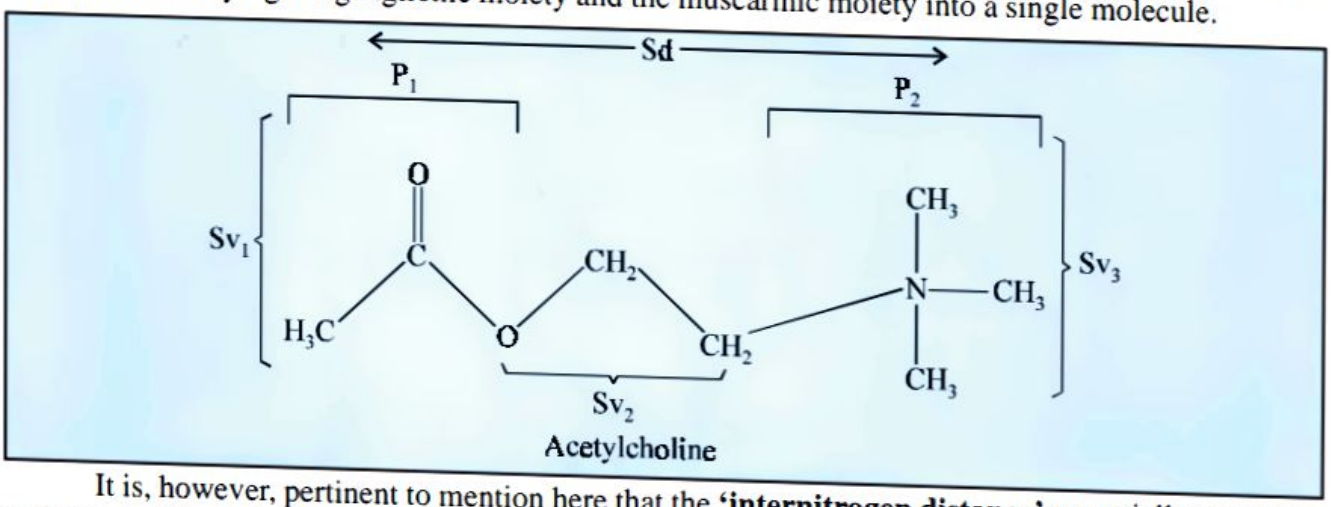
Acetylcholine is an effective postganglionic parasympathetic stimulant in doses that afford no appreciable changes in the ganglionic function ; whereas **hexamethonium** possesses only a slight action at postganglionic parasympathetic endings in doses that produce a high degree of ganglionic blockade.



(where Sv_1 = steric factor 1 ; Sv_2 = steric factor 2 ; Sv_3 = steric factor 3 ; Sd = steric distance factor ; P_1 = polarity factor 1 and P_2 = polarity factor 2).

The moiety requirements for postganglionic parasympathetic stimulant action (muscarinic moiety) have been duly summarized for convenience to the above structure of acetylcholine wherein the various operating factors have been highlighted.

The foregoing generalization of the muscarinic moiety on being studied in relation to the particular bisquaternary type of structure, *e.g.* hexamethonium, promptly suggests the following proposed design, thus embodying the ganglionic moiety and the muscarinic moiety into a single molecule.



Acetylcholine

It is, however, pertinent to mention here that the **'internitrogen distance'** essentially constitute an important factor in many series of bisquaternary salts that possess ganglionic blocking activity. It is worthwhile to note that this distance is almost similar to that present in hexamethonium in its most extended configuration.

However, the actual synthesis and pharmacological evaluation of the above **hexamethyl analogue** reveal the presence of both muscarinic stimulant and ganglionic blocking actions. Interestingly, the corresponding **hexaethyl analogue** possesses a ganglionic blocking effect and a weak muscarinic stimulant action.

7. DRUG DESIGN AND DEVELOPMENT : AN OVERVIEW

7.1. Preamble

The overwhelming qualified success in the evolution of **'ethical pharmaceutical industry'** in the twentieth century have not only registered an unquestionable growth in improving the fabric of society to combat dreadful diseases across the globe but also made a significant legitimate cognizance of an individual's quality of life and above all the life expectancy.

The twentyfirst century may obviously record and witness an apparent positive tilt in population demographics ultimately leading to a much healthier, stronger and happier elderly population.

However, in the 21st century, the **'ethical pharmaceutical industry'** has been fully geared towards the production of relatively safer, less toxic, more effective, higher therapeutic index, novel, innovative medicaments that will evidently help the mankind to afford a disease-free society ; besides, the elder ones with a glaring hope to live a still longer life span.

Following is the brief description in a chromological order for the development of **'ethical pharmaceutical industry'** in the world :

Year	Country	Historical Development
1600s	Japan	—Takeda in 1637*.
1800s	Europe and USA	—Fine chemical industries**.
1880s	Germany and UK	—Hoechst (Germany) and Wellcome (UK) for immunological drugs.
1889	UK	—Aspirin (as NSAID)
1990	France	—Rhone Poulenc
1914	Europe	—Engaged in US-operations
1929	USA	—Aureomycin (Lederle) ; Chloromycetin (Parke-Davis) ; Teramycin (Pfizer) ;
1950	France and Belgian	—Chlorpromazine [Rhone-Poulenc (France)] ; Haloperidol [Janssen (Belgium)]—both psychotropic drugs
1950s to 1970s	USA	—Pharmaceutical Industry showed a steady growth***
1970s	USA	—Greater advancement on molecular focus in the regimen of **'drug discovery'** picked up substantial momentum with the strategic induction of noted scientists in the US National Academy of Sciences, namely : Needleman P (Monsanto) ; Cuatrecasas P (Burroughs Wellcome) ; and Vagelos PR (Merck).

*Sneader WJ, **'Drug Discovery : The Evolution of Modern Medicines,'** John Wiley, Chichester, UK, 1997.

** Di Masi, d J *et al.* **Research and Development costs for new drugs for therapeutic category**, *Pharmaco.Econ.*, **7 :** *52, 169, 1995.*

***Drayer JI and Burns JP. From discovery to market : the development of pharmaceuticals. In : Wolff ME, ed, **Burgers Medicinal Chemistry and Drug Discovery**, 5th edn, Vol I, Wiley, New York, 1995, pp 251-300.

The various phases of transformations in **'ethical pharmaceutical industry'** between 1600 to 1970s brought about a sea-change with a significant shift from the core techniques of molecular pharmacology and biochemistry to those of molecular biology and genomics (biotechnology). Based upon these fundamental newer concepts amalgamated with various paradigm shifts resulted into the evolution of an exclusive progressive change in the scenario of both culture and the environment of the **'ethical pharmaceutical industry'** in developed as well as developing countries in the world.

7.2. Revolutions in Drug Discovery

A tremendous noticeable change in the **'process of drug discovery'** in the past three decades has been focused solely on the **'biotechnology revolution'.** In short, the techniques employed invariably in 'molecular biology' and 'biotechnology' opened up an altogether **'new trend in biomedical research'.**

In 1997, a staggering 1150 companies were established based on **'biotechnology'**, engaging three lacs research scientists working round-the-clock, and generated USD 12 billion. The six major biotech companies in USA, established in mid 1980s, now proudly enjoys the number one status not only in US but also in rest of the world, namely :

(*a*) **Genentech**—Presently subsidiaries of *Roche Biosciences ;*

(*b*) **Genetics Institute**—Presently subsidiaries of *American Home Products,*

(*c*) **Amgen ; Genzyme ; Chiron** and **Biogen**—Presently emerged as *major pharmaceutical companies.*

In the light of the huge accelerated costs for drug development, touching USD 359 million in 1991, to almost USD 627 million in 1995 and a projected USD 1.36 billion in 2000, have virtually pumped in lots of force geared towards superb efficacies and efficiencies in the pharmaceutical industry.* And this could only be accomplished through appreciable consolidation amalgamated with continued efforts of outsourcing of higher risk, early drug discovery to venture **capital-aided-biotech units ;** besides, clinical trials to the **clinical-research organizations** exclusively.

In order to significantly cut down the overhead expenses, and encash on sizable profitability various giants in the pharmaceutical industry have more or less adopted the following stringent measures to face the cut-throat competition in the global market and also survive gainfully, such as :

(*a*) To enhance the required productivity in the R and D activities of major pharmaceutical companies to sustain and maintain profitability,

(*b*) Increased productivity without enhancing R and D resources,

(*c*) Focusing on new research activities/strategies thereby creating a possible balance between internal research and external alliances,

(*d*) Merger and alliances in Pharmaceutical Industries dates back to 1970s with the formation of **Ciba-Geigy**** ; and till 2000 more than 20 such acquisitions/mergers have already been materialized across the globe.

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*Carr G : **The Alchemists : A survey of the Pharmaceutical Industry, Economist**, February 21, 1998, pp 3-18.

** de Stevens G., **Conflicts and Resolutions.**, *Med. Res Rev.*, 1995, **15**, pp 261-275.

7.3. Research and Development Strategies

It has been proved beyond any reasonable doubt that the *'rate of success'* in **drug discovery** is exclusively dependent on the ability to identify, characterize novel, patentable newer **'target-drug-molecules'** usually termed as **New Chemical Entities (NCEs)**, which essentially possess the inherent capability and potential in the management and control of a specific disease/ailment ; besides, being efficacious and safer in character. With the advent of latest technological advancements in the specialized areas related to **genomics and combinatorial chemistry** an appreciable advancement has been accomplished in the R & D strategies. It is, however, pertinent to mention here that a proprietary NCE status, position and recognition is an absolute must not only to ensure marketing exclusively but also to aptly justify the huge investment in the ensuing R & D process thereby making **medicinal chemitry** a more or less core element of the entire **'drug discovery process'.**

Interestingly, the **'drug discovery process'** may be categorized into **four** distinct heads, namely :

(*i*) Target identification and selection,

(*ii*) Target optimization,

(*iii*) Lead identification, and

(*iv*) Lead optimization.

The concerted efforts encompassing various intangible and critical methodologies that ultimately relate to the activities, expertise, wisdom and integration of the individual scientist directly or indirectly involved in **'drug discovery process'** virtually leads to advance drug discovery profiles.*

In short, the qualified success in the **'drug discovery process'** predominantly revolves around the following cardinal factors, namely :

- Articulated project management processes
- Prioritization
- Well-defined aims and objectives
- Company organization(s) and culture
- Resourcing *modus operandi*
- Prompt decision making factors.

8. MOLECULAR HYBRIDISATION

The **molecular hybridisation** essentially embodies the synthesis of strategically designed of altogether newer breeds of **'bioactive agents'** either from two or even more compounds having different characteristic features by the aid of **covalent-bond synthesis.**

Necki (1886) first conceived the interesting **'salol principle',** whereby he exploited the beneficial properties of phenols and carboxylic acids possessing potent antibacterial characteristic features into the **'design'** of newer drug molecules with better and improved pharmacological activities by means of simple esterification.

*Sapienza A.M., **Managing Scientists**, Wiley, New York, 1995.

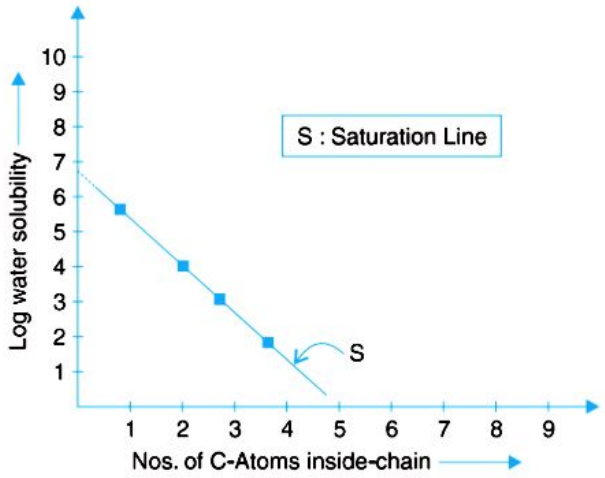


Fig. 2.1. Interaction between 'Saturation-Line S' and 'Log Water Solubility'.

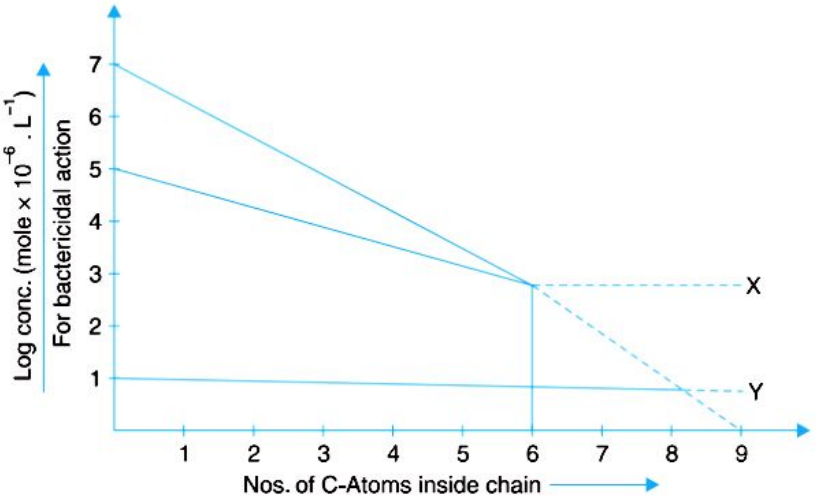


Fig. 2.2. Plot between Log Conc. and Nos. of C-Atoms Inside-chain.

2.9. Steric Factors

Interestingly, it is absolutely necessary for a **'drug molecule'** to engage into a viable and plausible interaction either with a **drug receptor** or with an **enzyme**, it has got to *first* approach ; and *secondly*, attach to a binding site. Obviously, this essentially demands certain specific criteria that a **'drug molecule'** must fulfil, for instance : bulk, size and shape of the **'drug'.** Precisely, the **'bulky substituent'** more or less serve as a shield that eventually hinders the possible and feasible interaction taking place between a **'drug'** and a **'receptor'.**

Meticulous and intensive in-depth studies in this particular aspect has practically failed to *justify* and *quantify* steric characteristics in comparison to quantifying either electronic or hydrophobic

characteristics. In fact, a plethora of methodologies have been tried and tested to ascertain the steric factor(s). In the present context only *three* such methods shall be discussed briefly, namely :

(*a*) Taft's Steric Factor (Es),

(*b*) Molar Refractivity (MR), and

(*c*) Verloop Steric Parameter.

2.9.1. Taft's Steric Factor (Es)

An attempt has been made to quantify the steric features of various substituents (*i.e.*, functional moieties) by the help of **Taft's steric factor (Es).**

In fact, there are *three* predominant constants, namely :

(*i*) Hammett substitution constant (σ),

(*ii*) Resonance effect (R), and

(*iii*) Inductive effect (F).

can only be employed for aromatic substituents ; and are hence suitable exclusively for such **'drugs'** that contain *aromatic rings.*

A. Hammett Substitution Constant (σ). It is a measure of either the **electron-withdrawing** or **electron-donating** capability of a substituent (*i.e.*, the functional moiety). **Hammet substitution constant** may be determined conveniently by actual measurement of the dissociation of a series of benzoic acid substituted derivatives *vis-a-vis* the dissociation of pure benzoic acid itself.

However, benzoic acid being a **'weak-acid'** gets partially ionized in an aqueous medium (H_2O) as depicted under :

Explanation. An equilibrium is established between the two distinct species *i.e.*, the *ionized* and *non-ionized* forms. Thus, the relative proportion of the said two species is usually termed as the **'dissociation'** or **'equilibrium'** constant ; and invariable designated by K_H (wherein the *'subscript H'* represents/signifies that there is no substituents normally attached to the aromatic nucleus *i.e.*, the phenyl ring).

$$\therefore \qquad K_H = \frac{[PhCOO^{\ominus}]}{[PhCOOH]}$$

As soon as a substituent is strategically positioned on the aromatic (phenyl) ring, this **'equilibrium'** gets imbalanced. At this juncture *two* situations may crop up distinctly by virtue of the fact that :

(*i*) An electron-withdrawing moiety, and

(*ii*) An electron-releasing (donating) moiety

could be present in the aromatic ring thereby giving rise to **altogether different electronic status** to the **'Aryl Nucleus'.**

(*a*) **Electron-Withdrawing Moiety.** A host of **electron-withdrawing groups**, such as : NO_2, CN, COOH, COOR, $CONH_2$, CONHR, $CONR_2$, CHO, COR, SO_2R, SO_2OR, NO ; cause and result in the aromatic ring (with a π electron cloud both on its top and bottom) having a marked and stronger electron withdrawing and stabilizing influence on the carboxylate anion as illustrated below. Hence,

the overall equilibrium shall influence and shift more to the ionized form thereby rendering the '**substituted benzoic acid**' into a **much stronger acid** (benzoic acid as such is a weak acid). The resulting substituted benzoic acid exhibits a larger K_X value (where, X designates the substituent on the aromatic nucleus) (see Fig. 2.3).

(*b*) **Electron-Donating Moiety :** A plethora of **electron-donating groups**, for instance : R, Ar, F, Cl, I, Br, SH, SR, O^-, S^-, NR_2, NHR, NH_2, NHCOR, OR, OH, OCOR, influence and render the ensuing aromatic ring into a distinctly much less stable to stabilize the *carboxylate ion.* Thus, the equilibrium gets shifted to the left overwhelmingly ; thereby ultimately forming a relatively **much weaker acid** having a smaller K_X value (see Fig. 2.3).

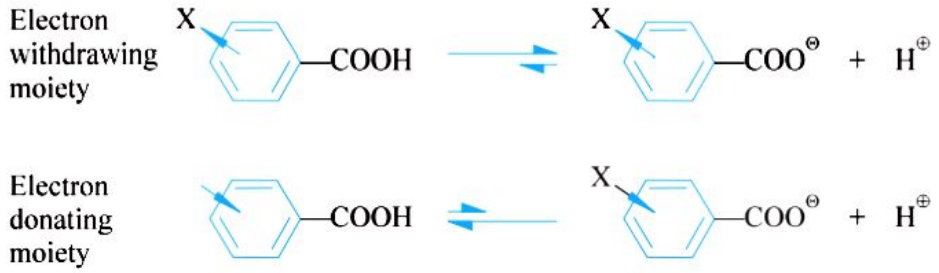


Fig. 2.3 : Influence of Substituent Moiety X on the Status of Equilibrium in Reaction.

Now, the **Hammett substitution constant [σ_X]** with reference to a specific substituent X is usually defined by the following expression :

$$\sigma_X = \log \frac{K_X}{K_H} = \log K_X - \log K_H$$

Therefore, for all benzoic acids essentially possessing electron-withdrawing substituents shall have larger K_X values than the parent benzoic acid itself (K_H) ; thereby the value of **Hammett substitution constant σ_X** for an electron-withdrawing substituent shall be always **positive**.

Similarly, for most benzoic acid variants essentially having electron-donating substituents shall have comparatively smaller K_X values than benzoic acid itself ; and, therefore, the value of **Hammett substitution constant σ_X** for an electron-donating substituent will always be **negative**.

Furthermore, the **Hammett substitution constant** essentially and importantly takes cognizance of *two* vital and critical supportive effects, such as : **resonance effect**, and **inductive effect**. Consequently, the value of σ with respect to a specific substituent may exclusively depend upon whether the attached *'substituent'* is located either at *meta*-or at *para*-position. Conventionally, such particular substituent is invariably indicated by the subscript *m* or *p* first after the symbol σ.

Example : The nitro ($-NO_2$) substituent on the benzene nucleus has two distinct σ values, namely : $\sigma_m = 0.71$ and $\sigma_p = 0.78$.

Explanation. From the σ values, one may evidently observe that the electron-withdrawing strength at the *para*-position is solely contributed by both **'inductive'** and **'resonance'** effects combinedly which justifies the greater value of σ_p, as shown in Fig. 2.4(*a*). Likewise, the *meta*-position, only affords the electron-withdrawing power by virtue of the **'inductive'** influence of the substituent ($-NO_2$ group), as shown in Fig. 2.4(*b*).

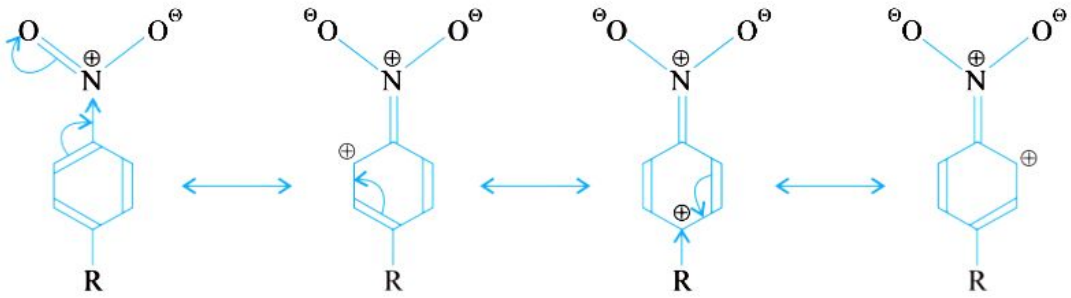


Fig. 2.4(*a*) Electronic Influence on R Caused due to Resonance and Inductive Effects of *p*-nitro Function.

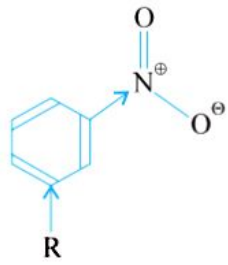


Fig. 2.4(*b*) Electronic Influence on R Caused due to Inductive Effect alone of *m*-nitro Function.

B. Resonance Effect (R) : It has been observed that **'resonance'** mostly gives rise to an altogether **different distribution of electron density** than would be the situation if there existed absolutely no resonance.

Examples : The resonance effects, as observed in *two* electron donating functional moieties, such as : $-NH_2$ (amino) ; and –OH (hydroxyl), attached to an aromatic nucleus, are depicted in Fig. 2.5(*a*) and (*b*) as under :

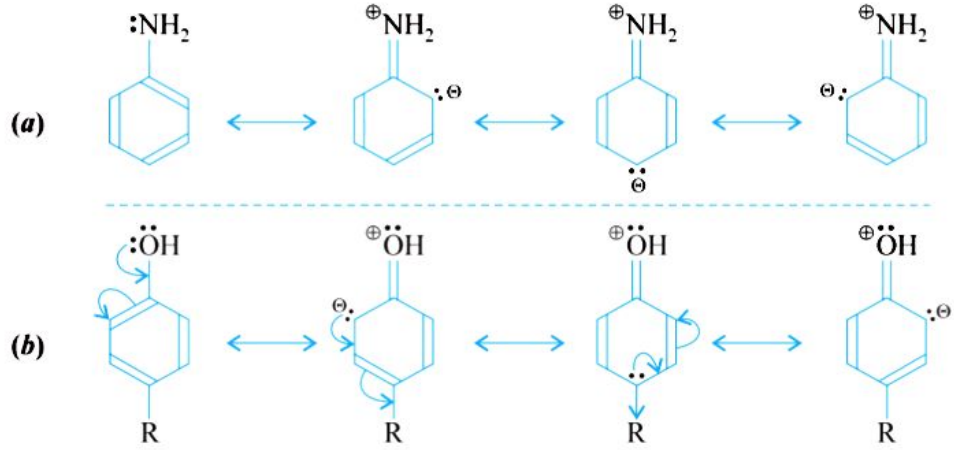


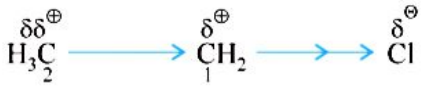
Fig. 2.5(*a*) :Resonance Structures of Aniline

Fig. 2.5(*b*) Electronic Influence on R Exclusively Dominated by Resonance Effects.

Explanations : **For Resonance Structures of Aniline [Fig. 2.5(*a*)] :** In case, the **first structure** happened to be the **'actual structure of aniline'**, the two unshared electrons of the N-atom would certainly reside exclusively on that particular atom. However, in true sense and real perspective the **first structure** is **not** the ideal and only structure for aniline but a **hybrid one** which essentially includes contributions from several canonical forms as shown, wherein the density of electrons of the unshared pair does not reside necessarily on the N-atom but gets spread out around the phenyl ring. In nut shell, this observed density of electron at one particular position (with a corresponding enhancement elsewhere) is invariably known as the **'resonance'** or **'mesomeric effect'.**

For Resonance Structures of Phenol [Fig. 2.5(*b*)] : Here, the influence of R at the *para* position, and the electron-donating effect caused due to resonance is more marked, pronounced and significant as compared to the electron-withdrawing influence due to induction.

C. Inductive Effect (F) : The C—C single bond present in **'ethane'** has practically no polarity as it simply connects two equivalent atoms. On the contrary, the C—C single bond in '**chloroethane**' gets solemnly polarized by the critical presence of the electronegative *chlorine-atom*. In fact, the prevailing polarization is actually the sum of *two* **separate effects.** *First*, being the C-1 atom that has been duly deprived of a part of its electron density evidently by the greater electronegativity of Cl. It is, however, compensated partially by drawing the C—C electrons located closer to itself, thereby causing polarization of this bond and consequently rendering a slightly positive charge on the C-2 atom as shown below :



Chloroethane

Secondly, the effect is caused not through bonds, but directly either through *space* or *solvent molecules*, and is usually termed as the **field effect.***

2.9.2. Molar Refractivity (MR)

Another vital and equally important criterion to measure the **'steric factor'** is adequately provided by a parameter called as **molar refractivity (MR)**. It is usually designated as a simple measure of the volume occupied either by an individual atom or a cluster (group) of atoms. However, the **MR** may be obtained by the help of the following expression :

$$MR = \frac{(n^2 - 1)}{(n^2 + 2)} \times \frac{MW}{d}$$

where, n = Index of refraction,

MW = Molecular Weight,

d = Density,

MW/d = Volume and

$\frac{n^2 - 1}{n^2 + 2}$ = Correction factor (*i.e.*, how easily the substituent can undergo polarization)

Molar refractivity is specifically significant in a situation when the substituent possesses either π *electron* or *lone pairs of electrons.*

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*Roberts ; Moreland., *J. Am. Chem. Soc.*, **75,** 2167, 1953.

2.9.3. Verloop Steric Parameter

The unique revelation and wisdom of a latest computer researched programme termed as **sterimol** has indeed helped a long way in measuring the **steric factor** to a reasonably correct extent. It essentially aids in the calculation of desired steric substituent values (otherwise known as **Verloop steric parameters**) based on various standard physical parameters, such as : Van der Waals radii, bond lengths, bond angles, and ultimately the proposed most likely conformations for the substituent under examination. It is, however, pertinent to mention here that unlike the **Taft's steric factor (E_S)** (see Section 2.9.1) the Verloop steric parameters may be measured conveniently and accurately for any substituent.

Example : **Carboxylic acid (say, Benzoic Acid) :** The ensuing **Verloop steric parameters** for a carboxylic acid moiety are duly measured as shown in Fig. 2.6 below, where L represents the length of the substituent, and $B_1 - B_4$ designate the radii (*i.e.,* **longitudinal** and **horizontal**) of the *two* functional groups *viz., carboxyl and hydroxyl* (—O—H).

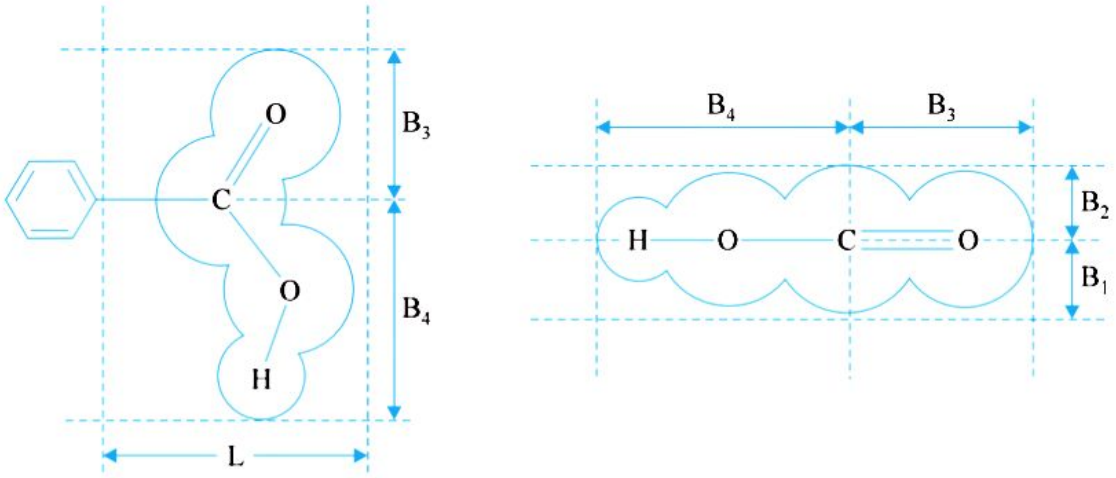

Fig. 2.6 Verloop Steric Parameters for a Carboxylic Acid (—COOH) Moiety.

Interestingly, most **quantitative structural activity relationship (QSAR)** studies usually commence by considering σ (**Hammett substitution constant**) and, in case there exists more than one substituent, the σ values are represented in a summed up manner as Σσ. Keeping in view the enormous quantum of **synthetic newer target drug molecules,** it has now become almost necessary and possible either to modify/refine or fine tune-up the QSAR equation. In fact, a substituent's **resonance effect (R)** and **inductive effect (F)** may be quantified as far as possible with the help of available **'tables of constants'.** In certain instances one may evidently observe that :

- a substituent's effect on biological activity is solely on account of F rather than R, and *vice versa.*
- a substituent exerts a more prominent and appreciable activity when strategically located at a specific position on the aromatic nucleus ; and moreover it may also be embeded in the '**equation**' appropriately.

2.10. Hansch Equation

Integrating various factors, namely : **Taft's steric factor, resonance, inductive, Verloop steric parameters** with the partition behaviour of **'drug molecules'** Hansch* and Fujita** exploited these principles in determining the establishing **quantitative structure-activity relationship (QSAR)** of **drugs,** which has undergone a sea change both in expansion and improvement with the help of **computer researched soft-wares**.

The **hydrophobic characteristic,** designated by π_x, may be correlated to a **drug's distribution pattern**, within which a given substituent '*x*' affects molecular behaviour and conduct with regard to its :

- ➤ distribution and transport, and
- ➤ drug-receptor activities.

The hydrophobic characteristic π_x of a drug substance may be expressed as :

$$\pi_x = \log P_x - \log P_{yH}$$

where, log P = logarithm of 1-octanol-water partition coefficient

y = A parent compound (*i.e.,* an unsubstituted reference compound/drug).

Salient Features : The various salient features of **Hansch equation** are as enumerated under :

(1) Value of π is indicative, to a certain extent, the behavioural pattern of a *'substituent'* contributing to the solubility behaviour of a molecule under investigation. It also reflects upon the manner it gets partitioned between lipoidal and aqueous interfaces in the reputed compartments it happens to cross as a **'drug'** so as to reach the **'site of action'** ultimately.

(2) It is, however, not very clear and definite whether the solid surface of a *'drug'* undergoes adsorption on colloidally suspended plasma proteins while establishing the **hydrophobic characteristics π.**

(3) Interestingly, the concurrent considerations of π and σ **(Hammett's constant)** has evolved gainful vital correlations existing between the biological activities of quite a few drug substances with their corresponding physical properties and chemical structures.

Therefore, **Hansch's correlations** piece together valuable information(s) of a newly designed **'drug molecule'** in a more plausible, predictive and quantifiable manner than before — and apply it to a biological system more logistically and judiciously. This particular concept and idea was further substantiated and expanded by assuming that all the *three* substituents *viz.*, π, σ and Es, exert a significant effect on the efficacy and hence the potency of a **'drug substance'** ; and are found to be additive in nature independently. Therefore, it has given rise to the underlying **linear Hansch equation** :

$$\log\left(\frac{1}{C}\right) = a \log P + b\, E_S + \rho(\sigma) + d$$

where , C = Concentration of drug producing the biological response being measured,

log P = Substituent constant for solubility (*i.e.,* π),

E_S = Taft constant (for steric effects),

ρ – (rho) Proportionality constant designating the sensitivity of the reaction to electron density.

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* Hansch *et al. J. Am. Chem. Soc.,* **85,** 2817, 1963, *ibid*, **86**, 1616, 1964 ;

** Fujita *et al. J. Am. Chem. Soc.,* **86,** 5175, 1964.

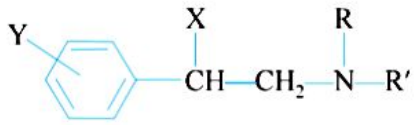
σ = Hammett substitution constant

a, b, d = Constants of the system (which are determined by computer to obtain the **'best fitting line').**

It is pertinent to state at this juncture that *not* all the parameters shall necessarily be significant.

Example : **β-Halo-arylamines :** The **adrenergic blocking profile** of **β-halo-arylamines** was observed to be solely related to the two constants, π and σ ; and specifically excluded the steric factor altogether.

i.e., $$\log\left(\frac{1}{C}\right) = 1.22\,\pi - 1.59\,\sigma + 7.89$$

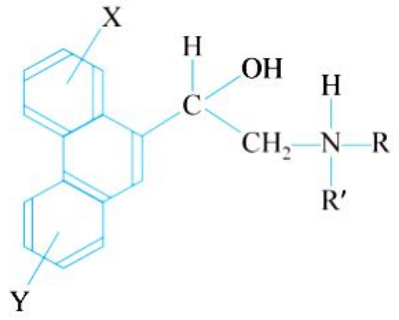


The aforesaid equation offers a dictum that the **'biological response'** gets enhanced if the substituents possess a positive π value and a negative σ value ; or more explicitely the substituents must preferentially be both hydrophobic in nature and electron donating in character.

It has been established beyond any reasonable doubt that there exists no correlation between the **π factor** and the **P value** ; therefore, it is quite feasible to have **Hansch equations** essentially comprising of these two stated components :

Example : **Phenanthrene aminocarbinols :** An analogous series of more than one hundred **phenanthrene aminocarbinols** were successfully synthesized and subsequently screened for their **antimalarial profile**. Interestingly, the analogous series fitted appropriately into the following version of **Hansch equation** :

$$\log\left(\frac{1}{C}\right) = -0.015\,(\log P)^2 + 0.14\log P + 0.27\,\Sigma\pi_x + 0.40\,\Sigma\pi_y + 0.65\,\Sigma\sigma_x + 0.88\,\Sigma\sigma_y + 2.34$$



PHENANTHRENE AMINOCARBINOL

Salient Features : The various characteristic **salient features** that may be derived from the above equation are, namely :

(1) As the **hydrophobicity** of the molecule (P) enhances there exists a very nominal increase in the **antimalarial activity**.

(2) The corresponding constant is low (0.14) which reflects that the increase in **antimalarial activity** is also low.

(3) The value of $(\log P)^2$ evidently reveals that there prevails a **maximum P value for activity**.

(4) Further the above equation suggests that the **antimalarial activity** gets enhanced appreciably when the hydrophobic moieties are strategically located either on ring 'X' or more specifically on ring 'Y'. It further ascertains that the **hydrophobic interaction(s)** are virtually taking place at these sites.

(5) The **electron-withdrawing substituents on rings 'X' and 'Y'** contribute enormously to the **antimalarial activity** ; however, the effect is more on ring 'Y' than in ring 'X'.

2.11. The Craig Plot

The **Craig plot** is nothing but an actual plot between the **'π factor'** taken along the **X-axis** and the **'σ factor'** taken along the **Y-axis**, thereby having a clear and vivid idea with regard to the relative properties of different functional moieties (substituents).

Fig. 2.7 illustrates the **Craig plot** of various *para* aromatic substituents for the σ and π factors respectively.

Salient Features : The various advantageous **salient features** of a **Craig plot** are enumerated as under :

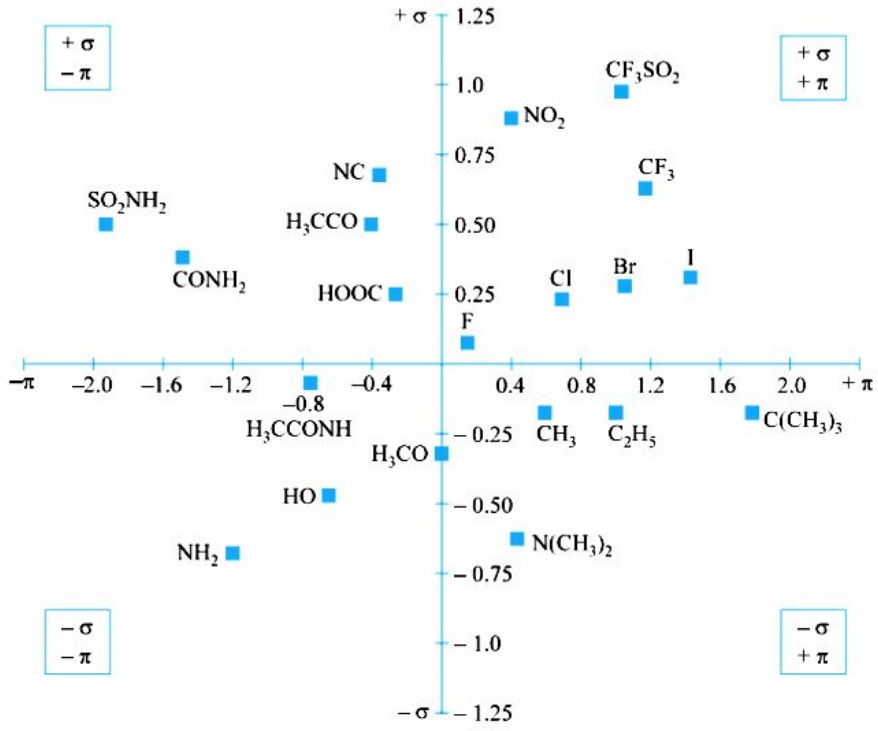


Fig. 2.7 The Craig Plot for the σ and π Factors of *para*-Aromatic Substituents.

(1) The **Craig plot** in Fig. 2.6 evidently depicts that there is absolutely no clearly defined overall relationship between the two **'key factors'** σ and π. However, the various functional moieties (*i.e.*, substituents) are strategically positioned around all the four quadrants of the plot based on their inherent physicochemical status and integrity.

(2) From the above **Craig plot** one may obviously identify the substituents that are particularly responsible for +ve π and σ parameters, –ve π and σ parameters, and lastly one +ve and one –ve parameter.

(3) Further it is quite convenient and easy to observe which substituents have nearly identical π values, such as : *dimethyl-amino, fluoro* and *nitro* on one hand ; whereas, *ethyl, bromo, trifluoromethyl,* and *trifluoromethyl sulphonyl* moieties on the other are found to be almost located on the same **'vertical line'** on the **Craig plot.** Thus, theoretically all these functional groups are legitamately interchangeable on a newly designed drug molecule wherein the major critical and principal factor that significantly affects the **'biological characteristics'** is essentially the π factor.

Interestingly, in the same vein, the various functional moieties that are located on the **'horizontal line'**, for instance : methyl, ethyl *tert-butyl* on one hand ; whereas, carboxy, chloro, bromo, and iodo moieties on the other can be regarded and identified as being *iso-electric* in nature or possessing identical σ values.

(4) **QSAR studies** are exclusively and predominantly governed and guided by the **Craig plot** with regard to the various substituents in a new drug molecule. Therefore, in order to arrive at the most preferred **'accurate equation'** essentially consisting of π and σ, —the various structural analogues must be synthesized having appropriate substituents pertaining to each of the four quadrants.

Examples :

(*i*) **Alkyl Moieties :** These substituents contribute exclusively +ve p values and –ve s values.

(*ii*) **Acetyl Moieties :** These are responsible for attributing –ve π values and +ve σ values.

(*iii*) **Halide Groups :** These functional moieties essentially enhance both electron-withdrawing characteristics and hydrophobicity in the **'drug molecule'** by virtue of their +ve σ and +ve π effects.

(*iv*) **Hydroxy Groups :** These functional moieties exert progressively more hydrophilic and electron-donating characteristics on account of the –ve π and –ve σ effects.

(5) Importantly, the very establishment and derivation of **Hansch equation** will certainly give a better reliable and meaningful clue with regard to attaining a reasonably good biological property based on the fact whether π and σ must be –ve or +ve in character. However, further improvements in the **'drug molecule'** could be accomplished by exploring various other possible substituents picked up judiciously from the relevant quadrant (see Fig. 2.6).

Example : In case, the **Hansch equation** rightfully demands that +ve σ and –π values are an absolute necessity, additional relevant substituents must be picked up from the top-left quadrant.

(6) The **Craig plot** may also be exploited to compare the **MR and hydrophobicity**.

2.12. The Topliss Scheme

Keeping in view the enormous cost incurred with regard to the synthesis of a large range of structural analogues necessarily required for a **Hansch equation,** it has become almost necessary to restrict the synthesis of a relatively lesser number of drug molecules that may be produced in a limited span of time having viable biological activity. Based on the actual outcome of the biological activity *vis-a-vis* the actual structure of the '**drug**' ultimately helps to determine the next analogue to be synthesized.

The **Topliss scheme** is nothing but an organized **'flow diagram'** which categorically permits such a procedure to be adopted with a commendable success rate.

In actual practice, however, there are *two* distinct **Topliss Schemes**, namely : (*a*) For **aromatic substituents ;** and (*b*) For **aliphatic side-chain substituents.** It is pertinent to mention here that the said *two schemes* were so meticulously designed by taking into consideration both **electronic** and **hydrophobicity** features (*i.e.*, substituents) with a common objective to arrive at the **'optimum biological active substituents'.**

It may be made abundantly clear and explicit that the **Topliss Schemes** are not a replacement for the Hansch analysis. Hence, the former may be made useful and effective only when a good number of tailor-made structures have been designed and synthesized.

[A] Fig. 2.8 represents the **Topliss Scheme for Aromatic substituents ;** and has been based on the assumption that the **'lead compound'** essentially possesses a single monosubstituted aromatic ring and that it has already been screened for its desired biological activity.

Salient Features : The various **salient features** with respect to the **Topliss scheme** for aromatic substituents are as described below :

(1) 4-chloro derivative happens to be the *'first structural analogue'* in this particular scheme perhaps because it is easy to synthesize.

(2) The π and σ values are both positive by virtue of the fact that the chloro substituent is much more hydrophobic and electron-withdrawing than hydrogen-atom.

(3) The synthesized chloro-analogue is subjected to the biological activity measurements accordingly.

(4) Three situations may arise, namely : (*a*) analogue possessing less activity (L) ; (*b*) equal activity (E) ; and (*c*) more activity (M). Thus, the type of observed activity is solely the determining factor as to which *'branch'* of the Topliss scheme is to be adopted next.

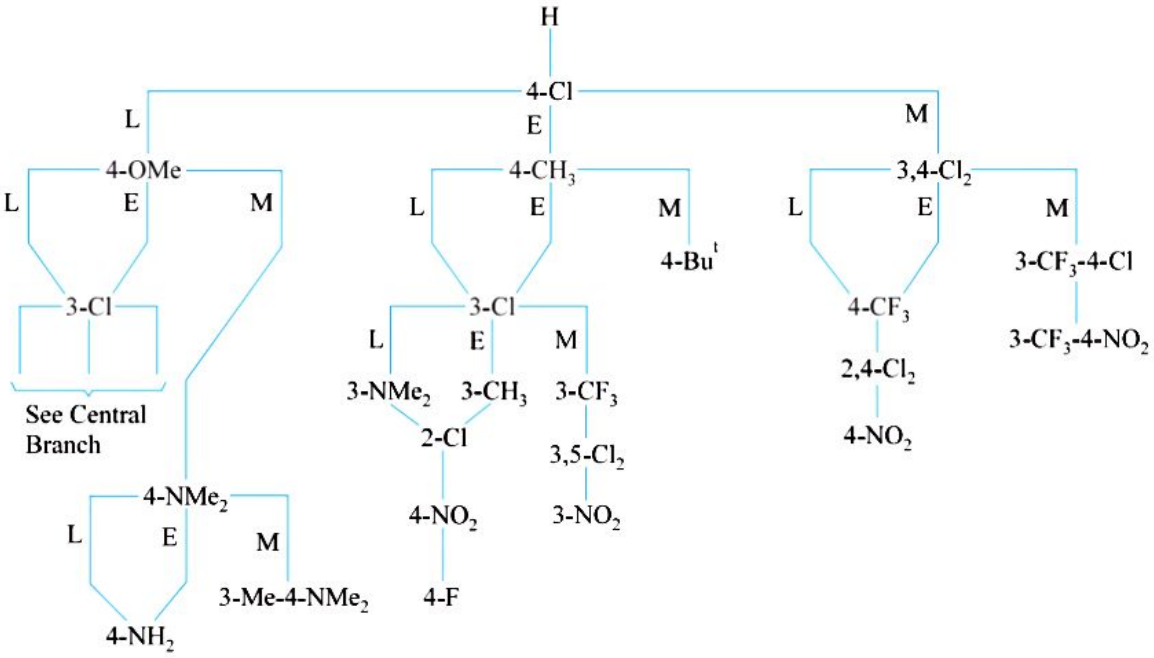


Fig. 2.7 : Topliss Scheme for Aromatic Substituents

(5) Further line of action towards the synthesis of structural analogues of 4-chloro aromatic substituents are entirely guided and based on the following *three* options, namely :

Biological Activity	Series Followed	Next Analogues Synthesized
(*a*) Increases	M-series	3, 4-Dichloro substituted derivatives
(*b*) Same profile	E-series	4-Methyl derivatives
(*c*) Decreases	L-series	4-Methoxy derivatives

(6) Let us consider the second analogous series which shows the same biological activity. The various situations that may arise are as follows :

(*i*) **4-Chloro derivative enhances the desired biological property :**

As the Cl-substituent exerts both positive π and σ values it evidently shows that either one or both of three characteristic features are quite critical and important to biological property. In case, both characteristic features are important, addition of the second Cl-moiety shall enhance the biological activity to the positive side furthermore. If it fails, there may exist either an excess hydrophobic character or an obstructive steric hindrance is exhibited. Thus, the situation demands further modification based on subsequent biological screening *vis-a-vis* the comparative importance and status of π as well as the steric features.

(*ii*) **4-Chloro derivative lowers the desired biological activity :**

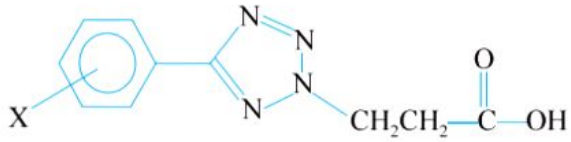
It gives a clue that either the location of the *para*-substituent is absolutely unsuitable sterically or the –ve π and/or σ values are prominently important with regard to the biological activity. It has been established that the reduced activity is solely attributed due to an unfavourable σ effect ; and hence, one may assign the *para*-methoxy moiety as the next probable substituent having a –ve σ factor. If by doing so there is an apparent improvement in activity, further alterations are accomplished with a view to ascertain the prevailing relative importance of the σ and π values. Now, if the above modifications *i.e.*, *para*-methoxy moiety fails to make any improvement in the activity, one may draw an inference that an undesired steric factor is playing the havoc, and the next possible entrance is of the *meta*-chloro group. However, further modifications of this functional group shall then be persued as depicted in the middle series of Fig. 2.8.

(*iii*) **4-Methyl derivative equals the desired biological activity :**

In this specific instance, the overall biological activity of the 4-chloro structural analogue exerts practically no change as compared to the **'lead compound'.** It might have emanated from the **'drug substance'** essentially looking for a negative π value and a positive σ value. As it is quite evident that the two said values attributed by the chloro moiety are apparently positive, the useful effect of the positive π value should have been nullified due to the detrimental influence of a positive σ value. Therefore, the most preferred substituent would be the *para*-methyl group, which adequately possesses positive π value and negative σ value. In case, it still exhibits no useful effect, one may draw a conclusion that there exists an unfavourable steric interaction prevailing at the *para*-position. Hence, the next preferable line of action would be the introduction of chloro group at the *meta*-position. However, any additional changes shall affect the values attributed by both π and σ factors.

The **Topliss scheme** has been thoroughly investigated, tested and above all validated by various researcher after evaluating their **structure-activity relationships (SARs)** for a host of **'drug substances'**.

Example : **Substituted phenyltetrazolylalkanoic acid :** A total of 28 structural analogues of **substituted phenyltetrazolylalkanoic acids** were synthesized in the laboratory and screened duly for their anti-inflammatory activities. Nevertheless, if the whole exercise would have been based on the **Topliss Scheme** only the first eight compounds (out of 28) should have yielded *three* most active compounds as given below :



Substituted Phenyltetrazolylalkanoic Acids

Sequence of Synthesis	X	Biological Activity (Observed)	Maximum Potency (Observed)
1	H	—	
2	*para*-Cl	L	
3	*para*-OCH_3	L	
4	*meta*-Cl	M	++++
5	*meta*-CF_3	L	++++
6	*meta*-Br	M	
7	*meta*-I	L	
8	3, 5—Cl_2	M	++++

L = Less Activity
M = More Activity
E = Equal Activity

[B] Fig. 2.9 designates the **Topliss Scheme** for the **Aliphatic** side-chains and adopted in the same vein and rationale as the aforementioned **'aromatic scheme'** (section 'A'). The present scheme is expanded exactly in the same fashion for the side functional moieties strategically linked to a variety of such functional groups as : **amine**, **amide** or **carbonyl**.

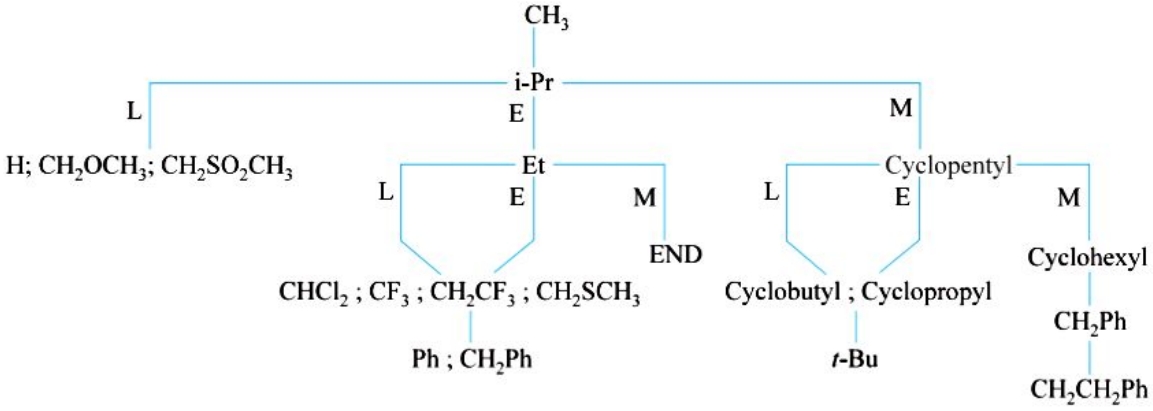


Fig. 2.9. Topliss Scheme for Aliphatic Side-chain Substituents.

Interestingly, the **Topliss Scheme** helps to make a clear cut distinction between the two pronounced physical characteristic features, namely : electronic effect, and hydrophobic effect, caused due to the various substituents ; and not the steric characteristic features. Perhaps that could be the possible line of thought judiciously utilized in the selection of appropriate substituents so as to reduce any steric differences. Let us have an assumption that the **'lead compound'** possesses a—CH_3 functional moiety.

A variety of typical situations may crop up during the said studies :

(*a*) **Rise in anti-inflammatory activity :** A cyclopentyl moiety is now utilized which provides a much larger π value, and simultaneously holds the steric influence to a bear minimum level. In case, a further rise in activity is observed one may institute more hydrophobic substituents. On the contrary if the activity fails to rise, there could be two possible reasons, namely : (*i*) optimum hydrophobicity has superseded ; and (*ii*) electronic effect (σ_1) has triggered action. Of course, an elaborated further study would reveal and ascertain the exact substituents to substantiate which of the two explanations stands valid.

(*b*) **Static anti-inflammatory activity :** The activity exerted by the isopropyl structural analogue almost remains the same as that of the methyl one. It could be explained most logically that both methyl and isopropyl moieties are actually located on either side of the **'hydrophobic optimum'**. Hence, an intermediate functional group *i.e.*, an *ethyl group*, possessing an intermediate π value, is employed as the next substituent (see Fig. 2.7). In case, it still registers practically no plausible or appreciable improvement in the activity profile, one may switch over to an electron-withdrawing moiety instead of an electron-donating moiety, having identical π values, as futuristic suggestive approach.

3. FACTORS GOVERNING ABILITY OF DRUGS TO REACH ACTIVE SITE

There are certain vital factors that govern the ability of a drug to reach the active site soon after its administration through various modes known to us. These factors essentially include **absorption, distribution, biotransformation (metabolism) and elimination**. However, in all these instances, the drug molecule has to cross a few biological membrane in one form or the other. These factors shall now be treated briefly with appropriate typical examples wherever necessary.

3.1. Absorption

Biological membranes play a vital role towards the absorption of a drug molecule. Soon after a drug is taken orally, it makes its way through the gastrointestinal tract, cross the various membranes and finally approach the site or cell where it exerts its desired pharmacological action.

It has been observed that a plethora of drug molecules normally cross biological membranes by passive diffusion from a region of high drug concentration (*viz* : gastrointestinal tract) to a region of low drug concentration (*viz* : blood). However, the rate of diffusion solely depends upon the magnitude of the concentration gradient (ΔC) across the biological membrane and may be represented by the following equation :

$$\text{Rate} = -K\Delta C = -K(C_{abs} - C_{bl}) \qquad ...(1)$$

where C_{abs} represents the concentration of drug at the absorption site and C_{bl} is the respective concentration present in the blood. The constant of proportionality K, is a complex constant which essentially includes the area and thickness of membrane, partition of drug molecule between aqueous phase and membrane and finally the **diffusion coefficient of the drug**. It may be assumed that the concentration of

drug in the blood is fairly negligible as compared to the concentration in the gastrointestinal lumen. Hence, equation (1) simplifies to

$$\text{Rate} = -KC_{abs} \qquad ...(2)$$

As one may observe from equation (2) that absorption by passive diffusion is nothing but a first-order process, hence the rate of drug absorption is directly proportional to the concentration of drug at the absorption site. In other words, the larger the concentration of drug, the faster is the rate of absorption. At any time after the administration of the drug, the percentage of the dose absorbed remains the same irrespective of the dose administered.

Lipid solubility of the drug is the determining factor for the penetration of cell membranes. Therefore, the passage of many drug molecules across the membranes of the skin, oral cavity, bile, tissue cells, kidneys, central nervous system and the gastrointestinal epithelium is very much related to the lipid solubility of the drug molecule.

3.2. Distribution

As soon as a drug finds its way into the blood stream, it tries to approach the site of biological action. Hence, the **distribution** of a drug is markedly influenced by such vital factors as tissue distribution and membrane penetration, which largely depends on the physico-chemical characteristics of the drug. For instance, the effect of the ultra-short acting barbiturate thiopental may be explained on its dissociation constant and lipid solubility. It is worthwhile to observe here that the duration of thiopental is not influenced by its rate of excretion or metabolism, but by its **rate of distribution**.

3.3. Metabolism (Biotransformation)

When a drug molecule gets converted into the body to an altogether different form, which may be either less or more active than the parent drug, the phenomenon is termed as **biotransformation**. Mostly the drug metabolism occurs in liver. In fact, a number of pathways are genuinely responsible for carrying out various diverse metabolism reactions in the body.

It may be pertinent to observe here that most of the metabolised products are usually more polar in character than the parent drug molecule. This increased polarity renders the metabolism less absorbable through the renal tubules and also makes it transient in the body.

A large number of **barbiturates** are metabolized by liver microsomes. **Isoniazid** is quickly metabolized in **Japanese race** to the extent of 86.7%, whereas approximately half of it (44.9%) in *American and* **Canadian whites.** This disparity is due to the genetic differences in the said races.

In a broader sense a plethora of metabolic processes which usually **detoxify** the foreign substances *in vivo*, such as : oxidation, reduction, hydrolysis, esterification or conjugation ; thereby rendering the **'drug substance'** normally more water-soluble, so as to enhance its excretion from the body. It has been duly observed that in a good number of cases a **'drug metabolite'** actually may serve as the *active compound,* almost showing identical biological activity to the original compound. Interestingly, after having undergone several **biotransformations**, the ultimate modified form of the drug is excreted finally.

Though liver is considered to be the **primary site** of **'detoxification'** ; however, many enzymatic degradation processes may also take place in the stomach, intestine, pancreas, and other locations in the body. Generally, the metabolic processes occurring in the liver may be conveniently categorized under the following **two** heads, namely :

(*a*) **Functional Group Changes :** Here, the **'drug substance'** undergoes functional group changes, for instance : side-chain or ring hydroxylation, reduction of nitrogroup, reduction, aldehyde oxidation, deamination or dealkylation, and

(*b*) **Conjugation :** In this instance, the **'drug substance'** undergoes conjugation whereby the metabolized product subsequently combines with various solubilizing groups, such as : **glycine** (an amino acid) or **glucuronic acid** (glucuronides) to result into the formation of excretable conjugates ultimately.

Hence, during the course of designing/development of a **'new target-drug-molecule'** the **'medicinal chemist'** must take into cognizance of such metabolic phenomena and modify the structure of the drug substance in question so as to alter the course in which it should have been metabolized otherwise.

3.4. Excretion

Excretion of drugs from their sites of action is of paramount importance and may be effectively carried out with the help of a number of processes, namely : renal excretion, biliary excretion, excretion through lungs and above all by **drug metabolism** (**biotransformation**).

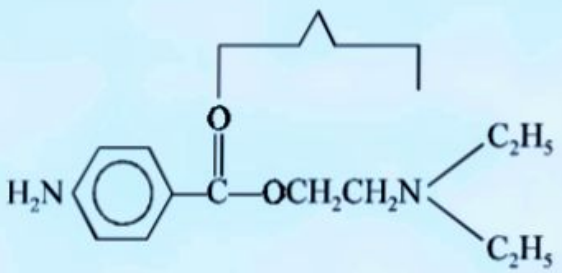
Drugs which are either water-soluble or get metabolized gradually are mostly eliminated through the kidneys by the aid of these three essential phenomena, *viz* : secretion, glomerular filtration and tubular reabsorption. For instance, **probenecid** considerably retards tubular secretion of **penicillin** thereby enhancing its duration of action appreciably.

Another aspect of excretion is the biliary excretion of drugs or its metabolites which essentially affects excretion of drugs by liver cells into the bile and subsequently into intestine. Invariably, a drug undergoes 'enterohepatic cycling', *i.e.*, instead of its elimination through the faeces it gains entry into the system through the intestines, *eg.*, **penicillin, fluorescein,** etc.

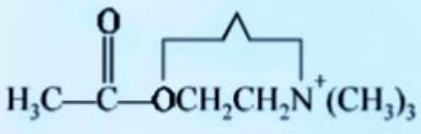
3.5. Intramolecular Distances and Biological Activity

The intramolecular distance is regarded as a structural feature of the drug molecule which falls within the regimen of physical property. It can be effectively measured either by X-ray or by electron diffraction measurements.

The intramolecular distance present in the grouping $-X\,CH_2CH_2N-$ between the nitrogen atom and X (where X = N, O etc.) that could be seen in a variety of medicinal compounds (*i* – *iii*) as stated below falls in the vicinity of 5A :



(*i*) **Procaine**
(local anaesthetic)



(*ii*) **Acetylcholine**
(parasympathomimetic)