Strategy of Drug Design: A Guide to Biological Activity

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PREFACE

This book was written to introduce organic chemists, medicinal chemists, pharmacologists, graduate students, and others to the techniques of applying mathematical models to the design of molecules with desired biological activities. It is hoped that the book will be a convenient desk reference for these techniques and serve as a "how-to-do-it" text. It is not intended to be a textbook on physical-organic chemistry, statistics, or quantum chemistry; other books are available which treat these subjects most adequately.

Chapter I introduces the subject, gives an historical review of the development of quantitative structure-activity relationships (QSAR) and presents some justification for the use of these tools in designing a molecule for a specific biological purpose. The rest of the book is devoted to two approaches in QSAR: the Linear Free Energy-Related (LFER) or Extrathermodynamic models (Chapters II-IV), which deal with the correlation of physicochemical properties of a molecule with its biological activity, and the De Novo model (Chapters V and VI), which is a statistical approach, independent of physicochemical properties, for ranking substituent group contributions to biological activity.

The section on the LFER models is divided into three chapters: the underlying theory (Chapter II); reference to the applications of the method and tables of hydrophobic, steric, and electronic parameters (Chapter III); and a simple hypothetical step-by-step example of two "real-life" examples (Chapter IV). These three chapters are

intended to serve different purposes and may be read independently or simply used as reference sources. In Chapter III, for example, we do not attempt to define and explain the Taft steric parameter (Table 3.2); rather we point out that it is used in the LFER model and give 22 references to it. Chapter IV was written to show the reader how to use the method by guiding him through a simple example. Two examples follow to bring the theory into perspective with real applications.

Chapter V and VI are analogous to the section on the LFER model. The main difference is that much less work has been done using the De Novo model; therefore, the theory is introduced in a short chapter followed by a detailed hypothetical example and two real examples in Chapter VI.

The reader may find some sections written like a review article and some sections written like a detailed teaching text. Our objectives are such that this style is intentional.

On a slightly philosophical note, we might add that we recognize that this approach does not represent a panacea to drug design and that biological systems are not ready to lie quietly while we dissect and probe with neat mathematical models and laws of physics. We do see tremendous potential in the application of mathematics, physics, and chemistry (including advances in computer technology) to problems of biological interest; further, we can envision a day when the biological activity data become more quantitative and the models become more refined and meaningful, and when one will be able to predict rather accurately the biological activity of a molecule before it is even synthesized.

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CHAPTER I

INTRODUCTION

The planning and architectural concepts underlying the selection of a molecule which would be a promising candidate as a useful therapeutic agent carry the label "drug design." This same activity, however, is being applied to the search for more effective herbicides, pesticides, and the like, and it is in this broad sense that structure-activity relationships are considered here. Even though the last 100 years produced more examples of attempts to correlate changes in molecular structure with changes in drug-like activities, the methodology is perfectly general and the spectrum of disciplines associated with the research continues to widen.

Until about the middle of the twentieth century, most of the correlation studies were empirical and qualitative, but more recent work shows a bold effort to make the correlations quantitative via mathematical models with predictive capabilities. Paralleling the growth of interest in quantitative structure-activity relationship (QSAR) studies, there has been improvement in the techniques for isolating the physicochemical factors associated with a particular biological mechanism. The ultimate goal is obvious: to predict the biological activity of a molecule prior to evaluation or even synthesis in order to reduce the costly and time-consuming synthetic work and biological screening. From another point of view, it is hoped that the application of QSAR studies will elucidate the mechanism of the interaction of a given molecule with a biological system.

Around 1865-1870, Crum-Brown and Fraser published what might be considered the first structure-activity relationship study of molecules of pharmacological interest (1). They showed that the gradual chemical modification in the molecular structure of a series of poisons produced some important differences in their actions. In a study of such compounds as strychnine, brucine, thebain, codeine, morphine, and nicotine, they observed distinct changes in the degree of activity paralleling somewhat minor changes in chemical structures (1,2). With their observations having been further substantiated by studies on atropine and conine, Crum-Brown and Fraser postulated that the physiological action, Φ, of a molecule is some function of its chemical constitution, C (1.1).

$$\Phi = f(C) \qquad (1.1)$$

They concurred that the only reason that such a correlation was not strictly mathematical was their inability to express the terms $\Delta C, \Phi$, and $\Phi+\Delta\Phi$ quantitatively as required for such a treatment. ΔC represents a defined change in chemical constitution and $\Delta\Phi$ symbolizes a corresponding incremental change in biological activity (1,2).

Studying the toxicities of a variety of ethers, alcohols, aldehydes, and ketones, Richet concluded in 1893 that their degree of activity was inversely related to their water solubility (3). This postulate, known as Richet's rule, was the first published experimental evidence of Crum-Brown and Fraser's theory. At the turn of the twentieth century Meyer and Overton applied Richet's work quite extensively to other series of liquid compounds (4-7). Studying the lipid solubility of congeners that possessed narcotic activity, they observed that most organic compounds foreign to the body penetrate tissue cells as though the membranes were lipid in nature. They further noted that passage across these barriers and the resulting narcotic activity paralleled their oil-water partitioning properties. This treatment was theorized to simulate the <u>in vivo</u> situation of a drug's partitioning between an aqueous exobiophase and a lipophilic receptor site. This is the first reported correlation between partition coefficients and biological activity.

Further investigations of the relationship between other physicochemical properties of molecules and their elicited biological responses were made by Traube in 1904 (8). In studies of a variety of narcotic agents he observed a linear relationship between the surface tensions

of the compounds and their narcotic activity. At approximately the same time Führer attempted the quantitative correlation between the narcotic action of a diverse group of molecules with the number of carbon atoms in the compound (9-11). He demonstrated that the decrease in the molecular concentration necessary to produce a defined response over the homologous series followed a geometric progression ($1:3:3^2:3^3$ . . .) corresponding to an increase in the number of carbon atoms (11). Moore used another physicochemical parameter in structure-activity studies in 1917 (12,13). As a result of a series of experiments with a large number of different chemicals, he observed that the toxicity to insects of the vapor of an organic compound is correlated directly with its volatility or boiling point (12-15). Later studies based on Traube's work led Warburg in 1921 to postulate a mechanism of narcotic action for these compounds (16).

A very important second step in QSAR was made by Ferguson in 1939 when he demonstrated an interrelationship among much of the earlier work (17). Using Equations 1.2 and 1.3,

$$C_r = kS_r^{1/n} \tag{1.2}$$

$$C_r = kp_r^{1/n} \tag{1.3}$$

he was able to calculate the toxic concentrations, C, of a series of compounds from solubility and vapor pressure data. In equations 1.2 and 1.3, C_r is the toxic concentration of the rth member of the series, S_r is its solubility in moles per liter, p_r is its vapor pressure, and k and n are constants with n always greater than one. From this study, a generalized equation (1.4) was postulated to describe the biological responses of several congeneric series (17-19):

$$C_i = kA_i^m \tag{1.4}$$

C_i is the concentration of the ith congener necessary to elicit a defined response, A_i is a physicochemical or descriptive parameter for the compound (e.g., partition coefficient, number of carbon atoms in a side chain, solubility, vapor pressure, etc.), and K and m are constants for the series. The negative logarithm of Equation 1.4 becomes Equation 1.5 which is more useful in QSAR studies:

$$-\log C_i = -\log k - m \log A_i \quad (1.5)$$

Incorporating the negative signs into constants k and m (i.e., by redefining k = -log k and m = -n), Equation 1.5 becomes the somewhat more familiar Equation 1.6:

$$\log 1/C_i = k + m \log A_i \quad (1.6)$$

Further correlations between physicochemical parameters and biological activity made by McGowan in 1951 (20-22). In the study of the physical toxicity of a variety of chemicals to different biological systems, he found that Equation 1.7 gave excellent correlations for the diverse systems (20):

$$\log C = (7.7 + S) + (4 \times 10^{23})p - 0.036\ [P] \quad (1.7)$$

In equation 1.7, C is the toxic concentration of vapor of the chemical in parts per million, S is a sensitivity factor based upon varying sensitivity of different biological systems to a series of compounds, p is the polarizability of the gas or vapor, and [P] represents the molecular volume or parachor of the chemical. His study led him to postulate that the biophase concerned is either very similar or identical in all organisms studied. Other studies by McGowan (21-24) extended his correlation studies to a variety of liquids and solutions with apparent success. These studies included the incorporation of partition coefficient, boiling point, and interaction terms into the equations.

Perhaps one of the most important contributions to the development of QSAR models was reported in 1956 by Bruice, Kharasch, and Winzler (25). Their empirical, mathematical model, which marked the beginning of studies which were to proliferate in the 1960s, was applied to the correlation of thyroxine-like activities of a series of congeners with the sum of constants assigned to different substituents on the molecules. Using Equation 1.8, they obtained excellent correlations between calculated and observed biological activities:

$$\log \%\ \text{thyroxine-like activity} = K\Sigma f + c \quad (1.8)$$

In Equation 1.8, $\Sigma f = (f_X + f_{X'} + f_{OR'})$, where f_X, $f_{X'}$, and $f_{OR'}$ are entirely empirical and were selected by a method similar to that of Hammett for the evaluation of sigma constants, and c is a constant. Subscripts X, X' and OR' represent substituent positions of the molecules

of interest (15).

An important contribution which will be treated in detail in Chapters V and VI is the development of a QSAR model by Free and Wilson in 1964 (26). It is an example of what we will categorize as the "de novo" model. They defined the biological response (BR) as equal to the sum of the contributions to the activity of the substituent groups plus the overall average activity (μ) which might be attributed to the activity contribution of the parent structure (Equation 1.9) (26):

$$BR = \Sigma \text{ (substituent group contributions)} + \mu \quad (1.9)$$

The main purpose of this treatment is to rank the biological activities of the substituent groups while noting possible structure-activity relationships and to predict the compounds of the series not tested, and possibly not synthesized, which would have the greatest potential for further investigation. The major limitation of the method lies in the fact that the activity contributions of the substituents must be additive.

At approximately the same time as Free and Wilson's work, Kopecký, Boček, and Vlachová introduced a similar mathematical QSAR model (27, 28). Based upon a multiplicative as well as an additive model, their method employed four basic equations (1.10-1.13):

$$BA = a_x - a_y \quad (1.10)$$

$$BA = b_x b_y \quad (1.11)$$

$$BA = c_x + c_y - d_x d_y \quad (1.12)$$

$$BA = c_x + c_y + d_x d_y \quad (1.13)$$

in which a, b, c, and d represent the substituent contributions to the total activities of the compounds while the subscripts x and y denote the substituent positions on the parent molecule, and BA represents the total biological activity for the molecule. Testing these equations for the expression of the quantitative difference between the log LD_{50} (LD_{50} = concentration necessary to kill 50% of the population) values of para- (27) and meta- (28) disubstituted benzenes and benzene, they found that neither the additive model (1.10), the multiplicative model (1.11), nor the combined difference expression (1.12) described the biological activity adequately. The combined summation expression (1.13), however, gave a statistically

significant correlation between substituent activity and total biological activity for both the meta- (28) and para- (27) disubstituted congeners.

At the same time as the postulation and first application of the mathematical model of QSAR were being made, the development of another type of approach, the linear free energy-related (LFER) model (now often called extrathermodynamic), was introduced (29). With the Hammett equation (30, 31) for the hydrolysis rates of benzoic acid derivatives (Equation 1.14) as a basis, i.e.,

$$\log (k_X/k_H) = \rho\sigma \qquad (1.14)$$

several investigators have attempted quantitative correlations between physicochemical properties of molecules and their biological responses (32, 33). In Equation 1.14, k_X and k_H are the equilibrium constants for the reactions of substituted and unsubstituted compounds, respectively, σ is a constant which is dependent entirely on the nature and position of the substituent, and ρ is a constant dependent on the type and conditions of the reaction as well as the nature of the compounds (31). When Equation 1.14 is solved for $\log k_X$, i.e.,

$$\log k_X = \rho\sigma + \log k_H \qquad (1.15)$$

the Hammett equation clearly illustrates the linear relationship between the substituent constant σ and the logarithm of the reactivity of the compound (k_X) (33, 34). Since the logarithm of an equilibrium constant is proportional to the change in Gibbs free energy (35), i.e.,

$$\Delta G^\circ = -RT \ln k \qquad (1.16)$$

Equation 1.15 and others like it are said to be "free energy-related" (34); therefore, this phrase will be used to include all models of this type. Since Hansch pioneered the approach, it is often called the Hansch model. In Equation 1.16, ΔG° is the change in Gibbs free energy, R is the ideal gas constant, T is the absolute temperature, and k is the equilibrium constant for the reaction. From about 1952 to 1966 several investigators have applied this Hammet LFER equation to many biological systems; however, they met with very limited degrees of success (32, 36-43). With a number of these applications as a basis, in 1962 Hansen proposed a "biological Hammett equation" (44):

$$-\log (H\sigma)_q + \log (Ho)_q = \rho\sigma \qquad (1.17)$$

Using Equation 1.17 in which $(H\sigma)_q$ and $(Ho)_q$ are the concentrations of the inhibitor of the substituted and parent compound, respectively, in a Hammett series necessary to give a defined percentage response q, while ρ and σ are the Hammett constants, Hansen was able to correlate successfully bacterial growth inhibition of several series of compounds with their Hammett sigma (σ) constants. In spite of its very restrictive set of conditions, however, the "biological Hammett equation" has met with only limited success (44).

The application of the Hammett equation was extended by Zahradník and co-workers to correlate other physicochemical parameters of homologous series of compounds with their biological activities (45). The basis of their correlations was Equation 1.18:

$$\log (\tau_i/\tau_{et}) = \alpha\beta \qquad (1.18)$$

where τ_i and τ_{et} are the molar concentrations of the ith congener and ethyl derivative, respectively, of an homologous series necessary to elicit a defined biological response, α is a constant which is dependent upon the nature of the series of compounds and the biological system, and β is a physicochemical parameter which is dependent upon the particular substituent group. Different β values (including Hammett and Taft constants) have been used on several homologous series of compounds in various biological systems (45-48). Again, the use of a single parameter, however, has given correlations of limited significance.

Recognizing the physicochemical nature of biological reactions and realizing, as did Overton and others several years prior to 1965 (49, 50), the importance of partitioning in a drug's transport to its ultimate site of action, Hansch and co-workers expanded the Hammett LFER expression to include additional physicochemical parameters (51-53). Following the approach used by Taft (54) in the linear combination of two physicochemical constants, they derived the ρ-σ-π equation (1.19) for the correlation of biological activity with molecular structure (51):

$$\log (1/C) = k_1\pi + \rho\sigma + k_2 \qquad (1.19)$$

In this equation C represents the molar concentration of a congener in the series necessary to elicit a defined

biological response, π is the substituent partitioning parameter defined as the difference between the logarithms of the octanol/water partition coefficients of the substituted and unsubstituted parent compounds in the series (55), σ is the Hammett substituent constant, and k_1, ρ, and k_2 are constants for the series generated by regression analysis of the data. Although all of these terms are free energy-related and approximate true thermodynamic constants, the expression is said to be "extrathermodynamic" since the parameters are used in systems other than those similar to the systems in which they were determined (51,56).

After meeting with a great deal of success in correlating the structure-activity data from hundreds of systems (57,58), this basic equation has been modified by the addition or substitution of a variety of parameters in attempts to find better correlations. One of the foremost modifications of this basic equation has been Hansch's postulate that the biological response to a drug is parabolically rather than linearly related to its partitioning properties. This resulted in the inclusion of the π^2 term (52,53,59) as shown in Equation 1.20 (in which k is also a constant generated by the regression analysis):

$$\log (1/C) = k\pi^2 + k_1\pi + \rho\sigma + k_2 \qquad (1.20)$$

Although it may seem that the parameters in Equation 1.20 are somewhat arbitrary and highly empirical, it can be shown that these variables can be derived from first principles if one assumes a random walk process by which a drug reaches its site of action (52).

An important advantage of this extrathermodynamic or LFER approach lies in its flexibility to modification by incorporation or deletion of physicochemical parameters to describe more adequately a particular biological phenomenon. For example, it has been used by Hansch and Deutsch to aid in the elucidation of the mechanism of drug action at the submolecular level by determination of the relative importance of each type of parameter in describing the biological response (60). Of course, the quantitative nature of the LFER model is limited by the accuracy of the biological data (as are all QSAR models), as well as by the accuracy of the experimental physicochemical parameters and their applicability to systems somewhat unrelated to those in which they were determined.

In addition to these attempts at QSAR model building, a theoretical, quantum chemical approach has been applied

to the study of chemical compounds of biological interest (61,62,33). Since 1950, the Pullmans have made major contributions in the application of quantum chemistry to biological phenomena (63-66). Their work on the possible mechanism of chemical carcinogenesis in terms of quantum mechanical properties as well as calculations on the nucleic acid constituents has laid much of the foundation for the increasing interest in quantum biology (63-66). At a somewhat more fundamental level, Löwdin has also been a pioneer in the application of quantum mechanics to the problems of biological and biochemical interest (67). He has proposed a mechanism of deoxyribonucleic acid (DNA) replication based on his theoretical calculations.

Other related work appeared in 1965 when Neely published an example of the utility of molecular orbital theory in biological activity correlation studies (68). He illustrated the use of quantum chemical calculations as an aid in the correlation of the submolecular structure of selected organophosphates and carbamates with their cholinesterase inhibitory potencies (68). Kier has been another pioneer in the utilization of these techniques to postulate the nature of several biological receptors. Through quantum mechanical calculations, he has predicted the preferred conformations of isolated molecules of biological interest and has related their lowest energy conformations to the nature of their receptors (69-75).

These methods have been used in the physicochemical approach to drug design. Applying the mathematical model of Free and Wilson (26), Beasley and Purcell have given the first example of a successful prediction of the activity of a compound three years prior to its synthesis (76). In 1965 they reported the calculated butyrylcholinesterase inhibitory potency of 1-decyl-3-(N-ethyl-N-methylcarbamoyl)piperidine hydrobromide (77). Three years later this compound was synthesized and evaluated biochemically. The observed and predicted response values agreed within the limits of experimental error (76). Ban and Fujita also obtained excellent correlations between calculated and observed response values in the study of the norepinephrine uptake inhibition of selected sympathomimetic amines (78).

More efforts, however, have been concerned with the attempts to correlate molecular structure and biological activity using physicochemical parameters in modification of the LFER expressions (79-83). Although the basic transport and electronic parameters are usually retained, the application of several parameters other than π and σ

has been studied. For example, Hansch and co-workers have obtained excellent correlations using log P, where P is the partition coefficient of the entire compound, in place of the summation of the substituent parameters π (84,85). Although partitioning systems other than that of octanol/water have been used for the *in vitro* simulation of the *in vivo* situation, very little improvement, if any, has been shown in the correlations using other systems (86,87). Others have obtained excellent correlations by use of the chromatographic parameter R_M to approximate the transport process (88-93).

Further extensive variation in parameters has been reported in the approximation of the electronic substituent parameters. In addition to the widely used Hammett σ parameter for aromatic systems, many investigators have applied the Taft σ^* parameter to aliphatic systems with varying degrees of success (29,54,56,79,83,94,95). McFarland has suggested the use of group dipole moments, μ, and the electronic polarizability parameter α in addition to σ values in order to explain the electronic factors involved in drug-receptor interactions (96,97). He has obtained excellent correlations between the inhibitory rate constants of *E. coli* and the properties of certain chloramphenicol analogs using these parameters (Equation 1.21) (96):

$$\log (1/C) = k_1\pi^2 + k_2\pi + k_3\sigma + k_4\mu + k_5\alpha + k_6 \quad (1.21)$$

More recently he has given an extensive derivation of the theoretical basis for the inclusion of these parameters; he also treated the parabolic relationship between drug potency and hydrophobicity (97).

In other applications of the method, Clayton and Purcell have illustrated the predictive utility of such expressions in a study of selected butyrylcholinesterase inhibitors (94). They obtained quantitative correlations between the calculated and observed biological activities by using Taft σ^* substituent parameters, amide group dipole moments and total dipole moment values, in addition to substituent partitioning parameters (94). Hansch and co-workers have used Taft steric parameters (E_s) (56) and pK_a values to achieve significant correlations (84). E_s has recently been shown to be quantitatively related to van der Waal's radii for symmetrical toplike substituents (98) while pK_a values have been used as a measure of the electron density distributions (99). Fukuto and co-workers have combined E_s and σ^* parameters in a physicochemical approach to elucidating the mode of action of organophosphorous insecticides (95).

Garrett et al. have used modified Hammett substituent constants (100) to describe the bacteriostatic activities of a series of sulfanilamides (101). The homolytic substituent constants E_R of Yamamoto and Otsu (102) were applied by Hansch to analyze the activity of selected chloramphenicol derivatives (103). The results of his study led to the hypothesis of a free-radical mechanism of chloramphenicol action. Other estimates of the electronic factors involved in drug-receptor interactions have been used by Sasaki and Suzuki (104). They approached the problem by using substituent measures of π-electron charge density distributions (σ_I and σ_π) (105) to illustrate the dependence of partition coefficients and biological activity on molecular electronic conditions (104).

In addition to these, other thermodynamic substituent constants have been investigated (33,79,106). For example, Ostrenga has considered molar attraction constants (107, 108) and Turner and Battershell have correlated chemical reactivities, vapor pressures, and partition coefficients of a series of isophthalonitriles with their fungicidal properties (109).

Jones and co-workers have used regression analysis to study the effects of field constants and resonance parameters (110) of some carbamate derivatives on their penetration and detoxication with some success (111). Similar studies have been made by Fukuto and co-workers using selected oximes and their anti-cholinesterase activities (112). Kakeya et al. have used chemical shifts and valence force constants in addition to other thermodynamic parameters in the structure-activity study of a series of sulfonamide carbonic anhydrase inhibitors (113).

The combination of quantum mechanical calculations and the LFER model presents a wider view in drug activity studies; a variety of indices obtained from the quantum chemical calculations have been utilized in these correlations (79,83,114-116). For example, Neely and co-workers have obtained excellent correlations between the energy of the highest occupied molecular orbital (HOMO), a relative measure of the ability of a molecule to donate an electron to an acceptor molecule, of a series of imidazolines and their analgetic potencies (117).

In an analysis of the linear free energy relationship in drug-receptor interactions, Cammarata has shown a theoretical interpretation of substituent constants in a biological context (118,119). He has separated the free energy change occurring in a reaction into its electronic, desolvation, and steric components; defined each

in terms of contributions made to it; and approximated these contributions with quantum mechanical indices (120, 121). Using atomic orbital coefficients and total electronic charge on certain portions of the molecule, Cammarata has obtained excellent correlations between quantum mechanical indices and sulfanilamide activity (122). He has also suggested the use of π-electrophilic and nucleophilic superdelocalizabilities and energy level differences to interpret drug-receptor interactions. When this approach was applied to selected cholinesterase inhibitors, he obtained very good correlations (123). Wohl has combined several quantum mechanical parameters determined from the Extended Hückel Theory in a LFER study of the biological potencies and electronic structures of several benzothiadiazine derivatives. The quantitative correlation that he obtained led to certain postulations concerning the centers of the molecules which are most responsible for the biological responses due to their electronic properties (115,116).

Hermann et al. have obtained good correlations between the relative substrate efficiencies of some acetophenones toward rabbit kidney reductase and selected quantum mechanical parameters (124). The substituent indices were derived from electron density calculations and energy differences between ground and incipient transition states (124). In the study of the DNA intercalation by chloroquine derivatives, Bass et al. (125) calculated the sigma-electron charge distributions and used these in addition to other substituent parameters to investigate a mechanism proposed by O'Brien and Hahn (126) for antimalarial activity. The derivation of and rationale behind the inclusion of this term into the Hansch equation were also given (125).

It may appear that the various structure-activity models and parameters are not truly as independent as they are presented here. Certainly this suspicion is justified. Singer and Purcell have evaluated the interrelationships among the quantitative structure-activity models and have illustrated their similarities (127). Also, the parameters used in these models cannot be completely independent of one another. In most of the literature, the investigators have merely attempted to find those parameters which alone or in combination best describe the biological activity. Along these lines, Leo et al. have reported a comparison of the parameters currently used in studies of this type (86).

Apart from their use in LFER equations, quantum mechanical calculations have been used in other ways in