Lipophilicity and drug activity

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1 Introduction

The understanding of drug potency in biological systems requires an understanding of chemical structures in terms of physical and chemical properties: transport and distribution of a drug in a biological multicompartment system, the affinity of the drug to a complementary – structurally unknown – receptor, and the interaction of the drug with its receptor obviously depend on these properties.

In drug design the first step is the more or less systematic variation of a lead compound to derive some hypotheses of relationships between chemical structure and biological activity. In the next step these hypotheses are used to arrive at improved derivatives of the original lead compound with minimal effort. The introduction of the Hansch model in 1964 enabled medicinal chemists to formulate their hypotheses of structure-activity relationships in quantitative terms and to check these hypotheses by means of statistical methods. From such quantitative structure-activity relationships (QSAR) it is possible to elucidate the influence of various physicochemical properties on drug potency and to predict activity values for new compounds within certain limits.

The main purpose of this review is to sum up some developments of QSAR since 1971, when the review 'On the understanding of drug potency' [1] appeared in this series. Three excellent books on QSAR have been published in the meantime, the introductory book by Purcell, Bass and Clayton [2] and two comprehensive monographs by Martin [3] and Seydel and Schaper [4]. Monographs on selected topics [5, 6], several symposia proceedings [7–10], review articles [11–28], and a rapidly increasing number of publications reflect the growing importance of QSAR in medicinal chemistry.

During the last decade QSAR started to develop from a merely intuitive and empirical discipline to a more and more theoretically based science. Drug design will remain a sophisticated art all the time; however, from QSAR medicinal chemists gained new insights which allow the application of more rational approaches, especially in lead structure optimization. The largest progress has been made in describing the lipophilicity of drugs and in understanding the dependence of drug activity on lipophilicity. Therefore special emphasis is placed on lipophilicity and drug activity in this review.

2 The additivity concept

The fundamental basis of all quantitative structure-activity analyses is the concept of additivity: all substructures of a drug are assumed to contribute to biological activity in an additive manner, each part of the structure irrespective of all other variations in the molecule. There is no sharp definition of the term substructure, each substituent and each partial structure with unique chemical properties can be regarded as a substructure: sometimes single atoms, e.g. the halogens, sometimes larger groups, e.g. a sulfonamido or pyridyl group, are taken as substructures.

The environment of a substructure has of course a significant influence on its chemical properties and therefore different activity contributions may be observed for identical groups in different positions of a molecule. For drugs interacting with a specific receptor additional differences result from the asymmetric topology of the receptor. Taking this into consideration the different biological activities of optical enantiomers are compatible with the additivity concept.

Is there a rationale of the additivity concept of drug-receptor interactions? There is one: if the affinity of a drug to its receptor depends only on the physicochemical properties of the complementary binding sites and if these physicochemical properties are additive themselves, also the receptor affinity of a drug should be an additive molecular property. It must be emphasized that the structure and the physicochemical properties of the receptor binding site need not be known because this part of the system remains constant. Such 'simple' drug-receptor interactions can be studied e.g. in isolated enzyme systems or in receptor preparations.

As far as hydrophobic interactions are concerned, the additivity concept can be illustrated by the driving forces of hydrophobic interactions (fig. 1) [3, 29, 30]. A nonpolar drug and a hydrophobic region of a receptor are surrounded by water molecules which are more or less ordered and therefore in a higher state of energy than in free solution. In the drug-receptor complex a smaller number of water molecules is in contact with hydrophobic surfaces; the resulting increase in entropy leads to a stabilization of the drug-receptor complex. It is obvious that the gain in free energy should be proportional to the number of water molecules changing from an ordered to an unordered state, i.e. proportional to the surface area of the nonpolar part of the drug. Specific polar, electronic and steric effects may add to these unspecific interactions.

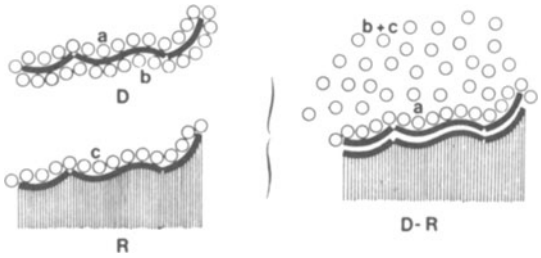

Figure 1
Schematic representation of hydrophobic interaction. R = hydrophobic part of receptor covered by *c* water molecules; D = approaching drug enveloped by *a* + *b* water molecules; D-R = drug-receptor interaction complex with *a* representing ordered water molecules covering D-R and *b* + *c* are the displaced, disordered water molecules (reprinted from [29] with permission of the copyright owner).

In more complex systems like isolated cells, bacteria, isolated organs, or whole animals the biological activity of a drug depends not only on the receptor affinity but also on the absorption and distribution of the drug: the more complex the system is, the more important will the influence of absorption and distribution be.

Lipophilicity is the main factor governing transport and distribution of drugs in biological systems. Although these drug characteristics are – for a given biological system – unequivocally a function of chemical structure and time, the relationships are not as simple as in the case of drug-receptor interactions. Nonlinear lipophilicity-activity relationships have been known since long but they could not be described mathematically until fifteen years ago; today the understanding of the dependence of drug distribution in biological systems on lipophilicity is much better than in the early days of QSAR.

However, there are some other effects which cause departures from the additivity concept. Metabolism of drugs is – because of the specifity of the involved enzymes – no simple function of a definite molecular property, but depends on the presence of certain substructures. As long as these substructures are common to all molecules of a series, one can be confident that a quantitative relationship can be derived for these metabolic conversions too. If the metabolic conversions take place at a position of substituent variation, the additivity concept is seriously disturbed. Examples for such metabolic conversions are e.g. the hydroxylation of aromatic rings, the reduction of nitro groups to amino groups and the cleavage of ethers, esters, amides and amines.

Other nonlinear effects may arise from steric crowding of substituents, leading to lower than predicted activity, and cooperative binding, leading to higher than predicted activity. While the effects from steric crowding are easy to understand, cooperative binding can be explained only in thermodynamic terms. Each interaction between a drug substructure and the complementary receptor site causes an enthalpy and an entropy change. Once a drug molecule is fixed at its binding site by one or more specific interactions, no entropy loss will result from further interactions. Hence, if two or more substructures of a drug molecule fit to a complementary structure, the overall binding force may be higher than the sum of the individual contributions. Although all single drug-receptor interactions are weak bonds, the high affinity and specifity of most drugs can be explained by this cooperative effect.

While we are far from a general mathematical model including all factors responsible for the relationships between chemical structure and biological activity, the linear free energy related Hansch model in its linear [eq. (1)] and parabolic form [eq. (2)] [31–34] and the de novo model of Free and Wilson [eq. (3)] [35] have proven their utility for the quantitative description of such relationships and have confirmed the additivity concept of biological activity group contributions.

$$\log 1/C = a\log P + b\sigma + c, \tag{1}$$

$$\log 1/C = a(\log P)^2 + b\log P + c\sigma + d, \tag{2}$$

$$\log 1/C = \sum_i a_i + \mu. \tag{3}$$

In these equations C is a molar concentration causing a standard biological response, e.g. an ED_{50} or LD_{50}, P is the partition coefficient, σ is the Hammett constant, and a, b, c and d are constants determined by linear multiple regression analysis. Other physicochemical parameters can be used instead of or in addition to P and σ in equations (1) and (2). In equation (3) a_i are the values of the substituent group contributions to biological activity, and μ is regarded to be the activity contribution of the parent system (in Fujita-Ban analysis [36, 37] μ is the theoretical biological activity value of the reference compound). Both the Hansch and Free-Wilson analysis have been reviewed in the literature [1–4, 11–19]; only new developments concerning the methodology will be discussed in this review.

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