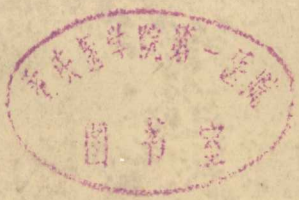
# DRUG DESIGN

*Edited by E. J. Ariëns*

VOLUME X



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# Preface

The positive responses to the previous volumes of *Drug Design* and the rapid development in this field have encouraged and stimulated us to continue this series.

The first two chapters examine procedures as applied in the practice of drug design. Chapter 3, "Bridging the Gap between Bioactive Peptides and Nonpeptides," opens promising perspectives in the highly actual field of bioactive peptides. A new physiological approach to drug design, i.e., "Dynamic Systems Analysis as a Basis for Drug Design," is outlined in Chapter 4, and Chapters 5 and 6 deal effectively with polymers in drug design in "Polymeric Drug Delivery Systems" and "The Design of Biocompatible Polymers," respectively. Chapter 7 presents the structure–activity relationships of insect repellents as a basis for the design of such agents, and Chapters 8 and 9 give approaches to the multivariate data analysis in structure–activity relationships, which is an essential aspect of drug design.

Again, as in previous volumes, the aim of the authors has been to offer the reader insights into promising and current developments in the field. The topics are presented in an informative, concise, systematic, and thought-provoking manner, in which speculations and new perspectives are encouraged. The contents of this volume and those preceding it are indicative of the wide scope, the interdisciplinary character, and the various perspectives of drug design, a discipline in which fundamental and applied science go hand in hand.

E. J. ARIËNS

# Contents

# Chapter 1 Practical Procedures in Drug Design

*V. Austel and E. Kutter*



## I. Introduction

During the last decade a continuous decrease in the number of newly introduced drugs has been observed. There are two main reasons for this


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development: (1) the steadily rising standards that new drugs have to meet and (2) the increasing complexity of synthetic pathways leading to new drugs. Nevertheless, progress in medicinal therapy is still needed especially since some very serious problems (e.g., cancer chemotherapy, treatment of arteriosclerosis and arthritis) have been solved only insufficiently or not at all. However, the experimental capacity for drug design cannot be extended indefinitely. Therefore, the only way out of the dilemma seems to be an optimal economization of the search for new drugs.

Drug design, like every other field of research, is primarily dependent on both the creativity of the scientist and the manner in which his ideas are actualized. Therefore, we have to look for procedures in drug design that allow the scientist to develop his ideas as unrestrictedly as possible but that at the same time allow him to focus them specifically, i.e., at the development of a new drug with specified biological properties. It is the intention of this chapter to outline drug design procedures, with special emphasis on creative and systematic elements and their interaction.

## II. General Aspects of Drug Development

The term "drug development" stands for the whole process that leads to the introduction of a new drug into practical therapy. Most of the medicinal chemist's contribution refers to the first part of this process wherein compounds are developed which, according to their biological properties in experimental animals, can be expected to exert the desired therapeutical effect in man. In the present context such compounds will be called "drugs." The nature of this effect is defined by the medicinal objective which normally specifies not only the main activity but which also refers to other pharmacodynamic and pharmacokinetic properties of the desired drug.

### A. Factors Governing the Output of New Drugs

Statistically, the medicinal chemist at present has to synthesize an average of 6,000 to 10,000 compounds for every newly introduced drug. This figure will probably increase in the future. It is therefore necessary to be aware of the factors that govern the success of the medicinal chemist in producing new drugs. Some of these factors, which we shall call external, can hardly be influenced by the medicinal chemist. The most important of these factors are (1) the requirements of the medicinal objective and (2) the quality of the available biological test systems. The higher the demands of the medicinal objective, the less likely it is for a compound to meet them. In statistical terms this amounts to an average increase in the number of compounds that have to be prepared before a new drug is obtained. Thus, it is relatively easy

to find a $\beta$-sympathomimetic drug. However, not every such drug is a selective $\beta_1$- or $\beta_2$-agonist. Therefore, statistically, a greater number of compounds has to be synthesized until such a selectivity requirement can be fulfilled. As an example, only isoproterenol, an agonist of $\beta_1$- and $\beta_2$-receptors, has initially been available as a bronchodilator, whereas selectively $\beta_2$-mimetic bronchodilators needed a longer development time. On the other hand, a $\beta_1$-mimetic compound, which affects neither heart rate nor blood pressure, would be a rather ideal cardiotonic agent. According to our present knowledge this aim is very hard to attain. In other words we need to synthesize a very large number of compounds in order to find one which eventually fulfills these requirements.

There are three features of the biological test system that influence the rate of success in drug development: (1) the capacity, i.e., the number of compounds that can be tested in a given time, (2) the discriminating power, i.e., how reliably promising compounds can be distinguished from undesirable ones, and (3) the clinical relevance, i.e., the correlation (not necessarily correspondence) between the measured biological effect and the required clinical activity. The first two features affect the feedback that the medicinal chemist needs in order to be able to proceed rationally.

A flow of information that is too slow reduces either the flow or the structural quality of the test compounds. Unreliable data may direct the medicinal chemist into inadequate structural areas, thus increasing the number of compounds that have to be synthesized in the search for a new drug. The same applies to test systems of questionable clinical relevance.

There are, however, also factors pertaining to the medicinal chemist that influence the rate of success in drug development considerably. These "internal" factors consist of: (1) the creativity of the medicinal chemist and (2) the degree to which this creativity can be (a) directed towards the medicinal objective and (b) put into practice economically. Undoubtedly, the chances for innovation in the field of drug therapy increase with both the number and the originality of the medicinal chemist's ideas. However, such ideas can only arise from a well-founded background of information (knowledge). In the present context this background consists of experience or knowledge in synthetic chemistry and molecular biology.

However, it would be uneconomical to put these ideas into practice indiscriminately. Therefore, we need systematic elements in drug design that allow the more promising ideas to be selected for further pursuit. The efficiency of these elements greatly influences the rate of innovation, i.e., the time needed to find a new drug.

Before discussing these aspects, it seems appropriate briefly to recall the activities that have to be undertaken by the medicinal chemist during the development of a new drug.

### B. Steps of Drug Development in the Chemical Laboratory

The contribution of the medicinal chemist to drug development is composed of three steps: (1) design of chemical structures, (2) design of synthetic pathways, and (3) chemical synthesis. The first step concerns the design of structures for those chemical compounds that ought to be synthesized and subjected to pharmacological testing. These compounds form a structure plan. The term "drug design" thus signifies the generation of structure plans in connection with the development of new drugs.

The second step refers to the development of synthetic routes that are likely to produce the compounds specified in the structure plan in sufficient quality and quantity. The result of this step may be called a synthesis plan.

The final step realizes the structure and synthesis plans through the actual synthesis of the test compounds. This step also implies the confirmation of the chemical structure, e.g., by spectroscopy.

The skill with which the last two steps are carried out controls to a great extent the time needed for the development of a new drug. Moreover, synthetic possibilities (ease of synthesis) are a major point of consideration in the first step, the design of structure plans. However, the two steps that refer to chemical synthesis do not have any specific bearing on medicinal chemistry. Therefore, we shall not discuss the design of synthetic pathways and the aspects of practical syntheses here. Instead the reader is referred to the respective literature (examples are given in Refs. *1a–g*).

## III. Procedures in Drug Design

### A. Classical Approach

The great majority of drugs presently in use were developed in classical manner through (1) isolation of natural products, (2) synthetic work pertaining to chemical concepts, or (3) exhaustive variation of known active compounds (mostly governed only by synthetic accessibility). The first procedure is aimed at the isolation and possibly structure elucidation as well as synthesis of the chemically pure active principles of medicinal plants.

As an example morphine, atropine, quinidine, or the cardiac glycosides originated from this procedure. The observation that biologically related organisms can produce the same or related active principles led to an extension of this procedure. Thus, it was noted that certain fungi and bacteria can produce antibacterial compounds. As a consequence, these species are nowadays examined intensively with the aim of finding new antibiotics.

It has become fashionable to isolate natural products from all kinds of (more or less arbitrarily chosen) organisms (e.g., seaweed) with the hope of

finding new active principles. The chances of obtaining new drugs in this manner are apparently not greater than with randomly chosen synthetic chemical compounds (*2,3*).

The second and third ways have been applied very successfully to the development of drugs. Thus, the barbiturates, the benzodiazepines, phenacetin, aspirin, the antibacterial sulfonamides, and antidiabetic sulfonylureas, for example, were found and developed by these procedures. Despite this success, it cannot be overlooked that the chances of finding new active principles among structures designed exclusively by chemical concepts remain very slight. It is also debatable whether indiscriminate variation of active structures is a very economical route to new drugs.

## B. QUANTITATIVE DRUG DESIGN

It has always been the aim of medicinal chemists to predict the biological activity of not yet synthesized or tested chemical compounds. Such predictions can be of a qualitative (e.g., whether a compound with certain structural features will be active or not) or a quantitative (that a particular compound shows, e.g., an $EC_{50}$ of $2.5 \times 10^{-6}$ M) nature and are dependent on the availability of respective structure–activity relationships. Quantitative drug design tries to find out by application of QSAR (quantitative structure–activity relationships) those chemical structures that show an optimal effect in a particular pharmacological test system.

The concept of quantitative drug design is based on the fact that the biological properties of a compound are a function of its physicochemical properties. There are two ways of accounting for these properties: (1) implicitly, by expressing structural changes in terms of particular substituents or substructures (Free–Wilson approach) or (2) explicitly, by measured or calculated physicochemical properties of these substituents or substructures (Hansch approach). Contrary to the classical procedure, quantitative drug design refers directly to the medicinal objective. This results in a high probability that the compounds conceived in this way will exert the desired pharmacological effect. However, quantitative drug design has so far not been as successful as originally expected. What are the reasons for this disappointing performance?

The shortcomings of quantitative drug design stem from two serious drawbacks of currently used QSAR.

1. The assumption of independent contributions to the activity from substructures must be considered an exception rather than a rule. The same applies to the thermodynamic basis of the Hansch approach, namely the validity of the linear free energy model in drug action. This is

especially true for the description of drug–receptor interactions, which cannot be expected to fulfill the entropy requirements of linear free energy relationships.

2. QSAR is so far of an empirical nature, which implies that it has been obtained retrospectively, i.e., from the known pharmacological activity of a number of active compounds belonging to the same structural type. Therefore, new types of active compounds cannot be discovered through QSAR. Moreover, QSAR like other empirical relationships is only valid within the experimental range from which it is derived; extrapolations frequently lead to false predictions. Thus, the application of QSAR is restricted to a relatively small area of closely related active structures, the optimal one of which may, however, be predicted rather accurately. Unfortunately, in practice, the optimal compound is often already a member of the initial set of test compounds from which the respective QSAR is derived, i.e., this compound was strictly speaking not conceived by quantitative drug design.

Nevertheless, there is one problem in drug design that may advantageously be tackled by QSAR, namely the question of whether a certain structural field deserves further investigation. In addition, QSAR can reveal structural features and physicochemical properties that are important for the activity of compounds, an information that can help discover insufficiently examined structural variations of a lead compound.

### C. Criteria for Adequacy of Procedures in Drug Design

The fundamental criterion for the quality of a procedure in drug design is whether or not it can be expected to minimize the time or experimental work needed to find a compound whose pharmacological properties meet the requirements of the medicinal objective: since drug design is greatly influenced by progress in chemical and biological science and technology, the value of a certain procedure will change with time. For instance, quantitative drug design may become much more important when QSAR can be derived prospectively.

What requirements must be met by a procedure in order to fulfill the minimization criterion? Considering the factors that play a major role in drug development (see Section II,A), it is possible to derive such requirements.

1. There ought to be, whenever possible, a rational reference of the structures to be designed to the medicinal objective.
2. The nature of the pharmacological test system (especially its capacity) ought to be taken into consideration.

3. There has to be sufficient room for the creativity of the medicinal chemist.
4. The synthetic accessibility of the structures to be designed should be considered.
5. The synthesizing capacity of the chemical laboratory must be accounted for.

To what extent are these conditions met by the various approaches to drug design outlined in Sections III,A and III,B? Procedures based exclusively on chemical concepts cannot, of course, meet the first condition. Since chemical concepts are *a priori* unrelated to the structural properties pertaining to a certain biological activity, the capacity of the pharmacological test system can only be accounted for by arbitrary reduction of the number of test compounds. Therefore, the second criterion is not properly fulfilled either. However, factors referring to the last three conditions can very well be taken into consideration.

Drug design based on structure–activity relationships fulfills only the first criterion ideally; the second one may also be met sufficiently (4). Since this approach is very strongly oriented toward the medicinal objective, only little room is left for the creativity of the medicinal chemist. In addition, the last two criteria cannot satisfactorily be accounted for either.

These considerations show that the chemical concept and the structure–activity relationship approaches are complementary, with a continuous spectrum of combinations lying between these extremes. Unfortunately, none of these combinations can meet all five conditions simultaneously. Thus, criteria (1) and (2) will frequently conflict with criteria (4) and (5) since the most desirable test compounds from the medicinal or pharmacological point of view are seldom those that are optimally accessible. Moreover, (3) is always to some extent restricted by the other four conditions.

Nevertheless, there is always a combination that accounts for all five conditions in an overall optimal manner. The degree to which the optimal combination resembles one or the other extreme will thereby vary with the type of problem that the medicinal chemist has to work on. Thus, in the optimization of a lead the optimal procedure will generally be based to a greater extent on structure–activity relationships than in the search for a new lead, in which the chemical concept even nowadays tends to play the predominant role.

## IV. Application of the Theory of Sets to Drug Design

From the last paragraph, it becomes obvious that the description of drug design procedures is a rather complex subject. We have found that the theory

of sets offers a very concise representation of drug design and therefore is very suitable for the discussion of drug design problems.

## A. SETS OF CHEMICAL COMPOUNDS

A group of chemical compounds, all of which have one or several characteristic properties in common, form a set. Such properties may, for example, refer to the presence of a methoxy group, or of a pyridine ring, or the absence of cyclic substructures, i.e., the criterion for membership in the respective set is in these examples provided by a structural feature. Similarly, a physicochemical property, such as acidity or lipophilicity, or some biological activity, such as antibacterial activity, could be chosen as the characteristic property. The members of a set are usually called elements of that set. We shall visualize sets by circles (see Fig. 1 in which two of the sets of chemical compounds mentioned above are shown).

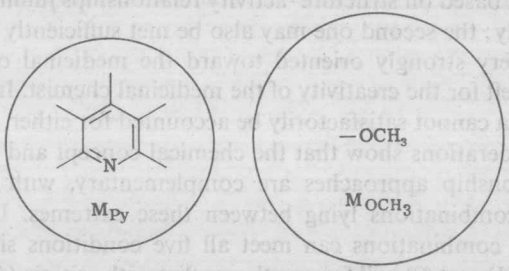


**Fig. 1.** Representation of two sets of chemical compounds: $M_{Py}$, set of chemical compounds that contain a pyridine ring; $M_{OCH_3}$, set of chemical compounds that contain a methoxy group.

The number of elements may vary from set to set. Our visualization can account for this by corresponding variations in the radii of the circles. Theoretically, sets of compounds like those shown in Fig. 1 are infinitely large. In practice, however, their size will always be limited. Therefore, in all our consideration we shall tacitly assume that, unless specified otherwise, all sets of compounds are finite. Generally, the set of compounds characterized by the presence of a pyridine ring ($M_{Py}$) will also include elements which, in addition, contain methoxy groups. These compounds form a subset ($T_{OCH_3/Py}$) of $M_{Py}$, which may consequently be visualized as a small circle completely surrounded by the circle representing $M_{Py}$ (Fig. 2). The elements of the subset $T_{OCH_3/Py}$ also form, of course, a subset ($T_{Py/OCH_3}$) of $M_{OCH_3}$ (Fig. 2).

In other words, $M_{Py}$ and $M_{OCH_3}$ have the subset $T_{OCH_3/Py} \equiv T_{Py/OCH_3}$ in common. Such a subset is called an intersection of two sets. We can visualize

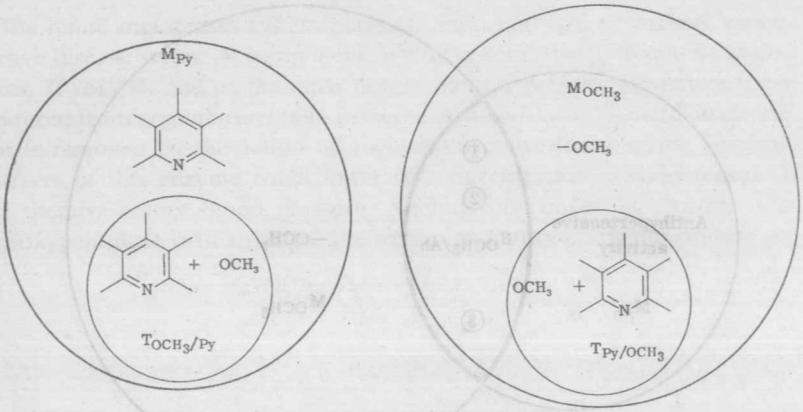


**Fig. 2.** Representation of subsets of chemical compounds: $M_{Py}$ and $M_{OCH_3}$, see Fig. 1; $T_{OCH_3/Py}$, subset of compounds of $M_{Py}$ that contain an $OCH_3$ group; $T_{Py/OCH_3}$, subset of compounds of $M_{OCH_3}$ which contain a pyridine ring. Note: $T_{OCH_3/Py} \equiv T_{Py/OCH_3}$.

an intersection (here $S_{Py/OCH_3}$) by the area of overlap between two circles (Fig. 3).

Intersections can also occur between a set of compounds that is characterized by structural features and one that is determined by physicochemical or biological properties. As an example, there is an intersection ($S_{OCH_3/Ah}$)

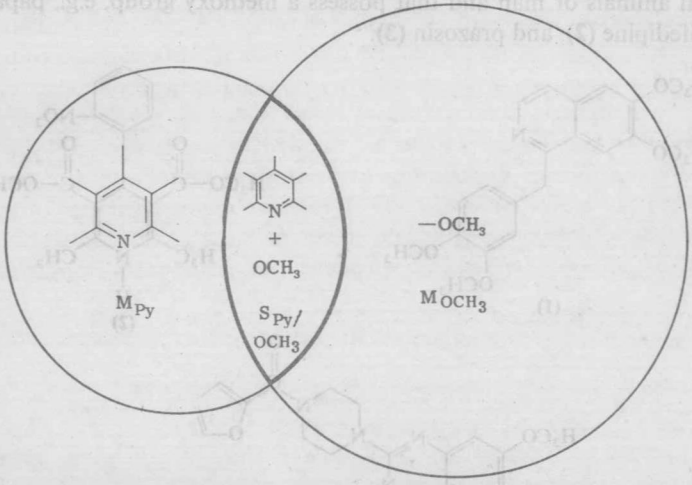


**Fig. 3.** Representation of an intersection of two sets of compounds: $M_{Py}$ and $M_{OCH_3}$, see Fig. 1; $S_{Py/OCH_3}$, intersection of the two sets $M_{Py}$ and $M_{OCH_3}$, i.e., the set of compounds which contain a pyridine ring as well as an $OCH_3$ group. Note: $S_{Py/OCH_3} \equiv T_{OCH_3/Py} \equiv T_{Py/OCH_3}$.