Encyclopedia of Pharmaceutical Technology

Volume 4

Editors
James Swarbrick
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ENCYCLOPEDIA OF PHARMACEUTICAL TECHNOLOGY

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VOLUME 4

DESIGN OF DRUGS TO DRYING AND DRIERS

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Design of Drugs: Basic Concepts and Applications

Introduction

This chapter provides the reader with some contemporary aspects of drug design, as well as with an insight into the history of the discipline, a presentation of the basic elements of construction of pharmacomolecules using the language of the disconnection [1] along with some examples of realizations, and an outlook at some near-future advances.

As such, the idea of designing a drug structure on a rational basis is nothing new. Beyond the fact that this rational approach has always created an extraordinarily high level of scientific attraction and even intellectual fascination is the economical interest of producing new therapeutic agents more rapidly at lower costs. Up to now, however, most of the discoveries of pharmacomolecules have been made by accident or mass screening.

Although we do indeed have some methodologies to improve the therapeutic characteristics of a pharmacomolecule, the crucial problem remains of discovering original chemicals with interesting biological properties (i.e., chemical leads). The intellectual sources of ideas for new drugs have virtually no limits. Ideas may result, for example, from adverse reactions produced by existing drugs: adverse reactions for one use of a known drug may serve as a new indication for the same drug or may stimulate the search for chemically related compounds that have more potent actions of the desired new type. For instance, the observation that morphine produces constipation resulted in the development of antidiarrheals.

Lead structures may have number of origins. Plants have been a source of drugs for millennia, and some important therapeutic agents still come from plants (e.g., digitalis glycosides, opium alkaloids, belladonna alkaloids); nonetheless, fewer and fewer drugs are derived from plants. Drugs have been obtained also from human and animal origins (e.g., adrenaline, insulin, vitamin B_{12}, thyroid and growth hormones). Biotechnology will certainly increase the importance of these natural sources, and nature has always been a source of inspiration. However, several other major processes are used to discover a new lead structure:

1. Random screening of a large number of chemicals
2. Random or directed modifications of old chemical leads or of known drugs
3. New chemical reactions allowing the production of novel and original (therefore patentable) compounds
4. New biological hypotheses
5. Use of new animal models [2]

Now that dramatic advances have been made in the biological sciences, efforts can be intensified to elucidate the mechanisms of a pathology and to discover the molecular bases of a disease. Once the defect at the level of a receptor, an enzyme, or a gene has been detected, *rational* drug design can then be undertaken. This requires an exact knowledge of the three-dimensional structure of the active site of an enzyme, a binding locus, or a particular DNA sequence. Construction of a molecule that blocks or activates the targets in question should in principle lead unequivocally to the desired pharmacologic effect.

This scenario, at present, is somewhat too idyllic, as many weak points exist in this strategy. In particular, determination of the molecular aspects of a pathology is often very difficult because of the complexity of the biological mechanisms. Three-dimensional structure determination of the biological targets is up to now carried out almost exclusively by x-ray diffraction, which requires suitable crystals that are not always available. Other techniques are foreseeable, namely, 2D-NMR or molecular design, but they have not yet reached a sufficient degree of maturity for us to rely on them solely.

Here we will focus our attention mainly on rather low-molecular-weight therapeutic agents and not consider biotechnology drugs. Most examples will be chosen from morphinic compounds.

Historical Background and Emergence of QSAR

Medicinal chemistry is the branch of chemistry that deals with the discovery, design, and development of therapeutic chemical agents [3]. Drug design appears therefore as one of the essential charismata of the medicinal chemist. As a scientific discipline, drug design has not reached the level of complete adulthood, but dependable predictions can be drawn on the structure manipulations one should make to tailor a lead compound to the various requirements of a clinically useful drug. One century ago, little was known about the basic reasoning underlying successful molecular modifications of natural compounds to more effective drugs. The history of drug design is not a linear one, and the date of its origin is not so obvious.

About a century ago, Nencki synthesized phenyl salicylate (Salol) in an effort to remove some of the undesirable properties of salicylic acid [4]; a decade later, acetylsalicylic acid (aspirin) was prepared by Hoffman and introduced by Dreser as an analgesic and anti-inflammatory agent [5]. This classic example is illustrative of a very common scenario. The original lead, a natural compound (salicin), was soon modified to Salol and aspirin by straightforward empirical manipulations, the process culminating later on by the selection of diflunisal out of 500 candidates [6] (Fig. 1).

In this connection, the discovery of morphine and the subsequent development of opioid compounds follow in many respects the same intellectual process. Morphine was isolated from *papaver somniferum* by the German pharmacist Sertürner in 1805 [7]; codeine (the corresponding 3-methyl ether derivative) was isolated from the same source in 1832 [8]. In 1898, Dreser, who previously had introduced aspirin, repeated the same acetylation process, which resulted in the discovery of heroin,

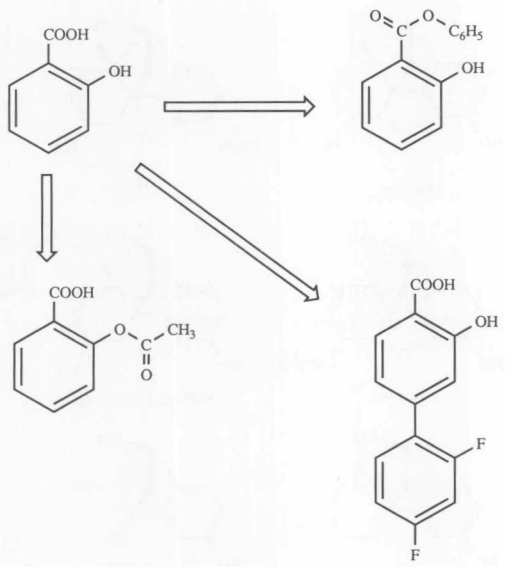


FIG. 1. Design of analgesic anti-inflammatory salicylic acid derived drugs.

considered at that time just as "a little more active" than morphine [9,10] but soon recognized as a potent addictive compound. Throughout the world, many projects were launched to dissociate the analgesic property and the liability of dependence.

Two approaches were used: either simple modifications were performed on morphine itself (oxidation, reduction, substitution, omission of a function) or successive deletion of various sections of the morphine skeleton, resulting in simplified structures such as morphinanes and benzomorphanes. These efforts, as well as the fortuitous discovery of the analgesic properties of meperidine and methadone (originally designed as potential acetylcholine blocking agents), failed to provide a nonaddictive opioid compound; they created, however, a thesaurus of abundant but disparate structure-activity relationship data [11] (Fig. 2).

General considerations on drug design should include various sections concerned with the methodologies involved in the molecular modifications carried out on a lead structure (e.g., chain homologation and branching, bioisosterism, considerations of drug metabolism, design of transition-state, analogs, suicide enzyme and active site-directed irreversible inhibitors, design of antagonists). A detailed description of these conventional methodologies is beyond our scope here. Moreover, these points have been treated in an excellent text by Alfred Burger [12]. A more appropriate introduction to the drug design topic is a short presentation of quantitative structure-activity relationships, which will allow us then to look at the concept of disconnection in drug design.

The early 1960s marked the emergence of *quantitative* studies of *structure-activity relationships* (QSAR), with Hansch and Fujita presenting the model of linear multiple regression [13] and Free and Wilson discussing the additive model [14]. Although these methods were not totally new and were based in part on what was known after the classic works of structure-reactivity relationships in physical organic

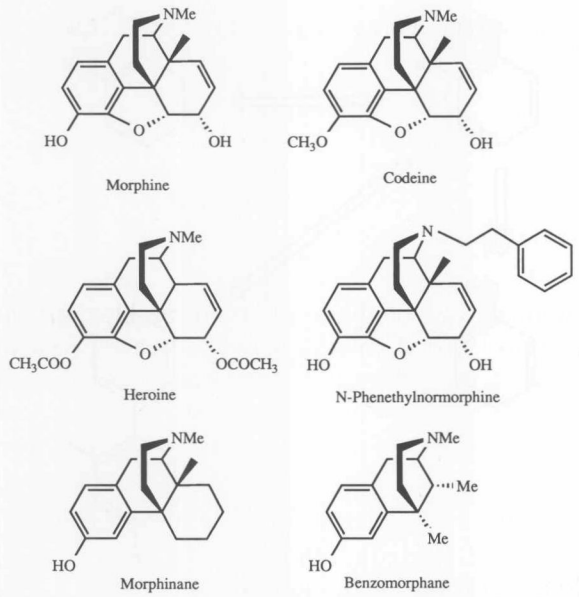


FIG. 2. Representative morphinic compounds for which morphine can be considered as lead structure.

chemistry (Hammet, Taft, etc.), they provided a practical tool to diminish the tremendous work required by the systematic and somewhat empirical molecular modification approach. The ideas, however, entered the routine practice in drug design only very slowly. A certain skepticism was even apparent in the 1970s: "Where are the drugs designed by QSAR?"

At the time, that a compound could not be elaborated simply on the basis of QSAR and that additional know-how had to be acquired were not obvious. Ganellin has described how, at various stages of the process (launched in 1964) that would ultimately result in the discovery of cimetidine, QSAR were helpful in making possible the right decision at the right stage to define the optimal structure [15]. Another significant improvement in the everyday use of QSAR was the introduction of the hydrophobic fragmental constants by Nys and Rekker [16,17] as an alternative to the Hansh π value, allowing prediction of the partition coefficient (P) of a compound, generally expressed as log P. Nys and Rekker's provision of log P is generally quite accurate and is considerably more time efficient than tedious experimental determination.

In the linear free energy or so-called extrathermodynamic method of Hansch, activity in a series of structurally related compounds is expressed in the form of Eq. (1).

$$\log(1/c) = k(\log P) + k'(\sigma) + k''(Es) + K \qquad (1)$$

where c represents a concentration parameter (ED_{50}, IC_{50}, LD_{50}, etc.) necessary to reach a certain level of biological activity; P is the partition coefficient of the active structure (generally between n-octanol and water); σ is the substituent parameter involving mainly electronic effects, according to Hammet; Es is another substituent parameter involving the steric effect according to Taft; and K is an additional residual constant [18].

The advantages of the introduction of quantitative aspects in what was, and still is, an art are in:

1. Deciding which additional derivatives should be synthesized
2. Finding exceptions and thereby potential new leads
3. Understanding complex processes involved in the analysis of multivariate data obtained from various test systems

As already mentioned, one of the most severe problems is the complexity of biological systems. The drug is, in this gigantic play, an actor involved in reestablishing perturbed equilibria in sequences of reactions intervening during transport, metabolism, and interactions between solute, carrier substrate, enzyme, hormone, and receptor. Drug action, therefore, strongly depends on two factors:

1. Recognition and affinity for an appropriate biologic target
2. Capability of reaching the critical biophase (where the target is located) after eventually a long and complex trajectory

The essential difference between a drug and an endogenous biological messenger (e.g., a hormone or a neurotransmitter) is that the latter is often secreted in the close vicinity or at least in the same biophase, whereas optimally a drug should be taken *per os*, which implicates the passage through several barriers before reaching the target organ or system.

If one contemplates Eq. (1) with these considerations in mind, the equation can be regarded as the summation of two types of contributions:

1. σ and Es (as well as various other terms commonly employed) refer to a description of the molecular electronic (σ) and steric (Es, local shape) constitution, factors that affect the recognition and the fit of the biological target
2. The term "log P" conditions the passage through membranes and the repartition between the different compartments

Although this dichotomic analysis may not be totally rigorous, it bears a sound truth that is too often forgotten when designing drugs, even with today's advanced computerized techniques: the pharmacomolecule designed in the very best way possible can act effectively only if it adequately reaches the target. *Affinity* and *transport* are the key words in drug design.

Although transport, convincingly enough, appears crucial for totally integrated in vivo systems, it may appear less important for isolated in vitro systems (tissue membranes, organelles). Recent evidence, however, does contradict this point. For example, in the case of opioid peptides, in addition to the prerequisite of ligand-receptor complementarity, specific concentrations of these peptides in various membrane compartments mediate their ability to interact selectively with a distinct receptor type. A model has indeed been proposed suggesting that the three major opioid receptor types (μ, δ, κ) are located in different subsections of the lipid bilayer membrane. The δ-receptor site should be exposed to an aqueous compartment in a

cationic environment. The μ-site would be situated in an anionic surrounding. The κ-site is assumed to be buried in a hydrophobic region of the membrane in the close vicinity of the anionic compartment. Thus, opioid peptides carrying a net positive charge, which can be solvated by water, would therefore accumulate in the μ-compartment; negatively charged analogs would preferentially concentrate in the δ-receptor surrounding; and opioid peptides with an amphiphilic character would exhibit κ-receptor selectivity. The membrane compartment concept [19] has been utilized by Schiller and associates to design dermorphin analogs carrying a net positive charge, which display considerable μ-opioid receptor preference. The tetrapeptide H-Tyr-D-Arg-Phe-Lys-NH_2, which is protonated at the physiological pH on the guanine moiety of the arginine residue, displays an enormous μ selectivity in in vitro binding studies [20]. Because of its high positive charge, at the in vivo level this tetrapeptide most likely will neither cross the blood-brain barrier to an appreciable extent nor produce any significant central analgesia.

The structure of any pharmacomolecule can a priori be schematized as the sum of a pharmacophore pole, responsible for recognition and affinity for the target, and a vector pole, responsible for the pharmacokinetic (and metabolic) behavior of the drug. If the chemical formulation of one of these poles is not correct, the compound will certainly not be active in vivo. The analysis of the structure of a pharmacomolecule in terms of pharmacophore and vectors constitutes the fundamental basis of the disconnection approach in drug design.

Disconnection in Drug Design: Nature and Constitution of the Pharmacophore

First, some basic terminology is necessary. A therapeutic agent or pharmacomolecule can be regarded as a molecular entity made up of two inner parts: the *pharmacophore* (**P**) and the *vector* (**V**). Such a concept may appear utopian because, in most drugs currently in use, **P** can barely be distinguished from **V**. This is so because such drugs were developed in a pragmatic way by simultaneously optimizing both their pharmacologic and pharmacokinetic characteristics. In this situation, the structural elements of **P** and **V** are generally intimately interconnected, if not superimposed, to form a *unitary* drug. Inversely, when **P** and **V** are eventually clearly separated by a connecting unit, sometimes called a *spacer* or *spanner* [21] and termed here *connector*, the resulting molecular edifice is then labeled *dichotomic*.

To understand the constitution of the pharmacophore, the "message-address" concept (initially employed by Schwyzer [22] and subsequently by Chavkin and Goldstein [23]) must be introduced to rationalize the selectivity of peptide hormones. In this concept, the "message" mediates the general type of activity and the "address" confers specificity. For example, Leu- and Met-enkephalins have differential behavior at *d* receptors, which can be explained by the fact that the common "message" segment (Tyr-Gly-Gly-Phe) confers opioid activity and the Leu- and Met-residues induce selectivity.

The pharmacophore (**P**) can be disconnected in pharmacons (Φ) and tensors (T) [24,25] (Fig. 3); they can be analyzed in terms of the message-address concept.

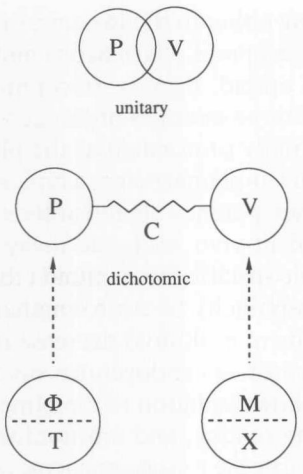
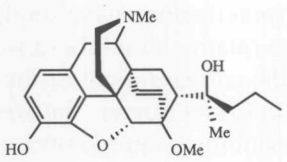


FIG. 3. Analysis of the structures of the pharmacomolecules by the disconnection method. *P* = pharmacophore; *V* = vector; *C* = connector; Φ = pharmacon; T = tensor; M = modifier, and X = carrier.

The *pharmacons* are groups of atoms representative of a qualitative structure-activity relationship within a therapeutic class; these groups are supposed to be in intimate contact with the functional subsites of the receptor site. They are necessary parts of the message; and their alteration or partial or total suppression leads to diminution, reversal (antagonism), or abolition of the pharmacologic activity. The *tensors* play an essentially topological role; they arrange the pharmacons in such a way as to obtain a correct fit with the receptor subsites, or they modulate the reactivity of a chemical function (enzyme inhibition). Tensors are quite variable in



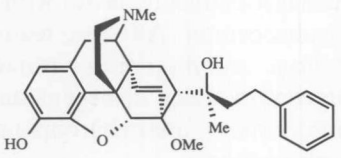


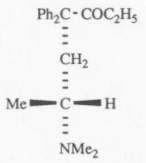
FIG. 4. Structures of etorphine and the corresponding phenyl analog, which contains the three essential opioid pharmacons and is 6 times more active than etorphine.

structure, and they may belong either to the message or to the address. To illustrate this point, some aspects of the opioid pharmacons and tensors follow (Fig. 4).

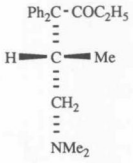
The structure of classic opioid ligands (morphine, etorphine, methadone, fentanyl) permits isolation of three essential pharmacons; phenol, phenyl moieties, and an amino group substantially protonated at the physiologic pH. Considerable evidence supports this view. In (–)-phenazocine, a typical 6,7-benzomorphan opiate, the phenethyl moiety increases potency significantly relative to the *N*-methyl derivative on both in vitro and in vivo analgesic assays. This increase in potency appears to be due to a favorable specific interaction at the receptor site rather than to a simple augmentation of lipophilicity because lengthening of this side chain from two to three methylenes results in a 100-fold decrease in in vivo activity. The same disconnection process performed on endogenous opioid ligands (Leu- and Met-enkephalins, β-endorphine) allows isolation of the same pharmacons (phenol of the Tyr residue, phenyl of the Phe residue, and ammonium of the Tyr residue). Note, however, that efforts to superimpose (–)-phenazocine with the enkephalins lead to energetically unfavorable conformers of the former with the *N*-phenethyl side chain positioned in the unfavorable axial position with respect to the piperidine ring. This is most likely a reflection of the fact the μ and δ opioid ligands possess different stereochemical requirements, which are fulfilled by a network of different tensors [26].

This last question can be further explored through a study of methadone congeners performed by Portoghese and associates [27] on (6*R*)-methadone, (5*S*)-isomethadone, (5*S*,6*S*)-*erythro*-5-methyl-methadone and (55*S*,6*R*)-*threo*-5-methyl-methadone) (Fig. 5). All these methadonoid compounds have the same atomic connectivity or normethadone and differ only by the implementation of a methyl group on the 5- and 6-positions, which strongly affects their binding characteristics. What is the effective role of these methyl groups? Do they really occupy a distinct hydrophobic pocket [different from the T (Tyr) and P (Phe) loci] [28]? If so, they should be considered as pharmacons. Or do they play the role of tensors by arranging in a correct orientation the phenyl and ammonium pharmacons vis-à-vis the corresponding subsites of either the μ- and δ-receptors? The more active enantiomers of methadone and isomethadone have similar potency both in vitro and in vivo, yet they have opposite relative (and also absolute) configuration at their chiral center. Conjunction of the configurations at the 5- and 6-positions yields an inactive compound, the *threo*-diastereoisomer. Surprisingly, the *erythro*-species is the most active of the series, exhibiting a predominant μ-character compared with methadone and isomethadone, which have a mixed μ/δ behavior in the guinea pig ileon (GPI) and mouse vas deferens (MVD) preparations. Analyzed in terms of stereostructure-activity relationships, methadone and isomethadone share quite similar relative orientation of the phenyl and ammonium pharmacons, whereas *erythro*-5-methyl-methadone has a distinct behavior with the NMe_2 and $Ph_2COC_2H_5$ moieties in an antiperiplanar disposition. All these features can be rationalized on the basis of the identity of the μ- and δ-opioid pharmacons and of the difference of topology of the μ and δ receptors. Such divergent stereochemical requirements can be produced only by tensors (here, methyl groups) pointing at directions complementary to those of the pharmacons.

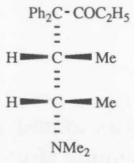
To substantiate further the essential role of the tensors in the architecture of the opioid ligands, we will develop some examples of the design of highly selective δ and



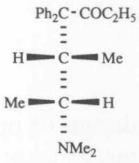
(6*R*)-Methadone



(5*S*)-Isomethadone



(5*S*,6*S*)-Erythro-
5-methylmethadone

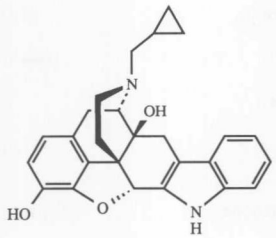


(5*S*,6*R*)-Threo-
5-methylmethadone

FIG. 5. Structures of some methadone congeners.

κ antagonists. Now that the existence of receptor subpopulations among different receptors is well recognized, advances in many areas of medicinal chemistry depend greatly on the availability of selective ligands that can be employed as receptor probes. Because cross-recognition of multiple receptor populations by a poorly selective ligand may lead to ambiguities in the analysis of structure-activity relationship studies, highly selective tools must be available for this purpose. This point is particularly relevant to opioid receptors, as this class has at least three major receptor types (μ, δ, κ). At this level, an important distinction should be made between a receptor probe or tool and a real drug. A receptor probe is intended to be active in vitro; it generally lacks a vector moiety and is therefore not optimized from the point of view of its pharmacokinetic metabolic susceptibility. A drug is designed, of course, to be active in vivo, which requires, as mentioned previously, efficiency in transport and affinity.

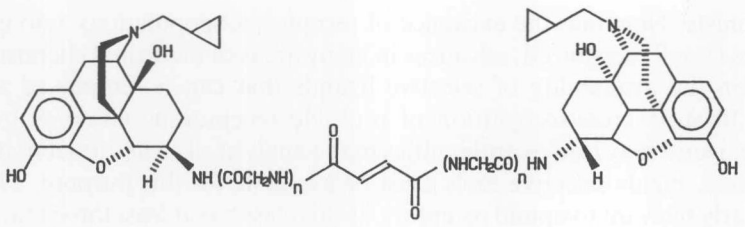
Taking into account the particular orientation of the *P* hydrophobic packet of the δ-receptor, Portoghese attached to naltrexone an additional phenyl pharmacon that could mimic the phenyl group of Phe[4] of the enkephalins; this phenyl group was rigidified in the correct orientation by insertion of a nitrogen or oxygen tensor, realizing in this way a fusion of an indole or benzofuran to the $C_{6\text{-}7}$ position of the C ring of the morphinan skeleton. In the GPI and NVD models, Naltrexindole (NTI) (Fig. 6) was found to be more than 300 times more δ-selective than allyl$_2$Tyr-Aib-Aib-Phe-Leu[5] (ICI 174864), a typical peptidic δ antagonist [29].



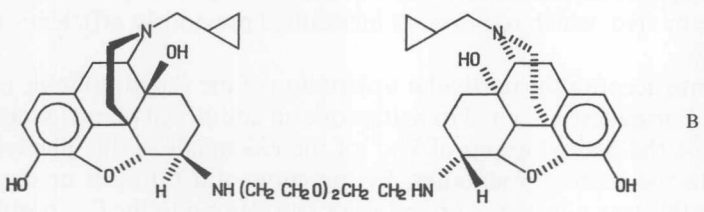
NTI

FIG. 6. Structure of naltrexindole (NTI).

Another example of design of opioid antagonists aimed at selectively targeting κ receptors is found in the concept of bivalent ligands (Fig. 7). The term *bivalent ligand* has been given to two pharmacophore groups linked through a connector. The rational basis behind this concept was that enhanced potency and selectivity could be conferred by the simultaneous occupation of proximal recognition sites of a multimeric receptor complex by both pharmacophore centers of a single bivalent ligand. In this context, the effectiveness with which two pharmacophores bridge proximal recognition sites depends on the length and conformational flex-



A



B

FIG. 7. Typical structures of opioid bivalent ligands. When $n = 2$, maximal μ antagonism is reached (A); with the more flexible polyethyleneoxy connector (B), a specific κ-antagonist is obtained.