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*Review*

# Drug Discovery—Today and Tomorrow: The Role of Medicinal Chemistry

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Novel drugs presently introduced in the market are largely not discovered by rational design or by random screening but, rather, are products of evolution of existing leads (analogue research). It is suggested that this will change in the near future. Progress in a number of scientific disciplines will make it likely that drug design, but also systematic screening, will contribute more and more to novel drug discovery.

KEY WORDS: drug design; drug screening; medicinal chemistry; new chemical entities.

## INTRODUCTION

The medicinal chemistry contribution to the drug discovery process consists of two major parts: lead detection and optimization. Lead detection can be defined as the observation of a useful biological property in a novel chemical. Optimization is the procedure that includes the acquisition of structure–activity relationship information on this chemical, the extension of this information to a group of related compounds, and the subsequent arrival at a drug candidate with optimal properties: the desired biological effect versus toxicity, stability, ease of preparation, etc. The latter part, while not exactly routine, creates no major problems; the full spectrum of possibilities from purely empirical via semiquantitative to mathematical structure–activity relationship methods is successfully being used (1). Optimization, in a broader sense, is still leading to better drugs using the previous generation as leads (analogue design research). As we will see, the majority of new chemical entities (NCE) presently introduced does not originate from de novo lead detection as defined below; these drugs are, rather, the product of evolution, incorporating the experience and knowledge gathered with older, related chemicals.

It is lead detection that really has been and still is the challenge for the medicinal chemist. Conceptually and practically, two possibilities exist and are being used to arrive at new and novel leads: screening and design.

Screening, of course, is the process of subjecting a more or less random selection of chemicals to one test or to a "battery" of tests in the hope of finding useful biological properties. The chances for success depend on the number and structural variety of the compounds and the reliability and relevance of the screening tests.

Drug design attempts to tailor the structure of one or a few chemicals in such a way that the drug interacts with known and well-understood biological systems in the desired manner, e.g., as ligand to a receptor. The influence of both methods, screening and design, on drug discovery in the future is discussed. To appreciate the anticipated change, the origin of the presently introduced drugs should be analyzed first.

### The 1985 New Chemical Entities (NCEs)

Figure 1 shows the 25 NCEs which were approved for marketing by the FDA in 1985. [The actual number approved was 30, but some diagnostics and radioopaque materials have been omitted, as they do not contribute to this discussion (2).]

A glance at the structures shows the medicinal chemist that most, if not all, are the result of evolution: the systematic process of changing established structures with established biological properties with the intention of improving the biological properties profile. Some cases are more obvious than others. The central nervous system (CNS) depressant effects of aryl-benzodiazepines, for example, are well known and are the starting point for a host of drugs; the hypnotic and anesthetic properties of Quazepam and Midazolan consequently appear as logical results of this process of evolution (3). It is equally obvious to the chemist that Betaxolol and Levobunolol were expected to be β-adrenergic blockers, both having the characteristic aryloxy-hydroxypropyl-isopropyl (or butyl) amine structure.

Some of the NCEs are products of this technique but in a different indication from the one intended: Terfenadine (4) has its conceptual roots no doubt in the butyrophenone-piperidine group of neuroleptics, yet it developed to a nonsedating antihistamine, the first breakthrough after 40 years of antihistamine research.

No matter how clear-cut or how elaborate the concept behind these new drugs is, probably none of the 1985 crop is the result of either random screening or de novo design as defined above. The author believes that advances in technol-

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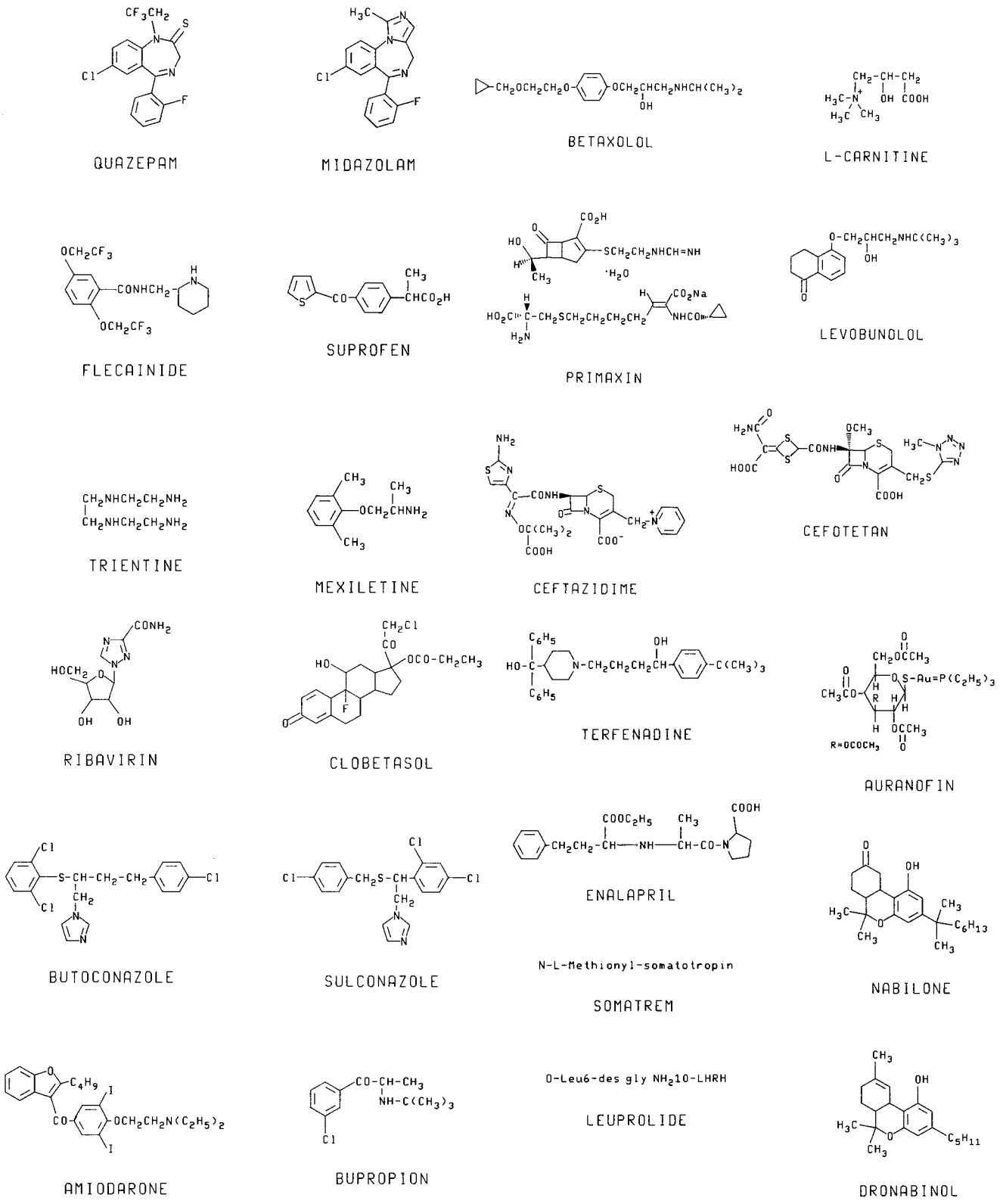



**Fig. 1.** 25 NCEs approved in 1985 by the FDA.

ogies and basic science will change this situation and that a number of drugs of the 1990s will be developed that originate from screening or design. Some of these advances are discussed below.

## FUTURE TRENDS

### Peptide Chemistry

The dramatic progress in this area will certainly con-

tribute greatly to the drug discovery process in the future. The perfection of the classical protection and coupling techniques combined with the automated solid-phase methodology and with the powerful tool of high-performance liquid chromatography will allow the synthesis of peptides up to the size of small enzymes, an achievement that, until very recently, was believed to be possible only through bioengineering.

As a consequence, tools for drug research will become available that will give the discovery process a more rational basis. These tools may be the enzymes, or neurotransmitters, or messenger molecules themselves, or intentional modifications thereof to study their active sites. Other peptides may be used as probes to investigate substrates or receptors, to understand specificity and conformation. But only in rare cases will peptide chemistry provide the actual drug. It is important to understand that the perfected modern peptide chemistry most likely will not produce peptide drugs but will be instrumental in providing the tools for the rational design of future drugs. Interestingly, the availability of these biomolecules for *in vitro* assays has its impact also on the second source of new leads, screening. This aspect is discussed later.

### Molecular Biology

It is the purpose of this review not to explain the techniques of recombinant DNA and bioengineering, which have reshaped today's science, but to estimate this discipline's impact on future drug discovery.

The first drugs manufactured by this process are on the market, one outstanding example being insulin. Several others are in the pipeline for development and some will reach the patient in the near-future, such as tissue plasminogen activator for the treatment of cardiac infarct. But there is no reason to believe that we will see a proliferation of new drug introductions like we saw in the 1950s. The limitations of this new technique for drug development are formidable. First and foremost, the instability of peptides and proteins toward hydrolyzing enzymes of the gastrointestinal tract necessitates administrations other than oral.

Second, the requirements for purity and stability—difficult enough for many synthetic drugs—are considerable for bioengineered products. Contamination with impurities of a similar, high molecular nature from biological sources, antigenicity, tertiary structure, degree of glycosylation, etc., are problems to be dealt with. If nothing else, this will have an impact on the price of these products. This—together with the handicap of administration—allows the prediction that peptides and proteins from molecular biology sources will become drugs in the future only for a few life-threatening indications.

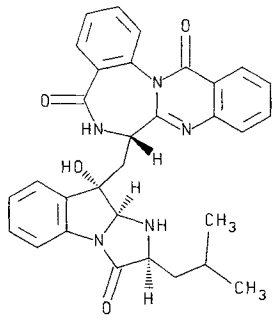
The availability of products from these sources, however, will have a great impact on rational drug design in the same way as that of the progress in peptide chemistry. Indeed, both methodologies complement each other and modern drug research establishments have recognized the importance of having both disciplines available to provide the tools for future drug design.

### Computer-Assisted Drug Design

The third discipline that undoubtedly will influence pharmaceutical research in the future is computer science. The broad term computer-assisted drug design (CADD) covers a wide spectrum of applications. At one end, computers can be used to facilitate the mathematics describing more or less empirical correlations between the biological effect and the physicochemical properties of groups of (related) chemicals. At the other end of the spectrum, it is possible, with the help of sophisticated programs and with information from physicochemical experiments such as nuclear magnetic resonance (NMR), to calculate de novo conformations and secondary structures of large macromolecules and to gain insight into active sites and receptor–ligand interactions. This process is already reducing the amount of trial-and-error syntheses and enhancing the probability that a newly synthesized compound has the desired biological properties.

### Screening

Interestingly, progress in the three technologies mentioned above not only will increase the chances for rational drug design, but also will revive the time-honored method of lead detection through screening. By definition, the therapeutic uses of all natural products must have been found by "screening" during the history of medicinal therapy. Some 120 natural products are presently in use in the United States (5) and many synthetic drugs are modifications of these leads. But screening on an industrial scale has not resulted in too many NCEs in the last decades, perhaps with the exception of antibiotics. The reason was that the relatively cumbersome animal models did not allow the evaluation of larger numbers of novel and unrelated compounds. This has changed now. The availability of bioengineered or synthetic enzymes, receptors, substrates, and inhibitors



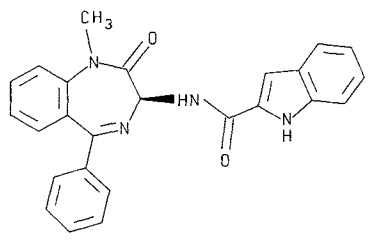




Fig. 2. The lead compound asperlicin and the optimized cholecystokinin inhibitor L-364,718.

combined with computer-driven robotics and computer handling of test data will allow the gathering of biochemical data on a large number of compounds.

The first results of this technique have become visible. A particularly beautiful example is the discovery of Asperlicin as "lead," from a screening program of fungal metabolites designed to find inhibitors of the enzyme cholecystokinin (6). The subsequent optimization which led to L-364,718 completed the professionally executed discovery process, of which we hopefully will see more in the future (Fig. 2) (7).

## CONCLUSION

It is still a long way from knowing a biochemical mechanism of action to a drug. "Classical" pharmacologists will always be needed, to observe the effects of drug candidates in whole animals and to suggest applications for therapy. We can expect, however, that the number of chemicals so evaluated will decrease because of these new techniques; a sharp reduction in the use of experimental animals will be another consequence.

In spite of all these advances in technologies, the road to better and safer drugs is still long and rocky; the medicinal chemist will also need in the future a measure of good luck and patience.

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