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# Drug Design and Development. A Realistic Appraisal*

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The discovery of new biologically–therapeutically active structures continues to depend on screening and on isolated observations of unexpected drug metabolites and drug activities. The selection of therapeutically improved and useful chemicals requires molecular modification. Refinements in intuitive and physicochemical methodology can provide shortcuts in random choices and permit extrapolations of some facets of activity with a variable degree of accuracy. The final decisions concerning the usefulness of a drug remain in the domain of experimental and clinical pharmacology.

The last four decades have witnessed progressive changes in the conception, design, and development of the structure of organic drugs. On the surface, the purely heuristic and empirical methods of earlier periods appear to have been replaced by more rational approaches[1] involving biochemistry, biophysics, enzymology, kinetics, statistical analysis, measurements of partition coefficients, and spectroscopic interpretations ranging from ultraviolet to NMR and x-ray diffractometry, the latter being the arbiter of stereochemical data obtained by chemical means and conformational analysis. Of the methods which have been the subject of intensive research, one is the quest for quantitative relationships of structure and biological activity. Since an early paper[2] this was continued in an illuminating series of publications which earned Corwin Hansch the first Smissman Award of the Division of Medicinal Chemistry of the American Chemical Society.[3]

Another broad method is the application of biochemical rationales to the discovery of structures of biologically active chemicals, be they hormones, drugs, agricultural fungicides, pesticides, pheromones, or other selectively toxic substances. Ideas and successes in these fields have been reviewed repeatedly.[4-6] The hope of correlating biochemical events with the structure of biologically active compounds has been based on the observation that analogues of enzymic substrates may affect the rates of enzymatic reactions. Whenever and *if* an abnormal or toxic state leading to a disease is induced by a proved enzymic reaction, the inhibition of such a reaction might ameliorate the damaging consequences of a noxious biochemical sequence.

On the other hand, among synthetic hormones (steroids, catecholamines, peptide hormones, etc.) as well as analogues of prostaglandins many potent agonists have been encountered. The structural modification of plant metabolites, such as alkaloids, and of microbial metabolites, such as antibiotics, has usually had the aim of improving potency and specificity, that is, properties agonistic relative to those of the prototype.

The increasing refinements of chromatographic separation methods and of spectroscopic and other analytical procedures have revealed a steadily growing number of enzymic substrates, biochemical intermediates and reaction products, cofactors, hormones, and neurotransmitters that can, in turn, serve as prototypes for the design of metabolite analogues. This has provided "lead" compounds in situations bearing real or at least putative relationships to disease states that can form a basis for the search for new therapeutic agents.

In the early stages of medicinal research, the screening of natural products provided the principal sources of "lead" materials. For 150 years plant materials were investigated more vigorously than other natural products, but if we total up the number of clinically useful alkaloids and divide it into the number of alkaloid-bearing plants extracted, the yield of useful drugs has been very low. This proportion is even less favorable when non-nitrogenous plant products are counted. This does not detract from the inestimable impact biologically active and inactive plant products have had on the development of deductive structural organic chemistry, and on the incentive they provided to synthesize them by ingenious schemes or to imitate Nature by elucidating their biosynthesis. But as a mission-oriented medicinal project, the chemistry of natural plant products has not been profitable. This has been corroborated by systematic contemporary searches. During the last three decades, many laboratories devoted a major effort to the screening especially of indole alkaloids with the hope of duplicating the success of the chemical and therapeutic study of reserpine. With the exception of the vinca alkaloids, the medicinal results of this effort have remained questionable. In one industrial laboratory, 600–700 plants were extracted monthly for several years and the extracts screened in several biological tests, without practical success.

Mammalian, amphibian, and marine animal hormones as well as the vitamins have the advantage as "lead"

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compounds in that their biological activity can be anticipated prior to their isolation and characterization. Animal toxins also approach this description because some venoms exhibit potentially useful pharmacological properties at low doses. In the field of naturally occurring antibiotics from microbial or botanical sources, inhibition of pathogens can be detected rapidly and routinely by screening extracts from soil samples or plants. In spite of the successes in this area over 30 years and the continuing discovery of second-generation antibiotics, the yield of novel, clinically useful agents of acceptable toxicity has decreased.

My reason for emphasizing natural products is that they remain one of the few de novo sources of drug discovery. Their direct medicinal value is rare and should really not be expected because natural products, with the exception of mammalian hormones, arise from the metabolism of organisms far removed from the evolutionary stages of man and metabolically related animals. As far as can be estimated, they have not been intended to be used as therapeutic agents. However, their unorthodox and often unexpected chemical structures derived from universal metabolites offer novel points of departure for molecular modification which, in many cases, has led to clinically valuable drugs.

Instead of screening natural products with or without therapeutic folklore for a given biological activity, random collections of chemicals can be screened regardless of their origin. Such a conglomerate consists mostly of synthetic substances. Some compounds can be eliminated a priori if experience predicts a lack of interesting biological properties, but many others with a doubtful chance are usually included. In spite of their low return of active compounds, such screening operations are still conducted on a massive scale in crash programs, where every attainable "lead" has to be considered, and one active or perhaps useful compound in many thousands may justify the wastefulness of the undertaking. The success of random screening depends on the availability of reasonably simple, rapid, and yet significant tests for the desired biological activity.

The second route to generating "lead" compounds is the study of biologically active metabolites of drugs. In a few cases such as imipramine and phenylbutazone, the drug has activity but also yields an active metabolite. Chlorguanide is inactive as an antimalarial and must be converted to a biologically active substance, cycloguanil, by metabolic reactions unrelated to the desired activity. Likewise, polynuclear aromatic hydrocarbons must undergo metabolism to epoxides[7] or carbonium ions derived from mesomethyl hydrocarbons[8] to become carcinogenic electrophiles.[9a] In other cases, a moderately active drug is metabolized to a more potent derivative. In either instance, the structurally new drug metabolites may serve as guides in subsequent molecular modification.

A few attempts have been made to rationalize these events. For example, bioreduction can convert quinonoid homocyclic and heterocyclic compounds to quinone methides which can then function as alkylating agents of nucleic acids.[9b] However, such activation occurred only in 48–63% of the cases studied.

All other pathways to biologically active structures are molecular modifications of existing "lead" compounds, motivated by various purposes.[10] These include the preparation of products competitive with a drug of commerce or, more commonly, the synthesis of compounds that represent improvements in potency and specificity. A more inspired type of molecular modification is the synthesis of analogues of essential substrates that alter the rate of enzymic reactions. In descending order, the greatest successes of this approach have been recorded in the field of invasive and infectious diseases,[11] in the control of neoplasms,[12] and a few functional and behavioral disorders.[13] A few isoenzymes have been recognized in different species and organs with a more selective sensitivity to certain metabolite antagonists.[14] Thus, for selective performance, blockade of any one of the enzymes in the de novo synthesis of dihydrofolic acid leads to selective poisoning of parasites that have no active transport system for folic acid. Or else, the invading cell, e.g., leukemia cells, may have an active transport system for a drug (e.g., methotrexate) that requires such a system for cell entry. The host may also be able to detoxify a chemotherapeutic antimetabolite such as 6-MP by a route (glucuronide formation) not available to the invading cell, or the latter may convert an intrinsically inactive compound to a lethal form whereas the host may lack such suicidal reactions.

However, these demonstrations of the value of the design of biochemical inhibitors as medicinal agents are dampened by the repeated discovery of equally or even more effective drugs by random screening or by serendipitous biological observations in tenuously related researches. In such cases, a biochemical explanation of the mechanism of action usually follows the chance discovery of activity.

A mechanistic refinement of preparing structural analogues of a substrate of an enzyme can be attained by predicting, on purely chemical grounds, transition states of the substrate and designing transition state analogues.[15,16] Such compounds are not likely to succeed in clinical utility, however, because the critical change is made at the molecular position where the substrate is expected to bind to the active site of the enzyme, i.e., where the enzymes from different cellular species show the greatest similarity or even identity.

Indiscriminate reactivity toward overlapping enzymes has also limited the utility of other agents for which mechanistic explanations could predict biological activity. Thus, the hundreds of natural and synthetic $\alpha,\beta$-unsaturated carbonyl compounds tested appear to act by Michael addition to biochemical nucleophiles but they add unselectively on the whole, giving rise to widespread toxic symptoms.[17-19] The relatively few sufficiently selective agents of this type which have found application in therapy owe their value to empirical manipulations of hydrophobic portions of their molecules or to steric differences whose functions have not yet been explained. The same limitations of selectivity are observed for other alkylating agents which also establish covalent linkages to macromolecular bioligands by predictable mechanisms. These more classical alkylating agents are again generally toxic, interestingly at similar cells and tissues as the $\alpha,\beta$-unsaturated carbonyl compounds. The least toxic and thereby most useful alkylating agents also appear to have a special balance of hydrophobic and hydrophilic regions.

It has been suggested repeatedly that an understanding of the chemoreceptor processes would enable a chemist to build molecular models that would fit the active domain of the drug receptors. This would amount to an ab initio design of a drug. Unfortunately, the many interesting attempts to clarify the active region of a receptor, and indeed the chemical nature of any receptor, have remained incomplete. Receptors have been described as proteins and sometimes as lipoprotein components of membranes, usually of high molecular weight and undefined structures. Receptors for acetylcholine,[20] estrogens and steroids,[21,22] insulin,[23] and glucagon[24,25] have been studied extensively.

In these cases their existence as molecular entities of usually high specificity, determined by receptor mapping with closely related compounds, has been confirmed. For adrenergic receptors, the participation of adenylyl cyclase and cAMP has been postulated.[26] Some drugs react with nucleic acids in a way that marks nucleic acids as their receptors.

It is more difficult to visualize receptors for drugs that have not yet been prepared. For potent analgetics, this question has been answered, in part, by the discovery of the enkephalins and endorphins.[27-29] The characterization of these endogenous analgetic peptides must be regarded as a biochemical breakthrough in illuminating pain perception, but these functionally specialized peptides are not unlike many others found in the animal body, especially in endocrine secretions. They react with receptors which, except for being recognizable as proteins, remain uncharacterized.[30-32] Except for having been spotted by unusually astute pharmacological observations, these peptides fall, however, into traditional patterns of the discovery of biologically active natural products and of subsequent synthetic modification.

A case suggestive of creating "lead" compounds is the facilitation of ion transport across membranes by ionophores. It could be argued that compounds which render cations lipid-soluble could be designed on theoretical grounds involving the ligating ability of polar functions and a prerequisite conformation, but in truth the ionophores, and especially the ionophoric peptides,[33] were discovered experimentally in another context.[34] A better case can be made for the design of free-radical scavengers that could be applicable as drugs in free-radical pathologies[35] or radiation damage.

One special case of biological input in which, however, chemists do not provide the innovative stimulus, approaches de novo drug conception when prototype drugs are recognized for unforeseen therapeutic uses. This occurs if a biologist observes a side effect of an experimental or clinical test drug which might have a bearing on a disease state unrelated to that of the principal action of the compound. The classical examples of such findings are several side effects of sulfanilamides, which have nothing to do with antibacterial action,[36] and of purine analogues conceived as antineoplastic agents, with biochemical and pharmacological side effects in several unrelated areas such as uricosuria.[14,37,38] Such observations have opened the way to molecular modifications which suppressed the original activity and raised the side action to decisive potency and specificity.

In other clinical instances of this type, chorthalidone, an antihypertensive–diuretic agent, and droperidol, a neuroleptic, are effective in Menière's disease and so is the antimanic lithium ion. Propranolol improves migraine headaches and causalgia, epinephrine is useful in cluster headaches, and the tricyclic antidepressant, imipramine, suppresses nightmares and prevents sleepwalking. Hemiballismus, a spastic disorder, yields to haloperidol. The antihistaminic agent, cyproheptadine, relieves the symptoms of Cushing's disease, and indomethacin retards premature labor. Molecular modification may well enhance these unusual activities.

But with the exception of pharmacological observations of activated drug metabolites or of unexpected effects of known drugs, the only way to the discovery of novel drug structures has remained screening, with its low return of useful medicinal agents. The overwhelming bulk of the actual development of new drugs encompasses molecular modification.

Almost nobody modifies molecules in the random manner as it was prevalent until the early 1930's. Rules concerning the isosteric replacement for the gradual and fairly rational modification of molecular functions and moieties emerged at that time[39,40] and were expanded subsequently[40] to accommodate new knowledge of electronic, hydrophobic, and steric conditions. Under the heading of bioisosterism they have lately placed more emphasis on biological than chemical similarities of diverse structures.[40,41]

Among the more recently used chemical exchanges are subtle variations in protonic functions, such as the replacement of phenolic hydroxyl by $CH_2OH$, $CH_2SO_2CH_3$, or $NHSO_2CH_3$ and that of carboxyl by tetrazolyl. In ring exchanges a revival of classical isosterism now often includes replacement of CH= by N=, and vice versa, and of cyclic methylene by oxygen, sulfur, and imino. This has been the successful basis of many new medicinal agents. Such structural changes often permit estimates of the quality and type of biological activity, although predictions of potency are harder to make and chemical prognoses of the therapeutic index, i.e., the probable usefulness of a drug, are still largely guesswork.

The last 15 years have witnessed intensive efforts to place structure–activity relationships on a quantitative basis. These researches have been reviewed repeatedly.[3,42,43] Hansch[3] has based his extensive correlations of structure and activity primarily on parameters reflecting hydrophobicity vs. polarity of the test compounds. In a given structural series these properties can be calculated from the Hammett constants of individual substituents, especially for aromatic compounds. The need to draw on Hammett constants previously determined can be circumvented by modifications[44,45] of the Free and Wilson model[46] in which substituent/position combinations are expressed as substructural variables. Both methods now frequently provide shortcuts if in a given series of structurally related compounds more potent analogues are to be extrapolated by decisions which would otherwise be based on chemical intuition only.

Quantitative structure–activity relationships are only as good as the biological test methods against which physicochemical parameters are plotted. Many of the biological tests used 25–30 years ago lacked the reliability required of similar tests today. Some of the earlier quantitative measurements had to use those older biological tests because more relevant data for series of structurally related compounds had not been recorded in the literature. As measurements of partition coefficients and similar methods are more widely adopted in laboratories which also carry out uniform biochemical and pharmacological tests with the same compounds, these difficulties are overcome to some extent. Even so, the physicochemical model must be consistent with the biological test if it is to have predictive value. For example, 3,5-dichlorosalicylic acid and *N*-(2,3-xylyl)anthranilic acid cause the same increase (20 mV) in the membrane potential of the mollusk buccal ganglion and have identical log *P* values.[41,47]

Reduced cost of computer time has made possible the inclusion of more physical parameters in calculations of structure–activity relationships. Nevertheless, it should be remembered that toxicity, the limiting factor in the utility of active drugs, depends inter alia on intrinsic activity, accumulation of toxic metabolites, and loss of the drug to serum and tissue proteins. In addition, pharmacokinetic and complex distribution factors which are a function of blood flow have not yet been treated adequately. The comparisons are much more meaningful for

the ability of a compound to inhibit an enzymic reaction in vitro.[3] Only inclusion of all pertinent data measured in at least two animal species will give an adequate account of the in vivo effectiveness and safety of a drug.

On the chemical side, steric factors[48] have been the hardest to incorporate into the required equations. As long as we do not have reliable evidence for the conformation of flexible molecules in solution where, as Cramer put it,[49] solvent molecules promenade around the sterically adaptable solute, the data for steric descriptions will be hard to get, especially for polar compounds. Qualitatively, an imaginative bioisosteric interpretation even of structures quite unlike in two-dimensional appearance may be of great value in explaining striking biochemical and pharmacological analogies. One example for such relationships is the comparison of the bisisoquinoline alkaloid, emetine, and the antibiotic, cycloheximide, which have similar biochemical actions and can be visualized as steric analogues in important molecular features.[50] A less sophisticated but nevertheless effective contribution to drug design is seen in various blocking agents—anticholinergics, antihistaminics, antipsychotics, anticonvulsants, antidepressants, antianxiety agents, etc.—in which flat or bulky moieties bear down protectively on functional groups that appear to be needed in receptor interaction.

Some investigators have felt that molecular orbital calculations of biologically active molecules would furnish more comprehensive descriptions which would minimize bioisosteric uncertainties. These hopes have materialized only partially. It may be that the complexity of medium-sized multiatomic and polyfunctional molecules still poses forbidding limits to such calculations. The need to use molecular orbital theory in conjunction with as many chemical disciplines as possible has been emphasized.[51]

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