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ADVANCED DRUG DESIGN AND DEVELOPMENT

a medicinal chemistry approach

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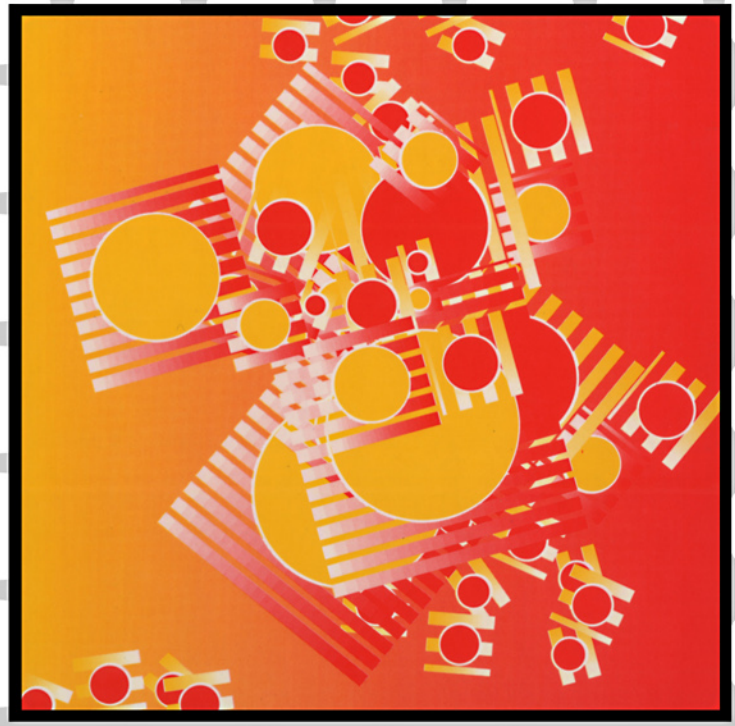
P. N. KOUROUNAKIS and E. REKKA



ADVANCED DRUG DESIGN AND DEVELOPMENT

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P.N.Kourounakis and E.Rekka

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DEDICATION

This volume is dedicated to our graduate students, worthy and motivated research workers in the science we all serve.

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Preface

The Department of Pharmaceutical-Medicinal Chemistry, School of Pharmacy, Aristotelian University of Thessaloniki, organizes, every other year, a graduate seminar in advanced medicinal chemistry, with international participation, in Thessaloniki. The purpose of this seminar is to help young and ambitious pharmaceutical scientists in this field by updating their knowledge and informing them about the new trends in our science, through the presentations of renowned invited speakers. It is also aimed to create a forum for exchange of ideas in medicinal chemistry, in a different informal environment, bringing internationally recognized medicinal chemists closer to their Greek colleagues. Some of the invited speakers in this series of seminars are: A.H.Beckett, A.Benakis, N.Bodor, D.D.Breimer, J.Caldwell, R.Ganellin, J.Gorrod, R.Franke, H.Kappus, P.Krogsgaard-Larsen, A.Makriyiannis, J.Seydel, H.Sies, J.Tollenaere and W.Wiegrebe.

This volume, entitled *Advanced Drug Design and Development: A Medicinal Chemistry Approach,* is a collection of lectures by most of the invited speakers in our second seminar.

We hope that this book will be a source of inspiration to all young medicinal chemists, providing examples in drug design from various pharmacochemical approaches.

Before closing, we would like to thank all our invited speakers presented in the text, and, last but not least, all our colleagues and staff at the Department of Pharmaceutical-Medicinal Chemistry, without whose hard work these seminars could not have materialized: V.Demopoulos, A.Geronikaki, D.Hadjipavlou-Litina, E.Sotiropoulou-Dimitriou, Ek. Tani, D.Spiriounis, I.Andreadou, A.Gavalas, G.Rekatas, R.Mgonzo, A.Alexidis, M.Tomi-Hadji, A.Polymerou-Kapoula, M.Diamanti and M.Triandaphyllidou.

P.N.Kourounakis
E.A.Rekka
Department of Pharmaceutical Chemistry
School of Pharmacy
Aristotelian University of Thessaloniki
Thessaloniki 540 06, Greece

1
Introduction

P.N.Kourounakis and E.A.Rekka

Department of Pharmaceutical Chemistry, School of Pharmacy, Aristotelian University of Thessaloniki, Thessaloniki 540 06, Greece

The discovery of drugs and drug molecules has always been the aim of pharmaceutical sciences and, in particular, of medicinal chemistry, which evolved from pharmaceutical chemistry. Half a century ago, pharmacochemistry, the modern expression of pharmaceutical chemistry, as a science whose main interest is the design and development of new pharmacomolecules, was at the beginning of its evolution. Drug design in its broad sense and structure-activity relationship studies are essential and at the heart of medicinal chemistry, and it is the progress and development of this field of research that has made medicinal chemistry the modern and enormously productive science it has become in recent decades [1]. Today, studies on structure-activity relationships and their influence on the design of new drugs have rendered them one of the most useful and thus important activities of pharmacochemistry, a modern component science in the group of pharmaceutical sciences [2].

Despite the advances in medical and pharmaceutical sciences, there are still many diseases which are incurable or can only be treated symptomatically, and at a great economic and social cost owing to only moderately effective or even to the lack of appropriate therapeutic agents. Of the 30000 or so diseases or disorders currently known, only one-third can somehow be treated with drugs. Furthermore, there are incurable maladies, like viral diseases (influenza, AIDS), CNS disorders (Alzheimer's disease), cancer and autoimmune disorders, which can be fatal or cause great suffering and disability [3]. Therefore, there is still a great need for more and better drugs—more active and selective, drugs with fewer undesired or toxic side-effects, agents useful in prophylaxis and drugs which will cause as little as possible harmful contamination in the already polluted environment.

In a systematically planned programme of drug discovery, several questions have to be answered:

— Is the research for the discovery of a certain drug justified by the medical expectation?
— How will the expected drug contribute to health?
— What would be the economic or other, more noble benefit that is expected from the drug?

— Is the state of the art of medicinal chemistry at a satisfactory level so that the risk of investing in the project should be taken? That is, have the coordinated attempts a favourable possibility for solving the problem in a reasonable time period?
— Does the specific disease affect sufficient people for the economic attempt to be justified? It is tragic that serious diseases, mainly in developing countries, are sometimes uncontrolled because of a lack of effective therapeutic agents due to the non-existent financial profit [3].

Because of the strict prerequisites of national drug authorities, which are becoming ever more demanding, the cost of drug discovery is steadily increasing. Thus, rational drug design becomes the main objective of medicinal chemistry today. Based on rational design, new structures can be developed with a high probability of possessing the required properties. The setting of clear rules to help in the access to information hidden in accumulated experimental data is necessary, and this requires studies on the quantitative relationships between (physicochemical) properties and (biological) activity.

We are thus led to the selection of a subsystem of compounds originating from an initial structure, the *lead compound,* the discovery of which is the most decisive step in the process of drug discovery. Methods used in lead compound discovery include: folk/ethno-pharmacy and therapeutics; massive pharmacological screening; fortuitous discovery; modification of bioactive natural products; exploitation of secondary or side-effects of drugs; study of the basic processes of life; body biochemistry and the use of metabolic analogues; study and exploitation of differences in molecular biology, differential cytology, biochemistry and endocrinology; study of the biochemistry of diseases; an approach through the molecular mechanism of drug action; analysis of the mechanism of action of multipotent compounds; drug metabolism (hard, soft, pro-drugs); and chemical delivery systems [2, 5–7].

The pharmacochemical manipulations following the discovery of the lead compound include: attempts aimed at the development of substitutes of existing biologically active molecules; attempts aimed at the alteration of the activity spectrum of biologically active molecules; attempts aimed at the modification of the pharmacokinetics of the compounds used as drugs or as lead compounds; structural changes in natural products; molecular transformations performed by microbes; and other chemical processes that follow the molecular manipulations on the lead compounds (for example, construction of homologous series, application of the rule of bioisosteric groups, resolution of stereoisomers) [2, 5].

It is evident that in the process of drug development the molecular structure is the main feature that determines the molecular properties, and thus whether the particular molecule finally reaches the patient [8].

Since, in the majority of drugs, action appears after the interaction of the pharmacomolecule with its receptor, it seems reasonable to study the drug structure in relation to its receptor site (the dynamic aspect). For a productive

drug-receptor interaction a good fit, determined by physicochemical properties, is required. Besides solving the basic synthetic problems, studies on the geometry and shape, conformational analysis and investigation of the influence of electronic and hydrophobic effects on drug-receptor interaction are performed. In quantitative structure-activity relationship studies attempts have been made, with success, to correlate quantitatively biological activity with molecular properties (electronic, hydrophobic, steric). This relationship has been based on the assumption that the relative importance of physicochemical properties for biological activity can be described numerically, for an objective evaluation of drug-receptor interactions. Numerous methods have been invented for the quantification of electronic, hydrophobic and steric effects of functional groups [9]. Statistical methods, mainly Hansch or extrathermodynamic analysis [10], as well as those of Free and Wilson [11], pattern recognition/principal components analysis and cluster analysis, can lead to the prediction and optimization of activity, and ultimately to the design of better drugs. The development of powerful, interactive computers and molecular graphics systems helps in the analysis and visualization of biologically active compounds and in a better understanding of drug-receptor interactions. Techniques have been developed for the determination and visual presentation of pharmacophores (receptor mapping), as well as techniques for drug design based on a knowledge of receptor structure (receptor fitting) [2, 12].

The pharmacomolecule, before interacting with its receptor (this interaction being direct or indirect, a simple binding—affinity—or a productive interaction yielding a biological effect—efficacy), must reach, intact and in satisfactory concentration, the immediate environment of the receptor site. Access to the receptor is also determined by the physicochemical properties of the molecule. Thus, structure plays a decisive role not only in the dynamics, but also in the kinetics of the drug molecule.

Molecular structure is usually altered by the body. Drug metabolism, basically an adaptive process, is a rather useful property of the (liver) cell, as a whole. Drug biotransformation usually leads to more polar compounds, and thus to faster elimination, and to substances with lower or no activity. Only rarely is an increase of activity observed after biotransformation. However, in certain cases, very dangerous highly (chemically) reactive metabolic intermediates are formed. During drug metabolism, and through the catalytic activity of enzymes like the cytochrome P-450 family, prostaglandin synthase and xanthine oxidase, free radicals may be formed, which participate in the initiation and propagation of chain reactions. Oxygen is activated, and the presence of active oxygen species ($O_2^{-}\cdot$, H_2O_2, $HO\cdot$) may lead, via lipid peroxidation or other cellular structure damage, to cell injury and necrosis [12]. Numerous pathophysiological conditions are probably due to radical attack and oxidative damage [13]. A knowledge of the pathophysiology of diseases constitutes a decisive step towards the discovery of lead compounds. This could be conducted in various ways, for example by the study either of free radical scavenging activity or of free radical formation.

Therefore, drug metabolism and, in particular, relationships between the structure of the drug molecule and the enzyme systems responsible for drug biotransformation, resulting in detoxification, but also in biotoxification, are currently subjects of active pharmacochemical investigation. The ever-increasing number of modern, improved drug molecules, the discovery of which is based upon a knowledge of drug biotransformations and oxygen activation, supports the argument for the prominent position held by drug metabolism and free radical pharmacochemistry in currently used rational drug design techniques.

This volume covers topics such as drug discovery and physicochemical properties, structure-activity relationships, structure-interaction with specific receptor subtypes, and in combating serious diseases that cause great financial and social problems, for example Alzheimer's disease and gastric ulceration. Also discussed is the dependence of the biological properties of a compound on chemical structure, in terms of quantitative structure-activity relationships, the merits and shortcomings of computational chemistry and the techniques applied to gaining insight into the complex molecular phenomena in innovative drug research, the characterization and prediction of drug metabolism in humans and the importance of labelling of bioactive compounds in the study of the dynamics but mainly the kinetics of a prospective drug.

These topics are presented by contributors, each one a specialist in his or her own field within the greater subject of pharmacochemistry. We are certain that the following chapters, tackling the subject of drug design from different viewpoints, will stimulate the creativity of those involved or interested in innovative drug research. Young medicinal chemistry investigators could be helped and inspired in their attempts to find new and better drug molecules among the structures waiting to be discovered.

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Structure-activity studies and drug design with antagonists at histamine H_2 receptors

C.R.Ganellin

Department of Chemistry, University College London, 20 Gordon Street, London WC1H 0AJ, UK

SUMMARY

H_2 receptor histamine antagonists now have a considerable diversity of chemical structure but incorporate at least two planar π-electron systems which are polar and have a propensity towards hydrogen bonding.

The activities of a series of antagonists structurally related to cimetidine have been compared to investigate the effect of replacing the cyanoguanidine moiety by other neutral, dipolar groups. Antagonist activity (measured *in vitro* on the histamine-stimulated right atrium of the guinea-pig) is very sensitive to relatively minor structural changes. Differences in activity are accounted for by dipole moment orientation and lipophilicity for 15 different structural groups according to the equation $-\log K_B = 9.1 \cos\theta + 0.60 \log P - 2.7$.

It is suggested that drug molecules in aqueous solution are in a water-solvent shell and have to undergo desolvation (log *P* octanol: water, representing a hydrophobic effect) and align themselves at a polar receptor; they then undergo hydrogen bonding and dipolar interactions with the receptor.

H_2 receptor histamine antagonists do not readily enter the brain and it appears that this may largely be due to their high polarity coupled with a relatively low lipophilicity. A physicochemical model relating to the difference between octanol/water and cyclohexane/water log *P* values, which is regarded as an approximate measure of hydrogen-bonding ability, correlates with brain/blood concentration ratios. A series of 3-(3-(l-piperidinylmethyl)phenoxy)propyl derivatives was sythesized with the aim of reducing hydrogen bonding ability whilst retaining H_2 antagonist potency, and several novel compounds were obtained which readily crossed the blood-brain barrier. In particular, zolantidine (SK&F 95282), an aminobenzo-thiazole derivative having an atrial pA_2 of 7.65 and a brain/blood concentration ratio of 1.4, has been identified for use in studying histaminergic H_2 receptor mechanisms in the brain.

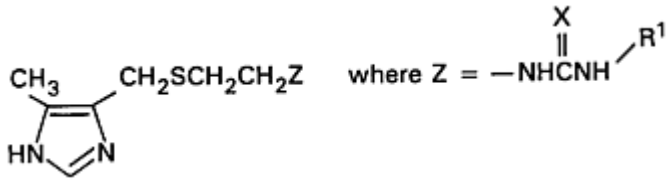

Fig. 1. General structure of a series of H_2 receptor histamine antagonists (cimetidine analogues).

INTRODUCTION

Three types of histamine receptor have now been characterized pharmacologically according to the antagonists and agonists which interact with them. They are designated H_1 [1], H_2 [2] and H_3 [3, 4]. This chapter describes some structure-activity studies concerned with designing antagonists at H_2 receptors as potential therapeutic drugs.

The first clinically valuable H_2 receptor histamine antagonist was cimetidine (Fig. 1, X=NCN, R^1=CH_3), which was introduced into many countries in 1977 and revolutionized the treatment of peptic ulcer disease [5–7]. In seeking alternative chemical structures as H_2 receptor antagonists various hydrogen-bonding polar groups were examined as alternatives to the cyanoguanidine group in cimetidine [8], including the isocytosine group (2-amino-pyrimidin-4-one).

It became of interest to study the chemical properties of these compounds to gain some insights into how they may interact with the H_2 histamine receptor. The analysis was simplified by concentrating on a series of antagonists depicted in Fig. 1 whose structures were closely related to cimetidine. The studies emphasized the importance of such physicochemical properties as geometry, acidity (pK_a), hydrophilicity (octanol-water partition, P) and dipole moment (electron density distribution).

In cimetidine, the cyanoguanidine moiety is regarded as a 'polar hydrogenbonding group' and initially a small chemically homogeneous series of 12 cimetidine analogues was studied (Fig. 1, X=O, S, N–CN, N–NO_2, N–CO– or $CHNO_2$).

The rules used of selection of structure in the first correlation analysis are as follows:

(1) The 'aromatic group' and chain are kept constant, that is, 2-[(5-methylimidazol-4-yl)methylthio]ethyl.
(2) Z is a planar, 1, 3-amidine NH system which is formally uncharged at pH 7. 4, that is, pK_a (proton gained) <5 and (proton lost) >9.

(3) In the 'hydrogen-bonding group', Z, alkyl substitution on C is excluded to avoid introducing new steric effects, but replacement of $NHCH_3$ by NH_2 is

permitted since this is of obvious importance to consideration of hydrophilicity; cyclic forms of acyl guanidine such as isocytosine are also included.

BIOLOGICAL ACTIVITY

In this study, the activity of H_2 receptor histamine antagonists was determined *in vitro* against the histamine-stimulated increase in the rate of beating of the guineapig right atrium at 34°C, by the method described by Parsons *et al*. [9]. Dose ratios *(A)* were calculated as the ratio of histamine concentrations required to produce half-maximal responses in the presence and absence of different concentrations *(B)* of antagonist, and dissociation constants *(K_B)* were derived from the equation $K_B=B(A-1)$. The compounds appeared to behave as simple competitive antagonists.

CORRELATION WITH OCTANOL-WATER PARTITION

For most of the compounds there appeared to be a good correlation between activity and a lipophilicity parameter (octanol–water partition for the model compounds HZ) in which a 10-fold increase in *P* brought about a 100-fold increase in activity. There were, however, two notable exceptions, namely the thiocytosine and the 1,1-diamino-2-nitroethene (see Ganellin [8]).

The thiocytosine was much less active (about one-hundredth) than predicted and the 1,1-diamino-2-nitroethene (Fig. 1, X=$CHNO_2$, R^1=CH_3) was much more active than predicted (approximately 30-fold), and it was concluded that some property other than the lipophilicity parameter was making a marked contribution to activity.

Partition coefficients were measured by a conventional shake-flask technique at 37°C [10]. The concentrations of the compound in the aqueous phase before and after partitioning were determined spectrophotometrically. Buffer salts were used to control the pH of the aqueous phase. Log *P* is the partition coefficient of the neutral form of the compound. It is assumed that only the neutral form of the compound partitions into the organic phase, whence log *P* is related to the apparent partition coefficient (P_a) of the compound, measured at a pH at which the neutral and monoprotonated forms are in equilibrium in the aqueous phase, and to the dissociation constant (K_a) of a proton from the most basic site in the molecule, by equation (1):

$$\log P = \log P_a + \log (1 + 10^{pK_a - pH}) \qquad (1)$$

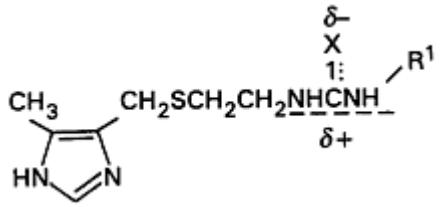

Fig. 2. General structures showing the partial charge separation in the 'polar H-bonding group'.

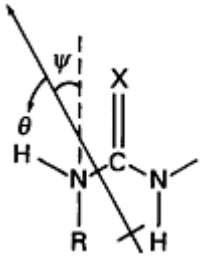

Fig. 3. Definition of the orientation parameter, that is, the deviation, from the optimal angle, of the dipole orientation with respect to the side-chain N-R bond. The optimum for ψ was found to be 30°, and the ideal orientation would have θ=0°.

CORRELATION WITH DIPOLE ORIENTATION

One property which cyanoguanidine has in common with other neutral moieties found in active analogues of cimetidine is high polarity. Simple derivatives of urea, thiourea, cyanoguanidine and 1,1-diamino-2-nitroethene have high dipole moments, especially in aqueous solution, where charge-separated canonical structures are believed to make important contributions to the overall electronic distribution (Fig. 2).

Consideration of the dipolar nature of the above groups prompted the measurement of the dipole moment of model compounds [11, 12] and led to the interesting proposition that it might be possible to account for activity by considering hydrophilicites and dipole orientation [13].

To investigate the importance of dipole orientation, CNDO/2 molecular orbital calculations were performed for each dipolar group, and estimates made of the dipole orientation with respect to the side-chain R–N bond, that is, angle ψ. The possible existence of an optimum value for ψ within the series was then examined by calculating the deviation θ (Fig. 3) from various arbitrary angles of ψ and assessing their biological significance.

In this study, only the *N*-methylated derivatives of the acyclic dipolar group were included (compounds **1**–**4**), together with four cyclic analogues **(5–8)**. For the eight compounds shown in Fig. 4, only a poor correlation was obtained using the dipole moment vector term, μ cos θ, but a surprisingly good correlation was obtained (correlation coefficient r=0.86) between antagonist activity and cos θ alone.