CHAPTER I

INTRODUCTION

One of the major goals of pharmaceutical chemistry is an understanding of the action of drugs based on their structure and physico-chemical properties. Empirical methods of approaching this goal have led in the past to a large number of highly useful medicinal agents; however, these qualitative techniques are admittedly oversimplified and uneconomical. It is estimated that out of every 5,000 to 10,000 compounds synthesized today only one is ultimately found to be a useful therapeutic agent. It should be possible to improve this proportion with the aid of recently developed theoretical and computational chemical methods.

With the increasing knowledge of the structure and physico-chemical properties of drug molecules and biochemical substances, it is now possible to investigate how a drug acts at the molecular level in the body. One attempts to determine the sites, called receptors, at which a drug acts, and the mechanism by which the action is brought about when the drug interacts with the receptor. A knowledge of the interaction forces involved in the binding of drug molecules to receptor sites is essential for understanding of drug action. Unfortunately, the experimental determination of these forces is difficult, and little has been accomplished along these lines.

On the theoretical level, quantum mechanical calculation of the electronic characteristics of molecules should prove to be a fruitful approach to the determination of drug-receptor interaction. Such quantum mechanical methods become increasingly difficult to apply to the determination of electronic characteristics as the molecules become larger, however, the use of certain simplifying assumptions and the application of high-speed electronic computers have permitted the application of quantum theory to the study of numerous chemical problems. Some beginning has already been made in the application of quantum theory to the study of drug design, stabilization of medicinal agents, and the interaction of drugs in solution (1,2). These applied fields of quantum mechanics are currently referred to in the literature as quantum chemistry, quantum biochemistry, or quantum pharmacology.

Drug scientists are becoming increasingly aware that the biological events induced by drug molecules are governed by physical and chemical properties and that the specific activity of any drug molecule is a function of its electronic structure. In the general sense, the term electronic structure encompasses the electron distribution, the stereochemistry, and the static and dynamic energy profiles of a molecule. To determine of these structural features has been the concern of scientists seeking to explain drug actions, to improve drug efficiency, and to design new drug molecules.

The traditional approach to deducing electronic influence on biologic activity has to synthesize and evaluate biologically a series of molecules with graded structural changes, permitting an intuitive

analysis of the electronic effect of the structural change within the series. The analysis and extrapolation to prediction of new compounds can be improved partly by involving statistical methods. A parallel approach to the understanding of the influence of electronic structure on biological activity is to evaluate the electronic structure from first principles.

About 100 years ago it was demonstrated that a gradual change in chemical structure could lead to a change in the biological activity of drugs. Since that time the rational prediction of the results of changing the structure of a drug molecule for the explicit purpose of custom designing a compound possesing particular therapeutic properties has been an important goal of medicinal chemists. One important technique is based on theoretical calculations of electronic structure by the molecular orbital methods of quantum chemistry. In these studies electronic indices are compared with biological response in an effort to gain a better understanding of active site of drugs and/or drug-receptor interactions.

1.1 Historical Outline of Antimalarial Drugs

Malaria has been one of the most prevalent of human diseases, affecting particularly the populations of tropical regions and also in the past those of temperate climates. The malaria situation throughout the world (Figure 1.1) causes increasing concern. The number of malaria cases in Southern Asia and middle America during the past few years shows a sharp increase; and the number of cases of malaria imported into the countries of

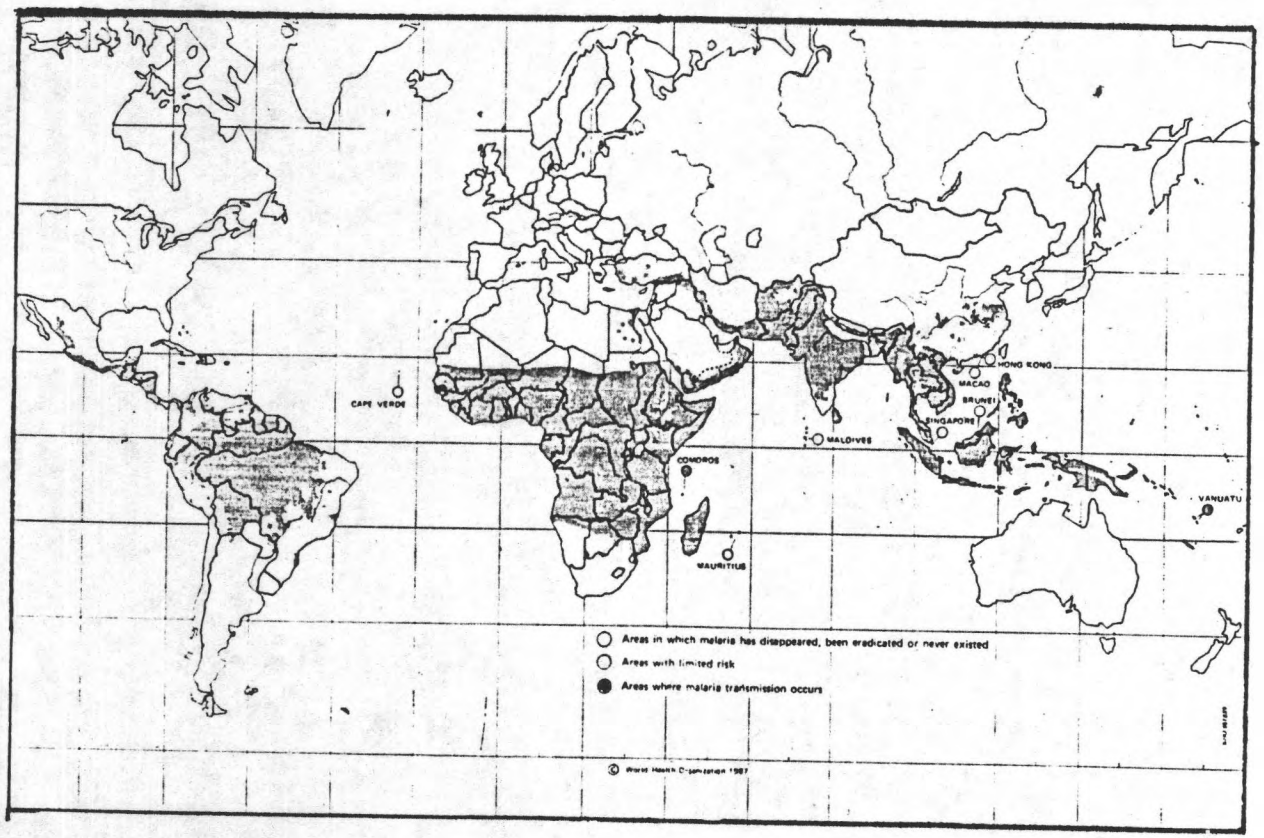

Figure 1.1 Malaria Situation in the World, 1985

(WHO, 1987)

the temperate zone has been rising every year, owing to the greater mobility of people as well as the deteriorating malaria situation in many tropical areas. At the end of 1979 some 2,350 million people were living in areas where the transmission of malaria has not ceased; at least one sixth of these people were still living in places where no organized antimalarial measures were being undertaken, especially in Africa, south of the Sahara. These figures show better than any other pointer that global eradication of malaria, however desirable, is an extremely difficult enterprise and that one of today's major tasks is not to lose the gains achieved during past decades.

In order to deal with the correlation of electronic distribution and the antimalarial activity of drugs by quantum pharmacological study, it is necessary to appreciate the historical features and the major chemical structures of antimalarial drugs.

For 200 years the crude bark of cincona was used for the preparation of powders and infusions. Many chemists attempted to isolate the active principle of the drug; it seems that, at the beginning of the nineteenth century, Antonio Gomez in Portugal and Th.I. Gize of Kharkov in Tussia obtained a crystalline substance from an alcoholic extract of the bark. But the final isolation of two basic alkaloids of cinchonine, qionine and cinchonine, was not accomplished until 1820, by the French chemists Pierre Pelletier and Joseph Caventou. Following the isolation of two other alkaloids of cinchona (quinidine and cinchonidine), the use of the alkaloids as such gained favor rapidly; quinine (Figure 1.2) owes its dominant position for the treatment of malaria with cinchona alkaloids to its

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prior isolation.

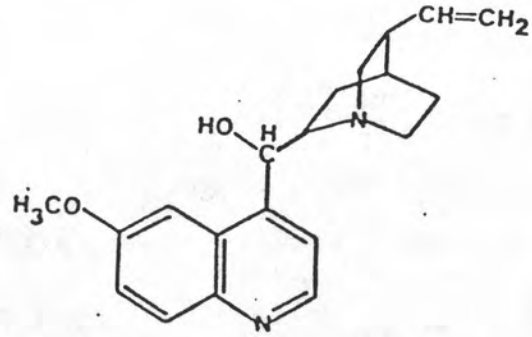

Figure 1.2 Quinine

The ruthless harvest of cinchona bark resulted in the near-extinction of the tree in the mid-nineteenth century, and efforts were made to introduce the species into India and Java. The British attempt was soon abandoned, and the Dutch East Indies came to supply almost all of the world's quinine. This limited geographical locale was the spur to research into synthetic antimalarials in both world wars.

After three centuries of reliance on cinchona bark and quinine, the development of synthetic antimalarials was initiated by German chemists and quick by the enemy control of quinine supplies in World War I. Their starting point was methylene blue, which had been shown to possess some antimalarial activity (3). Structural variations in the methylene blue molecule indicated that a dialkylamino side chain was essential for activity, and the researches culminated in the development of the first synthetic antimalarial drug. Plasmochin, later termed pamaquine. Further research in Germany on the attachment of the basic dialkyoaminoalkylamino side chain to other heterocyclic systems led

to the synthesis of Atebrin, now called quinacrine or mepacrine which continued to play an outstanding role in the prevention and treatment of malaria of Allied troops (4).

The value of the 4-aminoquinolines as antimalarial agents was not fully recognized until the early 1940s, although they had been developed in Germany some 10 years earlier (5). The stimulated resurgence of interest in the 4-aminquinolines resulted in the establishment of chloroquine (Figure 1.3) as one of the most effective drugs in antimalarial therapy.

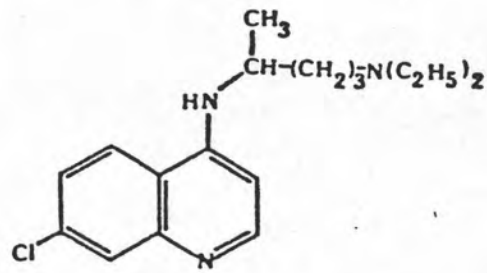

Figure 1.3 Chloroquine

On the basis of previous experimental work and field observations, it was believed that in human plasmodia the development of resistance to the 4-aminoquinolines was unlikely, to say the least. This complacency was shaken when the failure of chloroquine treatment to cure a Plasmodium falciparum infection originating in Columbia was reported in 1960. The possibility of widespread resistance of Plasmodium falciparum to chloroquine in south-East Asia, South America, and now in Africa and India, has posed very serious problems.

The drug screening programme carried out in the USA

that some of the most promising future drugs for the prevention and treatment of malaria will emerge from this far-seeing enterprise. The programme coordinated by the Walter Reed Army Institute of Research was designed to include the screening of available compounds (6). During the past 12 years, over 250,000 compounds have been screened in primary tests using mice infected with P. berghei. About 170 of the most active compounds were selected for advanced testing in monkeys infected with simian malaria. Pharmacological and toxicological studies were then carried out on selected compounds, and clinical and field tests on those which showed the greatest promise. By 1974, of the 26 new drugs or their combinations 11, had undergone full trials and of these several have demonstrated high activity against drug-resistant P. falciparum. The only new alternative antimalarial drug that is in an advanced state of development is mefloquine (Figure 1.4).

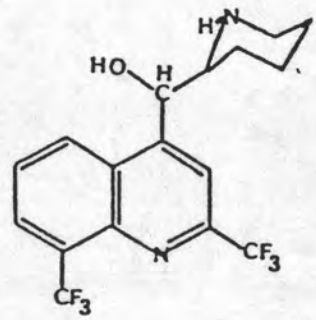

Figure 1.4 Mefloquine

This drug has been shown to be highly active against chloroquine-resistant falciparum starains in experimental animals

and in man, and it is also known to have a long half-life in human. Although mefloquine is by no means ideal, sufficient data are now available to show that it has a place in the treatment of malaria, particularly that caused by chloroquine-resistant Plasmodium falciparum. Even if another new drug were discovered today, it would take many years to bring it to the present status of mefloquine. Thus, it is possible that, in view of the serious situation posed by chloroquine-resistant malaria, mefloquine have been widely introduced despite of some important issues and problems still associated with the drug. This is a matter of grave concern for the successful use of mefloquine in the future. It must be appreciated that the difficulty of trials on cases of human malaria is due to the amount and complexity of preclinical information now required and to the extreme caution needed to carry out.

The history of the chemotherapy of malaria during this century shows the value of close collaboration between fundamental research in academic institutions, applied work carried out by the pharmaceutical industry, and field work in which national and international health authorities are involved. Such collaboration offers the best hope for success in fighting one of the world's oldest, most debilitating and most prevalent tropical diseases.

1.2 General Chemical Structure of Antimalarials

The benzene ring occurs in the molecular structure of all the classical antimalarials. Atoms other than carbon, called heteroatoms, may replace one or more of the carbon atoms of the

benzene ring, the product being called a heterocycle. If a single nitrogen atom replaces one of the carbon atoms of the benzene ring, the product is pyridine, the basis of a number of antimalarial compounds.

Ring systems may be joined in such a way that 2 carbon atoms are common to 2 or more rings. This process is known as ring fusion, and the resulting compound is said to be polycyclic. Fusion of a benzene ring and a pyridine ring in such a way that the 2^{nd} and 3^{rd} atoms of the latter are common to both rings gives quinoline (Figure 1.5). Substitution of a complex group at the 4 position of quinoline gives two of the important cinchona alkaloids, and additional substitution at the 6 position gives the other two important members of this group of alkaliods. Quinoline also is the basis of a number of synthetic antimalarial compounds. Substitution of an amino group at the 4 or the 8 position of quinoline gives 4-aminoquinoline and 8-aminoquinoline respectively, each of which is the basis of an important group of antimalarials.

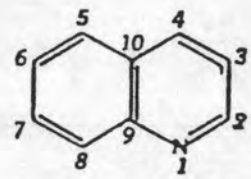

Figure 1.5 quinoline

Fusion of 2 benzene rings and a pyridine ring at the 2,3 and 5,6 positions of the latter produces acridine (Figure 1.6). Substitution of an amino group at the 9 position of the acridine ring

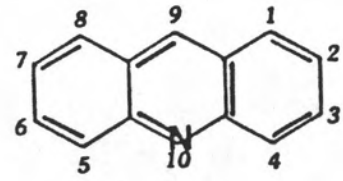

Figure 1.6 Acridine

Phenanthrene (Figure 1.7), another polycyclic compound on which a number of antimalarials are based, is produced by the fusion of 3 benzene rings.

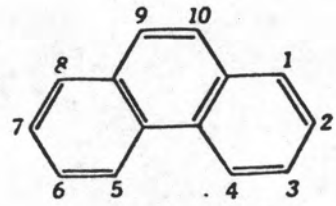

Figure 1.7 Phenanthrene

Finally, there are 3 groups of antimalarials that are based on noncyclic structures. These are the biguanides (Figure 1.8), the sulfones, and the sulfonamides. Two different systems are in use for assigning locants to the biguanide structure, as shown.

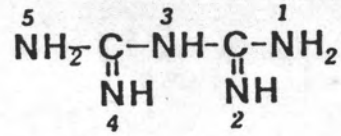

Figure 1.8 Biguanide

Sulfones (Figure 1.9) and sulfonamides (Figure 1.10) contain the groups shown. All antimalarial biguanides, sulfones, and sulfonamides have cyclic substituents that contain the benzene ring.

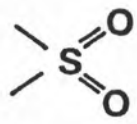

Figure 1.9 Sulfone

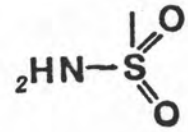

Figure 1.10 Sulfonamide

The presence of a quinoline ring in quinine, coupled with the preservation of schizontocidal activity in 4-aminoquinolines such as chloroquine and 4-aminoquinoline methanol such as mefloquine has led to the inclusion of the quinoline nucleus in the majority of compounds tested for antimalarial activity.

1.3 Quantitative Structure-Activity Relationships in Quantum Pharmacological Studies

Organic chemists and pharmacologists have attempted to relate quantitatively chemical structure and biological activity since before the turn of last century (7,8). Due to the complexity of the factors governing biological interactions such as structural flexibility of enzymes and receptors (9,10), the accompanying conformational changes (9-11),steric factors (12,13), hydrophobic (14-18), electronic interactions (19,20) and the complicated mathematical manipulations necessary to describe such interactions, progress to evaluate meaningful quantitative structure-activity

correlations has been slow. There is yet no panacea for the multiplicity of problems faced by investigators who strive towards making these correlations, but statistical techniques such as regression analysis have provided a method for obtaining approximate predictions of activity. This tool has a variety of uses, including measuring the relationships among variables, predicting one set of variables from another, and assessing the validity of hypotheses (21).

Prerequisites (22) essential to the application of regression analysis to quantitative structure-activity data are that:

(a) the series of compounds to be studied should be closely related analogs (to increase the probability that the mechanism of action of the members of the series under study will be similar)

(b) accurate biological data measured under uniform conditions must be utilized (23).

The mathematical models are those in which the biological activity is expressed as a function of the activity contributions associated with segments of the molecule; the values of these parameters are obtained by fitting the experimentally observed activities of a series of molecules by the method of multiple regression (24).

Hammett's (25) classic book on physical organic chemistry appeared in 1940 can be taken as a turning point in the study of organic reactions, showing the correlation of the electronic effects of substituents on the dynamics of aromatic side chain reactions into numerical terms. Taft (25) made a major advance by showing that

linear free energy relationships could be formulated for electronic and steric effects in aliphatic systems, Brown and his colleagues (26) extended the approach to the broad field of aromatic electrophilic substitution reactions. More recently, the technique has been extended to hydrophobic interactions in biochemical and medicinal chemical systems (27).

Before the general availability of computers, one often spoke of fitting an equation to data. This was a tedious and time-consuming process in which one simply could not consider many possibilities. The situation has changed completely now and one can readily explore hundreds or thousands of possible equations in studying the interrelationship of sets of data. On the frontiers of chemical structure-activity relationships, especially in biological and medicinal chemistry, still little solid theory is at hand on which to build all kinds of empirical ideas. Computerized statistical techniques promise to be of great help in sorting out important structure-activity features which can then be used to form more firmly based theory. Techniques such as pattern recognition (28,29), discriminate analysis (30), cluster analysis (31), molecular shape analysis (32) and regression analysis (33), which have been developed and used heavily outside of chemistry, are now beginning to be used by those working on structure-activity relationships.

Soon after numerical methods of quantum chemistry have become widely accessible to chemists in the sixties, their possible applications in pharmaceutical chemistry gained strong interest of a

large number of research groups. Several attempts at establishing quantitative relations between quantum chemical results and pharmacological data have also been made since that time. The main problem in this regard have been the very simplified calculation methods (e.g. Extended Hueckel) and/or prohibitively high computation costs for the use of more sophisticated quantitative molecular orbital methods in calculations of series of larger molecules. This dilemma was probably one of the reasons, that drug design has concentrated mostly on topological approaches rather than electronic structures. Molecular modelling has since become a most important discipline and is nowadays also supported by high-speed computational graphics. The computational effort for such graphics has almost reached the range of SCF calculations, and this-together with the enormous decrease of computational costs in the eighties-seems to suggest strongly new efforts to evaluate electronic structures of pharmacologically relevant molecules by more appropriate quantum chemical calculation methods. The most logical first approach in such attempts seems to be the comparison of electron density distribution with pharmaceutical activity of drugs, leading to quantitative relations for modelling and planning of new drugs of the same type and giving strong indications towards the nature of the drug's (and its receptor's) active center. The costs for even ab initio calculations of such molecules become by far less than those of synthesis. This seems to be a good reason from the economic view point to encourage efforts in this aspect.

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The present work is to examine relationships between electronic structure and reactivity, including the creation of a correlation equation between both within the framework of a standardized semiempirical MO-SCF method (CNDO/2) (34), using Mulliken's atomic populations (35) as electronic structure data within a series of rather rigid topology, in order to avoid lengthy geometry optimizations. A series of pharmacologically well-tested antimalarial drugs, chloroquine and mefloquine analogs has been chosen, where a large number of strongly varying modifications (side chains, aromatic nucleus substitutions) are known. These drugs deserve special interest due to the acute danger malaria still poses in most tropical countries and due to the rapid resistence of the malaria-causing plasmodia towards new drugs for prevention and therapy. The latter fact urges a continuous search for new antimalarials, which could be well assisted by quantum pharmacological approaches.