CHAPTER 1

History and Introduction

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A. Chemistry

Lesher et al. (1962) showed that 7-chloro-1,4-dihydro-1-ethyl-4-oxoquinoline-3-carboxylic acid, referred to as compound (a), which was obtained as an impurity during the manufacture of chloroquine, possessed antibacterial activity.

\[
\begin{align*}
\text{Cl} & \quad \text{N} & \quad \text{CH}_2\text{CH}_3 \\
\text{O} & \quad \text{COOH} & \quad \text{H} & \quad \text{N} & \quad \text{CH}(\text{CH}_2)_3 & \quad \text{N}(\text{C}_2\text{H}_5)_2
\end{align*}
\]

(a) chloroquine

Consequently many derivatives of compound (a) were synthesized and evaluated for their antibacterial potency.

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{O} & \quad \text{COOH} \\
\text{N} & \quad \text{N} & \quad \text{CH}_2\text{CH}_3
\end{align*}
\]

naldixic acid

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{Naphthyridine} \\
\text{Quinoline}
\end{align*}
\]

Dedication. In memory of J.T. Smith, who died unexpectedly in 1996 during the publication of this book. From the beginnings of quinolones, he made many significant contributions to the understanding of the mechanism of this class of antibacterials. He was a wonderful person to work with and we are grateful to have known him for so many years. We will hold him and his work in high regard.
Ultimately nalidixic acid was chosen as the optimum compound to treat human bacterial infections. Nalidixic acid was patented in 1962 and launched in 1965. It is curious that a naphthyridine became the chosen congener of compound (a) because neither chloroquine nor compound (a) are naphthyridines but rather are quinolines. In later years quinolines proved to be the 4-quinolones of choice rather than naphthyridines.

It is also worth noting that compound (a) is halogenated at the 7-position, while nalidixic acid was not halogenated. The very successful modern 4-quinolone antibacterials are all halogenated at the 6-position and some are halogenated at position 8 as well. It is worth remembering that fluorine at C-6, which is now a common substituent in modern drugs, was first adopted when flumequine was synthesized by the 3M group (Gerster 1973). This was done at their Riker laboratories, where this C-6 position was successfully fluorinated for the first time. It was rumoured that this occurred because 3M had assembled a team of fluorine chemists who so rapidly solved problems associated with the development of other products made by the group that they were asked to try to fluorinate 4-quinolone antibacterials. Flumequine was patented in 1973 and was launched as long ago as 1982. Its previous designation was R 802.

It is also interesting that a compound having another common substituent of modern 4-quinolones, the piperazine group at position 7, was first patented as early as 1974 in pipemidic acid (Matsumoto and Minami 1975); it was synthesized by the Dainippon laboratories and was used clinically for the first time in 1978.

Another curious feature of the 4-quinolone antibacterials is that, as mentioned before, their origin was chloroquine, which was then and still is an effective treatment for malaria. Sarma (1989) accidentally found that norfloxacin cured malaria in patients being treated for *Pseudomonas aeruginosa* infections. It is also worth noting that ICI-56780 is an antimalarial drug about 50 times more potent than chloroquine (Ryley and Peters 1970), and this compound bears more resemblance to the modern 4-quinolone antibacterials than to chloroquine.