Medicinal chemistry of the disease modifying anti-rheumatic drugs

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Introduction

The disease modifying anti-rheumatic drugs (DMARD) and the corticosteroids constitute a great variety of chemical compounds and, as is the case with all drugs, the chemical properties of the DMARD and corticosteroids are important aspects of their pharmacology. In this chapter, the medicinal chemistry of the various DMARD is discussed. The coverage includes the chemical factors that affect their handling by the body. In addition to the DMARD discussed in this book, the chemistry of penicillamine is also described. Although the use of penicillamine as an anti-rheumatic drug has declined in recent years, thiol compounds, such as penicillamine, are still of great interest because of their antioxidant activity and potential activities in inflammatory states.

Antimalarials (chloroquine and hydroxychloroquine)

At least three antimalarial drugs have anti-rheumatic activity in man. The first to be discovered, accidentally, was mepracrine (quinacrine). This drug is no longer used, but the discovery of its anti-rheumatic activity was followed by the successful testing of chloroquine and hydroxychloroquine for the treatment of rheumatoid arthritis (RA) (see the chapter by Bothwell and Furst). Hydroxychloroquine is now generally preferred to chloroquine because of its lesser toxicity.

These two antimalarials are very lipid soluble bases, as is indicated by their octanol/water partition coefficient ($P$) of the un-ionised forms. For chloroquine, the logarithm of the partition coefficient between octanol and water ($\log P$) is 4.72, while the octanol/water partition coefficient of hydroxychloroquine ($\log P = 3.85$) is lower because of hydrogen bonding of water to the hydroxyl group (Fig. 1). It should be noted that the lipid solubility of drugs is usually quoted as the partition between octanol and water because octanol has similar lipid-like characteristics to
The pKa values of hydroxychloroquine are 8.3 and 9.7 [1] and therefore the major form of hydroxychloroquine at pH 7.4 is the di-cation (two positive charges per molecule). The pKa values of quinine are 4.1 and 8.5 [2] and it follows that the mono-cation shown is the major form present at pH 7.4. The chiral centre in hydroxychloroquine is shown (*). There are four chiral centres in quinine, which is only one of the 16 possible isomers.

cell membranes. A high octanol/water partition coefficient, together with a molecular weight in the range of 200–400, is considered to predict ready passive diffusion through cell membranes.

In contrast to most basic drugs, chloroquine and hydroxychloroquine contain two basic nitrogen moieties, which are both highly ionized at pH 7.4 (Fig. 1) [1, 2]. Thus, they are di-cations at physiological pH values. At pH 7.4, the neutral species accounts for less than 0.05% of both antimalarials (Fig. 1). However, the un-ionised forms of both drugs are so lipid soluble that they still partition preferentially into octanol at pH 7.4. Thus, the logarithm of the distribution coefficients between octanol and buffer (log D) for chloroquine and hydroxychloroquine are 0.96 and 0.66 at pH 7.4, respectively (i.e., their partition coefficients are 9.1 and 4.6) [1].