Chapter 11 Quinolines and Isoquinolines

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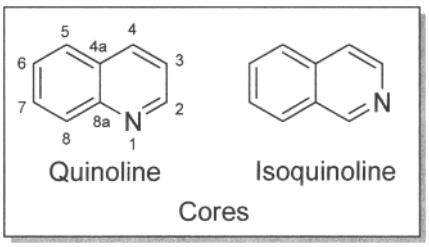
11.1 Introduction

Quinoline and isoquinoline are heterocycles in which a benzene ring and a pyridine ring are fused through carbon. The isomeric heterocycles 1- and 2-azanaphthalene, better known by their trivial names quinoline and isoquinoline, have been the subject of extensive studies since their discovery in the extracts of coal tar at the beginning of nineteenth century. Since then their heterocyclic ring systems were found incorporated in several hundreds of natural products and were used as pharmacophore units in dozens of pharmaceuticals especially anti-bacterials, better known under the general name of "Quinolones".[1]



The quinolines are historically among the most important anti-malarial drugs ever used. Throughout the 20th century, the immense use of chloroquine, the most famous drug of this group, along with quinine, provided well-founded hopes for the eradication of malaria before the World War II.[2] These drugs were followed by newer and more effective anti-malarials by decorating, most commonly C2-, C4- and C8-position of the quinoline core, with appropriate groups. Among them, amodiaquine, which was introduced in 1940, piperaquine in the late 1960s, and mefloquine in 1980, still provide important knowledge for the treatment of resistant malaria parasite of the future.

The chemotherapy of malaria basically involves killing the asexual parasites (hemozoin) and providing supporting therapy to the host to boost its immune system. Although the complete mechanism of action for quinoline anti-malarials is not known, it is believed that these drugs mostly act during the blood stages of the parasite's life cycle.[3] Quinoline drugs act as inhibitors of polymerization of heme in the food vacuole of the parasite, preventing the disposal of the polymers to the cytoplasm where hemozoin is formed.[4,5] This leads to intraparasitic accumulation of free heme, which is highly toxic to the parasite. In addition to heme, several other targets are postulated to