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**1.**

**Aryl aminoalcohol compounds: quinine, quinidine, chloroquine, amodiaquine, mefloquine, , lumefantrine, piperaquine, tafenoquine**

**Mechanism of Action**

The lysosomotropic character of chloroquine is believed to account for much of its antimalarial activity; the drug concentrates in the acidic food vacuole of the parasite and interferes with essential processes. Its lysosomotropic properties further allow for its use for in vitro experiments pertaining to intracellular lipid related diseases,[30][31] autophagy, and apoptosis.[32]

Inside red blood cells, the malarial parasite, which is then in its asexual lifecycle stage, must degrade hemoglobin to acquire essential amino acids, which the parasite requires to construct its own protein and for energy metabolism. Digestion is carried out in a vacuole of the parasitic cell.[citation needed]

Hemoglobin is composed of a protein unit (digested by the parasite) and a heme unit (not used by the parasite). During this process, the parasite releases the toxic and soluble molecule heme. The heme moiety consists of a porphyrin ring called Fe(II)-protoporphyrin IX (FP). To avoid destruction by this molecule, the parasite biocrystallizes heme to form hemozoin, a nontoxic molecule. Hemozoin collects in the digestive vacuole as insoluble crystals.[citation needed]

Chloroquine enters the red blood cell by simple diffusion, inhibiting the parasite cell and digestive vacuole. Chloroquine then becomes protonated (to CQ2+), as the digestive vacuole is known to be acidic (pH 4.7); chloroquine then cannot leave by diffusion. Chloroquine caps hemozoin molecules to prevent further biocrystallization of heme, thus leading to heme buildup. Chloroquine binds to heme (or FP) to form the FP-chloroquine complex; this complex is highly toxic to the cell and disrupts membrane function. Action of the toxic FP-chloroquine and FP results in cell lysis and ultimately parasite cell autodigestion.[33] Parasites that do not form hemozoin are therefore resistant to chloroquine.[34]

Resistance in malaria

**2.**

**Antifolate compounds (“antifols”): pyrimethamine, proguanil, chlorproguanil, trimethoprim**

**Mechanism of action**

Many are primarily DHFR inhibitors, but raltitrexed is an inhibitor of thymidylate synthase, and pemetrexed inhibits both and a third enzyme.

Antifolates act specifically during DNA and RNA synthesis, and thus are cytotoxic during the S-phase of the cell cycle. Thus, they have a greater toxic effect on rapidly dividing cells (such as malignant and myeloid cells, and GI & oral mucosa), which replicate their DNA more frequently, and thus inhibits the growth and proliferation of these non-cancerous cells as well as causing the side-effects listed.

3.

**Artemisinin compounds (artemisinin, dihydroartemisinin, artemether, artesunate)**

**Mechanism of action.**

Artemisinin derivatives are an important new class of antimalarial agents. These compounds contain endoperoxide bridges which are essential for antimalarial activity. Artemisinin is believed to act via a two-step mechanism. Artemisinin is first activated by intraparasitic heme-iron which catalyzes the cleavage of this endoperoxide. A resulting free radical intermediate may then kill the parasite by alkylating and poisoning one or more essential malarial protein(s). No clinically relevant artemisinin-resistant human malaria has yet been reported. However, an artemisinin-resistant strain of murine malaria has been developed and may offer clues to the kinds of resistance that may someday develop in human malarias.