Exploring the Solution Structures of Heme-Quinoline Complexes and their Relation to Antimalarial Activity

Timothy J. Egan[1], Tebogo E. Mabotha[1], Katherine A. De Villiers[1], and Helder M. Marques[2]

[1]*Department of Chemistry, University of Cape Town and* [2]*School of Chemistry, University of the Witwatersrand, Johannesburg, South Africa*

During their pathogenic blood stage, malaria parasites invade host erythrocytes where they digest hemoglobin. In the process, they release large quantities of potentially toxic hematin, which they convert to hemozoin. This is an insoluble microcrystalline product. The quinoline antimalarials, such as chloroquine form complexes with hematin and inhibit the formation of synthetic hemozoin (β-hematin). There is now considerable evidence that this may be their mechanism of biological action. The complexes of quinoline antimalarials with hematin form through interaction of the aromatic ring of the quinoline with the tetrapyrrole of the porphyrin. Recently Leed et al. [1] observed the effect of hematin concentration on the T_1 NMR relaxation of quinoline protons to derive proton-Fe(III) distances that were used in constrained molecular mechanics, molecular dynamics/simulated annealing (MM/MDSA) calculations to successfully derive solution structures of hematin-chloroquine, quinine and quinidine complexes.

Arising from our earlier studies on structure-activity relationships in 4-aminoquinolines with in vitro antimalarial activity [2], we have a unique library of compounds that have varying association strengths with hematin and abilities to inhibit β-hematin formation. T_1 NMR constrained MM/MDSA calculations have been carried out to explore the relationship between structures of 4-aminoquinoline-hematin complexes and their ability to inhibit β-hematin formation. These dynamic structures are very similar, with the quinoline ring lying over the outer part of the porphyrin ring and the 4-amino group usually oriented towards the center. There appears to be little difference between the complexes of quinolines that inhibit β-hematin formation strongly and those that inhibit weakly or not at all. This suggests that such inhibition probably arises from interactions with the crystallite surface, rather than in solution.

[1] A. Leed, K. DuBay, L. M. B. Ursos, D. Sears, A. C. de Dios, P. D. Roepe, Biochemistry 41 (2002) 10245-10255.

[2] T. J. Egan, R. Hunter, C. H. Kaschula, H. M. Marques, A. Misplon, J. C. Walden, J. Med. Chem. 43 (2000) 283-291