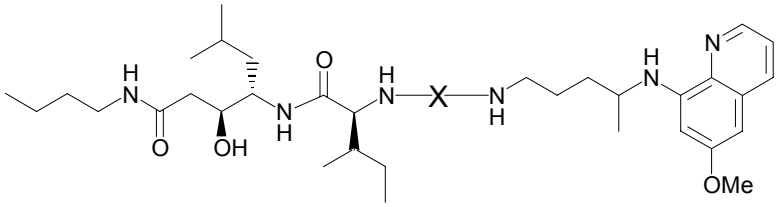
PLASMEPSIN II INHIBITION AND ANTIPLASMODIAL ACTIVITY OF PRIMAQUINE-STATINE "DOUBLE-DRUGS"

Sergio Romeo[a], Silvia Parapini[b], Mario Dell'Agli[c], Luca Rizzi[a], Germana Galli[c], Monica Mondani[b], Nicoletta Basilico[b], Donatella Taramelli[b], Enrica Bosisio[c]

[a]Istituto di Chimica Farmaceutica e Tossicologica
[b]Istituto di Microbiologia, [c]Dipartimento di Scienze Farmacologiche
School of Pharmacy, University of Milan, 20131 Milan, Italy

The diffusion of *Plasmodium falciparum* (*Pf*) strains resistant to traditional drugs is a major health problem, given the high mortality and morbidity rate of malaria in endemic countries. Inhibition of plasmepsin II (PLMII) is considered a valid strategy for the search of new drugs. PLMII inhibitors, including molecules with a statine-based core, have been developed: they possess low Ki values against the enzyme (nM order) but their effectiveness in killing the parasite is limited (IC_{50} range 2-20 μM). [1]
We developed statine-based inhibitors of PLMII with the characteristics of double drugs. [2] Several compounds were synthesized using statine as PLMII inhibitor bound to primaquine by means of different linkers. The compounds were tested *in vitro* for anti-PLMII and antiplasmodial activity against chloroquine-sensitive (D10) and chloroquine-resistent (W2) strains of *Pf*. All compounds inhibited PLMII in a nanomolar range (IC_{50} 0.5-400 nM). When tested for antiplasmodial activity, IC_{50} ranging between 0.2 – 5.0 μM were obtained. In conclusion, the newly synthesized compounds possess anti-PLMII activity greater than the statine-based molecules previously reported. The antiplasmodial activity is significantly improved, as well. A correlation was found between the inhibition of PLMII and the antiplasmodial activity, suggesting that parasite death is due to the inhibition of haemoglobin digestion by PLMII. Systematic modification of the linker indicate that the antiplasmodial activity is linearly correlated with calculated logP.



[1] Boss, C.,Richard-Bildstein, S.,Weller, T.,Fischli, W.,Meyer, S.,Binkert, C. *Current Medicinal Chemistry* **2003***, 10*, 883-907.
[2] Romeo S., Dell'Agli M., Parapini S., Rizzi L., Galli G., Mondani M., Sparatore A., Taramelli D., Bosisio E., *Bioorganic Medicinal Chemistry Letters,* **2004,** *14*, 2931.