Into the Odorous Realm of Isocyanides – Spectroscopic Binding Studies of Potential Antimalarials

Evelyn Fülöp, Lothar Brecker

Department of Organic Chemistry, University of Vienna, Währingerstraße 38-42, 1090 Vienna, Austria

Malaria, one the most threatening diseases, caused by the *Plasmodium* species, still claims many victims. Quinolines and artemisinin-based combination therapies, which can contain quinoline derivatives as partner drugs, are currently used for treatment. [1] These pharmaceuticals are based on the same impact. Before the parasite is able to form the nontoxic hemozoin from lethal free heme (Fe^{3+}), which has derived from digestion of ingested hemoglobin, molecular interaction occurs between the respective drug and heme. However, resistances of *Plasmodia* against these drugs and partner drugs, respectively, were recorded in recent years which requires the development of new potent antimalarials. [2]

Marine diterpene isocyanides have been discovered, showing antimalarial properties, which form complexes with heme through coordinative bonding of the isocyanide moiety to the iron of the porphyrin. This behavior would represent a new mode of action. [3]

Therefore, small artificial isocyanide derivatives were prepared to examine their binding type with heme. For this purpose, nine different amines were converted to the corresponding formamides, which were then dehydrated to the desired products. The interaction studies were conducted via NMR-, UV-Vis and IR- spectroscopy as well as mass spectrometry. Indeed, two 1:1 complexes of heme with different isocyanides could be verified.

[1] Hopkins Sibley, C.; J. Infect. Dis., **2015**, *211*, 667-669.

[2] Kumar, S., Guha, M., Choubey, V., Maity, P., Bandyopadhyay, U.; Life Sci., **2007**, *80*, 813-828.

[3] Wright, A., Wang, H., Gurrath, M., König, G. M., Kocak, G., Neumann, G., Loria, P., Foley M., Tilley, L.; J. Med. Chem.; **2001**, *44*, 873-885.