A223 Antitrypanosomal and antileishmanial activity of acylated triterpenoid saponins from *Maesa lanceolata*

S. Apers, S. van Miert, A. Vlietinck and L. Pieters
Department of Pharmaceutical Sciences, University of Antwerp, Universiteitsplein 1, B-2610 Antwerp, Belgium.

Ten acylated triterpenoid saponins were obtained by semi-preparative HPLC from a biologically active saponin mixture from leaves of *Maesa lanceolata* Forsskal var. *gonlungensis* Welw. (Myrsinaceae), which is used in Rwandan and East African traditional medicine. Their antiviral, haemolytic, molluscicidal and antiangiogenic activity has been reported before (1). In addition their antitrypanosomal and antileishmanial activity was evaluated and structure-activity relationships established.

Antitrypanosomal activity: Bloodstream forms of *T. brucei* were cultivated in HMI-9 medium in a 96-well microplate. Test compounds were added, and after 4 days IC_{50} values were determined. Parasite multiplication was measured colorimetrically (490 nm) following addition of MTT, which converts to an aqueous soluble formazan product.

Antileishmanial activity: An *in vitro* method against intracellular *Leishmania donovani* amastigotes was used, in which primary mouse peritoneal macrophages were seeded, incubated for 24 h and infected, followed by addition of the test compound. After incubation for 7 days, the drug activity was semiquantitatively scored as a percent reduction of the total parasite load, and the scoring was performed microscopically (2).

All the maesasaponins tested showed antitrypanosomal activity in the micromolar range. Maesasaponin VI2, a diester (3β-O-{α-L-rhamnosyl-(1→2)-β-D-galactosyl-(1→3)]-[β-D-galactosyl-(1→2)]-β-D-glucuronyl}-21β,22α-diangeloyl-oxy-13β,28-epoxy-olean-16α,28α-diol), the most potent molluscicidal compound, also showed the highest anti-trypanosomal activity, with an IC_{50} of 0.3 ± 0.1 µM, and the corresponding 21β-angeloyl, 22α-propanoyl diester (maesasaponin IV_3) showed an IC_{50} of 0.6 ± 0.3 µM. Some of the maesasaponins also exhibited antileishmanial activity in the micromolar range, although most compounds also were toxic to the macrophages used in the *in vitro* assay.

Acknowledgements: Antitrypanosomal and antileishmanial evaluation was performed at Tibotec-Virco NV, Mechelen, Belgium. S. Apers is a postdoctoral fellow of the Fund for Scientific Research (Flanders – Belgium).

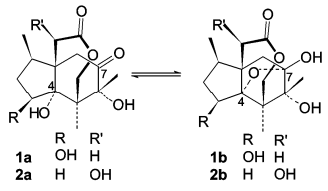
References: 1. Apers, S. et al. (2001) Planta Med. 67: 528–532. **2.** Girault, S. et al. (2000) J. Med. Chem. 43: 2646-2654.

A224 Bioactive isomers of GABA antagonistic insecticidal sesquiterpenes of the pseudoanisatin type from *Illicium* species and QSAR based on pseudoreceptor modelling

T.J. Schmidt [a] *and M. Gurrath* [b]
[a] Institut für Pharmazeutische Biologie, [b] Institut für Pharmazeutische Chemie; Heinrich-Heine-Universität Düsseldorf, Universitätsstrasse 1, Geb. 26.23, D-40225 Düsseldorf, Germany.

The *seco*-prezizaane type sesquiterpene lactones pseudoanisatin **1** and parviflorolide **2** from *Illicium* species were recently found to be potent non-competitive antagonists at *Musca domestica* γ-aminobutyric acid (GABA) receptors (1). As opposed to the convulsants anisatin and veranisatin, belonging to the same type of natural products but showing considerable toxicity to insects and mammals, these two compounds are non-toxic to mammals and showed high selectivity towards the insect receptor. They thus represent a new type of leads towards selective insecticides (1).

Both compounds were shown to exist in equilibria of the 4-hydroxy-7-oxo- (**1a**, **2a**) and cyclic 4,7-hemiketal structure (**1b**, **2b**) (2). We have now investigated by proton NMR spectroscopy the solvent-dependence of these equilibria. In acetone-d_6, a ratio of 79:21 for **1a** : **1b** and of 22:78 for **2a** : **2b** was found. Measurements in D_2O solution showed dramatic (but fully reversible) changes. Here, the 4-hydroxy-7-oxo form (**1a**, **2a**) constitutes 53 and 8 % showing a stabilizing effect of aqueous environment on the hemiketal form in both cases.



The difference in receptor affinity between **1** and **2** [IC_{50} 0.38 and 2.12 µM, resp. (1)] can be explained by the different equilibrium concentrations, assuming that the hemiketal form is inactive in both cases. Almost identical IC_{50} values of 0.177 and 0.175 µM are calculated for the ketoalcohol forms, **1a** and **2a**, which are therefore likely to represent the bioactive isomers.

Biological data for 13 *seco*-prezizaane and 17 picrotoxane and picrodendrane type terpenoids with respect to their specific binding to housefly GABA receptors (1) were analysed in a 3D-QSAR study by quasi-atomistic pseudoreceptor modelling using the program Quasar (3), which resulted in a QSAR model of high internal and reasonable external predicitivity. The pseudoreceptor model gives valuable information with respect to lead structure optimization.

References: 1. Kuriyama, T. et al. (2002) Bioorg. Med. Chem. 10: 1873. **2.** Schmidt, T.J. (1999) J. Nat. Prod. 62: 684. **3.** Vedani, A. et al. (1998) J. Amer. Chem. Soc. 120: 4471.