Design, synthesis and anthelmintic activity of 7-keto-sempervirol analogues

Alessandra Crusco [a,b], Andrew D. Westwell [b] and Karl F. Hoffmann [a]

[a] Institute of Biological, Environmental and Rural Sciences (IBERS), Penglais Campus, Aberystwyth University, Aberystwyth SY23 3DA, United Kingdom

[b] School of Pharmacy and Pharmaceutical Sciences, Cardiff University, Cardiff CF10 3NB, United Kingdom

Abstract

The plant-derived, diterpenoid 7-keto-sempervirol was recently reported to display moderate activity against larval stages of *Schistosoma mansoni* (IC_{50} = 19.1 μM) and *Fasciola hepatica* (IC_{50} = 17.7 μM). These related parasitic blood and liver flukes are responsible for the neglected tropical diseases schistosomiasis and fascioliasis respectively. As both diseases are predominantly controlled by single-class chemotherapies, praziquantel for schistosomiasis and triclabendazole for fascioliasis, the discovery of new anti-flukicidal drugs is imperative should parasite resistance against the current drugs develop. In this study, we aimed to increase the potency of 7-keto-sempervirol by total synthesis of 30 structural analogues. Subsequent screening of these new diterpenoids against juvenile and adult lifecycle stages of both parasites as well as the human HepG2 liver cell line and the bovine MDBK kidney cell line revealed structure-activity relationship trends. The most active analogue, **7d**, displayed improved dual anthelmintic activity over 7-keto-sempervirol (IC_{50} ≈ 6 μM for larval blood flukes; IC_{50} ≈ 3 μM for juvenile liver flukes) and moderate selectivity (SI ≈ 4 - 5 for blood flukes, 8 - 13 for liver flukes compared to HepG2 and MDBK cells respectively). Phenotypic studies using scanning electron microscopy revealed substantial tegumental alterations in both helminth species, supporting the hypothesis that the parasite surface is one of the main targets of this chemical family. Further modifications of **7d** could lead to greater potency and selectivity metrics resulting in a new class of broad-spectrum anthelmintic.