Amino ozonides exhibit in vitro activity against Echinococcus multilocularis metacestodes

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Artemisinin is an antimalarial sesquiterpene lactone that contains a 1,2,4-trioxane heterocycle. Dihydroartemisinin and artesunate demonstrated activity against Echinococcus multilocularis metacestodes in vitro but were not effective in a mouse model. In this study, the in vitro effects of a small library of synthetic ozonides (1,2,4-trioxolanes) were investigated. Initial compound screening against E. multilocularis metacestodes was performed at 20μM, and selected ozonides were further assessed in dose-response studies in metacestode cultures and mammalian cells. Transmission electron microscopy (TEM) was employed to characterise compound-induced structural alterations. At 20μM, the most potent ozonides (OZ401, OZ455, OZ491 and OZ494) led to death of ca. 60-100% of the parasites. Subsequent dose-response experiments demonstrated that OZ401, OZ455 and OZ491, which contain an aminopropylether substructure, were the most potent, with 50% inhibitory concentrations ranging from 11μM to 14μM. Cytotoxicity for these three ozonides, assessed in human foreskin fibroblasts, rat hepatoma cells and green monkey epithelial kidney (Vero) cells, was evident only at high concentrations. TEM demonstrated that OZ401 and OZ491 treatment induced considerable metabolic impairment in metacestodes at 1 day post exposure. At Day 3 post exposure, the germinal layer was severely distorted, although some intact cells were still visible, demonstrating that not all cell types in the parasite tissue were equally affected. Complete destruction of the germinal layer was noted at 5 days post exposure. Synthetic ozonides could represent interesting leads that will be further investigated in a suitable in vivo model of E. multilocularis infection.

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