Deazapurine nucleoside analogues for the treatment of *Trichomonas vaginalis*

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Trichomoniasis is an important sexually transmitted infection, caused by the human-only protozoan parasite *Trichomonas vaginalis*. Treatment of this disease is essentially by metronidazole although in recent years the related nitro-heterocyclic compound tinidazole is also increasingly used. However, resistance to either drug implies cross0resistance to the other, owing to their identical mechanism of action. In an effort to identify new anti-trichomonal treatments, we scaled-up our resorufin based fluorescence assay for medium throughput, using 386-well plates, automated liquid handling and improved micro-aerobic incubation conditions. A number of compound series were screened and a series of 7-deaza-7-substituted adenosine analogues displayed by far the most promising activity ibn vitro. The structure activity relationship was systematically explored through the synthesis of additional nucleoside analogues and the most promising lead, TH1012 displayed an E_{C50} of 0.035 ± 0.007 µM compared to an EC_{50} ~0.3 µM for metronidazole. Fluorescence microscopy with DAPI revealed that TH1012 disrupted proper nuclear division n trophozoites while growth curves showed almost immediate action on cell density in culture. TH1012 was curative in a mouse model of Tritrichomonas foetus, applied topically, despite being much less active against this species *in vitro*. We believe that these adenosine analogues have genuine promise as anti-trichomonal agents and are currently studying *T. vaginalis* adenosine transporters and attempting to create a TH1012-resistant cell line for studies of the mechanism of action.