Distamycin A derivatives: a new class of minor groove binders for the treatment of animal trypanosomiasis.

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Animal trypanosomiasis (Nagana) is one of the most important diseases of livestock in Africa, causing annual losses of billions of US$ and hampering agricultural production and animal husbandry. The disease is caused by tsetse-transmitted protozoa *Trypanosoma congolense*, *T. vivax* and *T. brucei brucei*. Control mainly relies on treatment with diminazene (for cure) and isometamidium (for prophylaxis). However, spreading resistance to these drugs is putting their future efficacy at risk. After decades of neglect, there is today renewed interest in developing new treatments for Nagana.

A library screen of a series of minor groove binders (S-MGBs) developed in our laboratories identified a number of hits against *Trypanosoma congolense* and *T. b. brucei.* The compounds are derivatives of distamycin A with proven antimicrobial activity. The S-MGBs concentrate within the nucleus and kinetoplast of the parasites, where they are expected to exert their action. Members of the diamidine class of drugs are also minor groove binders, however, there is no indication of cross-resistance between the S-MGBs and the diamidine diminazene, possibly due to different mechanisms of uptake or DNA binding specificity. Further work will focus on lead optimisation and study of the MOA of these S-MGBs.