Antiprotozoal activity and DNA binding of dicationic acridones

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Dicationic acridone derivatives were synthesized and their antiparasitic activity was evaluated. Acridones displayed in vitro nanomolar IC50 values against Trypanosoma brucei rhodesiense STIB900 with selectivity indices <1000. Compounds 1b, 3a, and 3b were as potent as the reference drug melarsoprol in this assay. Submicromolar-range activities were observed against wild-type (NF54) and resistant (K1) strains of Plasmodium falciparum, whereas no significant activity was detected against Trypanosoma cruzi or Leishmania donovani. Compounds 1a and 1b were curative in the STIB900 mouse model for human African trypanosomiasis. UV spectrophotometric titrations and circular dichroism (CD) experiments with fish sperm (FS) DNA showed that these compounds form complexes with DNA with binding affinities in the 10(4) M(-1) range. Biological and biophysical data show that antiparasitic activity, toxicity, and DNA binding of this series of acridones are dependent on the relative position of both imidazolinium cations on the heterocyclic scaffold.

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