Halogen scan study of a bisimidazoline DNA minor groove binder that targets the kinetoplast of Trypanosoma brucei

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Abstract:
The parasite Trypanosoma brucei, ethiological agent of sleeping sickness, contains a kinetoplast with the mitochondrial DNA (kDNA) comprising of >70% AT base pairs. Hence, DNA minor groove binding molecules represent an important class of anti-trypansomal agents. Diphenoxy-based bis(2-imidazolidinelines) are promising DNA minor groove binders that are curative in mouse models of stage 1 African trypanosomiasis but devoid of activity in the late-stage disease, possibly due to poor brain penetration caused by their dicatic nature.

As a strategy to reduce the pKₐ of the bis-2-imidazolidinelines groups, halogen atoms (Cl, F) were introduced in the structure of lead compound 1 [1]. The pKₐ of the new compounds was determined by UV-metric and pH-metric methods. A reduction of 1–2 pKₐ units for the imidazoline group linked to the substituted phenyl ring was observed [1,2].

In vitro activities (EC₅₀) against wild type and resistant strains of T. b. brucei were in the submicromolar range with four compounds being more active and selective than 1 (m=340) [3]. The 3-chloro substituted derivative 17 was curative in vivo in a mouse model of stage 1 infection by T. b. rhodesiensis.

To identify their cellular target inside the parasite a mechanistic study was performed. Altogether, our results show that 1 and 17 share the same mechanism of action against T. brucei, acting specifically on the integrity of the kinetoplast by altering the structure and replication of kDNA [4]. Surface plasmon resonance (SPR)-biosensor experiments show that the drug can displace IMS low-binding proteins essential for kDNA binding sites. The crystal structure of the complex of the di(dAAATT)₃ oligonucleotide with 1 and 17 showed that the drugs cover the minor grooves of DNA, displace bound water and interact with neighbouring DNA molecules, as cross-linking agents [4].

Lead compound

Abstract: