Derivatives of guanidine-based DNA minor groove binders as antiprotozoal agents

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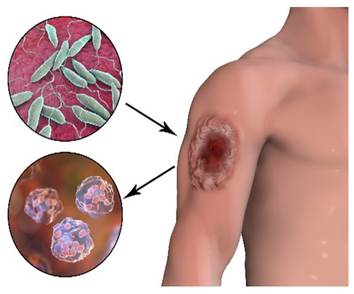
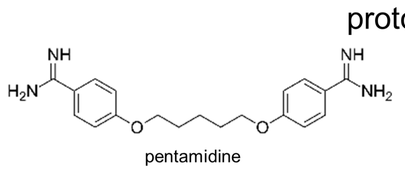
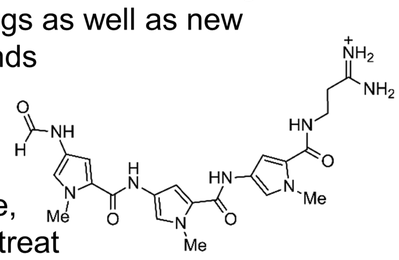
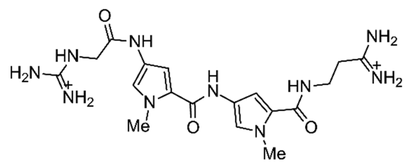
Introduction

Parasitic infectious diseases such as malaria, human African trypanosomiasis (HAT) and leishmaniasis are a major concern in developing countries. According to the WHO, in 2018, there were 228 million cases of malaria with death rates reaching 405,000.[1] In addition, in sub-Saharan Africa, HAT has a risk population of 65 million people and almost 1 million annual cases of leishmaniasis exist.[2] Current standard of care for malaria includes drugs such as quinolones (e.g. chloroquine), anti-folates (e.g. pyrimethamine) or artemisinin. However, because emergence of multi-drug resistant protozoans, the identification of new drugs as well as new therapeutic targets is needed. Compounds that bind into the DNA minor-groove (MGBs) are very promising for the treatment of diseases at the DNA level. Accordingly, MGBs such as pentamidine, distamycin-A and netropsin are used to treat parasitic diseases.[1,2]



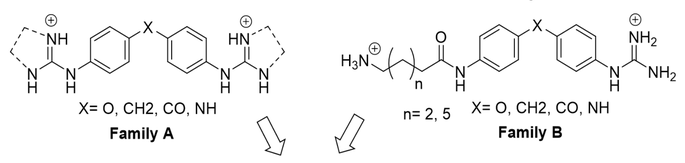




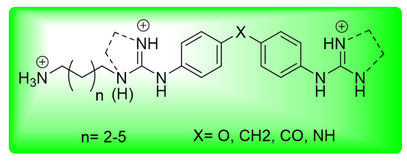


Objectives

Our lab has prepared a large number of symmetric and asymmetric dications that are strong MGBs.[3,5] Recently, a series of amino alkyl derivatives of di-aromatic guanidines with very promising anti-malarial activity were reported by us.[4] Based on these results, a novel series of amino-alkyl derivatives were designed. Hence, our objective is to computationally and biophysically study the interaction of these molecules with DNA and assess their ability as anti-protozoal agents.

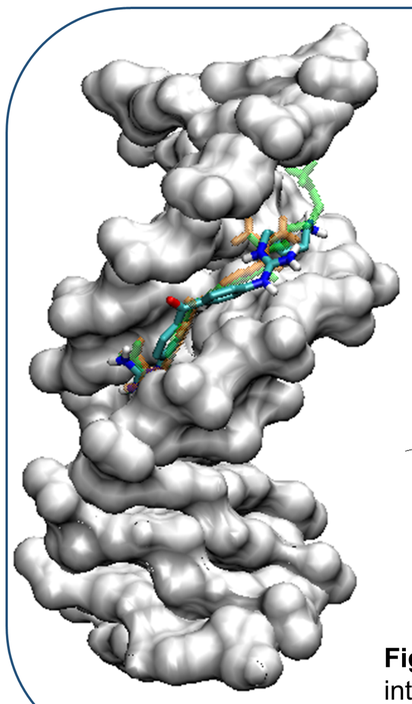


Objective: MGBs with antiprotozoal activity



Novel aminoalkyl derivatives of diaryl bisguanidine/2-aminoimidazolines

Molecular Modelling



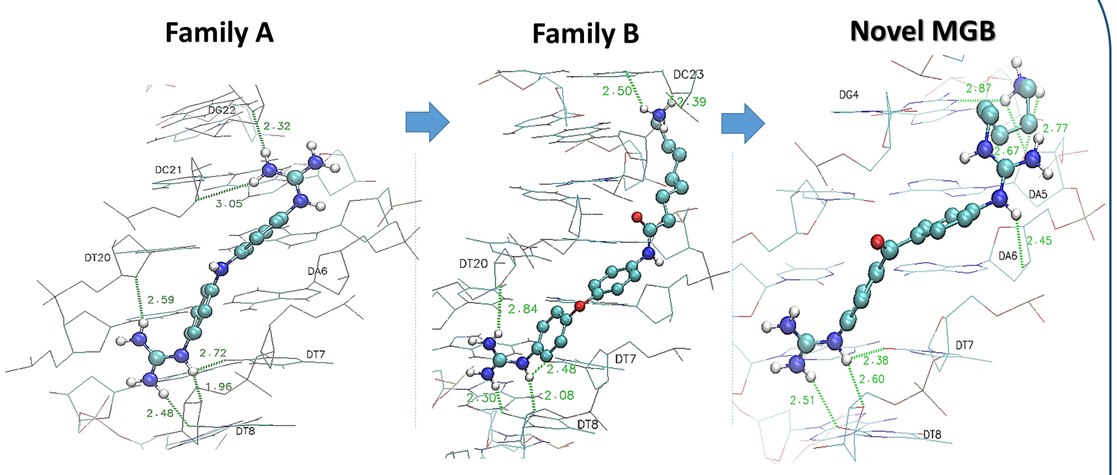
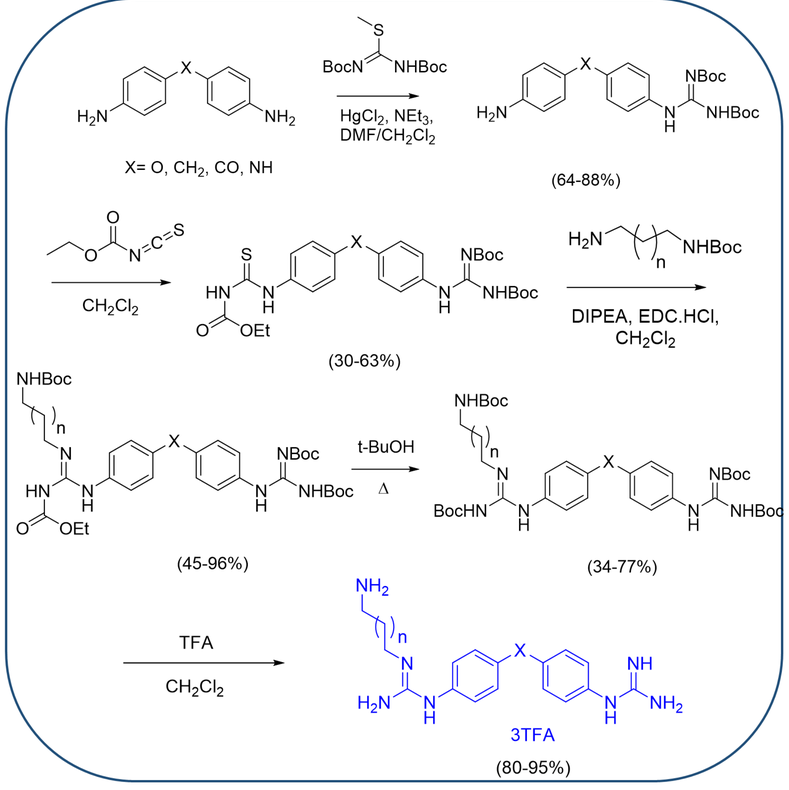


Fig1. Docking of previous Family A+B and novel series of aminoalkyl derivatives into the minor groove of DNA. Ligands were optimized using DFT (M06-2X/6-31+G) and docking was conducted using AutoDock Vina

Synthesis



Biophysical Analysis

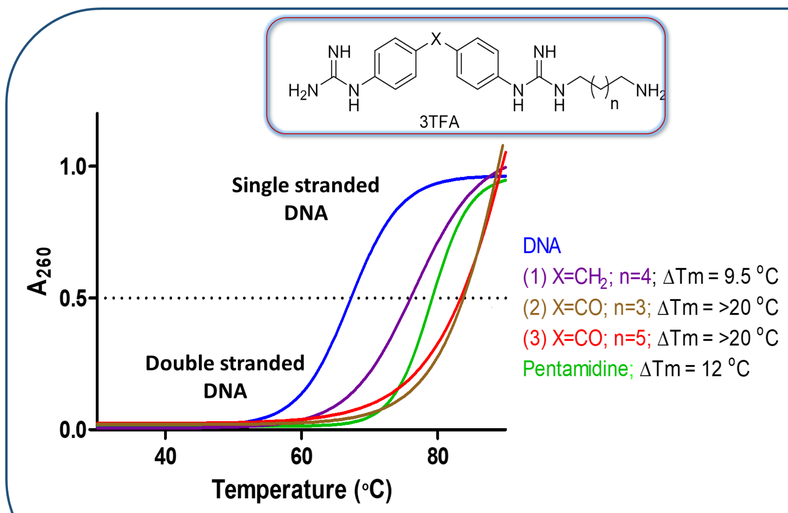


Fig2. UV-Thermal melting curves for novel guanidinoalkyl derivatives using salmon sperm DNA

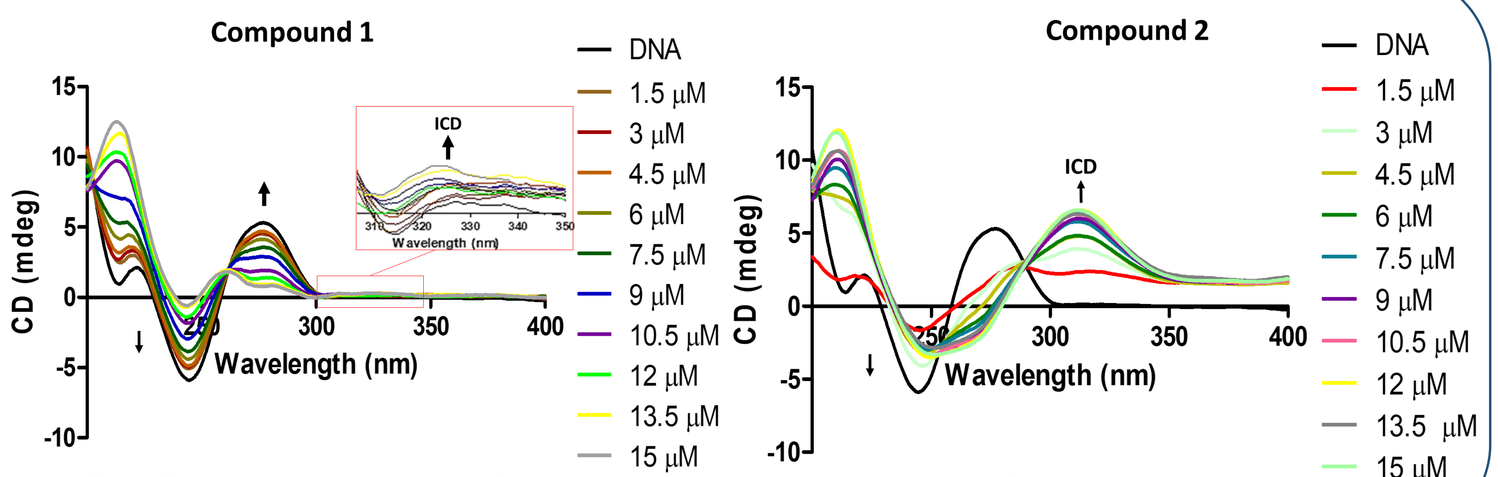


Fig3. Circular dichroism spectra of compounds 1 and 2 using salmon sperm DNA and indicating the induced signal (ICD)

References

1. http://www.who.int/malaria/publications/world-malaria-report-2019/en/
2. http://www.who.int/mediacentre/factsheets/fs259/en/ & /leishmaniasis/publications/en
3. Rodriguez, F.; Rozas, I.; Kaiser, M.; Brun, R.; Nguyen, B.; Wilson, W. D.; Garcia, R. N.; Dardonville, C., J. Med. Chem., 2008, 51, 909–923
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Acknowledgements

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Conclusion and Outlook

A series of mono- and di-aromatic guanidine based derivatives targeting *T. b. rhodesiense* and *P. falciparum* have been previously reported by our group. Strong DNA minor groove binding and correlation of early derivatives with selective anti-parasitic activity indicated a potential mechanism for their anti-trypanosomal action. Based on aforementioned findings, a novel series of derivatives were designed by combining structural features of previously produced families. With this new family, attachment of the aminoalkyl chain to the guanidine-like cation serves to introduce an additional positive charge and added hydrophobicity. Molecular docking studies have shown that derivatives among this family with more planar linkers such as CO and NH and those with longer alkyl chains possess better DNA binding. This is reinforced in our UV-thermal melting and circular dichroism studies which show strong DNA binding with groove binding specificity. Given the positive results obtained from these novel series of compounds, their *in vitro* anti-parasitic activity will be studied to asses their ability as potential antiprotozoal agents.

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