First Total Synthesis of Aerucyclamide B and Macrocycle Analogs as Antimalarial and Anti-Trypanosomal Agents

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INTRODUCTION

Human African Trypanosomiasis (HAT) and malaria are neglected tropical diseases caused by *Trypanosome* and *Plasmodium* parasites respectively. Globally, an estimated 3.3 billion people were at risk of malaria in 2011 and 60 million people of HAT in 2009.[1]

Aerucyclamides A, B, C and D (Figure 1) were isolated from the cyanobacteria *Microcystis aeruginosa* PCC 7806 by Gademann and co-workers.[2] Aerucyclamide B, displays potent and selective antiplasmodial activity against *P. falciparum* k_1 (IC_{50} = 0.7µM) and aerucyclamide C is the most active against *T. brucei rhodesiense* (IC_{50} = 9.2 µM).

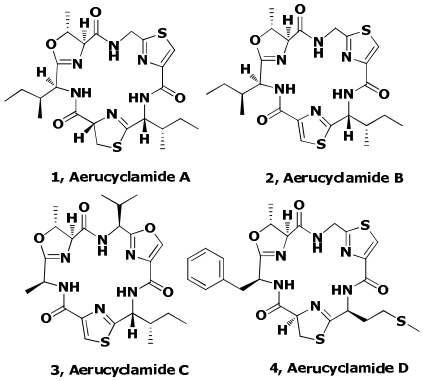

Figure 1. Aerucyclamides

As part of our search for antiparasitic agents,[3] in the present work we report the total synthesis of Aerucyclamide B[4] and the synthesis of antiparasitic cyclohexapeptides analogs. Some of the obtained products show enhanced activity compared with aerucyclamides.

RESULTS AND DISCUSSION

Aeruciclamide B was prepared by a convergent macrocycle assembly methodology, starting from two thiazoles and a dipeptide as building blocks. The last step of our route was the cyclodehydration reaction of the β-hydroxyamide, to obtain the oxazoline ring.

The open precursors of the hexacyclopeptides analogs were obtained by solid phase peptide synthesis (SPPS), Figure 2. The macrocyclization reaction was carried out in solution phase.

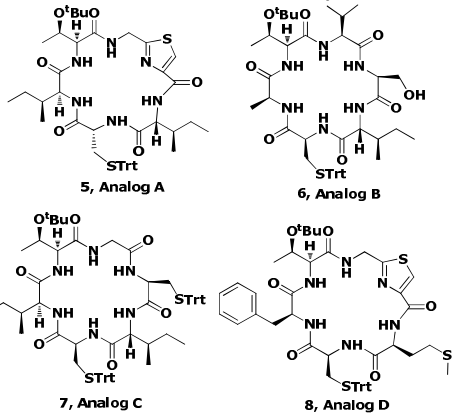

Figure 2. Synthesized analogs

The activities of the obtained compounds against *P. falciparum k1, T. brucei brucei* and the cytotoxicities on murine macrophages (cell line J774) were evaluated.

CONCLUSION

The first total synthesis of the antimalarial natural aerucyclamide B has been achieved in 9% overall yield. Four macrocycles analogues were obtained in good yield. The biological evaluation against *P. falciparum* and *T. brucei brucei* rendered promising results. The compounds present good selectivity for the parasites than murine macrophages.

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