Synthesis of a new highly fluorescent HDAC inhibitor against *Toxoplasma gondii*

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Palavras Chave: *cyclic tetrapeptide synthesis, HDAC inhibitor.*

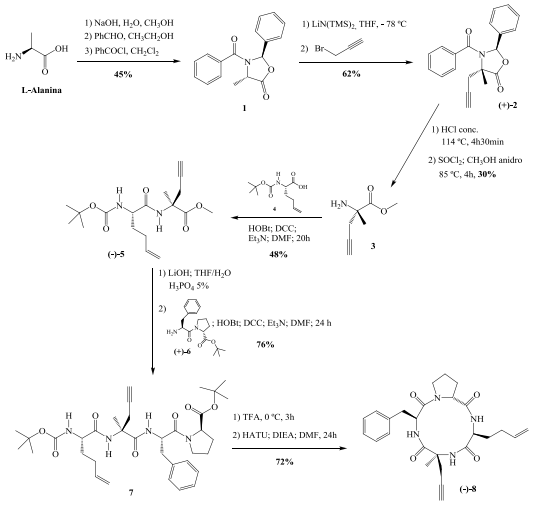
Introduction

Recently, the natural product cyclic tetrapeptide FR235222 was identified as a highly potent histone deacetylase inhibitor (HDACi), efficient at 10 nM on *Toxoplasma gondii*, the apicomplexa parasite responsible for toxoplasmosis.[1] Histone deacetylases (HDACs) play an important role in the regulation of the dynamic equilibrium of the chromatin, which is associated with gene expression regulation.[1] The inhibition of HDAC3 by FR235222 induced epigenetic modifications, which strongly affected strain virulence at the tachyzoite and bradyzoite (cystic) stages of the *Toxoplasma gondii* life cycle.[1,2] This dual efficiency with a bioactive molecule on two distinct stages of the parasitic life cycle is unprecedented and outlines the key potential of targeting the epigenetic mechanisms to control parasite proliferation. Synthetic analogs of FR235222 with improved potency have recently been obtained by our research group.[3]

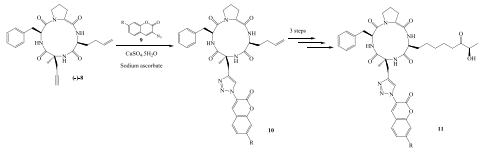
The aim of this work is the synthesis of a new fluorescent HDACi, analog of FR235222, to identify the cell penetration mechanism and quantify the penetration of HDACi on tachyzoite and bradyzoite (cystic) forms of the *Toxoplasma gondii*.

Results and Discussion

For the synthesis of the new fluorescent HDACi, the novel cyclic tetrapeptide **(-)-8** was obtained by convergent synthesis from dipeptides **(+)-6**[3] and **(-)-5**. This latter is novel and was synthesized from amino acids **4**[3] and *L*-alanine (**Scheme 1**). The cyclic tetrapeptide **(-)-8** is a key intermediate once it has a double and a triple bond which allow quick access to a large number of new diversely functionalized analogs. From this cyclic tetrapeptide, the new fluorescent HDACi **11** was obtained (**Scheme 2**) and the key step for the synthesis was click reaction.



Scheme 1. Synthesis of the cyclic tetrapeptide **(-)-8**.



Scheme 2. Synthesis of HDACi **11** from **(-)-8**.

Conclusions

In the present work, we report the synthesis of a new fluorescent analog of FR235222 to be used as a probe to unravel epigenetic mechanisms on *Toxoplasma gondii*.

Acknowledgments

CAPES, FAPEMIG, CNPQ, DQ/ UFMG, DPM/ UJF.

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