Design and Synthesis of Novel Peptide Conjugates: Piperine Tagged to the Fibronectin Receptor of *Trypanosoma cruzi*

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Abstract

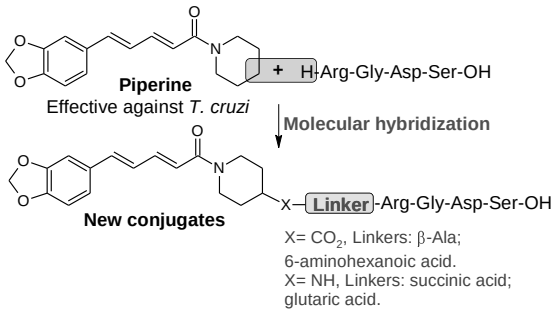
Design and synthesis of a series of novel piperine-peptide conjugates that binds on *Trypanosoma cruzi* cell surface have been discussed.

Introduction

Chagas' disease (American Trypanosomiasis) is a zoonosis caused by the protozoan *Trypanosoma cruzi* (Kinetoplastida: Trypanosomatidae). This parasitic infection is recognized by WHO as one of the thirteen most neglected diseases in the World.[1] There are only two drugs for the treatment of chagasic patients: the nitro-heterocyclic derivatives benznidazole and nifurtimox. However, none of them meets the criteria (i.e. parasitical cure both in acute as well as in chronic phase of the infection and reduced side effects) required to be an optimal drug to treat this illness.

Recently, we reported the trypanocidal effects of the natural amide piperine and its derivatives. Ouassi reported in 1986 that the presence of a fibronectin receptor (FNR) on the parasite`s cell membrane can recognize the peptidic sequence RGDS.[3] Despite the importance of this finding for the development of more selective drugs for the treatment of Chagas' disease, this information has never been exploited so far. Herein, we have taken a novel approach of combining these two chemical structures in a single molecule to achieve our goal in obtaining active and more selective molecules against *T. cruzi*.

Results & Discussion



Scheme 1. Design of novel piperine-peptide conjugates

A known trypanocidal natural product i.e. piperine and the tetrapeptide (Arg-Gly-Asp-Ser-OH) have been taken as reference for the design of our conjugates (**Scheme 1**). Piperine was extracted from powdered black pepper (*Piper nigrum*, Piperaceae) in 3-7% yield.[2] The derivatives having the suitable X-anchors in the piperidine ring (**Scheme 1)** were prepared from the reaction of piperic acid chloride and the suitable substituted piperidines.

Six conjugates with different types of spacers having different lengths were designed in order to examine the impact of spacer and its length. The piperine-peptide conjugates were prepared in solid phase employing Fmoc/^{t}Bu approach using 2-chlorotrityl chloride resin as a solid support. The steps of coupling and deprotection were confirmed by Kaiser Test. The final molecules were detached from the resin using TFA 1% in DCM and the deprotection of the side chains were achieved by using 0.1N HCl in HFIP.[4] The piperine derivatives were fully characterized by ^{1}H-NMR, ^{13}C-NMR and HRMS. The six new piperine-RGDS conjugates were characterized by HRMS.

The initial *in vitro* biological assays with the tetrapeptide (RGDS) and one of the derivatives (piperine-X directly linked to RGDS, **Scheme 1**) conducted against *T. cruzi* epimastigotes (Y strain) showed no toxic effects against epimastigotes. Studies with other conjugates are in progress.

Conclusions

A class of novel conjugates were designed and synthesized by combining the trypanocidal piperine and RGDS via linker. The approach developed herein is being used in the synthesis of a series of benznidazole-RGDS conjugates. The biological assays against *T. cruzi* trypomatigotes are in progress.

Aknowledments

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