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Evaluation of dipeptide nitriles as inhibitors of rhodesain, a major cysteine protease of *Trypanosoma brucei*

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ABSTRACT

A series of dipeptide nitriles known as inhibitors of mammalian cathepsins were evaluated for inhibition of rhodesain, the cathepsin L-like protease of *Trypanosoma brucei*. Compound **35** consisting of a Leu residue fitting into the S2 pocket and a triarylic moiety consisting of thiophene, a 1,2,4-oxadiazole and a phenyl ring fitting into the S3 pocket, and compound **33** with a 3-bromo-Phe residue (S2) and a biphenyl fragment (S3) were found to inhibit rhodesain in the single-digit nanomolar range. The observed steep structure-activity relationship could be explained by covalent docking simulations. With their high selectivity indices (ca. 200) and the good antitrypanosomal activity (8 µM) the compounds represent promising starting points for new rhodesain inhibitors.

Keywords:
Dipeptide nitrile
Cysteine protease
Rhodesain
Inhibitor
Trypanosoma

The cysteine protease rhodesain of the parasite *Trypanosoma brucei* which causes the human African trypanosomiasis (HAT, African sleeping sickness) is considered a target for new antitrypanosomal drugs due to its role in the parasite's iron homeostasis[1] and the parasite's ability to cross the blood-brain barrier.[2] Peptidic nitriles have widely been evaluated as inhibitors of cysteine cathepsins,[3,4,5,6,7] which are the human analogs of rhodesain, and non-peptidic nitriles have been shown to be excellent inhibitors of rhodesain and cathepsins.[8,9,10,11,12] In the latter case, the selectivity was successively optimized based on X-ray crystallographic studies of enzyme-inhibitor complexes and docking studies.[11] The nitrile group has been shown to function as an electrophilic warhead which undergoes a reversible addition reaction with the nucleophilic Cys residue of the cysteine protease yielding a thioimidate.[13,14,15,16]

In the present study, we evaluated the potency and selectivity of a series of known dipeptide nitrile-based cysteine cathepsin inhibitors (Table 1) as new inhibitors of rhodesain in order to gain insights into the structure-activity and structure-selectivity relationships. A special focus was put onto the substituents binding into the S2 (Xaa in Figure 1) and S3 (CG in Figure 1) pockets since previous studies on rhodesain and cathepsin L showed that variations of the substituents for the S1 pocket had only weak effects on affinity and selectivity.[11] The most active compounds were also analyzed for their antitrypanosomal activity (Table 3) by applying a previously described method.[17] The synthesis of compounds derived from the general structure shown in Figure 1 has already been published.[3,18,19,20,21,22,23]

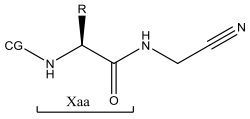

Figure 1. General structure of dipeptide nitriles. For "Xaa" and "CG"(capping group), see Table 1.

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