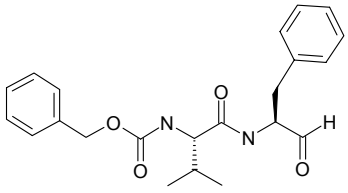
# CALPAIN INHIBITORS AS POTENTIAL DRUG CANDIDATES FOR THE TREATMENT OF DUCHENNE MUSCULAR DYSTROPHY

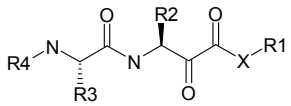
Cyrille Lescop[a], Hervé Siendt[a], Reto Bolliger[a], Marco Henneböhle[a], Holger Herzner[a], Philipp Weyermann[a], Andreas von Sprecher[a], Mark Foster[b], Isabelle Courdier-Fruh[b], Michael Erb[b], Alexandre Briguet[b] and Josef P. Magyar[b]

[a]Medicinal Chemistry Department and [b]Biology Department, Santhera Pharmaceuticals AG, Hammerstrasse 25, CH-4410 Liestal, Switzerland

Calpain I and II are calcium-dependent cytosolic cystein proteases which are widely distributed in mammalian cells. They hydrolyze physiologically important proteins when activated by elevated intracellular concentration of calcium cation and are therefore implicated in a variety of disorders such as muscular dystrophy [1,2].
Duchenne Muscular Dystrophy (DMD) is a fatal inherited neuromuscular disease which is caused by the mutation on the gene encoding for dystrophin. DMD is associated with progressive deterioration of muscle function and no effective treatment is currently available [3]. Calpains are over-activated in dystrophin-deficient muscles and contribute to muscle wasting through increased proteolysis. Inhibition of calpain is therefore regarded as a possible therapeutic strategy for the treatment of DMD.
Starting from known calpain inhibitor lead compounds such as MDL28170 **1**, we initiated a lead optimization program to develop calpain inhibitors **2** with improved uptake into muscle cells. The presentation will describe the synthesis and evaluation of peptide keto-carbonyl compounds. These inhibitors exhibited activity with IC50 value at nanomolar range and they showed greatly improved potency over reference compound MDL28170 in the cellular assay. Several drug candidates were tested *in vivo* in *mdx* mice [4], a well established mouse model for DMD. They showed positive effects on two histological parameters demonstrating their potential as a treatment option.




**1**, MDL28170




**2**

[1] Wells, G. J., Bihowsky, R. *Exp. Opin. Ther. Pat.* **1998**, *8*, 1707-1727.
[2] Donkor, I. O. *Curr. Med. Chem*. **2000**, *7*, 1171-1188.
[3] Khurana, T. S., Davies, K. E., *Nature Rev. Drug Discovery* **2003**, *2*, 379-390.
[4] Briguet A., Courdier-Fruh I., Foster M., Meier T., Magyar J. P. *Neuromusc. Disord.* **2004**, *14*, 675-682.