Peptidic α-ketoamides as PfSUB1 inhibitors

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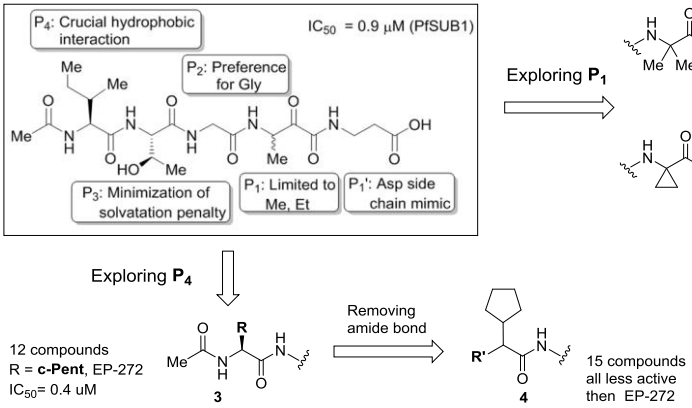
Malarial serine protease (PfSUB1) is involved in parasite invasion and egress of/from human red blood cells. Consequently, PfSUB1 has a potential to be exploited as anti-malarial drug target [1]. We have previously developed peptidic PfSUB1 inhibitors containing α-ketoamide warhead [2]. Preliminary SAR investigations revealed the crucial interactions of peptidic part of ketoamide inhibitors. Here we report additional studies to explore the optimal substituents for sub-pockets P_1 and P_4.



Geminal substitution at P_1 position provided inactive compounds **1** and **2**. Variation of P_4 position (compounds **3**) revealed c-Pent as the most optimal substituent leading to improved inhibitor EP-272. Further attempts were made to reduce the number of amide groups leading to series of inhibitors **4**. These compounds showed reduced activity compared to parent inhibitor EP-272.

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References:

1. Blackman, M. *Cell. Microbiol*. **2008**, *10*, 1925 − 1934
2. Kher, S. S.; Penzo M.; Fulle, S.; Finn, P. W.; Blackman, M. J.; Jirgensons, A. *Bioorg. Med. Chem. Lett.*, **2014**, *24*, 4486 – 4489.