Synthesis of peptidic α-ketoamide analogues of known PfSUB1 inhibitor

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INTRODUCTION

Malaria was considered to be endemic in 91 countries and territories in 2016, down from 108 in 2000. Most of the change can be attributed to the wide-scale deployment of malaria control interventions. Despite this remarkable progress, the global count of malaria in 2015 was 212 million new cases and 429 000 deaths [1].

Egress of plasmodium blood-stage merosoites relies on protease activity, so the enzymes involved have potential as antimalarial drug targets. As such, subtilisin-like serine protease called SUB1 is known to be involved in parasite invasion and egress within human red blood cells [2]. Recently, successful development of potent peptidyl PfSUB1 inhibitors bearing a difluorostatone moiety as a transition-state mimetic has been published [3] and also active inhibitors containing α-ketoamide warhead were developed, which ensures the binding to the protease by forming reversible covalent bond between the α-keto- group of the inhibitor and the serine of the catalytic triad [4].

RESULTS AND DISCUSSION

Based on the previous results of α-ketoamide moiety containing substrates (fig. 1.) [4] and their inhibitory activities, we planned to synthesize analogues and continue structure–activity relationship studies.

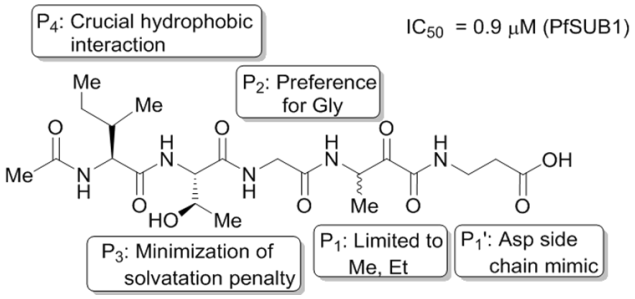
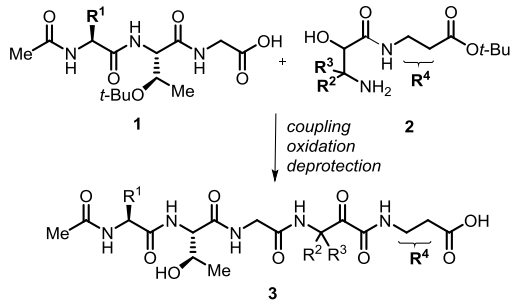


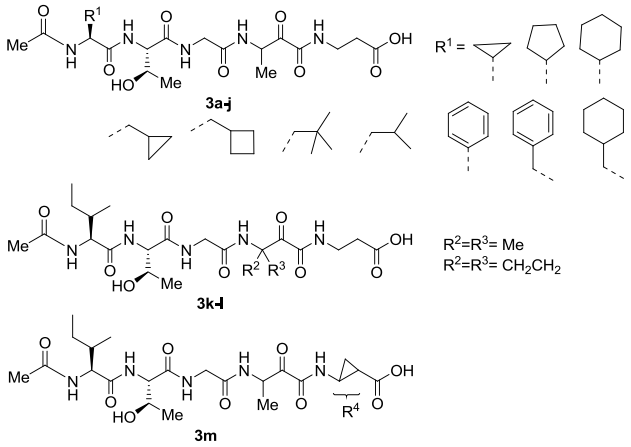
Figure 1. Peptidic α-ketoamide PfSUB1 inhibitor

We started our synthesis with previously described method shown in scheme 1. Initially, tripeptide **1** and amino alcohol containing building block **2** were coupled together forming amide bond, then oxidation of free alcohol functionality and deprotection of *t*-butyl groups gave final compound **3**.



Scheme 1. General synthesis of compounds **3**

Analogues were synthesized by changing substituents $R^{1,2,3 \text{ and } 4}$ (scheme 2).



Scheme 2. Analogues of known PfSUB1 inhibitor

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