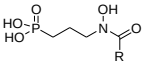
SYNTHESIS of β-ANALOGUES of FR900098 AS ANTIMALARIALS

Chofor René

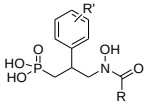
Laboratory for Medicinal Chemistry, Gent University, Harelbekestraat 72, 9000 Ghent

Background

Recently, the discovery of the mevalonate-independent pathway for isoprenoid biosynthesis opened interesting opportunities for the discovery of new antimalarial agents, as this alternative pathway is absent in humans. Two groups simultaneously discovered that fosmidomycin (**1**) potently inhibits 1-deoxy-D-xylulose 5-phosphate reductoisomerase (DXR),[1] which converts 1-deoxy-D-xylulose 5-phosphate (DOXP) to 2C-methyl-D-erithrytol phosphate (MEP), the second step in the non-mevalonate pathway. Its acetyl counterpart FR900098 (**2**) exhibits potent inhibition of DXR, and the former is currently in clinical trials of combination therapies for the treatment of malaria. They thus represent valuable leads, for further optimization in the quest for new antimalarials.



1 R = H
2 R = Me



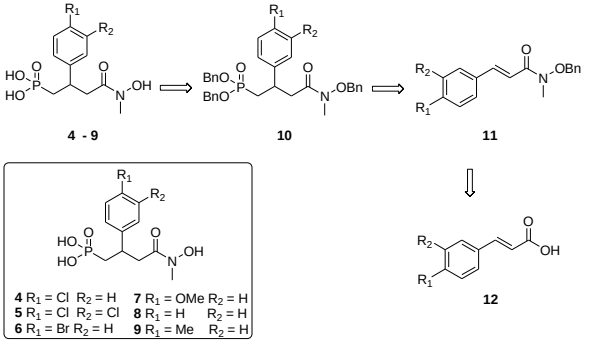
3 R = H or Me
R' = H, Cl, F, CO_2H, CH_3

Aim

Attempts to increase their potency by introducing various aromatic groups in α-position of the phosphonate, yielded analogues with increased cell-based activity.[2] Remarkably, substitution at the β-position has hitherto not been explored. In this poster, we present our ongoing efforts towards the synthesis of β-substituted analogues (**3**).

Methods-retrosynthesis

Conjugate addition of dibenzyl methylphosphonate to cinnamic hydroxamates or esters, offers a short synthetic plan, which also allows late introduction of the phosphonate moiety to yield a modified three carbon linker and hydroxamate of **3**. Thus, treatment of various cinnamic acids with N-methyl,O-benzylhydroxylamine affords appropriate intermediates **11** which serve as Micheal acceptors for complimentarily protected phosphonate donors. A single benzyl deprotection step of **10** would then give access to the desired target compounds **4** - **9**.



Results and conclusion

A short synthetic plan for modifying the three carbon spacer of FR900098 at the beta position has been developed and successfully executed. Biological evaluation will follow.

References

[1] Kuzuyama, T.; Shimizu, T.; Takahashi, S.; Seto, H. *Tetrahedron Lett.1998*, 39, 7913.

[2] Devreux, V.; Wiesner, J.; Jomaa, H.; Rozenski, J.; Van der Eycken, J.; Van Calenbergh, S. *J. Org. Chem.* **2007,** *72*, 3783-3789.