Getting fosmidomycin inside mycobacterial cells: a prodrug approach.

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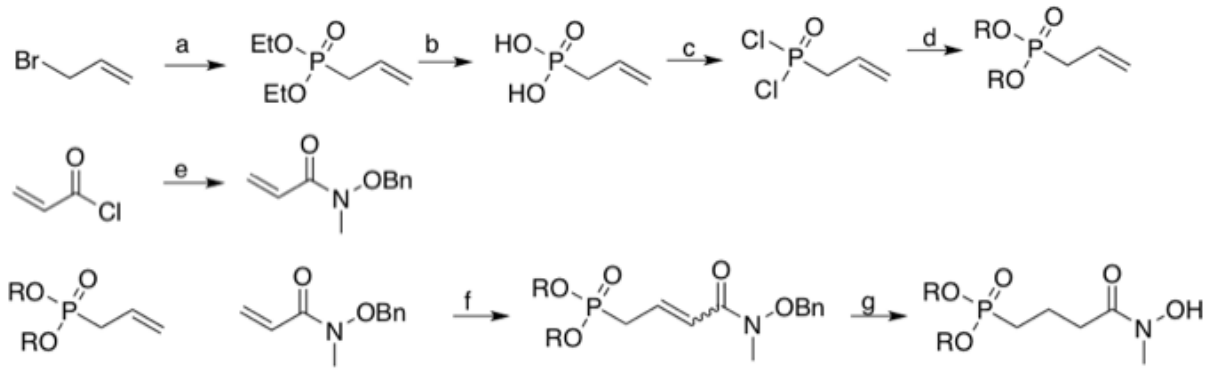
Antimalarial and antitubercular agents with new mechanisms of action are necessary to tackle *Plasmodium* parasites and *Mycobacteria* resistant to all current therapies. Fosmidomycin has been shown to be a well-tolerated, safe and efficacious antimalarial drug in combination treatment. However, its pharmacokinetic properties are less than ideal, with only moderate bioavailability and a short plasma half-life. Moreover, because of the unique highly lipophilic cell wall of *Mycobacteria*, fosmidomycin cannot cross the cell wall and thus, is not active against *Mycobacteria*.

A lot of research has been done on the design of highly active fosmidomycin analogs. However, the problem of low bioavailability remains. Conversion into hydrophobic phosphonate prodrugs can improve both oral bioavailability and cell penetration by passive diffusion. To date, only acyloxymethyl- and alkoxycarbonyloxymethyl prodrugs have been reported in the literature. The aim of this project is to synthesize a broad range of prodrugs of fosmidomycin analogs and to test them for whole cell activity against *Plasmodium* species and *Mycobacteria*.

In this poster, we will present the synthesis of HepDirect and alkoxyalkyl phosphonate esters. A short and broadly applicable synthesis route was designed, the key step being cross metathesis. We will also present our ongoing efforts towards the synthesis of phosphonamidate prodrugs.



a) $(EtO)_3P$, 150°C, 97%; b) TMSBr, DCM; c) oxalyl chloride, DMF, DCM, 45°C; d) $C_{16}H_{33}OC_3H_6OH$, DIPEA, pyr, DCM, 0°C, 47%; e) NH(Me)OBn, pyr, DCM, 0°C, 69%; f) Grubbs 2, DCE, 40°C, 55%; g) H_2, Pd/C, MeOH, q.