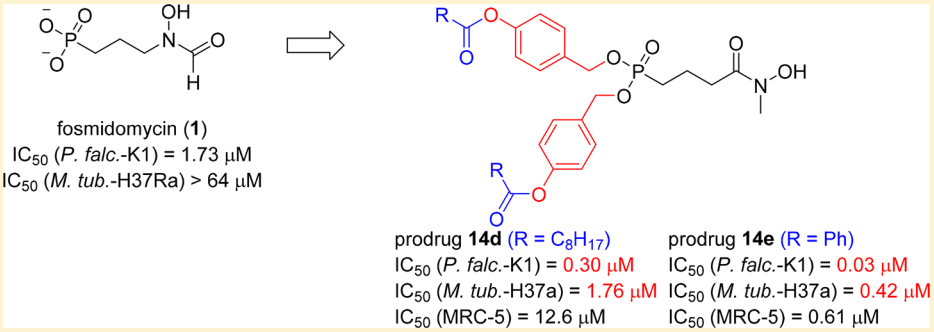
ACS Medicinal Chemistry Letters
Cite This: ACS Med. Chem. Lett. 2018, 9, 986−989
Letter
pubs.acs.org/acsmedchemlett

Acyloxybenzyl and Alkoxyalkyl Prodrugs of a Fosmidomycin Surrogate as Antimalarial and Antitubercular Agents

Charlotte Courtens,[†] Martijn Risseeuw,[†] Guy Caljon,[‡] Paul Cos,[‡] and Serge Van Calenbergh*[,†]

[†]Laboratory for Medicinal Chemistry, Ghent University, Ottergemsesteenweg 460, B-9000 Ghent, Belgium
[‡]Laboratory for Microbiology, Parasitology and Hygiene, University of Antwerp, Universiteitsplein 1 (S7), B-2610 Wilrijk, Belgium

Supporting Information



ABSTRACT: Two classes of prodrugs of a fosmidomycin surrogate were synthesized and investigated for their ability to inhibit *in vitro* growth of *P. falciparum* and *M. tuberculosis*. To this end, a novel efficient synthesis route was developed involving a cross metathesis reaction as a key step. Alkoxyalkyl prodrugs show decent antimalarial activities, but acyloxybenzyl prodrugs proved to be the most interesting and show enhanced antimalarial and antitubercular activity. The most active antimalarial analogues show low nanomolar IC_{50} values.

KEYWORDS: *Fosmidomycin, prodrugs, nonmevalonate pathway, isoprenoid biosynthesis, malaria, tuberculosis*

Despite considerable international efforts, malaria and tuberculosis remain two major challenges to public health.[1,2] Especially worrying are the emergence and spread of artemisinin resistant *Plasmodium falciparum*[3,4] and the rise of infections with multidrug resistant (MDR) and extensively drug resistant (XDR) *Mycobacterium tuberculosis*.[2] Therefore, new drugs that are free from cross-resistance with currently used antimalarial and antitubercular drugs are urgently needed. Toward this goal, inhibition of the methylerythritol (MEP) pathway for isoprenoid biosynthesis represents a promising strategy for the development of new antimalarial and antitubercular agents since it is essential in the aforementioned target pathogens and absent in humans.[5]

The first committed reaction step of the MEP pathway is catalyzed by IspC or DXR (1-deoxy-D-xylulose 5-phosphate reducto-isomerase).[6] Fosmidomycin (**1**, Figure 1) is a natural antibiotic acting as a slow, tight-binding inhibitor of this enzyme.[7] It has been shown to be a well-tolerated, safe, and efficacious antimalarial drug in combination treatment.[8−10] However, fosmidomycin's pharmacokinetic (PK) properties are suboptimal, with only moderate bioavailability (30%) and a short plasma half-life (2h).[11,12] Due to its highly polar character, mainly due to the phosphonate functionality, which is charged at physiological pH, fosmidomycin permeates cells only poorly via passive diffusion. This has important consequences not only for oral bioavailability but also for the

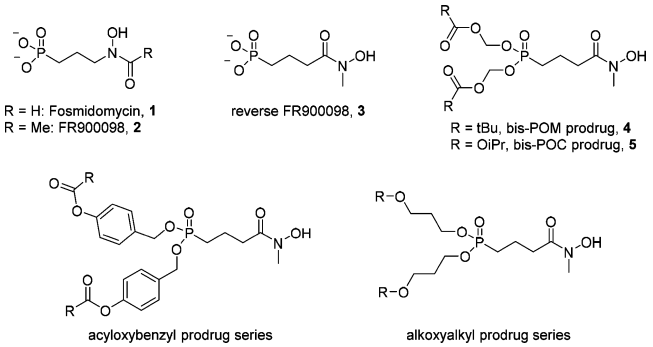


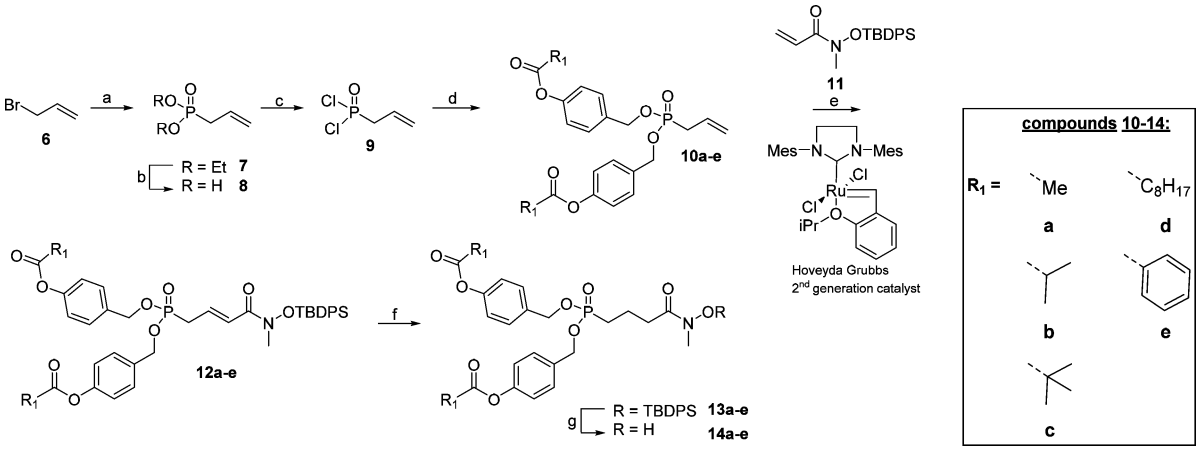
Figure 1. Structural formulas of fosmidomycin, FR900098 and its reverse analog **3**, and known prodrugs **4** and **5**. Acyloxybenzyl and alkoxyalkyl prodrugs are the focus of this work.

molecule to reach its intracellular target. In *E. coli*, the uptake of fosmidomycin has been shown to be dependent on the presence of a glycerol 3-phosphate transporter (GlpT).[13] Also *P. falciparum*-infected erythrocytes have been shown to use parasite-induced permeability pathways, to facilitate uptake of fosmidomycin in infected red blood cells.[14] For various

Received: May 14, 2018
Accepted: September 11, 2018
Published: September 11, 2018

DOI: 10.1021/acsmedchemlett.8b00223
ACS Med. Chem. Lett. 2018, 9, 986−989

Scheme 1. Synthesis of Acyloxybenzyl Prodrugs[a]



[a]Reagents and conditions: (a) triethyl phosphite, 150 °C (97%); (b) (i) TMSBr, DCM; (ii) H_2O, THF; (c) oxalyl chloride, DMF, DCM, 45 °C; (d) acyloxybenzylalcohol, DIPEA, pyridine, DCM (53−60% over 3 steps); (e) Hoveyda−Grubbs second generation catalyst, toluene, 70 °C (58−77%); (f) $NiCl_2 \cdot 6H_2O$, $NaBH_4$, THF (26−75%); (g) HF·pyridine, pyridine, THF, 0 °C (63−80%).

reasons, it would be interesting to enable fosmidomycin uptake independent of transporters. One such reason would be that sole dependence of uptake on one transporter increases the chances for bacterial resistance development. Indeed, it has been shown that fosmidomycin-resistant *E. coli* strains are often deficient in GlpT activity.[13,15] Liver-stage *Plasmodium berghei* has also been shown to be resistant to fosmidomycin due to the inability of this phosphonate antibiotic to enter hepatocytes.[14] *Mycobacteria* lack the GlpT transporter and additionally have a highly lipophilic cell wall. As a result, fosmidomycin is unable to penetrate *Mycobacteria* to reach its target.[16] Perusal of the literature shows that a lot of research has been dedicated to improve the potency of fosmidomycin.[17−19] However, the problem of low bioavailability and cellular penetration remains.

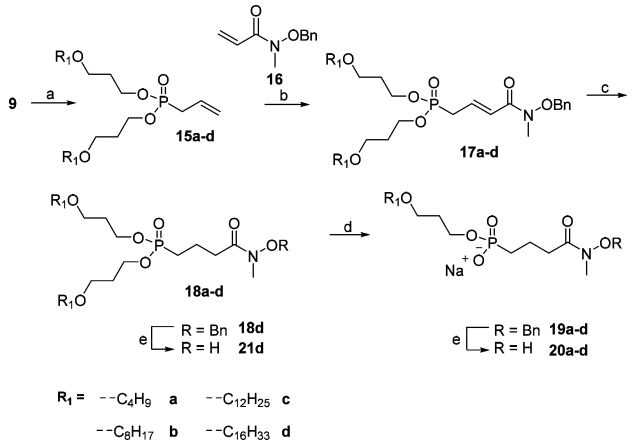
Prodrugs of fosmidomycin (analogues) have been obtained, mainly by conversion of the phosphonate moiety into acyloxymethyl (such as **4**, Figure 1) and alkoxycarbonyloxymethyl phosphonate esters (such as **5**, Figure 1) and have been shown to possess increased antimalarial and to some extent also antimycobacterial activity.[20−23] Previous research in our lab has confirmed that the hydroxamate counterparts of fosmidomycin (**1**, Figure 1) and FR900098 (**2**, Figure 1) have comparable inhibitory activity against both *Pf*DXR and *Mtb*DXR. Also, IC_{50} values of **2** and its reverse analog **3** (Figure 1) against the *P. falciparum* K1 strain have been shown to be comparable.[24] For reasons of synthetic ease and equipotent biological activity, **3** (Figure 1), a fosmidomycin surrogate, has been used as a starting point for the development of prodrugs. This Letter reports on the synthesis and *in vitro* antimalarial and antitubercular activity of two novel prodrug series of this fosmidomycin surrogate: the acyloxybenzyl and the alkoxyalkyl phosphonate esters (Figure 1). Both series are inspired by phosphonate and phosphate prodrugs successfully applied in the nucleoside field.[25] The acyloxybenzyl prodrug approach, developed by Meier and coworkers, has been shown to increase cellular uptake of nucleoside di- and triphosphates.[26−29] Cleavage of this prodrug class is based on hydrolysis of the acyl group by an esterase, followed by a rapid and spontaneous release of the resulting quinone methide and the parent phosphates.[29] The alkoxyalkyl prodrug approach, developed by Hostetler for nucleoside phosphonates, has been shown to facilitate diffusion in cells.[30] Intracellular cleavage of these prodrugs is mediated by phospholipase C, which hydrolyzes the lysophosphatidylcholine resembling phosphonate esters. We hypothesized that the acyloxybenzyl and alkoxyalkyl esters of **3** (Figure 1) might also enhance *in vitro* antimalarial and antitubercular activity as a result of increased cellular uptake.

The synthesis of both prodrug classes relies on a cross metathesis reaction between the appropriate allylphosphonate and *N*-acrylhydroxamate building blocks. This allows easy modifications on both sides. The phosphonate building blocks **10a−e** were synthesized starting from allyl bromide **6** (Scheme 1). Arbuzov reaction with triethyl phosphite yielded diethylphosphonate **7**, which was hydrolyzed to the phosphonic acid and subsequently converted into the phosphonic dichloride **9** upon treatment with oxalyl chloride. Treatment of **9** with the appropriate acyloxybenzylalcohols afforded phosphonate esters **10a−e**. Cross metathesis with *O*-silyl-protected acryl hydroxamate **11** using Hoveyda−Grubbs second generation catalyst yielded the protected unsaturated compounds **12a−e** in good yields.[31,32] Saturation of the alkene using a nickel boride reduction to give **13a−e** and subsequent silyl deprotection using HF·pyridine yielded the final compounds **14a−e**. The alkoxyalkyl prodrugs were synthesized in a similar way (Scheme 2). Reaction of phosphonic dichloride **9** with the corresponding alkoxyalkylalcohols to provide **15a−d** was followed by cross metathesis reaction with *O*-benzyl-protected acryl hydroxamate **16** to provide **17a−d**. After nickel boride reduction of the alkene, removal of the benzyl group by hydrogenation was preceded by monodealkylation using sodium azide, yielding monoesters **20a−d**. Immediate hydrogenation of the dialkylphosphonate ester **18d** afforded 21**d**.

The final compounds were screened for growth inhibition of asexual blood stage parasites of *P. falciparum* (Pf-K1) and an avirulent *M. tuberculosis* strain (H37Ra) (Table 1). Additionally, toxicity on MRC-5 fibroblasts was assessed. Compared to fosmidomycin, all acyloxybenzyl prodrugs showed improved antiplasmodial and antibacterial activity. The benzoyl analog **14e** displayed the best inhibitory activity of *P. falciparum* growth, while analogues **14b**, **14c**, and **14e** showed submicromolar antitubercular activities. Acetyl analog **14a** showed considerably weaker antitubercular activity than the

DOI: 10.1021/acsmedchemlett.8b00223
ACS Med. Chem. Lett. 2018, 9, 986−989

Scheme 2. Synthesis of Alkoxyalkyl Prodrugs[a]



[a]Reagents and conditions: (a) alkoxyalkylalcohol, DIPEA, pyridine, DCM (29−52% over 3 steps); (b) Hoveyda−Grubbs second generation catalyst, toluene, 70 °C (59−76%); (c) $NiCl_2.6H_2O$, $NaBH_4$, THF (27−58%); (d) NaN_3, DMF, 130 °C (40−84%); (e) H_2, Pd/C, MeOH (24−67%).

Table 1. Biological Evaluation of Novel Fosmidomycin Surrogate Prodrugs

compd	Pf-K1 IC_{50} [μM]	H37Ra IC_{50} [μM]	MRC-5 [μM]	SI (Pf-K1)	SI (H37Ra)
1	1.73[33]	>64	>64		
2	0.42[33]	>64			
3	0.26[24]	>64			
4	0.73	44.28	>64	>88	>1.4
5	0.08	>64	55.73	743	-
14a	0.49	19.68	15.49	32	0.8
14b	0.14	0.64	0.99	7.3	1.6
14c	0.16	0.43	0.98	6.1	2.3
14d	0.30	1.76	12.6	42	7.6
14e	0.03	0.42	0.61	20	1.5
20a	16	>64	>64	>4	
20b	1.9	>64	>64	>34	
20c	0.82	>64	55.87	68	
20d	0.95	>64	24.54	26	
21d	42	>64	>64	>1.5	

other analogues. This might at least partially be explained by the labile character of the phenolic acetyl ester. A stability experiment in human serum at 37 °C demonstrated that the stability of the compounds increased in the following order: **14a** < **14b** < **14d** < **14e** < **14c**. Even acetyl derivative **14a** with the shortest serum half-life was more stable than reference prodrugs **4** and **5** (details in Supporting Information). For use as antimalarials, limited serum stability of the prodrug promoieties is less of a problem since the released phosphonate can still be taken up via the parasite-induced permeability pathways. For *Mycobacterium*, however, passive diffusion in its prodrug form is expected to be the prevalent way of cellular uptake. Unfortunately, all acyloxybenzyl analogues decreased cell viability of MRC-5 fibroblasts, particularly **14b**, **14c**, and **14e**. This toxicity might at least partially be explained by the release of 2 equiv of the reactive electrophile quinone methide upon prodrug cleavage. Despite the observed toxicity, analogues **14d** and **14e** are considered interesting as they exhibited relatively selective antimalarial activity, as indicated by the favorable selectivity indices.

Remarkably, all monoalkoxyalkyl phosphonates were inactive against *M. tuberculosis* but showed good antiplasmodial activity. Dodecyl analog **20c** and hexadecyl analog **20d** showed submicromolar IC_{50} values, comparable to fosmidomycin. It is possible that very long alkyl chains are beneficial for passive diffusion and/or necessary for recognition by phospholipase C, which is hypothesized to be the activating enzyme. Double ester **21d** showed only weak antimalarial activity. Solubility issues during biological evaluation of this compound hampered accurate testing, which might explain this result.

In conclusion, we have successfully developed an efficient synthesis route for two classes of prodrugs of a fosmidomycin surrogate, involving a cross metathesis reaction as the key step. Acyloxybenzyl prodrug **14e** showed markedly improved *in vitro* antimalarial activity. This prodrug of a MEP pathway inhibitor may serve as a lead for future analog development of compounds that combine superior activity against their target microorganisms with an improved PK profile, combined with lower cytotoxicity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.8b00223.

Experimental details and characterization data for the reported compounds, NMR spectra, stability assay, and biological data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*Tel: +32 (0)9 264 81 24. Fax: +32 (0)9 264 81 46. E-mail: serge.vancalenbergh@ugent.be.

ORCID

Serge Van Calenbergh: 0000-0002-4201-1264

Author Contributions

All authors have given approval to the final version of the manuscript.

Funding

The authors gratefully acknowledge funding by the Research Fund Flanders (FWO).

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

C.C. is indebted to the FWO-Flanders for a PhD Scholarship. The authors would like to thank An Matheeussen and Izet Karalic for technical assistance and Bernardo Ercoli for assistance with the synthesis.

■ ABBREVIATIONS

MDR, multidrug resistant; XDR, extensively drug resistant; MEP, methylerythritol phosphate; DXR, 1-deoxy-D-xylulose 5-phosphate reductoisomerase; PK, pharmacokinetic; GlpT, glycerol 3-phosphate transporter; SI, selectivity index; TMSBr, trimethylsilyl bromide; DCM, dichloromethane; THF, tetrahydrofuran; DMF, dimethylformamide; DIPEA, diisopropylethylamine; MeOH, methanol

DOI: 10.1021/acsmedchemlett.8b00223
ACS Med. Chem. Lett. 2018, 9, 986−989

REFERENCES

(1) WHO. World malaria report. http://www.who.int/malaria/publications/world_malaria_report/en/ (accessed Mar 13, 2018).
(2) WHO. Tuberculosis. http://www.who.int/mediacentre/factsheets/fs104/en/ (accessed Mar 13, 2018).
(3) Dondorp, A. M.; Nosten, F.; Yi, P.; Das, D.; Phyo, A. P.; Tarning, J.; Lwin, K. M.; Ariey, F.; Hanpithakpong, W.; Lee, S. J.; et al. Artemisinin Resistance in *Plasmodium falciparum* Malaria. *N. Engl. J. Med.* **2009**, *361*, 455−467.
(4) Lu, F.; Culleton, R.; Zhang, M.; Ramaprasad, A.; von Seidlein, L.; Zhou, H.; Zhu, G.; Tang, J.; Liu, Y.; Wang, W.; et al. Emergence of Indigenous Artemisinin-Resistant *Plasmodium falciparum* in Africa. *N. Engl. J. Med.* **2017**, *376*, 991−993.
(5) Frank, A.; Groll, M. The Methylerythritol Phosphate Pathway to Isoprenoids. *Chem. Rev.* **2017**, *117*, 5675−5703.
(6) Murkin, A. S.; Manning, K. A.; Kholodar, S. A. Mechanism and Inhibition of 1-Deoxy-*D*-Xylulose-5-Phosphate Reductoisomerase. *Bioorg. Chem.* **2014**, *57*, 171−185.
(7) Mac Sweeney, A.; Lange, R.; Fernandes, R. P. M.; Schulz, H.; Dale, G. E.; Douangamath, A.; Proteau, P. J.; Oefner, C. The Crystal Structure of *E. Coli* 1-Deoxy-*D*-Xylulose-5-Phosphate Reductoisomerase in a Ternary Complex with the Antimalarial Compound Fosmidomycin and NADPH Reveals a Tight-Binding Closed Enzyme Conformation. *J. Mol. Biol.* **2005**, *345*, 115−127.
(8) Mombo-Ngoma, G.; Remppis, J.; Sievers, M.; Zoleko, R. M.; Endamne, L.; Kabwende, L.; Veletzky, L.; Nguyen, T. T.; Groger, M.; Lötsch, F.; et al. Efficacy and Safety of Fosmidomycin-Piperaquine as Non-Artemisinin-Based Combination Therapy for Uncomplicated *falciparum* Malaria - A Single-Arm, Age-de-Escalation Proof of Concept Study in Gabon. *Clin. Infect. Dis.* **2018**, *66*, 1823−1830.
(9) Borrmann, S.; Adegnika, A. A.; Matsiegui, P.-B.; Issifou, S.; Schindler, A.; Mawili-Mboumba, D. P.; Baranek, T.; Wiesner, J.; Jomaa, H.; Kremsner, P. G. Fosmidomycin-Clindamycin for *Plasmodium falciparum* Infections in African Children. *J. Infect. Dis.* **2004**, *189*, 901−908.
(10) Borrmann, S.; Adegnika, A. A.; Moussavou, F.; Oyakhirome, S.; Esser, G.; Matsiegui, P.-B.; Ramharter, M.; Lundgren, I.; Kombila, M.; Issifou, S.; et al. Short-Course Regimens of Artesunate-Fosmidomycin in Treatment of Uncomplicated *Plasmodium falciparum* Malaria. *Antimicrob. Agents Chemother.* **2005**, *49*, 3749−3754.
(11) Murakawa, T.; Sakamoto, H.; Fukada, S.; Konishi, T.; Nishida, M. Pharmacokinetics of Fosmidomycin, a New Phosphonic Acid Antibiotic. *Antimicrob. Agents Chemother.* **1982**, *21*, 224−230.
(12) Na-Bangchang, K.; Ruengweerayut, R.; Karbwang, J.; Chauemung, A.; Hutchinson, D. Pharmacokinetics and Pharmacodynamics of Fosmidomycin Monotherapy and Combination Therapy with Clindamycin in the Treatment of Multidrug Resistant *falciparum* Malaria. *Malar. J.* **2007**, *6*, 70.
(13) Sakamoto, Y.; Furukawa, S.; Ogihara, H.; Yamasaki, M. Fosmidomycin Resistance in Adenylate Cyclase Deficient (*Cya*) Mutants of *Escherichia coli*. *Biosci., Biotechnol., Biochem.* **2003**, *67*, 2030−2033.
(14) Baumeister, S.; Wiesner, J.; Reichenberg, A.; Hintz, M.; Bietz, S.; Harb, O. S.; Roos, D. S.; Kordes, M.; Friesen, J.; Matuschewski, K.; et al. Fosmidomycin Uptake into *Plasmodium* and *Babesia*-Infected Erythrocytes Is Facilitated by Parasite-Induced New Permeability Pathways. *PLoS One* **2011**, *6*, e19334.
(15) Nilsson, A. I.; Berg, O. G.; Aspevall, O.; Kahlmeter, G.; Andersson, D. I. Biological Costs and Mechanisms of Fosfomycin Resistance in *Escherichia coli*. *Antimicrob. Agents Chemother.* **2003**, *47*, 2850−2858.
(16) Brown, A. C.; Parish, T. Dxr Is Essential in *Mycobacterium tuberculosis* and Fosmidomycin Resistance Is Due to a Lack of Uptake. *BMC Microbiol.* **2008**, *8*, 78.
(17) Masini, T.; Hirsch, A. K. H. Development of Inhibitors of the 2*C*-Methyl-*D*-Erythritol 4-Phosphate (MEP) Pathway Enzymes as Potential Anti-Infective Agents. *J. Med. Chem.* **2014**, *57*, 9740−9763.
(18) Wang, X.; Dowd, C. S. The Methylerythritol Phosphate Pathway: Promising Drug Targets in the Fight against Tuberculosis. *ACS Infect. Dis.* **2018**, *4*, 278−290.
(19) Singh, N.; Cheve, G.; Avery, M. A.; McCurdy, C. R. Targeting the Methyl Erythritol Phosphate (MEP) Pathway for Novel Antimalarial, Antibacterial and Herbicidal Drug Discovery: Inhibition of 1-Deoxy-*D*-Xylulose-5-Phosphate Reductoisomerase (DXR) Enzyme. *Curr. Pharm. Des.* **2007**, *13*, 1161−1177.
(20) Ponaire, S.; Zinglé, C.; Tritsch, D.; Grosdemange-Billiard, C.; Rohmer, M. Growth Inhibition of *Mycobacterium Smegmatis* by Prodrugs of Deoxyxylulose Phosphate Reducto-Isomerase Inhibitors, Promising Anti-Mycobacterial Agents. *Eur. J. Med. Chem.* **2012**, *51*, 277−285.
(21) Uh, E.; Jackson, E. R.; San Jose, G.; Maddox, M.; Lee, R. E.; Lee, R. E.; Boshoff, H. I.; Dowd, C. S. Antibacterial and Antitubercular Activity of Fosmidomycin, FR900098, and Their Lipophilic Analogs. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 6973−6976.
(22) Brücher, K.; Gräwert, T.; Konzuch, S.; Held, J.; Lienau, C.; Behrendt, C.; Illarionov, B.; Maes, L.; Bacher, A.; Wittlin, S.; et al. Prodrugs of Reverse Fosmidomycin Analogues. *J. Med. Chem.* **2015**, *58*, 2025−2035.
(23) Wiesner, J.; Ortmann, R.; Jomaa, H.; Schlitzer, M. Double Ester Prodrugs of FR900098 Display Enhanced In-Vitro Antimalarial Activity. *Arch. Pharm. (Weinheim, Ger.)* **2007**, *340*, 667−669.
(24) Chofor, R.; Sooriyaarachchi, S.; Risseeuw, M. D. P.; Bergfors, T.; Pouyez, J.; Johny, C.; Haymond, A.; Everaert, A.; Dowd, C. S.; Maes, L.; et al. Synthesis and Bioactivity of β-Substituted Fosmidomycin Analogues Targeting 1-Deoxy-*D*-Xylulose-5-Phosphate Reductoisomerase. *J. Med. Chem.* **2015**, *58*, 2988−3001.
(25) Pradere, U.; Garnier-Amblard, E. C.; Coats, S. J.; Amblard, F.; Schinazi, R. F. Synthesis of Nucleoside Phosphate and Phosphonate Prodrugs. *Chem. Rev.* **2014**, *114*, 9154−9218.
(26) Jessen, H. J.; Schulz, T.; Balzarini, J.; Meier, C. Bioreversible Protection of Nucleoside Diphosphates. *Angew. Chem., Int. Ed.* **2008**, *47*, 8719−8722.
(27) Weinschenk, L.; Schols, D.; Balzarini, J.; Meier, C. Nucleoside Diphosphate Prodrugs: Nonsymmetric DiPPro-Nucleotides. *J. Med. Chem.* **2015**, *58*, 6114−6130.
(28) Gollnest, T.; Dinis de Oliveira, T.; Rath, A.; Hauber, I.; Schols, D.; Balzarini, J.; Meier, C. Membrane-Permeable Triphosphate Prodrugs of Nucleoside Analogues. *Angew. Chem., Int. Ed.* **2016**, *55*, 5255−5258.
(29) Gollnest, T.; de Oliveira, T. D.; Schols, D.; Balzarini, J.; Meier, C. Lipophilic Prodrugs of Nucleoside Triphosphates as Biochemical Probes and Potential Antivirals. *Nat. Commun.* **2015**, *6*, 8716.
(30) Hostetler, K. Y. Alkoxyalkyl Prodrugs of Acyclic Nucleoside Phosphonates Enhance Oral Antiviral Activity and Reduce Toxicity: Current State of the Art. *Antiviral Res.* **2009**, *82*, A84−A98.
(31) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. Efficient and Recyclable Monomeric and Dendritic Ru-Based Metathesis Catalysts. *J. Am. Chem. Soc.* **2000**, *122*, 8168−8179.
(32) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. A General Model for Selectivity in Olefin Cross Metathesis. *J. Am. Chem. Soc.* **2003**, *125*, 11360−11370.
(33) Verbrugghen, T.; Cos, P.; Maes, L.; Van Calenbergh, S. Synthesis and Evaluation of α-Halogenated Analogues of 3-(Acetylhydroxyamino)Propylphosphonic Acid (FR900098) as Antimalarials. *J. Med. Chem.* **2010**, *53*, 5342−5346.

DOI: 10.1021/acsmedchemlett.8b00223
ACS Med. Chem. Lett. 2018, 9, 986−989